CTC North

Placebo-controlled, double-blind, randomized trial to assess the efficacy and safety of Adrecizumab in subjects with cardiogenic shock

Clinical Study Report Synopsis

EudraCT-No.	2018-002824-17
Protocol-No.	Sponsor: ACCOST-HH / CRO: CTC181431
Version / date	1.0 / 18-JAN-2022
Study phase	Phase 2
Study start and completion date	Q1/2019 to Q2 2021
Sponsor	University Medical Center Hamburg-Eppendorf Phone +49 40 7410-57975 Fax +49 40 7410-40194
Principal investigator	Mahir Karakas, MD, MBA (LKP) University Heart Center Hamburg-Eppendorf Department of General and Interventional Cardiology

2 SYNOPSIS

Name of Sponsor/company: University Medical Center Hamburg-Eppendorf	**Individual study table referring to part of the dossier**	**(For National Authority Use only)**
Name of finished product: Adrecizumab	**Volume:**	
Name of active ingredient: Adrecizumab (IgG1 monoclonal antibody)	**Page:**	

Study title	Placebo-controlled, double-blind, randomized trial to assess the efficacy and safety of Adrecizumab against placebo in subjects with cardiogenic shock
Principal investigator	Mahir Karakas
Study center	University Heart Center Hamburg-Eppendorf Department of General and Interventional Cardiology Martinistrasse 52 20246 Hamburg, Germany
Publication (reference)	Not applicable
Protocol No.	ACCOST-HH (Sponsor), CTC181431 (CRO)
EudraCT-No.	2018-002824-17
Study period	Q1/2019 to Q2 2021
Phase of development	Phase 2
Primary objective	To evaluate the number of days through day 30 without need for cardiovascular (CV) organ support, including vasopressors, or mechanical support (VA-ECMO, Impella®) in patients with cardiogenic shock treated with Adrecizumab on top of standard of care (SOC).
Secondary objectives	To compare the active treatment and placebo / control substance (NaCl 0.9%) groups with respect to ventilation, (cardiovascular) death, length of ICU stay, medication, clinical condition, biomarker levels, quality of life, and re-hospitalization (stratified according to baseline ADM levels: above versus below Median level").
Methodology	Investigator-initiated, prospective, randomized, double-blinded, multi-center, controlled, interventional trial Eligible patients were randomized (1:1) to intravenous (i.v.) Adrecizumab or placebo / control substance (i.e. NaCl 0.9%), on top of SOC. The scheme of the trial is depicted in **Fehler! Verweisquelle konnte nicht gefunden werden.**.
Number of subjects	150
Indication	Cardiogenic shock

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Main criteria for inclusion	• Hospitalization for cardiogenic shock (at the discretion of the local investigator)
	• Cardiogenic shock is usually defined as:
	  • Systolic blood pressure < 90 mmHg > 30 min or inotropes required to maintain pressure > 90 mmHg during systole
	  • Signs of left heart insufficiency and/or pulmonary congestion
	  • Signs of impaired organ perfusion with at least one of the following:
	  • Altered mental status
	  • Cold, clammy skin
	  • Urine output < 30 ml/h
	  • Serum lactate > 2 mmol/l
	• Age above 18 years at time of screening
	• Body weight below 150 kg at time of screening
	• Females/males who agree to comply with the applicable contraceptive requirements of the protocol	

Test product, dose and mode of administration, batch no.	Adrecizumab on top of SOC Dosage form: Solution for injection in 200 mg vials Dose: 8 mg/kg body weight (BW), single dose Route: i.v. infusion over approximately 1 hour Batch No.: KPR/19040/01 KPR/200116/01 KPR/200128/01	
Duration of treatment	Single infusion over 60 min	
Reference product, dose and mode of administration, batch no.	Placebo / control substance (NaCl 0.9%) on top of SOC Route of administration corresponding to Adrecizumab	

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Criteria for evaluation **Efficacy and safety**	**Primary safety endpoint** • Rate of serious adverse events (SAEs) / adverse events (AEs) / suspected unexpected serious adverse reaction (SUSARs) (deemed to be related to investigational medicinal product [IMP]) in both arms within 30 days • Mortality related to Adrecizumab • Interruption of infusion due to intolerability to Adrecizumab • New treatment-emergent adverse events [TEAEs] (and changes in severity and frequency in these) related to Adrecizumab **Primary efficacy endpoint:** • Number of days through day 30 without need for CV organ support, including vasopressors, or mechanical support ((VA-ECMO, Impella®). In case of death the remaining days through day 30 count as days with need for support.	

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Statistical methods

Efficacy:

The statistical analysis of the primary endpoints was based on an ANCOVA, using a two-sided significance level of 5%. The primary analysis was adjusted for the stratification factors of the randomization. Randomization was carried out centrally using a computerized system.
A block randomization procedure was applied with stratification by age (above versus below 65 years), sex (male versus female), and type of underlying cardiogenic shock (acute myocardial infarction [AMI] versus other entities).

Description of the primary efficacy analysis and population:

The primary analysis population was intention-to-treat (ITT). All details on the analyses, including the definition of the analysis populations, are detailed in a statistical analysis plan (SAP), which was finalized prior to database lock and unblinding.

Effect size assumed for power calculation:

The primary objective was to evaluate the number of days through day 30 without need for cardiovascular CV organ support, including vasopressors, or mechanical support (VA-ECMO, Impella®).

Only adjudicated events were used for the analysis. Power calculations had been carried out using a series of scenarios. This was based on data from previous shock trials and data from our intensive care unit (ICU) database.
Based on these event-rates, we calculated that, at a significance level of 5%, 128 patients were required to have an 80% chance of detecting a clinically relevant decrease in the primary outcome measure. In order to compensate for potential drop-outs, a total of 150 patients had to be recruited.

Safety:

Was ascertained via the assessment of key safety endpoints, and compared between treatment groups by chi square tests. Safety endpoints for the Adrecizumab group were analyzed descriptively (event rates with two-sided 95% confidence intervals [CI]).

Secondary endpoint(s):

The analysis of the secondary endpoints with an assumed normal distribution followed the same lines of analyses of the primary outcome assessment.

The time to event outcomes were analyzed using the Cox proportional hazards model.

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Efficacy results	In this study no substantial differences between treatment with Adrecizumab on top of SOC compared to placebo were seen, therefore the primary aim of this study was not met. On average the duration of support for participants of the Adrecizumab group was 1.69 days longer compared to the placebo group. This mean difference was not statistically significant with a p-value of 0.367. Also, sensitivity analyses or alternative modelling in case of unmet assumptions did not show substantial differences regarding interpretation. The Adrecizumab group and the placebo group were comparable within the respective variability for all defined secondary endpoints: Mortality by days 30 and 90 was 40% and 48% in the Adrecizumab group as compared to 40% and 43% in the placebo group. Rates of CV death, the need for invasive mechanical ventilation, rates of re-hospitalization, length of initial stay at the ICU, length of mechanical ventilation and the distance of the 6-MWT did not differ statistically between both groups. The mini-mental state exam questionnaire (MMSE) could not be analyzed as specified in advance due to substantial amount of missing data and was therefore analyzed descriptively, only. The analysis of EQ-5D-scores is postponed. The additional not pre-specified subgroup analysis shows a dependency on the type of underlying shock with a negative impact on patients presenting with AMI.	

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Safety results	Safety analysis was performed in the safety set including 150 patients. All participants received the allocated treatment (Adrecizumab 8 mg/kg body weight or placebo, both on top of SOC). Patients were treated with a mean dose of Adrecizumab of 636.3 mg ± 122.5 mg, ranging from 360.0 to 960 mg. Occurrence of AEs (672 AEs in total) was comparable in both groups: 348 AEs occurred in the group treated with Adrecizumab and 325 AEs occurred in the placebo group. The corresponding mean of AEs was 4.5 in both groups. This was also the case for occurrence of SAEs (215 SAEs in total): 110 SAEs occurred in the group treated with Adrecizumab and 105 AEs occurred in the placebo group. The corresponding mean of SAEs was 1.4 in both groups. All AEs as well as all SAEs were considered as not related to treatment with Adrecizumab. Alltogether there was a total of 68 deaths that occurred during this study; 37 deaths were observed in the group treated with Adrecizumab and 31 deaths were reported in the placebo group. The main reason for deaths was cardiogenic shock (n = 41), followed by septic shock or sepsis (n = 5), and unknown reason (n = 5). There were no further observations related to safety.	
Conclusion	It can be concluded that the humanized monoclonal non-neutralizing adrenomedullin antibody Adrecizumab was well tolerated in patients presenting with acute cardiogenic shock, but did not improve morbidity and mortality outcomes.	
Date of report	18 JAN 2022	