Study Title:
ProAir Digihaler in COPD Disease Management: A real world study to assess ProAir Digihaler inhalation parameters thresholds and their use to identify deterioration in clinical practice

Study Site:
Pulmonary Research Institute of Southeast Michigan between May 19, 2021 and June 20, 2022

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Title: ProAir Digihaler in COPD Disease Management: A real world study to assess ProAir Digihaler inhalation parameters thresholds and their use to identify deterioration in clinical practice

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Background: Despite increasing awareness of the problems and needs, COPD remains the 3rd leading cause of death in the world and has significant impacts on patient function and quality of life. Even in those patients diagnosed with COPD, management is very poor, with over half of COPD exacerbations never reported. In addition, patients who do seek medical attention often delay reporting when they have symptoms of exacerbations. The consequences of these events are well known, with negative impacts on lung function, symptoms, quality of life, future exacerbations and increased mortality. Finding a way to assist patients and caregivers to better identify deterioration in COPD and improve disease management is essential to overcoming these issues.

Proposal:
A pilot study to explore the utilization of the TEVA ProAir Digihaler rescue medication use and inhalation parameters to identify disease deterioration to help in the management of COPD patients in clinical practice.
This study is designed to follow a small sample size of patients with COPD, monitor and collect inhalation parameters from the DIGIHALER dashboard, and changes in symptom control as measured by the COPD Assessment Test (CAT) to identify potential inhalation parameter thresholds that could be applied to the management of patients with COPD in clinical practice.

Objective(s):
Primary Objective:
1) Identify trends in Peak Inspiratory Flow (PIF) rates that associate with disease deterioration as defined by loss of symptom control and reduced lung function in patients with COPD.

Secondary Objectives:
1) Describe specific changes in ProAir Digihaler PIF (e.g. 10, 20, or 30% reduction in PIF from baseline for a minimum of 2 consecutive days) to identify an optimal threshold for characterizing trends in acute changes in the COPD Assessment Test (CAT)
2) Describe specific ProAir Digihaler SABA inhalations per day (Inhalations) above baseline (e.g. 2, 4 or 6 inhalations/day for a minimum of 2 consecutive days) to identify an optimal threshold for characterizing trends in acute changes in the CAT
3) Describe specific changes in ProAir Digihaler Inhalation Volume (IV) (e.g. 10, 20, or 30% reduction in IV from baseline for a minimum of 2 consecutive days) to identify an optimal threshold for characterizing trends in acute changes in the CAT

Exploratory Objectives:

1) Determine whether ProAir Digihaler changes in PIF and in SABA use above baseline thresholds are influenced by baseline COPD condition, as measured by:
   a) COPD Assessment Test (CAT)
   b) Modified Medical Research Council Dyspnea Scale (mMRC)
   c) GOLD group [A-D]
   d) FEV_1 severity/GOLD grade [I-IV]5)
   e) BODE score [Body Mass Index (BMI), Airway Obstruction (FEV_1), Dyspnea (mMRC), and Exercise Tolerance (6-minute walk)]
2) Determine if concomitant measurement of Anthonisen Exacerbation Criteria (dyspnea, sputum amount and color change) using the Breathlessness, Cough and Sputum Survey (BCSS) is associated with ProAir Digihaler changes in PIF below baseline thresholds
3) Determine if concomitant measurement of Anthonisen exacerbation criteria (dyspnea, sputum amount and color change) using the Breathlessness, Cough and Sputum Survey (BCSS) is associated with ProAir Digihaler changes in SABA use above baseline thresholds
4) Determine if concomitant measurement of Anthonisen exacerbation criteria (dyspnea, sputum amount and color change) using the Breathlessness, Cough and Sputum Survey (BCSS) is associated with ProAir Digihaler changes in Inspiratory Volume below baseline thresholds
5) Determine if Inspiratory Capacity (IC) correlates to Inhalation Volume (IV) measured by the ProAir Digihaler, at baseline and during the study

Primary Outcome Measure:

1) Change in Peak Inspiratory Flow (PIF) from Baseline as measured via the ProAir Digihaler device

Secondary Outcome Measures:

1. Change in SABA use (Inhalations) from Baseline
2. Change in Inhalation Volume (IV) use from Baseline
3. Change in CAT
4. Change in FEV_1

Other Outcome Measures:

1. Change in Anthonisen Exacerbation Criteria
2. Change in BCSS
3. Change in Inhalation Volume

Trial Population Entry Criteria:

Inclusion Criteria:

1) Documented history of COPD by ATS/GOLD criteria
2) Age > 45 years
3) Patient willing and able to:
   a) participate in the study, including all scheduled visits
   b) demonstrate the ability to use the ProAir Digihaler, including transfer of Digihaler data via blue-tooth to a smart device
   c) perform all required testing, including spirometry and walk tests
   d) complete all home questionnaires and participate in all telephone contacts
   e) switch current rescue inhaler/device to ProAir Digihaler
4) Baseline spirometry consistent with COPD (post bronchodilator FEV_1 < 80% predicted, FEV_1/FVC <70%)
5) Use of albuterol inhaler as primary device for administration of rescue therapy
6) Reported use of rescue inhaler at least twice (4 inhalations) a week in the previous 6 months
7) Access to smartphone with blue-tooth and cellular/internet access

Exclusion criteria:

1) Allergy, contraindication or inability to use albuterol sulfate
2) Frequent use of a nebulizer as rescue therapy (>1 time per day)
3) Current diagnosis of asthma
4) Unstable medical condition that could prevent the completion of the research trial
5) Pregnancy, planning to become pregnant or breast feeding
6) Failure to use rescue inhaler during Run-in period (minimum of at least 8 rescue inhaler inhalations over the 2 weeks)
7) Exacerbations that require discontinuation from study (during run-in period)

Variables Measured:

1) Digihaler inhalation parameters [PIF – L/Min, Inhalations (#), Inhalation Volume (L)]
2) COPD Assessment Test (CAT)
3) Modified Medical Research Council Dyspnea Scale (mMRC)
4) Anthonisen Exacerbation Criteria (AEC)
5) Breathlessness, Cough and Sputum Survey (BCSS)
6) Inspiratory Capacity [IC (L)]
7) Spirometry (pre and post bronchodilator) [FEV_1, FVC (L)]
8) Vital signs, including body mass index (BMI)
9) 6-minute walk distance (6MWD)
10) Maintenance COPD therapy
11) Healthcare resource utilization (HCRU) – ED/UC Visit, Hospitalization, Office Visits

Variables Derived:

1. Baseline peak inspiratory flow (**Baseline PIF**) measured via Digihaler Device
   PIF is the maximal flow occurring during an albuterol rescue inhalation effort, expressed in Liters/minute. Individual PIF measurements collected over 2 weeks at baseline will be measured using the Digihaler device. The mean value for PIF will be reported as the Baseline PIF.
2. Baseline albuterol inhalations per day (**Baseline Inhalations**) measured via Digihaler Device
   The number of albuterol rescue inhalations used and measured over 2 weeks at baseline using the Digihaler device. Baseline inhalations per day at baseline will be derived by the total number of inhalations divided by the total number of days during the baseline period and reported as inhalations per day or Baseline Inhalations/day.
3. Baseline Inhalation Volume (**Baseline IV**) measured via Digihaler device
   IV is the volume of air inhaled during an albuterol rescue inhalation effort, expressed in Liters. Individual IV measurements collected over 2 weeks at baseline will be measured using the Digihaler device. The mean value for IV during the baseline period will be reported as the Baseline IV.

Protocol Overview

The trial is an unblinded open label single center study designed to identify trends in Peak Inspiratory Flow (PIF) rates and Rescue Albuterol Inhaler usage (Inhalations) that associate with disease deterioration as defined by worsening of symptoms and reduced lung function in patients with COPD.

The study will consist of a run-in period of approximately 2 weeks, a treatment period of 6 months and a follow-up period of 1 week. Twenty (20) patients with COPD requiring intermittent short acting beta agonist (SABA) rescue inhaler usage, but not requiring frequent SABA nebulizer rescue usage, will be enrolled.

After signing informed consent, patients will undergo a screening evaluation. During the run-in period, patients will continue on their COPD maintenance treatments, while discontinuing all previously prescribed periodic use rescue medications. Upon completion of screening, all patients will be dispensed a ProAir Digihaler to be used exclusively as their rescue medication throughout the duration of the study. During the run-in period all rescue inhaler usage will be electronically monitored and patient data from the Digihaler Dashboard will be downloaded every other business day basis (Monday, Wednesday and Friday).

