Clinical trial results:
A prospective, active-controlled, randomized, open label, single-center, multiple dose, two-period crossover clinical trial to assess the efficacy, safety and pharmacokinetics of a budesonide inhalation solution (AQ001S) compared to a budesonide inhalation suspension (comparator) in adults with mild asthma

Summary

EudraCT number	2019-002849-38
Trial protocol	BE
Global end of trial date	21 December 2022

Results information

Result version number	v1 (current)
This version publication date	10 March 2024
First version publication date	10 March 2024

Trial information

Trial identification

Sponsor protocol code	AQ-PRO-005

Additional study identifiers

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

Notes:

Sponsors

Sponsor organisation name	Aquilon Pharmaceuticals SA
Sponsor organisation address	Quai de la Boverie, 59, Liège, Belgium, 4020
Public contact	Clinical Operations, Aquilon Pharmaceuticals, 32 042292800, nait@aquilonpharma.com
Scientific contact	Clinical Operations, Aquilon Pharmaceuticals, 32 042292800, nait@aquilonpharma.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	07 September 2023
Is this the analysis of the primary completion data?	Yes
Primary completion date	21 December 2022
Global end of trial reached?	Yes
Global end of trial date	21 December 2022
Was the trial ended prematurely?	No

Notes:

General information about the trial

Main objective of the trial:

The primary objectives of the clinical trial were:
- to compare the efficacy, i.e. the bronchoprotection, of AQ001S 0.125 mg/mL with the comparator
- to assess the safety of AQ001S 0.125 mg/mL

Based on the results of the non-clinical data, it was hypothesized that AQ001S 0.125 mg/mL would show a higher efficacy in treating asthma than the comparator used at the same dose.

Protection of trial subjects:

The study was conducted in accordance with the ethical principles that have their origin in the Declaration of Helsinki and in compliance with all International Conference on Harmonisation (ICH), Good Clinical Practice (GCP) guidelines and the Belgian regulations.
Each subject was given full and adequate oral and written information about the nature, purpose, possible risk and benefit of the study and it was ensured that the informed consent form was signed and dated before any study specific procedure was performed. Opportunity was given to ask questions and subjects were allowed time to consider the information provided. Subjects were also notified that they were free to discontinue from the study at any time. Written informed consent was obtained from all subjects prior to initiation of the study. Trial subjects were monitored at baseline and daily throughout the trial by the study nurse and monthly by the study investigator.

As-needed reliever medication (only short-acting beta2-agonist containing medication) were allowed.

Background therapy:

Relevant treatment (prior/current medications, including all prescription/non-prescription medications) received by the subject within 3 months prior the screening visit were recorded.
After a pre-trial visit, the study plan foresaw a wash out period of min. 60 days for subjects under inhaled corticosteroids.

Evidence for comparator:

The comparator Budesonide TEVA is indicated for patients with bronchial asthma, who require maintenance treatment with inhaled glucocorticosteroids, for control of the underlying airways inflammation. It is a liquid suspension of budesonide for nebulization. Budesonide is an inhaled corticosteroid approved since 1981 for the treatment of asthma.

Actual start date of recruitment	23 July 2021
Long term follow-up planned	No
Independent data monitoring committee (IDMC) involvement?	No

Notes:

Population of trial subjects

Subjects enrolled per country

Country: Number of subjects enrolled	Belgium: 23
Worldwide total number of subjects	23
EEA total number of subjects	23

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)	23
From 65 to 84 years	0
85 years and over	0

Subject disposition

Recruitment

Recruitment details:

Subjects were screened within 7 days prior to randomization from an asthma clinical center in Belgium. Subjects were to be aged 18 years to 65 years and have a documented clinical diagnosis of stable, persistent asthma for at least 3 months. Following all screening procedures, patients who satisfied eligibility criteria were randomized.

Pre-assignment

Screening details:

Screening included informed consent process, demographic data, review of exclusion criteria, medical and surgical history, respiratory and asthma history, medication history including respiratory medication, physical and clinical examination (ECG, spirometry, vital signs, laboratory tests, urine pregnancy test for females of reproductive age).

Pre-assignment period milestones

Number of subjects started	24[1]
Number of subjects completed	23

Pre-assignment subject non-completion reasons

Reason: Number of subjects	Consent withdrawn by subject: 1

Notes:

[1] - The number of subjects reported to have started the pre-assignment period are not the same as the worldwide number enrolled in the trial. It is expected that these numbers will be the same.
Justification: 24 patients were screened and signed informed consent. Among them, one subject withdraw his consent after the screening visit and was then not randomized. Only 23 subjects were randomized and received study medications.

