STUDY PROTOCOL

A Single Center, Open Label, Prospective, Observational Study Measuring Proportion of Patients with Suboptimal Peak Inspiratory Flow Rate (sPIFR) over 24 Weeks in an Ambulatory Setting among Moderate to Very Severe COPD Patients

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Complete Title: A single center, open label, prospective, observational study measuring proportion of patients with suboptimal Peak Inspiratory Flow Rate (sPIFR) over 24 weeks in an ambulatory setting among moderate to very severe COPD patients

Short Title: PIFR in COPD

Drug or Device Name(s): N/A

Protocol Date: February 18, 2021

Revision #1 Date: August 16, 2019

Summary of Revisions (August 16, 2019)

- Add Wixela® Inhub® as low-medium resistance inhaler
- remove two year window on prior confirmatory spirometry testing for inclusion
- Request to add Dr. Robert Burkes, MD as co-investigator

Revision #2 Date: May 21, 2020

Summary of Revisions (May 21, 2020)

- Remove performance of pre and post-bronchodilator spirometry testing
- change spirometry criteria to three year window with abstraction of previously completed spirometry data for enrollment data
- move all in-person procedures (positional PIFR, pre and post-bronchodilator PIFR measurements to V1 Enrollment
- Modify V6 to phone visit

Revision #3 Date: February 18, 2021

Summary of Revisions (February 18, 2021)

- Remove Dr. Robert Burkes, MD (co-investigator) as he has left UNC
- change spirometry criteria to any history of spirometry confirming COPD with abstraction of any previously completed spirometry data for enrollment data
- change exacerbation criteria to one or more exacerbations of COPD requiring systemic corticosteroids within last 3 years (changing from 2 years)

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A single center, open label, prospective, observational study measuring proportion of patients with suboptimal Peak Inspiratory Flow Rate (sPIFR) over 24 weeks in an ambulatory setting among moderate to very severe COPD patients

(Short Title: PIFR in COPD)

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Protocol Version: REVISION 3

Version Date: February 18, 2021

I confirm that I have read this protocol and understand it.

Principal Investigator Name: M. Bradley Drummond, MD, MHS

Principal Investigator Signature: _____

Date: _____

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Abbreviations and Definitions of Terms

Abbreviation	Definition
AE	Adverse Event
CAT	COPD Assessment Test
COPD	Chronic obstructive pulmonary disease
DPI	Dry Powdered Inhaler
FEV1	Forced expiratory volume in 1 second
FVC	Forced vital capacity
MDI	Metered dose Inhaler
mMRC	modified Medical Research Council
mBorg	modified Borg dyspnea scale
PIFR	Peak inspiratory flow rate
PRO	Patient reported outcome
RV	Residual Volume
sPIFR	Suboptimal peak inspiratory flow rate

Protocol Synopsis

Study Title	Peak Inspiratory Flow Rate in COPD Patients
Study Rationale	Recent studies have reported that some COPD patients may have a suboptimal ability to generate a sufficient inspiratory effort to achieve adequate lung delivery of inhaled medications through dry powder inhalers. Sparse data is available about the inspiratory capacity of these patients in the home setting, whether clinically stable or when experiencing worsened respiratory symptoms outside the acute care setting. Thus, we are undertaking this study to better understand the proportion of patients with suboptimal peak inspiratory flow rate (sPIFR) measurements amongst COPD patients receiving dry powder inhaler(s) (DPI) in the ambulatory setting. Further, we seek to characterize PIFR over time, the variability of PIFR measurements, and the associations with potential predictors (demographics, clinical, PRO, body position, and device) as well as exacerbations frequency and change in PIFR around period of exacerbation.
Study Endpoint(s)	<u>Primary Endpoint</u> For each patient, the occurrence of suboptimal Peak Inspiratory Flow Rate (sPIFR) over 24 weeks. sPIFR will be defined as any two consecutive measurements on different days below the optimal threshold for any prescribed DPI (e.g.,<30 L/min for Handihaler® (High resistance DPI), <60 L/min for Ellipta® (Medium resistance DPI)) <u>Exploratory Endpoints</u> • PIFR Endpoints ▪ Time to first occurrence of sPIFR (in days) ▪ Number and proportion of sPIFR ▪ Rate of sPIFR, defined as the number of sPIFR / number of days in the study, multiplied by 30 as sPIFR/month. • Exacerbation Endpoints Occurrence (yes/no), number, severity (mild, moderate, severe) and rate of COPD exacerbations over 24 weeks. Mild, moderate and severe exacerbations will be defined as: ▪ Mild – doubling use of inhaled rescue medication <u>≥</u> 48 hours and not meeting definition of moderate or severe ▪ Moderate – increased rescue medication and either oral corticosteroid or antibiotics, not requiring hospitalization; ▪ Severe – hospitalization for exacerbation

Test Article(s) *(If Applicable)*	Measurement of PIFR using the InCheck Dial® device and quantification of respiratory symptoms and COPD exacerbations using standardized questionnaires in the patient's home setting and during research visits in the clinic setting.
Funding Source	Boehringer Ingelheim Pharmaceuticals Inc.
Study Design	Prospective, monocenter, observational study in 120 COPD patients over a 24 week period with six study visits.
Subject Population key criteria for Inclusion and Exclusion:	Inclusion Criteria: • Age > 50 years-old • Spirometry-confirmed diagnosis of COPD (FEV1/FVC <0.70) • GOLD II-IV based on existing spirometry results • CAT score > 10 • For high resistance DPI, baseline PIFR < 90 L/min (InCheck DIAL®) and >=30 L/min; for medium resistance DPI, PIFR ≤ 90 L/min (InCheck DIAL®) and >=60 L/min. Handihaler is a high resistance DPI. Examples of medium resistance DPI: Anoro, Incruse, Breo Ellipta®, Advair® Diskus® DP or Wixela® Inhub® • History of smoking tobacco products > 10 pack years • Prescribed at least one daily maintenance DPI with no change in prescription within the four weeks prior to the Enrollment Visit • One or more exacerbations of COPD requiring systemic corticosteroids within last 3 years • Patients will be enrolled with regards to the below pre-specified characteristics based on gender and the prescribed maintenance inhaler(s) as follows (note that patients are commonly prescribed multiple inhalers): ▪ Male:Female ratio 1:1 (+ 10%) ▪ Target recruitment stratified to two treatment arms: ▪ N=60 patients receiving medium resistance DPI (Anoro, Incruse, Breo Ellipta®, Advair® Diskus® or Wixela® Inhub® DPI) with planned recruitment to include 50% of participants on Diskus®/ Inhub® and 50% on Ellipta® ▪ N= 60 patients receiving high resistance DPI (Spiriva Handihaler® DPI)

	Study participants may also receive another MDI, Respimat® inhaler, or DPI (e.g. Breo Ellipta® + Spiriva Respimat®, Symbicort MDI® + Spiriva Handihaler®, Advair Diskus® + Spiriva Handihaler®, Wixela® Inhub® + Spiriva Handihaler®) Subjects will be placed into one of the two cohorts based on the DPI, if on more than one DPI, they will be placed into the cohort for the DPI with the highest resistance (Handihaler>Ellipta=Diskus=Inhub). These strata are for recruitment only, and PIFR measurement for both DPIs will be recorded and used in analyses. Exclusion Criteria: • Inability to demonstrate proper technique for the InCheck DIAL® device • Inability to achieve minimum PIFR for prescribed DPI(s) at screening/enrollment visit (< 30 L/min for e.g., Handihaler® (High resistance DPI), < 60 L/min for Ellipta® (Medium resistance DPI)) • Neuromuscular disease associated with weakness • Any condition that, in the opinion of the site investigator, would compromise the subject's ability to participate in the study. • Pneumothorax within the past 4 weeks
Number Of Subjects	N=120
Study Duration	Each participant's duration of involvement will last 24 weeks.
Study Phases **Screening** **Study Enrollment** **Follow-Up**	 Visit 1- Screening Visit Visit 2- Enrollment Visit Home monitoring of PIFR and PRO over 24 weeks Visits 3, 4, 5, 6: Telephone Visits
Efficacy Evaluations	Changes in PIFR and dyspnea (modified Borg) that occur in the COPD population in the home setting during periods of stable respiratory symptoms and periods of worsening will be measured and recorded by participating subjects. PIFR measurements, PRO (mMRC, modified Borg, CAT) will also be undertaken in the research clinic setting. PRO will also be completed with each telephone-based study visit. This study will not be powered to definitely test for efficacy of different inhalers.

