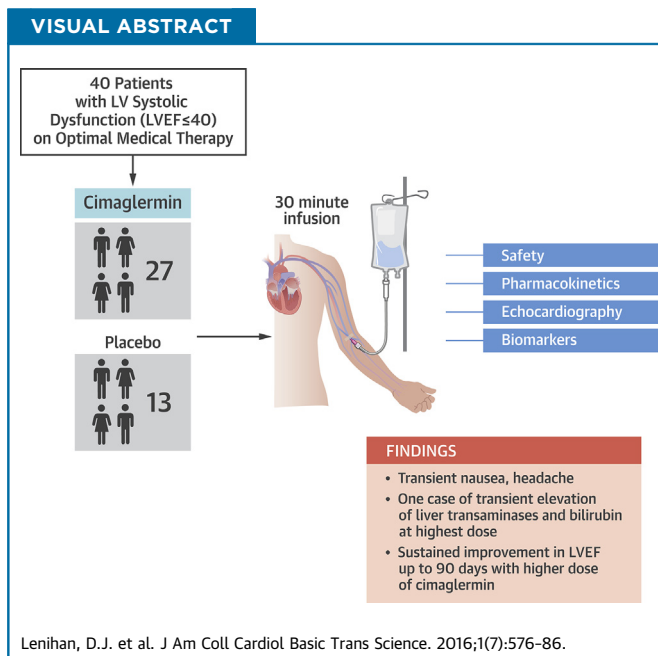


CLINICAL RESEARCH

A Phase I, Single Ascending Dose Study of Cimaglermin Alfa (Neuregulin 1 β 3) in Patients With Systolic Dysfunction and Heart Failure

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HIGHLIGHTS

- Cimaglermin is a recombinant neuregulin that appears to be important for essential cardiac repair processes.
- Forty patients with significant left ventricular dysfunction and heart failure were randomized in a phase 1 double blind, placebo controlled, single ascending dose study to examine safety and tolerability.
- An infusion of cimaglermin was generally tolerated except for transient nausea and headache.
- A dose-limiting toxicity of transient elevated liver transaminases and bilirubin was observed at the highest planned dose.
- There was a sustained improvement in left ventricular ejection fraction over 3 months at higher doses tested compared to lower doses or placebo.

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SUMMARY

A first-in-human, phase 1, double blind, placebo-controlled, single ascending dose study examined the safety, tolerability, and exploratory efficacy of intravenous infusion of a recombinant growth factor, cimaglermin alfa, in patients with heart failure and left ventricular systolic dysfunction (LVSD). In these patients on optimal guideline-directed medical therapy, cimaglermin treatment was generally tolerated except for transient nausea and headache and a dose-limiting toxicity was noted at the highest planned dose. There was a dose-dependent improvement in left ventricular ejection fraction lasting 90 days following infusion. Thus, cimaglermin is a potential therapy to enhance cardiac function in LVSD and warrants further investigation. (J Am Coll Cardiol Basic Trans Science 2016;1:576-86) © 2016 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/>).

ABBREVIATIONS AND ACRONYMS

AE = adverse event
AUC = area under the curve
DLT = dose-limiting toxicity
GGF = glial growth factor
HF = heart failure
LVEF = left ventricular ejection fraction
LVSD = left ventricular systolic dysfunction
NRG = neuregulin
NYHA = New York Heart Association functional class
TEAE = treatment-emergent adverse event

Heat failure (HF) is a complex clinical syndrome characterized by inadequate cardiac function and a characteristic pattern of hemodynamic, renal, and neurohormonal responses leading to poor peripheral perfusion and impaired exercise tolerance. HF is among the leading causes of mortality and morbidity worldwide (1). Despite advances in medical therapy, the mortality for HF remains elevated, with overall rates of 35% to 40% at 1 year and 50% at 5 years (2). A significant proportion of HF patients, particularly those with severe left ventricular systolic dysfunction (LVSD), do not adequately respond to current medical therapy that may include beta blockers, angiotensin-converting enzyme inhibitors, angiotensin receptor blockers, mineralocorticoid receptor antagonists, diuretics, and vasodilators (3). Despite many medication- and device-based improvements that have become guideline-based therapy, there is still a compelling clinical need to enhance cardiac function and outcomes in HF patients (4,5).

