Clinical trial results:
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

Summary

EudraCT number	2013-001951-11
Trial protocol	SE FI HU DK PL
Global end of trial date	13 November 2015

Results information

Result version number	v1 (current)
This version publication date	08 December 2018
First version publication date	08 December 2018

Trial information

Trial identification

Sponsor protocol code	AQX-1125-202

Additional study identifiers

ISRCTN number	-
ClinicalTrials.gov id (NCT number)	NCT01954628
WHO universal trial number (UTN)	-

Notes:

Sponsors

Sponsor organisation name	Aquinox Pharmaceuticals (Canada) Inc.
Sponsor organisation address	450 - 887 Great Northern Way, Vancouver, Canada, V5T 4T5
Public contact	Clinical Operations, Aquinox Pharmaceuticals (Canada) Inc., +001 604 629 9223, clinical@aqxpharma.com
Scientific contact	Clinical Operations, Aquinox Pharmaceuticals (Canada) Inc., +001 604 629 9223, clinical@aqxpharma.com

Notes:

Paediatric regulatory details

Is trial part of an agreed paediatric investigation plan (PIP)	No
Does article 45 of REGULATION (EC) No 1901/2006 apply to this trial?	No
Does article 46 of REGULATION (EC) No 1901/2006 apply to this trial?	No

Notes:

Results analysis stage

Analysis stage	Final
Date of interim/final analysis	13 November 2015
Is this the analysis of the primary completion data?	No

Global end of trial reached?	Yes
Global end of trial date	13 November 2015
Was the trial ended prematurely?	No

Notes:

General information about the trial

Main objective of the trial:

The primary objective is to evaluate the treatment effect of once daily administrations of AQX-1125 compared to placebo over 12 weeks on recurrent exacerbations as measured by EXACT (EXAcerbation of Chronic pulmonary disease Tool) in subjects with COPD following a recent exacerbation.

Protection of trial subjects:

The study was conducted in accordance with the ethical principles of the "Declaration of Helsinki" and International Conference on Harmonization guideline on Good Clinical Practice (GCP). This clinical trial was reviewed and approved by the appropriate Regulatory Health Agency and Ethics Committee. Before entering the study, the informed consent form was read by and explained to all subjects. Participating subjects were required to sign the informed consent form.

Background therapy: -

Evidence for comparator: -

Actual start date of recruitment	06 November 2013
Long term follow-up planned	Yes
Long term follow-up rationale	Safety
Long term follow-up duration	6 Months
Independent data monitoring committee (IDMC) involvement?	No

Notes:

Population of trial subjects

Subjects enrolled per country

Country: Number of subjects enrolled	New Zealand: 6
Country: Number of subjects enrolled	United States: 104
Country: Number of subjects enrolled	Poland: 156
Country: Number of subjects enrolled	Sweden: 1
Country: Number of subjects enrolled	Denmark: 26
Country: Number of subjects enrolled	Finland: 8
Country: Number of subjects enrolled	Hungary: 83
Country: Number of subjects enrolled	Australia: 16
Worldwide total number of subjects	400
EEA total number of subjects	274

Notes:

Subjects enrolled per age group	
In utero	0
Preterm newborn - gestational age < 37 wk	0
Newborns (0-27 days)	0
Infants and toddlers (28 days-23 months)	0
Children (2-11 years)	0
Adolescents (12-17 years)	0
Adults (18-64 years)	186
From 65 to 84 years	211
85 years and over	3

Subject disposition

Recruitment

Recruitment details:

The study was conducted in 8 countries: Australia, Denmark, Finland, Hungary, New Zealand, Poland, Sweden and US. US subjects participating in 6 month safety follow-up continued in the study until November 2015.

Pre-assignment

Screening details:

Four hundred subjects were randomized into two subsets: (1) Subjects suitable for outpatient treatment of a current exacerbation of COPD (within 3 days of diagnosis) & (2) Subjects who had been hospitalized in order to treat their exacerbation for not more than 7 days & were ready to be discharged or had been discharged within the last 3 days.

Period 1

Period 1 title	Overall Trial (overall period)
Is this the baseline period?	Yes
Allocation method	Randomised - controlled
Blinding used	Double blind
Roles blinded	Subject, Investigator, Carer, Assessor

Arms

Are arms mutually exclusive?	Yes
Arm title	AQX-1125

Arm description:

AQX-1125 (200 mg capsule), oral once daily for 12 weeks.

Arm type	Experimental
Investigational medicinal product name	AQX-1125
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Capsule, hard
Routes of administration	Oral use

Dosage and administration details:

AQX-1125 (200 mg capsule), oral once daily for 12 weeks.

