2. SYNOPSIS

Name of Sponsor: Aquinox Pharmaceuticals Inc. Name of finished product: AQX-1125 Name of active ingredient: AQX-1125 free base	Individual Study Table Referring to Part of the Dossier Volume: Page:	*(For National Authority Use only)*
Title of study:	A phase IIa, single-centre, randomised, double-blind, placebo-controlled, two-way, cross-over allergen challenge study to evaluate the effect of treatment with once daily AQX-1125 on the late asthmatic response (LAR) to inhaled allergen challenge (IAC) in subjects with mild to moderate atopic asthma	
Investigator:	Dr Brian Leaker	
Study centre:	Heart Lung Centre, 20 Queen Anne Street, London, WIG 8HU, UK	
Publication (reference):	None at the time of this report	
Study period (dates):	07 November 2011 to 13 April 2012	
Phase of development:	IIa	
Objectives:	The primary objective was to evaluate the effect of treatment with once daily AQX-1125 on the LAR to IAC in subjects with mild to moderate atopic asthma. Secondary objectives included evaluation of effect of treatment with AQX-1125 on the early asthmatic response (EAR), total asthmatic response (TAR), forced expiratory volume in 1 second (FEV_1), exhaled nitric oxide (eNO), bronchial hyper-reactivity measured using methacholine challenge, sputum inflammatory markers, pharmacokinetic (PK) parameters and safety and tolerability.	
Methodology:	This study was a two-way cross-over design in which AQX-1125 450 mg free base was compared to placebo to evaluate the effect on asthmatic responses in subjects with mild to moderate atopic asthma. A total of 22 subjects with asthma with a dual (early and late) asthmatic response to inhaled house dust mite, cat or grass pollen allergen were randomised to one of two treatment sequences (placebo then AQX-1125 or AQX-1125 then placebo) in a double-blind fashion. In each treatment period they received either oral AQX-1125 or matching placebo once-daily, for 7 days. The wash-out period was 14 to 21 days between the two treatment periods.	
Number of subjects (planned and analysed):	A total of 22 subjects were to be enrolled (in order to achieve 21evaluable subjects). Drop outs were not replaced. All 22 subjects who were screened were subsequently randomised and received study medication (10 subjects to AQX-1125 followed by placebo, and 12 to placebo followed by AQX-1125). All but 1 subject completed the study: Subject 11 was withdrawn at the end of Treatment Period 1 (AQX-1125 treatment) following a positive drugs screen on Day 1.	
Diagnosis and main criteria for inclusion:	Eligible subjects comprised otherwise healthy male or female adult steroid naïve subjects with a documented history of mild to moderate atopic bronchial asthma who had a demonstrable EAR and LAR and a provocative concentration of methacholine resulting in a 20% reduction in FEV_1 (PC_{20}) ≤16 mg/mL at screening.	
Test products, dose and mode of administration, batch number:	AQX-1125 was administered orally once per day for 7 days (3 capsules per day). Batch numbers: [redacted] and [redacted]	
Duration of treatment:	Two screening visits were conducted (either consecutively or a maximum of 1 day apart) 14 to 28 days prior to the first treatment period. Two treatment periods (each of 7 days) were completed, with a 14 to 21 day wash-out period between the treatment periods. A Follow-up Visit then took place 14 ±3 days later. The total study duration was between 59 and 90 days for each subject.	
Reference therapy, dose and mode of administration, batch number:	Matching placebo, [redacted], was packaged identically to the study drug and administered in an identical manner. Batch numbers: [redacted] and [redacted].	

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Criteria for evaluation:

Efficacy:

Primary Efficacy Parameter:

- LAR: baseline-corrected area under the curve (AUC) of FEV_1 from 4 to 10 hours ($AUC_{4\text{-}10h}$) after allergen challenge on Day 6 of each treatment period.

Secondary Efficacy Parameters:

- Induced sputum cell count on Day 7 of each treatment period.
- EAR: Minimum FEV_1 and baseline-corrected AUC of FEV_1 between 0-4 hours ($AUC_{0\text{-}4h}$) after allergen challenge on Day 6 of each treatment period.
- LAR: Minimum FEV_1 between 4-10 hours after allergen challenge on Day 6 of each treatment period.
- TAR: Minimum FEV_1 between 0-10 hours and baseline-corrected AUC of FEV_1 between 0-10 hours ($AUC_{0\text{-}10h}$) after allergen challenge on Day 6 of each treatment period.
- FEV_1 at each timepoint.
- Methacholine PC_{20} on Day 7 of each treatment period.
- Maximum eNO and baseline-corrected AUC of eNO on Days 6 and 7 ($AUC_{0\text{-}24h}$) of each treatment period.
- Induced sputum inflammatory mediators including but not limited to IL-4, IL-5, IL-13 and TNF-α on Day 7 of each treatment period.
- PK parameters of AQX-1125 (following a non-compartmental analysis).

Safety:

Safety assessments included monitoring adverse events (AEs), concomitant medications, vital signs, 12-lead electrocardiograms (ECGs), physical examination, clinical laboratory measurements and ophthalmological examination (including slit lamp).