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Recombinant neuregulin (NRG)-1 β is a naturally occurring growth factor that acts directly on cardiomyocytes and is being explored as a potential therapy for HF. NRG-1 β regulates cardiac development through receptor tyrosine kinases in the epidermal growth factor receptor family, ERBB2-4 (6). The importance of this NRG-1/ERBB signaling pathway in the adult heart was demonstrated clinically when unexpectedly high rates of cardiotoxicity were observed in association with the chemotherapeutic agent trastuzumab, a monoclonal antibody that blocks the ERBB2 receptor (7,8). These clinical results and the ability of NRG-1 β to activate cytoprotective mechanisms in cardiac myocytes has prompted investigations of its potential to enhance cardiac function in HF (9,10). Recent animal data support this notion. NRG-1 β is released in response to ischemia, stress, and exercise, and is beneficial in animal

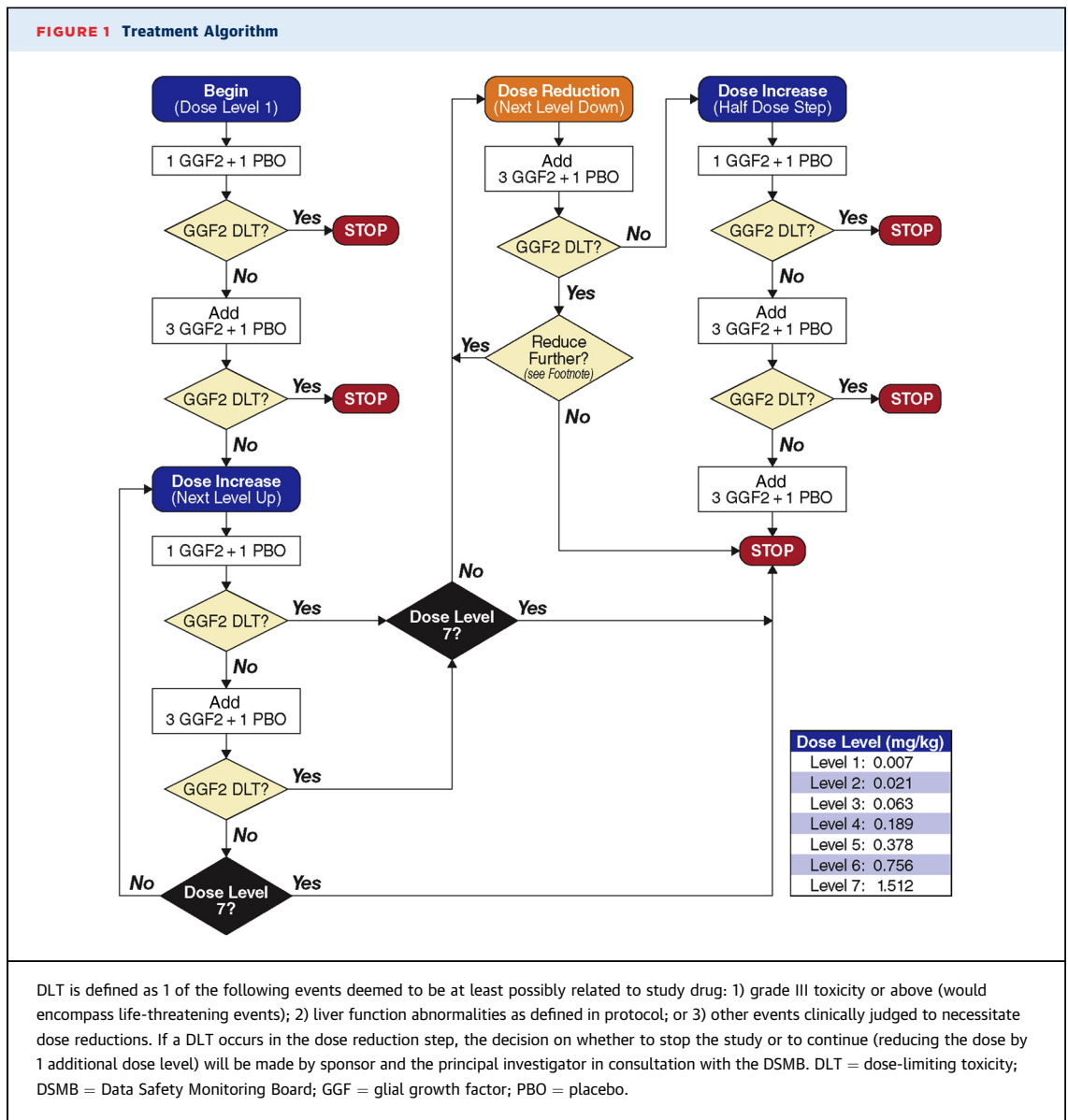
models of cardiac injury by promoting restorative remodeling (11-13). A recombinant peptide representing the epidermal growth factor-like domain of NRG-1 β (Neucardin, Zensun USA Inc., San Diego, California) has been studied in humans with stable chronic HF, where it improved hemodynamics acutely (14) and when given by prolonged infusion over many days increased left ventricular (LV) systolic function (15).