Period 1

Period 1 title	Cross-over by sequence (overall period)
Is this the baseline period?	Yes
Allocation method	Randomised - controlled
Blinding used	Not blinded

Blinding implementation details:

As this was an open-label study, no blinding procedure was used.

Arms

Are arms mutually exclusive?	Yes
Arm title	Sequence A: AQ001S - Comparator

Arm description:

AQ001S budesonide solution was administered for 29 (+2) days once daily (treatment period 1). Following a wash-out period of 14 (+2) days, the comparator Budesonide TEVA suspension was administered for 29 (+2) days once daily (treatment period 2).

Arm type	Experimental
Investigational medicinal product name	AQ001S 0.125 mg/mL
Investigational medicinal product code	
Other name	Budesonide 0.125 mg/mL inhalation solution
Pharmaceutical forms	Inhalation solution
Routes of administration	Inhalation use

Dosage and administration details:

Both products were administered by inhalation with a standard jet nebulizer using the same strength i.e. 0.125 mg budesonide/mL, according to the following administration scheme:
- 0.25 mg budesonide administration (2mL) at day 0 of each treatment period
- 0.125 mg budesonide daily administration (1mL) for 28 days per treatment period.

Investigational medicinal product name	Active comparator
Investigational medicinal product code	
Other name	Budesonide TEVA 0.125 mg/mL inhalation suspension
Pharmaceutical forms	Nebuliser suspension
Routes of administration	Inhalation use

Dosage and administration details:

Both products were administered by inhalation with a standard jet nebulizer using the same strength i.e. 0.125 mg budesonide/mL, according to the following administration scheme:
- 0.25 mg budesonide administration (2mL) at day 0 of each treatment period
- 0.125 mg budesonide daily administration (1mL) for 28 days per treatment period.

Arm title	Sequence B: Comparator - AQ001S

Arm description:

Comparator Budesonide TEVA suspension was administered for 29 (+2) days once daily (treatment period 1). Following a washout period of 14 (+2) days, AQ001S budesonide solution was administered for 29 (+2) days once daily (treatment period 2).

Arm type	Experimental
Investigational medicinal product name	Active comparator
Investigational medicinal product code	
Other name	Budesonide TEVA 0.125 mg/mL inhalation suspension
Pharmaceutical forms	Nebuliser suspension
Routes of administration	Inhalation use

Dosage and administration details:

Both products were administered by inhalation with a standard jet nebulizer using the same strength i.e. 0.125 mg budesonide/mL, according to the following administration scheme:
- 0.25 mg budesonide administration (2mL) at day 0 of each treatment period
- 0.125 mg budesonide daily administration (1mL) for 28 days per treatment period.

Investigational medicinal product name	AQ001S 0.125 mg/mL
Investigational medicinal product code	
Other name	Budesonide 0.125 mg/mL inhalation solution
Pharmaceutical forms	Inhalation solution
Routes of administration	Inhalation use

Dosage and administration details:

Both products were administered by inhalation with a standard jet nebulizer using the same strength, i.e., 0.125 mg budesonide/mL, according to the following administration scheme:
- 0.25 mg budesonide administration (2 mL) at D0 of each treatment period.
- 0.125 mg budesonide daily administration (1 mL) for 28 days per treatment period.

Number of subjects in period 1	Sequence A: AQ001S - Comparator	Sequence B: Comparator - AQ001S
Started	11	12
Completed	11	11
Not completed	0	1
Pregnancy	-	1

Baseline characteristics

Reporting groups

Reporting group title	Sequence A: AQ001S - Comparator

Reporting group description:

AQ001S budesonide solution was administered for 29 (+2) days once daily (treatment period 1). Following a wash-out period of 14 (+2) days, the comparator Budesonide TEVA suspension was administered for 29 (+2) days once daily (treatment period 2).

Reporting group title	Sequence B: Comparator - AQ001S

Reporting group description:

Comparator Budesonide TEVA suspension was administered for 29 (+2) days once daily (treatment period 1). Following a washout period of 14 (+2) days, AQ001S budesonide solution was administered for 29 (+2) days once daily (treatment period 2).

Reporting group values	Sequence A: AQ001S - Comparator	Sequence B: Comparator - AQ001S	Total
Number of subjects	11	12	23
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)	11	12	23
From 65-84 years	0	0	0
85 years and over	0	0	0
Adults	0	0	0
Age continuous Units: years			
arithmetic mean	36.3	29.1	
standard deviation	± 11.2	± 9.9	-
Gender categorical Units: Subjects			
Female	4	8	12
Male	7	4	11

Subject analysis sets

Subject analysis set title	AQ001S - efficacy population
Subject analysis set type	Per protocol

Subject analysis set description:

The efficacy population encompasses all subjects that completed both treatment periods and for which the primary efficacy parameter PC20 was available at baseline (Visit 1) and after both treatment periods (Visit 2 and Visit 4).

