TEVA Asthma Predictive Analytics Study

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Principal Investigator: Njira Lugogo

Co-Investigators: Stewart Wang, Michael Sjoding

TEVA Collaborators: Tanisha Hill, Amanda Boe

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Summary of Changes from Previous Version:

Affected Section(s)	Summary of Revisions Made	Rationale
Throughout Document	Updated Versioning	
Section 1.1 Synopsis	Clarified Endpoints and Objectives and updated Exploratory Objectives	
Section 3. Objectives and Endpoints	Clarified Endpoints and Objectives and updated Exploratory Objectives	

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STATEMENT OF COMPLIANCE

Provide a statement that the trial will be conducted in compliance with the protocol, International Council on Harmonization Good Clinical Practice (ICH GCP) and applicable state, local and federal regulatory requirements. Each engaged institution must have a current Federal-Wide Assurance (FWA) issued by the Office for Human Research Protections (OHRP) and must provide this protocol and the associated informed consent documents and recruitment materials for review and approval by an appropriate Institutional Review Board (IRB) or Ethics Committee (EC) registered with OHRP. Any amendments to the protocol or consent materials must also be approved before implementation. Select one of the two statements below. If the study is an ***intramural*** *NIH study, use the second statement below:*

The trial will be conducted in accordance with International Council on Harmonization Good Clinical Practice (ICH GCP), applicable United States (US) Code of Federal Regulations (CFR), and the [specify NIH Institute or Center (IC) [Terms and Conditions of Award. The Principal Investigator will assure that no deviation from, or changes to the protocol will take place without prior agreement from the funding agency and documented approval from the Institutional Review Board (IRB), and the Investigational New Drug (IND) or Investigational Device Exemption (IDE) sponsor, if applicable, except where necessary to eliminate an immediate hazard(s) to the trial participants. All personnel involved in the conduct of this study have completed Human Subjects Protection and ICH GCP Training.

The protocol, informed consent form(s), recruitment materials, and all participant materials will be submitted to the IRB for review and approval. Approval of both the protocol and the consent form(s) must be obtained before any participant is consented. Any amendment to the protocol will require review and approval by the IRB before the changes are implemented to the study. All changes to the consent form(s) will be IRB approved; a determination will be made regarding whether a new consent needs to be obtained from participants who provided consent, using a previously approved consent form.

1 PROTOCOL SUMMARY

1.1 SYNOPSIS

Title: **Utilizing Advances in Digital Inhaler Technology to Understand Heterogeneous Treatment Responses to Biologics in Severe Asthma**

Study Description: This real-world study aims to determine baseline inhalation parameters and patterns of use in patients receiving treatment with TEVA digital inhalers, and to develop predictive models for asthma exacerbations and response to biologics using data collected from these devices.

Objectives:

Primary Objective:
To determine the baseline inhalation parameters and patterns of use of both the maintenance (AirDuo®) Digihaler™ and rescue (ProAir®) Digihaler™ in patients with severe persistent asthma who are being treated with biologics.

Secondary Objectives:

1. To determine the predictive value of inhalation parameters, including peak inspiratory flow (PIF), inspiratory time and volume, and number of inhaled doses on asthma exacerbations in a population of severe asthma patients on biologics.

2. To determine whether inhalation measurements can serve as surrogates of standard expiratory flow measurements. Specifically, to determine the correlation between PIF with FEV1 and identify thresholds for changes in PIF that are associated with a clinically meaningful increases or decreases (10%) in lung function as measured by conventional spirometry (e.g., FEV1).

3. To determine the impact of variable degrees of adherence to maintenance therapy on outcomes to biologics. The Digihaler™ will allow us to collect accurate information on adherence that will be utilized to divide patients into groups and to assess asthma outcomes such as change in mean FEV1, exacerbations, oral steroid reduction, and asthma control (using the asthma control test scores over time) in patients receiving biologic therapies.

4. To determine the impact on inhalation parameters on categorical response to biologics. Response will be categorized as non-response, partial and complete response on the basis of six factors: a 50% reduction in exacerbations, any reduction in maintenance OCS dose, change of at least 10% in FEV1, improvement of 3 points in ACT score, and patient perception of global improvement in asthma.

Exploratory Objectives

5. To evaluate the asthma control and health care utilization of subjects as measured by the number of exacerbations (acute worsening of asthma requiring at least 3 days of corticosteroids or a doubling dose of maintenance steroids), Emergency and hospitalization encounters, and patient-reported perceptions of asthma control.

6. To employ machine learning techniques to a robust well characterized cohort with clinical, biological, and digital markers to develop a predictive algorithm aimed at identifying responders to biologics. In addition, we would aim to develop an algorithm that can detect early changes in measured parameters that can predict long-term improvements in asthma control and exacerbations when biologics are initiated. The latter objective will be achieved by focusing on the sub-group of patients initiating biologics for the first time or switching between biologics due to perceived inadequate response.

Endpoints:

Primary Endpoint:

Mean and median number of (daily) doses of ProAir® Digihaler™ and AirDuo® Digihaler™ utilized at baseline, temporal patterns in rescue and controller medication utilization, and within-patient parameter mean, median, and variance per-inhalation to establish baselines.

Secondary Endpoints:

1. Proportion of patients with different rates of adherence.
2. Proportion of Patients achieving non-response, partial-responses, and complete response to biologics.
3. Change in Main Peak Inspiratory volume from baseline up to one year.
4. Change in Mean Inspiratory Time from baseline up to one year.
5. Change in mean peak inspiratory flow (PIF) from baseline up to one year.
6. Change in mean forced expiratory volume in one second (FEV1) from baseline up to one year.

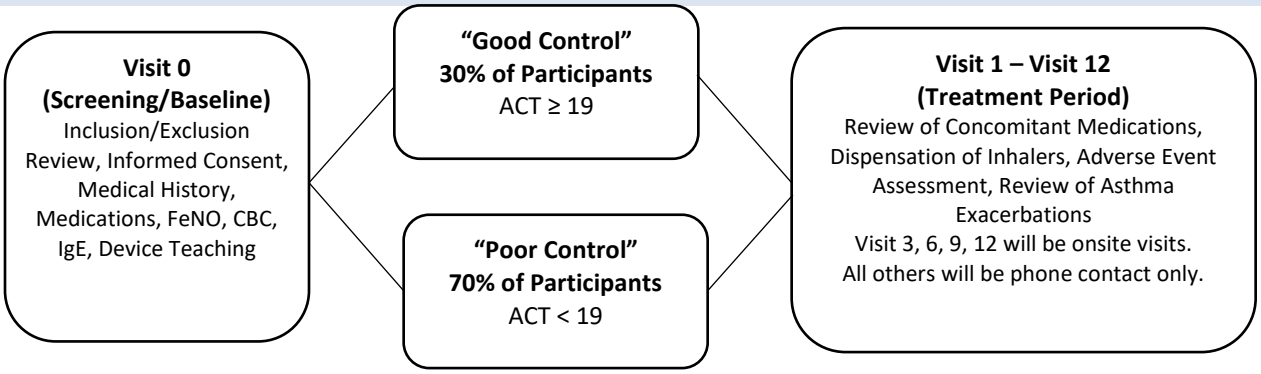
Exploratory Endpoints

7. Number of exacerbations from baseline up to one year.
8. Number of hospitalizations.

9. Number of emergency room visits.
10. Mean Asthma Control Test (ACT) scores.
11. Algorithm that produces a daily asthma exacerbation probability given a set of baseline and current inhalation parameters. A confusion matrix summarizing the algorithm's performance on training dataset and from which performance statistics (accuracy, sensitivity, specificity, etc.) can be computed.
12. Machine learning model developed for predicting responders to biologics (developed in collaboration with the University of Michigan Morphomic Analysis Group). Reporting key factors in the model that are associated with response, using inhalation parameters (digital markers), clinical factors, and biomarkers.

Study Population:	Adults > 18 years of age or older with severe persistent asthma as defined by ERS/ATS criteria that are currently receiving or awaiting approval for biologic therapies for asthma.
Phase:	Open Label Real World Study
Description of Sites Enrolling Participants:	All patients will be recruited from the Michigan Medicine Severe Asthma Clinics.
Description of Study Intervention:	Maintenance inhaler (AirDuo® Digihaler™) and two rescue inhalers (ProAir® Digihaler™) use in Severe Asthma patients currently receiving or awaiting approval for biologic therapies for asthma.
Study Duration:	2 years, including approximately 3-month start-up, 6 months' recruitment period, 12 months follow-up of the last subject in (LSI), 3-month data cleaning and analysis.
Participant Duration:	12 months

1.2 SCHEMA



1.3 SCHEDULE OF ACTIVITIES (SOA)

Study Visit	Screening/ Baseline	Visit 1	Visit 2	Visit 3	Visit 4	Visit 5	Visit 6	Visit 7	Visit 8	Visit 9	Visit 10	Visit 11	Visit 12/EOS	Follow Up
Study Week[1]	0	4	8	12	16	20	24	28	32	36	40	44	48	52
Location	Clinic	Phone	Phone	Clinic	Phone	Phone	Clinic	Phone	Phone	Clinic	Phone	Phone	Clinic	Phone
Informed Consent	X													
Enrollment to MiAsthma Registry	X													
Inclusion/Exclusion Review	X													
Demographics	X													
Smoking/Tobacco Use History	X													
Medical History- General/Asthma	X													
Conmeds- General/Asthma	X	X	X	X	X	X	X	X	X	X	X	X	X	X
Exacerbations/Healthcare Utilization	X	X	X	X	X	X	X	X	X	X	X	X	X	
Patient Reported Outcomes (PRO)[2]	X			X			X			X			X	
FeNO (Clinical)[3]	X			X			X			X			X	
CBC w. Differential (Clinical)[3]	X			X			X			X			X	
Immunoglobulin (IgE) (Clinical)[3]	X			X			X			X			X	
Inhaler Teaching	X													
Dispense Digihaler™	X	X	X	X	X	X	X	X	X	X	X	X	X	
Registration/Onboarding App	X													
Home Spirometry Teaching	X													
Dispense Home Spirometer	X													
Adverse Events	X	X	X	X	X	X	X	X	X	X	X	X	X	X
Subject Fee/Stipend	X			X			X			X			X	
Phone Call		X	X		X	X		X	X		X	X		X
Ship Drug (As Needed)		X	X		X	X		X	X		X	X		

1 Study visits have a ± 7 Day window.
2 Patient Reported Outcomes include the Asthma Control Test (ACT), AIRQ, and the St. George's Respiratory Questionnaire
3 Clinical activities will be captured if they are available but will not be done specifically for the study.

2 INTRODUCTION

2.1 STUDY RATIONALE & BACKGROUND

Severe asthma affects 10% of the adult population and these patients suffer an increased number of exacerbations and subsequent accelerated decline in lung function. Asthma exacerbations are poorly understood and the ability to predict exacerbations is limited. The factors associated with an increased risk of exacerbations include a prior history of exacerbations, elevated type 2 markers, lower lung function and increased short acting beta agonist (SABA) use. The ability to predict the onset of each isolated exacerbation event and to thus intervene is hampered by a lack of access to real-time information about both SABA use and lung function parameters. The Digihaler™ has demonstrated changes in both PIF and SABA doses surrounding acute asthma events (TEVA, unpublished data). The clinical utility of this information will be tested in future trials that aim to examine the impact of data from the Digihaler™ on clinical decision making. The data from the Digihaler™ coupled with clinical characteristics and biomarkers could be utilized to revolutionize how asthma is monitored and how exacerbations are detected.

Two-thirds of patients with severe asthma have evidence of type 2 inflammation that is targeted by five approved biologics for asthma. In clinical trials biologics have demonstrated significant impacts on exacerbation reduction, oral steroid sparing effects and improvements in quality of life. In all the clinical trials patients were required to remain on their maintenance inhaled (background) therapies and use of rescue bronchodilators was reported using patient self-report in symptom diaries. Little is known about how patients use their maintenance and rescue medications for asthma following the initiation of biologics and whether these patterns of use impact their response to these therapies. Furthermore, information about inhalation parameters such as peak inspiratory flow and inspiratory time and the importance of variability in these parameters that are measured in the Digihaler™ are lacking. The TEVA Digihaler™ offers an opportunity to obtain granular data about inhaler use in patients with severe asthma. Importantly, this data will be incorporated with clinical, biomarker, and digital data from the cohort, and machine learning methods will be utilized to determine if predictive algorithms can be developed to not only identify exacerbations but also provide a priori prediction of likelihood of response to biologics. These models will enhance our understanding of disease variability and characteristics, enable us to perform future trials testing the hypothesis that “baseline characteristics and early changes in lung function parameters and medication use will provide early and accurate predictions of future outcomes when biologics are initiated,” and could provide the basis for early discontinuation of ineffective therapies, saving money and time for patients who are currently subjected to long trials with biologics prior to switching or discontinuation.

Asthma is a highly prevalent disease that affects 30 million people in the United States. The vast majority of asthma patients are well controlled with conventional asthma therapies; however, 10% of patients have severe disease that is associated with significant comorbidity and exposure to high doses

of oral corticosteroids (OCS). This exposure to OCS increases the odds of developing co-morbid diseases such as diabetes, hypertension, cardiac disease and cataracts[1]. Severe asthma is associated with an increased risk of acute events/exacerbations that result in accelerated lung function decline[2] and increased morbidity and mortality. Exacerbations are difficult to characterize and what is currently known about the changes in lung function prior to, during, and after exacerbations is predominantly focused on expiratory flow and highly reliant on patient diaries and peak flow meters. The variability in inspiratory flow parameters during acute events is not well characterized and may significantly impact inhaled drug delivery. The Digihaler™ data could enable the development of next-generation asthma action plans and novel real-time asthma control monitoring. Furthermore, this technology will allow the development of novel methods to monitor asthma and enable earlier detection of acute asthma exacerbations. The early detection of asthma attacks would enable clinicians and empower patients to intervene and perhaps change the trajectory of illness.

The rapid development of new biologics approved for the management of severe asthma with type II inflammation has led to a revolution in asthma care [3-5]. The term "type II inflammation" refers to an increase in the levels of type II cytokines including interleukin IL-4, IL-5 and IL-13, which results in downstream production of IgE and eosinophils. Sixty percent of severe asthma patients have evidence of type II inflammation[6 7]. Surrogate biomarkers including peripheral eosinophils, fraction of exhaled nitric oxide (FeNO) and total IgE levels are used to phenotype patients with severe asthma and to guide biologic drug selection[8]. Eosinophils have been shown to predict response to IL5 and IL4 targeted therapies and FeNO is a predictor of response to anti-IL4 therapy[9 10].

The response to targeted biologic therapies is heterogeneous despite the use of biomarkers to select potential responders. Unfortunately, even when patients with a high likelihood of response are selected, 10-15% have complete non-response in all clinical parameters, 40% have a robust and complete response to therapy, and the remainder of patients have a partial response. This is likely related to the presence of overlapping inflammatory pathways, co-morbid eosinophilic diseases that affect response to therapy, possible sub-optimal dosing of drug, and the lack of highly specific biomarkers.

Little is known about how biologics impact the use of inhaled asthma therapies and whether the heterogeneity in responses to biologics could be partially attributed to nonadherence with maintenance therapies once biologic therapy is initiated. Data collection on use of both maintenance and inhaled therapies is based primarily on patient self-reporting. The Digihaler™ presents a unique opportunity to gain invaluable insights into both patterns of use of inhaled therapies and changes in inspiratory flow parameters in patients with severe asthma who are treated with biologics. In addition, coupling the maintenance and rescue Digihaler™ will allow the collection of a significant amount of information both about baseline therapies and exacerbations. Furthermore, the granular data collected from these inhalers will be invaluable in determining the impact of inhalation parameters on predicting asthma outcomes and in determining whether these measurements can serve as surrogates of expiratory flow measurements that are the cornerstone of asthma management but often challenging to obtain in real world settings. Coupling digital biomarkers from the inhaler with biological and clinical characteristics in a cohort of severe asthma patients will lead to an enhanced ability to not only understand the impact of

maintenance therapies on asthma outcomes but will also provide us with the opportunity to use machine learning algorithms to develop predictive models that may enhance our ability to predict response to biologics.

Precision medicine approaches to severe asthma are in their infancy and the application of complex techniques to help guide therapy are urgently needed. Currently, patients that are partial responders or non-responders to given therapies are switched between available biologics, and clinical response is assessed 4-6 months after the new therapy is initiated. This represents an inefficient approach that is both time consuming and costly to patients and payers.

We propose that variability in patterns of inhaler use, inhalation parameters, and overall medication adherence will significantly impact response to biologics in patients with severe asthma. Furthermore, the additive impact of predictive biomarkers, digital markers, and clinical characteristics will allow the development of a predictive algorithm that will help identify responders and enhance our understanding of the heterogeneous responses to therapy.

2.3 RISK/BENEFIT ASSESSMENT

2.3.1 KNOWN POTENTIAL RISKS

There is a risk of loss of PHI which will be mitigated by use of secure servers at the University of Michigan campus. The cloud that receives digital information from the inhalers is HIPAA compliant and under the control of TEVA. TEVA collaborating investigators will partner with a cross-functional internal team and principal investigator/sponsor to determine the appropriate AE/SAE reporting requirements and reporting structure.

Clinical Safety: A total of 1289 subjects were treated with PROAIR® RESPICLICK during the clinical development program. The most common adverse reactions (≥1% and >placebo) were back pain, pain, gastroenteritis viral, sinus headache, and urinary tract infection. In a long-term study of 168 patients treated with PROAIR® RESPICLICK for up to 52 weeks (including a 12-week double-blind period), the most commonly reported adverse events ≥5% were upper respiratory infection, nasopharyngitis, sinusitis, bronchitis, cough, oropharyngeal pain, headache, and pyrexia. In a small cumulative dose study, tremor, palpitations, and headache were the most frequently occurring (≥5%) adverse events.

2.3.2 KNOWN POTENTIAL BENEFITS

Participants in this study will receive free asthma maintenance and rescue inhalers and access to information in the Digihaler™ app that may have a positive impact on their health behaviors.

2.3.3 ASSESSMENT OF POTENTIAL RISKS AND BENEFITS

This is a minimal risk study that will focus on real world use of approved medications with an emphasis on understanding patterns of use, inhalational parameters, and changes in these measurements during acute episodes of asthma. Patients will be encouraged to follow the clinical guidance that is provided by the treating physician.

The ProAir® Digihaler™ is a rescue/reliever agent that includes an eModule on top of the approved PROAIR® RESPICLICK inhaler. The system consists of the ProAir® Digihaler™, the App, the cloud solution, and the dashboard. The ProAir® Digihaler™ can be used with or without the additional devices (App, cloud solution, and dashboard) that are being evaluated in this study. The on-board electronics and power source in the Digihaler™ are fully integrated into the inhaler and are designed to operate for the life of the inhaler without intervention. The eModule records timestamped pre-defined events. The inclusion of the eModule has been shown to have no impact on the dose delivery compared with the approved product without the eModule (performance and functional testing on file at Teva). Furthermore, the steps to take a dose of ProAir® Digihaler™ are identical to that of the currently approved PROAIR® RESPICLICK. Therefore, it is unlikely that the inclusion of the eModule will add additional risk to the approved product. In summary, the benefit and risk assessment for ProAir® Digihaler™ is favorable following review of the outlined data.

3 OBJECTIVES AND ENDPOINTS

OBJECTIVES	ENDPOINTS	JUSTIFICATION FOR ENDPOINTS
Primary		
To determine the baseline inhalation parameters and patterns of use of both the maintenance (AirDuo®) and rescue (ProAir®) Digihaler™ in patients with severe persistent asthma who are being treated with biologics from baseline through the duration of the 12-month treatment period	• Mean number of daily doses of ProAir® Digihaler™ • Mean number of daily doses of AirDuo® Digihaler™ • Median number of daily doses of ProAir® Digihaler™ • Median number of daily doses of AirDuo® Digihaler™	The number of inhalations of rescue and maintenance bronchodilator use varies amongst and within patients with severe asthma and is impacted by changes in asthma control. This is a clinically meaningful measurement that is included in assessments of disease activity and control. PIF, inspiratory time and volume vary with changes in baseline asthma control and may be important in identifying acute exacerbations of asthma. Maintenance therapies can impact asthma control and confound the response to biologics. In addition, the patterns of use of maintenance therapies and the potential discordance with rescue inhaler use would be important to delineate in this severe asthma population.
Secondary		
To determine the impact of variable degrees of adherence to maintenance therapy on outcomes to biologics. The Digihaler™ will allow us to collect accurate information on adherence that will be utilized to divide patients into groups and to assess asthma outcomes such as change in mean FEV1, exacerbations, oral steroid reduction, and asthma control (using the asthma control	• Proportion of patients with different adherence rates. **Tests:** Summary, chi-squared test, and Tukey's HSD test statistics of asthma outcomes by adherence group.	Adequate understanding of adherence is essential for guiding treatment decisions in clinical asthma care. It may impact response to biologics particularly in patients that are partial responders to targeted therapies. The degree of asthma control while on biologics may be altered by

OBJECTIVES	ENDPOINTS	JUSTIFICATION FOR ENDPOINTS
test scores over time) in patients receiving biologic therapies. **Definitions:** Adherence rates will be defined as: high (>80% of puffs), moderate (50-80% of puffs) and low levels (<50% of puffs) of adherence to maintenance inhalers (assuming an expected baseline usage of two puffs per day).		non-adherence to inhaled therapies and lead to incorrect conclusion that the biologic is not effective. In addition, little is known about how patients with severe asthma utilize their inhalers once biologics are initiated and more importantly if it is safe to discontinue these therapies altogether.
To determine the impact on inhalation parameters on categorical response to biologics. Response will be categorized as non-response, partial and complete response on the basis of six factors: a 50% reduction in exacerbations, any reduction in maintenance OCS dose, change of at least 10% in FEV1, improvement of 3 points in ACT score and patient perception of global improvement in asthma.	• Proportion of patients achieving non-response, partial and complete response to biologics. **Tests:** Summary, chi-squared test, and Tukey's HSD test statistics of inhalation parameters by response group.	Response to biologics is heterogeneous, and it is unclear if inhalational parameters measured by the Digihaler™ are correlated with degree of response.
To determine whether inhalation measurements can serve as surrogates of standard expiratory flow measurements. Specifically, to determine the correlation between PIF with FEV1 and identify thresholds for changes in PIF that are associated with a clinically meaningful increases or decreases (10%) in lung function as measured by conventional spirometry (e.g., FEV1).	• Change in Main Peak Inspiratory volume from baseline up to one year • Change in Mean Inspiratory Time from baseline up to one year • Change in mean peak inspiratory flow (PIF) from baseline up to one year • Change in mean forced expiratory volume in one second (FEV1) from baseline up to one year **Tests:** Correlation coefficients, regression equations, and regression summary statistics (e.g., R-squared,	FEV1 is a well-established and accepted measure of lung function in asthma. Changes in FEV1 are noted during acute episodes and clinically meaningful changes have been established. Little is known about the correlation between FEV1 and PIF and whether change in PIF could serve as a surrogate for change in FEV1.

OBJECTIVES	ENDPOINTS	JUSTIFICATION FOR ENDPOINTS
	mean absolute error) for PIF vs. FEV1, PIF vs. FVC. Identification of change in PIF thresholds (increase and decrease thresholds) that are clinically meaningful. Univariate/multivariate regression statistics between inhalation parameters and asthma outcomes such as asthma control score, number of exacerbations, and number of hospitalizations. Reported confusion matrix for change in PIF versus asthma exacerbations and poor asthma control.	
Exploratory		
To evaluate the asthma control and health care utilization of subjects as measured by the number of exacerbations (acute worsening of asthma requiring at least 3 days of corticosteroids or a doubling dose of maintenance steroids), Emergency and hospitalization encounters, and patient-reported perceptions of asthma control.	• Number of exacerbations from baseline up to one year • Number of hospitalizations • Number of emergency room visits • Mean Asthma Control Test (ACT) scores	Understanding the healthcare utilization and perceptions of asthma control can help researchers better understand how/whether the digihalers are helping the patients achieve better asthma control.
To determine the predictive value of inhalation parameters, including peak inspiratory flow (PIF), inspiratory time and volume, and number of inhaled doses on asthma exacerbations in a population of severe asthma patients on biologics. To determine the impact on inhalation parameters on categorical response to biologics. Response will be categorized as non-response, partial and complete response on the basis of six factors: a 50% reduction in exacerbations, any reduction in maintenance OCS dose, change of at least 10% in FEV1, improvement of 3 points in ACT score and patient	Algorithm that produces asthma exacerbation probability given a set of baseline and current inhalation parameters. A confusion matrix summarizing the algorithm's performance on training dataset and from which performance statistics (accuracy, sensitivity, specificity, etc.) can be computed.Proportion of patients achieving non-response, partial and complete response to biologics. Summary, chi-squared test, and Tukey's HSD test statistics of inhalation parameters by response group.	PIF, inspiratory time and volume are expected to vary within a patient over time; however, significant changes in these variables may indicate the development of acute exacerbations of asthma during the early phase when interventions may help change the progression of these events.Response to biologics is heterogeneous, and it is unclear if inhalational parameters measured by the Digihaler™ are

OBJECTIVES	ENDPOINTS	JUSTIFICATION FOR ENDPOINTS
perception of global improvement in asthma.		correlated with degree of response.
To employ machine learning techniques to a robust well characterized cohort with clinical, biological and digital markers to develop a predictive algorithm aimed at identifying responders to biologics. In addition, we would aim to develop an algorithm that can detect early changes in measured parameters that can predict long-term improvements in asthma control and exacerbations when biologics are initiated. The latter objective will be achieved by focusing on the sub-group of patients initiating biologics for the first time or switching between biologics due to perceived inadequate response.	Machine learning model developed for predicting responders to biologics (developed in collaboration with the University of Michigan Morphomic Analysis Group). Reporting key factors in the model that are associated with response, using inhalation parameters (digital markers), clinical factors, and biomarkers.	Predictive analytics have been utilized in many diseases to develop robust ways to identify response, and the use of machine learning methods has enhanced our ability to identify responders to antibiotics, predict those with a risk of poor surgical outcomes, and identify those likely to have disease progression. We will use our experience with machine learning to develop new predictive models that can help us to shift the treatment paradigm, improving our ability to make early predictions of therapeutic response in patients receiving biologics for asthma.

4 STUDY DESIGN

4.1 OVERALL DESIGN

This is an open-label real world study that has been designed to determine the patterns of use and impact of inhalation parameters on both predicting asthma exacerbations and response to biologics in patients with severe asthma. The digital inhalers used in this trial are unique in their ability to seamlessly record multiple parameters as the patients use their inhalers. There are no external devices required for device use recording. We aim to leverage the information collected by the digital inhaler to understand the impact of exacerbations on inhalation parameters, to determine the clinically meaningful differences in these measurements, and to determine their correlation to FEV1, which is the most widely accept measure of airflow in patients with severe asthma. Home spirometry is challenging and expensive and if inspiratory flow measures can be used as surrogates of expiratory flow, this would revolutionize our ability to track lung function in patients with severe asthma. The digital parameters will be incorporated with clinical, digital, and biological markers in an attempt to identify predictive algorithms that can identify responders to biologics early in the treatment course, facilitating decisions about continuation or discontinuation of therapy.