A larger full-length recombinant NRG-1 β 3 known as cimaglermin alfa (cimaglermin; also known as NRG-1 β 3, glial growth factor [GGF]-2) is also being examined as a possible treatment for HF (12,13). Although cimaglermin and Neucardin both act on ERBB receptor tyrosine kinases, the larger cimaglermin is distinct in structure, containing kringle and immunoglobulin-like domains (16,17), and is manufactured in a mammalian cell expression system leading to complex glycosylation. The other domains of cimaglermin, beyond the epidermal growth factor-like domain, provide additional differences from the fragment including receptor binding, signaling, recycling, and extracellular matrix binding (18-22). Cimaglermin improves cardiac function in rats and swine after myocardial infarction, even when administered as brief intravenous infusions twice per week (11-13). In addition to the HF models, cimaglermin has been shown to protect cardiomyocytes from toxicity both in vitro (23,24) and in vivo (25).

Given the preclinical promise of cimaglermin, we conducted a first-in-human, phase 1, randomized, placebo-controlled clinical trial to examine the safety and tolerability of single intravenous infusions of cimaglermin over a range of doses in human subjects with LVSD (left ventricular ejection fraction [LVEF] \leq 40%) and HF.

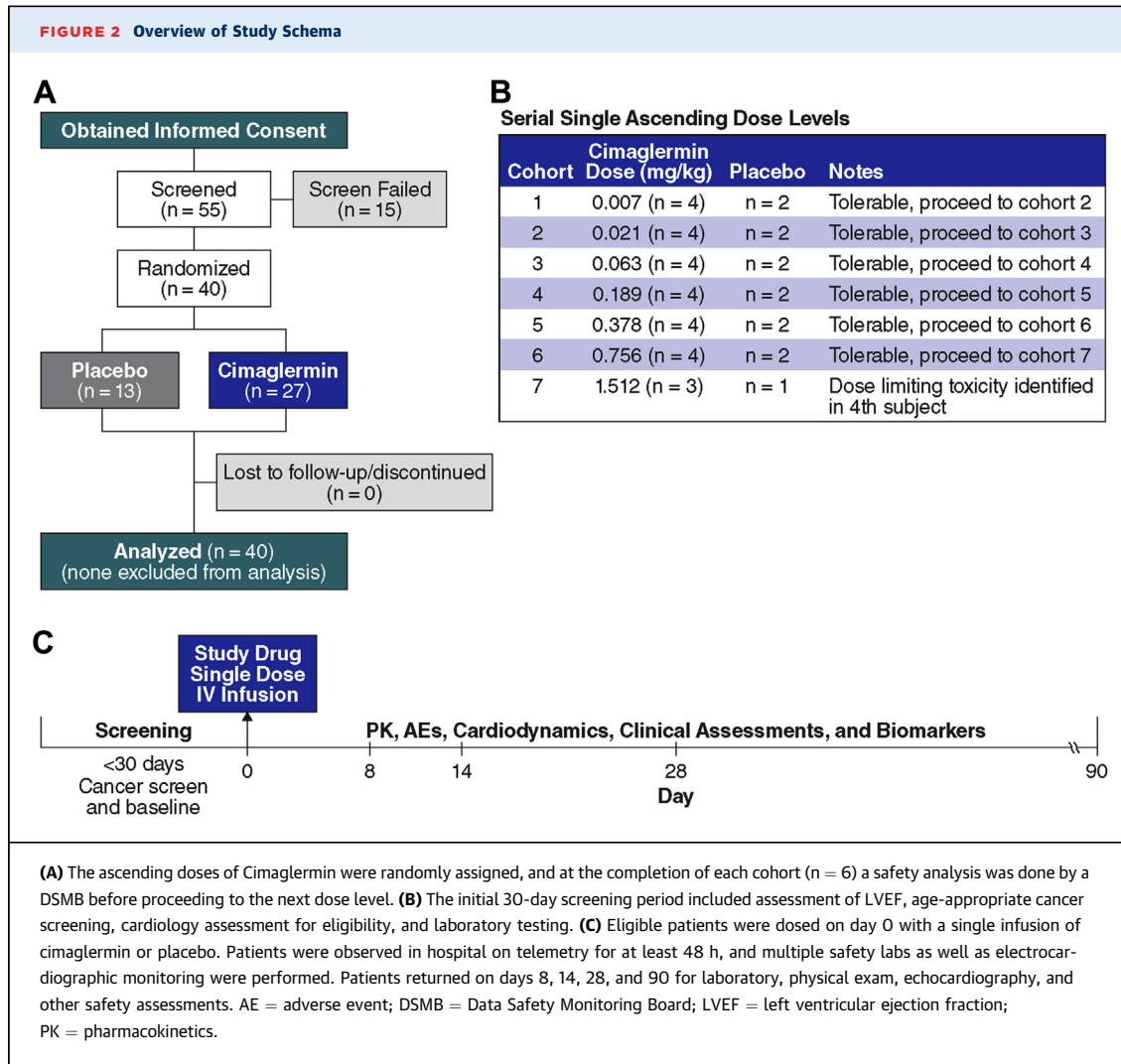
METHODS

HUMAN SUBJECTS. All patients had New York Heart Association (NYHA) functional class II to III HF and



were maintained on an optimal medical regimen for at least 3 months before enrollment at Vanderbilt University Medical Center or Emory Heart and Vascular Center at Emory Saint Joseph's. All patients had an LVEF $\leq 40\%$ on screening, no significant renal or liver disease, and an existing implantable cardioverter-defibrillator. Given the theoretical risk of administering a growth factor, patients with a history of cancer were excluded and an age-appropriate cancer screen was completed before enrollment. After informed consent, 40 patients with symptomatic HF were randomized (4:2) to cimaglermin or placebo in 7 ascending dose cohorts (0.007 mg/kg, 0.021 mg/kg, 0.063 mg/kg, 0.189 mg/kg, 0.378

mg/kg, 0.756 mg/kg, and 1.512 mg/kg). Each cohort of 6 patients was treated in 2 sequences. In sequence 1, 1 patient received placebo and 1 patient received cimaglermin. If no dose-limiting toxicities (DLTs) were observed, sequence 2 was initiated with 1 patient receiving placebo and 3 patients receiving cimaglermin. A dose escalation committee evaluated clinical, laboratory, and electrocardiographic safety before advancing to the next sequence or dose cohort (Figure 1). Patients were observed in a hospital for at least 48 h and then evaluated for adverse events (AEs) for 24 weeks after infusion with study visits at 1, 2, 4, and 12 weeks. AEs were graded using the Common Terminology Criteria for Adverse Events, version