At the completion of at least 2 weeks of run-in (with a minimum of at least 8 rescue inhaler usages) and with documentation of stable clinical status throughout run-in, the patient will return for baseline testing; including vital signs, health related quality of life and Anthonisen Exacerbation questionnaires, pre and post bronchodilator spirometry and 6-minute walk testing (see table/flow chart). Average Peak Inspiratory Flow (Baseline PIF) and average Number of Rescue Inhalations per day (Baseline Inhalations) will be determined from the Digihaler Dashboard Data downloads during run-in.

In the event that the patient does not meet number of rescue inhaler usages or does not have a stable clinical status during run-in, an additional 2 weeks of run-in may be obtained. If at the end of the extended run-in period so that Baseline PIF and Baseline Inhalations cannot be determined or the patient continues to be clinically unstable, the patient will be discontinued from the study. If the patient has an upper respiratory tract infection or COPD exacerbation during run-in, they will also be discontinued from the study. Patients may be re-screened one time at a later date, when stable.

Once run-in and baseline testing are complete, all patients will continue on their maintenance COPD medications and use the ProAir Digihaler rescue SABA exclusively for the next 6 months. Patients will be provided with paper forms of the CAT, BCSS and Anthonisen Exacerbation criteria, to be completed at home on a weekly basis and mailed to the research center upon completion).

Throughout the treatment period, all rescue inhaler usage will be electronically transmitted to, monitored at and downloaded from the Digihaler Dashboard by the research center on every other business day basis (Monday, Wednesday and Friday). At the completion of each Digihaler Dashboard Data Download, comparisons of Daily PIF (average PIF of all rescue inhalations in a day) and Daily Inhalations (number of rescue inhalations in a day) to Baseline PIF and Baseline Inhalations will be made.

All patients with Daily Inhalations exceeding Baseline Inhalations by ≥4 Inhalations per day and/or with a Daily PIF ≤80% of Baseline PIF for 2 consecutive days will be DEFINED as "at risk". For each "at risk" event, the patient will be contacted, their health status reviewed, and CAT and Anthonisen Exacerbation questionnaires will be administered. Based on symptoms, patients may also be advised to seek additional medical care.

All patients will be contacted on a monthly basis, irrespective of "risk" findings and seen in person every 3 months. All medication usage (including ProAir Digihaler medication usage), changes in medical care, healthcare contacts and usage, and any adverse events will be recorded. All office records for the intervening time period will be reviewed and Information for any non-office healthcare contacts and usage will be requested to provide detailed clinical information for comparison to Digihaler usage records.

At months 3 and 6 on treatment, all subjects will return to the research center, where vital signs, Anthonisen Exacerbation and CAT questionnaires, and post bronchodilator spirometry will be assessed. All medication usage (including ProAir Digihaler medication usage), changes in medical care, healthcare contacts and usage, and any adverse events will be recorded. All office records for the intervening time period will be reviewed and Information for any non-office healthcare contacts and usage will be requested to provide detailed clinical information for comparison to Digihaler usage records. Three (3) new ProAir Digihalers will be dispensed at month 3.

Throughout the treatment period, all rescue inhaler usage will be electronically monitored and downloaded from the Digihaler Dashboard by the research center on an every other business day basis (Monday, Wednesday and Friday). At the completion of each Digihaler Dashboard Data Download, comparisons of Daily PIF (average PIF of all rescue inhalations in a day) and Daily Inhalations (number of rescue inhalations in a day) to Baseline PIF and Baseline Inhalations will be made.

All patients with Daily Inhalations exceeding Baseline Inhalations by ≥4 Inhalations per day and/or with a Daily PIF ≤80% of Baseline PIF for 2 consecutive days will be DEFINED as "at risk". For each "at risk" event, the patient will be contacted, their health status reviewed, and CAT and Anthonisen Exacerbation questionnaires will be administered. Based on symptoms, patients may also be advised to seek additional medical care.

At the conclusion of the 6-month treatment period the patients will return to the research center for a final visit, returning all study medication not previously returned. The patient will be advised to resume usage of their prior rescue inhaler medication at that time. A telephone call will be made to the patient 1 week after their final in-person visit, to assess vital status and any adverse events that may have occurred subsequent to discontinuing the ProAir Digihaler.

