Peak Inspiratory Flow (PIF) in COPD
Protocol ID: 001

Investigator Initiated Research Protocol

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Scientific Rationale/ Background

Inhaled medications are the cornerstone of therapy for respiratory airways diseases such as asthma and COPD, delivering medication directly to the organ of concern and allowing for reduced systemic exposures and side effects of needed drugs. Since medication delivery to the lungs is essential for this form of therapy, the delivery device chosen plays a critical role in the effectiveness of these medications.

Multiple factors can lead to ineffective handheld inhaler drug delivery, including components unique to how the drug is compounded, unique characteristics of each delivery device and various individual patient limitations (e.g cognitive impairment, mechanical usage difficulties in patients with arthritis and neuromuscular diseases, and respiratory muscle dysfunction).

Dry powder inhalers (DPIs) are one of the most common handheld delivery systems used by respiratory patients and present with many unique features. Importantly, they are breath actuated, which helps many patents with timing and ease of device use. However, DPIs require a certain level of inspiratory effort to create an inspiratory flow sufficient to inhale the medication from the inhaler and disaggregate the medication from its excipient carrier creating respirable medication particles needed for effective drug delivery.

Failure of effective drug delivery will lead to failure of whatever clinical outcome for which an inhaled device is being used. It has recently been suggested that a low peak inspiratory flow (PIF) during DPI usage can contribute to inpatient and outpatient treatment failures in patients with COPD. Indeed, a subset of patients with low PIF in an observational hospital study were noted to have higher readmission rates when treated with a DPI compared to those treated with nebulizers. However, other investigators have observed that a low PIF is a minor clinical problem in outpatients and inpatients with COPD. Overall, specific information about how PIF measurements are made and how they relate to therapeutic and clinical responses in the use of DPIS for COPD patients is lacking.

Peak Inspiratory Flow (PIF)

Ohm's law defines the relationship between inspiratory pressures, inspiratory airflows and resistances. For any given resistance, the level of airflow generated is directly dependent on the pressure gradient across the resistance. In the case of DPIs, each device has a defined fixed resistance. Thus, the inspiratory flow generated is directly related to the inspiratory pressure applied to the device. The inspiratory pressure generated, in turn, depends on the degree of effort applied by the patient, the manner in which the effort is performed and any medical conditions that might reduce or limit a patient's capabilities to generate an inspiratory muscle force (even with a maximal effort).

Identifying the level of effort required to properly use a DPI is further challenged by the multiple different DPIs that are commercially available, each having different resistances and varying instructions for how to inhale when using the device. Clinical patient data is limited related to the degree of effort and flow needed by a patient for effective drug delivery for any given DPI, with even less known about the clinical consequences of inadequate DPI usage.

Various patient characteristics have been suggested that might predict patients with risk for poor inspiratory flow capabilities leading to impaired DPI medication delivery, including female gender, short stature, severe airflow limitation and lung hyperinflation. However, none of these are sensitive and specific enough to prospectively identify patients in a clinical situation who may not be able to effectively use a DPI.

Inspiratory flow rates are often measured as a part of spirometry and these measurements might be useful to identify patients who are unable to generate inspiratory airflows sufficient to effectively use a DPI. However, airflows measured during spirometry are obtained using a large bore mouthpiece with virtually no resistance and peak inspiratory flows measured during spirometry maneuvers have been suggested to not correlate well with inspiratory airflows achieved when inspiring through a resistance typically found in a DPI.

InCheck Dial Device

Recently, it has been suggested that the InCheck Dial, a device originally designed to train and coach patients on how to use their inhalers correctly, might be used to determine whether a patient's peak inspiratory flow (PIF) is sufficient for effective DPI drug delivery, by maximally inspiring though a resistance appropriate to the DPI being used by the patient. It has also been suggested that there may be a suboptimal PIF below which effective medication delivery from a DPI begins to drop, leading to a risk of a lower clinical effectiveness. A minimal or critical PIF has also been suggested, below which no medication is effectively delivered. Since DPI devices have varying resistances, measured PIF will vary based on the resistance against which it was measured, with implications for suboptimal and minimal PIF changing accordingly. Nevertheless, the concept of suboptimal PIF as a tool to help identify patients who might not be able to effectively use a DPI and that an alternative delivery system should be considered for their respiratory medications is reasonable.

PIF Measurement Technique

Before any diagnostic tool can be used in clinical practice, it must meet criteria showing the robustness of the test and defining any limitations that the test may have. Ideally, test sensitivity, specificity, positive and negative predictive values and receiver operator characteristics (ROC) should be determined. In the case of PIF, none of these qualities have been determined to date. In spite of this and based on modest data from drug impactors and limited observational studies, it has been suggested that a PIF of <60 l/min is suboptimal and a PIF <30 l/min is minimal for DPI usage. Recommendations about the use of PIF to dictate device selection has also been made based on these results.

Critical questions remain for PIF, including at what resistance it should be measured and exactly how the PIF effort should be performed. To be most meaningful, the effort should mimic the effort used when the patient inhales with their DPI, which should match the effort recommended by the DPI device maker, and the outcome measured should relate to the expected clinical response desired for the medication being used.

Common variables that change with patient inspiratory effort include the intensity, speed, depth and duration of the inspiratory effort. Each can change the pressure applied to the DPI and alter the inspiratory flow. By definition, one might assume that PIF would best be measured as a maximal effort, since it is "peak". However, to achieve such a "peak" measurement, one needs to inhale with a very sharp, rapid, intense effort starting from residual volume (RV). Although breathing down to RV provides maximal stretch of the respiratory muscles and offers their greatest force generation, breathing down to RV can be difficult. Lesser degrees of forced exhalation prior to a PIFR effort would then be expected to provide a lower "PIF" measurement, even when otherwise performing a sharp, maximal efforts. On the other hand, a sharp, maximal effort may give a "peak" inspiratory flow, but might not be able to effectively performed during routine DPI usage and may go against device maker recommendations for their DPI usage. An intense "peak" effort could also lead to increased oropharyngeal drug impaction, reducing the amount of medication delivered to the lower airways.

What level of reproducible effort is needed to provide a reliable PIF measurement is also uncertain. Three efforts has been suggested, but the variability allowed between efforts and whether the best or average PIFR should be used is also unclear. These decisions become critically important when performing "effort-dependent" testing, since variable submaximal efforts will give inadequate results and could inappropriately define a patient with a "suboptimal" PIF when, in fact, they are fully capable of inhaling sufficiently to use a DPI.

Study Purpose

The purpose of this research is to determine whether PIF is clinically important when using the Ellipta DPI device. In addition, the study will validate the best/most clinically appropriate way to perform a PIF maneuver, to determine the testing capabilities of the preferred PIF maneuver and to relate this PIF measurement to meaningful clinical outcomes in COPD patients.

Hypothesis

A standardized method for determining PIFR can be developed

- to determine if low PIF is a meaningful clinical problem in patients with COPD using the Ellipta DPI
- to identify what clinical features predict a risk of inadequate response to an inhaled medication delivered by the Ellipta DPI
- to detect the presence, prevalence and risk of low PIF in patients with COPD
- to identify what clinical features in COPD patients may predict a lower PIF

Objectives/Questions

Primary

- Determine if an inhaled short acting bronchodilator delivered by a non-DPI delivery device (Ventolin pMDI with a spacer) produces added clinical bronchodilation added to Trelegy has been delivered by the Ellipta DPI if a suboptimal or minimal PIF is present in COPD patients.