4 (26,27). The trial was performed in accordance with the Declaration of Helsinki, Good Clinical Practice, and applicable regulatory requirements. The study was performed at 2 institutions; the protocol was approved by the institutional review boards, and all participants gave written informed consent. The Trial Registration Identifier is [NCT01258387](https://clinicaltrials.gov/ct2/show/study/NCT01258387).

DRUG ADMINISTRATION. Cimagerlin was produced under Good Manufacturing Practices in Chinese Hamster Ovary cells using animal-component-free media. The growth factor was purified to homogeneity using a series of standard chromatography steps. Patients received a 20- to 30-min intravenous bolus infusion of cimagerlin in 100 ml of dilution buffer or placebo (dilution buffer) without any premedication. Patients previously on strong CYP3A4 inhibitors had dose

adjustments 2 weeks before receiving study drug, as cimagerlin was observed to affect CYP3A4 activity in vitro, which is being explored clinically ([NCT01944683](https://clinicaltrials.gov/ct2/show/study/NCT01944683)).

STUDY CONDUCT. Two-dimensional echocardiography was performed at screening (day 0) and on days 8, 14, 28, and 90. LVEF, left ventricular end-diastolic volume (LVEDV) and left ventricular end-systolic volume (LVESV) were measured from orthogonal apical views using the Biplane Simpson's method (28). Ultrasound contrast was used for technically difficult studies according to the American Society of Echocardiography guidelines (29). All studies were reviewed in a blinded fashion by 2 experienced cardiologists with echocardiographic expertise. Blood sampling for safety assessments (hematology, biochemistry, and liver function), standard clinical

TABLE 1 Characteristics of the Patients at Baseline

	All (N = 40)	Placebo (n = 13)	Cimaglermin	
			Low Dose (n = 12)	High Dose (n = 15)
Age, yrs	57.4 ± 9.8	54.7 ± 13.2	55.8 ± 7.8	60.9 ± 7.0
Male	33 (83)	12 (92)	8 (67)	13 (87)
Race				
African American	4 (10)	1 (8)	2 (17)	1 (7)
Caucasian	36 (90)	12 (92)	10 (83)	14 (93)
Weight, kg	93.8 ± 21.5	102.2 ± 23.1	89.0 ± 21.8	90.4 ± 17.8
Duration of HF (months)	95.0 ± 94.9	95.0 ± 63.5	69.6 ± 59.9	114.5 ± 134.0
Ischemic/nonischemic				
Ischemic	29 (73)	9 (69)	9 (75)	11 (73)
Nonischemic	11 (28)	4 (31)	3 (25)	4 (27)
NYHA functional class				
II	24 (60)	7 (54)	7 (58)	10 (67)
III	16 (40)	6 (46)	5 (42)	5 (33)
Baseline LVEF (%)	27.5 ± 1.3	29.2 ± 2.9	27.5 ± 1.9	26.0 ± 1.9

