Statistical Analysis Plan

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

Study Number ABS-AS-40138

NCT03890666

SAP Approval Date: 13 October 2021

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

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

Feasibility Study

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

Approval Date: 13 October 2021

Sponsor

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STATISTICAL ANALYSIS PLAN APPROVAL

Study No.: **CONN**ected **E**lectronic Inhalers Asthma **C**ontrol **T**rial 1 ("CONNECT 1"), a 12-Week Treatment, Multicenter, Open-Label, Randomized, Parallel Group Comparison, Feasibility Study to Evaluate the Effectiveness of the Albuterol eMDPI Digital System, to Optimize Outcomes in Patients at Least 13 Years of Age or Older with Asthma

Study Title: ABS-AS-40138

Statistical Analysis Plan for:

- ☐ **Interim Analysis**
- ☒ **Final Analysis**
- ☐ **Integrated Summary of Efficacy**
- ☐ **Integrated Summary of Safety**

Amendment: Not applicable

Author: [redacted]
Teva Global Statistics

Approver: [redacted] **Date** [redacted]

Approver: [redacted] **Date**

Executed signature pages are maintained separately within the Trial Master File

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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
CC	concurrent control
CI	confidence interval
CRF	case report form
CSR	clinical study report
DHP	Digital Health Platform
DS	Digital System
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 provider
iHCP	investigational center healthcare provider
IMP	investigational medicinal product
ITT	intent-to-treat
LAMA	long-acting muscarinic antagonist
MAR	missing at random
MedDRA	Medical Dictionary for Regulatory Activities
MI	multiple imputation
MIF	maximal inhalation flow
mITT	modified intent-to-treat
R&D	Research and Development
RTSM	Randomization and Trial Supply Management
SABA	short-acting $beta_2$ agonist
SAP	statistical analysis plan
SD	Standard Deviation

Abbreviation	Term
SE	Standard Error
SOC	system organ class
SOP	standard operating procedure
SUS	System Usability Scale
WHO	World Health Organization

INTRODUCTION

This Statistical Analysis Plan (SAP) describes the planned analysis and reporting for Teva Branded Pharmaceutical Products Research and Development (R&D) study ABS-AS-40138 (**CONN**ected **E**lectronic Inhalers Asthma **C**ontrol **T**rial 1 ("CONNECT 1"), a 12-Week Treatment, Multicenter, Open-Label, Randomized, Parallel Group Comparison, Feasibility Study to Evaluate the Effectiveness of the Albuterol eMDPI Digital System, to Optimize Outcomes in Patients at Least 13 Years of Age or Older with Asthma), 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 concurrent control (CC) group.	The primary endpoint is the proportion of patients for the DS and CC groups achieving meaningful improvement, which is defined as an Asthma Control Test (ACT) score greater than or equal to 20 at the end of the 12-week treatment period or an increase of at least 3 units on the ACT score from baseline at the end of the 12-week treatment period.
The **secondary objective (#1)** is to describe the asthma management actions by 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 between patient and healthcare provider (HCP) regarding inhaler technique or adherence • number of adjustments of therapy including: o increased or decreased doses of inhaled medication o change to different inhaled medication o additional inhaled medication o addition of a systemic corticosteroid medication for asthma or another controller, including a long-acting muscarinic antagonist (LAMA) or biologics • frequency of intervention to manage comorbid conditions associated with poor asthma control (gastroesophageal reflux disease [GERD], sinusitis, etc.)
The **secondary objective (#2)** is to evaluate short-acting $beta_2$ agonist (SABA) usage and the number of SABA-free days in the DS group.	This secondary endpoint is the change from baseline in the mean weekly SABA usage and the change from baseline in the number of SABA-free days over the 12-week treatment period for the DS group.
The **secondary objective (#3)** is to assess the usability and acceptability of the DS by patients in the DS group and the investigational center personnel.	This secondary endpoint is the assessment of the DS (eMDPI, App and dashboard) acceptability and usability, utilizing the System Usability Scale (SUS), completed by the patients in the DS group, 18 years of age or older, and the investigational center personnel at the end of the study.

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

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

1.2. Exploratory Objectives and Endpoints

Exploratory objectives and endpoints are as follows:

[redacted]

2. STUDY DESIGN

2.1. General Design

This is a 12-week treatment, multicenter, open-label, randomized, parallel group comparison feasibility study to evaluate the effectiveness of the Albuterol eMDPI DS, including inhaler, App, 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 visit, a 12-week open-label treatment period, and a follow-up telephone call (2 weeks following treatment completion).

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

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

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

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

For all patients, at Visit 2 and at each Clinically Driven Assessment, if necessary, the iHCP will record answers to Asthma Management questions regarding what interventions occurred as a

consequence of the Clinically Driven Assessment, including discussions regarding adherence, or inhaler technique, treatment adjustments, or additions of new treatments, including biologic medication usage. Additionally, for patients in the DS group, the iHCP will be asked whether or not the contact with the patient was originated from the iHCP interaction with the dashboard.

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

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

Study procedures and assessments with their timing are summarized in Table 3 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 CC group in a 1:1 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.

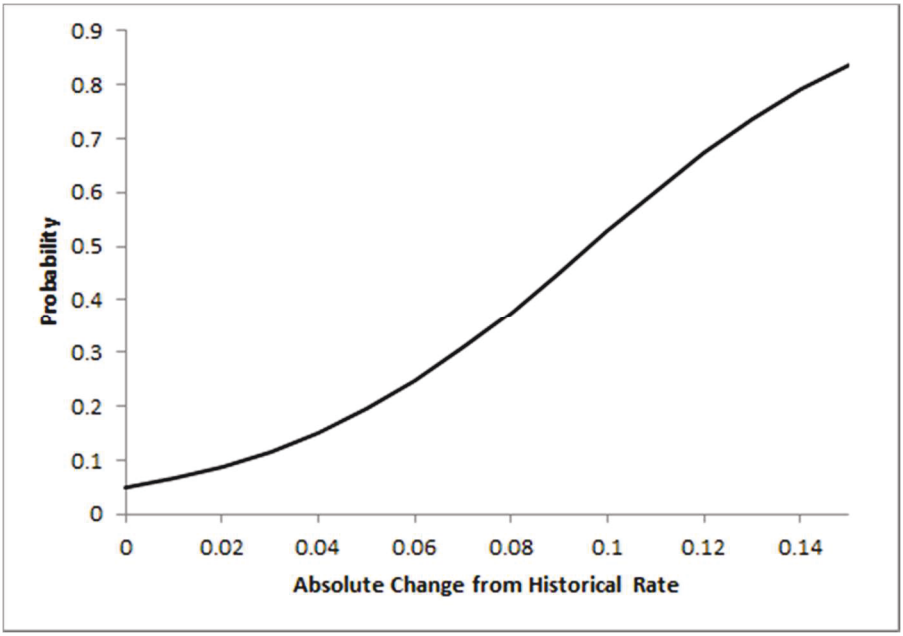
2.4. Sample Size and Power Considerations

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

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

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

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



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. 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.

3.2. 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 investigational medicinal product (IMP) (IMP is albuterol eMDPI for the DS group and standard-of-care albuterol-administering rescue medication for the CC group) and at least 1 postbaseline assessment on any of the study endpoints (primary, secondary, or exploratory).

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

3.3. Safety Analysis Set

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

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.

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 Albuterol eMDPI DS.

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

6.2. Primary Endpoint and Analysis

6.2.1. Definition

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

6.2.2. Primary Analysis

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

1. Analysis will be performed on the mITT analysis set.

2. A binary distribution is assumed for the primary endpoint. Patients who discontinue early due to technology failure, disliking the digital platform, disease worsening, adverse experience or disliking the IMP will be counted as treatment failures. For those who discontinue early not due to these reasons, the ACT value assessed at the ET visit will be used.

3. Summary measure: A successful differentiation between the 2 groups will be determined by a Bayesian posterior probability for $\beta_1 > 0$ greater than 0.95 (1-sided). The following statistical methods will be utilized:

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

$$\ln\left(\frac{pij}{1-pij}\right) = \beta_0 + \beta_1 x_i + \beta_2 baseline\ ACT\ value \quad + Center_{\text{j}}$$

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.

Non-informative priors will be assumed for all coefficients. 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 CC, and probability of ($\beta_1 > 0$) and probability of ($Odd\ Ratio >$ clinical meaningful value) 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-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);
  beta1_gt0 = beta1 > 0;
run;
```

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

To include study center into the model, the study centers may be pooled according to the number of patients enrolled at each center by keeping the largest centers intact and pooling the remainder of the larger sites with smaller sites to form pooled sites. A final plan for pooling will be made and documented in Statistical Data Review meeting minutes prior to database lock. In addition, summary statistics for the ACT score will be presented at baseline, and the end of treatment and ET visits. ACT score values and changes from baseline to each visit will be summarized using descriptive statistics.

6.2.3. Sensitivity Analysis

Sensitivity analysis will be performed for the primary analysis by imputing missing ACT values using the multiple imputation (MI) method assuming missing at random (MAR). Those who discontinue early due to technology failure, disliking the digital platform, disease worsening, adverse experience 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;
  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 _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;
  modeleffects estimate;
  stderr stderr;
  ods output paramestimates=or;
run;
```

6.3. Secondary Endpoints and Analysis

6.3.1. Secondary Endpoint #1 – Description of Asthma Management Actions by the Investigational Center Healthcare Providers

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 therapy adjustments 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 12-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 = post2
  monitor = (beta0-beta3 sigma2 beta1_gt0 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);
  beta1_gt0 = beta1 < 0;
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 12-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 7.

6.3.2.2. Analysis

Weekly average SABA use, change from week 1 in weekly average SABA use and weekly SABA-free days will be summarized using descriptive statistics.

6.3.3. Secondary Endpoint #3 – Usability and Acceptability of the Digital System

6.3.3.1. 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 #3 is the assessment of the DS (eMDPI, App and dashboard) acceptability and usability, utilizing the SUS, completed by the patients in the DS group, 18 years of age or older, and investigational center personnel at the end of the study. The SUS will be completed after all other questionnaires.

6.3.3.2. Analysis

The SUS score (completed by patients and investigator sites) at the end of treatment and ET visits will be summarized as continuous data 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 7. 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 CC 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.

6.4. Exploratory/Other Endpoints Analysis

6.4.1. Definition

The exploratory endpoints are:

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, …, >11 to ≤12 weeks, and > week 12. 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.

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.

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 12-week treatment period are the values from the inhalation with the median PIF during the entire 12-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 12-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 1.

Table 1 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 1: 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 statisics 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

There are no changes to analyses specified in the study protocol.

12. REFERENCES

Merchant, RK, Inamdar R, Quade, RC. Effectiveness of population health management using the Propeller Health Asthma Platform: a randomized clinical trial. J Allergy Clin Immunol Pract. 2016 May-Jun;4(3):455-63.

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.