Safety Evaluations	Minimal risk

Statistical And Analytical Plan	Primary analysis will be descriptive. The primary endpoint will be described as the proportion of patients with suboptimal PIFR and reported with 95% confidence intervals. Suboptimal PIFR will be defined as any two consecutive measurements on different days below the optimal threshold for any prescribed DPI (<30 L/min for High resistance, <60 L/min for Medium resistance). Descriptive analysis of PIFR measurements, including mean (SD), median (IQR), range over time per patient per device, and in different body positions, will be conducted. The time of first occurrence of sPIFR will be reported in days and will be plotted with a Kaplan-Meier curve. We will explore, for each device, with logistic regression (binary) or negative binomial (count) the clinical and demographic factors associated with sPIFR measurements. Correlation of PIFR with CAT score, mBORG and mMRC score will be conducted. The associations between exacerbations and PIFR will be explored in different ways, for all exacerbation, stratified by severity of exacerbations, and stratified by device. See section 6.1 to 6.3 for detailed statistical plan.
Data and Safety Monitoring Plan	Data will be managed on REDCap, developed by PI of study. The PI and study staff will review data collection forms on an ongoing basis for data completeness and accuracy as well as protocol compliance. The PI will be responsible for data quality management and ongoing assessment of safety.

1 BACKGROUND AND RATIONALE

1.1 Introduction

The optimal management of chronic obstructive pulmonary disease (COPD) is important at population and health system levels due to substantial costs, morbidity and mortality. At the individual patient level, experiencing shortness of breath, often on a daily basis, with periods of worsening symptoms, can have a big impact on quality of life, productivity, and outcomes. Inhaled medications are the most effective therapies for symptom relief and available for COPD patients–particularly when given in combination. (GOLD 2017) Inhaled therapies are available as metered dose inhalers (MDI), soft-mist inhalers (SMI), dry powder inhalers (DPI), and by nebulization. Although DPI's are breath-actuated and tend to be easier for patients to use than the MDI or SMI, there is emerging evidence that delivery from DPI and drug stability of the powder is suboptimal in some patients and settings. It has recently been shown that COPD patients can exhibit suboptimal inspiratory rates during exacerbations in the hospital (Loh, Sharma) as well as in the outpatient setting (Sulaiman 2017a, Jansenns); it is unclear what impact this this may have on the efficacy and safety of DPIs. Several population-based studies from the United Kingdom report that a DPI (Diskus® inhaler), with relatively low respirable mass (portion delivered into target airways) and larger particle size is associated with greater COPD exacerbation frequency and oropharyngeal side-effects compared to inhalers with a higher respirable mass in both COPD and asthma patients. (Price, Jones, Dekhuijzen) Although published evidence regarding suboptimal delivery from DPIs in the COPD population is emerging, substantial knowledge gaps exist, including peak inspiratory flow in ambulatory COPD patients when clinically stable and during periods of worsened respiratory symptoms. This specific knowledge gap is the principal basis of our investigation.

1.2 Name and Description of Procedures

This is an observational study but certain study procedures and PROs will be measured in the study. The proposed procedure is measurement of peak inspiratory flow rate (PIFR), using a device called In-Check DIAL® (Alliance Tech, Granbury, TX), and recording of respiratory symptoms in COPD patients in the home setting. This device has been used in the clinical and research settings for more than a decade.

1.3 Relevant Literature and Data

Factors that can influence optimal delivery of inhaled drug therapy in the obstructive lung disease population include the inhalational device as well as the drug and formulation and patient characteristics such as cognition, disease severity, and clinical status of the patient. Important device characteristics include overall ease of use, aerosol particle size, fine particle fraction or dose, and in the case of DPIs, the inspiratory resistance inherent to the inhaler. Of the three types of multi-dose inhalers, the MDI is the most difficult device to use correctly, particularly in the elderly COPD patient, whereas DPI breath-activated devices tend to be easier to use. The fine particle fraction, the portion of the emitted dose in the respirable range of 1-5 microns that is most likely to reach target airways, varies widely among different multi-dose inhalers: 12-35% for DPIs, 10-50% for MDI, and ~ 30% for SMI. It has been shown that a higher fine particle fraction can result in greater lung delivery into the peripheral airways (Pitcairn) - COPD is a disease that also affects the small airways. For the SMI and MDI, a slow, deep inspiration delivers the most respirable particles, whereas for the DPI, a rapid deep breath is required to de-agglomerate the powder. As noted previously, some COPD patients are not able to generate an adequate inspiratory effort with the DPI in order to achieve adequate lung drug delivery.

Depending on the DPI, the minimum peak inspiratory flow rate (PIFR) ranges from 30 L/min for the Handihaler® to 60 L/min for the Diskus® and Ellipta® DPI's. (Ghosh 2017, Mahler 2017). The Handihaler® is a high-resistance DPI, whereas the Ellipta® and Diskus® are classified as medium-resistance inhalers. In vitro studies indicate that the fine particle dose from Diskus®, and Ellipta® DPIs can be reduced when inspiratory flow rate decreases below 60 L/min (Buttini, Feddah, Yokohama, Grant, Prime), whereas other studies showed little effect. (Hamilton) Recent studies in humans are finding that inhaled drug delivery with the Diskus® is suboptimal when the PIFR decreases below 60 L/min. In a study of healthy volunteers using the Diskus® inhaler, a decrease in the PIFR from 60 to 30 L/min resulted in 30% decrease in blood levels of albuterol and fluticasone (Sulaiman 2017b), indicative of decreased lung delivery. (Lipworth) A recent study evaluated errors made by COPD patients using the Diskus® over a one month period in the ambulatory setting post-hospitalization. For this study, an audio monitoring device (INCA) was attached to the inhaler to measure the inspiratory flow rate and monitor adherence. Subjects were educated on the proper use of the inhaler prior to discharge from the hospital. The most frequent error made by patients was an inadequate inspiratory effort in nearly one-half of the COPD patients. (Sulaiman 2017b) It is possible that PIFR may have been lower as a consequence of the recent exacerbation. In a study conducted in an outpatient research setting, using an instrumented Ellipta® inhaler, it was found that severe to very severe COPD patients had shorter inspiratory times and tended to have impaired inspiratory flow (< 60 L/min) through the device. (Prime) It appears that lung

delivery with the Diskus® and Ellipta® may be suboptimal between 30 L/min and 60 L/min. The aforementioned data is the basis for the use of target PIFR values for Handihaler®, Diskus®, and Ellipta® devices (30 L/min, 60L/min, and 60 L/min, respectively) for the current study. We have also chosen to only enroll patients with a PIFR $\leq$ 90 L/min at a medium resistance PIFR setting (Ellipta®) in order to select a cohort that has a reasonable probability that their PIFR may approach the minimally acceptable value for their prescribed DPI(s) with worsened symptoms.

Patient-related impediments to achieving this minimum inspiratory flow in the COPD population include age, gender, and stature (Seheult, Mahler 2013). Mahler reported that persons most likely to have an impaired PIFR are the elderly and females, (Mahler 2013), thus the rationale for having an equivalent number of males and females participate in the present study. Another factor that could affect inspiratory flow in the COPD patient is the physical position of the patient when using their DPI (standing, sitting, supine). It has been shown that peak expiratory flow rate (Wade) and other pulmonary function test measures (Wallace) including forced residual capacity are lower in a supine position than in a standing position. Therefore it is possible that a hospitalized COPD patient in a supine position, particularly with worsened respiratory status, could have decreased lung deposition from a DPI because of impaired inspiratory ability. Another scenario that a COPD patient could have impaired inspiratory capability is a morbidly obese subject using their DPI in a sitting position, where the diaphragm is displaced upwards and thus the lungs are less capable to generate a strong inspiratory effort. To our knowledge, the effect of physical position of the COPD patient on PIFR has not been investigated.

