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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Session: B39
Poster: A2889
Board: A30

Abstract

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 PIP3-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 NHVs 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 (EXAcerbation of Chronic pulmonary disease Tool) in subjects with COPD following a recent exacerbation.

Secondary objectives are to evaluate effects on: COPD Assessment Tool (CAT) score; Pulmonary function (including FEV_1); Safety by AEs, physical examination, vital signs, ophthalmic 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 in each of the 2 years prior to screening; At least 2 documented exacerbations in previous 18 months; Post-bronchodilator FEV_1/ FVC ratio of <0.70 and predicted FEV_1 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 roflumilast or theophylline within 1 month; Lobar pneumonia within last 3 months; Hospitalisation for >7 days for current acute exacerbation, or intubation; 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 candidate in a new paradigm of COPD study – the unstable, frequent exacerbator, using a recently developed patient reported outcome.

Study Design

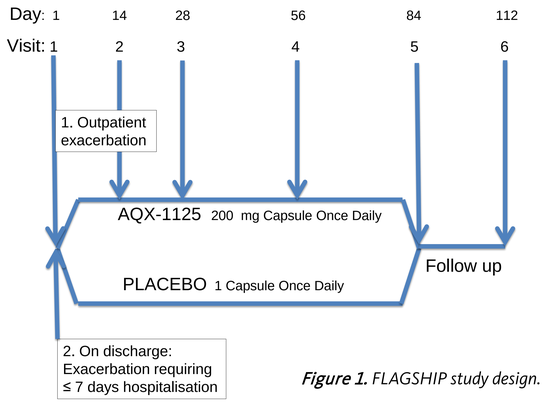

Figure 1. FLAGSHIP study design.

INTRODUCTION

SHIP1 Activation

AQX-1125 is a small molecule, SHIP1 activator with the biological effects of the earlier generation SHIP1 activators[1,2], 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 molecules and induce an anti-inflammatory phenotype, without causing the immunosuppression seen with PI3 kinase inhibition.

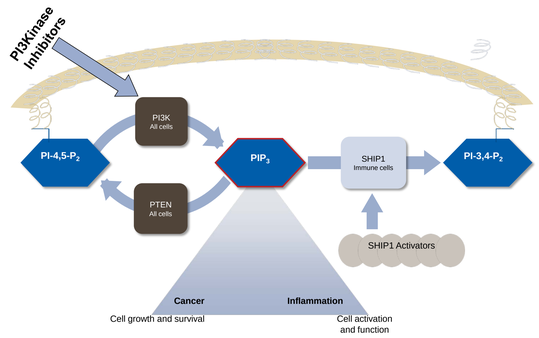

Figure 2. SHIP1 and PI3K signalling. SHIP1 activators redirect PI3K signalling, PI3K inhibitors block PI3K signalling.

AQX-1125 Clinical Development Program

In previous trials, more than 100 subjects have been dosed with AQX-1125, demonstrating good tolerability (up to 542 mg with no dose limiting toxicity), highly desirable PK properties, and two positive Proof-of-Concept inhaled challenge trials (of LPS and allergen), suggesting the prospect of an effective once daily oral drug for inflammatory pulmonary disease.

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. Safety and PK was monitored in all 3 parts (Presented: ATS 2012) [2].

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[4] looking at sputum neutrophil count), and aeroallergen to mild asthmatics as an asthma PoC[5] (looking at reduction in the Late Asthmatic Response). Both trials met their primary endpoints (Presented at ATS 2013), suggesting AQX-1125 has broad anti-inflammatory effects 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 of the EXACT-PRO, a specifically developed PRO for assessing the onset, duration and severity of acute exacerbations of COPD.

COPD and Acute Exacerbations of COPD

COPD and AECOPD

COPD is a leading cause of global morbidity and mortality. In 2001 it was #5 leading cause of death in high-income countries, (3.8% of total deaths), and #6 in nations of low and middle income, (4.9% of total deaths)[6].

As the global population ages, but smoking remains prevalent, COPD is predicted to become more frequent, accounting for huge healthcare spending for patients when stable and during exacerbations.

USA, in 2003, the estimated total costs (direct and indirect) of COPD were US$32.1 billion, with direct costs of US$18.0 billion[6].

Acute exacerbations of COPD (AECOPD) are usually treated with oral steroids and/or antibiotics but with significant side effects including osteoporosis, cataracts and immunosuppression (steroids) and increasing bacterial resistance and other side effects (antibiotics). During an AECOPD, the inflammation in the airways increases.

Hypothesis: A once-daily, oral, well tolerated, disease-modifying drug that reduced exacerbation severity, frequency and duration and improved the underlying inflammatory process would be useful to healthcare providers. The FLAGSHIP trial aims to assess whether AQX-1125 could be such a drug.

Objectives

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

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

Secondary Objectives:
- The COPD Assessment Tool (CAT) score
- Pulmonary function (FEV_1, FVC, FEV_1/FVC and % predicted)
- AEs, physical exams, vitals, ophthalmic examination, lab tests, weight, ECG and concomitant medications
- PK of AQX-1125 in plasma in COPD patients

Study design

This Phase 2, multi-centre, randomised, parallel group, double-blind, placebo-controlled, 12-week treatment trial of ~400 patients suffering from a recent exacerbation of COPD (Figure 1).

Two subsets will be recruited: (1) those AECOPD suitable for treatment on an outpatient basis, and (2) those hospitalised for not more than 7 days ready to be discharged, or discharged within the last 3 days.

The trial will consist of 6 visits; a baseline visit at Day 1, visits at Day 14, Day 28, Day 56, day 84 and a follow up visit at Day 112.

The trial is currently enrolling in ~ 40 centres in Sweden, Denmark, Finland, Hungary and Poland with ~ 15 sites being added in Australia and New Zealand.

Top line data expected: 1Q 2015.

ClinicalTrials.gov Registration Number: NCT01954628

Major inclusion and exclusion criteria

See abstract.

EXACT PRO

EXACT PRO

Developed by Evidera (previously United Biosource Corp.)
- Designed to standardize the evaluation of the frequency, severity, and duration of AECOPD
- Patient reported outcome (PRO) of 14 daily questions utilizing eDiaries (taking ~ 2 minutes to complete)
- Developed with considerable regulatory consultation (FDA and EMA)
- FDA guidance published January 2014

EXACT development funded by pharma consortium:
- AZ
- Almirall
- Bayer
- BI
- Forest
- GSK
- Novartis
- Ortho-McNeil
- Pfizer
- Sepracor

Figure 3. Example of a hand held device (e.g. a Smartphone) which can provide EXACT questions to enrolled subjects one screen/question at a time.

Summary

Acute exacerbations of COPD remain a major global unmet healthcare need

A once-daily, oral, well tolerated treatment for COPD that modifies the disease, reduces airway inflammation and corresponding exacerbations has been elusive

AQX-1125 may be that drug: The FLAGSHIP trial has been designed to answer that question

References

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For additional information

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