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Effects of a Novel Nitroxyl Donor in Acute Heart Failure

The STAND-UP AHF Study

G. Michael Felker, MD, MHS,[a] John J.V. McMurray, MD,[b] John G. Cleland, MD,[c] Christopher M. O'Connor, MD,[d] John R. Teerlink, MD,[e] Adriaan A. Voors, MD, PhD,[f] Jan Belohlavek, MD, PhD,[g] Michael Böhm, MD,[h] Maria Borentain, MD,[i] Hector Bueno, MD, PhD,[j] Robert T. Cole, MD,[d] Mary M. DeSouza, PhD,[i] Justin A. Ezekowitz, MBBCh, MSc,[k] Gerasimos Filippatos, MD,[l] Ninian N. Lang, MD, PhD,[b] Paul D. Kessler, MD,[i] Felipe A. Martinez, MD,[m] Alex Mebazaa, MD, PhD,[n] Marco Metra, MD,[o] Arend Mosterd, MD,[p] Peter S. Pang, MD,[q] Piotr Ponikowski, MD, PhD,[r] Naoki Sato, MD, PhD,[s] Dietmar Seiffert, MD,[i] June Ye, PhD[i]

ABSTRACT

OBJECTIVES The primary objective was to identify well-tolerated doses of cimlanod in patients with acute heart failure (AHF). Secondary objectives were to identify signals of efficacy, including biomarkers, symptoms, and clinical events.

BACKGROUND Nitroxyl (HNO) donors have vasodilator, inotropic and lusitropic effects. Bristol-Myers Squibb-986231 (cimlanod) is an HNO donor being developed for acute heart failure (AHF).

METHODS This was a phase IIb, double-blind, randomized, placebo-controlled trial of 48-h treatment with cimlanod compared with placebo in patients with left ventricular ejection fraction ≤40% hospitalized for AHF. In part I, patients were randomized in a 1:1 ratio to escalating doses of cimlanod or matching placebo. In part II, patients were randomized in a 1:1:1 ratio to either of the 2 highest tolerated doses of cimlanod from part I or placebo. The primary endpoint was the rate of clinically relevant hypotension (systolic blood pressure <90 mm Hg or patients became symptomatic).

RESULTS In part I (n = 100), clinically relevant hypotension was more common with cimlanod than placebo (20% vs. 8%; relative risk [RR]: 2.45; 95% confidence interval [CI]: 0.83 to 14.53). In part II (n = 222), the incidence of clinically relevant hypotension was 18% for placebo, 21% for cimlanod 6 μg/kg/min (RR: 1.15; 95% CI: 0.58 to 2.43), and 35% for cimlanod 12 μg/kg/min (RR: 1.9; 95% CI: 1.04 to 3.59). N-terminal pro–B-type natriuretic peptide and bilirubin decreased during infusion of cimlanod treatment compared with placebo, but these differences did not persist after treatment discontinuation.

CONCLUSIONS Cimlanod at a dose of 6 μg/kg/min was reasonably well-tolerated compared with placebo. Cimlanod reduced markers of congestion, but this did not persist beyond the treatment period. (Evaluate the Safety and Efficacy of 48-Hour Infusions of HNO (Nitroxyl) Donor in Hospitalized Patients With Heart Failure [STANDUP AHF]; NCT03016325) (J Am Coll Cardiol HF 2021;9:146–57) © 2021 The Authors. Published by Elsevier on behalf of the American College of Cardiology Foundation. This is an open access article under the CC BY-NC-ND license (http://creativecommons.org/licenses/by-nc-nd/4.0/).

From the [a]Duke University School of Medicine and the Duke Clinical Research Institute, Durham, North Carolina, USA; [b]British Heart Foundation Cardiovascular Research Centre, University of Glasgow, Glasgow, United Kingdom; [c]Robertson Centre for Biostatistics, Institute of Health and Wellbeing, University of Glasgow, Glasgow Royal Infirmary, Glasgow, United Kingdom and National Heart & Lung Institute Imperial College, London, United Kingdom; [d]Inova Heart and Vascular Institute, Falls Church, Virginia, USA; [e]Section of Cardiology, San Francisco Veterans Affairs Medical Center and School of Medicine, University of California San Francisco, San Francisco, California, USA; [f]University of Groningen, Department of Cardiology, University Medical Center Groningen, Groningen, the Netherlands; [g]2nd Department of Internal Medicine, Cardiovascular Medicine, General University Hospital, Charles University in Prague, Czech Republic; [h]Klinik für Innere Medizin III, Universitätsklinikum des Saarlandes, Saarland University, Homburg/Saar, Germany; [i]Bristol-Myers-Squibb, Princeton, New Jersey, USA; [j]Cardiology Department, Hospital Universitario 12 de Octubre and Instituto de Investigación Sanitaria Hospital 12 de Octubre, Madrid, Spain; [k]Canadian VIGOUR Centre at the University of Alberta, Edmonton, Alberta, Canada; [l]National and Kapodisrian University of Athens, School of Medicine, Athens, Greece; [m]Instituto DAMIC, Cordoba National University Cordoba, Argentina; [n]Department of Anaesthesiology and Critical Care Medicine, Saint Louis Lariboisière University Hospitals, Assistance Publique - Hôpitaux de Paris, Université

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Attempts to develop effective new therapies for patients hospitalized with acute heart failure (AHF) have been unsuccessful, and intravenous (IV) loop diuretic agents remain the mainstay of management. Current treatment guidelines recommend vasodilators (e.g., nitroglycerin) in patients with elevated blood pressure (1), although high-quality data supporting this recommendation are sparse, and recent studies have called this strategy into question (2). Although signs and symptoms of AHF usually improve with treatment, congestion is often persistent at hospital discharge, contributing to high rates of recurrent hospitalization and death (3).

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HNO gas (nitroxyl) is a chemical sibling of nitric oxide. Although nitric oxide and HNO appear to be closely related chemically, the physiological effects and biologic mechanisms of HNO and nitric oxide action are distinct (4). The biologic effects of HNO are mediated by direct post-translational modification of thiol residues in target proteins, including SERCA2a, phospholamban, the ryanodine receptor, and myofilament proteins in cardiomyocytes (5–8). In vitro, HNO increases the efficiency of calcium cycling and improves myofilament calcium sensitivity, which enhances myocardial contraction and relaxation (9). HNO also mediates peripheral vasodilation through endothelial soluble guanylate cyclase (5). HNO does not induce tachyphylaxis in peripheral vessels, unlike nitric oxide (10).

