Statistical Analysis Plan

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

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SAP Approval Date: 04 April 2022

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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

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STATISTICAL ANALYSIS PLAN APPROVAL

Study No.: **CONN**ected **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

Study Title: FSS-AS-40139

Statistical Analysis Plan for:

☐ **Interim Analysis** ☐ **Integrated Summary of Efficacy**

☒ **Final Analysis** ☐ **Integrated Summary of Safety**

Amendment: Not applicable

Author: [redacted]
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Approver: [redacted] **Date**
[redacted], Clinical Statistics

Approver: [redacted] **Date**
[redacted], Medical Affairs

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LIST OF ABBREVIATIONS AND DEFINITIONS OF TERMS

Abbreviation	Term
ACT	Asthma Control Test
App	smart device application
BIPQ	Brief Illness Perception Questionnaire
BMI	body mass index
BMQ	Beliefs about Medicines Questionnaire
CAE	clinical asthma exacerbation
CI	confidence interval
CRF	case report form
CSR	clinical study report
DHP	Digital Health Platform
DS	Digital System
DTP	direct-to-patient
ED	emergency department
ET	early termination
eMDPI	multidose dry powder inhaler with integrated electronic module
GERD	gastroesophageal reflux disease
GINA	Global Initiative for Asthma
HCP	healthcare professional
ICS	inhaled corticosteroid
iHCP	investigational center healthcare provider
IMP	investigational medicinal product
IRT	interactive response technology
ITT	intent-to-treat
LABA	long-acting $beta_2$ agonist
LAMA	long-acting muscarinic antagonist
MAR	missing at random
MedDRA	Medical Dictionary for Regulatory Activities
MI	multiple imputation
Mini-AQLQ	Mini Asthma Quality of Life Questionnaire
mITT	modified intent-to-treat
PIF	peak inhalation flow
R&D	Research and Development
RTSM	Randomization and Trial Supply Management

Abbreviation	Term
SABA	short-acting beta$_2$ agonist
SAP	statistical analysis plan
SD	standard deviation
SE	standard error
SoC	standard of care
SOC	system organ class
SOP	standard operating procedure
SUS	System Usability Scale
WHO	World Health Organization
WPAI	Work Productivity and Activity Impairment

INTRODUCTION

This Statistical Analysis Plan (SAP) describes the planned analysis and reporting for Teva Branded Pharmaceutical Products Research and Development (R&D) study FSS-AS-40139 (**CONN**ected **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), and was written in accordance with GSD_SOP_702 (SAP).

The reader of this SAP is encouraged to read the study protocol for details on the conduct of this study, the operational aspects of clinical assessments, and the timing for completing the participation of a patient in this study.

The SAP is intended to be in agreement with the protocol, especially with regards to the primary and all secondary endpoints and their respective analyses. However, the SAP may contain more details regarding these particular points of interest, or other types of analyses (e.g. other endpoints). When differences exist in descriptions or explanations provided in the study protocol and this SAP, the SAP prevails; the differences will be explained in the Clinical Study Report (CSR).

1. STUDY OBJECTIVES AND ENDPOINTS

1.1. 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 Digital System (DS) compared to a Standard of Care (SoC) group.	The primary endpoint is the proportion of patients for the DS and SoC groups achieving meaningful improvement, which is defined as an Asthma Control Test (ACT) score 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 healthcare providers (iHCPs) for all patients in both groups.	This secondary endpoint will describe 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: o increased or decreased doses of inhaled medication o change to different inhaled medication o additional inhaled medication o addition of a systemic corticosteroid medication for asthma or another controller, including a long-acting muscarinic antagonist (LAMA) or biologics • frequency of intervention to manage comorbid conditions associated with poor asthma control (gastroesophageal reflux disease [GERD], sinusitis, etc.)
The **secondary objective (#2)** is to evaluate short-acting beta$_2$ agonist (SABA) usage and the number of SABA-free days in the DS group.	This secondary endpoint is the change from baseline in the mean weekly SABA usage and the change from baseline in the number of SABA-free days over the 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 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, smart device application [App], and dashboard) acceptability and usability, utilizing the System Usability Scale (SUS), completed by the patients in the DS group, 18 years of age or older, and the investigational center personnel at the end of the study.
The **secondary objective (#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, Digital Health Platform [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.