Disease related factors that could affect a patient's inspiratory ability include diaphragmatic dysfunction, air trapping, narrowing of the airways, and worsening respiratory symptoms such as during an exacerbation. (Broeder, Jansenns, Malmberg, Taube, Loh, Sharma). In COPD patients with air trapping, it was shown that in addition to a reduced forced residual capacity and decreased inspiratory capacity, the inspiratory flow was also reduced. (Taube) Decreased inspiratory flow has been shown when COPD patients are clinically stable (Ghosh, Janssen, Mahler, Seheult) and during exacerbations requiring hospitalization. (Broeder, Loh, Sharma) Studies by Loh and Sharma found that impaired PIFR, below minimums for DPIs, occurred in a third or more of COPD patients with acute exacerbations requiring hospitalization. The study by Loh indicated patients with impaired PIFR were at a greater risk of all cause 90-day re-hospitalization, whereas this was not found in the study by Sharma. In the study by Loh, the PIFR was performed in patients while in a sitting position. (personal communication) The decrease in inspiratory flow and capacity apparently persists for some time after exacerbations. Broeder reported that PIFR, using the InCheck DIAL®, increased between 17% and 22% between hospital admission and 5 weeks later when patients were clinically stable in the outpatient setting. There are no published studies that

have measured longitudinal changes in PIFR in ambulatory COPD patients when clinically stable and during periods of worsened respiratory symptoms and recovery.

The In-Check DIAL® has been used for both clinical and research purposes for over 15 years to mimic the resistance to inspiration through DPIs. The In-Check G16 DIAL® (Alliance Tech Medical, Granbury TX) is a simple hand-held device that measures PIFR via a brief inspiratory maneuver. Measurement consists of a simple, 1-2 second inhalation requiring less user effort than an incentive spirometer. The best of three efforts are recorded. The InCheck DIAL® is designed to simulate the internal resistance of different inhalers and measure the PIFR against a specific level of resistance, either to assess a patient's ability to achieve a minimum effort recommended for DPI or to train patients on the proper inspiratory effort needed for a specific inhaler. The InCheck DIAL® measures PIFR between 15 and 120 L/min with a +/- 10% accuracy and has a repeatability of 5 L/min. Calibration of the device was shown to meet American Thoracic Society (ATS) standards through testing with an ATS waveform generator. The device includes a one-way disposable mouthpiece, measurement diaphragm, and a directly visualized PIFR scale. Importantly, the device also includes an adaptor with adjustable resistances to mimic nine resistance groups encompassing the popular MDIs and DPIs currently commercially available. These have been used repeatedly for both research and clinical purposes since 1991 (Broeder). Using these measurements against a set resistance, one can assess the frequency and degree of suboptimal PIFR in COPD patients with moderate to very severe obstruction in the home setting.

To inform this application, Dr Drummond and Ghosh have previously obtained IRB approval for a study to measure PIFR using the In-Check DIAL® in a clinic-based, stable COPD patient population prescribed maintenance inhalers and free of recent exacerbation, as well as a group of healthy controls (UNC IRB 16-3343; PI Ghosh; data presented by Ghosh et al ATS 2017). Over a four month period, 27 COPD patients and 19 healthy controls were recruited (Ghosh 2018). Among COPD patients, 20/27 (74%) were able to generate PIFR >120 L/min when no internal resistance was applied. However, PIFR (mean±SD) was 61±13 L/min with Diskus® resistance and 36±10 L/min with Handihaler® resistance. In the COPD patients, 11 used a medium resistance DPI alone, 25 a high resistance DPI alone, and 14 were receiving both a medium and high-resistance DPI.

Among the healthy controls, 19/19 (100%) were able to generate PIFR >120 L/min when no internal resistance was applied. PIFR was 97±13 L/min with Diskus® resistance and 55±7 L/min with Handihaler® resistance. Overall, 15 (55%) of COPD patients were not able to generate optimal PIFR (defined as >45L/min for this study) on at least one prescribed DPI. Compared to COPD patients able to generate optimal PIFR, discordant COPD participants had a greater prevalence of uncontrolled COPD (defined as COPD Assessment Test≥10): 93% versus 83%. Among nine

participants with repeated measures over two weeks, there were no statistical differences between intersession measurements for any inhaler resistance setting. These preliminary data demonstrate that suboptimal PIFR is common in stable COPD and may correlate with symptom burden.

Preliminary data has also demonstrated stability in PIFR over 2-4 weeks, suggesting this is inadequate duration to capture full spectrum of variability. Specifically, preliminary data from 15 COPD participants who underwent repeated measures at two to four weeks showed that participants using low-medium resistance inhalers did not have a difference in PIFR measurements at baseline versus follow-up (65 L/min on visit 1 and 64 L/min on visit 2; p=0.69). Of the 14 participants on a high resistance inhaler, there was no difference in baseline and repeated PIFR measurement (38 L/min on visit 1 and 38 L/min on visit 2; p=0.46). A study duration of 24 weeks has been selected to ensure adequate duration to capture normal variability of PIFR as well as need for adequate duration to capture COPD exacerbation events (an important exploratory outcome).

2 STUDY OBJECTIVES

2.1 Objectives:

- The primary objective of the study is to determine the proportion of patients with suboptimal peak inspiratory flow rate (sPIFR) measurements amongst COPD patients receiving dry powder inhaler(s) (DPI) in the ambulatory setting.
- The exploratory objectives are to characterize PIFR over time, the variability of PIFR measurements, and the associations with potential predictors (demographics, clinical, PRO, body position, device)
- Additionally, we will explore the exacerbations frequency and change in PIFR around period of exacerbation.

3 INVESTIGATIONAL PLAN

3.1 Study Design

This prospective, monocenter, observational study will be conducted over 24 weeks. The **Study Procedures and Assessments** (Appendix 1) are shown in the table and are also described further

3.2 Allocation to Treatment Groups and Blinding

All enrolled subjects will undergo the same procedures. There will be no blinding of subjects or study personnel to any aspect of the study.

3.3 Study Duration, Enrollment and Number of Subjects

Study duration and timeline: The duration of study is 24 weeks.

Enrollment: Participants will be recruited from UNC Clinics.

Number of subjects: One hundred twenty patients will be enrolled into this study.

Enrollment to ensure balance of seasonal effects across all arms: Enrollment such that the 24 week study period for each subject includes >2 months during the 'exacerbation season' of October – March (this translates into April and May being the only months to not enroll patients). Screening visits can be undertaken during these two months (April and May).

3.4 Study Population

Our study population will be outpatients with moderate, severe, or very severe COPD. Participants will be recruited from multiple sources as described above.

Inclusion Criteria:

- Age > 50 years-old
- Spirometry-confirmed diagnosis of COPD (FEV1/FVC <0.70)
- GOLD II-IV based on existing spirometry results
- CAT score > 10
- For high resistance DPI, baseline PIFR < 90 L/min (InCheck DIAL®) and >=30 L/min; for medium resistance DPI, PIFR ≤ 90 L/min (InCheck DIAL®) and >=60 L/min. Handihaler is a high resistance DPI. Examples of medium resistance DPI: Anoro, Incruse, Breo Ellipta® ,Advair® Diskus®, or Wixela® Inhub® DPI
- History of smoking tobacco products > 10 pack years
- Prescribed at least one daily maintenance DPI with no change in prescription within the four weeks prior to the Enrollment Visit
- One or more exacerbations of COPD requiring systemic corticosteroids within last 3 years
- Patients will be enrolled with regards to the below pre-specified characteristics based on gender and the prescribed maintenance inhaler(s) as follows (note that patients are commonly prescribed multiple inhalers):
  - Male : Female ratio 1:1 (+ 10%)
  - Target recruitment stratified to two treatment arms:

- N=60 patients receiving medium resistance DPI (Anoro, Incruse, Breo Ellipta®, Advair® Diskus®, or Wixela® Inhub® DPI) with planned recruitment to include 50% of participants on Diskus® and 50% on Ellipta®
- N= 60 patients receiving high resistance DPI (Spiriva Handihaler® DPI)

For all study participants, participants may also receive another MDI, Respimat® inhaler, or DPI (e.g. Breo Ellipta® + Spiriva Respimat®, Symbicort MDI® + Spiriva Handihaler®, Advair Diskus® + Spiriva Handihaler®, Wixela® Inhub® + Spiriva Handihaler®) Subjects will be placed into one of the two cohorts based on the DPI, if on more than one DPI, they will be placed into the cohort for the DPI with the highest resistance (Handihaler>Ellipta=Diskus=Inhub). These strata are for recruitment only, and PIFR measurement for both DPIs will be recorded and used in analyses.