In large animal models of heart failure, HNO donors directly enhanced myocardial contractility and relaxation, and reduced pre-load and afterload without increasing heart rate or myocardial oxygen consumption (11,12). This combination of physiological effects makes HNO pro-drugs potentially attractive therapeutic candidates in heart failure. Bristol-Myers Squibb-986231 (cimlanod) is an HNO donor being developed for AHF. Short-term treatment with cimlanod has caused venous and arteriolar dilation and may have had inotropic effects in hospitalized patients with advanced heart failure (13). We now report the results of the STAND-UP AHF (Study Assessing Nitorxyl Donor Upon Presentation with Acute Heart Failure) trial, a phase II, randomized, double-blind, placebo-controlled clinical trial of cimlanod in patients hospitalized for AHF.

ABBREVIATIONS AND ACRONYMS

AHF = acute heart failure
CI = confidence interval
HNO = nitroxyl
IV = intravenous
NT-proBNP = N-terminal pro-B-type natriuretic peptide
RR = relative risk
SBP = systolic blood pressure

METHODS

STUDY DESIGN. The detailed rationale and design of this trial was published previously (NCT03016325) (14). The study was approved by the relevant institutional review boards/ethics committee at each study site, and all patients provided informed consent. Briefly, STAND-UP AHF was an international, multicenter, randomized, double-blind, placebo-controlled ascending dose clinical trial of continuous 48-h IV infusions of cimlanod or placebo in patients with heart failure with reduced ejection fractions who were hospitalized with AHF. Cimlanod or matching placebo was administered in addition to background therapy. The primary objective was to evaluate the effects of various doses of cimlanod compared with placebo on the risk of clinically relevant hypotension (defined as systolic blood pressure [SBP] <90 mm Hg or symptoms of hypotension). The trial consisted of 2 sequential parts, each with a unique cohort of patients. In part I, 100 patients were randomized in a 1:1 ratio to escalating doses of cimlanod (3 μg/kg/min for 4 h, then 6 μg/kg/min for another 4 h, then 12 μg/kg/min for the remaining 40 h) or escalating doses of placebo. In part II of the study, 222 patients were randomized in a 1:1:1 ratio to 1 of the 2 highest tolerated doses of cimlanod in part 1 (6 and 12 μg/kg/min) or placebo.

To mitigate the risks of hypotension, the study protocol specified down titration of infusions (50% decrease) if a patient experienced SBP <95 mm Hg (confirmed by repeat measurement within 15 min). If SBP fell to <85 mm Hg or if there were symptoms of hypotension, the study drug was interrupted for at

de Paris, Inserm 942-MASCOT, FHU PROMICE, Paris, France; [o]Institute of Cardiology, ASST Spedali Civili di Brescia and Department of Medical and Surgical Specialties, Radiological Sciences, and Public Health, University of Brescia, Brescia, Italy; [p]Department of Cardiology, Meander Medical Center, Amersfoort, the Netherlands and Dutch Network for Cardiovascular Research, Utrecht, the Netherlands; [q]Indiana University School of Medicine, Indianapolis, Indiana, USA; [r]Wroclaw Medical University, Wroclaw, Poland; and the [s]Cardiology and Intensive Care Unit, Nippon Medical School, Musashi-Kosugi Hospital, Kawasaki, Japan. Barry Greenberg, MD, served as Guest Editor for this paper.
The authors attest they are in compliance with human studies committees and animal welfare regulations of the authors' institutions and Food and Drug Administration guidelines, including patient consent where appropriate. For more information, visit the Author Center.

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TABLE 1 Baseline Characteristics

	Part I		Part II		
	Placebo (n = 48)	Cimlanod (titration) (n = 49)	Placebo (n = 71)	Cimlanod 6 μg/kg/min (n = 71)	Cimlanod 12 μg/kg/min (n = 72)
Age, yrs	66 ± 12	65 ± 12	67 ± 12	69 ± 11	70 ± 12
Female	17	20	25	28	21
Race, Black	23	22	6	10	6
LVEF, %	26 ± 8	27 ± 7	28 ± 8	27 ± 9	26 ± 7
Hospitalizations for HF in past year	1.5 ± 1.0	1.4 ± 1.0	0.6 ± 0.8	0.5 ± 1.1	0.7 ± 0.9
Atrial fibrillation	46	49	52	41	46
Diabetes	52	61	47	31	49
MI	44	43	37	30	46
Hypertension	83	88	76	82	79
SBP, mm Hg	126 ± 15	125 ± 16	123 ± 15	122 ± 13	123 ± 16
HR, beats/min	80 ± 16	81 ± 15	82 ± 16	82 ± 16	80 ± 16
NT-proBNP, pg/ml	8,763 (5,700)	8,675 (5,576)	7,423 (5,515)	8,499 (5,810)	8,043 (5,218)
Creatinine, mg/dl	1.5 ± 0.5	1.4 ± 0.5	1.3 ± 0.4	1.2 ± 0.3	1.2 ± 0.4
Time since presentation, h	11.8 ± 6	11.9 ± 5	19.6 ± 9.9	17.3 ± 7.9	17.1 ± 9.5
Background medications					
BB	81	82	85	90	85
RAAS inhibitors (ACEi/ARB/ARNi)	73	65	80	83	74
Sacubitril/valsartan	13	4	10	6	6
MRA	48	43	68	79	54

Values are mean ± SD, %, or mean (median).

ACEi = angiotensin-converting enzyme inhibitor; ARB = angiotensin receptor blocker; ARNi = angiotensin receptor-neprilysin inhibitor; BB = beta-blocker; HF = heart failure; HR = heart rate; LVEF=left ventricular ejection fraction, MI = myocardial infarction; MRA = mineralocorticoid receptor antagonist; NT-proBNP = N-terminal pro–B-type natriuretic peptide; RAAS = renin-angiotensin-aldosterone system; SBP = systolic blood pressure.

least 1 h and then resumed at 50% of the previous rate if SBP was 105 mm Hg and symptoms of hypotension had resolved. After dose reductions, the dose was not further increased. After a dose decrease, infusions were permanently discontinued if criteria for dose reduction or interruption were met again.

PATIENTS. Enrolled patients were hospitalized for AHF with signs and symptoms of congestion that required treatment with IV loop diuretics. Patients were required to have a history of chronic heart failure with a reduced ejection fraction with a documented ejection fraction ≤40% within the previous 18 months. Patients with SBP <105 mm Hg or >160 mm Hg were ineligible. Patients could not be receiving IV vasodilators or IV inotropic agents at the time of randomization, with the exception of IV nitroglycerin at a stable dose of <100 μg/min with a SBP of >120 mm Hg. Patients were required to have increased plasma concentrations of natriuretic peptides (N-terminal pro-B-type natriuretic peptide [NT-proBNP] ≥1,600 pg/ml or B-BNP ≥400 pg/ml [≥2,400 pg/ml NT pro-BNP or 600 pg/ml BNP if atrial fibrillation was present at baseline]). For part I, patients had to be randomized within 18 h of their initial dose of IV loop diuretics. This time window for enrollment was expanded to 48 h for part II.

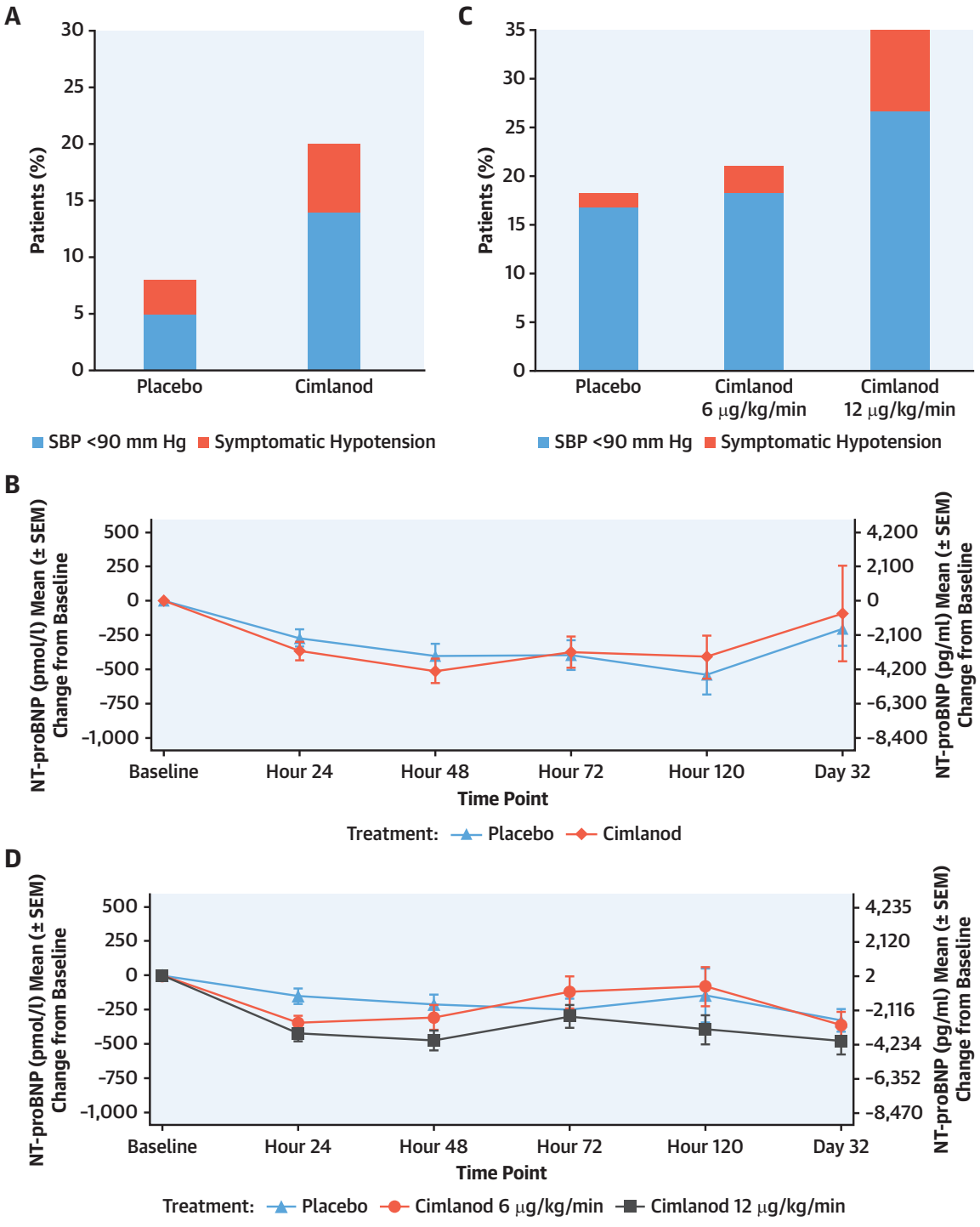
ENDPOINTS. The primary endpoint was the incidence of clinically relevant hypotension, defined by either SBP <90 mm Hg (confirmed by repeat measurement) or symptoms of hypotension, which occurred up to 6 h after the end of study drug infusion. Secondary endpoints were a change in plasma concentrations of NT-proBNP from baseline at various time points and a change in patient-reported resting dyspnea using the area under the curve of an 11-point numeric rating scale from baseline to 72 h. Other endpoints of interest included symptoms of dyspnea and patient global assessment measured by Likert scales, the incidence of worsening heart failure (defined as worsening signs or symptoms of heart failure that required escalation of heart failure therapy) through day 5 or hospital discharge, changes in renal function, changes in signs and symptoms of congestion, length of stay, and post-discharge death or rehospitalization through day 32. Patients were followed through day 182 for cardiovascular and all-cause mortality as a safety endpoint.

STATISTICAL ANALYSIS. The primary objective of the study was to evaluate the effects of various doses of cimlanod compared with placebo on clinically relevant hypotension. In part I, approximately 50 patients per group were randomized by 1:1 ratio. Assuming an incidence rate of clinically relevant hypotension in the placebo group ranged from 5% to 10%, the study required >80% power to detect a ≥3-fold increase in incidence in the cimlanod group compared with the placebo group.

At the conclusion of part I, an interim analysis was conducted to select doses of cimlanod for use in part II. This analysis was conducted in an unblinded fashion by the study executive committee and the study sponsor, with input from the data safety monitoring committee. The doses selected for part II (based on the overall totality of the available safety and efficacy data from part I) were the 2 highest doses administered in part I, specifically 6 and 12 μg/kg/min.

For part II, approximately 70 patients per group were randomized by 1:1:1 ratio into 3 groups. Under the same assumption of clinically relevant hypotension incidence in the placebo group, part II would have at least 80% of power to detect a ≥2.5-fold increase in incidence for each cimlanod group compared with placebo without multiplicity adjustment. The relative risk (RR) of clinically relevant hypotension between cimlanod and placebo and its