4.2 SCIENTIFIC RATIONALE FOR STUDY DESIGN

We designed an open label, single site study and intend to enroll patients in a sequential manner via screening of the EMR system for patients currently receiving biologics or with a pending approval for biologics for asthma. The open label design was selected as we are interested predominantly in inhalation parameters that are collected without any specific actions from participants, thus decreasing any potential changes in medication utilization. We intend to educate the patients on the use of the inhaler and how it has been prescribed but will make no efforts to intervene to encourage compliance with medication utilization, as we are interested in patient behavior and interaction with the device. The application that collects information about inhaler use will be stored on the patients' smart phone, and therefore they may choose to review the information and make changes in their adherence. We will not require patients to utilize the application and will passively record whether patients report using the app or not. We will design a questionnaire that determines patients' opinions of the app if they are utilizing it. All clinical parameters will be collected from the EMR.

Our main objective is to determine baseline inhalation parameters (e.g., peak inspiratory flow) using sample means. According to one study (https://www.ncbi.nlm.nih.gov/pmc/articles/PMC5328129/) the PIF mean was 115 and standard deviation was 15. Assuming a 100 patient sample, the 95% CI of our estimate of the PIF sample mean would be plus or minus 3, e.g., 115 (95% CI 112 – 118), which we deem to be of sufficient power for our analysis (http://statulator.com/SampleSize/ss1M.html).

Our secondary objective includes training a machine learning model, and one common measure to evaluate model performance is discrimination, assessed by an area under the ROC curve (AUROC). Again, assuming a 100 patient sample and a 50% event rate, we would have adequate power to conclude that a model with an AUROC performance of >0.65 has confidence intervals that won't cross 0.5 (which would be a model that is no better than chance) (http://www.biosoft.hacettepe.edu.tr/easyROC/).

4.3 JUSTIFICATION FOR DOSE

We intend to use the approved dosage of the IMP. No changes to therapy were warranted in this study.

4.4 END OF STUDY DEFINITION

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

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

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

If the whole study is stopped, patients who are terminated early will be followed according to withdrawal criteria and procedures for the patient.

5 STUDY POPULATION

5.1 INCLUSION CRITERIA

1. A history of severe persistent asthma as defined by ERS/ATS criteria which includes the presence of poor asthma control on high dose ICS/LABA OR the need for high dose ICS/LABA to maintain asthma control OR oral steroids for maintenance therapy for more than 50% of the prior year.

2. Age >18 years of age or older.

3. Presence of current biologic use or planned initiation of biologics following study enrollment.

4. Patients will be categorized on the basis of asthma control (ACT< 19 will be considered poor asthma control). We will cap the patients with good asthma control at 30% and will no longer enroll those patients once the strata have been fully enrolled.

5. Willingness to switch maintenance inhalers to AirDuo® Digihaler™ and/or to use ProAir® Digihaler™ for rescue therapy. Use of nebulized albuterol will be discouraged but not prohibited. We will require patients to document nebulizer use. Patients that discontinue Pro-Air will be asked to document use of their rescue inhalers in their diaries.

6. Can read and communicate in English and is familiar with and is willing to use his/her own smart device and download and use the study application. If their smart device is not compatible with the study software; willingness to use an alternative device that will be provided by the study team.

7. Ability to provide informed consent.

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

5.2 EXCLUSION CRITERIA

1. Clinically important pulmonary disease including COPD, primary bronchiectasis, idiopathic pulmonary fibrosis, cystic fibrosis and interstitial lung disease.
2. Any disorder that is either not stable or could in the opinion of the investigator affect the ability of the subject to safely participate in the study or could adversely affect study results.
3. History of HIV or other primary immunodeficiency syndrome.

4. Malignancy other than skin cancer that has occurred within the past year and that will impact survival thus limit participation in the clinical trial.

5. Current documented alcohol abuse or drug use. Patients with a history of abuse and are in remission are eligible to enroll.

6. Any life-threatening diseases that will impact the patient's ability to complete the 12-month study period.

7. Inability to provide informed consent.

5.3 LIFESTYLE CONSIDERATIONS

There are no lifestyle considerations for this study.

5.4 SCREEN FAILURES

Patients will - be removed from the study if they do not get started on a biologic or if they discontinue therapy with biologics for any reason.

Patients who screen fail do not need to be replaced to reach the target enrollment number.

5.5 STRATEGIES FOR RECRUITMENT AND RETENTION

Patients will be recruited from the Severe Asthma Clinics at the University of Michigan. The program currently has 300 patients receiving biologics for asthma. We will also recruit patients from other clinics that are receiving biologics as long as the providers are willing to obtain and document detailed information on biologic response to therapy.

6 STUDY INTERVENTION

6.1 STUDY INTERVENTION(S) ADMINISTRATION

6.1.1 STUDY INTERVENTION DESCRIPTION

The Teva Digihaler™ System consists of 4 devices. Device 1 is the ProAir® Digihaler™, which is the test IMP. The 3 investigational medical devices are: Device 2 - Patient-facing App; Device 3 - DHP (cloud solution); and Device 4 - Provider-facing dashboard. Patients will receive 2 ProAir® Digihaler™ devices at the face-to-face visits and can request additional devices if these devices have been completely used. A three-month supply of maintenance AirDuo® Digihaler™ will be provided at each in person visit and only after verification that data from the previous device has been downloaded. Patients will receive instructions for using the ProAir® Digihaler™ and AirDuo® Digihaler™ from the investigational center personnel. Patients will be instructed to return all inhalers to the investigational center at the end of treatment visit or at early termination. These devices will be brought to the in-person visits and the data download will be confirmed, after which the devices will be discarded.

6.1.2 DOSING AND ADMINISTRATION

Patients will receive the ProAir® Digihaler™ 90mcg and the AirDuo® Digihaler™ at a dose that is equivalent to the patients current inhaled therapy dose. Most patients will likely require the high dose inhaler: 232/14 device. This medication will be administered twice daily. The ProAir® Digihaler™ will be utilized up to six times per day as needed for acute asthma symptoms.

6.2 PREPARATION/HANDLING/STORAGE/ACCOUNTABILITY

6.2.1 ACQUISITION AND ACCOUNTABILITY

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

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

Only patients enrolled in the study may receive IMP, and only authorized personnel at the investigational center may supply or administer IMP. All IMP must be stored in a secure, environmentally controlled, and monitored (manual or automated) area in accordance with the labeled storage conditions or appropriate instructions with access limited to the investigator and authorized personnel at the investigational center. The investigator (or designee) will instruct the patient to store the IMP according to the instructions on the label, if applicable; or will give instructions in an appropriate form. Patients will be instructed to return all IMP (empty, partially used, and unused inhalers) to the investigational center at the final visit or at early termination.

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

A record of IMP accountability (i.e., IMP and other study materials received, used, retained, and returned) must be prepared and signed by the principal investigator or designee, with an account given for any discrepancies. All empty, partially used, and unused inhalers will be collected at the end of the study and will be returned to the sponsor or designee per sponsor instructions.
Further guidance and information are provided in the Study Reference Manual.

6.2.2 FORMULATION, APPEARANCE, PACKAGING, AND LABELING

The prescribed dose of ProAir® Digihaler™ used in this study (i.e., 90 mcg, 1 to 2 inhalations every 4 to 6 hours, as needed) was selected based on the prescribing information for PROAIR® RESPICLICK, which has the same drug delivery design as ProAir® Digihaler™. The prescribed dose of AirDuo® Digihaler™ is based on current FDA approval for the AirDuo® inhaler. The inhaler used in this study will have the digital interface for data collection, and this should not impact the drug delivery in any way. The digital inhaler is longer than the conventional inhaler but is otherwise used similarly.

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

6.2.3 PRODUCT STORAGE AND STABILITY

The IMP must be stored at room temperature (15°C to 25°C [59°F to 77°F]) and not exposed to extreme heat, cold, or humidity. The investigational drug (IDS) pharmacy at the University of Michigan will be responsible for acknowledging receipt of the IMP. All study drug will be dispensed by the IDS pharmacy.

6.2.4 PREPARATION

There is no medication preparation required.

6.3 MEASURES TO MINIMIZE BIAS: RANDOMIZATION AND BLINDING

There is no randomization in this study. Subjects will be pre-screened prior to clinical visits and all eligible subjects will be approached. Once the controlled strata have been filled then we will no longer approach patients that do not meet criteria for poor asthma control (ACT >/=19).

6.4 STUDY INTERVENTION COMPLIANCE

We will determine medication compliance by assessing the data collected from the inhaler. These inhalational parameters and medication use data will be transferred from the Digihaler™ to the patients' phone app and then to the server powering the dashboard. If a patient switches to ProAir® Digihaler™ /Airduo™ and determines that one of the inhalers is ineffective they can switch back to their original inhaler and remain in the study. The patient will need to agree to use at least one of the two digital inhalers to remain in the study (ie either the rescue or maintenance inhaler) as this will allow us to obtain the inspiratory parameters required in this study. We also ask that all non-digital inhaler use be documented in the patient diary. We will allow a maximum of 10% of the study population to switch their medications during the study.