Subject analysis set title	Comparator - efficacy population
Subject analysis set type	Per protocol

Subject analysis set description:

The efficacy population encompasses all subjects that completed both treatment periods and for which the primary efficacy parameter PC20 was available at baseline (Visit 1) and after both treatment periods (Visit 2 and Visit 4).

Subject analysis set title	AQ001S - safety population
Subject analysis set type	Safety analysis

Subject analysis set description:

The safety population includes all randomized subjects who received at least one dose of AQ001S 0.125 mg/ml.

Subject analysis set title	Comparator - safety population
Subject analysis set type	Safety analysis

Subject analysis set description:

The safety population includes all randomized subjects who received at least one dose of the comparator Budesonide TEVA.

Reporting group values	AQ001S - efficacy population	Comparator - efficacy population	AQ001S - safety population
Number of subjects	22	22	23
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)	22	22	23
From 65-84 years	0	0	0
85 years and over	0	0	0
Adults	0	0	0
Age continuous			
Units: years			
arithmetic mean			
standard deviation	±	±	±
Gender categorical			
Units: Subjects			
Female			
Male			

Reporting group values	Comparator - safety population		
Number of subjects	23		
Age categorical			
Units: Subjects			
In utero	0		
Preterm newborn infants (gestational age < 37 wks)	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)	23		

From 65-84 years	0		
85 years and over	0		
Adults	0		
Age continuous Units: years			
arithmetic mean			
standard deviation	±		
Gender categorical Units: Subjects			
Female			
Male			

End points

End points reporting groups

Reporting group title	Sequence A: AQ001S - Comparator

Reporting group description:

AQ001S budesonide solution was administered for 29 (+2) days once daily (treatment period 1). Following a wash-out period of 14 (+2) days, the comparator Budesonide TEVA suspension was administered for 29 (+2) days once daily (treatment period 2).

Reporting group title	Sequence B: Comparator - AQ001S

Reporting group description:

Comparator Budesonide TEVA suspension was administered for 29 (+2) days once daily (treatment period 1). Following a washout period of 14 (+2) days, AQ001S budesonide solution was administered for 29 (+2) days once daily (treatment period 2).

Subject analysis set title	AQ001S - efficacy population
Subject analysis set type	Per protocol

Subject analysis set description:

The efficacy population encompasses all subjects that completed both treatment periods and for which the primary efficacy parameter PC20 was available at baseline (Visit 1) and after both treatment periods (Visit 2 and Visit 4).

Subject analysis set title	Comparator - efficacy population
Subject analysis set type	Per protocol

Subject analysis set description:

The efficacy population encompasses all subjects that completed both treatment periods and for which the primary efficacy parameter PC20 was available at baseline (Visit 1) and after both treatment periods (Visit 2 and Visit 4).

Subject analysis set title	AQ001S - safety population
Subject analysis set type	Safety analysis

Subject analysis set description:

The safety population includes all randomized subjects who received at least one dose of AQ001S 0.125 mg/ml.

Subject analysis set title	Comparator - safety population
Subject analysis set type	Safety analysis

Subject analysis set description:

The safety population includes all randomized subjects who received at least one dose of the comparator Budesonide TEVA.

Primary: Change from baseline in PC20 after each treatment period

End point title	Change from baseline in PC20 after each treatment period

End point description:

Bronchoprotection was asssessed by PC20, as determined by methacholine challenge test. The primary efficacy endpoint were the change from baseline (visit 1) in PC20 after each treatment period.

End point type	Primary

End point timeframe:

visit 1 (randomization/baseline) - visit 2 (end of treatment period 1) - visit 4 (end of treatment period 2)

End point values	AQ001S - efficacy population	Comparator - efficacy population		
Subject group type	Subject analysis set	Subject analysis set		
Number of subjects analysed	22	22		
Units: mg/mL				
arithmetic mean (confidence interval 95%)	3.7 (0.9 to 6.5)	1.2 (-0.7 to 3.0)		

Statistical analyses

Statistical analysis title	AQ001S vs Comparator

Statistical analysis description:

The primary efficacy endpoint is the change from baseline in PC20 after each treatment period (baseline is defined at Visit 1).
For primary efficacy analysis, the mean PC20 changes from baseline between AQ001S 0.125 mg/ml and the comparator were compared by analysis of covariance (ANCOVA) for crossover design. A p-value was calculated for the difference of the parameter between AQ001S 0.125 mg/ml and comparator. Additionally, an adjusted 95%-CI for the mean difference was obtained by the ANCOVA

Comparison groups	AQ001S - efficacy population v Comparator - efficacy population
Number of subjects included in analysis	44
Analysis specification	Pre-specified
Analysis type	superiority[1]
P-value	= 0.000813 [2]
Method	ANCOVA
Parameter estimate	difference/ratio of least square means
Point estimate	180.6
Confidence interval	
level	95 %
sides	2-sided
lower limit	106.42
upper limit	306.48

Notes:

[1] - in a cross-over design, groups examined should not be added. The number N = 44 (subject in this analysis) is an innate error of the EudraCT database system. Actual number of subjects in the analysis is 22.

[2] - The difference/ratio of Least Square means [95%-CI] between the treatments was 180.60 [106.42; 306.48]. The p-value of 0.000813 for the difference of PC20 between AQ001S and Budesonide TEVA is significant showing a better bronchoprotection of AQ001S.

Adverse events

Adverse events information

Timeframe for reporting adverse events:

adverse events/serious adverse events were recorded from the time the subjects signed the informed consent until the last study visit.

Adverse event reporting additional description:

Treatment-emergent adverse events are reported and defined as AEs that started or worsened in severity on or after the first dose of study medication. The safety population was used to evaluate AEs. The safety population included all randomized subjects who received at least one dose of the study medication (AQ001S or comparator budesonide TEVA).

Assessment type	Systematic

Dictionary used

Dictionary name	MedDRA
Dictionary version	24.0

Reporting groups

Reporting group title	AQ001S - safety population
Reporting group description: -	
Reporting group title	Budesonide TEVA - safety population

Reporting group description: -

Serious adverse events	AQ001S - safety population	Budesonide TEVA - safety population	
Total subjects affected by serious adverse events			
subjects affected / exposed	0 / 23 (0.00%)	0 / 23 (0.00%)	
number of deaths (all causes)	0	0	
number of deaths resulting from adverse events	0	0	

Frequency threshold for reporting non-serious adverse events: 1 %

Non-serious adverse events	AQ001S - safety population	Budesonide TEVA - safety population	
Total subjects affected by non-serious adverse events			
subjects affected / exposed	5 / 23 (21.74%)	2 / 23 (8.70%)	
Injury, poisoning and procedural complications			
Contusion			
alternative assessment type: Non-systematic			
subjects affected / exposed	1 / 23 (4.35%)	0 / 23 (0.00%)	
occurrences (all)	1	0	
Limb injury	Additional description: right thumb wound		
alternative assessment type: Non-systematic			

subjects affected / exposed	1 / 23 (4.35%)	0 / 23 (0.00%)	
occurrences (all)	1	0	
Nervous system disorders			
Headache			
alternative assessment type: Non-systematic			
subjects affected / exposed	1 / 23 (4.35%)	1 / 23 (4.35%)	
occurrences (all)	1	1	
Gastrointestinal disorders			
Toothache			
alternative assessment type: Non-systematic			
subjects affected / exposed	1 / 23 (4.35%)	0 / 23 (0.00%)	
occurrences (all)	1	0	
Respiratory, thoracic and mediastinal disorders			
Asthmatic crisis			
alternative assessment type: Non-systematic			
subjects affected / exposed	0 / 23 (0.00%)	1 / 23 (4.35%)	
occurrences (all)	0	1	
Dyspnoea			
alternative assessment type: Non-systematic			
subjects affected / exposed	0 / 23 (0.00%)	1 / 23 (4.35%)	
occurrences (all)	0	1	
Musculoskeletal and connective tissue disorders			
Arthralgia	Additional description: shoulder pain		
alternative assessment type: Non-systematic			
subjects affected / exposed	1 / 23 (4.35%)	1 / 23 (4.35%)	
occurrences (all)	1	2	
Infections and infestations			
COVID-19 pneumonia			
alternative assessment type: Non-systematic			
subjects affected / exposed	1 / 23 (4.35%)	1 / 23 (4.35%)	
occurrences (all)	1	1	

More information

Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? Yes

Date	Amendment
21 August 2020	After IEC review (Comité d'Ethique Hospitalo-Facultaire Universitaire de Liège) dated 24 March 2020 of the original CTA and subsequent CTA withdrawal, amendment 1 was resubmitted with the following substantial modifications: - Removal of CT scans and related FRI endpoints - Emphasis on the primary efficacy parameter, e.g. PC20, explaining the need for this assessment at Visits 1 (baseline), Visit 2 (end of first treatment period) and Visit 4 (end of second treatment period) - Addition of HIV and COVID-19 infections as exclusion criterion - Add of assessment of COVID-19 symptoms in physical and clinical examination

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.

No limitations or caveat are reported for this trial.

Notes: