ABBREVIATED CLINICAL STUDY REPORT

Protocol Number:	APG101_CD_018
Investigational Medicinal Product:	APG101
Indication:	Moderate to Severe COVID-19 Disease
Phase:	III
Sponsor:	Apogenix GmbH Im Neuenheimer Feld 584 69120 Heidelberg, Germany
Coordinating Investigator	Prof. Dr. med. Frederik Trinkmann Röntgenstraße 1 69126 Heidelberg, Germany
First Patient, First Visit:	02 November 2022
Early Study Termination:	30 June 2023
Last Patient, Last Visit:	18 August 2023
Date of Report:	25 April 2024
Report Version:	1.0

The study was conducted according to the protocol and in compliance with Good Clinical Practice (GCP), with the Declaration of Helsinki and with other applicable regulatory requirements.

2. SYNOPSIS

Name of Company: Apogenix GmbH	**Volume:** Not applicable	(For national authority use only)
Name of Finished Product: Not available at the time of the report	**Page:** Not applicable	
Name of Active Ingredient(s): APG101 (Asunercept)		

Title of Study:

A Multicenter, Randomized, Placebo-controlled, Double-blind, Phase III Trial to Evaluate the Efficacy of Asunercept for the Treatment of Hospitalized Patients with Moderate to Severe COVID-19 Disease

Protocol Number: APG101_CD_018

Study Period: **Study Phase:** III

Date of first patient, first visit: 02 November 2022

Date of last patient, last visit: 18 August 2023

Coordinating Investigator:

Prof. Dr. med. Frederik Trinkmann

Study Center(s):

Nine sites located in 4 countries (Georgia, France, India, South Africa) enrolled study subjects.

Publication(s):

None at the time of writing this report.

Objectives and Endpoints:

Objective	Endpoints
Primary	
• To estimate the efficacy of Asunercept in the treatment of hospitalized patients with moderate to severe coronavirus disease 2019 (COVID-19) when given as add on to Standard of Care (SoC)	Time to sustained recovery, defined as sustained improvement (i.e., without decrease) of ≥2 points on the World Health Organization (WHO) 10-point clinical progression scale or discharge from hospital followed by being alive and at home for 14 consecutive days prior to day (D) 56, whichever occurs first
Key Secondary	
• To estimate the efficacy of Asunercept when given as add on to SoC in reducing progression to more severe disease (i.e., invasive mechanical ventilation [IMV]) or death	• All-cause mortality or progression to IMV by D28
Secondary	
• To estimate the efficacy of Asunercept when given as add on to SoC in reducing the all-cause mortality in patients with moderate to severe COVID-19	• D56 all-cause mortality
• To estimate the efficacy of Asunercept when given as add on to SoC in reducing the	• Proportion of patients with symptoms associated with PCS on D28, D35, D42, D49, and D56; assessed using EuroQol-5 Dimension-5 Level

occurrence of post-COVID syndrome (PCS) in patients with moderate to severe COVID-19	(EQ-5D-5L) and Post-Covid Functional Scale (PCFS) questionnaires
• To estimate the efficacy of Asunercept when given as add on to SoC in reducing the need for oxygen therapy in patients with moderate to severe COVID-19	• Proportion of patients being alive and free of respiratory failure on D8, D15, D22, and D28 (Respiratory failure is defined as the need for invasive or non-invasive mechanical ventilation, high-flow oxygen, or extra corporeal membrane oxygenation)
• To estimate the efficacy of Asunercept when given as add on to SoC on preventing progression of disease in patients with moderate to severe COVID-19	• Proportion of patients admitted to intensive care unit (ICU) until D28 after randomization • Length of ICU stay (in days) • Duration of hospitalization
• To estimate the effect of Asunercept when given as add on to SoC on the trajectory of COVID-19 until hospital discharge on an individual patient basis	• Proportion of patients with each severity scoring on the WHO 10-point clinical progression scale on a daily basis until hospital discharge Mean change in the scoring on the WHO 10-point clinical progression scale from baseline (assessment once daily) • Disease progression as evidenced by chest X-ray (CXR)/computed tomography (CT), if performed at investigator's discretion.
• To estimate the safety of treatment with Asunercept when given as add on to SoC in the treatment of moderate to severe COVID-19	• Cumulative incidence of adverse events (AEs)

Study Design:

Trial APG101_CD_018 was a prospective, multicenter, randomized, double-blind, placebo-controlled Phase III study conducted in hospitalized patients with moderate to severe COVID-19 corresponding to score 5 or 6 on the World Health Organization (WHO) 10-point clinical progression scale (Grade 0-10).

Asunercept was administered at a dose of 100 mg intravenously (IV) once weekly for a period of 4 weeks (1 dose each on D1, D8, D15, and D22) in addition to the treatment recommended by international, national, or local treatment guidelines (SoC) and was compared with the control arm (i.e., placebo + SoC).

Randomization and start of treatment occurred within 72 hours after admission to the hospital. Subjects were randomized in a 1:1 ratio (Asunercept 100 mg: placebo). The randomization was stratified according to the severity of the disease (Score 5 or 6 on the WHO 10-point clinical progression scale) and regions with similar SoC (Europe [including Georgia]/India/Africa).

In the statistical analysis plan (SAP), Apogenix prospectively defined subgroup analyses addressing the outcome of combination treatment with Asunercept. Safety was supervised by an unblinded Data Safety Monitoring Board (DSMB). After 100, 200, and 400 subjects have been randomized, safety data were to be reviewed by the DSMB to determine safety signals. The study was ended prematurely prior to enrolment of the first 100 subjects due to insufficient subject enrolment rates.

Trial Population:

Inclusion Criteria:

1.	The patient or his/her legal authorized representative (in case the patient was temporarily unable to give own consent due to his/her acute medical condition; in France, India, and South Africa only) had given informed consent to participate in the trial and to adhere to the procedures stated in the protocol.
2.	The patient was a male or female adult aged ≥18 years at the time of giving informed consent.
3.	The patient was admitted to a hospital (maximum 72 hours prior to randomization) due to COVID-19 and had a positive SARS-CoV-2 polymerase chain reaction (PCR) test.
4.	The patient had clinical symptoms indicative of moderate or severe illness (corresponding to score 5 [oxygen by mask or nasal prongs] or 6 [oxygen by non-invasive ventilation or high flow] on the

	WHO 10-point clinical progression scale) with COVID-19 prior to trial treatment on D1: Radiologically confirmed pneumonia due to COVID-19 and/ or clinical signs suggestive of moderate/severe illness with COVID-19.
5.	The patient agreed to not participate in another clinical trial from screening until d56 (in Georgia only).
6.	The patient was willing to follow effective measures of contraception during the trial.

Exclusion Criteria:

1.	The patient was moribund or had an estimated life expectancy <1 month (e.g., terminal cancer, etc.).
2.	The patient was pregnant or breastfeeding.
3.	The patient was anticipated to be discharged from hospital within 48 hours.
4.	The patient required anti-inflammatory medicines beyond SoC (SoC are drugs that are approved for treatment of COVID-19. In addition, SoC comprises medicines that have been recommended in treatment guidelines of national health authorities and/or professional organization).
5.	The patient required invasive mechanical ventilation.
6.	The patient was known to have active tuberculosis.
7.	The patient was known to have hereditary fructose intolerance.
8.	The patient was known to have co-infection with Influenza viruses or other viral respiratory infections (respiratory syncytial virus, parainfluenza viruses, respiratory adenoviruses).
9.	The patient was participating in any investigational clinical study, other than observational, within 30 days prior to enrolment (in France, India, and South Africa only).

Number of Patients (planned and analysed): Approximately 636 patients were planned to be enrolled into the trial to achieve 600 events. Sponsor prematurely terminated the study due to low recruitment rates after only 38 patients had been screened at 9 clinical centers in period between November 2022 and June 2023. 34 patients have been randomized at 8 centres during this period.

Test Product, Dose and Mode of Administration, and Lot Number(s): APG101 (Asunercept), 100 mg IV once per week administration, LOT number: F006G/2149HMF001

Reference Therapy, Dose and Mode of Administration, and Lot Number(s): Saline (Sodium chloride [NaCl]) for infusion served as a placebo reference therapy

Duration of Treatment: 4 weeks

Patient Duration: 56 days for each individual patient after randomization

Criteria for Evaluation:

Efficacy

Efficacy was assessed by:

- WHO 10-Point Clinical Progression Scale
- All-cause mortality rate
- EQ-5D-5L
- PCFS
- Hospitalization rate and duration
- CXR/CT
- Oxygen use
- Ventilation status

Safety

Safety was assessed through incidence of AEs, laboratory parameters, physical examination, vital signs, and 12-lead electrocardiograms (ECGs).

Pharmacokinetic, Anti-drug Antibody, and Biomarker Assessments

Pharmacokinetic (PK) parameters were to be evaluated in this study. In addition, Asunercept-anti-drug antibodies (ADAs) were to be determined in serum samples employing screening, confirmation, and titre assays. PK and ADA assessments were to be performed at selected trial sites only with separate Informed Consent.

In addition, the serostatus for anti-SARS-CoV-2 antibodies was to be determined, calprotectin levels were to be measured, and lymphocytopenia was assessed.

Collection of samples for exploratory biomarker research was also part of this study.

- Plasma samples were collected to analyze biomarker candidates thought to play a role in COVID-19 disease progression. Biomarkers were to include, e.g., inflammatory biomarkers.
- Bronchial lavage samples were to be analyzed from patients under ICU care to determine CD95L levels with separate Informed Consent (consent collected at inclusion of patients for the case that collection of bronchial lavage samples may become necessary at deteriorating disease stages).
- All samples were collected according to the schedule described in the Schedule of Activities and as detailed in a laboratory manual provided separately to trial sites.

The analysis of PK parameters, ADAs, serostatus for anti-SARS-CoV-2 antibodies, calprotectin, biomarkers, and CD95L levels in bronchial lavage were planned to be conducted as central analyses at the end of the study. Due to the low recruitment rates and resulting premature termination of the study, considerably less samples than anticipated were collected. It was decided to not analyze the collected samples as no statistically interpretable data was expected.

Statistical Methods:

Sample Size Calculation

Based on results from the APG101_CD_017 trial, median time to sustained recovery was assumed to be 15 days for the SoC arm, and 11.5 days for the Asunercept 100 mg arm. A sample size of approximately 636 patients to achieve 600 events, was calculated to provide approximately 90% power using a 2-sided log-rank test with alpha of 0.05 to reject the null hypothesis of no difference between groups.

Statistical Analysis

Primary: The median time to sustained recovery and associated 95% confidence interval (CI) for each treatment arm was estimated using the Kaplan-Meier method. Comparisons between treatment arms were performed using a log-rank test, stratified by baseline severity and region.

Key Secondary: The null hypothesis of no difference in proportion of all-cause mortality or progression to invasive mechanical ventilation by d28 in the 2 treatment arms was tested by using a Cochran-Mantel-Haenszel test stratified by baseline severity and region at a 2-sided 0.05 significance level. The difference in proportions between the 2 groups as well as corresponding standard deviation (SD), and 95% Miettinen-Nurminen CI were provided.

Efficacy analyses were conducted in the enrolled sample size.

Interim Analysis

One interim analysis was planned when 300 events had accrued. The analysis was to be conducted by an unblinded statistician who is not involved in the day-to-day conduct of the trial. No unblinding of any members of the operational team was to occur. No interim analysis was conducted, as the study was terminated prior to reaching the defined target for events required for the interim analysis.

Safety

Safety assessments were performed for Safety Population, defined as all patients who have received any study drug. Each AE was coded in accordance with Medical Dictionary for Regulatory Activities (MedDRA) and graded for severity using the classifications of National Cancer Institute Common Terminology Criteria for AEs. Treatment emergent AEs (TEAEs) were those events that occurred after the first administration of the study drug

until the subjects' last visit. Total number of TEAEs and number of subjects reporting TEAEs were summarized by the treatment arm and overall population, by system organ class and by preferred term as well as by severity and relationship. Absolute values and change from baseline for safety laboratory parameters were summarized using descriptive statistics by visit.

Safety Results:

- There were in total 6 SAEs reported during the study, 50% (3 SAEs) resulted in death (2 were reported in Asunercept + SoC treatment arm and 1 was reported in the Placebo + SoC treatment arm), while 50% (3 SAEs) resolved by the end of the study. None of the reported SAEs was assessed as related to study drug. Apart from the reported fatal outcomes, there were no other TEAEs leading to study or study drug discontinuation.
- Incidence of TEAEs was evenly distributed between both treatment arms as, of 30 total TEAEs in 16 subjects, 15 TEAEs in 8 (47.1%) subjects were reported in both, the Asunercept + SoC as well as the Placebo + SoC treatment arm.
- No differences were observed in the rates of reported TEAEs by SOC between the two treatment arms.
- The majority of the reported TEAEs were Grade 2 (moderate) in intensity in both the treatment arms.
- Treatment-emergent AEs assessed as related to study drug were reported in 1 (5.9%) subject in each of the treatment arms, TEAE bradycardia (severity: grade 2, moderate) in the Asunercept + SoC treatment arm and TEAE hepatic enzyme increased (severity: grade 1, mild) in the Placebo + SoC treatment arm.
- No TEAEs related to clinically abnormal changes in hematology parameters were reported in the study. Treatment-emergent AEs of hepatic enzyme increased (severity: grade 1, mild) and hypoalbuminaemia (severity: grade 2, moderate) were reported in the Placebo + SoC treatment arm. No other TEAEs related to chemistry parameters were reported in the study.

Conclusions:

No significant efficacy trends were noted due to the small number of patients recruited in the APG101_CD_018 study, but the results support Asunercept's Mode of Action of blocking activation-induced cell death of lymphocytes and show that Asunercept has the potential to prevent deterioration of and accelerate recovery from lymphocytopenia.

The safety and tolerability of Asunercept, and the incidence of TEAEs in both treatment arms, were evaluated. Asunercept was safe and well tolerated. Thus, the risk-benefit ratio of the current presentation of Asunercept justifies further clinical development.

Date of Report, version: 25 April 2024, v1.0