Values are mean ± SD or n (%).
HF = heart failure; LVEF = left ventricular ejection fraction; NYHA = New York Heart Association.

and exploratory biomarkers, and assessment of antitherapeutic and neutralizing antibody formation were performed at similar time intervals. More frequent sampling was performed the first day for pharmacokinetics. Safety monitoring for rhythm disturbances included continuous telemetry, Holter monitoring, and electrocardiography at multiple time points during the initial hospital stay and at each subsequent visit. The final patient evaluation was at day 90 post dose, and patients were contacted by

TABLE 2 Concomitant Medications at Baseline

Medication Class	All (N = 40)	Placebo (n = 13)	Cimaglermin	
			Low Dose (n = 12)	High Dose (n = 15)
Beta-blocker	39 (98)	12 (92)	12 (100)	15 (100)
ACEI or ARB	32 (80)	10 (77)	11 (92)	11 (73)
Diuretic	35 (88)	10 (77)	11 (92)	14 (93)
MRA	27 (68)	5 (38)	8 (67)	14 (93)
Statin or other cholesterol-lowering	34 (85)	11 (85)	10 (83)	13 (87)
Aspirin	28 (70)	10 (77)	10 (83)	8 (53)
Other antiplatelet	16 (40)	4 (31)	4 (33)	8 (53)
Anticoagulant	14 (35)	6 (46)	4 (33)	4 (27)
Antiarrhythmic	10 (25)	5 (38)	2 (17)	3 (20)
Digoxin	18 (45)	5 (38)	9 (75)	4 (27)
Vasodilator	34 (85)	11 (85)	10 (83)	13 (87)

Values are n (%). Patients previously on strong CYP3A/4 inhibitors had dose adjustments 2 weeks prior to receiving study drug, as cimaglermin was observed to affect CYP3A4 activity in vitro, which is being explored clinically.
ACEI = angiotensin-converting enzyme inhibitor; ARB = angiotensin receptor blocker; MRA = mineralocorticoid receptor antagonist.

telephone at 6 months for status assessment. **Figure 2** summarizes protocol events.

STATISTICAL METHODS. Given the small size of each dose cohort, patients were pooled by dose levels into approximately equal groups (placebo, low-, and high-dose groups) in a post-hoc manner. The low-dose group (n = 12) comprises the 0.007-mg/kg, 0.021-mg/kg, 0.063-mg/kg cohorts and the high-dose group (n=15) comprises the 0.189-mg/kg, 0.378-mg/kg, 0.75-mg/kg and 1.5-mg/kg groups. Additionally, the initial dose levels were anticipated to be sub-therapeutic based on preclinical studies and were included to ensure safety in a first-in-human study. Descriptive statistics were used to summarize the data by treatment group. Continuous variables were summarized using descriptive statistics such as mean and standard error; categorical variables were summarized using frequencies and percentages. Additional exploratory analyses were performed on echocardiography measurements of LVEF to evaluate the treatment effects of cimaglermin compared with placebo. LVEF was pre-defined as the first exploratory efficacy measure. Treatment differences were considered statistically significant if the p values were <0.05. To show the overall treatment effect over time, the area under the curve (AUC) as a summary score was evaluated. The derived AUC scores were analyzed via the analysis of covariance model, with treatment group as a factor and corresponding baseline measure as a covariate. Dunnett's test was used to adjust for the experiment-wise type I error rate. A mixed model repeated measures was also conducted to show the time profile. The treatment group, corresponding baseline measure, visit, and treatment by visit interaction effects were included in the mixed model repeated measures model. The unstructured variance-covariance and Kenward-Roger degree of freedom adjustment were used. Nominal p values were presented to show the entire clinical picture. The relationship of change in LVEF with dose was tested using the Jonckheere-Terpstra test. All statistics were performed with SAS version 9.4 software (SAS Institute, Cary, North Carolina).

RESULTS

Forty patients of a planned 42 (7 cohorts of 6 patients) were enrolled as study recruitment was suspended following a serious adverse event (SAE) in the 40th patient. Eighty-three percent (n = 33) of patients enrolled were male, 60% had NYHA functional class II, and 40% had NYHA functional class III symptoms.