Exclusion Criteria:

- Inability to demonstrate proper technique for the InCheck DIAL® device
- Inability to achieve minimum PIFR for prescribed DPI(s) at screening/enrollment visit (< 30 L/min for e.g., Handihaler® (High resistance DPI), < 60 L/min for Ellipta® (Medium resistance DPI))
- Neuromuscular disease associated with weakness
- Any condition that, in the opinion of the site investigator, would compromise the subject's ability to participate in the study.
- Pneumothorax within the past 4 weeks

4 STUDY PROCEDURES

4.1 Home Monitoring

Subjects will record their PIFR using the InCheck DIAL®and modified Borg dyspnea score three times weekly (MWF) when clinically stable and daily while respiratory symptoms worsen per patient self-assessment. At each session, the participant will repeat efforts three times, with the highest of the three repeated efforts being recorded by the participant. They will be asked to perform the PIFR for the DPI(s) they are receiving at home (Ellipta®, Inhub®, Diskus®or Handihaler®) using the InCheck DIAL®. If on more than one DPI, patient will record PIFR for each device. PIFR will be recorded with best approximation to nearest 1 L/min.

4.2 Study Visits

There will be six study visits/encounters over a 22-26 week period as shown in the Study Procedures and Assessments Table. Two study visits will occur at the UNC Clinics (Visits 1 and 2)

and four visits will only involve a telephone interview of subjects by study personnel (Visits 3, 4, 5, and 6).

Visit 1- Screening Visit

At Visit 1, after obtaining written informed consent, a clinical history will be obtained from the patient and if the subject meets all inclusion and exclusion criteria, a CAT score will be determined. The patient will be undergo PIFR assessment based on prescribed DPI. PIFR will be recorded with best approximation to nearest 1 L/min. Subjects will be excluded if PIFR > 90 L/min based on Ellipta® and Diskus® setting or inability to achieve minimum PIFR for prescribed DPI setting (< 30 L/min for Handihaler®, < 60 L/min for Ellipta® , Diskus® , or Inhub®). The PIFR will be performed in triplicate by the patient at the recommended device setting (based on patient's DPI specific internal resistance) in the physical position (e.g. sitting) that the patient normally uses to self-administer their inhaler(s). Further, they will be instructed to perform the PIFR consistent based on the manufacturer instructions for proper DPI inhalation technique (e.g. Ellipta®, Diskus® DPI, , Inhub®) "Breathe out gently and breathe in steadily and deep"). For the Handihaler®, subjects will be instructed as follows – "Breathe out completely in one breath. Empty your lungs of air. Breathe in deeply until your lungs are full." If the patient meets the inclusion and exclusion criteria including a PIFR < 90 L/min, they can proceed to Visit 2 (Enrollment) either during the same encounter or scheduled within 30 days. If there is greater than 30 days between Visit 1 and 2, another informed consent will be reviewed and signed.

For inclusion, historical spirometry is required to be documented to ensure patients meet the GOLD definition of COPD using airflow obstruction. Most recent spirometry data will be used for characterization of the enrolled cohort. No spirometry testing will be performed as part of this study.

Visit 2- Enrollment Visit

- A physical examination including measurement of waist circumference (measured in inches horizontally through the narrowest part of the torso, between the lowest rib and the iliac crest)
- Medical history (includes exacerbations history)
- COPD medication use (maintenance and reliever)
- Patient-reported outcomes (PROs)
    - CAT score (COPD Assessment test)
    - mMRC score (modified Medical Research Council)
    - mBorg score (modified Borg dyspnea score)

- PIFR measurement in three different physical positions – sitting, standing, and lying tilted at 45^{o} with head forward. (repeated using PIFR setting for each DPI patient is receiving)
- Pre- and post-bronchodilator PIFR measurement in sitting position
- Subject instructed on proper use of PIFR device and recording of PIFR measurement and modified Borg dyspnea score using the provided Study Notebook
- Subject instructed to mail PIFR and modified Borg dyspnea score on a monthly basis to the research team using supplied self-addressed, stamped envelopes

Visits 3, 4, 5, and 6 - Telephone Visits

At Visits 3, 4, 5, and 6 (at 4, 8, 12 , and 24 weeks after Visit 2 -permissible $\pm$2 week window for each visit), study personnel will contact the participant by telephone to obtain PIFR and symptom questionnaires recordings during the preceding 2 weeks. A time period less than 2 weeks is acceptable if the subject had mailed in their monthly log recently. PIFR measurements and respiratory symptom questionnaires (modified Borg dyspnea score only) will have been recorded by study participants using a Study Notebook. PIFR will be recorded for each DPI the patient is receiving. A CAT score, mBorg, and mMRC will also be determined by study personnel as part of each visit. Ascertainment of exacerbations, medication adherence, and change in inhaler regimens will be completed. In part, the telephone visit will be undertaken to increase subject's compliance to study procedures.

4.3 Unscheduled visits

No unscheduled visits will be incorporated into this protocol.

4.4 Concomitant Medication documentation

All COPD medications within 30 days of study enrollment and during the 24 week study period will be recorded.

4.5 Rescue medication administration (if applicable)

Inhaled albuterol 2 puffs by metered dose inhaler will be administered as part of pre- and post-PIFR measurement at Visit 2

4.6 Subject Completion/ Withdrawal procedures

If a patient decides to withdraw for any reason our contact information will be provided and they can email any member of the research team. If participants have a change in their prescribed DPI during study, study procedures will continue using previously prescribed DPIs and noting prescription changes.

4.7 Screen failure procedures

All consented participants will receive a study ID number. Those who fail initial screening will be excluded and no information will be collected. If a participant failed initial screening due to temporary exclusion criteria (e.g., failed due to recent exacerbation, recent change in meds), the participant will be offered a re-screening visit for a future date outside of the exclusion window. Last name and partial MRN for participant failing screening will be retained during study recruitment on a secured document to prevent re-screening.

5 STUDY EVALUATIONS AND MEASUREMENTS

5.1 Data collection

5.1.1 Data abstracted from electronic medical charts

- Historical spirometry
- Evidence of any COPD exacerbation requiring systemic corticosteroids within the last three years
- Concurrent diseases
- Prescribed COPD medications
- Demographics: age, height, weight, gender

5.1.2. Questionnaires

The questionnaires administered will be the modified Borg dyspnea scale, modified Medical research Council, and the COPD Assessment Test. Additional questionnaires will capture exacerbations, medication adherence, and inhaler regimens. The questionnaires will be self-administered by study subjects or conducted by study personnel with the subjects when appropriate. For the mMRC (APPENDIX 2), mBorg (APPENDIX 3), and CAT (APPENDIX 4), the time period for subjects to self-assess symptoms is not specified. The modified Borg dyspnea scale will be used for home monitoring of respiratory status, whereas modified Medical Research Council

score, modified Borg scale, and CAT will be used for clinic visits (2, 6) as well the 4 telephone visits (3, 4, 5). In addition, CAT will be determined at the enrollment visit (Visit 1).

When questionnaires are administered by study personnel, they will be completed using a polite, professional, and non-judgmental tone. Pacing of the interview will be adjusted to each participant. Interviewers will be familiar with the forms and questionnaires they are administering. Familiarity allows the coordinator to maintain eye contact with the participant, which helps build rapport. The interviewer must be careful not to inadvertently change the wording of questions or instructions because he or she has partially memorized the interview. If a participant appears to not understand the question or provides an incomplete answer, the interviewer may employ several techniques to improve participant response. In the case of misunderstood questions, the interviewer may re-read the question with a different emphasis, stressing the part of the question the subject appears to have misunderstood. The interviewer should not modify the question wording. For incomplete answers, interviewers may use probing to further clarify a participant's answer. The most commonly used probing technique is silence. In this situation the interviewer waits for the participant to provide an answer. Participants may require time to recall events or consider how to respond. If the participant seems uneasy with the length of time he or she is taking to answer a question, the coordinator may reassure the participant, i.e., "Take your time" or "There is no rush."

5.1.3. Spirometry:

Historical spirometry will be abstracted from medical charts. If multiple spirometry records are available, the most contemporaneous will be abstracted. This will also include the age, height and weight at the time of spirometry.

5.1.4. PIFR Measurements

Study visits PIFR: PIFR measurements will be collected using the In-Check G16 DIAL® which is a simple, hand-held low range inspiratory flow device that measures PIFR via a brief inspiratory maneuver (APPENDIX 5). The device includes a one-way disposable mouthpiece, measurement diaphragm, and a directly visualized PIFR scale. The device also includes an adaptor with adjustable resistance to mimic nine resistance groups encompassing the popular MDIs and DPIs currently available. After each inspiratory maneuver to a set resistance, the PIFR score will be visualized on the scale and recorded. Subjects will perform the PIFR in the following manner:

Patients receiving Handihaler® and/or Ellipta® and/or Diskus® and/or Inhub®

- For testing during study visits, perform PIFR in the physical position they most commonly use when self-administering their maintenance inhaler(s)
- Perform PIFR using the inspiratory effort described by the manufacturer (Ellipta®,Diskus®, and Inhub®)- breathe out fully, then take a long, steady deep breath'; 'breathe out all the way, then breathe in slowly and deeply') For the Handihaler®, subjects will be instructed as follows – "Empty your lungs of air. Breathe in deeply until your lungs are full."
- Measurements will be collected on each prescribed DPI resistance setting. PIFR will be recorded with best approximation to nearest 1 L/min. Ample time will be given to any patients who may be feeling short of breath or fatigued.

Home measurement of PIFR: Using the In-Check G16 DIAL®

- Perform PIFR in physical position most commonly used when self-administering maintenance inhaler(s)
- Perform PIFR (proper setting) for each maintenance DPI patient is receiving
- Use maximum inspiratory effort, by first breathing out fully, and breathing in as hard and fast as possible, and as above, repeat the maneuver two more times, recording the highest value.

5.1.4.1 Efficacy Evaluation (if applicable)

Changes in PIFR and dyspnea (modified Borg) that occur in the COPD population in the home setting during periods of stable respiratory symptoms and periods of worsening will be measured and recorded by participating subjects. PIFR measurements, PRO (mMRC, modified Borg, CAT) will also be undertaken in the research clinic setting. PRO will also be completed with each telephone-based study visit.

5.1.4.2 Safety Evaluations

Measurement of PIFR will be deferred or not performed for those with chest, abdominal, oral or facial pain; stress incontinence; dementia; recent myocardial infarction (6 weeks), chest or abdominal or ocular surgery (6 weeks), those with prior significant difficulties with spirometry or participant refusal.

6 STATISTICAL CONSIDERATION

6.1 Primary Endpoint

For each patient the occurrence of suboptimal Peak Inspiratory Flow Rate (sPIFR) over 24 weeks. sPIFR will be defined as any two consecutive measurements on different days below the optimal threshold for any prescribed DPI (e.g.,<30 L/min for Handihaler® (High resistance DPI), <60 L/min for Ellipta® (Medium resistance DPI))

6.2 Exploratory Endpoints

PIFR Endpoints:

1. Time to first occurrence of sPIFR (in days)
2. Number and proportion of sPIFR
3. Rate of sPIFR, defined as the number of sPIFR / number of days in the study, multiplied by 30 as sPIFR/month.

Exacerbation Endpoints:

Occurrence (yes/no), number, severity (mild, moderate, severe) and rate of COPD exacerbations over 24 weeks. Mild, moderate and severe exacerbations will be defined as:

1. Mild – doubling use of inhaled rescue medication > 48 hours and not meeting definition of moderate or severe
2. Moderate – increased rescue medication and either oral corticosteroid or antibiotics, not requiring hospitalization
3. Severe – hospitalization for exacerbation

6.3 Statistical Methods

Analysis populations

Full analysis set (FAS): all screened patients with informed consent and at least two consecutive PIFR measurements on different days.

Descriptive Statistics

Using the FAS, the following variables will be described using descriptive statistics (mean and standard deviation, min, max, median) and graphical displays (boxplots, histograms). Data transformation will be used if applicable, and extreme values will be verified and their effect on analysis results will be reported.

- demographics and clinical variables
- patient reported outcomes (CAT, mBORG and mMRC)
- concomitant diseases and medications

Primary analysis

The primary endpoint will be described as the proportion of patients with suboptimal PIFR and reported with 95% confidence intervals, on the FAS. The proportion of sPIFR will be computed from the Kaplan-Meier curve.

Subgroup analyses of the primary endpoint:

- per DPI device type (moderate vs. high resistance)
- per gender
- per GOLD stage based on spirometry results.

Analysis of exploratory endpoints: on FAS.

We will analyze the PIFR measurements over time, specifically:

- Descriptive analysis of PIFR measurements, including mean (SD), median (IQR), range over time per patient per device, and in different body positions (standing, sitting, supine at 45 degrees). PIFR curves per patient/device can be explored. Descriptive analysis for different time's period (week, month) may be explored.
- The time of first occurrence of sPIFR will be reported in days and will be plotted with a Kaplan-Meier curve. A patient will be considered censored for sPIFR at the time of the latest documented visit or PIFR measurements, the end of the study, the switching of device (between medium and high resistance DPI) or death (whichever occurs earlier), if they did not experience a sPIFR before. Associations with possible demographics and clinical variables will be explored using a Cox regression analysis.
- The proportion of suboptimal PIFR measurements will be reported with 95% CI, and also the rates. This analysis will also be performed per device in patients that used two devices with different resistances (e.g. Advair + Spiriva HH).
- We will explore, for each device, with logistic regression (binary) or negative binomial (count) the clinical and demographic factors associated with sPIFR measurements.
- We will use mixed models to explore associations of monthly PFIR averages over time and clinical and demographic factors. Subjects will be considered as random factor, other variables will be considered fixed effects.
- Association of PIFR with CAT score, mBORG score and mMRC
  - Association of PIFR and CAT scores at V1, V3, V4, V5,V6 (for PIFR, use the measurement in the week of each telephone follow-up, or the month average)

- Correlation of change in CAT scores with change in PIFR from baseline after 24 weeks
- Association of PIFR and mBORG score at V2, V3, V4, V5, V6
- Association of PIFR and mMRC scores at V1, V3, V4, V5,V6 (for PIFR, use the measurement in the week of each telephone follow-up, or the month average)

For COPD exacerbation analyses, the proportion of patients with COPD exacerbations (from Kaplan Meier curve) and the rate of exacerbations occurring during follow-up will be reported along with 95% CI. A patient will be considered censored for exacerbations at the time of the last documented visit, the end of the study, the switching of device (between medium and high resistance DPI) or death (whichever occurs earlier), if they did not experience an exacerbation before. The exacerbations will be reported overall and stratified by severity. The associations between exacerbations and PIFR will be explored in different ways, for all exacerbation, stratified by severity of exacerbations, and stratified by device.

- The rate of exacerbations and sPFIR will be analyzed with negative binomial models (or another model if more appropriate).
- For patients with exacerbations, the mean of PIFR in the week before, of, and after each exacerbation will be calculated and reported.

All tests with p value < 0.05 will be interpreted nominally as statistically significant.

Missing data

- No imputation for PIFR
- No imputation for COPD exacerbations
- No imputation for CAT, mBORG and mMRC

Sample Size and Power

In this application, we propose to recruit 120 COPD participants for study enrollment. There are several rationales for this sample size selection.

The primary outcome focuses on characterizing the proportion of participants with suboptimal PIFR. There are no available data on prevalence of sPIFR from home measurements in COPD, highlighting the novelty of this proposal. While there is no established clinical threshold of variability of proportion with suboptimal PIFR, it is felt that a precision of <10% (95% CI range <20%) is desirable for clinical interpretation of sPIFR prevalence. From pilot study data, we observed that 40% of patients had sPIFR. We have generated three scenarios with different ranges of proportion of sPIFR (30%, 40%, and 50%) along with the required sample sizes to obtain a range of precisions (see table). Given that clinical expertise and judgement suggests that a precision of <10% is acceptable for this study, one can see that sample size range of N=105 to 125 will achieve this precision across a range of possible sPIFR proportions (highlighted column).

	Precision (half of Confidence Interval)				
sPIFR proportion	5%	8.8%	10%	15%	20%
30%	323	105	81	36	21
40%	369	120	93	41	24
50%	385	125	97	43	25

Interim Analysis

None planned

7 STUDY PROCEDURES

This is an observational study but certain study procedures and PROs will be measured in the study. Procedures includes performing pre- and post-bronchodilator PIFR as well as completion of PROs during clinic visits. In the home setting, subjects will be expected to record PIFR and modified Borg score three times weekly (MWF), or more often with worsened symptoms.