1.2. [redacted]

2. STUDY DESIGN

2.1. General Design

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, Digital Health Platform (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 1), stratified by investigational center.

Table 1: 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 Digital System (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 inhaled corticosteroid (ICS) with long-acting beta$_2$ agonist (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 a new Albuterol 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 investigational medicinal product (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 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, Global Initiative for Asthma [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 of the study protocol, 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.

Study procedures and assessments with their timing are summarized in Table 5 of the study protocol.

2.2. 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 Randomization and Trial Supply Management (RTSM) system. Since this an open-label study, blinding is not applicable.

2.3. Data Monitoring Committee

There will be no Data Monitoring Committee for this study.

2.4. Sample Size and Power Considerations

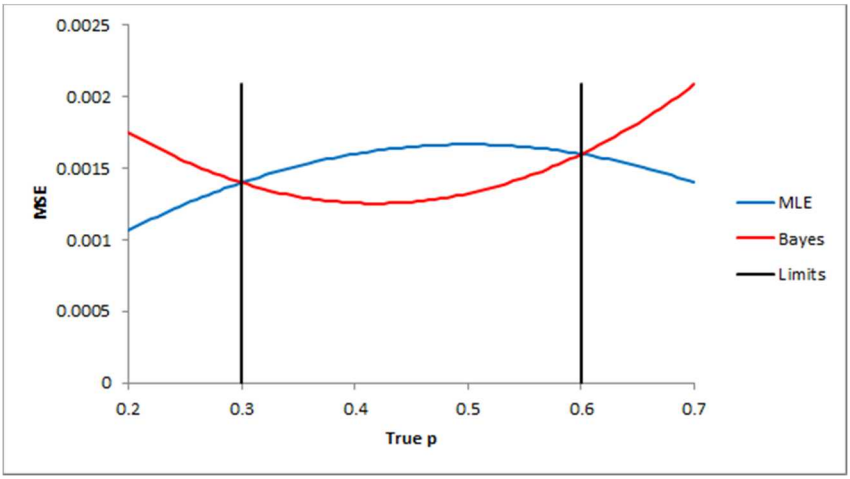
The sample size was selected based on a Bayesian approach which allows for a range of underlying proportions rather than a fixed predefined value.

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 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%.

2.5. Sequence of Planned Analyses

2.5.1. Planned Interim Analyses

There will be no formal interim analysis for this study.

2.5.2. Final Analyses and Reporting

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

This SAP and any corresponding amendments will be approved before database lock, in accordance to SOP GBP_RD_702 (SAP).

3. ANALYSIS SETS

3.1.1. 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.

3.1.2. 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 ACT assessment.

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 set will be used for all primary, secondary, [redacted] endpoint analyses.

3.1.3. 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.

4. GENERAL ISSUES FOR DATA ANALYSIS

4.1. General

Descriptive statistics for continuous variables include n, mean, standard deviation (SD), standard error (SE), median, minimum, and maximum. Descriptive statistics for categorical variables include patient counts and percentages, missing category will be displayed as appropriate.

Treatment dates are defined as follows:

- Treatment start date: date of randomization/the screening/baseline visit date.
- Treatment end date: the end of treatment/early termination (ET) visit date. If the end of treatment/ET date is missing then the last contact date will be used.

4.2. Specification of Baseline Values

Baseline is the data observed at that screening/baseline visit, unless otherwise specified.