Seventy-three percent (n = 29) had known significant coronary disease and established ischemic HF. The mean age was 57.4 ± 9.8 years. Other patient characteristics and concomitant medications during the study period are shown in **Tables 1** and **2**. Patients were maintained on optimal medical therapy for at least 3 months before enrollment in the trial (**Table 2**). Given the small size of the study, the demographics were relatively well matched. There were no clinically significant treatment effects of a single dose of cimaglermin on hematologic, electrical, or the majority of biochemical safety laboratory testing performed, with the exception of the DLT described in more detail below.

There were no acute AEs leading to termination of drug infusion. There were no study withdrawals due to AEs. The most frequently observed treatment-emergent adverse events (TEAEs) are shown in **Table 3**. A TEAE was defined as an event with a date of onset, or worsening, on or after the start of double-blind treatment and no more than 28 days from the start date of double-blind treatment. A higher percentage of patients receiving cimaglermin had symptoms of a headache (9 of 27, 33% vs. 0 of 13, 0%) as well as nausea compared with placebo (7 of 27, 26% vs. 2 of 13, 16%). The summary of serious AEs is shown in **Table 3**. Four patients, each in a different cohort (levels 1, 2, 4, and 7), had 1 serious AE. The serious AEs occurred in 2 of 12 patients (17%) of the total low-dose group (cohorts 1 to 3) and 2 of 15 (13%) of the total high-dose group (cohorts 4 to 7); they were viral infection requiring admission (cohort 1; 0.007 mg/kg); angina requiring nitroglycerin treatment (cohort 2; 0.021 mg/kg); worsening HF requiring admission (cohort 4; 0.189 mg/kg); and transient liver transaminase elevation and hyperbilirubinemia meeting the criteria of Hy's law (cohort 7; 1.512 mg/kg) (30). These events, with the exception of viral infection, were considered by the investigator to be possibly or probably related to the investigational product. All of the patients recovered with observation and medical treatment and without longer-term sequelae. No serious AEs were reported in the following treatment groups: placebo, cohort 3 (0.063 mg/kg), cohort 5 (0.378 mg/kg), and cohort 6 (0.756 mg/kg).

The transient liver transaminase elevation and hyperbilirubinemia that occurred in 1 patient who received 1.5 mg/kg of cimaglermin, the highest planned dose, defined a DLT. This patient presented to a local emergency department approximately 48 h after release from the study hospital with abdominal pain and was found to have elevated liver transaminases and bilirubin. Normalization of the liver enzymes and

TABLE 3 Treatment-Emergent Adverse Events

	Placebo (n = 13)	Cimaglermin	
		Low Dose (n = 12)	High Dose (n = 15)
TEAEs			
Headache	0	5 (42)	4 (27)
Nausea	2 (15)	1 (8)	6 (40)
Fatigue	1 (8)	2 (17)	4 (27)
Diarrhea	0	1 (8)	4 (27)
Cough	0	1 (8)	3 (20)
Dyspnea	0	2 (17)	1 (7)
Elevated GGT	0	0	3 (20)
Hypotension	0	0	3 (20)
Abdominal distension	0	0	2 (13)
Elevated BNP	0	0	2 (13)
Decreased appetite	0	0	2 (13)
Dysgeusia	0	0	2 (13)
Nasal congestion	0	2 (17)	0
Upper-respiratory tract symptoms	0	0	2 (13)
Severe TEAEs*			
Angina pectoris	0	1 (8)	0
Congestive heart failure	0	0	1 (7)
Hy's law case	0	0	1 (7)
Viral infection	0	1 (8)	0

Values are n (%). *Common Terminology Criteria for Adverse Events grade 3 or higher.
 BNP = B-type natriuretic peptide; GGT = gamma-glutamyl transferase; TEAE = treatment-emergent adverse event.

bilirubin, along with resolution of abdominal pain, occurred over 96 h under careful observation and symptom management. At the next observed time point of 14 days after dosing, the liver enzymes returned to baseline values.

All study patients had age-appropriate cancer screenings that were negative before enrollment. One patient with intermittent microscopic hematuria before enrollment was ultimately diagnosed with bladder cancer 3 months after receiving study drug. External review of the details of this case by an expert urogenital oncologist determined that this was not likely related to study drug based upon the natural history and risk factors for the development of bladder cancers.

