# SIROCCO 1 clinical study
# Summary report

**Report date:** 26 June 2023

**Termination Date:** 18 December 2022

**EudraCT :** 2021-000014-42

**Sponsor :** Aquilon Pharmaceuticals S.A.
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**Study title** : " A randomized, in hospital double-blind followed by outpatient open-label, placebo-controlled, parallel, trial to determine the safety and efficacy of inhaled AQ001S in the management of acute COVID-19 symptoms"

**Protocol :** AQ-PRO-013 V6.0 22Nov2021

# TABLE OF CONTENTS

TABLE OF CONTENTS ..... 2
ACRONYMS AND ABBREVIATIONS ..... 3
1 General information about the clinical trial ..... 4
2 Main objectives and reasons to conduct the clinical trial ..... 5
3 Subject Population ..... 6
3.1 Eligibility criteria ..... 6
3.2 Subject demography and exposure ..... 7
4 Investigational Medicinal Products used ..... 8
5 Safety Data ..... 8
5.1 Non-serious Adverse Events (AEs) ..... 8
5.2 Serious Adverse Events (SAEs) ..... 8
5.2.1 Deaths ..... 8
5.3 Safety Conclusions ..... 9
6 Efficacy ..... 9
6.1 General efficacy analysis ..... 9
6.2 Pulmonary tests ..... 10
7 Overall conclusions on the clinical trial ..... 10

# ACRONYMS AND ABBREVIATIONS

| | |
|---|---|
| ACQ | Asthma Control Questionnaire |
| AE | Adverse Event |
| ALT | Alanine Transaminase |
| AST | Aspartate Transaminase |
| BID | Bis in Die (twice a day) |
| BMI | Body Mass Index |
| COPD | Chronic Obstructive Pulmonary Disease |
| COVID-19 | Coronavirus Disease 2019 |
| CT-scan | Computed Tomography scan |
| DLCO | Diffusion capacity for carbon monoxide |
| ECG | Electrocardiogram |
| EOS | End of Study |
| EP | Evaluation Parameter |
| FEV1 | Forced Expiratory Volume in 1 second |
| FVC | Forced Vital Capacity |
| GFR | Glomerular Filtration Rate |
| ICS | Inhaled Corticosteroid |
| ICU | Intensive Care Unit |
| IDMC | Independent Data Monitoring Committee |
| IMP | Investigational Medicinal Product |
| mMRC | Modified Medical Research Council |
| PCR | Polymerase Chain Reaction |
| POC | Proof Of Concept |
| QID | Quater in die (4 times a day) |
| RT-PCR | Reverse Transcriptase Polymerase Chain Reaction |
| SAE | Serious Adverse Event |
| SARS-CoV-2 | Severe acute respiratory syndrome coronavirus 2 |
| SD | Standard Deviation |
| SUSAR | Suspected Unexpected Serious Adverse Reaction |
| WOCBP | Woman of Childbearing Potential |

# 1 General information about the clinical trial

| | | |
|---|---|---|
| Study title | A randomized, in hospital double-blind followed by outpatient open-label, placebo-controlled, parallel, trial to determine the safety and efficacy of inhaled AQ001S in the management of acute COVID-19 symptoms | |
| EudraCT number | 2021-000014-42 | |
| Name of test drug/investigational medicinal product (IMP) | 1) AQ001S 0.125 mg/ml (budesonide 0.125 mg/ml inhalation solution)<br>2) Placebo (normal saline, i.e. NaCl 0.9%)<br>administered by inhalation (nebulization). | |
| Indication | COVID-19 related respiratory disease | |
| Study design | Randomized, double-blind (at hospital), open-label at home, placebo-controlled, parallel, clinical trial | |
| Protocol identification | AQ-PRO-013 | |
| Development phase of study | Phase 2a | |
| Principal investigator | Dr Doriane Calmès (dcalmes@chuliege.be)<br>Centre Hospitalier Universitaire de Liège<br>Pneumology department<br>Avenue Hippocrate, 15<br>4000 Liège<br>Belgium | |
| Independent data monitoring committee (IDMC) involvement? | ☒Yes | ☐No |
| Study initiation date (First Subject Enrolled): | 4 November 2021 | |
| Data Lock Point | 12 April 2022 | |
| Termination Date | 18 December 2022 | |
| Was the study ended prematurely? | ☒Yes | ☐No |

