2 SYNOPSIS

Name of Sponsor/Company: AiCuris Anti-infective Cures AG	Individual trial table referring to part of the Dossier Volume: Page:	*(For National Authority Use only)*
Name of finished product:		
Name of active ingredient: AIC649		

Title of the trial

A randomized, double-blind, placebo-controlled trial to evaluate the efficacy and safety of AIC649 in the treatment of otherwise healthy subjects with asymptomatic or mildly symptomatic SARS-CoV-2 infection

Principal Investigators:

Site 1 (sole recruiting site):
Dr. Frank Zollmann, (PHARMA CONSULT), Emovis GmbH

Site 2: (no subjects recruited)
Dr. Anel Pretorius, FARMOVS (Pty) Ltd

Trial center(s)

Site 1:
Emovis GmbH, Wilmersdorfer Str. 79, 10629 Berlin, Germany

Site 2: (no subjects recruited)
FARMOVS (Pty) Ltd, Pharmacology Building, Building No. 80, Block C, Dekaan Street, University of the Free State, 205 Nelson Mandela Drive, Park West, Bloemfontein, 9301, South Africa.

Publication (reference)

Not applicable

Trial period (years)	**Phase of development**
First Subject First Visit: 06Feb2022 Last Subject Last Visit: 06May2022	1b/2a

Objectives

Primary

- To investigate the safety and tolerability of multiple dosing of AIC649

Secondary

- To investigate the impact of AIC649 on the clinical course of SARS-CoV-2 infections
- To investigate the impact of AIC649 on SARS-CoV-2 virus replication and viral shedding (from daily throat wash)
- To investigate the effect of AIC649 on the serum immunological pattern of subjects with SARS-CoV-2 infections

Key features of trial design

This was a double-blind, placebo-controlled trial conducted in 2 clinical sites.

It was planned that up to 60 otherwise healthy male and female subjects tested SARS-CoV-2 positive based on quantitative reverse transcriptase polymerase chain reaction (qRT-PCR, with $\geq 10^5$ viral

Name of Sponsor/Company: AiCuris Anti-infective Cures AG	Individual trial table referring to part of the Dossier	*(For National Authority Use only)*
Name of finished product:	Volume:	
Name of active ingredient: AIC649	Page:	

genome copies at screening obtained by throat swab in SARS-CoV-2 non-vaccinated subjects or not fully vaccinated subjects; qRT-PCR positive without threshold for SARS-CoV-2 fully vaccinated subjects) with at most mild COVID-19 symptoms (excluding: moderate [defined as ≥38.5°C] or severe fever, and/or moderate or severe cough) at screening were to be randomized 1:1 to receive intravenously either:

- AIC649 (10^9 viral particles in 1 mL) as bolus on Days 1, 3, and 5,
  or
- 0.9% w/v saline solution as Placebo (1 mL) administered as bolus on Days 1, 3 and 5.

Subjects were considered fully vaccinated according to local requirements. A sentinel approach was followed using separate sentinel groups for subjects based on SARS-CoV-2 vaccination status, ie, SARS-CoV-2 fully vaccinated and SARS-CoV-2 non-vaccinated or not fully vaccinated. Within each sentinel group, one of the first 2 subjects randomized received AIC649, the other placebo treatment. The next 4 subjects (2 on AIC649, 2 on placebo) in each sentinel group were to be dosed starting at least 7 days after the 2nd subject received his/her first dose. Clinical safety data (until Day 7) of those 6 sentinel subjects were to be evaluated by a Risk Benefit Committee (RBC) before dosing further subjects with the respective vaccination status. The RBC consisted of at least the Principal Investigator, the responsible physician of AiCuris and the Pharmacovigilance Manager of AiCuris.

On Day -1, subjects tested positive for SARS-CoV-2 by RT-PCR or qRT-PCR or antigen test for the first time signed the ICF (in the case of SARS-CoV-2 non-vaccinated subjects or not fully vaccinated subjects, this had to be done within 3 days after the sample that lead to the positive test result was taken; in the case of SARS-CoV-2 fully vaccinated subjects, no time frame was applied). Subjects were hospitalized on Day -1 for screening until the morning of Day 1 (when all screening results were available). If a subject was a screening failure, they were released from the clinical site immediately to continue any applicable SARS-CoV-2 quarantine measures according to applicable current regulations. If all the inclusion and none of the exclusion criteria were fulfilled, subjects were randomized 1:1 to receive either AIC649 or 0.9% w/v saline solution (placebo arm) on Days 1, 3, and 5. Randomization was stratified based on consent to epigenetic sampling using a centralized randomization system.

Subjects were discharged from the clinical site on Day 7 (6 days after first and 2 days after last Investigational Medicinal Product [IMP] administration) at the earliest. Subjects were only to be discharged if they had no, or only mild COVID-19 symptoms. Subjects with fever (defined as ≥38°C) were not to be discharged. Antipyretic drugs could be administered, but for discharge fever was not permitted to return after the antipyretic was withdrawn and its effects had abated.

Subjects with mild symptoms, including fever and cough, were not to be considered as treatment failures. If a subject had developed a moderate, severe, or critical SARS-CoV-2 infection during the trial, if a cytokine storm had been diagnosed, or if the safety laboratory risk score had been positive (and confirmed by a control determination), this subject would have been considered a treatment failure and transferred to a hospital for consultation and further diagnostics and treatment, if needed, after Early Termination examinations, if possible. These subjects were to be followed up for 4 weeks to capture the most severe grade of COVID-19 disease. If a subject had been hospitalized beyond this 4-weeks period, this follow-up would have been extended until discharge. In such cases, the subject (or

Name of Sponsor/Company: AiCuris Anti-infective Cures AG	Individual trial table referring to part of the Dossier	*(For National Authority Use only)*
Name of finished product:	Volume:	
Name of active ingredient: AIC649	Page:	

their relatives or the hospital) were to be contacted by weekly calls until resolution or/and discharge. A discharge letter from the hospital was to be provided to the Investigator, if available.

Depending on the applicable local regulations, the subject may have been required to follow SARS-CoV-2 related home quarantine time after discharge from the clinical site.

Between discharge from the clinical site and the End-of-Trial examinations, SARS-CoV-2 sampling was performed daily by the subject at home (gargling/throat wash method) until Day 14 and afterwards every 3rd day until End-of-Trial examination. Subjects could call the site/Investigator at any time, and they were called every day to check for adverse events, COVID-19 related symptoms, and concomitant medication until the End-of-Trial examinations. On these days respiratory rate, body temperature, pulse rate, and SpO2 were always measured by the subjects themselves, during the calls, and documented in a diary. If the results indicated worsening of COVID-19 grading, subjects were to be transported to the site as soon as possible to verify the results and appropriate measures were taken. If the situation was judged to be a medical emergency by the site staff / Investigator / physician on call, an emergency vehicle had to be sent to the subject for appropriate intervention.

An on-site visit was performed on Day 14.

End-of-Trial examinations were performed on Day 28 in all subjects being discharged from the clinical site between Day 7 and Day 21; if the subject was discharged on Day 22 or later, the End-of-Trial examination was performed one week after discharge.

Number of subjects (planned and analyzed)

Planned: 60 subjects in total. 30 placebo and 30 AIC649 treatment

Analyzed: 8 subjects in total. 4 placebo and 4 AIC649

Diagnosis and main criteria for inclusion

Adult otherwise healthy male and female subjects, 18-55 years-of-age inclusive for SARS-CoV-2 nonvaccinated- or not fully vaccinated subjects and 18-65 years-of-age inclusive for SARS-CoV-2 fully vaccinated subjects, of any ethnic origin, with RT-PCR or qRT-PCR positive, asymptomatic or with at most mild COVID-19 symptoms (excluding: moderate [defined as ≥38.5°C] or severe fever and/or moderate or severe cough).

Test product, dose and mode of administration, batch number(s)

AIC649 lyophilizate (1 vial containing 1 x 10^9 viral particles) to be reconstituted with 1.1 mL water for injection (WFI) and given as 1 mL bolus intravenous injection

Batch number: 0020810

Duration of Treatment

Treatment was administered on Days 1, 3 and 5.

Reference therapy, dose and mode of administration, batch number(s)

0.9% w/v saline solution, 1 mL, as Placebo for bolus intravenous administration.

Batch number: 941504

Name of Sponsor/Company: AiCuris Anti-infective Cures AG	Individual trial table referring to part of the Dossier Volume: Page:	*(For National Authority Use only)*
Name of finished product:		
Name of active ingredient: AIC649		

Criteria for evaluation

The trial was principally designed to study the safety and tolerability of three doses of AIC649 and all efficacy and pharmacodynamic parameters are only exploratory.

Primary endpoints

Safety and tolerability endpoints

The following safety variables were recorded at regular intervals during the trial:

- Nature, frequency, duration, severity and causality of adverse events (AEs) and serious adverse events (SAEs)
- Clinical laboratory tests (hematology, clinical chemistry and urinalysis)
- Vital signs (supine blood pressure [BP], pulse rate, oxygen saturation (SpO2), body temperature and respiratory rate [RR])
- Standard 12-lead Electrocardiogram (ECG)
- Concomitant medication assessments
- Physical examinations
- Local tolerance

Secondary endpoints

Clinical efficacy

- Proportion of patients in each COVID-19 symptom severity category (SARS-CoV-2 infection without symptoms, Mild COVID-19, Moderate COVID-19, Severe COVID-19, and Critical COVID-19) during the course of the trial
- Proportion of patients requires O_2 supplementation during the course of the trial
- Proportion of patients requires COVID-19 specific medication during the course of the trial
- Time to COVID-19 progression

Virological efficacy

- Mean viral load (SARS-CoV-2 RNA) as measured by quantitative polymerase chain reaction (PCR) during the course of the trial
- Change from baseline in viral load (SARS-CoV-2 RNA) as measured by PCR during the course of the trial
- Area under the viral load (SARS-CoV-2 RNA) - time curve (AUC)
- Time to viral load (SARS-CoV-2 RNA) free status as measured by PCR

Immune response

- Proportion of patients with anti-SARS-CoV-2 IgG and IgM at baseline and at the end of the trial.
- Pharmacodynamic chemokines/cytokine-panel at baseline and during the course of the trial.
- Determination of the cellular immune status at baseline and during the course of the trial.

Name of Sponsor/Company: AiCuris Anti-infective Cures AG	Individual trial table referring to part of the Dossier Volume: Page:	*(For National Authority Use only)*
Name of finished product:		
Name of active ingredient: AIC649		

Statistical methods

Sample size justification

No formal statistical sample size calculation has been performed for the clinical trial. The numbers of subjects have been chosen based on practical grounds and previous experience on the proposed design.

Efficacy analyses

Clinical efficacy, virology, immune response and immunogenicity data were summarized using descriptive statistics.

Safety analyses

The safety variables were summarized using descriptive statistics

SUMMARY AND CONCLUSIONS

Efficacy results

Within the restraints of small sample size: overall, TE symptoms of COVID-19 affected fewer subjects in the AIC649 group than in the placebo group. The likelihood of COVID-19 progression (to moderate severity or worse) was unaffected by AIC649 treatment. The time to disease progression could not be derived due to the low incidence.

Comparisons of viral load showed no meaningful differences in the changes from Baseline. Although the time to SARS-CoV-2 clearance was shorter in the AIC649 group, the viral load at Baseline was also lower in the AIC649 group than in the placebo group as 2 AIC649 subjects and 1 placebo subject had no detectable viral load at Baseline. Nonetheless, the kinetics of viral load were similar between the placebo and AIC649, and it was therefore concluded that AIC649 had no relevant treatment effect on viral load.

No AIC649 treatment effects were apparent in the analyses of cytokine/chemokine or cellular immune responses. It was noted that although anti-SARS-CoV-2 antibodies were detected in all subjects by EoT, they were detectable earlier on average in the AIC649 group.

Pharmacokinetics results

Not applicable.

Safety results

Multiple doses of AIC649 (3 times 1 x 10^9 viral particles) were systemically well tolerated in 4 otherwise healthy subjects with asymptomatic or mildly symptomatic SARS-CoV-2 infection.

Local tolerability was in general good, but it appeared minimally better in the placebo group vs AIC649. The maximum VIP score during the treatment period in the AIC649 group was 2 (early stage of phlebitis). No systemic hypersensitivity reaction against AIC649 was observed.

The profiles of AEs were comparable between treatment groups, although events of moderate intensity were slightly more common in the placebo group than in the AIC649 group.

Name of Sponsor/Company: AiCuris Anti-infective Cures AG	Individual trial table referring to part of the Dossier Volume: Page:	*(For National Authority Use only)*
Name of finished product:		
Name of active ingredient: AIC649		

AIC649 had no apparent effect on clinical laboratory, vital signs, pulse oximetry, respiratory rate, body temperature, ECG, physical examination.

Conclusions:

- Multiple doses of AIC649 (3 times 1 x 10^9 viral particles) were systemically well tolerated.
- Local tolerability appeared minimally better in the placebo group vs AIC649.
- The low population size in both treatment groups prohibits meaningful conclusions in the comparison of AIC649 with placebo treatment on the clinical course of subjects with at worst mild COVID-19.
- Comparisons of absolute viral load, time to clearance of viral load, cytokine/chemokine levels, cellular immune responses showed no apparent treatment effect from AIC649 when compared with placebo.
- AIC649 treatment appeared slightly better than placebo regarding the likelihood of new COVID-19 symptoms and time to detectable anti-SARS-CoV-2 antibodies, but the relevance of these differences is unclear.

Date of report: 19Apr2023