Serial echocardiogram measurements were measured and evaluated in a blinded fashion. The results of LVEF, LVEDV, LVESV, heart rate, and blood pressure are summarized in **Table 4**, and the primary exploratory efficacy measure of LVEF is displayed in **Figure 3** with additional data provided in the **Supplemental Figure**. There was a sustained, dose-related increase in LVEF through 90 days after dosing in the high-dose cimaglermin group when compared with the placebo group, (p < 0.01) (**Figures 3** and **4B**). There was no change in LVEF in

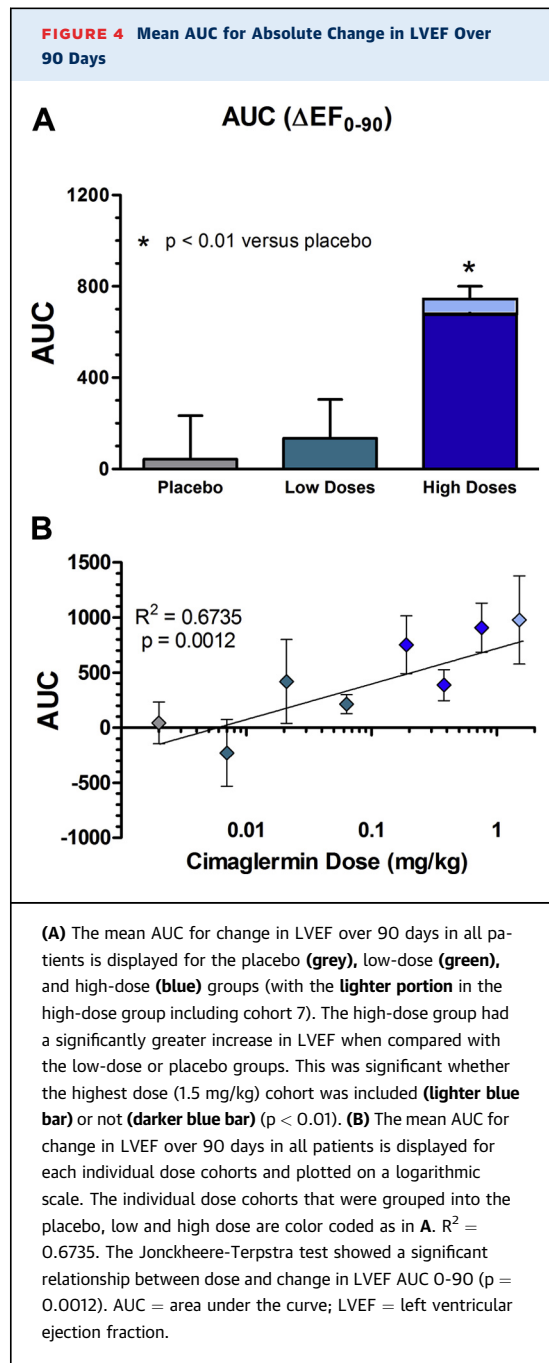
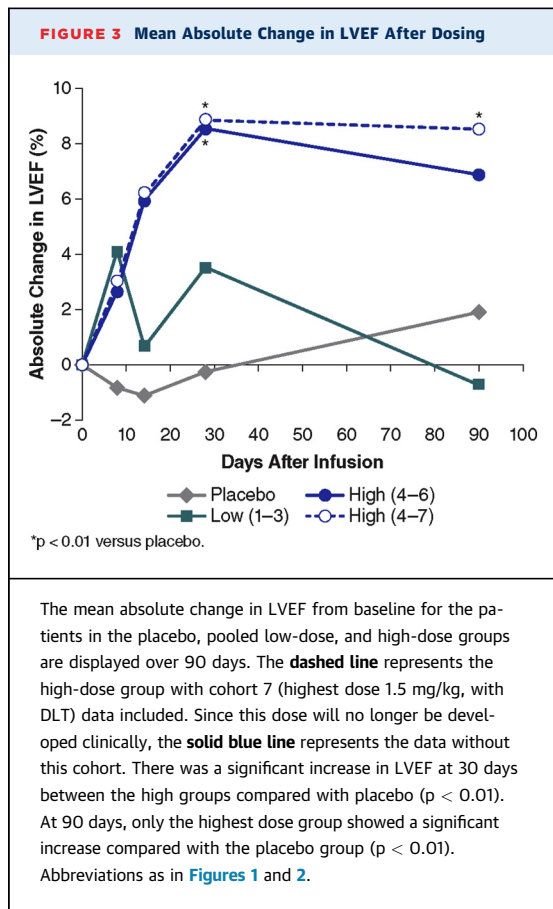
TABLE 4 Cardiac Parameters and Biomarkers					
	Days Post Treatment				
	0	8	14	28	90
Parameters					
LVEF					
Placebo	29.2 ± 10.5	28.4 ± 6.0	28.1 ± 7.8	28.9 ± 6.8	31.1 ± 7.4
Low dose	27.5 ± 6.6	31.6 ± 8.1	28.2 ± 9.3	31.0 ± 8.0	26.8 ± 6.4
High dose	26.0 ± 7.5	29.0 ± 7.9	32.2 ± 11.6	34.9 ± 7.3	34.5 ± 8.0
LVESV					
Placebo	195.5 ± 120.7	194.6 ± 86.0	176.5 ± 82.3	192.1 ± 91.0	182.9 ± 95.8
Low dose	164.7 ± 107.3	161.2 ± 98.6	161.7 ± 91.8	167.8 ± 103.1	175.9 ± 102.7
High dose	151.0 ± 74.2	139.5 ± 64.1	126.9 ± 67.3	131.1 ± 73.4	127.8 ± 85.2
LVEDV					
Placebo	284.6 ± 112.7	269.7 ± 109.1	243.0 ± 94.8	258.8 ± 95.1	258.9 ± 77.6
Low dose	221.2 ± 124.0	227.4 ± 115.7	217.4 ± 99.3	235.1 ± 116.3	235.7 ± 119.9
High dose	202.8 ± 91.3	198.9 ± 80.8	180.0 ± 82.9	196.7 ± 100.3	184.2 ± 109.1
HR					
Placebo	67.9 ± 8.6	72.5 ± 11.1	ND	71.0 ± 10.6	ND
Low dose	69.9 ± 6.5	73.4 ± 9.1	ND	69.9 ± 10.2	ND
High dose	68.4 ± 13.2	67.5 ± 9.6	ND	69.6 ± 9.9	ND
MAP					
Placebo	80.4 ± 6.9	82.2 ± 6.4	ND	84.5 ± 5.2	ND
Low dose	79.6 ± 10.9	86.1 ± 13.5	ND	79.0 ± 10.2	ND