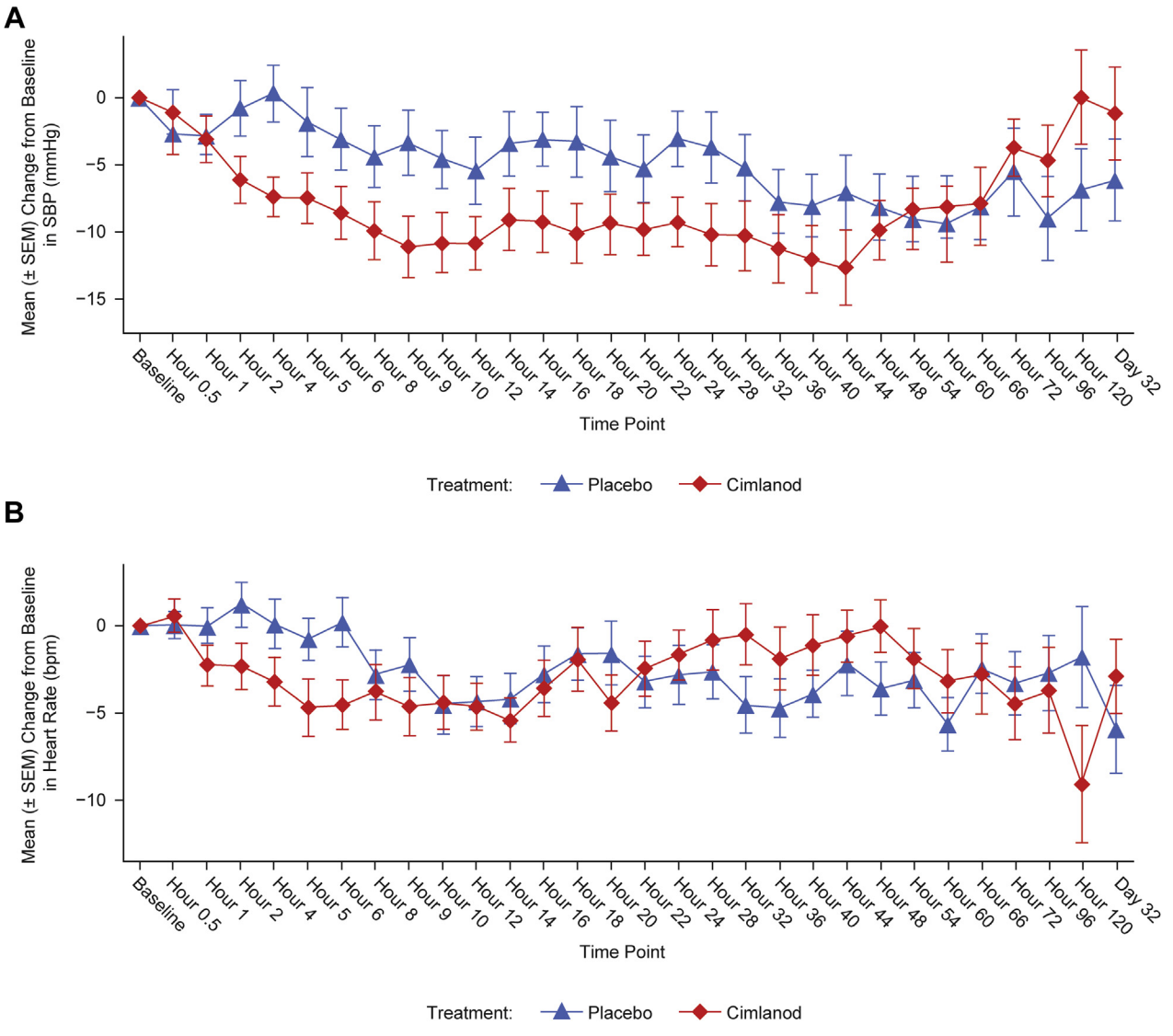
CENTRAL ILLUSTRATION **Incidence of Clinically Relevant Hypotension and Effects on Natriuretic Peptides**



Felker, G.M. et al. J Am Coll Cardiol HF. 2021;9(2):146-57.

Incidence of clinically relevant hypotension (primary endpoint) and changes in N-terminal pro-B-type natriuretic peptide (NT-proBNP) after study drug treatment for **(A and B)** part I and **(C and D)** part II. For clinically relevant hypotension, patients having both symptomatic hypotension and systolic blood pressure (SBP) <90 mm Hg were included in the symptomatic group **(orange bars)**.

FIGURE 1 Change in BP and Heart Rate



Change in blood pressure (BP) and heart rate during and after study drug infusion for **(A and B)** part I and **(C and D)** part II. beats/min = beats per minute; SBP = systolic blood pressure.