8 DATA COLLECTION AND MANAGEMENT

Each participant will be given a unique identifier which will be assigned serially with study enrollment starting with P001. The linking form will be the only form linking study ID to name or medical record number. All study related forms (regardless of identified or de-identified) will be placed in locked drawers. Hard copies of questionnaires marked with unique study numbers will not contain identifying information. The linking form will be kept on a secure password protected document on REDCap. This de-identified data will be entered and retained on a secure network via REDCap which has been developed to provide a mechanism for retaining a confidential, secure database with valid and accurate records. The system is comprehensive, thorough and constantly monitored on many levels. Protection against loss of data is provided through scheduled backup of data files by a central REDCap support center. The PI and study staff will review data collection forms on an ongoing basis for data completeness and accuracy as well as protocol compliance. Data managers write programs for data verification of all data collected, including field range limits and logical checks to help identify and eliminate data-entry errors. Hard copies of questionnaires will be saved should data entry questions arise, and will again be kept in a locked drawer. Follow up scheduling will be maintained on the REDCap Database and events will be recorded using only Study ID.

9 CONSENT PROCESS

HIPPA authorization will allow us to screen patients' medical record after permission from primary pulmonologist. This will allow us to screen for inclusion criteria prior to approaching the patients and minimize the likelihood of approaching patients who would not qualify. Informed consent is the first data collection form administered during the research encounter. A signed informed consent means the patient fully understands the requirements of the procedures and assessments included in the study as well as the risks of those procedures/assessments. It is important that the patient fully comprehends the time commitment required for participation, as well as the potential implications of specimen storage and dissemination of study findings.

- Reception

Upon arrival at the clinical center the study coordinator should greet the patient and confirm patient's identity. No data can be collected until the full informed consent has been obtained.

- Administration

The study coordinator and/or investigator should take the patient to a quiet, private area to review the informed consent. The coordinator should provide a copy of the consent to the participant, and ask the participant whether he or she would like to read the consent form or have it read to them by the staff person. If the participant is visually handicapped, the coordinator should read the form to him or her. If the participant chooses to read the form, the coordinator should still review, although not read, the consent form with the participant to ensure he or she is fully informed. This should be handled sensitively, so as not to imply poor comprehension on the part of the patient. The coordinator should encourage the participant to ask for clarification or any questions he or she may have. The original signed copy of the informed consent should be kept with the participant's study information. A copy of the consent form should be provided to the participant.

- Training and Certification

All study personnel interacting with participants must have received appropriate training and certification in confidentiality, privacy, and informed consent prior to having any contact with participants.

- Data and Collection

Informed consents are collected on paper.

- Ability to Comprehend the Informed Consent

The ability to provide informed consent is a requirement for participation in the study. In order to remain in compliance with ethical and regulatory standards, study coordinators should make every effort to ensure the patients understand their rights and risks when participating in this study. It can be difficult to determine whether a participant understands the informed consent. Behaviors and patterns to look for that might indicate poor comprehension include repetitive behaviors and speech patterns and looking to spouses and companions for assistance answering questions. If the coordinator doubts the patient's comprehension, he or she can ask the patient to explain the rights

and risks detailed in the consent form in his or her own words. If the coordinator continues to question the ability of the patient to consent, he or she should speak with the PI.

10. MANAGEMENT AND REPORTING OF ADVERSE EVENTS/ADVERSE REACTIONS

10.1 DEFINITIONS OF ADVERSE EVENTS

Adverse event
An adverse event (AE) is defined as any untoward medical occurrence in a patient or clinical investigation subject administered a medicinal product and which does not necessarily have a causal relationship with this treatment. An adverse event can therefore be any unfavorable and unintended sign (e.g. an abnormal laboratory finding), symptom, or disease temporally associated with the use of a medicinal product, whether or not considered related to the medicinal product.

Adverse reaction (ADR)
An adverse reaction is defined as a response to a medicinal product which is noxious and unintended. Response in this context means that a causal relationship between a medicinal product and an adverse event is at least a reasonable possibility. Adverse reactions may arise from use of the product within or outside the terms of the marketing authorization or from occupational exposure. Conditions of use outside the marketing authorization include off-label use, overdose, misuse, abuse and medication errors.

Serious adverse event
A serious adverse event is defined as any AE which

- Results in death,
- Is life-threatening
- requires in-patient hospitalization, or
- Prolongation of existing hospitalization,
- Results in persistent or significant disability or incapacity, or
- Is a congenital anomaly/birth defect

Life-threatening in this context refers to a reaction in which the patient was at risk of death at the time of the reaction; it does not refer to a reaction that hypothetically might have caused death if more severe.

Medical and scientific judgement should be exercised in deciding whether other situations should be considered serious reactions, such as important medical events that might not be immediately life threatening or result in death or hospitalization but might jeopardize the patient or might require intervention to prevent one of the other outcomes listed above. 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 development of dependency or abuse. Any suspected transmission via a medicinal product of an infectious agent is also considered a serious adverse reaction.

Adverse Event of Special Interest (AESI)
The term AESI relates to any specific AE that has been identified at the project level as being of particular concern for prospective safety monitoring and safety assessment within this study, e.g. the potential for AEs based on knowledge from other compounds in the same class.

No AESIs have been defined for this study.

10.2 ADVERSE EVENT AND SERIOUS ADVERSE EVENT COLLECTION AND REPORTING

The investigator shall maintain and keep detailed records of all AEs in their patient files.

INSTITUTION/Investigator will be responsible for reporting AEs which occur during the conduct of the Study, (i.e. from signing of informed consent to end of data collection), to the competent regulatory authorities, accredited Institutional Review Boards and/or Independent Ethics Committee(s) ("IRB/IEC(s)") in accordance with the applicable laws and regulations.

10.3 ADVERSE EVENT REPORTING TO BOEHRINGER-INGELHEIM (BI)

INSTITUTION shall report
(i) All ADRs (serious and non-serious)
(ii) All AEs with fatal outcome
(iii) Pregnancies in female subjects and partners of male subjects

which are associated with the BI Drug (Spiriva, Combivent, Stiolto, Striverdi, Atrovent), administered for the disease (COPD) in scope of the study by fax to the BI Unique Entry Point as specified in Safety Data Exchange Agreement using BI NIS SAE report form in following timelines.

< BI Unique Entry Point>
Boehringer Ingelheim Pharmaceuticals, Inc.
900 Ridgebury Road
Ridgefield, CT
Fax: 1-203-837-4329
Email: PVIRTGlobalCaseManagement.ING@boehringer-ingelheim.com

All Serious ADRs and AEs with fatal outcome shall be forwarded immediately (within twenty four (24) hours or next business day whichever is shorter). All non-serious ADRs and Pregnancy Monitoring Forms shall be forwarded within seven (7) calendar days. The investigator carefully assesses whether an AE constitutes an ADR using the information below.

Causal relationship of adverse event: The definition of an adverse reaction implies at least a reasonable possibility of a causal relationship between a suspected medicinal product and an adverse event. An adverse reaction, in contrast to an adverse event, is characterized by the fact that a causal relationship between a medicinal product and an occurrence is suspected.

Medical judgment should be used to determine the relationship, considering all relevant factors, including pattern of reaction, temporal relationship, de-challenge or re-challenge, confounding factors such as concomitant medication, concomitant diseases and relevant history.

Causality should be assessed for each event as either “yes” or “no”. No other variation should be reported.

Intensity of adverse event: The intensity of the AE should be judged based on the following:
Mild: Awareness of sign(s) or symptom(s) which is/are easily tolerated
Moderate: Enough discomfort to cause interference with usual activity
Severe: Incapacitating or causing inability to work or to perform usual activities

Pregnancy:
In rare cases, pregnancy might occur in a study. Once a subject has been enrolled into the study, after having taken BI Drug administered for the disease in scope of the study, the investigator must report any drug exposure during pregnancy, which occurred in a female subject or in a partner to a male subject to the Sponsor by means of BI Pregnancy Monitoring Form provided.

In the absence of a reportable AE, only the Pregnancy Monitoring Form must be completed, otherwise the NIS AE form is to be completed and forwarded as well within the respective timelines.