6.5 CONCOMITANT THERAPY

6.5.1 RESCUE MEDICINE

The patients will utilize the ProAir® Digihaler™ for rescue. Nebulized albuterol and atrovent will be allowed for severe symptoms during exacerbations and patients will be required to report when these medications were utilized. We will encourage preferential use of the inhaler if symptoms are not severe enough to warrant nebulized medications.

Any concomitant medication a patient is taking at screening and up to the final visit will be recorded on the CRF. Trade name and international nonproprietary name (if available), indication, dose, and start and end dates of the administered medication will be recorded.

7 STUDY INTERVENTION DISCONTINUATION AND PARTICIPANT DISCONTINUATION/WITHDRAWAL

7.1 DISCONTINUATION OF STUDY INTERVENTION

Patients will be discontinued from study intervention if they are no longer willing or able to comply with study procedures or if they withdraw consent. If a patient switches to ProAir® Digihaler™ /Airduo™ and later has a preference for their original controller or short-acting beta agonist, then switches will be allowed as long as the patient remains on at least one of the two digihaler devices. The patient will need to agree to use at least one of the two digital inhalers to remain in the study (ie either the rescue or maintenance inhaler) as this will allow us to obtain the inspiratory parameters required in this study.

7.2 PARTICIPANT DISCONTINUATION/WITHDRAWAL FROM THE STUDY

1. Patient withdraws consent or withdrawal from the study for any reason
2. Patient experiences an adverse event or other medical condition which indicates to the investigator that continued participation is not in the best interest of the patient.
3. Patient develops an illness that would interfere with his/her continued participation.
4. Patient is noncompliant with the study procedures and assessments in the opinion of the investigator.

Patients should be treated with standard of care after withdrawal from or termination of the study as appropriate. We will obtain information on patients in the case of withdrawal from the study or discontinuation from IMP. Results of any evaluations and observations, together with a narrative describing the reason(s) for withdrawal from the study or discontinuation from IMP, must be recorded in the source documents. The case report form (CRF) must document the primary reason for withdrawal from the study or discontinuation from IMP.

7.3 LOST TO FOLLOW-UP

A patient will be considered lost to follow-up if he/she repeatedly fails to return for scheduled visits and is unable to be contacted by the investigational center.
The following actions must be taken if a patient fails to return to the investigational center for a required study visit:

- The investigational center must attempt to contact the patient and reschedule the missed visit as soon as possible, counsel the patient on the importance of maintaining the assigned visit schedule and ascertain whether or not the patient wishes to and/or should continue in the study.
- In cases in which the patient is deemed lost to follow-up, the investigator or designee must make every effort to regain contact with the patient (where possible, 3 telephone calls and, if

necessary, a certified letter to the patient's last known mailing address, or local equivalent methods). These contact attempts should be documented in the patient's medical record.

- Should the patient continue to be unreachable, he/she will be considered to have withdrawn from the study with a primary reason of 'lost to follow-up'.

8 STUDY ASSESSMENTS AND PROCEDURES

8.1 EFFICACY ASSESSMENTS

The efficacy of the drug product will not be evaluated in this study. The focus of this study is the current behavior of severe asthmatics with regard to their inhaler use.

8.1.1 STUDY VISITS

8.1.1.1 SCREENING/BASELINE VISIT (V0)

Patients will be pre-screened and recruited as they attend standard of care visits in the Severe Asthma Clinic at Michigan Medicine. The following events will take place during the screening/baseline visit:

- Informed Consent
- Enrollment into the MiAsthma Registry
- Review of Inclusion/Exclusion Criteria
- Collection of Medical and Procedure History
- Collection of Smoking/Tobacco Use History
- Review of Past and Current Medications
- Review of Asthma Exacerbations and Healthcare Utilization
- Collection of Clinical Variables (*if available*) including FeNO, CBC w. Differential, and Immunoglobulin E (IgE) Levels
- Dispensation of Inhaler
    - Education on Inhaler Use and Registration to Inhaler Application
- Dispensation of Home Spirometer
    - Education on Use of Home Spirometer
- Collection of Patient Reported Outcomes
    - Asthma Control Test (ACT), AIR-Q, SGRQ

8.1.1.2 IN PERSON/CLINICAL VISITS (V3, V6, V9, V12)

Patients will return to clinic every three months to check in with the study team and to provide-additional inhalers for the study. During the in-person visits the following events will take place:

- Review of Current Medications
- Review of Asthma Exacerbations and Healthcare Utilization
- Collection of Clinical Variables (*if available*) including FeNO, CBC w. Differential, and Immunoglobulin E (IgE) Levels
- Dispensation of Inhaler
- Adverse Event Assessment
- Collection of Patient Reported Outcomes

- Asthma Control Test (ACT), AIR-Q, SGRQ
- Device Re-Education (As Needed)

8.1.1.3 INTERIM PHONE CONTACT (V1, V2, V4, V5, V7, V8, V10, V11)

Patients will be contacted monthly between in person visits to assess the following:

- Review of Current Medications
- Review of Asthma Exacerbations and Healthcare Utilization
- Shipping of Inhaler (As Needed)
- Adverse Event Assessment
- Device Re-Education (As Needed)

8.1.2 STUDY PROCEDURES

8.1.2.1 ENROLLMENT INTO MIASTHMA REGISTRYSCREENING/BASELINE VISIT (V0)

All clinical data elements will be abstracted from the EMR and entered into an existing asthma registry at the University of Michigan (MiAsthma Registry) that focuses on severe asthma. A separate consent is required for entry into the database and will be obtained at the same time as initial consent for this study. Variables captured in the MiAsthma Registry include medical and procedure history, review of past and current medications (both asthma and non-asthma related) and collection of clinically assessed PRO's. Relevant medical history may include any of the following: asthma history, co-morbid conditions such as nasal polyps, allergic rhinitis, hives, eosinophilic disease other than asthma, obesity and sleep apnea, age of asthma onset, number of exacerbations in the past year, lifetime hospitalizations, yearly ER visits, oral steroid dependence, history of life-threatening asthma as indicated by prior intubation and mechanical ventilation.

8.1.2.2 CLINICAL VARIABLES AND BIOLOGICAL MARKERS

When available FeNO, peripheral eosinophils (the three highest values in the past 12 month) collected via CBC with Differential, total IgE, presence or absence of positive specific IgE results will also be recorded. Prior lung function measurements and spirometry data (all available within 12 months prior to initiation of biologic therapy) will be abstracted via the MiAsthma Registry when available. No study specific testing will take place (with the exception of home spirometry).

8.1.2.3 ASTHMA EXACERBATIONS

During the study, an asthma exacerbation will be defined as a worsening of asthma symptoms (defined below) that leads to any of the following:

- Administration of a bolus/burst of systemic corticosteroids (one dose of IV or IM steroids or at least consecutive three days of oral corticosteroids).
- An emergency room or urgent care visit for asthma related symptoms that required oral/IV/IM corticosteroids.
- An inpatient hospitalization (defined as admission to an inpatient facility and/or evaluation and treatment in a healthcare facility for ≥ 24hrs) due to asthma.

For the protocol, the start date of the exacerbation will be based on the day of ER, urgent care visits or hospitalization. For those that did not experience one of these events, the day of the first dose of OCS will be used as the initial day of the exacerbation. The last day of systemic corticosteroids will be used as an end date of the exacerbation. If less than 7 days has elapsed between the end of the first exacerbation and the beginning of new symptoms, then this will be considered a relapse of the initial episode rather that a new episode. Subjects that experience exacerbations post enrollment will be treated per standard of care by the patient's physician.

8.1.2.4 DIGIHALER™, TEACHING, AND ONLINE APPLICATION

Education for the appropriate use of the Digihaler™ will be provided at the Screening/Baseline visits and again as needed throughout the study. The study team will assist in registering for the digital inhaler application and periodically check to ensure data is being captured appropriately.

Inhalation parameters and number of doses will automatically be collected using the Digihaler™.

Application

The software App is a user facing software/focused smart device application for patients using the Digihaler™ product. The smart device app is used to track medication usage and allow users to self-assess their respiratory symptoms on a daily basis, share information on local environmental conditions, and produce user reports to review data over time.

The software consists of a smart device application compatible for iPhone operating systems (iOS) and Android operating systems that will store data locally on the patient's smart device. The App will receive a patient's health data automatically from the inhaler devices via Bluetooth on a smart device. The smart device camera will be used for scanning and pairing. The data will allow the patient to track their usage of medication, inhalation results, and self-assessments related to their asthma. The App will get environmental information from 1 or more web services.

TEVA Digital Health Platform

The TEVA DHP is a system that stores and transfers health data collected from the App. The cloud solution automatically synchronized with the App after events and/or at predetermined time periods/intervals. An internet connection to the smart device (e.g., wireless or cellular phone network) is required in order for communication to be established between the App and the cloud solution. The

cloud solution will not send any notifications to the App. The cloud solution does not create, modify, or delete patient information.

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

8.1.2.5 SPIROMETRY

Home spirometry will be performed with the Go Spiro device that is coupled with an avatar that provides coaching and real time feedback about whether the testing has met ATS criteria. Patients will be asked to perform spirometry a *least* three days per week, at least one of which occurs on the weekend. Patients will be asked to make a maximum of three attempts to obtain data. Patients will be encouraged to complete more than three readings per week whenever possible. The spirometry should be obtained at approximately the same time of each day.

The vendor providing central spirometry services will be responsible for assuring that the spirometer used by patients at home meets ATS/ERS criteria and that study staff educating participants on home spirometry have been properly certified to provide this training.

Subjects should be instructed to follow the required restrictions below prior to performing spirometry. If the required restrictions have not been adhered to the visit should be rescheduled to the earliest possible time to maintain the visit windows.

Home Spirometry Testing

An electronic hand-held spirometer will be provided to the subject at the screening visit. Subjects will be trained on how to obtain at home PEF and FEV1 measurements at the screening visit. Training should include explanation of the device functionality and proper use of the PEF meter.

Home PEF measurements will be taken in the morning (prior to taking morning medications) and/or in the evening at bedtime (prior to taking pm medications for asthma) on the days that spirometry is done. FEV1 will be measured at home using accepted ATS/ERS criteria via the use of an avatar guided maneuver. Subjects should perform 3 successive maneuvers while sitting or standing but in the same position at every testing. Adherence to peak flow measurements must be checked by the study coordinator at every in-person visit. A low compliance trigger will be sent to the study site if the subject had completed less than 80% of the expected measurements over a seven-day period.

8.1.2.6 PATIENT REPORTED OUTCOMES

Asthma Control Test (ACT)

The ACT captures asthma symptoms and short acting bronchodilator usage. Questions will be weighted equally and scored per the standardized questionnaire (REF). An ACT score of <19 is consistent with uncontrolled asthma.

Asthma Impairment and Risk Questionnaire (AIRQ)
The AIRQ™ is a patient assessment tool intended to help identify patients 12 years of age and older whose health may be at risk because of uncontrolled asthma. This assessment is based on a series of patient-facing questions about asthma medications, respiratory symptoms, and utilization of health care resources. Depending on the patient's responses to these questions, the patient will receive a score reflecting their level of asthma control.

St. George's Respiratory Questionnaire
The St. George's Respiratory Questionnaire (SGRQ) is a patient reported questionnaire designed to measure impact on overall health, daily life, and perceived well-being in patients with obstructive airways disease. Scores range from 0 to 100 with higher scores indicating more limitations.

8.2 SAFETY AND OTHER ASSESSMENTS

In this study, safety will be assessed by qualified study personnel by evaluating reported adverse events, device safety (as assessed by adverse device effects and serious adverse device effects), and use of concomitant medications.

8.3 ADVERSE EVENTS AND SERIOUS ADVERSE EVENTS

8.3.1 DEFINITION OF ADVERSE EVENTS (AE)

Safety Considerations: The external sponsor/collaborator shall have the sole responsibility for the collection and recording of all reported Adverse Events (AEs),Serious Adverse Events (SAEs), Pregnancies, Adverse Device Effects and Serious Adverse Device Effects throughout the entire study. In keeping with good clinical practice or good pharmacovigilance practice, and 21 C.F.R. Part 314 as the case may be, the external sponsor/collaborator will be required to report and notify the FDA, Institutional Review Boards (IRBs), Teva Pharmaceuticals (Teva), and any other collaborators/investigators of all situations mentioned below, within twenty-four (24) hours from receiving information of the situation. The event will be reported to Teva by submitting the collected information to the Teva Local Safety Officer.

(a) All related Serious Adverse Events

(b) All Serious Adverse Device Effects.

(c) Any medical event which may reasonably be believed to impair the integrity, validity or ongoing viability of the Study

Pharmacovigilance approved definitions of AEs and SAEs and reporting and recording procedures will be followed as noted below.

In this study, safety will be assessed by qualified study personnel by evaluating reported adverse events and device safety (as assessed by adverse device effects and serious adverse device effects). The external sponsor/collaborator will be responsible for the collection and recording of all reported Adverse Events (AEs), Serious Adverse Events (SAEs) Pregnancies, Adverse Devise Effects and Serious Adverse Device Effects throughout the entire study.

Definitions:

Adverse Event

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

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

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

- intercurrent illnesses
- physical injuries
- events possibly related to concomitant medication
- significant worsening (change in nature, severity, or frequency) of the disease under study or other pre-existing conditions
- drug/drug or drug/device or device/device interactions
- events occurring during diagnostic procedures of this study

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

8.3.2 ADVERSE DEVICE EFFECT AND REPORTING

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

medical device, including any event resulting from user error or from intentional misuse of the investigational medical device.

A serious adverse device effect is an adverse device effect that has resulted in any of the consequences characteristic of a serious adverse event as described in section 8.3.3.

AE=adverse event; ADE=adverse device effect; SADE=serious adverse device effect; SAE=serious adverse event.

8.3.3 DEFINITION OF SERIOUS ADVERSE EVENTS (SAE)

Serious Adverse Event

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

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

  Hospitalizations scheduled before the patient signed the ICF will not be considered serious adverse events, unless there was worsening of the pre-existing condition during the patient's participation in this study.
- results in persistent or significant disability/incapacity (refers to a substantial disruption of one's ability to conduct normal life functions)
- is a congenital anomaly/birth defect
- an important medical event that may not result in death, be life-threatening, or require hospitalization, but may jeopardize the patient and may require medical intervention to prevent 1 of the outcomes listed in this definition

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

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

- alanine aminotransferase or aspartate aminotransferase increase of >3x the upper limit of normal (ULN)
- total bilirubin increase of >2x ULN

- absence of initial findings of cholestasis (i.e., no substantial increase of alkaline phosphatase)

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

8.3.4 SERIOUS ADVERSE EVENT REPORTING

In keeping with good clinical practice or good pharmacovigilance practice, and 21 C.F.R. Part 314 as the case may be, the external sponsor/collaborator will be required to report and notify the FDA, Institutional Review Boards (IRBs), Teva Pharmaceuticals (Teva), and any other collaborators/investigators of all situations mentioned below, within twenty-four (24) hours from receiving information of the situation. The event will be reported to Teva by submitting the collected information to the Teva Local Safety Officer.

(a) All related Serious Adverse Events

(b) All Serious Adverse Device Effects

(c) Any medical event which may reasonably be believed to impair the integrity, validity or ongoing viability of the Study

Adverse Event. Sponsor/collaborator acknowledges that Company is required to comply fully and promptly with all regulatory safety reporting requirements regarding its products. The investigator being the sponsor of the study has sole responsibility for reporting of adverse events to the FDA, IRBs and/or investigators. For informational purposes any correspondence to the FDA regarding adverse events or other safety issues will be simultaneously copied to the Company via email (us.clinops.sae@tevapharm.com) or facsimile (215-795-4243). The Investigator will communicate the occurrence of any serious adverse events which he or she believes to be definitely, likely, possibly or probably related to the Study Product, and any exposure of a pregnant study participant to the Study Product, within 24 hours of becoming aware of the event. In the case of non-interventional studies, the Investigator also will communicate all related, non-serious adverse events to Company within 24 hours of becoming aware of the event. Please note that the reporting period begins when a patient signs the informed consent, and ends 30 days after the discontinuation of dosing or completion of the patient's participation in the Study if the last scheduled visit occurs at a later time. In addition, the Investigator must notify Company of any serious adverse events that may occur after this time period which he or she believes to be definitely, likely, possibly or probably related to the Study Product.

The MedWatch 3500A form should be utilized to report serious adverse events to the FDA.

A serious adverse event or reaction is any untoward medical occurrence that at any dose:

- Results in death;
- Is life-threatening (meaning that the patient was at immediate risk of death as the event occurred, but not including events that could cause death if they occurred in a more severe form);
- Requires inpatient hospitalization or prolongation of existing hospitalization;
- Results in a persistent or significant disability/incapacity;
- Is a congenital anomaly or birth defect;

- Results in the development of drug dependency or drug abuse;
- An important medical event that may not result in death, be life threatening, or require hospitalization, but may jeopardize the patient and require medical intervention to prevent one of the outcomes listed above.

For the purpose of this Agreement, these terms shall have the same meaning as the terms used in the provisions of the Code of Federal Regulations governing drug and biologic safety reporting. See 21 CFR 314.80(a); 600.80(a). Additionally, pregnancy exposure and any safety information as reasonably requested by Company, will also be deemed to be adverse events for purposes of this Agreement. Investigator shall use his/her judgment to determine the relationship between the serious adverse event and the Study Product. In the event the IRB requests additional safety information from Investigator, Investigator shall notify Company of such request within one (1) business day.

Investigator and Institution further agree to report all Adverse Events in compliance with all applicable legal and regulatory requirements, and in accordance with any requirements provided by Company.

8.3.5 REPORTING EVENTS TO PARTICIPANTS

Events that involve device failure that will affect drug delivery as noted by the sponsor or any other new safety requirements that may be required by the FDA will be reported to participants.

8.3.6 EVENTS OF SPECIAL INTEREST

There are no events of special interest anticipated in this study.