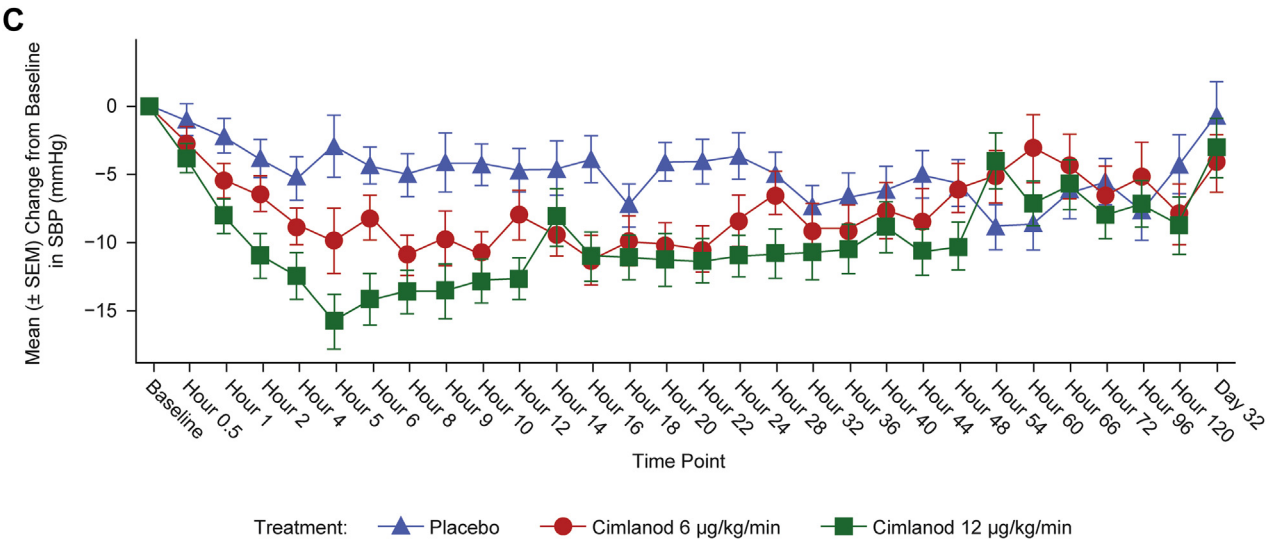
Continued on the next page

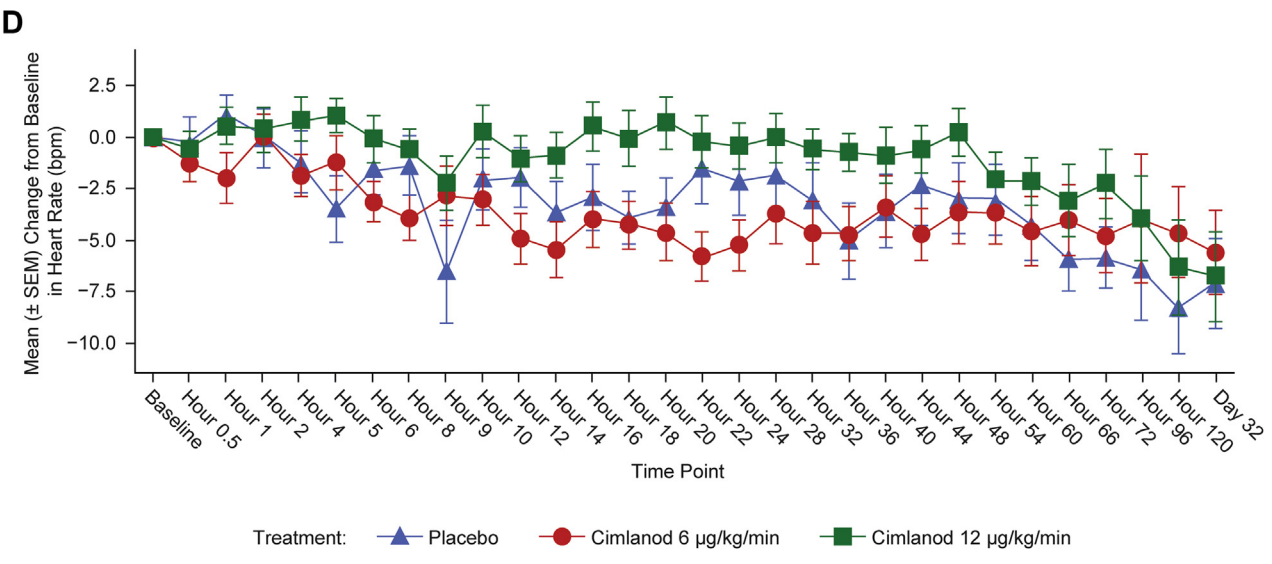
corresponding 95% confidence intervals (CIs) were calculated using an exact procedure that inverted the 2-sided test statistics.

RESULTS

PATIENTS AND STUDY TREATMENT. Enrollment of patients into part I began on April 24, 2017, and the final patient was enrolled in part II on May 15, 2019. A total of 322 patients were randomized (100 in part I and 222 in part II) in 13 countries in North America, Europe, South America (part II only), and Japan (part II only). Baseline characteristics for both cohorts are shown in Table 1 and were broadly balanced between randomized groups. In part I, the mean age was 65 years (vs. 69 years in part II); 19% were women (vs. 25% in part II), the mean left ventricular was similar in the 2 parts (27%), mean SBP was 125 mm Hg (vs. 123 mm Hg in part II), and median NT-proBNP was 5,686 pg/ml (vs. 5,529 pg/ml in part II). As anticipated, because of the expansion of the enrollment time window from 18 to 48 h, a notable difference

FIGURE 1 Continued





between parts I and II was the time from initial presentation to randomization, which was mean 12 h in part I versus 18 h in part II.

Background medical therapy for heart failure with reduced ejection fraction included treatment with beta-blockers (50% in part I and 86% in part II), modulators of the renin-angiotensin system (75% in part I and 79% in part II), and mineralocorticoid receptor antagonists (50% in part I and 65% in part II). All patients were treated with IV loop diuretic agents as required by trial inclusion criteria.

In part I, 83% of patients completed the 48-h infusion of placebo compared with 71% who completed the infusion of cimlanod. In part II, 87% of patients completed the 48-h infusion of placebo, 79% completed the infusion of cimlanod 6 µg/kg/min, and 75% completed the infusion of cimlanod 12 µg/kg/min.

OUTCOMES. Blood pressure and heart rate. Results of the primary endpoint analysis are summarized in the **Central Illustration**. In part I, clinically relevant hypotension was more common in patients randomized to cimlanod than placebo (20% vs. 8%; RR: 2.45; 95% CI: 0.83 to 14.53; $p = 0.10$). In most patients, this endpoint reflected asymptomatic SBP <90 mm Hg, and the incidence of symptomatic hypotension was low in both groups (6% in the cimlanod group and 2% in the placebo group; RR: 2.94; 95% CI: 0.31 to 75.47; $p = 0.30$). Changes in heart rate over time were generally similar between patients

TABLE 2 Secondary and Exploratory Endpoints

	Part I			
	Placebo	Cimlanod	Treatment Effect vs. Placebo (95% CI)	p Value
Secondary endpoints				
NT-proBNP change, % change at 48 h	−36	−50	−14.3 (−26.28 to −2.32)	0.02*
Dyspnea by NRS, AUC >72 h	−173 ± 17	−175 ± 16	2.5 (−45.89 to 50.96)	0.90†
Exploratory endpoints				
Dyspnea improvement by Likert scale at 24 h, % with moderate or marked improvement	69	67	0.98 (0.73 to 1.32)	0.90
Patient global assessment improvement by Likert scale at 24 h, % with moderate or marked improvement	65	69	1.07 (0.80 to 1.47)	0.6‡
Worsening HF through day 5	4 (8.3)	3 (6.1)	0.73 (0.10 to 3.31)	0.70‡
Daily urine volume at 24 h, ml	2,580 (2,200) ± 1,672	2,932 (2,391) ± 1,545	NA	0.10‡
Worsening renal function§ through day 5	25 (52)	25 (51)	0.98 (0.65 to 1.48)	0.90§
Mean change in body weight from baseline, kg				
Day 1	−0.8	−1.3	−0.6 (−1.62 to 0.49)	0.30*
Day 2	−1.9	−1.8	−0.2 (−1.56 to 1.06)	0.70*
Day 5	−2.1	−3.5	−1.8 (−4.01 to 0.49)	0.10*
Length of stay, median days	6.5	6	NA	0.20‡

TABLE 2 Continued

	Part II						
	Placebo	Cimlanod 6 μg/kg/min	Cimlanod 12 μg/kg/min	Treatment Effect (Placebo vs. 6) (95% CI)	p Value	Treatment Effect (Placebo vs. 12) (95% CI)	p Value
Secondary endpoints							
NT-proBNP change, % change at 48 h	−23	−32	−44	−9.2 (−23.68 to 5.23)	0.20*	−20.7 (−34.99 to 6.39)	0.005*
Dyspnea by NRS, AUC >72 h	−178 ± 20	−201 ± 19	−198 ± 19	−22.1 (−61.70 to 17.55)	0.30†	−19.2 (−58.18 to 19.82)	0.30†
Exploratory endpoints							
Dyspnea improvement by Likert scale at 24 h, % with moderate or marked improvement	61	65	60	1.07 (0.82 to 1.41)	0.60‡	0.99 (0.74 to 1.31)	0.90‡
Patient global assessment improvement by Likert scale at 24 h, % with moderate or marked improvement	61	62	58	1.02 (0.78 to 1.35)	0.90‡	0.96 (0.72 to 1.29)	0.80‡
Worsening HF through day 5	5 (7)	0 (0)	4 (6)	0 (0.00 to 0.94)	0.02‡	0.79 (0.18 to 3.21)	0.70‡
Daily urine volume at 24 h, ml	2,676 (2,425) ± 1,380	2,543 (2,100) ± 1,504	2,668 (2,125) ± 1,972	NA	0.30‡	NA	0.20‡
Worsening renal function§ through day 5	29 (41)	40 (56)	25 (35)	1.38 (0.97 to 2.04)	0.06‡	0.85 (0.54 to 1.32)	0.40‡
Mean change in body weight from baseline, kg							
Day 1	−1.4	−0.9	−1.1	0.7 (−0.05 to 1.35)	0.07*	0.4 (−0.33 to 1.05)	0.30*
Day 2	−2.1	−1.6	−1.8	0.5 (−0.30 to 1.35)	0.20*	0.4 (−0.45 to 1.19)	0.40*
Day 5	−2.6	−3	−3.2	0.1 (−1.01 to 1.30)	0.80*	−0.5 (−1.63 to 0.71)	0.50*
Length of stay, median days	6	7	6	NA	0.10‡	NA	0.70‡

Values are n (%), mean ± SD, or mean (median) ± SD. *F-statistic. †Mixed model. ‡Chi-square test. §Worsening renal function defined as increase from baseline in cystatin C values by ≥0.3 mg/l or in serum creatinine by ≥0.3 mg/dl (27 μmol/l).

AUC = area under the curve; CI = confidence interval; NRS = numerical rating scale; RR = relative risk; other abbreviations as in Table 1.

randomized to cimlanod or placebo (Figure 1). Based on review of these data by the executive committee, data safety monitoring committee, and study sponsor, the 2 highest doses (6 and 12 μg/kg/min) from part I were selected for further study in part II.

In part II, the incidence of clinically relevant hypotension was 18% for placebo, 21% for cimlanod 6 μg/kg/min (RR: 1.15; 95% CI: 0.58 to 2.43; p = 0.70), and 35% for cimlanod 12 μg/kg/min (RR: 1.9; 95% CI: 1.04 to 3.59; p = 0.03). Symptomatic hypotension occurred in 1% on placebo, 3% on 6 μg/kg/min (RR: 2.0; 95% CI: 0.18 to 54.35; p = 0.60), and 8% on 12 μg/kg/min (RR: 5.92; 95% CI: 0.91 to 159.72; p = 0.06). Dose reduction was required in 13% of patients on placebo, 14% on 6 μg/kg/min (RR: 1.1; 95% CI: 0.47 to 2.85; p = 0.80), and 35% on 12 μg/kg/min (RR: 2.74; 95% CI: 1.34 to 6.89; p = 0.002), whereas dose discontinuation due to hypotension occurred in 10% on placebo, 18% on 6 μg/kg/min (RR: 1.86; 95% CI: 0.80 to 5.11; p = 0.10), and 21% on 12 μg/kg/min (RR: 2.1; 95% CI: 0.92 to 5.85; p = 0.07). Compared with patients randomized to placebo, heart rates were generally higher over time in patients randomized to the highest dose (12 μg/kg/min) of cimlanod but generally lower in patients randomized to the lower dose (6 μg/kg/min) (Figure 1).

EFFICACY. Although this study was not powered for efficacy, there were a variety of efficacy signals of interest as secondary and exploratory endpoints, the results of which are summarized in Table 2. Changes in NT-proBNP over time for cimlanod versus placebo are shown in the Central Illustration. In both parts I and II, an NT-proBNP decrease during treatment was greater during the 48 h of active treatment with cimlanod than that with placebo. In part I, the decrease in NT-proBNP at 48 h was 36% in the placebo group and 50% in the cimlanod group. The proportion of patients who experienced a ≥30% decrease in NT-proBNP by 48 h was significantly greater in patients treated with cimlanod than those who received the placebo (76% vs. 54%; p = 0.03). Similarly, in part II, the decrease in NT-proBNP at 48 h was 23% in the placebo group, 32% in the cimlanod 6 μg/kg/min group, and 44% in the cimlanod 12 μg/kg/min group. The proportion of patients who experienced a ≥30% decrease in NT-proBNP by 48 h was again significantly greater in patients treated with cimlanod compared with those who received placebo: 71% versus 62% versus 47% for cimlanod 12 μg/kg/min, 6 μg/kg/min, and placebo, respectively (p = 0.06 for 6 μg/kg/min vs. placebo, and p = 0.003 for 12 μg/kg/min vs. placebo). Overall, these data suggested a dose-dependent effect of cimlanod on plasma concentrations of NT-proBNP. However, in both parts I and II, these differences in NT-proBNP waned after the 48-h active treatment period was completed (Central Illustration).

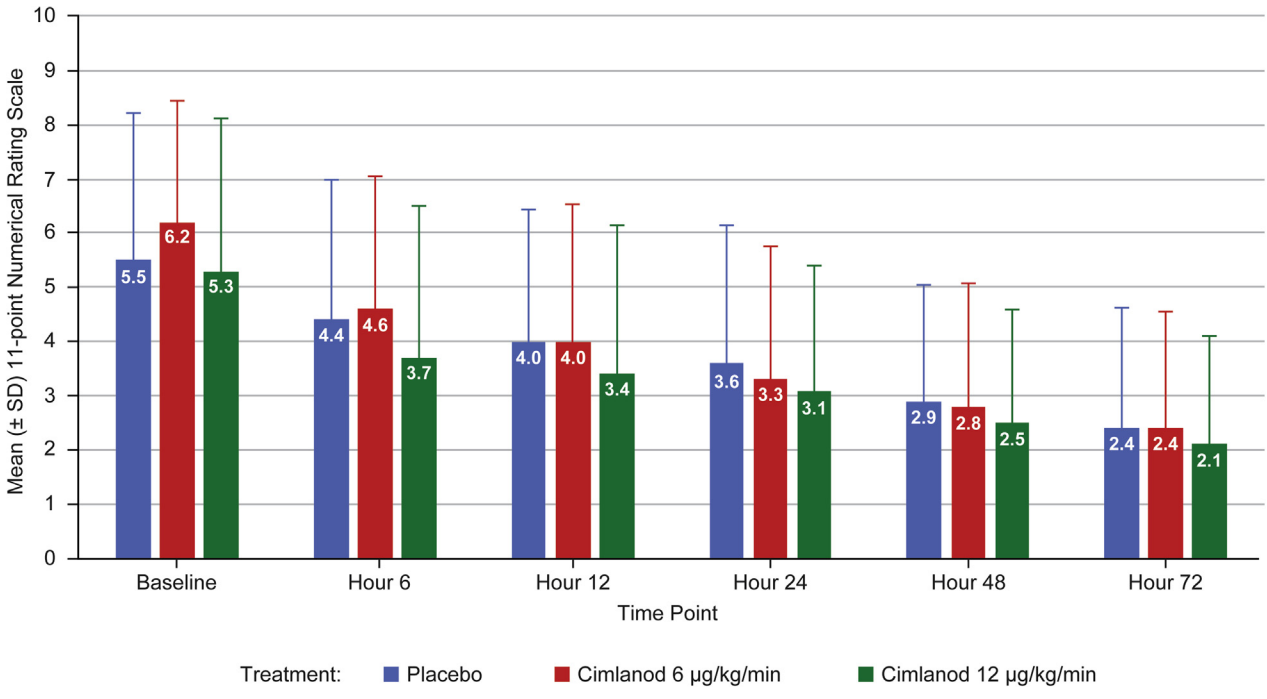
Symptoms of dyspnea by numerical rating scale improved in all groups during hospitalization, and the improvement was generally similar for patients assigned to either cimlanod or placebo (Figure 2). Physical examination findings of congestion, urinary volumes, and changes in body weight were also generally similar between the study groups in both parts I and II.

In addition to the NT-proBNP results described previously, laboratory data were generally consistent with an unloading effect during cimlanod infusion, which waned when treatment was stopped (Figure 3). Serum creatinine increased transiently during cimlanod treatment compared with that of placebo, but this difference did not persist after treatment was discontinued. Serum bilirubin concentrations markedly decreased during cimlanod infusion compared with placebo. Cardiac troponin did not differ significantly over time between patients randomized to cimlanod or placebo.

Data on post-discharge events are provided in Table 3. Because this program was not powered for clinical outcomes and the numbers of events were small, we pooled clinical outcomes data from parts I and II for analysis. Length of stay (from randomization to hospital discharge) was similar in both groups (median 6 days in both groups), and rates of post-discharge events were not different. The incidence of cardiovascular death or rehospitalization at 32 days from randomization was 5.7% in patients treated with cimlanod and 9.6% in patients treated with placebo. The incidence of cardiovascular death at 182 days was 8.3% in cimlanod-treated patients and 10.1% in those treated with placebo.

ADVERSE EVENTS. Safety events are summarized in Table 4. In pooled data (part I and part II combined), 74% of patients randomized to cimlanod had an adverse event compared with 66% randomized to placebo. In contrast, serious adverse events were more common in patients in the placebo group (29%) versus those in the cimlanod group (23%). The most common adverse event leading to drug discontinuation was hypotension, which was more common in the cimlanod group (19%) than in the placebo group (9%).

FIGURE 2 Patient-Reported Dyspnea



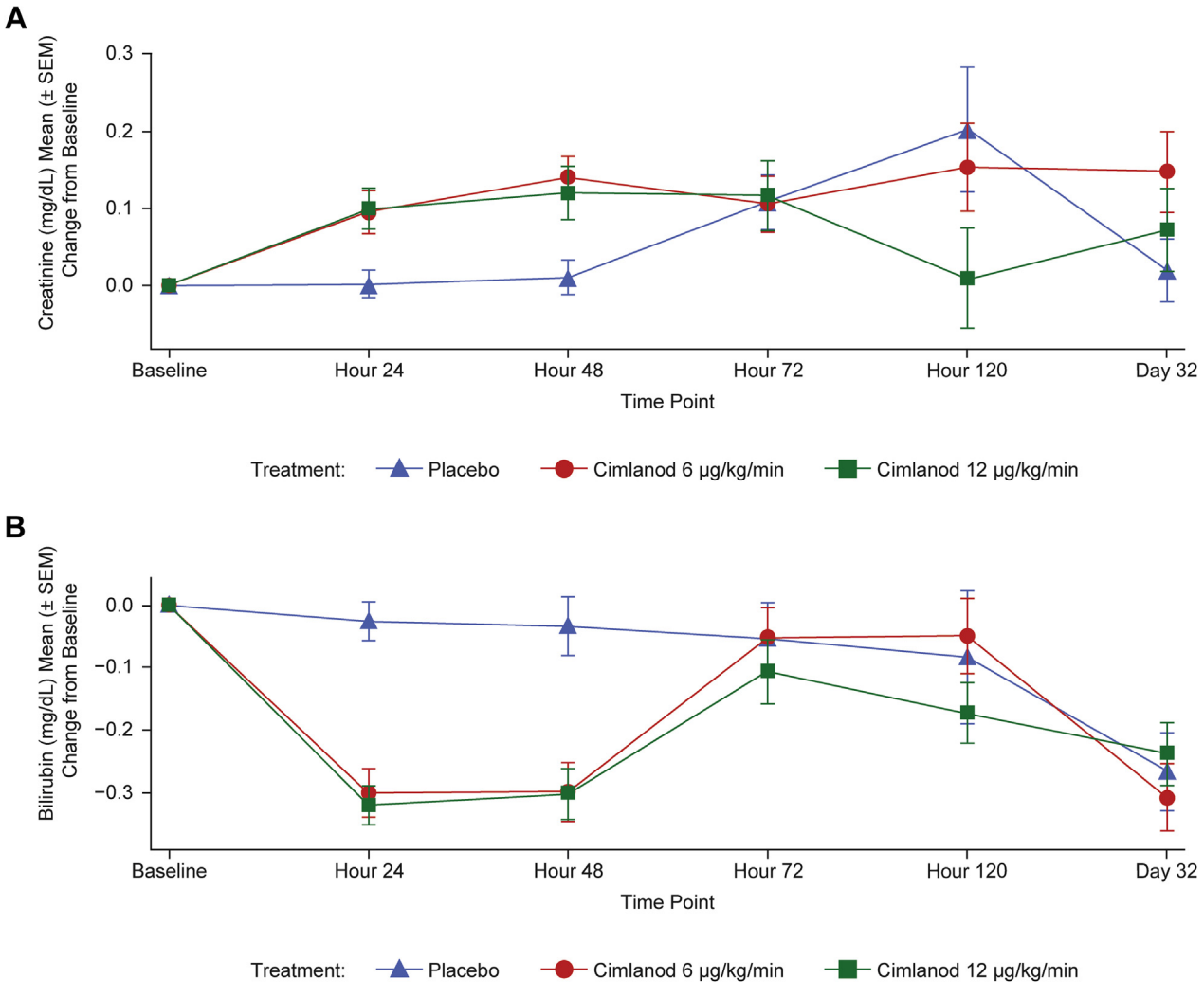
Patient reported dyspnea using a 11-point numerical rating scale over 72 h.

DISCUSSION

The primary goal of the present study was to identify a dose or doses of cimlanod that had acceptable rates of hypotension in the target population (patients with heart failure with reduced ejection fraction hospitalized for AHF) that could be used in future clinical outcome studies. As anticipated for an IV agent with vasodilator properties, both the 6 and 12 μg/kg/min doses of cimlanod were associated with a higher incidence of clinically significant hypotension than that of placebo. Although the patient characteristics and specific definitions of hypotension differed between the present trial and previous studies of AHF, the rates of hypotension observed with cimlanod were generally similar to those seen in other trials of IV vasodilators in AHF, such as nesiritide (27% in ASCEND-HF [Acute Study of Clinical Effectiveness of Nesiritide in Decompensated Heart Failure]) (15), serelaxin (19% in RELAX-AHF-2 [Relaxin in Acute Heart Failure-2]) (16), and ularitide (22% in TRUE-HF [Trial of Ularitide Efficacy and Safety in Acute Heart Failure]) (17). Rates of hypotension with the highest studied dose of cimlanod (12 μg/kg/min) were greater (35%) than that in the other study arms, and a substantial proportion of patients who received this dose required dose reduction or discontinuation (35% and 21%, respectively). This finding suggested that 6 μg/kg/min had a more acceptable safety profile in the population studied in the present trial. Gradual up-titration to the highest tolerated dose (as performed in part I) could allow for more individualized dosing and could also be a viable alternate strategy.

Because of the putative mechanisms of cimlanod in HF, including vasodilator, inotropic, and lusitropic effects, we hypothesized that treatment with cimlanod would facilitate more rapid and complete decongestion, potentially improving the in-hospital clinical course and decreasing post-discharge events. We assessed several clinical and laboratory measures of ventricular unloading. Plasma concentrations of NT-proBNP, a biomarker of myocardial stress, fell during infusion of cimlanod compared with placebo, but these differences did not persist beyond the 48-h treatment period. Changes in cardiac troponin, a marker of myocardial injury, did not differ between groups. Serum creatinine rose modestly during cimlanod infusion compared with placebo. This suggested a decongestive effect similar to that seen with a high dose versus a low dose

FIGURE 3 Change in Serum Creatinine



Change in **(A)** serum creatinine and **(B)** bilirubin after study drug treatment.

diuretic therapy in the DOSE (Diuretic Optimization Strategies Evaluation) trial (18). Bilirubin, a marker of adverse outcomes in AHF (19,20), also transiently improved with cimlanod compared with placebo. Collectively, these data suggested a greater reduction in congestion with cimlanod compared with placebo. The mechanism of the observed effect on congestion was not clear from this study, because we did not find significant differences in urine output, symptoms, or changes in body weight. The transient improvements in measures of congestion during treatment that waned with treatment cessation were similar to data from other trials of vasodilators in AHF, in particular with serelaxin (21,22)

TABLE 3 Post-Discharge Clinical Events

	Part I		Part II		
	Placebo	Cimlanod	Placebo	Cimlanod 6 µg/kg/min	Cimlanod 12 µg/kg/min
Median days alive and out of hospital through day 32	24	26	25	25	25
HF hospitalization or CV death through day 32, %	4	4	10	7	6
CV death through day 180, %	6	4	13	14	6

CV = cardiovascular; HF = heart failure.

TABLE 4 Adverse Events

	Placebo (n = 119)	Cimlanod (n = 192)
Patients with an AE	79 (66.4)	142 (74.0)
Deaths	6 (5.0)	8 (4.2)
Patients with serious AEs	34 (28.6)	44 (22.9)
Patients with AEs leading to discontinuation	12 (10.1)	41 (21.4)
Discontinuation due to hypotension	11 (9.2)	37 (19.3)
Drug-related AEs (including hypotension)	20 (16.8)	76 (39.6)

Values are n (%).
AE = adverse event.

and ularitide (17). A key question is whether these short-term effects on congestion translate into longer term benefits. In theory, more effective acute treatment of congestion could improve the in-hospital course, reduce rates of in-hospital worsening heart failure and other adverse events, shorten length of stay, and reduce rehospitalizations for heart failure. However, these hypothesized longer term benefits have not been confirmed in trials of short-term infusions of novel vasodilators. A recent randomized trial of clinically available vasodilators (primarily nitrates and oral hydralazine) given acutely to patients with AHF also failed to demonstrate longer term clinical benefits (2). Measures of clinical status in the hospital (in-patient worsening heart failure, length of stay) and post-discharge events (heart failure rehospitalizations through day 32 and cardiovascular deaths through day 182) did not differ between cimlanod and placebo. Other than the expected adverse effect of hypotension, cimlanod was generally well tolerated, with an overall rate of adverse events and serious adverse events similar to placebo.

STUDY LIMITATIONS. We enrolled patients with a history of chronic heart failure and a left ventricular ejection fraction of ≤40%. Patients with de novo heart failure or patients with heart failure and preserved ejection fraction were excluded, which limited our ability to draw conclusions about these patient groups. As a phase II study, STAND-UP AHF was not powered to draw conclusions about clinical endpoints.

CONCLUSIONS

Treatment with cimlanod (6 μg/kg/min) in patients with AHF and reduced systolic function improved some parameters related to congestion at the cost of a modest increase in hypotension rates. We did not identify persistent effects of cimlanod after the infusion was stopped. Other ongoing trials are evaluating the effects of cimlanod on hemodynamics, renal function, and diuresis (A Study of Continuous Infusions of HNO (Nitroxyl) Donor in Patients With Heart Failure and Impaired Systolic Function; NCT03357731 and An Investigational Study of Continuous 8-Hour Intravenous Administrations of Bristol-Myers Squibb-986231 in Participants With Heart Failure and Reduced Heart Function Given a Standard Dose of Loop Diuretic; NCT03730961). Collectively, the results of these studies will inform the continued development of cimlanod for patients with heart failure.

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ADDRESS FOR CORRESPONDENCE: Dr. G. Michael Felker, Duke Clinical Research Institute, Division of Cardiology, 200 Morris Street, Durham, North Carolina 27705, USA. E-mail: michael.felker@duke.edu.

PERSPECTIVES

COMPETENCY IN MEDICAL KNOWLEDGE: For patients with AHF, the novel HNO donor cimlanod provided short-term improvements in some clinical measures of congestion but these effects did not persist after discontinuation of therapy.

TRANSLATIONAL OUTLOOK: The development of new therapeutics for AHF remains an important unmet need. Treatments that can be given acutely to patients with AHF and provide longer term clinical benefits remain elusive.

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