Statistical methods:

Efficacy: Descriptive summaries were presented using summary statistics [e.g. number (n), mean, geometric mean, standard deviations (SD), coefficient of variance as a percentage (%CV), median, minimum, maximum] and 95% confidence intervals (CI) for continuous parameters or frequency distributions (n, %) for categorical parameters. Comparison between treatments was carried out using an analysis of variance/covariance for a cross-over design with subject (sequence and subject within sequence), period and treatment as factors of the model and baseline value as a covariate, if applicable. The least square adjusted treatment means, the pair-wise treatment effect along with the 95% CIs and the probability were shown. Where appropriate, the data were analysed following a log transformation using base 2, and all results from the analysis were presented after they had been back-transformed.

Safety: The incidence of AEs was summarised by system organ class (SOC), preferred term (PT) and maximum severity or strongest relationship to study treatment for each treatment. Serious Adverse Events (SAEs) and AEs leading to early withdrawal from the study were also listed. Clinical safety laboratory tests data were listed by subject and visit, with values falling outside the normal range flagged. Shifts from abnormally low/normal/abnormally high at baseline to the end of the study were shown. Data on vital signs, ECG and ophthalmological procedures were summarised.

SUMMARY OF RESULTS

EFFICACY RESULTS:

Results quoted are for the Evaluable Population; results from the modified intention to treat (mITT) Population were similar and only differed by 1 subject. The results of the primary analysis of the LAR showed a significant treatment effect (using adjusted means), with subjects receiving AQX-1125 having a lesser decrease in FEV_1 after the IAC compared to when they were receiving placebo (p=0.0268) (Figure 1). A secondary, confirmatory, analysis was performed using the observed data, with the treatment effect just missing statistical significance in this analysis (p=0.0744).

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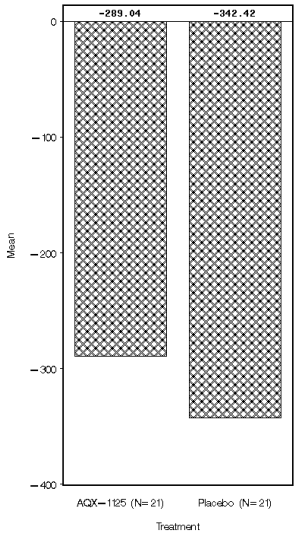
Figure 1: Allergen Challenge on Day 6 – LAR Response (AUC_{4-10h}) (min•L): Mean Per Treatment (Evaluable Population)



Minimum FEV_1 also showed a significant treatment effect for LAR (p=0.0137). Trends in sputum cell counts favoured AQX-1125, however, due to the relatively low numbers of subjects who had evaluable data and the high level of variability, significance was not achieved. The results of the analyses of other secondary efficacy endpoints (sputum cytokines, EAR, TAR, methacholine PC_{20}, and eNO) showed no significant treatment effect for any of the analyses.

The time to maximum plasma concentration at steady state ($C_{max,ss}$) indicated that AQX-1125 was rapidly absorbed. The median time to the maximum plasma concentration at steady state ($T_{max,ss}$) was 1.50 hours and ranged from 1.00 to 4.00 hours. The mean $C_{max,ss}$ and $AUC_{0-24\,h,ss}$ values were 1507.64 ng/mL and 17228.307 hr.ng/mL and the inter-subject variability in exposure parameters was within or close to expected physiological variability. The %CV based on mean values for $C_{max,ss}$, $AUC_{0-24h,ss}$ and the minimum plasma concentration at steady state ($C_{min,ss}$) was 38.62%, 25.73% and 37.73% respectively.

SAFETY RESULTS:

AEs were reported by 16 subjects overall (72.7%): 7 on AQX-1125 only, 1 on placebo only, and 8 on both. The most common AE was headache, which was reported by 4 subjects (18.2%) in the AQX-1125 treatment period and 3 subjects (14.3%) in the placebo treatment period. More subjects during the AQX-1125 treatment period reported gastrointestinal AEs compared to during the placebo treatment period (3 subjects reported dyspepsia and 1 reported 6 events of nausea and upper abdominal pain versus 0 subjects during placebo treatment). Wheezing was also reported by 3 subjects during AQX-1125 treatment compared to 0 subjects during placebo treatment. The majority of AEs were considered mild, with no severe AEs being reported. Seven subjects (31.8%) reported AEs that were considered related to treatment: 5 (22.7%) in the AQX-1125 treatment period and 2 (9.5%) in the placebo treatment period. The most common drug-related AEs were headache (reported by 1 subject in each treatment period) and dyspepsia (reported by 2 subjects in the AQX-1125 treatment period). There were no deaths, SAEs or withdrawals due to AEs. There were also no clinically meaningful changes in laboratory results, vital signs or ophthalmic tests.

CONCLUSIONS:

- The primary objective of the study was met, with significant improvements in the LAR (FEV_1 AUC_{4-10h} and minimum FEV_1) following treatment with AQX-1125 (versus placebo) in subjects with mild to moderate atopic asthma.
- Even though the treatment ratio for eosinophils, neutrophils and macrophages all favoured AQX-1125 treatment, none reached statistical significance. Greater subject numbers are required to adequately assess the effect on sputum leukocytes.
- AQX-1125 was rapidly absorbed after once daily oral administration. Inter-subject AQX-1125 plasma exposure based on $AUC_{0-24h,ss}$, $C_{max,ss}$ and $C_{min,ss}$ was within or close to expected physiological variability.
- AQX-1125 was well tolerated in this population of subjects with mild to moderate asthma in terms of

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AEs, laboratory data, vital signs data and ophthalmic examinations.

- The results of this study support further clinical development of AQX-1125 in asthma and potentially in other inflammatory lung conditions.

Date of report: 17 September 2012