- All study information, including study app login information, will be labeled with a subject code number and will not include subject name, initials, address, telephone number or e-mail address.
- A secured master spreadsheet will provide the link between required subject identification information and the subject code number.
- The link between subject identification information and subject code number will not be shared.
- All data provided to Teva will only be transmitted using the subject code number.

Visit Schedule

Screening visit (V1):

- Review and sign consent
- Obtain demographic and medical history, including exacerbation and past medical history
- Obtain smoking status and history
- Review all current medications, including all rescue therapies
- Review safety issues, device issues and adverse events
- Review inclusion and exclusion criteria
- Obtain vital signs, including BMI
- Perform Pregnancy test (if of child-bearing potential)
- Complete physical examination
- Complete Health Questionnaires [CAT, mMRC, Anthonisen Exacerbation criteria and BCSS]

- Dispense ProAir Digihaler and establish smartphone connectivity and internet access to the Digihaler Dashboard
- Instruction and training in the proper use of the ProAir Digihaler
- Provide paper copies of CAT, BCSS and Anthonisen Exacerbation criteria, to be completed at home on a weekly basis, along with instructions and stamped envelopes for questionnaire return upon completing
- Instructions for pre-spirometry medication washout prior to visit 2
- Schedule visit 2 for approximately 14 +/- 3 days after visit 1

Run-in visit (V2):

- Review medications, including all rescue therapies and medication washout
- Review safety issues, device issues and adverse events
- Review inclusion and exclusion criteria
- If medication washout has not occurred, reschedule v2 within 1 week
- If medication washout has occurred, complete health questionnaires [CAT, mMRC, Anthonisen Exacerbation criteria and BCSS]
- Perform Pregnancy test (if of child-bearing potential)
- Review and compare health history during the run-in period, returned paper questionnaires and visit 2 health questionnaires to screening medical information and questionnaires to ensure stable baseline clinical condition
- Download Digihaler Dashboard Data and determine if the minimum number of rescue inhalations required during run-in have occurred
- If clinical conditions are not stable or if inadequate numbers of inhalations have occurred during run-in, re-schedule v2 for 2 weeks later
- If clinical conditions remain unstable or inadequate inhalations occur during the extended run-in, withdraw patient from the study
- If medication washout, clinical stability and adequate rescue inhalation criteria during run-in have been meet, perform vital signs
- Perform pre-bronchodilator Inspiratory Capacity (see testing)
- Perform pre-bronchodilator Spirometry (see testing),
- Administer 4 inhalations of albuterol via the ProAir Digihaler
- Perform post-bronchodilator Inspiratory Capacity (see testing)
- Perform post-bronchodilator Spirometry 20-30 minutes after albuterol dosing (see testing)
- If post-bronchodilator spirometry entry criteria are not met (inclusion criteria), withdraw subject from the study
- If post-bronchodilator study spirometry criteria are met, instruct patient to self-administer their maintenance COPD medications
- Perform 6-minute walk testing I hour after maintenance medication administration

- Based on spirometry, CAT, and 6-minute walk results, determine GOLD group, airflow/FEV_1 severity and BODE score
- Dispense 2 additional ProAir Digihalers and establish smartphone connectivity and internet access to the Digihaler Dashboard
- Instruction and training in the proper use of the ProAir Digihaler
- Provide paper copies of CAT, BCSS and Anthonisen Exacerbation criteria, to be completed at home on a weekly basis, along with instructions and stamped envelopes for questionnaire return upon completing
- Instruct patient to continue use of all maintenance medications and to use the ProAir Digihaler as their rescue inhaler as needed
- Schedule month 1 and 2 telephone contacts
- Schedule in-clinic visit 3 for approximately for approximately 3months from v2

3-month follow-up (visit 3)

