Efficacy, tolerability and safety of a range of doses of an orally inhaled, particle engineered, drug-only, suspension of glycopyrronium bromide in male and female patients with moderate or severe Chronic Obstructive Pulmonary Disease (COPD)

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Rationale
Chronic Obstructive Pulmonary Disease (COPD): COPD is predicted to become the third leading cause of death by 2020, despite being both preventable and treatable.

No existing COPD medications have been conclusively shown to modify the long-term decline in lung function.

Pharmacologic therapy aims to control and prevent the symptoms and/or exacerbations, and to improve health status and exercise tolerance.

Glycopyrronium bromide (GB) is a good candidate for COPD treatment.

Competitive inhibitor of parasympathetic acetylcholine receptors, acting on smooth muscle that is responsive to acetylcholine, including that not innervated by cholinergic fibers, and exocrine glands.

Mode of action of GB in COPD:
- Reduction of bronchial smooth muscle constriction
- Control of excessive pharyngeal, tracheal and bronchial secretions.

Experience with inhaled GB to date:
- Single aerosolised doses (500 to 2000 µg) of the parenteral form of GB as a bronchodilator for treatment of patients with COPD
- Extensive investigation of orally inhaled formulations by a range of companies
- The dry powder formulation (Novartis Pharmaceuticals AG, Seebri® Breezhaler®, 44 µg delivered dose) is approved (in 2012).
- To date there have been no unexpected or concerning safety findings.

Why develop a pMDI formulation of GB?
- Particle engineered form of GB (PSX1002-GB pMDI), using focused ultrasound directed-crystallisation which allows:
  - Unprecedented control of the drug particle size and form
  - No jet mulling
  - No excipients other than the hydrofluoroalkane (HFA) propellant.

This formulation of GB has been engineered to provide effective airway delivery with a particle size designed to minimise non-pulmonary deposition.

Objectives and Endpoints
To determine the efficacy, tolerability and safety of a range of single doses of orally inhaled PSX1002-GB, administered via pMDI, in patients with COPD.

Primary Endpoint:
- Forced expiratory volume in first second (FEV1) time-adjusted AUC (0-24 hours), using an ANCOVA model (SAS® 9.2) with FEV1 AUC (0-24) as a dependent variable and treatment, period and subject as fixed effects; pre-dose FEV1 was used as a covariate.

Secondary Endpoints:
- FEV1 time-adjusted AUC (0-12 hours)
- FEV1 time-adjusted AUC (12-24 hours)
- Serial FEV1 time-points to 26 hours
- Forced vital capacity (FVC) time-adjusted AUC (0-24 hours)
- Pharmacokinetic (PK) profile of PSX1002 GB over 24 hours.

Safety Endpoints:
- Safety and tolerability of PSX1002 GB pMDI adverse events (AE), clinical examination, pulmonary flow measures, electrocardiogram, and clinical laboratory findings.

Methods
Study Design:
Randomised (not Latin Square), placebo-controlled, double-blind, five-way (seven study visits) crossover, single-dose design.

Key Inclusion Criteria:
- Adults (40-75 years old) with diagnosed moderate to severe COPD and FVC <65% from predicted; FVC > 50% from predicted with post-bronchodilator FEV1/FVC > 70%;
- History of tuberculosis, bronchiectasis or other non-specific pulmonary disease;
- Need for recent increase in treatment for COPD or systemic steroids;
- Inability to be trained and/or inability to demonstrate good inhaler technique;
- History of asthma; any other significant medical condition;
- Excessive bronchial secretions;
- First or second-degree relative with COPD;
- Former smoker with a smoking history of ≤10 pack years;
- Not pregnant, planning pregnancy or breastfeeding;
- No history of drug or alcohol abuse;
- Ability to perform acceptable spirometry according to the ATS/ERS guidelines; and
- Willing and able to provide written informed consent.

Key Exclusion Criteria:
- Current evidence or recent history of any clinically significant disease, or hospitalisation due to an exacerbation of airway disease;
- Need for recent increase in treatment for COPD or systemic steroids;
- Primary diagnosis of asthma;
- History of tuberculosis, bronchiectasis or other non-specific pulmonary disease;
- Inability to be trained and/or inability to demonstrate good inhaler technique with the Vitalograph AM.

Treatments Administered:
PSX1002 GB pMDI: inhalation suspension delivered using a pressurised metered dose inhaler. Single actuations from 2 inhalers were administered to deliver five doses (Placebo, 12.5, 25, 50 and 100µg).

Efficacy Measures:
Assessments were made for 26 hours post dose on five separate study days according to the study protocol (see Table 1).

Secondary Efficacy Analyses:
Analysis of FEV1 AUC (0-12 hours) and FEV1 AUC (12-24 hours) also confirmed a clinical response to PSX1002 GB is elicited following a single administration of PSX1002 GB at each of the active doses tested (12.5 µg, 25 µg, 50 µg and 100 µg).

In summary, data demonstrated the rapid onset and prolonged duration of action; the serial time plot demonstrates dose ordering and clear separation between active doses from 5 minutes and up to 20 hours following administration. All active doses are separated from placebo throughout the 26 hour observation period.

Safety Analyses:
- 52 treatment emergent adverse events (TEAEs) reported in 25 patients (67.6%);
- 45 AEs were mild and 9 AEs were moderate in intensity;
- 4 adverse drug reactions (ADR) were reported in eight patients (21.6%);
- One serious adverse event (atypical flutter, not related to PSX1002-GB);
- No serious or life-threatening AEs and no AE led to study discontinuation;
- No difference between the number of ADRs reported across all treatment groups (all active doses and placebo).

Table 2: Summary of FEV1 time adjusted AUC (0-24h) and difference between doses and placebo

Table 3: Summary of FEV1 time adjusted AUC (0-12) and difference between doses and placebo

Table 4: Summary of FEV1 time adjusted AUC (12-24h) and difference between doses and placebo

Table 5: Summary of FVC endpoints

Table 6: Summary of FEV1 time adjusted AUC (24-72h) and difference between doses and placebo

Conclusions
FEV1 AUC analyses support the efficacy of all active doses of PSX1002-GB compared to placebo (p<0.001), with clear dose ordering. Furthermore, data support a rapid onset and prolonged duration of action; the serial time plot demonstrates dose ordering and clear separation between active doses from 5 minutes and up to 20 hours following administration. All active doses are separated from placebo throughout the 26 hour observation period.

Overall these data demonstrate the safety, tolerability and efficacy of a range of single doses of PSX1002, and support further clinical development as a once-daily suspension formulation of glycopyrronium bromide administered via pMDI. As a proof of principle study, the results also support development of other mono and combination suspension formulations for pMDI products using this novel technology.

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