9 STATISTICAL CONSIDERATIONS

9.1 STATISTICAL HYPOTHESES

- Primary Efficacy Endpoint(s): Establish group-level daily/weekly baseline normative values for: (1) mean and median number of doses of ProAir® Digihaler™ and AirDuo® Digihaler™, and per-inhalation baseline normative values for (2) peak inspiratory flow (PIF), (3) inspiratory time and (4) volume. We will test the hypothesis that patient-specific baseline usage values are significantly different from usage values collected during or leading up to exacerbation events.

- Secondary Efficacy Endpoint(s): 1. Test the hypothesis that imminent exacerbation events can be predicted using Digihaler™ inhalation parameter measurements. 2. Test the hypothesis that PIF is linearly (or non-linearly) related to FVC and FEV1. Test the hypothesis that there exists a threshold for change in PIF that is associated with a clinically meaningful change (>10%) in lung function. 3. Test the hypothesis that patients with low, moderate, and high adherence to maintenance inhalers have significantly different asthma outcomes. 4. Test the hypothesis that non-responders, partial, and complete responders have significantly different Digihaler™ inhalation parameters. 5. Test the hypothesis that future response to biologics can be predicted using clinical, biological, and digital (inhalation) markers.

9.2 SAMPLE SIZE DETERMINATION

Sample size calculations were based on peak inspiratory flow measurements.

Based on population-based estimates of peak inspiratory flow: https://www.ncbi.nlm.nih.gov/pmc/articles/PMC5328129/ The mean was 115 and standard deviation was 15. With a 100-patient sample, 95% CI of our estimate of the mean would be plus or minus 3, e.g. 115 (95 CI 112 – 118).

The machine learning model will be performed based on the most common measure to evaluate performance which is discrimination that is assessed by an AUROC. If we have a 100-patient sample and assume a 50% event rate (http://www.biosoft.hacettepe.edu.tr/easyROC), we would have adequate power to conclude that a model with an AUROC performance of > 0.65 has confidence intervals that won't cross 0.5 (which would be a model that is no better than chance).

9.3 POPULATIONS FOR ANALYSES

University of Michigan patients currently receiving biologics or with a pending approval for biologics for asthma.

9.4 STATISTICAL ANALYSES

9.4.1 GENERAL APPROACH

We will perform a retrospective analysis of prospectively enrolled patient data. Following completion of the study's data collection period, data from the Digihaler™ asthma inhalers will be downloaded to secure servers, joined to clinical data from the electronic medical record (including exacerbation event data) and patient questionnaire responses, and analyzed using R statistical analysis software. The University of Michigan Morphomics Analysis Group will collaborate with the TEVA analytics team to produce a rigorous and reproducible research result. An alpha level of 0.05 will be used to determine "statistical significance" with a Bonferroni correction (alpha / # tests) applied to account for multiple testing when appropriate.

9.4.2 ANALYSIS OF THE PRIMARY EFFICACY ENDPOINT(S)

To establish normative baseline values, summary statistics (mean, standard deviation, median, IQR) will be computed for the number of doses taken per individual, stratified by type of inhaler (maintenance, rescue), and aggregated per day and for particular times of day (morning, midday, afternoon, evening, overnight). Per-inhalation summary statistics will be computed for PIF, inspiratory time, and inspiratory volume. Inhalation data within +/- 14 days of an acute exacerbation event will be identified and excluded from normative baseline calculations.

9.4.3 ANALYSIS OF THE SECONDARY ENDPOINT(S)

1. To develop an algorithm that can identify probable imminent exacerbation events using Digihaler™ inhalation parameter measurements, we will compare the performance of several different machine learning regression models. Since we expect our training set to be relatively small with a low event rate, we plan to use the entire inhalation parameter dataset for model training but will employ repeated k-fold cross-validation to reduce variance (over-fitting) and include non-linear features to reduce bias (under-fitting). Examples of features that could be computed and included in this model include but are not limited to: difference between current value and patient-specific 7-day moving average, difference between current value and patient-specific 24-hour moving average, 7-day sample entropy, 24-hour sample entropy, difference in Min-Max over last 24 hours, etc.

A logistic regression model would treat the outcome (exacerbation) as a binary (Yes/No) event. The output of this model would be a daily probability between 0 and 1 that an exacerbation event will occur within a certain period of time. Different models will be fit for different periods of time (e.g., 24, 48, 72 hours) and the performance of each model assessed and compared to others. A recurrent event survival model would treat the exacerbations as discrete events in time. The output of this model would be the predicted time (e.g., in decimal days or hours) until the next event. Other models may include convolutional and/or recurrent neural networks (RNN) with LSTM or GRU architecture with varied numbers of hidden layers.

2. To determine whether and how PIF is associated with FEV1 and FVC, we assess the linearity and strength of the relationship using scatter plots, calculate the paired correlations (Pearson, Kendall, and Spearman), and compute univariate linear regression equations with PIF as the predictor and FEV1 or

FVC as the response. If non-linearity is found, we will determine the appropriate PIF transformation or polynomial term to use in the regression. Regression summary statistics (e.g., R-squared, Mean Absolute Error, Coefficients, and p-values) will be reported.

3. Patients will be assigned to one of three adherence groups (low, moderate, high) based on Digihaler™ inhalation usage parameters over the previous month. We will use the Chi-squared test to determine if group differences exist for each asthma outcome over the next month, and Tukey's Honest Significant Difference test to determine which groups are significantly different.

4. Patients will be assigned to one of three biologics response groups (non, partial, complete) based on six asthma factors (described earlier). We will use the Chi-squared test to determine if group differences exist for each inhalation parameter, and Tukey's Honest Significant Difference test to determine which groups are significantly different.

5. To develop an algorithm that can predict patients that will respond to biologics regression or classification models. Since we expect our training set to be relatively small with a low event rate, we plan to use the entire inhalation parameter dataset for model training but will employ repeated k-fold cross-validation to reduce variance (over-fitting) and include non-linear features to reduce bias (under-fitting). We do not know a priori whether regression or classification would be the appropriate approach to this question so we will test models using both approaches. The classification approach can be formulated as either a two-class problem – Non vs. Partial or Complete responders, or Non or Partial vs. Complete responders – or a three-class problem – Non vs. Partial vs. Complete. The regression approach requires a two-class formulation using logistic regression. Different models will be fit for different formulations and the performance of each model assessed and compared to others.

9.4.4 SAFETY ANALYSES

We will track and document safety events related to the device during the clinical trial.

9.4.5 BASELINE DESCRIPTIVE STATISTICS

Count, mean, standard deviation, median, IQR will be computed for continuous variables and percentages for categorical variables – daily, time-of-day, and per-inhalation parameters, exhalation spirometer variables, clinical and demographic variables, asthma outcomes, radiographic variables. Summaries will be computed for males vs. females, adherence group, and response group.

9.4.6 PLANNED INTERIM ANALYSES

We will perform the initial analysis once 50% of the study population has completed six months of follow-up within the study.

9.4.7 SUB-GROUP ANALYSES

See secondary endpoints #3 (adherence groups) and #4 (responder groups).

9.4.8 TABULATION OF INDIVIDUAL PARTICIPANT DATA

We do not plan to tabulate or report individual participant data, except in the case where we determine that one or more participant's data would be useful for explaining a general concept or idea, or is representative of an overall trend, and as such may be displayed (without any identifying information) in a data graphic or visualization with or without an accompanying data table.

9.4.9 EXPLORATORY ANALYSES

We plan to conduct extensive exploratory analyses including but not limited to: data cleaning and aggregation, outlier analysis, multicollinearity (correlation) analysis, sex effect analysis, age effect analysis, time series analysis, unsupervised cluster analysis, univariate testing (T-tests, Fisher's Exact Test, Wilcoxon Test, Chi-Squared Test, Tukey's Honest Significant Difference (HSD) Test), multivariable linear and non-linear regression, feature creation and selection for machine learning models, feature scaling and centering, training machine learning models using repeated k-fold cross-validation, and extensive data visualization for correlations and time series analysis.

10 SUPPORTING DOCUMENTATION AND OPERATIONAL CONSIDERATIONS

10.1 REGULATORY, ETHICAL, AND STUDY OVERSIGHT CONSIDERATIONS

10.1.1 INFORMED CONSENT PROCESS

It is the responsibility of the named investigator to assure that all study subjects undergo an appropriate process of written informed consent that has been reviewed and approved by their local Institutional Review Board. The investigators will inform all subjects as to the nature, aims, duration, potential hazards, and procedures to be performed during the study and that his/her medical records and study-related documents may be reviewed by the FDA or sponsoring companies in a manner designed to protect their confidentiality. This protocol must receive approval by the Institutional Review Board at each participating site prior to implementation of the study at that site. Investigators must also disclose to subjects any existing conflicts of interest and explain that patients are completely free to refuse to enter the study or to withdraw from it at any time without prejudice to their medical care.

10.1.1.1 CONSENT/ASSENT AND OTHER INFORMATIONAL DOCUMENTS PROVIDED TO PARTICIPANTS

Consent will be copied and provided to the patient after it has been signed. The documentation will then be scanned into the EMR per University of Michigan protocol.