4.3. Handling Withdrawals and Missing Data

For the primary endpoint, patients who discontinue early due to technology failure, disliking the digital platform, disease worsening, adverse experience or disliking the IMP will be counted as treatment failures. For those who discontinue early not to these reasons, the ACT value assessed at ET visit will be used. Those who discontinue early and do not have an ET visit will be counted as treatment failures.

For the SUS items 1, 3, 5, 7, and 9, if response to 1 item is missing, the missing item will be replaced by the average of the remaining 4 responses. For items 2, 4, 6, 8, and 10, if response to 1 item is missing, the missing item will be replaced by the average of the remaining 4 responses. If response to 2 or more of items 1, 3, 5, 7, and 9 are missing, or 2 or more of items 2, 4, 6, 8, and 10 are missing, the overall SUS score will be set to missing.

For the BMQ subscales, if response to 1 item within a subscale is missing, the missing response will be replaced with the average of the remaining responses within the subscale. If response to 2 or more items within a subscale are missing, the missing responses will not be replaced and the subscale score will be set to missing.

For the BIPQ cognitive subscale, if response to 1 item within the subscale is missing, the missing response will be replaced with the average of the remaining responses within the subscale. If response to 2 or more items within the subscale is missing, the missing responses will not be replaced and the subscale score will be set to missing. For the emotional subscale, if 1 of the responses is missing then the subscale will be set to missing.

For an incomplete mini-AQLQ, the overall score for a particular visit will not be calculated if 1 or more responses are missing; total scores for the domains will be regarded as missing if 1 or more item will be incomplete.

4.4. Study Days and Visits

Study days are numbered relative to the treatment start date (ie, ..., –2, –1, 1, 2, ...; with day 1 being the treatment start date and day –1 being the day before the treatment start date).

Weeks are defined in 7-day intervals (days 1 to 7, 8 to 14, …, 78 to 84). Day 1 is defined as the treatment start date (i.e., date of randomization/Visit 1 visit date).

By-visit (or by-week) summaries will include baseline, and the end of treatment and ET visits. The ET visit will be summarized as a separate visit.

5. STUDY POPULATION

5.1. General

The ITT analysis set will be used for all study population summaries, unless otherwise specified. Summaries will be presented by treatment group and for all patients.

5.2. Patient Disposition

Patients screened and screened but not randomized (with reason not randomized) will be summarized only for all patients using patient counts. Patients in the ITT analysis set, ITT analysis set who did not attempt to download the App, ITT analysis set who did not use the inhaler, safety analysis set, and mITT analysis set, patients who completed and withdrew from treatment (with reason for withdrawing), and patients who completed and withdrew from the study (with reason for withdrawal) will be summarized using descriptive statistics. The summary will be based on all patients. The denominator for calculating the percentages will be the number of patients in the ITT analysis set.

5.3. Demographics and Baseline Characteristics

The continuous variables of patient age, weight, height, and body mass index (BMI) will be summarized using descriptive statistics. The categorical variables of subject sex, race, and ethnicity will be summarized using descriptive statistics for each category. Missing categories will be presented if necessary.

5.4. Medical History

All medical history will be coded using the Medical Dictionary for Regulatory Activities (MedDRA). The incidence of medical history abnormalities will be summarized using descriptive statistics by system organ class (SOC) and preferred term. Patients are counted only once in each SOC category, and only once in each preferred term category.

5.5. Prior Therapy and Medication

Any prior therapy or medication a patient is taking at the screening/baseline visit will be recorded on the CRF. All prior therapies and medications will be coded using the World Health Organization (WHO) drug dictionary (WHO Drug).

The incidence of prior therapies and medications will be summarized using descriptive statistics by therapeutic class and preferred term. Patients are counted only once in each therapeutic class category, and only once in each preferred term category. Prior therapies and medications will include all medications taken and therapies administered before the treatment start date.

5.6. Study Protocol Deviations

Data from patients with any important protocol deviations during the study will be summarized overall and for each category using descriptive statistics.

6. DATA ANALYSIS

6.1. General

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.

The mITT analysis sets will be used for all data analyses, unless otherwise specified. Summaries will be presented by treatment group, as randomized.

6.2. Primary Endpoint and Analysis

6.2.1. Definition

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 primary endpoint is the proportion of patients for the DS and SoC groups reaching well-controlled asthma as defined by an ACT score of greater than or equal to 20, or a clinically important improvement in asthma control as defined by an increase of at least 3 units on the ACT score from baseline at the end of the 24-week treatment period (responder analysis of DS versus SoC group with responders defined by an ACT score of greater than or equal to 20 or an increase by greater than or equal to 3 units on the ACT score).

6.2.2. 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 digital platform, adverse event related to IMP, or disliking the 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.

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

$$\ln(\frac{pij}{1-pij}) = \beta_0 + \beta_1 x_i + \beta_2 baseline\ ACT\ value \quad + Center_j$$

where x_i = treatment group i , p_{ij} = response proportion of treatment group i at Center j, $Center_j$ = random center effect of center j.

An informative prior of Beta [9.52, 11.88] for SoC group and a non-informative prior of Beta [0.5,0.5] for the DS group will be assumed. Those priors will be converted to Normal(mean = -0.231, var = 0.192) for β_0 and Normal(mean = 0.236, var = 9.912) for β_1 respectively. Estimates of mean response rate and corresponding 95% credible intervals for individual proportions, histograms of the posterior response rates, odds ratio with corresponding 95% credible intervals for DS versus SoC, and probability of ($\beta_1 > 0$) will be presented.

The SAS code for the primary analysis is as follows:

```
proc mcmc data = x nbi = 1000 nmc = 500000 thin = 20 seed = 159 outpost =
post1 monitor = (beta0-beta2 sigma2 beta1_gt0 pi pi0 pooled or)
statistics=(summary intervals);

  parms beta0-beta2 0;

  parms sigma2 1;


  prior beta0 ~ normal (mean = -0.231, var = 0.192);

  prior beta1 ~ normal (mean = 0.236, var = 9.912);

  prior beta2 ~ normal(mean = 0, var = 1000);


  prior sigma2 ~ igamma(shape = 0.001, scale = 0.001);

  random b0 ~ normal(mean = 0, var = sigma2) subject = CENTER;


  eta = beta0 + b0 + beta1*trt + beta2*y0;

  pi = logistic(eta);

  pi0 = logistic(beta0 + b0 + beta2*y0);

  model count ~ binomial(n = total, p = pi);

  array or[<# of sites>];
```

```
  or[CENTER] = exp(b0 + beta1);

  pooled = exp(beta1);

run;
```

where count = number of responders and total = number of patients.

In addition, summary statistics for the ACT score will be presented at baseline, visit 2, visit 3, and ET visits. ACT score values and changes from baseline to each visit will be summarized using descriptive statistics.

In addition, summary statistics for question 4 of the ACT will be presented at baseline, visit 2, visit 3, and ET visits. Question 4 of the ACT values and changes from baseline to each visit will be summarized using descriptive statistics.

6.2.3. Sensitivity Analyses

Sensitivity analysis 1: This analysis will be performed by imputing missing ACT values using the multiple imputation (MI) method assuming missing at random (MAR). Those who discontinue the treatment before Week 24 due to technology failure, disliking the digital platform, adverse event related to IMP, or disliking the IMP will be considered having missing data. For those who discontinue early not due to these reasons, the ACT value assessed at the ET visit will be used. Those who discontinue early and do not have an ET visit will be considered having missing data.