Secondary

- Determine if a suboptimal or a minimal PIF in COPD patients predicts clinical response to medication delivered using the Ellipta DPI device.
- Determine the best way to measure PIF for the Ellipta device and are there suboptimal or minimal PIF thresholds that can be identified to predict response to a DPI?
  - What inspiratory effort should a patient exert when measuring PIF?
  - What lung volume should a patient start from when measuring PIF?
  - What reproducibility criteria should be used when measuring PIF?
- Determine if best PIF correlates with FEV1, FVC, IC or peak inspiratory flow measured during spirometry.

Study Population

- outpatients of either sex
- age ≥ 40 years with a clinical diagnosis of COPD
- smoking history >10 pack years
- post-bronchodilator FEV1 <50% predicted
- post-bronchodilator FEV1/FVC <70%
- female participants are eligible to participate if they are not pregnant, not breastfeeding, and at least one of the following conditions applies:
  - not a woman of childbearing potential OR
  - agree to follow the contraceptive guidance during the treatment period and until the safety follow-up contact after the last dose of study treatment
- stratification requiring at least 1/3 of patients having a PIF of < 60L/min (AM pre-dose based on using the level 2 InCheck Dial resistance setting with a sharp maximal effort starting after exhaling fully)

Exclusion Criteria

- any subject with unstable disease, including
  - COPD exacerbation in the last 6 weeks
  - upper respiratory tract in in the last 4 weeks
  - COPD or upper respiratory tract infection during run-in
    (subjects may be re-screened x 1 when stable after an acute event)
  - pulmonary disease other than COPD
  - any lung resection
  - unstable cardiac conditions
    (at the discretion of the investigator)
  - other unstable medical conditions
    (at the discretion of the investigator)

- participants who are medically unable to withhold their albuterol/salbutamol for the 4-hour period required prior to spirometry testing at each study visit
- participants who are unable to perform acceptable study test maneuvers
- women who are pregnant or lactating or are planning on becoming pregnant during the study
- a history of allergy or hypersensitivity to any corticosteroid, anticholinergic/muscarinic receptor antagonist, β_2-agonist, lactose/milk protein or magnesium stearate or a medical condition such as narrow-angle glaucoma, prostatic hypertrophy or bladder neck obstruction that, in the opinion of the Investigator, contraindicates study participation
- risk factors for pneumonia: immune suppression (e.g. advanced human immunodeficiency virus [HIV] with high viral load and low CD4 count, collagen vascular diseases on immunosuppressants) or other risk factors for pneumonia (e.g. neurological disorders affecting control of the upper airway, such as Parkinson's Disease, Myasthenia Gravis) that in the opinion of the investigator would increase risk of pneumonia
- participants at risk of non-compliance, unable to comply with the study procedures and the proposed treatment regimen, or have any infirmity, disability, or geographic location that would limit compliance for scheduled visits

Study Design and Methods Rationale

- The expected FEV1 response to a bronchodilator is uncertain as multiple factors influence this measure, including severity of disease, day to day variability, varying reversibility in COPD patients, the delivery of the drug to a patient and the effectiveness of the medication delivered. Thus, the measurement of an acute bronchodilator response after delivering a long acting bronchodilator may not identify whether a medication has been effectively delivered to a patient.
- However, if a long acting bronchodilator has not been effectively delivered to the lung, then subsequent delivery of a short acting bronchodilator should produce a significant additional bronchodilator response. On the other hand, if a long acting bronchodilator has been effectively delivered to the lung, then subsequent delivery of a short acting bronchodilator should not produce any further significant bronchodilation.
- Based on this rationale, comparison of the acute bronchodilator response to a short acting bronchodilator after receiving a long acting should identify whether drug delivery is ineffective in a selected patient population, irrespective of baseline FEV1 and of any partial response to the long acting bronchodilator. Comparison of the short acting bronchodilator measurement between patient groups with differing PIF thresholds should identify whether PIF has an impact of drug delivery of a long acting bronchodilator via a DPI.
- **Open label design comparing the acute bronchodilator response after delivery of a long acting bronchodilator via Ellipta DPI in patients with normal, suboptimal and minimal PIF.**

Number of subjects

- 30 stratified to recruit 10-15 subjects with a baseline PIF < 60 l/min at with an Incheck level 2 resistance

Ellipta Device Selection

- the Ellipta is the most commonly used DPI device in the United States
- the medium/low (level 2) resistance setting on the InCheck Dial device closely approximates the resistance found in the Ellipta device
- suggested peak inspiratory flows of 60 l/min for suboptimal and 30 l/min for minimal are most commonly based on using the medium/low (level 2) resistance setting on the InCheck Dial device
- manufacturer recommendations for Ellipta device usage describe the inspiratory effort required as a "breathe out fully, then take one long, steady, deep breath".

Trelegy Selection

- Trelegy is an effective COPD therapy shown to produce maximal bronchodilation in patients with COPD, both acutely (day 1) and chronically
- A low PIF likely has the greatest incidence in more severe COPD patients who require triple therapy
- Use of Trelegy as compared to a LABA/LAMA eliminates any concern over ICS withdrawal in patients with chronic ICS usage prior to study participation and ads minimal risk to those not taking an ICS prior to study participation
- All subjects will have their maintenance COPD medications discontinued and will be provided Trelegy Ellipta maintenance therapy throughout the study

Visit 1

Consent

Baseline Measurements

- Demographics
- History and Physical
- CAT
- Exacerbation history in the last year (# moderate and # severe)
- Pre Ventolin PIF measured with the Incheck Valve set to a low/mid level 2 resistance and measured after instructions to exhale fully followed by a sharp maximal inhalation (minimum of 3 efforts)
- Pre and 15-30 minutes Post Ventolin spirometry

Visit 2 (1-8 days post visit 1)

Pre Dose Measurements

- Review COPD medications and ensure effective washout
    - prn SAMA/SABA at least 6 hours
    - bid LAMA, LAMA/LABA or LABA/ICS at least 12 hours
    - qd LAMA, LAMA/LABA, LABA/ICS or LAMA/LABA/ICS at least 24 hours
- Adverse Event assessment

- PIFR measured with the In-check Dial resistance set at R2, low/mid (e.g. Ellipta)
    - Technique 1
        Standing, “exhaling fully” (after instructions, but without coaching to full exhalation), “deep full inhalation”
    - Technique 2
        Sitting, “exhaling fully” (after instructions, but without coaching to full exhalation), “deep full inhalation”
    - Technique 3
        Sitting, “exhaling fully” (after instructions, but without coaching to full exhalation), “sharp maximum inhalation”
    - Technique 4
        Sitting, “exhaling fully to RV” (with coaching to exhale completely before effort), “sharp maximum inhalation”
    - Minimum of 3 efforts performed at each setting, best effort recorded
- Inspiratory Capacity
- Spirometry with flow volume loops and inspiratory flows

Intervention 1 – Trelegy Ellipta 1 puff

Post Trelegy Ellipta Measurements
- IC – 115 minutes post dosing with Trelegy Ellipta
- Spirometry – 30, 60, 120 minutes post dosing with Trelegy Ellipta

Intervention 2 – Ventolin pMDI 2 puffs with spacer
(to be given after 120 minutes post Trelegy Ellipta spirometry is completed)

Post Ventolin pMDI Measurements
- IC – 55 minutes post dosing with Ventolin
- Spirometry – 30 and 60 minutes post dosing with Ventolin

Intervention 3 – Trelegy Ellipta QD x 2 weeks

Visit 3 (12-14 days post visit 2)

Pre Dose Measurements
- Review COPD medications and ensure adherence to Trelegy therapy
- Adverse Event assessment
- PIFR measured with the In-check Dial resistance set at R2, low/mid (e.g. Ellipta)
    - Technique 1
        Standing, “exhaling fully” (after instructions, but without coaching to full exhalation), “deep full inhalation”
    - Technique 2
        Sitting, “exhaling fully” (after instructions, but without coaching to full exhalation), “deep full inhalation”
    - Technique 3

Sitting, “exhaling fully” (after instructions, but without coaching to full exhalation), “sharp maximum inhalation”

- Technique 4
  Sitting, “exhaling fully to RV” (with coaching to exhale completely before effort), “sharp maximum inhalation”
- Minimum of 3 efforts performed at each setting, best effort recorded

- Inspiratory Capacity
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(to be given after 120 minutes post Trelegy Ellipta spirometry is completed)

Post Ventolin pMDI Measurement

- IC – 55 minutes post dosing with Ventolin
- Spirometry – 30 and 60 minutes post dosing with Ventolin

Study Endpoints

Primary

- Post BD response to Trelegy Ellipta at Visits 2 and 3 by PIF (normal, suboptimal, minimal)
- Post BD added response to Albuterol after Trelegy Ellipta at Visits 2 and 3 by PIF (normal, suboptimal, minimal)

Secondary

- Acceptability and Reproducibility of PIF Testing during various testing efforts
- Correlation of various methods of PIF Testing to
  - Acute (visit 2) IC and FEV1 response to Trelegy Ellipta
  - Added benefit of Ventolin to Trelegy Ellipta
  - Chronic (visit 3) IC and FEV1 response to Trelegy Ellipta
- Predictors of Trelegy Ellipta response

Safety Data Collection

- Any adverse event determined by the principal investigator/designee to a) put the subject at clinical risk or b) to make the subject unable to perform appropriate clinical testing during a visit
  - in the event that such an event occurs, a visit may be re-scheduled for up to 1 week later

- Any serious adverse event considered to be reasonably attributed to Trelegy Ellipta study medication/medical device by the principal investigator/designee, regardless of the investigator/external parties expectedness assessments.
- Any medical device (Ellipta) incidents or malfunction
- Pregnancy in any subject exposed to Trelegy Ellipta study medication/medical device
- All events will be reported in a non-statistical tabular format

Statistical Plan of Analysis

A change in FEV1 of less than 50 ml has been defined by many studies as a level of bronchodilation that defines non-inferiority between bronchodilators. However, a comparative study between Anoro and Spiriva determined that to achieve a 1 sided 2.5% significance level with a within subject standard deviation of 140 ml and a 90% power to detect 50 ml noninferiority would require a sample size of 220 patients to determine non-inferiority. Although within subject standard deviation for short-acting bronchodilator after long acting bronchodilator in COPD patients with an FEV1 <50% predicted likely has a smaller FEV1 standard deviation, the projected numbers to determine non-inferiority in this study are too large to be obtained by a single center.

We therefore propose this study as an observational and an exploratory study that will likely be underpowered for meaningful comparison. Noninferiority and subsequent superiority will be assed within the study to provide estimates for potential future evaluations. Our proposed numbers are in line with previously reported studies that have been used for current recommendations for suboptimal and minimal PIF measures. In spite of these statistical limitations, we believe this information will provide significant added information about PIF and the use of the Ellipta device.

Limitations

Statistical limitations as described above.

The challenge of finding subjects with a PIF of <60 l/min in outpatient COPD patients (estimated at <20% of severe/very severe COPD patients).

References

Altman P, Wehbe L, Dederichs J, et al. Comparison of peak inspiratory flow rate via the Breezhaler(R), Ellipta(R) and HandiHaler(R) dry powder inhalers in patients with moderate to very severe COPD: a randomized cross-over trial. *BMC Pulm Med.* 2018;18:100.

Bender BG. Editorial--How Important Are Inhaler Technique Errors? *Chronic Obstr Pulm Dis.* 2019;6:203.

Clark AR, Hollingworth AM. The relationship between powder inhaler resistance and peak inspiratory conditions in healthy volunteers--implications for in vitro testing. *J Aerosol Med.* 1993;6:99.

de Koning JP, van der Mark TW, Coenegracht PM, Tromp TF, Frijlink HW. Effect of an external resistance to airflow on the inspiratory flow curve. *Int J Pharm.* 2002;234:257.

Duarte AG, Tung L, Zhang W, Hsu ES, Kuo YF, Sharma G. Spirometry Measurement of Peak Inspiratory Flow Identifies Suboptimal Use of Dry Powder Inhalers in Ambulatory Patients with COPD. *Chronic Obstr Pulm Dis.* 2019;6:3.

Duarte-de-Araujo A, Teixeira P, Hespanhol V, Correia-de-Sousa J. COPD: misuse of inhaler devices in clinical practice. *Int J Chron Obstruct Pulmon Dis.* 2019;14:1209.

Feldman GJ, Sousa AR, Lispon DA, et al. Comparative Efficacy of Once-Daily Umeclidinium/Vilanterol and Tiotropium/Olodaterol Therapy in Symptomatic Chronic Obstructive Pulmonary Disease: A Randomized Study. Adv Ther. 2017;34:2518.

Ghosh S, Pleasants RA, Ohar JA, Donohue JF, Drummond MB. Prevalence and factors associated with suboptimal peak inspiratory flow rates in COPD. *Int J Chron Obstruct Pulmon Dis.* 2019;14:585.

Ghosh S, Ohar JA, Drummond MB. Peak Inspiratory Flow Rate in Chronic Obstructive Pulmonary Disease: Implications for Dry Powder Inhalers. *Journal of aerosol medicine and pulmonary drug delivery.* 2017;30:381.

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.

Kawamatawong T, Khiawwan S, 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.

Kocks JWH, Chrystyn H, van der Palen J, et al. Systematic review of association between critical errors in inhalation and health outcomes in asthma and COPD. *NPJ Prim Care Respir Med.* 2018;28:43.

Lewis A, Torvinen S, Dekhuijzen PN, et al. The economic burden of asthma and chronic obstructive pulmonary disease and the impact of poor inhalation technique with commonly prescribed dry powder inhalers in three European countries. *BMC Health Serv Res.* 2016;16:251.

Loh CH, Peters SP, Lovings TM, Ohar JA. Suboptimal Inspiratory Flow Rates Are Associated with Chronic Obstructive Pulmonary Disease and All-Cause Readmissions. *Ann Am Thorac Soc.* 2017;14:1305.

Mahler DA. Peak Inspiratory Flow Rate as a Criterion for Dry Powder Inhaler Use in Chronic Obstructive Pulmonary Disease. *Ann Am Thorac Soc.* 2017;14:1103.

Mahler DA. Peak Inspiratory Flow Rate: An Emerging Biomarker in Chronic Obstructive Pulmonary Disease. *Am J Respir Crit Care Med.* 2019;199:1577.

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 Deliv.* 2014;27:103.

Mahler DA, Waterman LA, Gifford AH. Prevalence and COPD phenotype for a suboptimal peak inspiratory flow rate against the simulated resistance of the Diskus(R) dry powder inhaler. *J Aerosol Med Pulm Drug Deliv.* 2013;26:174.

Malmberg LP, Rytila P, Happonen P, 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.

Molimard M, Raherison C, Lignot S, et al. Chronic obstructive pulmonary disease exacerbation and inhaler device handling: real-life assessment of 2935 patients. *Eur Respir J.* 2017;49:2.

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(R) Dry Powder Inhaler. *J Aerosol Med Pulm Drug Deliv.* 2015;28:486.

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, Mahler DA, Mayorga VM, Deering KL, Harshaw O, Ganapathy V. Prevalence of Low Peak Inspiratory Flow Rate at Discharge in Patients Hospitalized for COPD Exacerbation. *Chronic Obstr Pulm Dis.* 2017;4:217.

Usmani OS, Lavorini F, Marshall J, et al. Critical inhaler errors in asthma and COPD: a systematic review of impact on health outcomes. *Respiratory research.* 2018;19:10.

In-Check Dial. Available at http://alliancetechmedical.com/educationclinicals/. Accessed June 27, 2019.