# 2 Main objectives and reasons to conduct the clinical trial

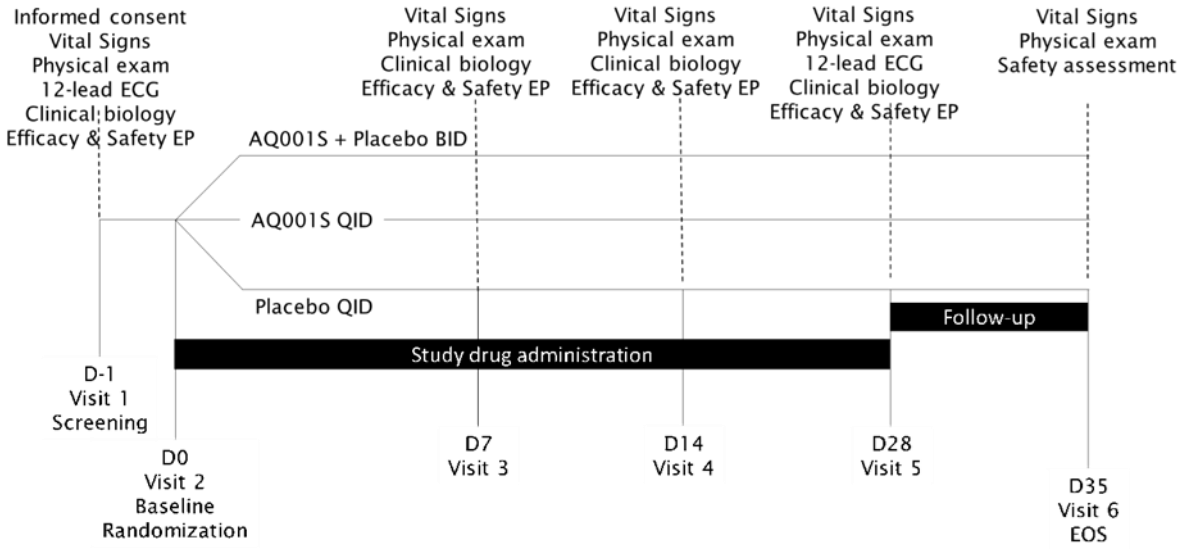
Aquilon Pharmaceuticals S.A. (Aquilon) conducted the SIROCCO 1 proof-of-concept (POC) study, a randomized, double-blind (at hospital) followed by outpatient open-label, placebo-controlled, parallel, trial to determine the safety and efficacy of inhaled AQ001S in the management of acute COVID-19 symptoms.
AQ001S is an innovative budesonide inhalation solution developed by Aquilon to be administered by the inhalation route with a nebulizer.

Several clinical studies investigating the efficacy of budesonide as a treatment for the COVID-19 patients suffering acute and chronic pulmonary symptoms were started and supported the hypothesis that ICS such as budesonide could be a therapeutic alternative for the management of acute and chronic COVID-19 symptoms.

One strength of AQ001S (i.e., 125 µg/mL) in two regimens (i.e., BID and QID) were tested in the SIROCCO 1 clinical trial on acute COVID-19 patients to assess the safety and efficacy of the AQ001S solution on adult patients (≥ 18 years old). Ninety-nine (99) patients were planned to be recruited.

SIROCCO1 clinical trial duration and general procedures are presented schematically in **Erreur ! Source du renvoi introuvable.**.

**FIGURE 1 SIROCCO1 CLINICAL TRIAL DESIGN**




Efficacy EndPoints: COVID-19 clinical progression scale, Pulmonary function test, DLCO, mMRC dyspnea scale and pulmonary CT Scan assessments; COVID-19 clinical endpoints. Safety EndPoints: (S)AEs, general tolerability, laboratory parameters, safety and tolerability including respiratory rate and oxygen saturation, and local tolerability,.
Exam= Examination

The recruitment started in November 2021 and the study was prematurely terminated by Aquilon on 18 December 2022 given the improvement of the COVID-19 status in Belgium and the lack of patients to recruit.

An Independent Data Monitoring Committee (IDMC) was set up beside the SIROCCO1 trial to monitor the safety profile and efficacy of AQ001S, ensuring the trial was being conducted with the highest scientific and ethical standards and making appropriate recommendations based on the data collected.

This summary report includes safety and efficacy data from SIROCCO 1 available at the data lock point (i.e., 12 April 2022), which were reviewed by the IDMC. At data lock point, twenty-one (21) patients were enrolled, of which sixteen (16) received at least one dose of the IMP (safety population) and seven (7) completed the clinical trial (efficacy population). They were all recruited until 10 February 2022.
No patients were recruited nor treated after the above-mentioned data lock point, which led to the early termination of the clinical trial.

# 3 Subject Population

## 3.1 Eligibility criteria

Patients **entered** in the clinical trial if they met the following criteria:

1. Patient admitted to hospital due to the severity of his/her confirmed or suspected COVID-19 disease.
2. Positive virus test for SARS-CoV-2 using RT-PCR (nasal swab).
3. Patient with COVID-19 clinical progression scale score ≥ 4 (hospitalized; no oxygen therapy).
4. Male or female, ≥18 years of age at the time of consent.
5. Patients who have given written informed consent.
6. Reliable patients who are willing to be available for the duration of the clinical trial and willing to comply with clinical trial procedures.
7. Patients who have the ability to understand the requirements of the clinical trial.
8. Female patients of childbearing potential (women of childbearing potential, WOCBP) should have a negative pregnancy test at Screening Visit.
9. Female patients of childbearing potential (women of childbearing potential, WOCBP) using a highly effective method of contraception (i.e., pregnancy rate of < 1% per year) on a stable regimen, for at least 28 days, and pursuing this contraception during the trial and for 28 days after the last administration of the IMP. The highly effective methods of contraception must be one of the following: combined estrogen and progestogen hormonal contraception with inhibition of ovulation, progestogen-only hormonal contraception associated with inhibition of ovulation, intrauterine device, intrauterine hormone-releasing system, bilateral tubal occlusion, vasectomized partner, or agreement on continuous abstinence from heterosexual intercourse.

Trial patients **were not entered** into the SIROCCO1 trial if any of the following applies:

1. Intensive care patients
2. Inability to use a nebulizer with a mouthpiece.
3. History of hypersensitivity to corticosteroid or to any of the excipients in the drug preparation.
4. Untreated oral candidiasis.

5. Evidence of symptomatic chronic or acute respiratory infection other than COVID-19 in the previous 8 weeks.
6. Proven diagnosis of asthma or bronchiectasis.
7. Proven diagnosis of COPD treated with ongoing ICS and/or corticosteroid treatment within 3 months prior to randomization.
8. Pulmonary malformations, tuberculosis, cystic fibrosis.
9. History or presence of severe hepatic impairment (i.e. alanine transaminase (ALT) and aspartate transaminase (AST) greater than 15 times the upper limit of normal)
10. History or presence of severe renal impairment considered as clinically significant according to the investigator's discretion (i.e. stage 4 (GFR = 15-29 mL/min))
11. Anticipated transfer to another hospital within 72 hours.
12. Use of ICS, at a strength at least equivalent to 200 µg of beclomethasone per day, within 7 days before Screening Visit.
13. Female patients who are breast-feeding, lactating, pregnant or intending to become pregnant.
14. Any condition, including findings in the patients' medical history or in the pre-randomization study assessments that, in the opinion of the Investigator, constitute a risk or a contraindication for the participation of the patient into the study or that could interfere with the study objectives, conduct or evaluation.
15. Current or previous participation in another clinical trial where the patient has received a dose of an IMP containing small molecules within 30 days or 5 half-lives (whichever is longer) prior to entry into this study or containing biologicals within 3 months prior to entry into this study.

## 3.2 Subject demography and exposure

The patient population was categorized in terms of age, gender, SARS-Cov-2 PCR, BMI and smoking status. Summaries of demographics for all patients who were recruited until the data lock point are provided in **Erreur ! Source du renvoi introuvable.**.

**TABLE 1 DEMOGRAPHY**

| | **All patients (n = 21)** | **Safety population (n=16)** |
|---|---|---|
| **Age** | | |
| Mean (SD) | 60 (14) | 58 (15) |
| **Gender** | | |
| Male (%) | 53% | 56% |
| Female (%) | 47% | 44% |
| **SARS-Cov-2 RT-PCR** | | |
| Positive (%) | 100% | 100% |
| **BMI** | | |
| Mean (SD) | 26.19 (10.69) | 29.28 (5.28) |
| **Smoking status** | | |
| Yes (%) | 10% | 13% |

At data lock point, safety and efficacy data were available for 21 patients (aged from 36 to 85 years old) randomized until 10 February 2022, from which 16 patients were exposed at least to one dose of the study drug (5 to placebo, 6 to AQ001S BID and 5 to AQ001S QID). These 16 patients constitute the safety population, which is defined as *all randomized subjects who received and used the study product* for whom safety and efficacy data are available to the sponsor.

# 4 Investigational Medicinal Products used

The patients received one of these treatments, at hospital and/or at home:

1) AQ001S 0.125 mg/ml (budesonide 0.125 mg/ml inhalation solution), QID
2) Placebo (normal saline, i.e. NaCl 0.9%), QID
3) AQ001S 0.125 mg/ml BID and placebo BID

# 5 Safety Data

From the safety population, 9 patients terminated the study prematurely: 2 patients were transferred to ICU, 2 patients were lost to follow up, 3 patients withdrew their consent and 2 patients died.

All adverse events, reported until data lock point, were also included in the safety analysis.

## 5.1 Non-serious Adverse Events (AEs)

From the 16 patients exposed to at least one dose of the IMP, 16 non-serious non-related AEs and 1 non-serious possibly related AE (nausea) were reported.

## 5.2 Serious Adverse Events (SAEs)

From the 16 patients of the safety population, a total of 7 SAEs were reported in 6 patients. All these SAEs were assessed as not related to the study drug by the investigator except for one case of rhabdomyolysis, which was considered as possibly related to the study drug. Thus, this SAE was qualified as a SUSAR.

### 5.2.1 Deaths

From the 16 patients who received the study drug, 2 deaths occurred as an outcome of an adverse event (altered neurological status with myoclonus and the SUSAR rhabdomyolysis).
In addition, 2 patients died due to the aggravation of the COVID-19 disease (respiratory failure and respiratory deterioration).

## 5.3 Safety Conclusions

In the SIROCCO 1 study, at data lock point, 16 patients have been exposed to the IMP at the occasion of 818 administrations:

- 5 patients received the placebo for a total of 336 administrations.
- 6 patients received AQ001S BID (twice a day) for a total of 207 administrations.
- 5 patients received AQ001S QID (four times a day) for a total of 275 administrations.

No clinically significant vital signs findings were detected during the SIROCCO1 study over the time between Screening (Visit 1) and Visit 5.
Laboratory evaluation did not reveal any clinically relevant findings over the time between Screening and Visit 5.

In addition, most of the (serious) adverse events observed were related to the severity of the disease for which patients were seeking hospital care.
No new safety findings including important potential safety risks have been identified.

# 6 Efficacy

During the interim analysis, efficacy was assessed based on the following endpoints from baseline:

- COVID-19 clinical progression scale
- COVID-19 clinical endpoints:
    - Time to discharge,
    - Time to ICU admission,
    - Length of ICU stay,
    - Time to hospital readmission,
    - Length of hospital readmission,
    - Time to mechanical ventilation,
    - Occurrence of death within 60 days.
- Changes in mMRC (Modified Medical Research Council) Dyspnea Scale, ACQ-5 and Saint-Georges respiratory questionnaires.
- Changes in the pulmonary function: Forced expiratory volume in the first second (FEV1), forced vital capacity (FVC), FEV1/FVC ratio.
- Changes in the diffusion capacity for carbon monoxide (DLCO)

## 6.1 General efficacy analysis

Only 7 patients completed the study (dosing period of 28±2 days): 3 under placebo, 3 under AQ001S BID and 1 under AQ001S QID. The sample size was not sufficient to show any statistically significant changes.

***Covid-19 clinical progression scale***
A similar decrease in the COVID-19 clinical progression scale was observed in all 3 arms showing an improvement of the patient clinical status.

***Covid-19 clinical endpoints***

The patient population included in the clinical trial was not sufficient to conclude on any Covid-19 clinical endpoint differences among the treatment arms.

***mMRC score Progression***
The patient population included in the clinical trial was not sufficient to conclude on any mMRC score result differences among the treatment arms.

***ACQ-5 and Saint-Georges respiratory questionnaire***
ACQ-5 and Saint-Georges result analysis for the 7 patients who completed the study tends to show improved ACQ-5 and Saint-Georges scores when using AQ001S compared to the placebo arm (with dose-relationship).

## *6.2* Pulmonary tests

The pulmonary tests could not be performed appropriately to all patients and at all visits due to the health conditions of the patients. Seven patients completed the study and could perform at least two pulmonary tests.

The interim analysis at data lock point of the efficacy results showed that the DLCO and the functional respiratory tests (FCV, FEV1 and FEV1/FVC) have been improved in patients using AQ001S, while they have been not at all improved in patients using the placebo (Table 2).

TABLE 2 PULMONARY FUNCTION TESTS AND DLCO CHANGES FROM BASELINE

| | DLCO* | FEV1 | FVC | FEV1/FVC |
|---|---|---|---|---|
| Placebo | 5% | 4% | 6% | -20% |
| AQ001S BID | 22% | 22% | 19% | 3% |
| AQ001S QID | 20% | 37% | 24% | 16% |

** DLCO changes from baseline was calculated from v3 as patients were not able to perform DLCO measurement at visit 2*

# 7 Overall conclusions on the clinical trial

This clinical trial aimed at determining the safety and efficacy of inhaled AQ001S in the management of acute COVID-19 symptoms.

This summary report includes safety and efficacy data from SIROCCO 1 available at the data lock point reviewed by the IDMC. At data lock point, twenty-one (21) patients were enrolled, of which sixteen (16) received at least one dose of the IMP (safety population) and seven (7) completed the clinical trial (efficacy population). No patients were recruited nor treated after the data lock point due to the disease status in Belgium, and this led to an early termination of the clinical trial.

No clinically significant vital signs findings were detected during the SIROCCO1 study (16 patients included in the safety analysis). Laboratory evaluation did not reveal any clinically relevant findings.

Most of the (serious) adverse events observed were related to the severity of the disease for which patients were seeking hospital care.
No new safety findings including important potential safety risks have been identified.

The sample size was not sufficient to show any statistically significant changes in efficacy.
The analysis of interim results (7 patients included in the efficacy analysis) showed that the DLCO and the functional respiratory tests (FVC, FEV1 and FEV1/FVC) have been improved in patients using AQ001S, while they have been not at all improved in patients using the placebo.
We also observed an improvement in symptoms and quality of life of patients treated with AQ001S compared to the placebo.