The following steps will be performed for the analysis:

- Create complete datasets using imputation. The SAS code is as follows:

```
proc mi data = yy out = yy2 seed = 4192 nimpute = 500 minimum = 5 maximum = 25;
  class trt;
  var trt actbase v2 v3;
  monotone regpmm;
run;
```

- For each dataset, the clinically important improvement in asthma control variable will be derived for each patient as defined in Section 6.2.1.
- Analyze each dataset using the model described below for the primary endpoint.

```
ods output Diffs = dif LSMeans = lsm;
  proc genmod data = indata;
    by visit _imputation_;
    class trt;
    model y = trt actbase / dist = binomial;
    lsmeans trt/pdiff cl diff exp;
  run;
ods output close;
```

- The output datasets from the above analysis will contain odds ratio estimates from each of the 500 datasets. An overall estimate will be generated using PROC MIANALYZE . The SAS code is as following:

```
proc mianalyze data=zz;
  by visit;
  modeleffects estimate;
  stderr stderr;
  ods output paramestimates=or;
run;
```

Sensitivity analysis 2: The primary variable will be analyzed using the same method as defined in Section 6.2.2 excluding the random site effect from the logistic model. The SAS code will be used for the analysis:

```
proc mcmc data = x nbi = 1000 nmc = 500000 thin = 20 seed = 159 outpost =
post2 monitor = (beta0-beta2 sigma2 pi pi0 pooled or) statistics=(summary
intervals);

  parms beta0-beta2 0;

  prior beta0 ~ normal (mean = -0.231, var = 0.192);

  prior beta1 ~ normal (mean = 0.236, var = 9.912);

  prior beta2 ~ normal(mean = 0, var = 1000);

  eta = beta0 + beta1*trt + beta2*y0;

  pi = logistic(eta);

  pi0 = logistic(beta0 + beta2*y0);

  model count ~ binomial(n = total, p = pi);

  pooled = exp(beta1);

run;
```

where count = number of responders and total = number of patients.

6.2.4. Supplementary Analysis

A supplementary analysis for the proportion of patients for the DS and SoC groups reaching well-controlled asthma as defined by an ACT score of greater than or equal to 20, or a clinically important improvement in asthma control as defined by an increase of at least 3 units on the ACT score from baseline at the end of 12-weeks during the treatment period (responder analysis of DS versus SoC group with responders defined by an ACT score of greater than or equal to 20 or an increase by greater than or equal to 3 units on the ACT score) will also be performed using the same analysis method as defined for the primary endpoint (see Section 6.2.2).

6.3. Secondary Endpoints and Analysis

6.3.1. Secondary Endpoint #1 – Frequency and Types of Interventions Done to Improve Asthma Control

6.3.1.1. Definition

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

- number of discussions between patient and HCP 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.)

6.3.1.2. Analysis

Frequency and types of interventions during the 24-week treatment period will be summarized as count data using descriptive statistics. In addition, similar Bayesian analysis specified for primary endpoint will be performed for those variables separately using Poisson regression. The suggested SAS code for the analyses is as follows:

```
proc mcmc data = x nbi = 1000 nmc = 100000 thin = 20 seed = 159 outpost = post3
  monitor = (beta0-beta3 sigma2 lambda lambda0 pooled) statistics=(summary intervals);
  parms beta0-beta3 0;
  parms sigma2 1;
  prior beta0-beta3 ~ normal(mean = 0, var = 1000);
  prior sigma2 ~ igamma(shape = 0.001, scale = 0.001);
  random b0 ~ normal(mean = 0, var = sigma2) subject = CENTER;
  eta = beta0 + b0 + beta1*trt + beta2*logt + beta3*y0;
  lambda = exp(eta);
  lambda0 = exp(beta0 + b0 + beta2*logt + beta3*y0);
  model hosp ~ poisson(lambda);
  array lmda[<# of sites>];
  lmda[CENTER] = exp(b0 + beta1 + beta2*logt + beta3*y0);
  pooled = exp(beta1);
run;
```

6.3.2. Secondary Endpoint #2 – Evaluation of Short-Acting Beta$_2$ Agonists Usage

6.3.2.1. Definition

Secondary endpoint #2 is the change from week 1 in the mean weekly SABA usage and the change from week 1 in the number of SABA-free days over the 24-week treatment period for the DS group. SABA usage and SABA-free days. Weekly average SABA use will be defined as ((number of inhalations in a week)*90 ug/7) and change from week 1 in weekly average SABA use will be defined as (week i – week 1). Weekly SABA-free days will be defined as number of days a patient does not use the rescue medication in a week. If no inhalations done for any week, the amount of the SABA use will be 0 and SABA-free days for week will be 7.

6.3.2.2. Analysis

Weekly average SABA use, change from week 1 in weekly average SABA use, weekly SABA-free days, change from week 1 in weekly SABA-free days, weekly total number of inhalations and inhalation attempts, and change from week 1 in total number of inhalations and inhalation attempts will be summarized using descriptive statistics.

6.3.3. Secondary Endpoint #3 – Adherence to Maintenance Treatment

6.3.3.1. Definition

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. Daily adherence to maintenance treatment will be defined as 100*(number of inhalations/2) if number of inhalations <= 2 (ie, for number of inhalations = 0, 1 and 2). Daily adherence to maintenance treatment will be defined as 100% if number of inhalations > 2.

Weekly adherence to maintenance treatment will be defined as total daily adherence in 7 days/7. Monthly adherence to maintenance treatment will be defined as total daily adherence in 28 days/28.

6.3.3.2. Analysis

Weekly adherence to maintenance treatment and change from week 1 in weekly adherence to maintenance treatment will be summarized using descriptive statistics. Monthly adherence to maintenance treatment and change from month 1 in monthly adherence to maintenance treatment will be summarized using descriptive statistics.

6.3.4. Secondary Endpoint #4 – Assessment of Behavioral Correlates of Responsiveness to Digital Health Technology

6.3.4.1. Definition

The BMQ is used to assess cognitive representations of medicine. The BMQ-Specific (BMQ-S11) is an 11-item questionnaire that assesses representation of medication prescribed for personal use. The specific necessity subscale is the sum of items 1, 3, 5, 7, and 10, and the

specific concern subscale is the sum of items 2, 4, 6, 8, 9, and 11. The BMQ should be the second questionnaire completed during a study visit following the ACT.

The BIPQ is a 9-item questionnaire designed to rapidly assess cognitive and emotional representations of illness. The BIPQ uses a single-item scale approach to assess perception on a 0-10 response scale. 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. The cognitive subscale is the sum of items 1 to 5, and the emotional representation subscale is the sum of items 6 and 8. The BIPQ should be the third questionnaire completed during a study visit following the BMQ.

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.

6.3.4.2. Analysis

Summary statistics for the BMQ and BIPQ subscales will be presented at baseline, and the end of treatment and ET visits. BMQ and BIPQ subscales values and changes from baseline to each visit will be summarized using descriptive statistics.

6.3.5. Secondary Endpoint #5 – Evaluation of Work Productivity and Activity Impairment

6.3.5.1. Definition

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.

The following scores will be derived based on the WPAI questionnaire. Multiply scores by 100 to express in percentages.

- percent work item missed due to asthma: $\frac{Q2}{Q2+Q4}$
- percent impairment while working due to asthma: $\frac{Q5}{10}$
- percent overall work impairment due to asthma: $\frac{Q2}{Q2+Q4} + \left[\left(1 - \frac{Q2}{Q2+Q4}\right) \times \frac{Q5}{10}\right]$
- percent activity impairment due to asthma: $\frac{Q6}{10}$

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.

6.3.5.2. Analysis

Summary statistics for the WPAI questionnaire scores will be presented at baseline, and Visit 3 and ET visits. WPAI questionnaire scores values and changes from baseline to each visit will be summarized using descriptive statistics.

6.3.6. Secondary Endpoint #6 – Usability and Acceptability of the Digital System

6.3.6.1. Definition

The SUS is used to explore device acceptability and usability for patients in the DS group. It is a 10-item tool that provides a composite measure of the overall usability of the system being studied. Responses for each item range from 1 (strongly disagree) to 5 (strongly agree). To calculate the SUS score, first sum the responses from each item. Each item's contribution will range from 0 to 4. For items 1,3,5,7, and 9 the score contribution is the response minus 1. For items 2,4,6,8 and 10, the score contribution is 5 minus the response. Multiply the sum of the scores by 2.5 to obtain the overall SUS score. SUS scores have a range of 0 to 100.

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 investigational center personnel at the end of the study. The SUS will be completed after all other questionnaires.

6.3.6.2. Analysis

The SUS score (completed by patients and investigator sites) at Visit 3 and ET visits will be summarized as continuous data using descriptive statistics.

6.4. [redacted]

[redacted]

[redacted]

[redacted]

7. MULTIPLE COMPARISONS AND MULTIPLICITY

No multiplicity adjustment is needed since there is no hypothesis testing in this study, Bayesian methods for primary endpoint and secondary endpoint #1 and descriptive nature of all other endpoints.

8. SAFETY ANALYSIS

8.1. General

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.

No clinical laboratory tests, physical examinations, and ECGs are scheduled to be performed during this study.

The safety analysis set will be used for all safety analyses. Summaries will be presented by treatment group and for all patients.

8.2. Duration of Exposure to IMP

Since the dosing of the test IMP is on an as-needed basis, there is no set maximum exposure.

Duration of exposure to IMP is the number of days from date of the 2nd dose (since the 1st dose is used for testing at the study site on date of randomization) to date of last dose of IMP (last dose of IMP date – 2nd dose of IMP date + 1). If the 1st dose is not used on date of randomization, the duration of exposure to IMP will be calculated as last dose of IMP date – 1st dose of IMP date + 1 assuming no testing is done at study site for the patient. Number and percent of patients will be summarized by duration of exposure to IMP categories ≤ 1 week, >1 to ≤2 weeks, …, >23 to ≤24 weeks, and > week 24. Duration of exposure to IMP (days) and number of inhalations will also be summarized as continuous data using descriptive statistics.

The number of days a patient takes IMP will be summarized as continuous data using descriptive statistics. If a patient takes more than 1 IMP treatment on the same day, the patient will be counted only once in the summary; if a patient does not take any IMP treatment on a given day the patient will be counted as zero on that day. Summaries will be presented separately for FS eMDPI and Albuterol eMDPI.

8.3. Inhalation Flow Parameters

Inhalation flow parameters (peak inhalation flow [PIF], inhalation volume, inhalation duration, and time to PIF) values will be calculated for each week in the treatment period. This will be done separately for FS eMDPI and Albuterol eMDPI.

The inhalation parameters for each week are defined as the values from the inhalation with the median value of PIF during each week. If the number of inhalations is an even number, the later of the two inhalations in the middle will be deemed as the inhalation for the week. If no inhalations are done in a week, no inhalation parameters are defined for the week. Similarly the inhalation parameters for the entire 24-week treatment period are the values from the inhalation with the median PIF during the entire 24-week treatment period. Any inhalation with PIF > 120 L/min will be excluded from derivations.

Summary statistics for inhalation flow parameters will be presented by week in the treatment period, and the entire 24-week treatment period. Actual values and changes from week 1 to each week and overall will be summarized using descriptive statistics.

Statistical analyses of inhalation flow parameters will be performed outside of the scope of this SAP. The big data team will analyze this date and a separate SAP will be devolved for this.

8.4. Adverse Events

All adverse events will be coded using the MedDRA. Adverse events occurring on or after the treatment start date will be included in the summary tables while all of the adverse events will be listed in data listings.

A summary will be presented for adverse events in the following categories: all adverse events, adverse events determined by the investigator to be related to study drug, severe adverse events, serious adverse events, adverse events leading to withdrawal from the study, non-serious adverse events, device-related adverse events (DS group only), asthma related adverse events, and CAE related adverse events. The incidence of patients with an adverse event in each category will be summarized using descriptive statistics.

Summaries will be presented for all adverse events (overall and by severity), adverse events determined by the investigator to be related to study drug (overall and by severity), serious adverse events, adverse events leading to withdrawal from the study, non-serious adverse events, and device-related adverse events (DS group only).

The incidence of adverse events will be summarized using descriptive statistics by SOC and preferred term (all AEs overall will also be presented by just preferred term category). Patients are counted only once in each SOC category, and only once in each preferred term category. For the summaries by severity, patients are counted at the greatest severity. Adverse events with the missing flag indicating serious will be excluded from the summary of serious adverse events but included in the summary of non-serious adverse events.

8.5. Deaths

If any patient dies during the study, all relevant information will be discussed in the patient's narrative included in the CSR.

8.6. Vital Signs

Summary statistics for vital signs (pulse, systolic and diastolic blood pressure, and respiratory rate) will be presented at baseline, and the end of treatment and ET visits. Vital signs values and changes from baseline to each visit will be summarized using descriptive statistics.

Summaries of potentially clinically significant abnormal values will include all postbaseline values (including scheduled, unscheduled, and early termination visits). The incidence of potentially clinically significant abnormal values will be summarized using descriptive statistics with the criteria specified in Table 2.

Table 2 specifies the criteria for identifying vital signs as potentially clinically significant abnormal values. Note that in order to qualify as potentially clinically significant abnormal, a value needs to meet both criteria below: ie, have a value beyond the criterion value and a change of at least the magnitude specified in the change relative to baseline column.

Table 2: Criteria for Potentially Clinically Significant Vital Signs

Vital Sign	Criterion value	Change relative to baseline
Pulse	≥120 bpm	Increase of ≥15 bpm
	≤50 bpm	Decrease of ≥15 bpm
Systolic blood pressure	≥180 mm Hg	Increase of ≥20 mm Hg
	≤90 mm Hg	Decrease of ≥20 mm Hg
Diastolic blood pressure	≥105 mm Hg	Increase of ≥15 mm Hg
	≤50 mm Hg	Decrease of ≥15 mm Hg
Respiratory rate	<10 breaths/min	

8.7. Concomitant Medications or Therapies

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

The incidence of concomitant medications and therapies will be summarized using descriptive statistics by therapeutic class category and preferred term. The incidence of concomitant medications for asthma at baseline will also be summarized using descriptive statistics by therapeutic class category and preferred term. Patients are counted only once in each therapeutic class, and only once in each preferred term category. Concomitant medications will include all medications taken from the day of treatment start through the end of treatment.

9. TOLERABILITY VARIABLES AND ANALYSIS

Tolerability is not applicable to this study.

10. STATISTICAL SOFTWARE

All data listings, summaries, and statistical analyses will be generated using SAS® version 9.4 or later.

11. CHANGES TO ANALYSES SPECIFIED IN THE STUDY PROTOCOL

The definition of the mITT analysis set (see Section 3.1.2) has been updated to include patients with at least 1 postbaseline ACT assessment rather than including patients with at least 1 postbaseline assessment on any of the study endpoints.

The analysis for the primary endpoint (see Section 6.2.2) has been updated to allow for different response rates at enrolling investigational centers.

Patients who discontinue treatment due to an adverse event related to IMP will be considered a nonresponder in the analysis for the primary endpoint (see Section 6.2.2) and in the sensitivity analyses (see Section 6.2.3).

12. REFERENCES

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Schatz M, Sorkness CA, Li JT, Marcus P, Murray JJ, Nathan RA, et al. Asthma Control Test: reliability, validity, and responsiveness in patients not previously followed by asthma specialists. J Allergy Clin Immunol 2006;117(3):549-56.