2 SYNOPSIS

NAME OF SPONSOR:	University Medical Center Hamburg-Eppendorf Martinistrasse 52, 20246 Hamburg, Germany
NAME OF ACTIVE INGREDIENT: Adrecizumab (in addition to standard of care)	
TITLE OF STUDY:	Adrecizumab (HAM8101) to improve proGNosis and outcomES in covid-19 Trial (AGNES-19) EudraCT No.: 2020-001336-10 CTgov.: NCT05156671
PRINCIPAL/COORDINATING INVESTIGATOR NAME: Prof. Dr. med. Stefan Kluge University Medical Center Hamburg-Eppendorf, Department of Intensive Care Medicine	
STUDY CENTRE(S): A total of 7 German sites participated in this study and had screened at least 1 patient (31 screened patients overall). Finally, a total of 16 patients were randomized at 6 study sites.	
PUBLICATION (REFERENCES): None so far.	
STUDY PERIOD:	First patient randomized: 06-Oct-2022 Last patient's last visit: 25-Aug-2023
PHASE OF DEVELOPMENT: Phase 2b	
BACKGROUND AND RATIONALE FOR THE STUDY: The main reason for admission to an intensive care unit (ICU) and need for mechanical ventilation of patients with COVID-19 is acute lung injury within a broad pneumonic spectrum, increased ventricular filling pressures, and resulting congestion. Sepsis, often seen in these patients, is a life-threatening condition that results in organ dysfunction caused by a dysregulated host response to infection. Septic shock is the most severe form of sepsis and is driven by severe loss of vascular integrity: a breakdown of the endothelial barrier, which results in uncontrolled leakage of intravascular fluid and other compounds into the extravascular space leading to congestion and edema. It is hypothesized that adrenomedullin (ADM) is a key player in the (dys)-regulation of vascular integrity. Adrecizumab is the first-in-class humanized monoclonal anti-adrenomedullin antibody and acts as a long-lasting plasma ADM enhancer stabilizing barrier function at a reasonable safety profile. Thus, the current study was performed to evaluate the efficacy as well as safety and tolerability of adrecizumab on top of standard of care (SoC) in hospitalized patients with moderate to severe COVID-19 that showed signs of with endothelial dysfunction (as indicated by elevated bio-ADM plasma levels).	

OBJECTIVES:

The overall objective of the AGNES-19 study was to demonstrate efficacy, safety, and tolerability of adrecizumab in patients with moderate to severe COVID-19. All outcome measures were defined in accordance with highest scientific standards. In order to generate meaningful data, patient-related endpoints were chosen as the primary efficacy outcome. The secondary endpoints were also patient-related and could be precisely assessed.

- The **primary objective** was to evaluate, if improvement of vascular integrity with adrecizumab on top of SoC is superior to placebo/control substance (NaCl 0.9%) on top of SoC in reduction of the endpoint "time to clinical improvement" until Day 28 in patients with moderate to severe COVID-19.
- The **secondary objectives** of the AGNES-19 trial intended to evaluate the effect of adrecizumab in comparison with placebo, with i) respect to safety and tolerability of Adrecizumab on top of SoC in patients with moderate to severe COVID-19, ii) clinical status at Day 28, iii) all-cause mortality, iv) rate of new invasive mechanical ventilation, v) length of invasive mechanical ventilation, vi) length of initial stay at ICU, vii) rate of renal replacement therapy, viii) change in SOFA score, ix) clinical status according to ordinal WHO scale for COVID-19, and x) quality of life (QoL) as assessed by EQ-5D-5L.

METHODOLOGY:

This study was a prospective, randomized, placebo-controlled, double-blinded, multi-center, national interventional Phase 2b trial. Eligible patients were randomized (1:1) to intravenous (IV) adrecizumab or placebo/control substance (NaCl 0.9% solution), on top of SoC. Randomization was carried out centrally using a computerized system. A block randomization procedure was applied with stratification by age (>65 years vs. ≤65 years) and sex (male vs. female). Investigational medicinal products (IMPs) were administered a single-dose treatment; the subsequent follow-up period was 90 days.

The primary endpoint was the time to clinical improvement, defined as the time from randomization to an improvement of 2 points (from the status at randomization) on the WHO 8-point ordinal scale or live discharge from the hospital, whichever occurred first. This endpoint of clinical improvement was used in previous influenza and COVID-19 studies and was also recommended by the WHO R&D Blueprint expert group.

An unblinded interim analysis was planned in the course of the study after the enrollment of 75% of initially estimated patients in order to allow for sample size re-assessment as well as stopping for futility and efficacy, respectively. In fact, no interim analysis was performed.

NUMBER OF SUBJECTS:

The original sample size estimation required a total of 180 patients to be randomized. Due to lacking recruitment, this study was prematurely terminated after the screening of 31 patients and randomization of 16 patients. As a general consequence, the reported study outcomes based on these 16 randomized patients (10 placebo and 6 adrecizumab) are not appropriately robust, and the descriptive statistical between-group tests are grossly underpowered. Therefore, all study results should be interpreted with due caution.

DIAGNOSIS AND MAIN CRITERIA FOR INCLUSION AND EXCLUSION:

Adult patients suffering from COVID-19 were to be enrolled in the study.

Key inclusion criteria were:

- Hospitalization with moderate to severe COVID-19, defined as fulfilling at a minimum the following clinical status category on the WHO 8-point ordinal scale:
  - "score 4" [oxygen via mask or nasal]
- Laboratory-confirmed SARS-CoV-2 infection at index hospitalization as determined by PCR or other validated commercial or public health assay
- Bio-ADM ≥50 pg/mL or ≥30% increase until the end of the next day (with a minimum of 35 pg/mL at all)
- DPP3 ≤30 ng/mL
- Age ≥18 years at time of screening
- Body weight ≤150 kg at time of screening
- Informed consent

Key exclusion criteria were:

- Life expectancy less than 3 months before COVID-19 at the discretion of the investigator
- Invasive mechanical ventilation ≥72 hours at time point of randomization
- Resuscitation >45 minutes
- Known or assumed hypersensitivity to the active substance, to adrecizumab or any of its excipients, or known serious hypersensitivity to other monoclonal antibodies
- Uncontrolled hematological/oncological malignancies
- Absolute neutropenia <500 per µL
- Pre-existing severe chronic liver disease (i.e., Child-Pugh C) before COVID-19 hospitalization

ECMO initiated during current COVID-19 hospitalization was not an exclusion criterion.

TEST PRODUCT, DOSE, MODE OF ADMINISTRATION, BATCH NUMBER(S):

The IMP to be tested in this study was the humanized IgG1 monoclonal antibody adrecizumab (HAM 8101) on top of SoC. Adrecizumab was administered as a single IV infusion over 60 minutes at a dose of 2 mg/kg body weight (BW). Precautionary measures to prevent allergic reactions under infusion were to be administered as deemed required.

The study sites were provided by the Sponsor with the test product. Adrecizumab was labelled in accordance with GCP/GMP regulations for IMPs. Test product (and reference product) were provided to the study sites in a blinded manner.

The following product batch number was used: 1069792

DURATION OF TREATMENT: Test products were administered once as single dose treatment on Day 1. The follow-up duration in this study was 90 days.

REFERENCE THERAPY, DOSE, MODE OF ADMINISTRATION, BATCH NUMBER(S):

Reference treatment in this placebo-controlled study was NaCl 0.9% solution for IV infusion and was to be handled in the same way as the test product. The study sites were provided by the Sponsor with the reference product, which was labelled in accordance with GCP/GMP regulations for IMPs. Reference product (and test product) were provided to the study sites in a blinded manner.

No batch numbers were available for placebo.

CRITERIA FOR EVALUATION:

The primary efficacy endpoint was the time to clinical improvement, defined as the time from randomization to an improvement of 2 points (from the status at randomization) on the WHO 8-point "ordinal scale for clinical improvement", or live discharge from the hospital, whichever occurred first.

Secondary efficacy endpoints were:

- Clinical status at Day 28, as measured on the WHO 8-point ordinal scale
- Survival (time-to-event) until Day 28 and end of follow-up (90 days)
- Rate and length of invasive mechanical ventilation until Day 28 and Day 90, defined as use of endotracheal or tracheostomy tube assisted ventilation
- Rate and length of ECMO therapy until Day 28 and Day 90
- Length of stay at ICU after application of IMP up to a total of 90 days
- Length of hospital stay after application of IMP up to a total of 90 days
- All-cause re-hospitalization within 90 days
- Rate of renal replacement therapy (RRT) until day 28 and Day 90
- Change in SOFA score sum (only during hospitalization on ICU) within 24 hours of IMP administration (start of infusion), 48 hours, and Day 7 post-infusion
- Change in clinical status on the WHO 8-point ordinal scale for COVID-19 at Days 7, 28, and 90
- Between-group difference in QoL as assessed by EQ-5D-5L at discharge, Day 28, and Day 90

Major safety endpoints were:

- Frequency and severity of serious adverse events (SAEs) / adverse events (AEs) / suspected unexpected serious adverse reactions (SUSARs) in both arms occurring within 28 days
- Mortality related to adrecizumab

- Interruption of infusion of adrecizumab due to intolerability to adrecizumab
- New treatment-emergent AEs (TEAEs) (and changes in severity and frequency in these) related to adrecizumab

Moreover, an expanded safety composite endpoint including death, myocardial infarction (MI), stroke, recurrent hospitalization, acute kidney injury, and gastrointestinal disorders was to be analyzed (actually not analyzed).

STATISTICAL METHODS:

General considerations

All applicable statistical tests were two-sided and performed using a 5%-significance level. Thus, all presented confidence intervals (CIs) encompassed 95% and were two-sided. Analyses of secondary efficacy outcomes were performed exploratory without adjustment for multiple testing. Categorical data were summarized by absolute and relative frequencies. Continuous data were summarized by mean, standard deviation (SD), median, interquartile range (IQR), and range. The numbers of available observations and numbers of missing observations were presented for the treatment groups separately.

Due to the small sample size, analysis models were not adjusted for stratification factors.

Primary efficacy endpoint

The primary endpoint was the time to clinical improvement, defined as the time from randomization to an improvement of at least 2 points (from the status at randomization) on the WHO 8-point ordinal scale or live discharge from the hospital, whichever occurred first. The primary efficacy analysis was a test for difference (2-sided significance level of 5%) performed on the ITT population applying a Cox proportional hazards model. Hence, an estimated hazard ratio (HR) was provided for the comparison of treatment groups.

Cumulative event rates were estimated according to Kaplan-Meier; deaths and failure of clinical improvement within 28 days were censored at 28 days.

Secondary efficacy endpoints

Metric outcomes and dichotomous/ordinal outcomes

Effects (i.e., treatment contrasts) were expressed as difference in means for metric outcomes and odds ratios (ORs) for dichotomous and ordinal outcomes from linear, logistic or ordinal regressions, respectively. Adjustment for stratification factors, as specified in the statistical analysis plan (SAP), was not possible due to the small sample size.

Overall survival

OS was analyzed in the same way as with the analysis of the primary endpoint; differences in mortality were expressed as HR with 95%-CI. In addition, survival probabilities at Days 28 and 90 were estimated using the Kaplan-Meier method.

WHO-8, SOFA score, and EQ-5D-5L

Changes from baseline in WHO-8 scores and SOFA score, and absolute mean values in EQ-5D-5L, were analyzed with estimated marginal means (EMM) and EMM differences using a linear mixed model with random intercepts for patient. The models for WHO-8 score and SOFA score were adjusted for baseline scores.

SUMMARY OF RESULTS AND CONCLUSIONS:

Subject Disposition:

A total of 31 patients were screened and 16 patients randomized to either the placebo group (N=10) or to the adrecizumab group (N=6). These 16 patients represented the ITT population and were used for the analyses of efficacy and safety. All 16 patients completed the study as defined in the protocol.

Demography and Baseline Characteristics:

The randomized patient population (N=16) consisted of 5 females and 11 males at a mean age of 74 ± 10 years (median: 78 years, range: 54 to 84 years). The placebo group comprised 3 females and 7 males (median age: 81 years; age range: 58-84 years) and the adrecizumab consisted of 2 females and 4 males (median age: 71 years; age range: 54-84 years). Thus, the median age in the placebo group was higher than in the adrecizumab group. Generally, the baseline homogeneity of treatment groups e.g., in terms of disease severity could not be checked.

Efficacy Results:

The outcome of the primary efficacy analysis (time from randomization to clinical improvement of at least 2 points on the WHO-8 scale or live discharge within 28 days) is summarized in Synopsis Table A. A total of 7 patients (70.0%) in the placebo group and 4 patients in the adrecizumab group (66.7%) experienced a relevant improvement within the observation period of 28 days. The resulting incidence per 100 patient days (PDs) was minimally higher in the adrecizumab group than in the placebo group (5.0 vs. 4.9/100 PDs), and the resulting HR was 1.02 (adrecizumab/placebo) and associated with a broad 95%-CI of [0.30; 3.47] and a non-significant p-value of p=0.980. Overall, no relevant treatment group difference was found with the primary efficacy analysis, which was, however, grossly underpowered.

Synopsis Table A: Primary efficacy analysis

	Placebo group (N=10)	Adrecizumab group (N=6)	Estimate / [95%-CI] [a]	p-value
No. of patients (%)	7 (70.0)	4 (66.7)	---	---
Incidence/100 PDs [b]	4.9 [2.0; 10.1]	5.0 [1.4; 12.8]	HR=1.02 [0.30; 3.47]	0.980

CI=Confidence interval; HR=Hazard ratio; PD=Patient day
a: An HR estimate of >1.0 indicates better outcome in the adrecizumab group (higher incidence of pts. with improvement).
b: With 95%-CI.

The mortality through Day 90 was 5/10 patients (50.0%) in the placebo group and 2/6 patients (33.3%) in the adrecizumab group. Vice versa, the survival probability after 3 months (Day 90) was 50% (95%-CI: [27; 93]) in the placebo group and 67% (95%-CI: [38; 100]) in the adrecizumab group. Synopsis Table B summarizes the outcomes of the secondary efficacy endpoint analyses over up to 90 days. Generally, the results of these endpoint analyses were consistent with that seen in the analysis of the primary endpoint and mostly showed slightly more favorable outcomes in the adrecizumab group compared with the placebo group, but the differences were quite small and not nominally significant (i.e., no descriptive p-values <0.05).

Synopsis Table B: Analysis of secondary efficacy endpoints

Variable		Placebo group (N=10)	Adrecizumab group (N=6)	Estimate / (95%-CI)	p-value
WHO-8 score					
Ordinal scale analysis		see full analysis	see full analysis	OR=0.8 [0.1, 5.1] [a]	0.818
WHO-8 score [b]	Day 7	0.01 [-1.77; 1.78]	-0.81 [-3.09; 1.46]	-0.82 [-3.78; 2.14]	0.566
	Day 28	0.51 [-1.27; 2.28]	-1.61 [-3.89; 0.66]	-2.12 [-5.08; 0.84]	0.149
	Day 90	-0.37 [-2.14; 1.41]	-3.01 [-5.29; -0.74]	-2.64 [-5.60; 0.32]	0.077
Mortality					
No. of patients, n (%)		5 (50.0)	2 (33.3)	---	---
Mortality/100 PDs [c]		0.9 [0.3; 2.1]	0.5 [0.1; 1.9]	HR=0.70 [0.14; 3.61] [a]	0.669
Survival probability					
	Day 28, % [c]	60 [36; 100]	67 [38; 100]	---	---
	Day 90, % [c]	50 [27; 93]	67 [38; 100]	---	---
MV	Rate, n (%) [d]	5 (50.0)	5 (83.0)	OR=5.0 [0.5; 115.6] [a]	0.203
MV (days)					
Mean time ± SD		12.0 ± 10.1	8.0 ± 6.5	-4.0 [-20.0; 12.0] [e]	0.580
LoS on ICU					
Mean time ± SD		12 ± 8	11 ± 10	-1.4 [-11.0; 8.2] [e]	0.760
LoS on normal ward					
Mean time ± SD		17 ± 10	20 ± 13	3.0 [-9.8; 15.8] [e]	0.621
RRT	Rate, n (%) [d]	3 (30.0)	3 (50.0)	OR=2.3 [0.3; 21.1] [a]	0.428
ECMO	Rate, n (%) [d]	0	1 (16.7)	nc	nc
SOFA score [b]					
	24 hrs. (± 6 hrs.)	0.35 [-1.72; 2.41]	-0.18 [-3.29; 2.94]	-0.53 [-4.58; 3.53]	0.784
	48 hrs. (± 12 hrs.)	-0.65 [-2.72; 1.41]	-1.71 [-4.87; 1.45]	-1.06 [-5.15; 3.03]	0.587
	Day 4	-0.23 [-2.32; 1.86]	-0.46 [-3.62; 2.70]	-0.23 [-4.34; 3.87]	0.905
	Day 5	-0.48 [-2.57; 1.61]	-0.71 [-3.87; 2.45]	-0.23 [-4.34; 3.87]	0.905
	Day 6	-0.58 [-2.70; 1.53]	-1.46 [-4.62; 1.70]	-0.88 [-4.99; 3.24]	0.655
	Day 7	-0.17 [-2.32; 1.97]	-1.71 [-4.87; 1.45]	-1.54 [-5.67; 2.60]	0.440
EQ-5D index score [f]					
	Discharge	0.49 [0.12; 0.85]	0.90 [0.39; 1.42]	0.42 [-0.22; 1.05]	0.181
	Day 28	0.36 [-0.01; 0.72]	0.88 [0.47; 1.29]	0.52 [-0.03; 1.07]	0.061
	Day 90	0.47 [0.15; 0.80]	0.86 [0.45; 1.27]	0.38 [-0.14; 0.91]	0.138
EQ-VAS [f]	Discharge	62.08 [33.09; 91.08]	56.11 [19.31; 92.91]	-5.97 [-52.78; 40.83]	0.785
	Day 28	36.41 [9.64; 63.19]	65.00 [31.03; 98.97]	28.59 [-14.57; 71.75]	0.170
	Day 90	39.04 [14.20; 63.88]	81.81 [45.02; 118.61]	42.77 [-1.60; 87.14]	0.057

CI=Confidence interval, ECMO=Extracorporeal membrane oxygenation; EMM=Estimated marginal means; hrs.=Hours; ICU=Intensive care unit; LoS=Length of stay (in days); MV=Mechanical ventilation; nc=Not calculable; OR=Odds ratio, RRT=Renal replacement therapy; SD=Standard deviation

a: An estimate of <1.0 indicates better outcome in the adrecizumab group.

b: Estimated marginal means (EMM) change from baseline and 95%-CI at time point per treatment group and resulting treatment contrast ([change in adrecizumab group] minus [change in placebo group]) with 95%-CI. Generally, lower score values indicate better clinical conditions.

c: With 95%-CI.

d: Number of patients with event (percentage).

e: Treatment group difference for means (adrecizumab minus placebo) with 95%-CI.

f: Estimated marginal mean (EMM) values and 95%-CI at time point per treatment group and resulting treatment contrast ([mean in adrecizumab group] minus [mean in placebo group]) with 95%-CI. Generally, higher score values indicate better clinical conditions.^

Safety Results:

Adverse events were analyzed on the event level (Synopsis Table C) and on the patient level (Synopsis Table D).Overall, 16 AEs occurred in the adrecizumab group and 64 AEs in the placebo group. These included 2 SAEs in the adrecizumab group and 13 SAEs in the placebo group. Thus, the event incidence was clearly higher in the placebo group than in the adrecizumab group. The most common AEs in the total study population (i.e., ≥3 events at the preferred term level) were "delirium" (8 events), "multiple organ dysfunction syndrome" (4 events), "pleural effusion" (3 events), and "septic shock" (3 events). Only 1 AE was reported that was considered to be at least possibly related to adrecizumab. This event occurred in the adrecizumab group and was related to blood creatinine phosphokinase (CPK) increase. This event was non-serious, of mild severity, and the outcome was reported as recovered/resolved. Thus, no SARs or SUSARs were reported in this study.

On a patient basis, AEs were reported in all 6 patients (100.0%) in the adrecizumab group and in 9 patients (90.0%) in the placebo group. The most commonly reported SOC in the total population were "infections and infestations (2 patients [33.3%] in the adrecizumab group vs. 9 patients [90.0%] in the placebo group; overall 11 patients [68.8%]), "metabolism and nutrition disorders" (no patients in the adrecizumab group vs. 9 patients [90.0%] in the placebo group; overall 9 patients [56.2%]), and "general disorders and administration site conditions" (2 patients [33.3%] in the adrecizumab group vs. 7 patients [70.0%] in the placebo group; overall 9 patients [56.2%]). At the PT level, the most common AEs in the total population were "delirium" (7 patients, 43.8%), "multiple organ dysfunction syndrome" (4 patients, 25.0%), "septic shock" (3 patients, 18.8%), and "pleural effusion" (3 patients, 18.8%; see Synopsis Table D). Only 2 SAEs were documented in 2 patients in the adrecizumab group (MOF and ARDS, respectively), and none of the documented SAEs had a reasonable possibility for a relationship with study treatment. In conclusion, the numerical AE and SAE incidences were higher in the placebo group than in the adrecizumab group, and the only AE considered to be at least possibly related to adrecizumab was a mild and transient increase in blood CPK.

Synopsis Table C: Adverse event experience (event-based analysis)

	Adrecizumab group n	Placebo group n	Total n
Number of any AEs	**16**	**64**	**80**
Number of SAEs	**2**	**13**	**15**
Number of unrelated AEs [a]	**15**	**64**	**79**
Number of related AEs [a]	**1**	**0**	**1**
Most common AEs by MedDRA PT [b]			
Delirium	2	6	8
Multiple organ dysfunction syndrome	1	3	4
Pleural effusion	0	3	3
Septic shock	0	3	3

AE=Adverse event; SAE=Serious adverse event
Note: All data in this table are based on number of events.
a: "Related" means at least possibly related to study drug. The only related event occurred in the adrecizumab group and was non-serious "blood creatine phosphokinase increased" (mild severity; outcome: recovered/resolved).
b: At least 3 events at the preferred term (PT) level in the total population.

Synopsis Table D: Adverse event experience (patient-based analysis)

	Adrecizumab group (N=6) n (%)	Placebo group (N=10) n (%)	Total (N=16) n (%)
Patients with any AEs	**6 (100.0)**	**9 (90.0)**	**15 (93.8)**
Patients with SAEs	**2 (33.3)**	**6 (60.0)**	**9 (56.3)**
Patients with related AEs [a]	**1 (16.7)**	**0**	**1 (6.2)**
Most common AEs by MedDRA PT [b]			
Delirium	2 (33.3)	5 (50.0)	7 (43.8)
Multiple organ dysfunction syndrome	1 (16.7)	3 (30.0)	4 (25.0)
Pleural effusion	0	3 (30.0)	3 (18.8)
Septic shock	0	3 (30.0)	3 (18.8)
All SAEs by MedDRA PT			
Multiple organ dysfunction syndrome	1 (16.7)	3 (30.0)	4 (25.0)
Septic shock	0	3 (30.0)	3 (18.8)
Cardiac arrest	0	2 (20.0)	2 (12.5)
Acute respiratory distress syndrome	1 (16.7)	0	1 (6.2)
Anastomotic leak	0	1 (10.0)	1 (6.2)
Renal failure	0	1 (10.0)	1 (6.2)
Respiratory failure	0	1 (10.0)	1 (6.2)
Transient ischaemic attack	0	1 (10.0)	1 (6.2)

AE=Adverse event; SAE=Serious adverse event
Note: All data in this table are based on number of patients with event.
a: "Related" means at least possibly related to study drug. The only related event occurred in the adrecizumab group and was non-serious "blood creatine phosphokinase increased" (mild severity; outcome: recovered/resolved).
b: At least 3 patients involved at a given PT in the total population

Overall conclusions:

No statistically/nominally significant treatment group differences at all were observed in the efficacy analyses performed in the AGNES-19 trial. Likewise, no obvious trends were observed in favor of adrecizumab. However, the reported efficacy outcomes based on just 16 patients (instead of 180 planned) were not appropriately robust, and the descriptive statistical between-group tests were grossly underpowered. Therefore, the current efficacy results of the AGNES-19 study are not suitable to evaluate the potential beneficial effects of adrecizumab vs. placebo in the clinical management of moderately to severely ill COVID-19 patients with endothelial barrier dysfunction.

The analysis of AEs and SAEs among the 16 randomized showed an event pattern that was consistent with a severely ill study population of COVID-19 patients at an advanced age, and no potential safety issues were observed with the IMP adrecizumab compared with placebo.

Overall, additional trials with an appropriate number of patients would be required to solidly evaluate the clinical value of adrecizumab in the treatment of moderately to severely ill COVID-19 patients with assumed endothelial barrier dysfunction.

DATE AND VERSION OF THIS REPORT: Final 1.0; dated 27-Jan-2025