Reporting of related Adverse Events associated with any other BI drug
The investigator is encouraged to report all adverse events related to any BI drug other than the BI drug taken for the disease in scope of the study according to the local regulatory requirements for spontaneous AE reporting at the investigator’s discretion by using the locally established routes and AE report forms. The term AE includes drug exposure during pregnancy, and, regardless of whether an AE occurred or not, any abuse, off-label use, misuse, medication error, occupational exposure, lack of effect, and unexpected benefit.

11 REFERENCES

- Broeders ME, Molema J, Hop WC, Vermue NA, and Folgering HT. The course of inhalation profiles during an exacerbation of obstructive lung disease. Respir Med 2004;98:1173-1179.

- Buttini F, Brambilla G, Copella D et al. Effect of flow rate on in vitro aerodynamic performance of NEXThaler® in comparison with Diskus® and Turbohaler® dry powder inhalers. J Aerosol Med Pulm Drug Delivery 2016;29: 167-78.
- Dalby RN, Eicher J, Zierneberg B Development of Respimat® Soft Mist™ inhaler and its clinical utility in respiratory disorders. Med Devices: Evidence Res. 2011:4 145–155.
- Dekhuijzen PNR, Batsiou M, Bjermer L etal. Incidence of oral thrush in patients with COPD prescribed inhaled corticosteroids : effect of drug, dose, and device. Respir Med 2016;120:54-63.
- Feddah MR , Brown KR, Gipps E et al. in vitro characterization of metered dose inhaler versus dry powder inhaler glucocorticoid products: influence of inspiratory flow rates. J Pharma Sci 2000;3:317-24.
- Ferguson GT, Ghafouri M, Dai L, Dunn LJ. COPD patient satisfaction with ipratropium bromide/albuterol delivered via Respimat: a randomized, controlled study. Int J Chron Obstruct Pulmon Dis. 2013;8:139-50.
- Ghosh S, Ohar JA, Drummond MB. Peak inspiratory flow Rate in chronic obstructive pulmonary disease: implications for dry powder inhalers. J Aerosol Med Pulm Drug Delivery 2017;30:1-7.
- Ghosh S, Pleasants RA, Donohue JF, Ohar JA, Drummond MB. Device-specific suboptimal peak inspiratory flow rates are common in COPD. Submitted as research abst for ATS 2018.
- Global Initiative for Chronic Obstructive Lung Disease Guidelines. http://goldcopd.org/wp-content/uploads/2016/12/wms-GOLD-2017-Pocket-Guide.pdf.
- Goldin JG, Tashkin DP, Kleerup EC, et al. Comparative effects of hydrofluoroalkane and chlorofluorocarbon beclomethasone dipropionate inhalation on small airways: assessment with functional helical thin-section computed tomography. J Allergy Clin Immunol 1999;104:S258-S67.
- Grant AC, walker R, Hamilton M et al. The ELLIPTA® dry powder inhaler: design, functionality, in vitro dosing performance and critical task compliance by patients and caregivers. J Aerosol Med Pulm Drug Delivery 2015:28:1-12.
- Hamilton M, Leggett R, Pang C et al. In vitro dosing performance of the ELLIPTA® dry powder inhaler using asthma and COPD patient inhalation profiles replicated with the Electronic Lung (eLungTM). J Aerosol Med Pulm Drug Delivery 2015:28:1-9.
- Janssens W, VandenBrande P, Hardeman E et al. Inspiratory flow rates at different levels of resistance in elderly COPD patients. Eur Respir J 2008;31-78-83.
- Jones R, Martin J, Thomas V et al. The comparative effectiveness of initiating fluticasone/salmeterol combination therapy via pMDI versus DPI in reducing exacerbations and treatment escalation in COPD: a UK database study. Int J COPD 2017:12 2445–2454.
- Kawamatawong T, Khiawwan S, and Pornsuriyasak P. Peak inspiratory flow rate measurement by using In-Check DIAL for the different inhaler devices in elderly with obstructive airway diseases. J Asthma Allergy 2017;10:17-21.
- Loh CH, Peters SP, Lovings TM, and Ohar JA. Suboptimal inspiratory flow rates are associated with chronic obstructive pulmonary disease and all cause readmissions. Ann Am Thorac Soc 2017;14:1305–1311

- Mahler DA, Waterman LA, and Gifford AH. Prevalence and COPD phenotype for a suboptimal peak inspiratory flow rate against the simulated resistance of the Diskus® dry powder inhaler. J Aerosol Med Pulm Drug Delivery 2013;26:174-179.
- Mahler DA, Waterman LA, Ward J, Gifford AH. Comparison of dry powder versus nebulized beta-agonist in patients with COPD who have suboptimal peak inspiratory flow rate. J Aerosol Med Pulm Drug Delivery 2014;27(2):103–109.
- Mahler DA, Peak inspiratory flow rate as a criterion for dry powder inhaler use in chronic obstructive pulmonary disease Ann Amer Thorac Soc 2017;14:1103–1107.
- Malmberg LP, Rytila P, Happonen P, and Haahtela T. Inspiratory flows through dry powder inhaler in chronic obstructive pulmonary disease: age and gender rather than severity matters. Int J Chron Obstruct Pulmon Dis 2010;5:257-262.
- Nielsen KG, Bojsen AK, Ifversen M et al. Clinical effect of Diskus™ dry-powder inhaler at low and high inspiratory flow-rates in asthmatic children. Eur Respir J 1998; 11: 350–354.
- Pitcairn G, Reader S, Pavia D, et al. Deposition of corticosteroid aerosol in the human lung by Respimat® Soft Mist™ inhaler compared with deposition by metered dose inhaler or by Turbuhaler® dry powder inhaler. J Aerosol Med 2005;18:264–72.
- Price D, Roche N, Virchow JC. Device type and real-world effectiveness of asthma combination therapy: an observational study. Respir Med 2011;105:1457e1466.
- Prime D, de Backer W, Hamilton M et al. Effect of disease severity in asthma and chronic obstructive pulmonary disease on inhaler-specific inhalation profiles through the Ellipta® dry powder inhaler. J Aerosol Med Pulm Drug Delivery 2015;28:486–497.
- Ramal Sk, Fisser FJ, Hop WCJ et al. Effects of long-acting bronchodilators and prednisolone on inspiratory lung function parameters in stable COPD. Pulm Pharmacol Ther 2014; 28:158e164.
- Seheult JN, O'Connell P, Tee KC et al. The acoustic features of inhalation can be used to quantify aerosol delivery from a Diskus® dry powder inhaler. Pharm Res (2014) 31:2735–2747.
- Seheult JN, Costello S, Tee KC et al. Investigating the relationship between peak inspiratory flow rate and volume of inhalation from a Diskus® Inhaler and baseline spirometric parameters: a cross-sectional study. Springerplus. 2014;3:496.
- Sharma G MD, Mayorga VM, Deering KL, Harshaw Q, and Ganapathy V. Prevalence of low peak inspiratory flow rate at discharge in patients hospitalized for COPD exacerbation. J COPD Found 2017;4:217-224.
- Sulaiman I, Cushan B, Greeen G et al. Objective assessment of adherence to inhalers by patients with chronic obstructive pulmonary disease. Am J Respir Crit Care Med 2017;195:1333–1343.
- Sulaiman I, Seheult J, Sadasivuni N et al The impact of common inhaler errors on drug delivery: investigating critical errors with a dry powder inhaler. J Aerosol Med Pulm Drug Delivery 2017;30:247-55.
- Tamura G, Sakae H, Fujina S. In vitro evaluation of dry powder inhaler devices of corticosteroid preparations. Allergology International 2012;61:149-154.

- Taube C, Rydzy L, Eich A et al. Use of a portable device to record maximum inspiratory flow in relation to dyspnoea in patients with COPD. Respir Med 2011;105, 316e321
- Yokohama H, Yamamura Y,Oseki T. Analysis of relationship between peak inspiratory flow rate and amount of drug delivered to lungs following inhalation of fluticasone propionate with a Diskhaler®. Biol Pharm Bull 2007;30:162—164.

16 APPENDIX 1. STUDY PROCEDURES AND ASSESSMENTS

Visit number	**V1** [a]	**V2**	**V 3,4,5,6**
Procedures and assessments	**Screening Visit**	**Enrollment Visit**	**Telephone Follow-up Visits**
Target time(s) and allowable time frames		**At same time as or within 1 month of Screening Visit**	**At 4, 8, 12, 24 weeks after V2 (± 2 weeks)**
Informed consent	X		
Clinical history	X	X	
Prior medication history	X	X	
Inclusion and exclusion criteria	X	X	
Physical examination including waist circumference		X	
Vital signs measurement		X	
Peak Inspiratory Flow Rate (Performed in triplicate at resistance of all DPIs the patient is receiving)	X	Pre- and post-bronchodilator (albuterol) Perform PIFR in three positions (sitting, standing, and lying at 45^{o} angle with head tilted forward)[#]	Done 3x/wk. (each session in triplicate with highest value recorded) at home by patient after enrollment[#] (Daily during worsened symptoms)
COPD Assessment Test score (CAT) questionnaire	X	X	X
Modified Borg Dyspnea Score (mBorg)		X	X Done 3x/wk at home by patient after enrollment
Modified Medical Research Council questionnaire (mMRC)		X	X
COPD exacerbation history[*]	X	X	X
COPD medication use and adherence	X	X	X

[*] *Mild, moderate and severe exacerbations will be defined as:*

Mild – doubling use of inhaled rescue medication ≥ 48 hours and not meeting definition of moderate or severe; Moderate – increased rescue medication and oral corticosteroid, not requiring hospitalization; Severe – hospitalization for exacerbation

PIFR will be performed before performing spirometry (if spirometry is performed at that visits) using InCheck Dial settings for each DPI patient is receiving

APPENDIX 2. Modified Medical Research Council questionnaire (mMRC)

Grade	Description of Breathlessness
Grade 0	I only get breathless with strenuous exercise
Grade 1	I get short of breath when hurrying on level ground or walking up a slight hill
Grade 2	On level ground, I walk slower than people of the same age because of breathlessness, or I have to stop for breath when walking at my own pace on the level
Grade 3	I stop for breath after walking about 100 yards or after a few minutes on level ground
Grade 4	I am too breathless to leave the house or I am breathless when dressing

APPENDIX 3. mBORG

Modified Borg Dyspnoea Scale

0	NOTHING AT ALL
0.5	VERY, VERY SLIGHT (just noticeable)
1	VERY SLIGHT
2	SLIGHT
3	MODERATE
4	SOMEWHAT SEVERE
5	SEVERE
6	
7	VERY SEVERE
8	
9	VERY, VERY SEVERE (almost maximal)
10	MAXIMAL

APPENDIX 4. COPD ASSESSMENT TEST

Name: Today's Date:

CAT™
COPD Assessment Test

How is your COPD? Take the COPD Assessment Test (CAT)

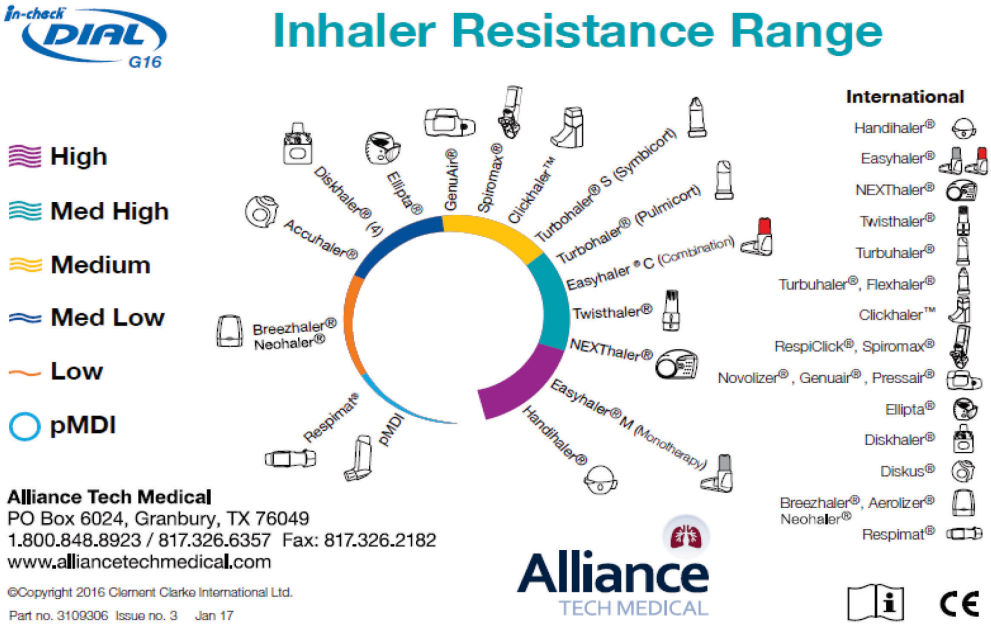
This questionnaire will help you and your healthcare professional measure the impact COPD (Chronic Obstructive Pulmonary Disease) is having on your wellbeing and daily life. Your answers and test score, can be used by you and your healthcare professional to help improve the management of your COPD and get the greatest benefit from treatment.

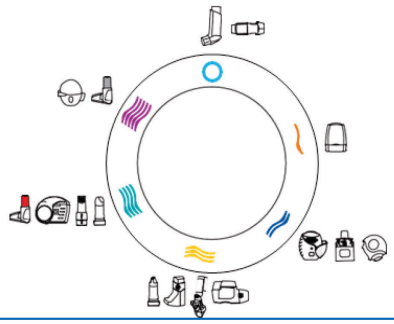
Example: I am very happy 0 X 2 3 4 5 I am sad

			SCORE
I never cough	0 1 2 3 4 5	I cough all the time	
I have no phlegm (mucus) in my chest at all	0 1 2 3 4 5	My chest is full of phlegm (mucus)	
My chest does not feel tight at all	0 1 2 3 4 5	My chest feels very tight	
When I walk up a hill or one flight of stairs I am not breathless	0 1 2 3 4 5	When I walk up a hill or one flight of stairs I am very breathless	
I am not limited doing any activities at home	0 1 2 3 4 5	I am very limited doing activities at home	
I am confident leaving my home despite my lung condition	0 1 2 3 4 5	I am not at all confident leaving my home because of my lung condition	
I sleep soundly	0 1 2 3 4 5	I don't sleep soundly because of my lung condition	
I have lots of energy	0 1 2 3 4 5	I have no energy at all	

CLICK TO GET YOUR TOTAL SCORE!

APPENDIX 5. In-Check G16 DIAL®



Icon	Product	Icon	Product	Device Resistance
	*Handihaler®		Spiromax®	
	*Easyhaler®		*GenuAir®	
	NEXThaler®		Ellipta®	
	Twisthaler®		*Diskhaler®	
	*Turbohaler® P		*Accuhaler®	
	Turbohaler® S		*Breezhaler® Neohaler®	
	*Clickhaler™			
			Respimat®	

Please Note:

All trademarks and product names are the property of their respective owners, see IFU booklet for details.

*Indicates device specific adaptor is available, see IFU booklet.

Assessing inspiratory flow rate for clinical efficacy:
Select appropriate resistance setting, inhale through meter, assess achieved flow rate.
For DPIs values between 30-90 L/min are generally associated with clinical efficacy.
For pMDIs values between 20-60 L/min are preferred.

Bibliography:

1. Pedersen S, Dubus JC, Crompton G. 5) Inhaler selection in children with asthma. *Prim Care Respir J* 2010;**19**(3):209-16
2. Lavorini F, Levy ML, Corrigan C, Crompton G. 6) Training tools for inhalation devices. *Prim Care Respir J* 2010;**19**(4):335-41
3. Capstick, T. G., & Clifton, I. J. (2014). Inhaler technique and training in people with chronic obstructive pulmonary disease and asthma. *Expert review of respiratory medicine.*
4. Broeders MEAC, Vincken W, Corbetta L. 7) Ways to improve pharmacological management of COPD: the importance of inhaler choice and inhalation technique. *Prim Care Respir J* 2011;**20**(3):338-43
5. Laube, B. L., Janssens, H.M., de Jongh, F.H., Devadason, S.G., Dhand, R., Diot, P., & Chrystyn, H. (2011). What the pulmonary specialist should know about the new inhalation therapies. *European Respiratory Journal*, **37**(6) 1308-1417.