Arm title	Placebo

Arm description:

Placebo (matching AQX-1125 capsule), oral, once daily for 12 weeks.

Arm type	Placebo
Investigational medicinal product name	Placebo
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Capsule, hard
Routes of administration	Oral use

Dosage and administration details:

Placebo (matching AQX-1125 capsule), oral, once daily for 12 weeks.

Number of subjects in period 1	AQX-1125	Placebo
Started	200	200
Completed	169	173
Not completed	31	27
Consent withdrawn by subject	14	13
Physician decision	4	1
Non-Compliance	1	-
Adverse event, non-fatal	6	7
Death	1	1
COPD Exacerbation	1	1
Sponsor Decision	-	1
Lost to follow-up	1	1
Protocol deviation	3	2

Baseline characteristics

Reporting groups	
Reporting group title	AQX-1125
Reporting group description:	
AQX-1125 (200 mg capsule), oral once daily for 12 weeks.	
Reporting group title	Placebo
Reporting group description:	
Placebo (matching AQX-1125 capsule), oral, once daily for 12 weeks.	

Reporting group values	AQX-1125	Placebo	Total
Number of subjects	200	200	400
Age categorical Units: Subjects			
In utero	0	0	0
Preterm newborn infants (gestational age < 37 wks)	0	0	0
Newborns (0-27 days)	0	0	0
Infants and toddlers (28 days-23 months)	0	0	0
Children (2-11 years)	0	0	0
Adolescents (12-17 years)	0	0	0
Adults (18-64 years)	86	100	186
From 65-84 years	113	98	211
85 years and over	1	2	3
Age continuous Units: years			
arithmetic mean	65.8	64.4	
standard deviation	± 8.2	± 8.5	-
Gender categorical Units: Subjects			
Female	99	91	190
Male	101	109	210
Ethnicity (NIH/OMB) Units: Subjects			
Hispanic or Latino	4	3	7
Not Hispanic or Latino	193	193	386
Unknown or Not Reported	3	4	7
Race (NIH/OMB) Units: Subjects			
American Indian or Alaska Native	0	0	0
Asian	0	0	0
Native Hawaiian or Other Pacific Islander	0	0	0
Black or African American	11	9	20
White	188	189	377
More than one race	1	2	3
Unknown or Not Reported	0	0	0
Region of Enrollment Units: Subjects			

New Zealand	3	3	6
Sweden	0	1	1
Hungary	40	43	83
United States	51	53	104
Finland	5	3	8
Denmark	13	13	26
Poland	81	75	156
Australia	7	9	16
Smoking Status Units: Subjects			
Current Smoker	69	103	172
Former Smoker	131	97	228
Nicotine Replacement Therapy Use Units: Subjects			
Yes	196	195	391
No	4	5	9
Body Mass Index Units: Kg/m2			
arithmetic mean	28.1	27.2	
standard deviation	± 6.6	± 6.1	-
Number of COPD Exacerbations in Last 18 months Units: Number of exacerbations/18 months			
arithmetic mean	3.1	3.0	
standard deviation	± 1.7	± 1.4	-
Number of Previous Hospitalizations for COPD Units: Number of previous hospitlizations			
arithmetic mean	1.1	0.9	
standard deviation	± 3.0	± 1.6	-
Years Since COPD Diagnosis Units: Years			
arithmetic mean	8.2	7.8	
standard deviation	± 5.7	± 5.9	-
Smoking Pack Years Units: pYears			
arithmetic mean	40.2	41.2	
standard deviation	± 22.0	± 20.9	-
Post-bronchodilator FEV1/FVC Ratio Units: Ratio			
arithmetic mean	0.51	0.52	
standard deviation	± 0.11	± 0.11	-
Post-bronchodilator FEV1% of Predicted Units: % Predicted			
arithmetic mean	50.2	50.9	
standard deviation	± 13.9	± 13.2	-

End points

End points reporting groups	
Reporting group title	AQX-1125
Reporting group description:	
AQX-1125 (200 mg capsule), oral once daily for 12 weeks.	
Reporting group title	Placebo
Reporting group description:	
Placebo (matching AQX-1125 capsule), oral, once daily for 12 weeks.	

Primary: Area Above Curve (AAC) on Daily Exact Score	
End point title	Area Above Curve (AAC) on Daily Exact Score
End point description:	
The primary variable (endpoint) of this study is the difference in the Area Above the Curve (AAC) for the daily EXACT score from baseline to Week 12 between subjects treated with AQX-1125 and placebo.The EXACT questionnaire is a patient reported outcome (PRO) measure designed to standardise the method for evaluating the frequency, severity and duration of acute exacerbations of COPD. The EXACT is a 14-item daily questionnaire where each item is assessed on a 5 or 6 point ordinal scale. Participants completed the EXACT questionnaire on a daily basis via an electronic diary from Day 1 (pre-dose) to Day 84 (week 12). Higher scores on the daily EXACT questionnaire indicate a more severe health state. When the post-treatment EXACT scores are lower (i.e. improved symptoms) than baseline EXACT, the AACs are positive.	
End point type	Primary
End point timeframe:	
During the 12-week Treatment Period	

End point values	AQX-1125	Placebo		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	179	183		
Units: AAC on Daily Exact Score				
least squares mean (confidence interval 95%)	415.4 (290.7 to 540.1)	391.7 (268.2 to 515.1)		

Statistical analyses

Statistical analysis title	AAC for Daily EXACT Scores During the 12-week TP
Comparison groups	AQX-1125 v Placebo
Number of subjects included in analysis	362
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.759
Method	ANOVA
Parameter estimate	Mean difference (final values)
Point estimate	23.7

Confidence interval	
level	95 %
sides	2-sided
lower limit	-128.3
upper limit	175.7

Secondary: Change From Baseline in COPD Assessment Tool (CAT) Score

End point title	Change From Baseline in COPD Assessment Tool (CAT) Score

End point description:

The secondary objective is to evaluate the treatment effect of once daily administrations of AQX-1125 compared to placebo over 12 weeks on the COPD Assessment Tool (CAT) score.The CAT questionnaire measures the impact of COPD on wellbeing and daily life. Participants answer 8 questions on a scale from 0 (best) to 5 (worst). The total score ranges from 0 to 40 with higher scores indicating more impact. A negative change from baseline indicates improvement. The change in total CAT score from Day 1, before taking study drug (baseline), to end of the 12 week treatment period was compared between the two treatments using an ANOVA model adjusting for treatment and region and including the baseline score as a covariate.

End point type	Secondary

End point timeframe:

12 weeks

End point values	AQX-1125	Placebo		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	179	182		
Units: COPD Assessment Tool Score				
least squares mean (confidence interval 95%)	-4.05 (-5.06 to -3.04)	-3.71 (-4.71 to -2.71)		

Statistical analyses

Statistical analysis title	Change From Baseline in COPD Assessment Tool (CAT)
Comparison groups	Placebo v AQX-1125
Number of subjects included in analysis	361
Analysis specification	Pre-specified
Analysis type	equivalence
P-value	= 0.588
Method	ANOVA
Parameter estimate	Mean difference (final values)
Point estimate	-0.34
Confidence interval	
level	95 %
sides	2-sided
lower limit	-1.57
upper limit	0.89

Secondary: Analysis of the Number of COPD Exacerbations (Medically Treated Event (MTE))

End point title	Analysis of the Number of COPD Exacerbations (Medically Treated Event (MTE))

End point description:

The secondary objective is to evaluate the treatment effect of once daily administrations of AQX-1125 compared to placebo over 12 weeks on the number of COPD exacerbations (MTE).

COPD exacerbations were referred to as Medically Treated Exacerbations (MTEs) and identified as a change in symptoms and/or signs of COPD requiring prescription of one or both of: (1) Course of oral corticosteroids or (2) Antibiotic(s).

End point type	Secondary

End point timeframe:

12 weeks

End point values	AQX-1125	Placebo		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	200	198		
Units: Number of exacerbations/year				
least squares mean (confidence interval 95%)	1.776 (1.374 to 2.297)	1.641 (1.261 to 2.135)		

Statistical analyses

Statistical analysis title	Number of COPD Exacerbations (MTE)
Comparison groups	AQX-1125 v Placebo
Number of subjects included in analysis	398
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.646
Method	Negative binomial regression model
Parameter estimate	Mean difference (final values)
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.771
upper limit	1.52

Secondary: Time to First COPD Exacerbation

End point title	Time to First COPD Exacerbation

End point description:

Evaluate the treatment effect of once daily administrations of AQX-1125 compared to placebo over 12

weeks on the time to first exacerbation requiring medical intervention of oral corticosteroids and/or antibiotics.

End point type	Secondary

End point timeframe:

12 weeks

End point values	AQX-1125	Placebo		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	200	198		
Units: Days				
arithmetic mean (standard deviation)	38.1 (± 21.3)	43.9 (± 24.1)		

Statistical analyses

No statistical analyses for this end point

Secondary: Number of Subjects With at Least One COPD Exacerbation

End point title	Number of Subjects With at Least One COPD Exacerbation

End point description:

Number of subjects that presented with a COPD exacerbation during the 12 week treatment period.