- Review medications, including all rescue therapies and medication washout
- Review safety issues, device issues and adverse events
- Perform Pregnancy test (if of child-bearing potential)
- Complete health questionnaires [CAT, mMRC, Anthonisen Exacerbation criteria and BCSS]
- Download Digihaler Dashboard Data
- Recover the 3 dispensed ProAir Digihalers
- Review any changes in health history, health care contacts, changes in medications and any healthcare utilization
- Review paper questionnaires submitted over the prior 3 months and any clinic or other healthcare records
- Perform vital signs
- Determine timing of maintenance medication usage that morning will be recorded
- Administer 4 inhalations of albuterol via the ProAir Digihaler
- Perform post-bronchodilator Inspiratory Capacity (see testing)
- Perform post-bronchodilator Spirometry 20-30 minutes after albuterol dosing (see testing)
- Dispense 3 additional ProAir Digihalers and establish smartphone connectivity and internet access to the Digihaler Dashboard
- Instruction and training in the proper use of the ProAir Digihaler
- Provide paper copies of CAT, BCSS and Anthonisen Exacerbation criteria, to be completed at home on a weekly basis, along with instructions and stamped envelopes for questionnaire return upon completing
- Instruct patient to continue use of all maintenance medications and to use the ProAir Digihaler as their rescue inhaler as needed

- Schedule month 4 and 5 telephone contacts
- Schedule in-clinic visit 4 for approximately for approximately 3months from v3

6-month follow-up (visit 4)

- Review medications, including all rescue therapies and medication washout
- Review safety issues, device issues and adverse events
- Perform Pregnancy test (if of child-bearing potential)
- Complete health questionnaires [CAT, mMRC, Anthonisen Exacerbation criteria and BCSS]
- Download Digihaler Dashboard Data
- Recover the 3 dispensed ProAir Digihalers
- Review any changes in health history, health care contacts, changes in medications and any healthcare utilization
- Review paper questionnaires submitted over the prior 3 months and any clinic or other healthcare records
- Perform vital signs
- Determine timing of maintenance medication usage that morning will be recorded
- Administer 4 inhalations of albuterol via the ProAir Digihaler
- Perform post-bronchodilator Inspiratory Capacity (see testing)
- Perform post-bronchodilator Spirometry 20-30 minutes after albuterol dosing (see testing)
- Dispense 3 additional ProAir Digihalers and establish smartphone connectivity and internet access to the Digihaler Dashboard
- Instruction and training in the proper use of the ProAir Digihaler
- Provide paper copies of CAT, BCSS and Anthonisen Exacerbation criteria, to be completed at home on a weekly basis, along with instructions and stamped envelopes for questionnaire return upon completing
- Instruct patient to continue use of all maintenance medications
- Instruct patient to resume use of the original rescue inhaler(s) as needed
- Schedule 1-week safety telephone contacts

Months 1, 2, 4 and 5 Telephone Contact:

- Contact patient at scheduled date and time by telephone
- Review changes in health history, health care contacts, changes in medications, any healthcare utilization and any safety issues
- Review paper questionnaires submitted over the prior month
- Download Digihaler Dashboard Data
- Provide reminders and instructions, as needed.

Safety Telephone contact:

- Contact patients at scheduled date and time by telephone 1-week after visit 4
- Review patient health status and any safety issues that may have occurred after discontinuation of study medication

Testing

CAT questionnaire: (see appendix) will be self-administered at home on a weekly basis and at all clinic visits.

Anthonisen Exacerbation Criteria (AEC): (see appendix) will be self-administered at home on a weekly basis and at all clinic visits.

BCSS questionnaire: (see appendix) will be self-administered at home on a weekly basis and at all clinic visits.

mMRC questionnaire: (see appendix) will be self-administered at clinic visits 1 and 2.

Vitals signs, BMI, History, Physical Examination will be performed as per clinical standards.

Medication washout: Medication washout will occur prior to visit 2 as per the following:

SABA – 6 hours
SAMA – 6 hours
BID LABA or LABA/ICS – 12 hours
BID LAMA – 12 hours
BID LABA/LAMA/ICS – 12 hours
QD LABA or LABA/ICS – 24 hours
QD LAMA – 24 hours
QD LABA/LAMA/ICS – 24 hours

Inspiratory Capacity: Inspiratory Capacity will be performed as per ATS standards. A minimum of 3 efforts and maximum of 8 efforts will be performed for each test, with ATS standards for baseline FRC/EELV established and reproducible standards required for all test results.

Spirometry: Spirometry will be performed as to ATS standards. A minimum of 3 efforts and maximum of 8 efforts will be performed for each test, with ATS acceptable and reproducible standards required for all test results. Pre and post bronchodilator spirometry will be performed at visit 2. Pre dose spirometry will be performed in the morning after documented inhaler medication washout. Post dose spirometry will be performed at visit 2, 3 and 4. 4 inhalations of albuterol delivered via ProAir Digihaler will be administered under direct supervision. 20-30 minutes after SABA administration, post dose spirometry will be performed (reference).

6-minute walk: 6-minute walk will be performed in duplicate. Baseline heart rate, oximetry and Borg dyspnea scale will be measured prior to testing. Walk testing will be performed in a continuous unimpeded path with recommended encouragement and continuous pulse and oximetry monitoring as per recommended guidance. A 15-minute rest will then occur, after which a second walk will be performed. The average of the 2 walk distances will be recorded as the measured walk distance (reference).

BODE score: BODE score will be derived from the measured BMI, post bronchodilator FEV_1, mMRC and 6-minute walk distance test results obtained at baseline (reference).

Airflow/FEV1 severity/GOLD stage: Airflow severity will be defined as per GOLD.

GOLD ABCD Group: GOLD ABCD group will be defined as per GOLD based on CAT score and exacerbation history obtained at baseline.

Investigational Product (IP):
FDA approved ProAir Digihaler IP will be provided by TEVA Pharmaceuticals. IP will be stored at room temperature (59-77 degrees F) in a temperature controlled, monitored, secure location at all times prior to dispensing. All dispensed IP will be recorded for each subject. All IP will be returned by the subjects as instructed per protocol, with IP return recorded. All used and unused IP will be returned to sponsor for destruction, unless otherwise instructed.

Medication Restrictions
SABA, pMDI - not allowed throughout the study
SAMA pMDI - not allowed throughout the study
SAMA/SABA pMDI – not allowed throughout the study
Nebulized SABA – allowed to be used on an infrequent basis (no more than once a day) delivering albuterol nebulizer solution
Nebulized SAMA - not allowed throughout the study
Nebulized SABA/SAMA - not allowed throughout the study

SAFETY ASSESSMENTS

Before participating in the study, subjects will be asked about history of intolerance to albuterol. The study team will also confirm that the participant is using albuterol on a regular basis (defined as at least one puff weekly for each of the last four weeks). If the safety of albuterol use cannot be assured, the subject will be excluded from the study. If any AE's or SAE's are detected, they will be followed by the investigator until symptoms have resolved.

Definition of Adverse Events (AEs) and Adverse Device Effects (ADEs)
An adverse event means any untoward medical occurrence associated with the use of an intervention in humans, whether or not considered intervention-related (21 CFR 312.32 (a)). Preexisting condition (i.e., a disorder present before the adverse event reporting period started) should not be reported as an adverse event unless the condition worsens or episodes

increase in frequency during the adverse event reporting period. This is particularly relevant for subjects with COPD who may have substantial symptoms at baseline.

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.

Definition of Serious Adverse Events (SAE)

An adverse event (AE) or suspected adverse reaction is considered "serious" if, in the view of the investigator, it results in any of the following outcomes: death, a life-threatening adverse event, inpatient hospitalization or prolongation of existing hospitalization, a persistent or significant incapacity or substantial disruption of the ability to conduct normal life functions, or a congenital anomaly/birth defect. Important medical events that may not result in death, be life-threatening, or require hospitalization may be considered serious when, based upon appropriate medical judgment, they may jeopardize the participant and may require medical or surgical intervention to prevent one of the outcomes listed in this definition.

A serious adverse device effect is an adverse device effect that has resulted in any of the consequences characteristic of a serious adverse event. Generally, adverse events reported from clinical trials associated with hospitalization or prolongation of hospitalization are considered serious. Any initial admission (even if less than 24 hours) to a healthcare facility meets these criteria. Admission also includes transfer within the hospital to an acute/intensive care unit (e.g., from the psychiatric wing to a medical floor, medical floor to a coronary care unit, neurological floor to a tuberculosis unit).

Because of the nature of the disease population being studied, and the fact that that part of the study includes studying subjects experiencing a COPD exacerbation with may require hospitalization, hospitalization will NOT immediately be considered an SAE for this study. Hospitalization will be reported as an SAE if, in the discretion of the investigator, it is temporally related to albuterol use.

Hospitalization does not include the following:

- Rehabilitation facilities;
- Hospice facilities;
- Respite care (e.g., caregiver relief);
- Skilled nursing facilities;
- Nursing homes;
- Same day surgeries (as outpatient/same day/ambulatory procedures).

Hospitalization or prolongation of hospitalization in the absence of a precipitating, clinical adverse event is not in itself a Serious Adverse Event. Examples include:

- Admission for treatment of a preexisting condition not associated with the development of a new adverse event or with a worsening of the preexisting condition (e.g., for work-up of persistent pretreatment lab abnormality);
- Social admission (e.g., subject has no place to sleep);
- Administrative admission (e.g., for yearly physical exam);
- Optional admission not associated with a precipitating clinical adverse event (e.g., for elective cosmetic surgery);
- Preplanned treatments or surgical procedures should be noted in the baseline documentation for the entire protocol and/or for the individual subject.

CLASSIFICATION OF AN ADVERSE EVENT

Severity of Event

The following guidelines will be used to describe severity.

- **Mild** – Events require minimal or no treatment and do not interfere with the participant's daily activities.
- **Moderate** – Events result in a low level of inconvenience or concern with the therapeutic measures. Moderate events may cause some interference with functioning.
- **Severe** – Events interrupt a participant's usual daily activity and may require systemic drug therapy or other treatment. Severe events are usually potentially life-threatening or incapacitating. Of note, the term "severe" does not necessarily equate to "serious".

RELATIONSHIP TO STUDY INTERVENTION

All adverse events (AEs) and Adverse Device Effects (ADEs) must have their relationship to study intervention assessed by the clinician who examines and evaluates the participant based on temporal relationship and his/her clinical judgment. The degree of certainty about causality for adverse events will be graded using the categories below.

The Relationship of an Adverse Event to the IMP

Term	Definition	Clarification
No reasonable possibility (not related)	This category applies to adverse events that, after careful consideration, are clearly due to extraneous causes (disease, environment, etc.) or to adverse events that, after careful medical consideration at the time they are evaluated, are judged to be unrelated to the IMP.	The relationship of an adverse event may be considered "no reasonable possibility" if it is clearly due to extraneous causes or if at least 2 of the following apply: • It does not follow a reasonable temporal sequence from the administration of the IMP. • It could readily have been produced by the patient's clinical state, environmental or toxic factors, or other modes of therapy administered to the patient. • It does not follow a known pattern of response to the IMP. • It does not reappear or worsen when the IMP is re-administered.
Reasonable possibility (related)	This category applies to adverse events for which, after careful medical consideration at the time they are evaluated, a connection with the administration of IMP cannot be ruled out with certainty.	The relationship of an adverse event may be considered "reasonable possibility" if at least 2 of the following apply: • It follows a reasonable temporal sequence from administration of the IMP. • It cannot be reasonably explained by the known characteristics of the patient's clinical state, environmental or toxic factors, or other modes of therapy administered to the patient. • It disappears or decreases on cessation or reduction in dose. There are important exceptions when an adverse event does not disappear after discontinuation of the IMP, yet an IMP relationship clearly exists. • It follows a known pattern of response to the IMP.

EXPECTEDNESS

The principal investigator or co-investigators will be responsible for determining whether an adverse event (AE) is expected or unexpected. An AE will be considered unexpected if the nature, severity, or frequency of the event is not consistent with the risk information previously described for the study intervention.

TIME PERIOD AND FREQUENCY FOR EVENT ASSESSMENT AND FOLLOW-UP

The occurrence of an adverse event (AE) or serious adverse event (SAE) may come to the attention of study personnel during study visits and interviews of a study participant presenting for medical care, or upon review by a study monitor.

All ADEs, SAEs, and AEs including local and systemic reactions not meeting the criteria for SAEs will be captured on the appropriate CRF. Information to be collected includes event description, time of onset, clinician's assessment of severity, relationship to study product (assessed only by those with the training and authority to make a diagnosis), and time of resolution/stabilization of the event. All AEs occurring while on study must be documented appropriately regardless of relationship. All AEs will be followed to adequate resolution.

Any medical condition that is present at the time that the participant is screened will be considered as baseline and not reported as an AE. However, if the study participant's condition deteriorates at any time during the study, it will be recorded as an AE.

Changes in the severity of an AE will be documented to allow an assessment of the duration of the event at each level of severity to be performed. AEs characterized as intermittent require documentation of onset and duration of each episode.

The study coordinator will record all reportable events with start dates occurring any time after informed consent is obtained until 24 hours after the last day of study participation. Events will be followed for outcome information until resolution or stabilization. Given the duration of the study, these events will be collected during the monthly phone calls by the study coordinator, unless the information is voluntarily provided by the subject in between study visits or phone calls.

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 investigator will be required to report and notify the Teva Pharmaceuticals (Teva) 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. The event will also be reported to the FDA, Institutional Review Boards (IRBs), and any other collaborators/investigators according to national, and local safety reporting requirements.

(a) All related Serious Adverse Events

(b) All Serious Adverse Device Effects

(c) Any exposure of a pregnant Study participant to the Study Drug within thirty (30) days of exposure

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

Each adverse event is to be classified by the investigator as serious or non-serious. This classification determines the reporting procedures to be followed. If a serious adverse event occurs, expedited reporting will follow IRB regulations. If an adverse event is both serious and unexpected, reporting will follow IRB reporting regulations as appropriate. SAEs are reportable from the time that the subject provides informed consent, which is obtained prior to the subject's participation in the trial (i.e., prior to undergoing any trial-related procedure through and including 24 hours after the final call). Any serious adverse event occurring at any other time during the study must be promptly reported if a causal relationship to study drug is suspected.

If a serious adverse event occurs, the Institutional IRB will be notified within five business days of awareness of the event by the investigator. The study coordinator may initiate the IRB notification, but it must be filed by the study investigator or co-investigators. If the serious adverse event is fatal or life threatening, notification to the Institutional IRB must be made within 24 hours, irrespective of the extent of available adverse event information. This timeframe also applies to additional new information (follow-up) on previously forwarded serious adverse event reports.

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

All adverse events (serious and non-serious) will be reported on the adverse event page(s) of the CRF. Adverse events should be reported using concise medical terminology on the CRFs. Non-serious AE's will be reported annually to the IRB as appropriate.

STATISTICAL ANALYSIS

Primary Outcome Measure:

1) Change in Peak Inspiratory Flow (PIF) from Baseline as measured via the ProAir Digihaler device

Secondary Outcome Measures:

1. Change in SABA use (Inhalations) from Baseline
2. Change in Inhalation Volume (IV) from Baseline
3. Change in CAT
4. Change in FEV_1

Other Outcome Measures:

1. Change in Anthonisen Exacerbation Criteria
2. Change in BCSS
3. Change in Inhalation Volume

All data is exploratory, with no calculated power or expected predictive probabilities. Statistical thresholds, comparisons, correlations and regressions, sensitivity/specificity/ROC analysis will be performed using Wizard 1.9.45 Statistics. Additional statistical analysis may be performed as per TEVA biostatistics.

PLANNED ANALYSIS

1. Average of PIF value and number of PIF events at 10%, 20% , 30%, 40% below Baseline PIF for 2 or more days per patient
2. Average summary statistics PIF values and frequency of PIF events across all patients
3. Number of inhalations per day that are 4 or more Inhalations above Baseline Inhalations for 2 or more days
4. Frequency of IV events that are 20% below Baseline (see Derived measurements) for 2 or more days
4. Frequency of combined events of PIF and IV 20% below Baseline and 4 or more Inhalations per day above Baseline for 2 or more days combined
5. Frequency of CAT events (defined as increase in CAT score by 2 above Baseline CAT score)
6. Correlation and regression analysis of PIF, Inhalations and IV events with CAT events
7. Correlation and regression analysis of PIF and/or Inhalations events at varying thresholds
    a. Daily PIF 10, 20, 30 or 40% below Baseline PIF
    b. Daily Inhalations at 2, 4 or 6 Inhalations above Baseline Inhalations
    c. Daily PIF and/or Inhalations duration of 2, 3 or 4 or more days outside of Baseline
8. Frequency and duration of AEC events of 2 or more major symptoms (Type I and Type II)
9. Frequency and duration of BCSS events (increase in BCSS by 2 above Baseline BCSS)
10. Correlation and regression analysis of PIF, Inhalations and IV events with AEC events
11. Correlation and regression analysis of PIF, Inhalations and IV events with BCSS event
12. Correlation of Digihaler changes in PIF above baseline and changes in CAT
13. Correlation off changes in SABA use above baseline with changes in CAT
14. Correlation of Digihaler changes in Inhalation Volume above baseline with changes in CAT
15. Descriptive sub-group analysis of PIF, Inhalations and IV thresholds by FEV1 severity, GOLD groups and BODE at Baseline.

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