The FLAGSHIP Study: A 12-week Phase II Study to Evaluate the Efficacy and Safety of AQX-1125 Following Exacerbations in Patients with Chronic Obstructive Pulmonary Disease (COPD) by Targeting the SHIP1 Pathway


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ABSTRACT

Study Design: Randomised, double-blind, placebo-controlled, parallel group, study of unstable COPD. Approximately 400 subjects with a recent exacerbation in two subsets: (1) at least 100 presenting for outpatient treatment and (2) at least 100 hospitalised for not more than 7 days and discharged within the last 3 days.

Rationale: Based on human and animal studies, AQX-1125, by activating SHIP1 and reducing the activation of several PI3K-mediated kinases, alters the migration and activation of various inflammatory cells, including neutrophils, mast cells and lymphocytes.

Oral AQX-1125 daily has been well tolerated for up to 10 consecutive days in normal healthy volunteers (NHV) and 7 consecutive days in NHV’s challenged with inhaled lipopolysaccharide. Generally mild AEs were observed, similar to placebo.

Objective: Effect of oral AQX-1125 over 12 weeks on recurrent exacerbations as measured by EXACT (EXAmination of Chronic pulmonary disease Trial) in subjects with COPD following a recent exacerbation.

Secondary objectives are to evaluate effects on: COPD Assessment Tool (CAT) score; Pulmonary function (including FEV1); Safety by AEs, physical examination, vital signs, serology, examination, laboratory tests, weight, ECG, and concomitant medications; Plasma PK.

Selected Inclusion Criteria: Male or female aged ≥40 years; COPD for at least 18 months; Chronic productive cough for at least 3 months each of the 2 years prior to screening; At least 2 documented exacerbations in previous 18 months; Post-bronchodilator FEV1/FVC ratio of >0.70 and predicted FEV1, 30%-80% of normal; Former smoker or current smoker (at least 10 pack years); Contraception if sexually active.

Selected Exclusion Criteria: Other lung disease; Treatment with inhaled or systemic glucocorticosteroids within 1 month; Lobar pneumonia within last 3 months; Hospitalisation for >7 days for current acute exacerbation, or for other conditions; Previous exacerbations required >3 weeks to stabilise.

Timeline: Results 1Q 2015

Conclusion: A potentially disease-modifying drug for unstable COPD is urgently needed. This study examines one such novel recent exacerbation in two subsets: (1) at least 100 presenting for frequent exacerbator, using a recently developed patient reported outpatient treatment and (2) at least 100 hospitalised for not more than 7 days ready to be discharged, or discharged within the last 3 days.

The Phase 1 program consisted of a 3-part trial in healthy human volunteers: a Single Ascending Dose part where 6 groups received up to 542 mg; a Multiple Ascending Dose part where 3 groups received up to 542 mg once daily for 10 days; and a Food Effect part where 12 subjects received 200 mg AQX-1125 after a fast or a high fat meal.

The Phase 2 program consisted of two different aerosol challenges. Both were Proof of Concept, placebo controlled, crossover trials, with subjects dosed for 7 days, challenged and, after a washout, dosed with the alternative regimen. Data was compared within subjects for the two challenge studies. The challenges were: LPS (to healthy volunteers) as a COPD PoC looking at sputum neutrophil count, and aerosolised to mild asthmatics as an asthma PoC (looking at reduction in the Late Asthma Response). Both trials met their primary endpoints (Presented at ATS 2013), suggesting AQX-1125 has broad anti-inflammatory affects across various cell types and in different airway disease challenge models.

The FLAGSHIP trial is the first, large trial in unstable COPD patients (recent exacerbations of COPD) using AQX-1125, and benefiting from the recent validation that SHIP1 is a potent and current a newly discovered target for assessing the onset, duration and severity of acute exacerbations of COPD.

INTRODUCTION

SHIP1 Activation

AQX-1125 is a small molecule, SHIP1 activator with the biological effects of the earlier generation SHIP1 activators1-2, but an improved drug scaffold and superior drug-like properties. This small molecule activates SHIP1 through an interaction with the C2 domain, and is anti-inflammatory in cellular and murine models. By redirecting degradation of PIP3 to PI-3,4-P2, SHIP1 activators alter the ratio between these two lipids. SHIP1 activators redirect PI3K signalling, PI-3,4-P2 and superior drug-like properties. This small molecule activates SHIP1 through an interaction with the C2 domain, and is anti-inflammatory in cellular and murine models. By redirecting degradation of PIP3 to PI-3,4-P2, SHIP1 activators alter the ratio between these two lipids. SHIP1 activators redirect PI3K signalling, PI-3,4-P2 and PI-4,5-P2.

The purpose of this study is to evaluate the efficacy and safety of orally administered AQX-1125 in subjects with COPD over 12 weeks of treatment compared to placebo using:

Primary Objective: Recurrent exacerbations as measured by EXACT (EXAmination of Chronic pulmonary disease Trial) in subjects following an AECOPD (recorded daily using an electronic diary)

Secondary Objectives: The COPD Assessment Tool (CAT) score; Pulmonary function (FEV1, FVC, FEV1/FVC % and predicted); AEs, physical examination, vital signs, serology, examination, laboratory tests, weight, ECG, and concomitant medications; Plasma PK of AQX-1125 in plasma in COPD patients

Figure 2. SHIP1 and PI3K signalling. SHIP1 activators redirect PI3K signalling, PI-3,4-P2 and PI-4,5-P2.

Figure 3. The FLAGSHIP Study design.