End point type	Secondary

End point timeframe:

12 weeks

End point values	AQX-1125	Placebo		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	200	198		
Units: Participants	48	51		

Statistical analyses

No statistical analyses for this end point

Secondary: Change From Baseline in FEV1

End point title	Change From Baseline in FEV1

End point description:

Evaluate the treatment effect of once daily administrations of AQX-1125 compared to placebo over 12 weeks on forced expiratory volume in 1 second [FEV1]. FEV1 was determined from post-bronchodilator spirometry testing done at clinic visits.

End point type	Secondary

End point timeframe:
12 weeks

End point values	AQX-1125	Placebo		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	184	185		
Units: litre(s)				
least squares mean (confidence interval 95%)	-0.02 (-0.06 to 0.02)	0.01 (-0.03 to 0.06)		

Statistical analyses

Statistical analysis title	Change From Baseline in FEV1
Comparison groups	AQX-1125 v Placebo
Number of subjects included in analysis	369
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.226
Method	ANOVA

Secondary: AQX-1125 Concentrations in Plasma (Trough Values)

End point title	AQX-1125 Concentrations in Plasma (Trough Values)

End point description:
Evaluate the pharmacokinetics (PK) of AQX-1125 in plasma.

End point type	Secondary

End point timeframe:
12 weeks

Statistical analyses

No statistical analyses for this end point

Adverse events

Adverse events information	
Timeframe for reporting adverse events:	
12 weeks treatment; up to 6 months safety follow-up.	
Adverse event reporting additional description:	
SAEs listed occurred in >1 subjects per treatment arm.	
Assessment type	Systematic

Dictionary used	
Dictionary name	MedDRA
Dictionary version	16.0

Reporting groups	
Reporting group title	AQX-1125
Reporting group description:	
AQX-1125 (200 mg capsule), oral once daily for 12 weeks.	
Reporting group title	Placebo
Reporting group description:	
Placebo (matching AQX-1125 capsule), oral, once daily for 12 weeks.	

Serious adverse events	AQX-1125	Placebo	
Total subjects affected by serious adverse events			
subjects affected / exposed	7 / 200 (3.50%)	12 / 200 (6.00%)	
number of deaths (all causes)	1	1	
number of deaths resulting from adverse events	1	1	
Respiratory, thoracic and mediastinal disorders			
Acute respiratory failure			
subjects affected / exposed	2 / 200 (1.00%)	2 / 200 (1.00%)	
occurrences causally related to treatment / all	0 / 2	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 1	
Chronic obstructive pulmonary disease			
subjects affected / exposed	1 / 200 (0.50%)	8 / 200 (4.00%)	
occurrences causally related to treatment / all	0 / 1	1 / 9	
deaths causally related to treatment / all	0 / 0	0 / 0	
Hypoxia			
subjects affected / exposed	1 / 200 (0.50%)	0 / 200 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 1	0 / 0	

Frequency threshold for reporting non-serious adverse events: 5 %

Non-serious adverse events	AQX-1125	Placebo	
Total subjects affected by non-serious adverse events			
subjects affected / exposed	21 / 200 (10.50%)	21 / 200 (10.50%)	
Nervous system disorders			
Headache			
subjects affected / exposed	12 / 200 (6.00%)	13 / 200 (6.50%)	
occurrences (all)	12	14	
Gastrointestinal disorders			
Diarrhoea			
subjects affected / exposed	11 / 200 (5.50%)	9 / 200 (4.50%)	
occurrences (all)	13	9	

More information

Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? Yes

Date	Amendment
29 July 2013	Clarification that the blood sample collection for biomarkers.
18 October 2013	Exclusion of women of child-bearing potential from being enrolled.
07 January 2014	Removal of biomarker sampling and analysis from the study. Clarification of the timing of the pulmonary function testing at each visit. Clarification of the time frame for the measurement of predicted FEV1 value in inclusion criterion No. 7.

Notes:

Interruptions (globally)

Were there any global interruptions to the trial? No

Limitations and caveats

Limitations of the trial such as small numbers of subjects analysed or technical problems leading to unreliable data.

Secondary objective of "The frequency and severity of AEs and changes in physical exam, vital signs, ophthalmic exam, laboratory tests, weight, ECG, and con meds" was monitored throughout the study, clinically significant events were reported as AEs.

Notes: