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ORIGINAL ARTICLE

The ADESTE trial: A phase 2 study of enibarcimab, a monoclonal antibody targeting adrenomedullin, in acute heart failure

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Abstract

Aims This study aimed to conduct a phase 2 proof-of-concept and safety study to evaluate the effect of ENIBARCIMAB (EN), a non-neutralizing humanized monoclonal antibody targeting the N-terminus of adrenomedullin (ADM), administered immediately after stabilization with standard of care (SoC) treatment, in patients hospitalized for acute heart failure (AHF).

Methods and results This prospective, open-label, controlled, interventional, multicenter, dose-escalation study was conducted at two cardiology sites in Indonesia. Patients were divided into two interventional groups sequentially receiving 0.5 mg/kg (SoC + EN 0.5 mg/kg, n = 10; first cohort) and 2 mg/kg (SoC + EN 2 mg/kg, n = 10; second cohort) of EN via 1-h intravenous (IV) infusion within 48 h after admission for AHF. The control group (n = 10) was treated with SoC therapy for AHF therapy. All patients were monitored continuously within 24 h post-infusion and subsequent daily until discharge. Treatment-related serious adverse events (SAEs) were recorded during hospitalization and up to 90 days after discharge. Both EN dosages were well-tolerated, and no significant safety issues were identified during hospitalization and up to 90 days of follow up. SAEs occurred in 10% of patients in each EN group but were deemed not related to treatment. No significant differences in the occurrence of SAEs were found between the groups. Five deaths occurred: three (30%) in the control group as compared with two deaths (20%) in the SoC + EN 2 mg/kg group. EN led to a significant increase in plasma bio-ADM levels within 24 h post-infusion, with the SoC + 2 mg/kg group showing the highest increase. Within 1 h from IV EN infusion, SoC + EN 2 mg/kg compared with 0.5 mg/kg, resulted in a significant percentage reduction in systolic, diastolic blood pressure, and mean arterial pressure. However, it did not result in severe hypotension and the need for drug discontinuation.

Conclusions In this pilot safety study of patients hospitalized for AHF, IV infusion of EN 0.5 and 2 mg/kg increased circulating plasma bio-ADM levels and was well-tolerated without treatment-related SAEs occurring during hospitalization and up to 90 days after discharge.

Keywords Acute heart failure; Bio-adrenomedullin; ENIBARCIMAB; Safety; Tolerability

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Introduction

The prevalence of heart failure (HF) is globally increasing due to the increase in life expectancy, improved survival rates after acute coronary events, and enhanced treatment modalities.[1,2] Current lingering effects of COVID-19 disease also contribute to the HF increased prevalence.[3] Nevertheless, mortality and rehospitalization rates after acute HF (AHF) remain high, particularly among individuals aged >65 years.[4,5] Evidence indicates that the initiation and optimization of medical therapy during hospitalization for AHF are linked to reduced rates of short-term rehospitalization.[6] However, to date, no prospective randomized studies have conclusively shown that treatments administered during the acute phase of HF significantly improve short- to medium-term clinical outcomes.[6,7]

Adrenomedullin (ADM) is a peptide hormone of 52 amino acids synthesized by endothelial and vascular smooth muscle cells,[8] circulating between blood compartments and the interstitium.[9] From proADM, its precursor peptide, a proteolytic fragmentation leads to the formation of four fragments (proADM NH2-terminal 20 peptide, midregional proADM, C-terminally glycine-extended ADM [ADM-Gly], and C-terminal proADM).[10] ADM-Gly, an inactive form of ADM, is then partly transformed into the biologically active C-terminally amidated ADM or bio-ADM.[10] Blood levels of bio-ADM can be measured using an assay from sphingotest® bio-ADM (SphingoTec GmbH, Germany).[10] In patients with AHF, bio-ADM blood level reflects the severity of congestion and predict the likelihood of rehospitalizations and mortality.[11]

In previous studies on healthy volunteers and patients with septic shock, the administration of a single dose of ENIBARCIMAB (EN), a humanized monoclonal antibody targeting the N-terminus of ADM resulted in dose-dependent increases in circulating bio-ADM levels.[12] EN retains its effect on bio-ADM with a half-life of approximately 15 days.[12] EN high affinity for bio-ADM, and its large molecular weight prevents it from crossing the endothelial barrier, leading to increased bio-ADM levels in the blood compartment[13] and consequent hypothesized improvement in vascular integrity. Animal sepsis models have demonstrated that EN, while reducing inducible nitric oxide synthase expression, improves haemodynamics, renal function, and systemic inflammation.[14,15]

In a phase 2 clinical trial for the treatment of early septic shock, EN showed no relevant safety issue after the single infusion of 2 and 4 mg/kg body weight.[16] No safety concerns were observed in all preclinical studies and in two phase 1 studies in which 0.5, 2, and 8 mg/kg of EN were administered.[12]

In AHF, the pathogenesis of oedema and congestion extends beyond elevated hydrostatic pressure, being significantly influenced by impaired endothelial barrier function. Plasma bio-ADM plays a critical role in maintaining vascular integrity and preventing the disintegration of the endothelial barrier.[13] We hypothesize that enhancing ADM activity within the endothelium could mitigate the progression of congestion. This could be achieved by increasing bio-ADM levels in circulation through the administration of intravenous EN in patients with AHF. Based on this premise, a phase 2 proof-of-concept and safety study was initiated to evaluate a novel investigational medicinal product (IMP), EN, designed to elevate plasma bio-ADM concentrations and thereby restore and stabilize vascular integrity and function in AHF patients.

This study aimed to conduct a phase 2 proof-of-concept and safety study to evaluate EN infusion at increasing doses in AHF inpatients already clinically stabilized by receiving standard of care (SoC) treatment as recommended by the European Society of Cardiology (ESC) Guidelines of acute and chronic HF.[17]

Methods

Study design

This study was a prospective, open-label, controlled, interventional, multicenter, safety, and tolerability dose-ranging, phase 2 study with EN, at 0.5 and 2 mg/kg, and enrolled inpatients with AHF. The study was conducted in accordance with the International Conference on Harmonization guidelines on Good Clinical Practice. Institutional review board approval for the study protocol was obtained from the respective Medical and Health Research Ethics Committees (MHREC) at the Faculty of Medicine, Public Health and Nursing Universitas Gadjah Mada-Dr. Sardjito Hospital, Yogyakarta, and Universitas Brawijaya-Dr. Saiful Anwar Hospital, Malang, Indonesia. The study, titled **A**drecizumab (ENIBARCIMAB) **D**ose-**E**scalation **S**afety and **T**olerability **E**valuation (ADESTE), was registered at ClinicalTrials.gov (NCT04252937).

Serious adverse events (SAEs) were collected and carefully monitored throughout hospitalization and the 90-day follow up period. For laboratory and haemodynamics safety evaluations and organ's function assessment, plasma, urine samples, and cardiac haemodynamic parameters were collected daily from the first day of treatment until hospital discharge. In addition, daily electrocardiograms (ECGs) were taken. An independent data and safety monitoring board (DSMB) periodically reviewed the safety data.

As a secondary objective, the initial efficacy and pharmacodynamics of EN in patients with AHF were also assessed. This evaluation occurred throughout the hospitalization period, typically anticipated to last for 7 days, or until discharge if occurring earlier or later than the anticipated duration.

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Study population

Inpatients with AHF were recruited from two study centers in Indonesia. The recruitment sites were Dr. Sardjito Hospital in Yogyakarta, Indonesia, and Dr. Saiful Anwar Hospital in Malang, Indonesia. The inclusion criteria were as follows: (1) age ≥18 years; (2) hospitalization for AHF and stabilization according to the ESC guidelines for HF, (3) New York Heart Association (NYHA) functional classes II–IV, (4) enrolled within 48 h from the hospital presentation, (5) body weight 40–120 kg, and (6) provision of written informed consent. The exclusion criteria are shown in *Table S1*.

Because the study focused on safety and was exploratory proof-of-concept, no formal calculation of the sample size was performed.[18,19] A written MHREC-approved informed consent form (ICF) was obtained from each patient before initiating any procedures. Patients admitted to hospitals for AHF were screened for eligibility by site investigators after evaluation using inclusion and exclusion criteria, within 48 h after admission.

Screening and recruitment

Assessments during the screening phase determined patients' eligibility for the study and their ability to comply with protocol requirements by completing all assessments. The following assessments were performed at screening and conducted before EN administration: written MHREC-approved ICF, demographics, medical history and co-morbidity, diagnostic workup of AHF based on 2016 ESC guidelines,[17] NYHA functional classification, inclusion and exclusion criteria, physical examination including HF signs and symptoms, dyspnoea assessment by the visual analogue scale (VAS), composite clinical congestive score (CCS), systolic and diastolic blood pressure (also mean arterial pressure), heart rate, respiratory rate, pulse oxygen saturation, clinical laboratory tests, plasma bio-ADM, 12-lead ECG, chest X-ray, transthoracic echocardiography (TTE), and current and previous medications. A diagnostic workup was conducted, which involved a detailed review of symptoms, a thorough physical examination with particular attention to signs and symptoms of congestion and/or hypoperfusion, and additional investigations by ECG, and TTE. The HF decompensation etiologies/precipitants were identified, and specific treatments were subsequently initiated by attending physicians at each study centre.

Drug administration

The EN vials were stored in hospital refrigerators at a temperature range of 2°C–8°C and shielded from light, maintaining temperature-controlled until administration. Vials were allowed to reach room temperature (approximately 20–25°C) for 1 h before use, after which the product was diluted with sterile 0.9% NaCl for infusion. Treatment involved administering a body weight-adjusted dose of EN, up to a maximum body weight of 120 kg. The EN was then administered as an intravenous (IV) infusion over 1 h using an infusion pump. The study was conducted in an open-label format. Standard treatment in each hospital was at the discretion of attending physicians based on the ESC standard HF treatment guidelines.[17] Other medications could be used as indicated according to the discretion of the attending physicians. All medications were recorded in the electronic case report form (eCRF).

Two cohorts of patients were included, each receiving one of two escalating doses of EN, which was administered as an IV infusion. The first 10 patients enrolled in the study received EN at a dose of 0.5 mg/kg (SoC + EN 0.5 mg/kg), and the second 10 patients received 2 mg/kg on top of SoC (SoC + EN 2 mg/kg). The third dose of 8 mg/kg EN planned in the initial version of the study protocol could not be conducted because of the COVID-19 pandemic that occurred during this trial and the expiration of the study drug in the meantime. In addition, a third cohort of patients with AHF received SoC without EN infusion (SoC alone), as the control group.

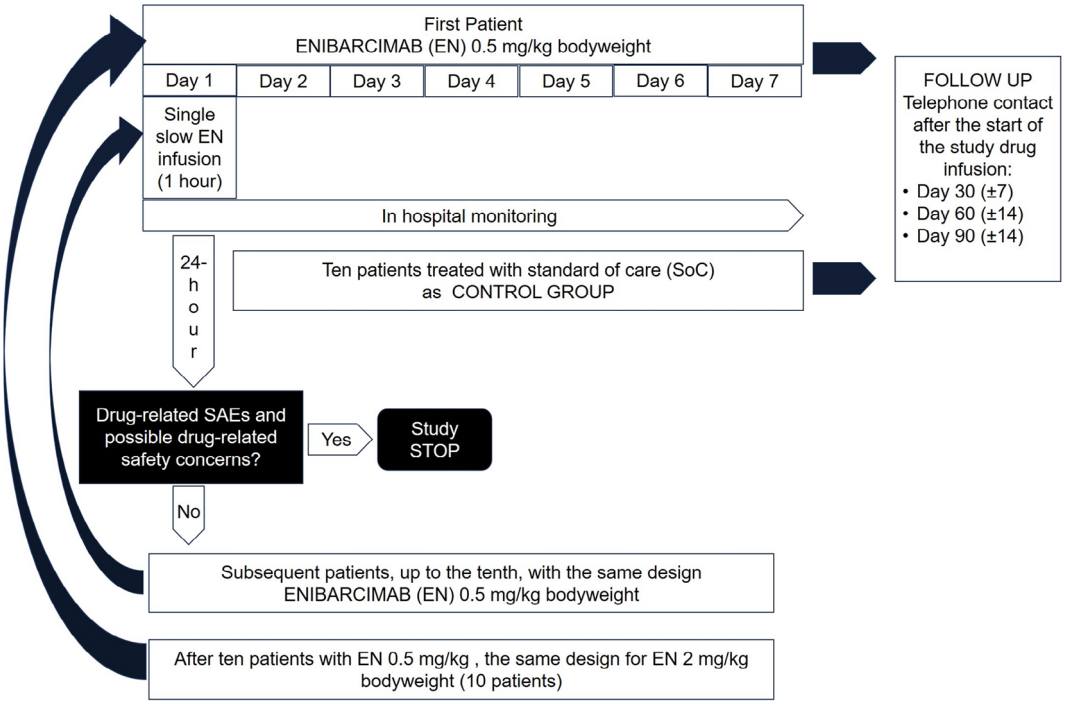
During EN infusion, patients were closely monitored for vital cardiorespiratory functions and signs of intolerability, a practice that continued for 24 h post-infusion. Throughout the 24-h observation, the safety of EN was evaluated in each patient. After 10 patients had been treated with 0.5 mg/kg with no critical safety findings related to EN identified by the investigators and by the appointed independent DSMB, the subsequent cohort of 10 patients was recruited for treatment with a dose of 2 mg/kg EN (SoC + EN 2 mg/kg) via IV infusion followed by 24-h observation., and were monitored in both inpatient and outpatient settings (*Figure 1*).

The evaluation after EN administration was assessed at predose (T-0) and then 30 min, 1 h, 2 h, 6 h, 12 h, and 24 h from the onset of the test dose: adverse events, HF signs and symptoms, systolic and diastolic blood pressure (and mean arterial pressure), heart rate, respiratory rate, pulse oxygen saturation, dyspnoea VAS score, and composite CCS. Blood pressure was measured by standardized aneroid sphygmomanometer (average value from three measurements, applicable also in subjects with atrial fibrillation). Diuresis was monitored by the insertion of a permanent urinary catheter. Body weight and height were obtained to calculate the body mass index (BMI).

Inpatient evaluation

Inpatient evaluation was performed from admission until day 7 of hospitalization or discharge if occurred earlier. Vital

Figure 1 The adrecizumab (ENIBARCIMAB) dose-escalation safety and tolerability evaluation or ADESTE study design.



cardiorespiratory functions were monitored noninvasively. Blood pressure was measured by standardized aneroid sphygmomanometer daily in the morning, disregarded the medication timing. During hospitalization, symptoms and signs of residual congestion (as a composite CCS and dyspnoea VAS score) were assessed daily. To detect any clinically significant changes and abnormalities, a 12-lead ECG was taken at baseline and repeated daily.

Clinical haematology was measured daily from baseline to 7 days or until discharge. Clinical chemistry, consisting of blood urea nitrogen, creatinine, aspartate aminotransferase (AST), alanine aminotransferase (ALT), sodium, potassium, glucose, uric acid, and albumin, was measured every other day from baseline to 7 days or until discharge. HbA1c and procalcitonin were measured at baseline. Levels of NT-proBNP and hs-troponin I were measured daily from baseline to 7 days or until discharge. These laboratory tests were routinely performed in study sites.

For bio-ADM measurement, blood was drawn into ethylenediaminetetraacetic acid tubes, and plasma was isolated by centrifugation at room temperature. Samples for bio-ADM measurements were taken daily from pretreatment to 7 days or until discharge. Plasma samples were stored in a −80°C freezer at the central hospital laboratory. Bio-ADM was quantified (sphingotest® bio-ADM) following the instructions provided by SphingoTec GmbH and was conducted using a microtiter plate (MTP) luminometer.

Study followup

After hospital discharge, patients were followed up as outpatients for 90 days. Specifically, they were contacted by telephone at 30 (±7), 60 (±14), and 90 (±14) days after the start of the EN infusion to assess the occurrence of SAEs, cardiovascular deaths, and rehospitalizations for AHF or renal failure (*Figure 1*).

Study endpoints

The primary objectives were safety and tolerability. The safety endpoints consisted of the interruption of EN infusion because of intolerability, and the frequency of treatment-emergent AEs during hospitalization (inpatient phase), including cardiovascular and non-cardiovascular treatment-emergent SAEs, treatment-emergent AEs defined by laboratory clinically significant abnormal findings, renal impairment, and clinically significant ECG changes. Changes in systolic and diastolic blood pressures and mean arterial pressures were assessed during EN infusion and 24 h. The exploratory endpoints were treatment-emergent SAEs due to any reason after discharge at 30, 60, and 90 days of follow up, including (1) emergency visits, (2) rehospitalization days, (3) number of rehospitalizations, and (4) number of deaths due to AHF, renal failure, and all other causes. In every occurring SAE,

investigators reported to the DSMB which indicated the causality assessment: (1) reasonable causal relationship with the study drug (related or possibly related) and (2) no reasonable causal relationship with the study drug (not related).

The secondary objectives were to evaluate the preliminary efficacy and pharmacodynamics of EN infusion. The preliminary efficacy encompassed (1) changes in AHF signs and symptoms, systolic and diastolic blood pressures, mean arterial pressure, and heart rate assessed within 1 and 24 h from the onset of EN infusion and daily until day 7 or discharge, (2) length of hospital stay, (3) changes in the dyspnoea VAS score, and the composite CCS assessed daily until day 7 or discharge, (4) 24-h urine output and net renal fluid balance, and (5) changes in plasma NT-proBNP levels from baseline and daily until day 7 or discharge.

The pharmacodynamic endpoint was the change in plasma bio-ADM from baseline and daily until day 7 or discharge.

Statistical analysis

Statistical analyses were conducted on three distinct sets: full-analysis set (FAS), per-protocol analysis set (PP), and safety analysis set (SAF), encompassing patients who were enrolled and completed the 90-day followup period. Continuous data are presented as means, standard deviations and medians, interquartile range (Q1–Q3) and categorical data are reported in absolute frequency (n) and percentage (%).

To assess differences among the groups (SoC, SoC + EN 0.5 mg/kg, and SoC + EN 2 mg/kg), either one-way analysis of variance (ANOVA), nonparametric Kruskal–Wallis test, or, where appropriate, the chi-square or Fisher exact test, was employed. Posthoc pairwise comparisons were performed using the Mann–Whitney test. A mixed model was utilized to evaluate clinical and laboratory parameters of interest during hospitalization, considering days, groups, and their interaction as fixed variables and patients as the random variable. Estimated mean and relative standard error of mean (SEM) were reported. The *p*-values were not adjusted for multiple comparisons. Each analysis was reported individually for each group. A p-value < 0.05 was considered significant. All statistical analyses were conducted using SAS® version 9.4, and figures were generated using GraphPad Prism version 8.0.1.

Results

Baseline characteristics

Participant enrolment started on 13 December 2019, whereas the last participant was enrolled on 24 August 2021, and the 90th day of follow up was 10 November 2021. This study was completed using two incremental EN doses of 0.5 and 2 mg/kg. Because the COVID-19 pandemic significantly decelerated participant enrolment and drug expiration, the planned EN 8 mg/kg dose could not be administered and evaluated in this study. The effect of the pandemic on enrolment was beyond the control of the study organizers, leading to the inability to complete the study as originally planned (ClinicalTrials.gov Identifier: NCT04252937).

A total of 34 patients were consecutively screened and enrolled in this study from two sites in Indonesia. Four patients exhibited major deviations, namely, an issue of the drug temperature excursion during storage, and were subsequently excluded from the study. Consequently, their data were not analysed (*Figure S1*). Therefore, out of the 34 patients screened and enrolled, 30 were included in the FAS, PP, and SAF statistical analyses, which overlapped. All patients, Asian in ethnicity, were allocated into three cohorts, namely, SoC (n = 10), SoC + EN 0.5 mg/kg (n = 10), and SoC + EN 2 mg/kg (n = 10), groups.

The baseline patient characteristics are described in *Table 1*. Demographics, clinical parameters, medical history and co-morbidities, echocardiogram parameters, medical treatments on admission, and clinical congestion parameters were well balanced among groups, except for hypertension (90%), which mostly occurred in the SoC + EN 2 mg/kg group, and the median composite CCS, which was significantly higher in the SoC group than in the EN groups. However, the CCS was comparable between the SoC + EN 0.5 mg/kg and SoC + EN 2 mg/kg groups (P = 0.481). Medical treatment and its daily dose on admission and at discharge are shown in Supplementary (Table S2).

The baseline clinical laboratory measurements of each group allocation are shown in *Table 2*. The laboratory parameters were generally comparable across the groups, with the exception of NT-proBNP level. The NT-proBNP level was significantly lower in the SoC + EN 0.5 mg/kg group compared to the SoC + EN 2 mg/kg group (P = 0.004). Additionally, the baseline levels of hs-troponin I and bio-ADM were comparable among the groups.

The median onset time of EN IV infusion from hospital admission (clinical stabilization time) was not significantly different between the SoC + EN 0.5 mg/kg and SoC + EN 2 mg/kg groups (median (Q1–Q3): 44.07 (40.04–47.40) h vs. 34.91 (33.59–45.18) h, P = 0.089).

The median duration of hospitalization for all patients was 6.0 (Q1–Q3: 6.0–8.0) days. The length of hospital stay did not significantly vary among the SoC, SoC + EN 0.5 mg/kg, and SoC + EN 2 mg/kg groups (median (Q1–Q3): 6.5 (6.0–8.0), 7.5 (6.0–9.0), and 6.0 (5.0–6.0) days, respectively; P = 0.051).

BIO-ADM changes during hospitalization

The EN in SoC + EN 0.5 mg/kg and SoC + EN 2 mg/kg caused a dose-dependent increase in bio-ADM levels 24 h after infusion, which persisted until discharge (*Figure 2*). In contrast,

Table 1 Baseline characteristics of the subjects of the ADESTE study.

Baseline parameters	SoC (n = 10)	SoC + EN 0.5 mg/kg (n = 10)	SoC + EN 2 mg/kg (n = 10)	P value
Demography				
Age (years), mean ± SD	58.10 ± 13.55	60.40 ± 7.11	55.40 ± 7.14	0.443
Male sex, *n* (%)	8 (80%)	9 (90%)	8 (80%)	0.787
Body weight (kg), mean ± SD	64.62 ± 11.38	57.16 ± 9.75	61.94 ± 9.77	0.285
Clinical parameters				
NYHA functional class, *n* (%)				0.369
II	0	1 (10%)	0	
III	10 (100%)	8 (80%)	10 (100%)	
IV	0	1 (10%)	0	
Systolic blood pressure (mmHg), mean ± SD	115.00 ± 23.67	115.90 ± 25.67	122.60 ± 20.63	0.754
Diastolic blood pressure (mmHg), mean ± SD	82.30 ± 12.87	71.70 ± 13.32	74.40 ± 7.18	0.157
Mean artery pressure (mmHg), mean ± SD	93.20 ± 14.1	86.43 ± 16.09	90.47 ± 9.56	0.539
Heart rate (b.p.m.), mean ± SD	80.60 ± 16.71	79.30 ± 8.60	84.60 ± 18.26	0.720
Respiratory rate (x/m), mean ± SD	20.50 ± 2.27	20.60 ± 1.90	19.90 ± 2.60	0.760
Pulse oxygen saturation (%), mean ± SD	97.50 ± 1.35	98.00 ± 1.70	98.30 ± 1.57	0.416
Co-morbidities				
Diabetes mellitus, *n* (%)	2 (20)	2 (20)	2 (20)	1.00
Hypertension, *n* (%)	3 (30)	5 (50)	9 (90)	0.022
History of coronary or ischaemic heart disease, *n* (%)	3 (30)	5 (50)	7 (70)	0.202
Atrial fibrillation, *n* (%)	3 (30)	2 (20)	1 (10)	0.535
Chronic kidney disease, *n* (%)	0	0	1 (10)	0.355
Echocardiogram parameters				
LV ejection fraction (%), mean ± SD	37.67 ± 17.13	32.60 ± 9.37	29.5 ± 12.41	0.412
LV ejection fraction >50%	2 (20)	1 (10)	1 (10)	0.662
LV ejection fraction <40%	6 (60)	8 (80)	9 (90)	
Medical treatments on admission				
Furosemide, *n* (%)	10 (100)	10 (100)	10 (100)	N.A
Thiazide, *n* (%)	0 (0)	0 (0)	1 (10)	N.A
Spironolactone, *n* (%)	6 (60)	7 (70)	6 (60)	0.866
ACE/ARB/ARNI, *n* (%)	9 (90)	10 (100)	9 (90)	0.585
Beta-blockers, *n* (%)	5 (50)	5 (50)	7 (70)	0.394
Nitrates, *n* (%)	2 (20)	4 (40)	5 (50)	0.366
Clinical congestion parameters				
Dyspnoea VAS score, median (Q1–Q3)	35.0 (20.0–50.0)	20.0 (0.0–40.0)	27.5 (0.0–50.0)	0.544
Composite CCS, median (Q1–Q3)	7.0 (4.0–9.0)	3.5 (2.0–6.0)	3.0 (2.0–5.0)	0.025*

Abbreviations: ACE, angiotensin-converting enzyme; ARB, angiotensin receptor blocker; ARNI, angiotensin receptor/neprilysin inhibitor; b.p.m., beat per min; CCS, clinical congestive score; EN, ENIBARCIMAB; LV, left ventricle; NYHA, New York Heart Association; SoC, standard of care; VAS, visual analogue scale; x/m, times per min.
*Mann–Whitney test: SoC + EN 0.5 mg/kg versus SoC + EN 2 mg/kg, P = 0.481.

bio-ADM levels decreased over time in the SoC group. The consistently significant percentage increase in plasma bio-ADM, from the baseline level, occurred in the SoC + EN 2 mg/kg group (*Figure 2B*). At discharge, the SoC + EN 2 mg/kg group had the highest plasma bio-ADM level compared with the SoC + EN 0.5 mg/kg (mean ± SEM: 72.72 ± 17.06 vs. 31.18 ± 20.90 pg/mL, P = 0.060) and SoC (72.72 ± 17.06 vs. 45.85 ± 18.34 pg/mL, P = 0.215) groups (*Figure 2A*).

Primary objectives: Safety and tolerability of EN

When comparing the effects of a 1-h IV EN infusion at doses of SoC + EN 2 mg/kg to SoC + EN 0.5 mg/kg and control, a significant reduction in the absolute values of systolic blood pressure, diastolic blood pressure, and mean arterial pressure was observed 1 h after starting the infusion. This trend of reduction persisted up to 24 h post-infusion (*Table 3*). A significant percentage reduction of systolic blood pressure was observed in the SoC + EN 2 mg group at 1-h IV EN infusion. In contrast, no significant changes were observed in the SoC + EN 0.5 mg/kg or the control groups (*Figure 3*). However, at the 24-h mark after IV EN infusion, no significant differences in absolute value and percentage changes in systolic and diastolic blood pressure and mean arterial pressure were found among the SoC, SoC + EN 0.5, and SoC + EN 2 mg/kg groups (*Figure S2* and *Table 3*). This observation was also similar from baseline until discharge (*Figure 3*).

Throughout the 1-h IV EN infusion, no patients discontinued the treatment because of symptomatic hypotension or intolerance. In addition, no SAEs were reported during the 1-h infusion period or within 24 h after infusion.

During hospitalization, SAEs occurred in 1 (10%) patient in the SoC + EN 0.5 mg/kg group, who had a prolongation of in-hospital stay due to pneumonia, whereas 1 more patient (10%) in the SoC + EN 2 mg/kg group, needed a prolongation of hospitalization stay because of HF (*Table 3*). No SAEs

Table 2 Baseline clinical laboratory measurements of the subjects of the ADESTE study.

Baseline parameters	SoC (n = 10)	SoC + EN 0.5 mg/kg (n = 10)	SoC + EN 2 mg/kg (n = 10)	P value
Leucocytes (10^3/μL), mean ± SD	7.68 ± 2.75	8.12 ± 2.19	8.34 ± 2.19	0.824
Haemoglobin (g/dL), mean ± SD	13.85 ± 1.72	13.04 ± 1.43	14.58 ± 2.28	0.195
AST (g/dL), mean ± SD	19.5 (16.8–65.5)	15.5 (8.8–22.0)	21.5 (13.5–54.8)	0.241
ALT (g/dL), mean ± SD	30.0 (21.0–70.5)	19.0 (14.0–24.25)	29.0 (17.3–42.5)	0.107
Urea nitrogen (g/dL), mean ± SD	27.90 ± 17.24	22.70 ± 21.20	24.60 ± 7.56	0.316
Creatinine (g/dL), mean ± SD	1.34 ± 0.48	1.36 ± 0.48	1.39 ± 0.36	0.870
Sodium (mmol/L), mean ± SD	136.40 ± 5.06	138.00 ± 4.00	137.40 ± 3.10	0.686
Potassium (mmol/L), mean ± SD	3.67 ± 0.67	3.94 ± 0.64	3.77 ± 0.56	0.627
Glucose (g/dL), mean ± SD	115.60 ± 35.00	122.90 ± 46.22	103.20 ± 44.67	0.580
Uric acid (g/dL), mean ± SD	9.57 ± 3.63	9.46 ± 3.42	10.50 ± 2.17	0.721
Albumin (g/dL), mean ± SD	3.93 ± 0.29	3.67 ± 0.61	3.59 ± 0.39	0.241
HbA1C (%), mean ± SD	6.96 ± 1.29	6.23 ± 0.63	7.20 ± 1.65	0.219
Procalcitonin, (ng/mL), median (Q1–Q3)	0.095 (0.050–0.240)	0.065 (0.050–0.173)	0.105 (0.073–0.500)	0.400
NT-proBNP (pg/mL), median (Q1–Q3)	11 970.0 (3635.50–17 149.50)	3979.0 (1804.50–7974.00)	15 214.50 (7424.50–21 640.25)	0.019*
hs-troponin I (ng/L), median (Q1–Q3)	21.02 (11.12–245.80)	25.00 (12.27–53.71)	53.70 (36.78–96.05)	0.091
Bio-ADM, (pg/mL), median (Q1–Q3)	35.50 (27.00–71.00)	19.00 (15.00–35.00)	27.00 (19.00–48.00)	0.127

Abbreviations: ADM, adrenomedullin; ALT, alanine aminotransferase; AST, aspartate aminotransferase; EN, ENIBARCIMAB; HbA1C, glycated haemoglobin; hs, high sensitivity; NT-proBNP, N-terminal pro B-type natriuretic peptides; SOC, standard of care.
*Mann–Whitney test: SoC + EN 0.5 mg/kg versus SoC + EN 2 mg/kg, P = 0.004.

Figure 2 Absolute value (pg/mL) (A) and percentage (%) changes (B) of plasma bio-ADM level from baseline to discharge day among SoC, SoC + EN 0.5 mg/kg, and SoC + EN 2 mg/kg groups. Data are expressed as the mean ± standard error of the mean (SEM). The differences among groups were analysed using mixed-effects model: *$P < 0.05$ compared with the SoC group; #$P < 0.05$ compared with baseline. EN, ENIBARCIMAB; SoC, standard of care.

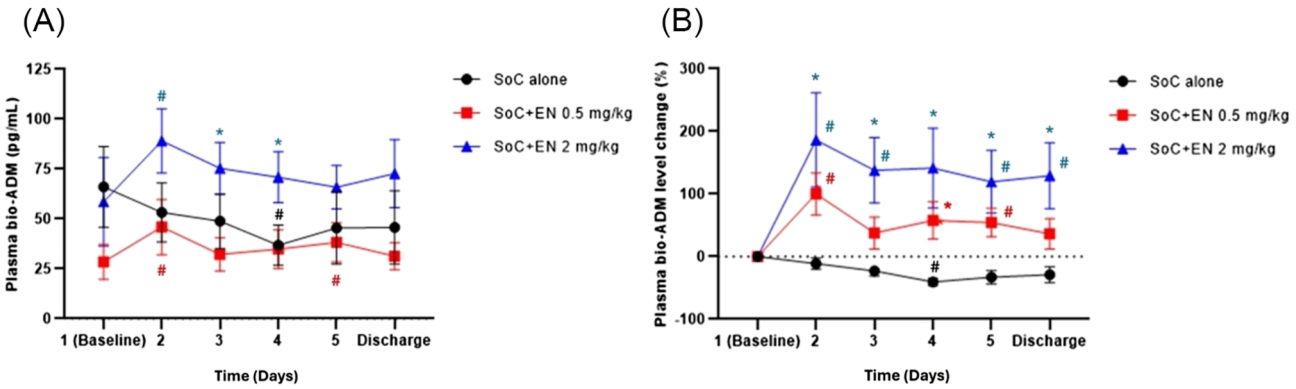
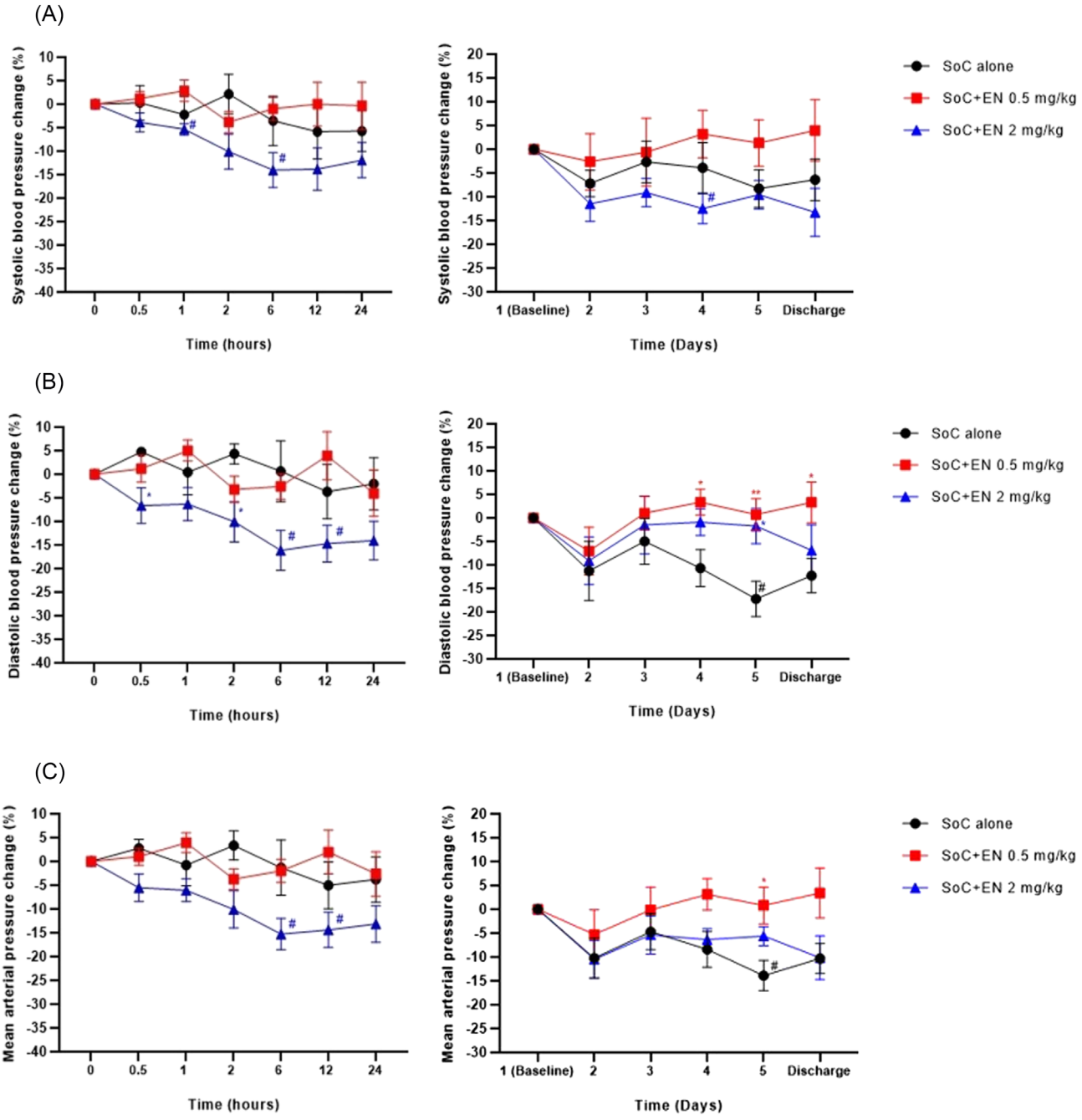


Table 3 Absolute value changes (Δ) of the systolic blood pressure, diastolic blood pressure, and mean arterial pressure at 1 and 24 h after ENIBARCIMAB IV infusion (0 h) and serious adverse events during hospitalization among groups.

Endpoints	SoC alone* (n = 10)	SoC + EN 0.5 mg/kg (n = 10)	SoC + EN 2 mg/kg (n = 10)	P value
0 h (before ENIBARCIMAB infusion) to 1 h ENIBARCIMAB IV infusion				
Δ Systolic BP (mmHg)	−3.50 (−9.00 to 2.00)	3.00 (−4.25–7.25)	−6.50 (−9.00 to −3.00)	0.007
Δ Diastolic BP (mmHg)	−0.00 (−4.00 to 4.00)	2.50 (0.75–5.00)	−4.00 (−10.75 to −0.25)	0.012
Δ MAP (mmHg)	−1.17 (−5.67 to 3.33)	1.80 (0.00–4.42)	−5.66 (−12.33 to −1.42)	0.008
0 h (before ENIBARCIMAB infusion) to 24 h ENIBARCIMAB IV infusion				
Δ Systolic BP (mmHg)	−4.5 (−23.25 to 0.0)	2.5 (−19.75–11.25)	−12.0 (−23.75 to −2.75)	0.240
Δ Diastolic BP (mmHg)	−1.00 (−15.00 to 5.00)	0.50 (−10.50–2.00)	−7.00 (−19.00 to −3.25)	0.191
Δ MAP (mmHg)	−9.5 (−20.08 to −1.25)	1.17 (−17.33–6.25)	−6.5 (−21.75 to −4.92)	0.141
Serious adverse events (SAEs) during hospitalization				
SAEs, n (%)	0 (0%)	1 (10%)	1 (10%)	0.585

Note: Values are given in median (Q1–Q3).
Abbreviations: BP, blood pressure; EN, ENIBARCIMAB; MAP, mean artery pressure; SAEs, serious adverse events; SoC, standard of care.
*For the SoC alone group, 0 h was at baseline (day 1) and 24 h was at day 2.

Figure 3 Left panel: percentage (%) changes in systolic blood pressure (A), diastolic blood pressure (B), and mean arterial pressure (C) within 24 h from the initiation of ENIBARCIMAB IV infusion among the SoC, SoC + EN 0.5 mg/kg, and SoC + EN 2 mg/kg groups. Right panel: Percentage changes (%) in systolic blood pressure (A), diastolic blood pressure (B), and mean arterial pressure (C) from baseline (day 1) to discharge day among the SoC, SoC + EN 0.5 mg/kg, and SoC + EN 2 mg/kg groups. Data are expressed as the mean ± standard error of the mean (SEM). The differences among groups were analysed with mixed-effects model: *$P < 0.05$ compared with the SoC group, #$P < 0.05$ compared with baseline. EN, ENIBARCIMAB; SoC, standard of care.



occurred in the control group (SoC alone). Both SAEs were not related to EN, the decision commissioned by DSMB after carefully considering investigators' report. No other SAEs related to significant laboratory value changes (haematology parameters, liver function tests, hs-troponin I value, and electrolytes), renal impairments (creatinine levels changes), and ECG were observed during hospitalization in all patients (*Figure S3*).

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Table 4 Treatment-emergent SAEs after hospital discharge within 90 days of follow-up.

Serious adverse events	SoC alone (n = 10)	SoC + EN 0.5 mg/kg (n = 10)	SoC + EN 2 mg/kg (n = 10)	P value
Subjects with SAEs, n (%)	4 (40)	2 (20)	4 (40)	0.700
Death subjects, n (%)	3 (30)	0 (0)	2 (20)	0.698
Death due to heart failure	1 (20)	0 (0)	2 (20)	
Death due to other causes	2(20)	0 (0)	0 (0)	
Subjects with at least one hospitalization, n (%)	4 (40)	2 (20)	4 (40)	0.700
Hospitalization due to heart failure	2 (20)	2 (20)	3 (30)	
Hospitalization due to other cause	2 (20)	0 (0)	1 (10)	
Cumulative SAEs within 90 days, n (%)	5 of 18 (27.8)	7 of 18 (38.9)	6 of 18 (33.3)	0.700
SAEs at 30 days, n (%)	2 of 18 (11.1)	2 of 18 (11.1)	2 of 18 (11.1)	0.787
SAEs at 60 days, n (%)	2 of 18 (11.1)	1 0f 18 (5.6)	3 of 18 (16.7)	0.535
SAEs at 90 days, n (%)	1 of 18 (5.6)	4 of 18 (22.2)	1 of 18 (5.6)	0.587

Abbreviations: EN, ENIBARCIMAB; SAEs, serious adverse events; SoC, standard of care.

The exploratory endpoints are presented in *Tables 4* and *S3*. After hospital discharge and throughout the 90-day follow up period, a total of 10 (33.3%) patients experienced at least one hospitalization: 4 (40%) in the SoC group, 2 (20%) in the SoC + EN 0.5 mg/kg group, and 4 (40%) in the SoC + EN 2 mg/kg group (P = 0.700). A total of 18 SAEs occurred in 10 patients: specifically, 5 (27.8%) events in 4 patients in the SoC group, 7 (38.9%) in 2 patients in the SoC + EN 0.5 mg/kg group, and 6 (33.3%) in 4 patients in the SoC + EN 2 mg/kg group. The comparison among the three groups did not reveal a significant difference in the percentage of patients experiencing at least one SAE (P = 0.700). Regarding mortality, 5 deaths occurred (16.7%): 3 in the SoC group and 2 in the SoC + EN 2 mg/kg group (P = 0.698). Among these deaths, 3 were attributed to HF (1 in the SoC group and 2 in the SoC + EN 2 mg/kg group), whereas the other 2 deaths were unrelated to HF and/or renal failure (both in the SoC group).

Secondary objectives: Preliminary efficacy of EN

Both SoC + EN 0.5 mg/kg and SoC + EN 2 mg/kg, as well as SoC alone, produced comparable 24-h urine output increase (median (Q1–Q3): 1750.0 (1237.5–2812.5) mL, 2250.0 (1960.0–3192.5) mL, and 2225 (1577.5–3387.5) mL, P = 0.161, respectively) and 24-h net fluid balance reduction (median (Q1–Q3): −350.0 (−1417.5 to −106.3) mL, −1023.5 (−2106.5 to −932.5) mL, and −1382.5 (−2040.0 to −487.75) mL, P = 0.076, respectively).

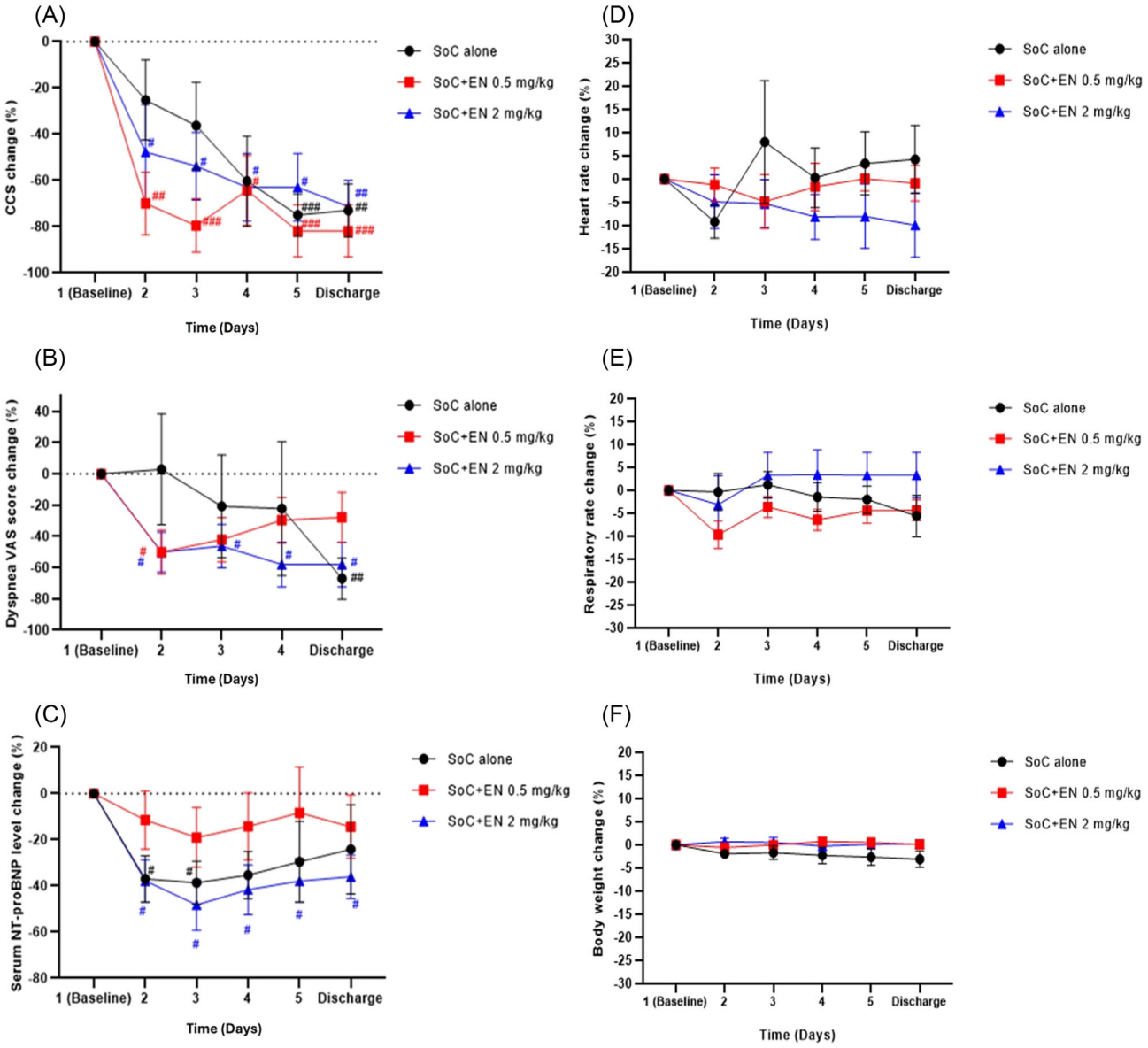
Both SoC + EN 0.5 mg/kg and SoC + EN 2 mg/kg, as well as SoC alone, produced equivalent percentage reduction of composite CCS and dyspnoea VAS scores from baseline to discharge and absolute values at discharge (*Figure 4A,B* and *Table 5*). No significant difference was found between the SoC + EN 0.5 mg/kg and SoC + EN 2 mg/kg groups, as well as in the SoC group, on changes in body weight, heart rate, and respiratory rate and pulse oxygen saturation as well, from baseline to discharge day (*Figure 4D–F*). The SoC + EN 2 mg/kg group had a significant percentage reduction of serum NT-proBNP levels from baseline to discharge (P = 0.033) (*Figure 4C*). No significant difference was noted when comparing the percentage and absolute changes in NT-proBNP levels at discharge among the three groups (*Figure 4C* and *Table 5*).

Discussion

This study evaluated the safety and tolerability of escalating doses of infusion of EN at doses of 0.5 mg/kg, 2 mg/kg bodyweight plus the SoC, or standard treatment alone in patients with clinically stabilized AHF within 48 h after hospital presentation. EN at both doses met the primary objectives of good safety and tolerability profile for treatment in inpatients with AHF. No significant differences in any of the explored efficacy parameters were observed in EN at both 0.5 and 2 mg/kg within 24 h after infusion and daily until discharge and 90 days of follow-up. While both doses produced increased plasma bio-ADM levels, EN at 2 mg/kg infusion produced the earliest and most significant increases in plasma bio-ADM levels, which persisted until hospital discharge. In this pilot study, both doses of EN at 0.5 and 2 mg/kg showed similar safety profiles.

A previous study indicated that the increase in bio-ADM levels occurs rapidly, within minutes of infusion, and persists for >15 days,[12] reflecting the half-life of EN. EN, being a high affinity, non-neutralizing antibody targeting the N-terminus of ADM, possesses properties that prevent it from crossing the endothelial barrier because of its high molecular weight.[13] However, it can effectively mobilize preexisting ADM from the interstitial space into the bloodstream.[13] This mechanism results in a net elevation in the levels of functional plasma ADM, known as bio-ADM, through the relocation of bio-ADM from the interstitial space to the circulation. This leads to an augmented bio-ADM activity in the bloodstream, which is beneficial for endothelial cells while simultaneously mitigating its vasodilatory effects. Our findings demonstrate that 0.5 and

Figure 4 Percentage (%) changes of composite CCS (A), dyspnoea VAS score (%) (B), NT-proBNP levels (%) (C), heart rate (D), respiratory rate (E), and bodyweight (F) from baseline to discharge day among SoC alone, SoC + EN 0.5 mg/kg, and SoC + EN 2 mg/kg groups. Data are expressed as the mean ± standard error of the mean (SEM). The differences among groups were analysed with mixed-model effects: #$P < 0.05$ as compared with baseline; ##$P < 0.01$ as compared with baseline; ###$P < 0.001$ as compared with baseline. CCS, composite congestion score; EN, ENIBACIMAB; NT-proBNP, N-terminal pro-B-type natriuretic peptide; SoC, standard of care; VAS, visual analogue score.



2 mg/kg EN induce a dose-dependent increase in plasma bio-ADM levels among patients with AHF.

Besides the increased hydrostatic pressure, deranged endothelial barrier function affects oedema and congestion in AHF. Plasma bio-ADM controls endothelial barrier function by supporting vascular integrity and endothelial barrier.[13,20] Therefore, it would be reasonable to hypothesize that in patients with AHF, improved endothelial function by increased bio-ADM levels in the circulation could reduce the development of pulmonary congestion leading to pulmonary oedema. The effect of ADM on increasing diuresis and natriuresis was mediated through the inhibition of the renin–angiotensin–aldosterone system.[21] The effect of ADM is dependent on the location of the molecule: interstitial ADM acts on vascular smooth muscle cells and leads to vasodilation, whereas plasma ADM was thought to act on endothelial cells and restore impaired vascular integrity.[12,21] Consequently, the therapeutic option would be to increase the functional plasma bio-ADM levels to foster the protective effect of ADM against vascular leakage in the endothelium. This

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Table 5 Absolute value changes (Δ) from baseline to discharge and values at discharge of the dyspnoea VAS score, composite CCS, and NT-proBNP level among the groups.

Endpoints	SoC alone (n = 10)	SoC + EN 0.5 mg/kg (n = 10)	SoC + EN 2 mg/kg (n = 10)	P value
Δ Dyspnoea VAS score, median (Q1–Q3)	−15.0 (−32.50 to −3.75)	−2.50 (−20.0 to 0.0)	−25.0 (−46.25 to −0.0)	0.281
Δ Composite CCS, median (Q1–Q3)	−3.0 (−4.5 to −1.75)	−1.5 (−3.0 to −1.0)	−2.0 (−3.25 to −1.0)	0.290
Δ NT-proBNP (pg/mL), median (Q1–Q3)	−2681.50 (−8048.50 to 1521.75)	−656.05 (−3017.00 to 313.25)	−4892.65 (−8686.75 to −1793.50)	0.107
Δ hs-troponin I (ng/L), median (Q1–Q3)	−2.6 (−9.5 to 2.3)	−6.8 (−11.8 to 3.1)	4.6 (−4.9 to 36.4)	0.468
Dyspnoea VAS score, median (Q1–Q3)	2.5 (0.0–12.5)	0.0 (0.0–11.25)	0.0 (0.0–5.0)	0.465
Composite CCS, median (Q1–Q3)	0.5 (0.0–2.25)	0.0 (0.0–0.25)	0.0 (0.0–1.25)	0.329
NT-proBNP (pg/mL), median (Q1–Q3)	5634.0 (2523.0 to 11 661.5)	2969.5 (1785.0 to 6217.0)	9218.5 (4989.75 to 17 069.75)	0.133
hs-troponin I (ng/L), median (Q1–Q3)	22.05 (12.7–281.6)	17.7 (8.6–34.5)	94.3 (42.1–107.3)	0.085

CCS, clinical congestive score; EN, ENIBARCIMAB; hs, high sensitivity; NT-proBNP, N-terminal pro B-type natriuretic peptides; SoC, standard of care; VAS, visual analogue scale.

strategy was proven to be safe and tolerable in patients with sepsis.[12]

The PROTECT trial revealed that out of all biomarkers, including BNP and clinical variables, bio-ADM was the strongest indicator of congestion remaining at day 7 after hospitalization.[22] Furthermore, in patients with AHF, the GREAT AHF trial showed that persisting congestion mirrored by bio-ADM was related with short-term mortality.[23] In the AdrenOSS-2 trial, a greater initial EN concentration was found at the 4 mg/kg dose compared with the 2 mg/kg dose with an elimination half-life of 7–8 days.[16] This study demonstrated a dose-dependent EN-induced elevation of plasma bio-ADM levels without a change in midregional-proADM, which proved that the increase in bio-ADM levels is not the effect of ADM de novo synthesis.[16] This current study corroborated a consistent increase in plasma bio-ADM levels with the higher dose of EN at 2 mg/kg, compared with 0.5 mg/kg, which persisted until the day of discharge. However, in this study we did not measure the concentration of EN, which is a limitation worth mentioning.

This study also investigated indicators of the preliminary efficacy of EN in AHF. The overall AHF signs and symptoms improved and were not different among the studied groups, whereas EN 2 mg/kg was associated with persistent reduction in systolic and diastolic blood pressures without any clinical intolerability. The reduced blood pressure was prominent within 24 h of drug infusion. The groups receiving EN infusion and standard treatment alone had similar lengths of hospital stay. Because the sample size for efficacy outcome in this study is too small, further larger clinical trials are needed to investigate the efficacy of EN among patients with AHF. For this purpose, EN 2 mg/kg can be proposed as the starting dose to be administered in a future efficacy trial which may incorporate pharmacokinetic measurements as well.

Limitations

This pilot study had limited ability to detect clinically significant differences across various outcomes and might not demonstrate any adverse effects which presented in <1/10 patients because of insufficient power and sample size. In addition, it was unable to establish a clear dose–response relationship for EN, as pharmacokinetic measurements were not conducted. The ADESTE trial, given its limitations, did not assess the concentration of EN. Nonetheless, the study demonstrated the safety and tolerability of a higher EN dose of 2 mg/kg for patients with AHF. In this study, drug therapy was initiated within 48 h of admission to the emergency department, allowing for initial stabilization. Notably, no significant difference was observed between the two drug doses in terms of this initial stabilization period. However, the potential for earlier initiation of this drug merits further investiga-

tion. The study did not include a cohort of patients receiving EN at a dose of 8 mg/kg. Other limitations of this study were the lack of blinding among the investigators to the study drug and the absence of randomization. These factors constrained the study's results, as they did not account for potential unmeasured confounders.

In summary, among patients hospitalized with AHF, the administration of ENIBARCIMAB, a novel humanized monoclonal antibody targeting ADM, at both 0.5 and 2 mg/kg doses, led to high plasma bio-ADM levels. Importantly, this intervention was well-tolerated and demonstrated a favourable safety profile both during hospitalization and after discharge.

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Conflict of interest statement

Claudia Knothe was employed by Adrenomed AG, the company holding patent rights for the ENIBARCIMAB (formerly known as ADRECIZUMAB) compound. Andreas Bergmann holds shares in Adrenomed AG. Salvatore Di Somma is a consultant for Adrenomed AG. The rest of the authors declare no conflict of interest.

Supporting information

Additional supporting information may be found online in the Supporting Information section at the end of the article.

Figure S1. Patients' flowchart from two study center hospitals in Indonesia. From 34 screening and enrolment, 4 patients had major study deviation, and were excluded from analysis. The analysis was performed for 30 patients who completed the study.

Figure S2. Absolute value (mmHg) (left panel) and percentage changes (%) (right panel) of systolic blood pressure (A), diastolic blood pressure (B), and mean arterial pressure (C) within 24 hours from pre-dose (0 hour) of ENIBARCIMAB IV infusion among SoC alone, SoC + EN 0.5 mg/kg and SoC + EN 2 mg/kg, Data are expressed as the mean ± standard error of the mean (SEM). The differences among groups were analysed with mixed-model effects: #$P < 0.05$ as compared with pre-dose (0 hour or baseline for SoC alone) since ENIBARCIMAB IV infusion. EN: enibarcimab; SoC: standard of care.

Figure S3. Percentage (%) changes of haematology parameters (haemoglobin) (A), leukocyte count (B), platelet count (C)), liver function tests (ALT level (D), AST level (E)), hs-Troponin I (F), creatinine (G), potassium (H), and sodium (I)) from baseline to discharge among SoC alone, SoC + EN 0.5 mg/kg and SoC + EN 2 mg/kg. Data are expressed as the mean ± standard error of the mean (SEM). The differences among groups were analysed with mixed-model effects. ALT: alanine transaminase; AST: aspartate aminotransferase; hs-Trop I: high-sensitivity troponin I; EN: enibarcimab; SoC: standard of care.

Table S1. Exclusion criteria in the ADESTE study.

Table S2. Medical Treatment and Its Daily Dose on Admission and at Discharge.

Table S3. Subjects (n = 10) with serious adverse events (SAE) (18 events) after hospital discharge and within 90 days follow up.

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