10.1.1.2 CONSENT PROCEDURES AND DOCUMENTATION

The protocol will be discussed in detail with all potentially eligible patients and the essential components of the informed consent process personally confirmed by a responsible investigator before the consent is signed and countersigned. The subject will sign the informed consent document prior to any procedures being done specifically for the study. All revisions of the protocol must be reviewed by the IRB and reflected in the consent form. Patients will receive copies of all consent documents and HIPAA forms for their records and these documents will detail emergency contact numbers for the study and independent reporting numbers for the local IRB in the event that they have any concerns or questions about the process of consent or the handling of human subjects.

10.1.2 STUDY DISCONTINUATION AND CLOSURE

The investigators and/or sponsor reserve the right to terminate the study at any time. If this becomes necessary, appropriate procedures for continuing long-term follow-up and assuring the adequate treatment and safety of the participating subjects will be arranged after review and approval by the study sponsor, Institutional Review Boards and the FDA.

10.1.3 CONFIDENTIALITY AND PRIVACY

Every participating clinical site will maintain appropriate medical and research records for this trial, in compliance with ICH E6 and regulatory and institutional requirements for the protection of confidentiality of subjects. Participating clinical sites will also obtain institutional authorization for external monitoring by the Sponsor, Data Coordinating Center and the FDA to examine (and when

permitted by applicable law, to copy) clinical records for the purposes of quality assurance reviews, audits, and evaluation of the study safety, progress, and data validity.

10.1.4 FUTURE USE OF STORED SPECIMENS AND DATA

Source data are defined as all information, original records of clinical findings, observations, or other activities in a clinical trial necessary for the reconstruction and evaluation of the trial. Examples of these original documents and data records include, but are not limited to, hospital records, clinical and office charts, laboratory notes, memoranda, subject's memory aids or evaluation checklists, pharmacy dispensing records, recorded audio tapes, recorded data from automated instruments, copies or transcriptions certified after verification as being accurate and complete, microfiches, photographic negatives, microfilm x-rays, and subject files and records kept at the pharmacy, at the laboratories, and medico-technical departments involved in the clinical trial. It is acceptable to use CRFs as source documents when the data is collected and recorded there as the primary source of information, but CRFs will not constitute the only form of source document information for this trial.

10.1.5 KEY ROLES AND STUDY GOVERNANCE

Principal Investigator	**Medical Monitor**
Njira Lugogo, MD	Not applicable
Co-Investigators	
Stewart Wang, MD	
Mike Sjoding, MD	

10.1.6 SAFETY OVERSIGHT

DSMB will not be required for this study. Safety events will be tracked in a log and reviewed by the principle investigator on a monthly basis. These safety events will also be reviewed with the sponsor during monthly calls.

10.1.7 CLINICAL MONITORING

No clinical monitoring will be required for this study. Oversight for the accuracy of data entry will be the responsibility of the Clinical Research Project Manager that will be overseeing the coordinator working on this study.

The clinical research project manager will ensure that:

- Data collected and entered into the database are verifiable against source documents for the subjects.
- Appropriate consent is obtained for each subject prior to study procedures.
- The rights and well-being of subjects are being protected.

- The study is conducted in accordance with the currently approved protocol (including study treatment being used in accordance with the protocol), with any other study agreements, with GCP and with applicable regulatory requirements.
- Will work with the research pharmacy on drug accountability and will review logs on a bimonthly basis.

10.1.8 QUALITY ASSURANCE AND QUALITY CONTROL

The clinical trial site has established a set of standard operating procedures (SOPs) governing the processes used to ensure patient privacy and data confidentiality, including the use of anonymous subject IDs on CRFs and in reports. Redcap® enables compliance with Good Clinical Practice (GCP) and regulatory requirements by providing differentiated user roles and privileges, password and user authentication security, electronic signatures, SSL encryption, and comprehensive auditing to record and monitor access and data changes.

10.1.9 DATA HANDLING AND RECORD KEEPING

10.1.9.1 DATA COLLECTION AND MANAGEMENT RESPONSIBILITIES

Data collection is the responsibility of the clinical trial staff at the site under the supervision of the site PI. The investigator is responsible for ensuring the accuracy, completeness, legibility, and timeliness of the data reported. In addition to the protocol, the DCC will prepare a Manual of Operations will provides additional detail on data collection procedures, including source documentation, eCRF completion guidelines, data handling procedures and procedures for data monitoring and quality control that ensure these data are accurate, consistent, complete and reliable and in accordance with ICH 36.

10.1.9.2 STUDY RECORDS RETENTION

Study documents are to be retained for a minimum of at least 6 years have elapsed since the formal discontinuation of clinical development of the investigational product for the studied purpose. These documents should be retained for a longer period, however, if required by local regulations. No records will be destroyed without the written consent of the sponsor, if applicable. It is the responsibility of the sponsor to inform the investigator when these documents no longer need to be retained.

10.1.10 PROTOCOL DEVIATIONS

A protocol deviation is any noncompliance with the clinical trial protocol requirements. The noncompliance may be either on the part of the subject, the investigator, or the study site staff. It is the responsibility of the site to use continuous vigilance to identify and report deviations per local IRB and DCC reporting requirements after identification of the protocol deviation or scheduled protocol-required activity. The investigator will work with the research project manager to ensure that all protocol deviations are documented and addressed in a timely fashion.

10.1.11 PUBLICATION AND DATA SHARING POLICY

The study will comply with Section 801 of the Food and Drug Administration Amendments Act of 2007, and this clinical trial will be registered in ClinicalTrials.gov, a freely available public registry sponsored by the National Library of Medicine.

In addition, an explicit goal of this study is to present the primary and related outcomes of this study at Scientific Meetings and to publish, as possible, in peer-reviewed Scholarly Journals to assure dissemination of the findings. The authority to do so resides with the subject investigators and not with any sponsor.

10.1.12 CONFLICT OF INTEREST POLICY

The investigators and sponsors will comply with the FDA regulations governing financial disclosure by clinical investigators, 21 CFR part 54, in case a new drug application should be filed in conjunction with the work supported by this clinical trial. As per the regulations, applicants will certify the absence of certain financial interests and arrangements of clinical investigators that could affect the reliability of data submitted to FDA, or alternatively disclose those financial interests and arrangements to the agency and identify steps taken to minimize the potential for bias (21 CFR § 54.4(a)).

In addition to FDA regulations, Investigators at the University of Michigan will follow institutional Conflicts of Interest and Conflicts of Commitment policies (https://research-compliance.umich.edu/coi-policies).

- Conflicts of Interest and Conflicts of Commitment standard practice guideline
- Policy for Identification and Management of Conflicts of Interest in Research, Sponsored Research, and Technology Transfer - includes outside interest disclosure requirements for individual or personal COI.
- Unit Policies - Michigan Medicine Outside Interests and Conflicts of Interest Policy, 01-04-003
- Policy for Institutional Conflicts of Interest in Research - U-M Office of President policy (effective July 1, 2018) includes oversight requirements when U-M, as an institution, has financial interests that may affect/appear to affect research.

10.2 ADDITIONAL CONSIDERATIONS

None

10.3 ABBREVIATIONS

ACT	Asthma Control Test
AE	Adverse Event
AIRQ	Asthma Impairment and Risk Questionnaire
ANCOVA	Analysis of Covariance

CFR	Code of Federal Regulations
CLIA	Clinical Laboratory Improvement Amendments
CMP	Clinical Monitoring Plan
COC	Certificate of Confidentiality
CONSORT	Consolidated Standards of Reporting Trials
CRF	Case Report Form
DCC	Data Coordinating Center
DHHS	Department of Health and Human Services
DSMB	Data Safety Monitoring Board
DRE	Disease-Related Event
EC	Ethics Committee
eCRF	Electronic Case Report Forms
FDA	Food and Drug Administration
FDAAA	Food and Drug Administration Amendments Act of 2007
FFR	Federal Financial Report
GCP	Good Clinical Practice
GLP	Good Laboratory Practices
GMP	Good Manufacturing Practices
GWAS	Genome-Wide Association Studies
HIPAA	Health Insurance Portability and Accountability Act
IB	Investigator's Brochure
ICH	International Conference on Harmonization
ICMJE	International Committee of Medical Journal Editors
IDE	Investigational Device Exemption
IND	Investigational New Drug Application
IRB	Institutional Review Board
ISM	Independent Safety Monitor
ISO	International Organization for Standardization
ITT	Intention-To-Treat
LSMEANS	Least-squares Means
MedDRA	Medical Dictionary for Regulatory Activities
MOP	Manual of Procedures
MSDS	Material Safety Data Sheet
NCT	National Clinical Trial
NIH	National Institutes of Health
NIH IC	NIH Institute or Center
OHRP	Office for Human Research Protections
PI	Principal Investigator
QA	Quality Assurance
QC	Quality Control
SAE	Serious Adverse Event

SAP	Statistical Analysis Plan
SGRQ	St George's Respiratory Questionnaire
SMC	Safety Monitoring Committee
SOA	Schedule of Activities
SOC	System Organ Class
SOP	Standard Operating Procedure
UP	Unanticipated Problem
US	United States

10.4 PROTOCOL AMENDMENT HISTORY

Version	**Date**	**Description of Change**	**Brief Rationale**
2	01OCT2021	Updates to exclusion criteria and expectations for use of spirometry and rescue inhalers.	Provide clarity for inclusion and to lessen study burden on patients to improve compliance with protocol procedures.

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