High dose	73.1 ± 7.5	89.8 ± 9.7	ND	87.0 ± 10.0	ND
SBP					
Placebo	119.6 ± 12.0	109.6 ± 8.6	ND	112.1 ± 10.4	ND
Low dose	115.9 ± 18.8	116.8 ± 20.8	ND	107.9 ± 12.9	ND
High dose	114.2 ± 14.3	117.1 ± 11.4	ND	115.5 ± 11.8	ND
DBP					
Placebo	71.1 ± 4.7	68.5 ± 7.1	ND	70.6 ± 4.3	ND
Low dose	65.9 ± 9.1	70.8 ± 12.9	ND	64.5 ± 10.4	ND
High dose	70.9 ± 10.1	76.1 ± 9.7	ND	72.7 ± 10.8	ND
Biomarkers					
BNP (pg/mL)					
Placebo	230 (108, 299; 191)	202 (89, 317; 228)	ND	177 (115, 237; 122)	ND
Low dose	279 (140, 432; 292)	332 (188, 447; 258)	ND	267 (116, 405; 289)	ND
High dose	108 (80, 301; 221)	230 (185, 619; 434)	ND	162 (74, 342; 268)	ND
NT-proBNP (fmol/mL)					
Placebo	898 (527, 1,495; 968)	877 (536, 1,467; 931)	ND	800 (564, 1,044; 480)	ND
Low dose	831 (513, 947; 434)	843 (658, 937; 279)	ND	910 (508, 1,161; 653)	ND
High dose	552 (310, 1,134; 824)	1193 (702, 1,598; 896)	ND	653 (328, 1,194; 866)	ND
Tn-I (ng/l)					
Placebo	20 (20, 30; 10)	20 (10, 30; 20)	ND	10 (10, 30; 20)	ND
Low dose	10 (10, 10; 0)	10 (10, 15; 5)	ND	10 (10, 10; 0)	ND
High dose	10 (10, 20; 10)	10 (10, 25; 15)	ND	10 (10, 30; 20)	ND

Values are mean ± SD or median (25th, 75th; interquartile range).

DBP = diastolic blood pressure; HR = heart rate; LVEDV = left ventricular end diastolic volume; LVEF = left ventricular ejection fraction; LVESV = left ventricular end systolic volume; MAP = mean arterial pressure; ND = not done; NT-proBNP = N-terminal pro-B-type natriuretic peptide; SBP = systolic blood pressure; Tn-I = troponin I.

placebo-treated patients. In low-dose cimaglermin treated patients, there was a small nonsignificant increase in LVEF which returned to baseline by 90 days. In the high-dose cimaglermin treated patients, there was a mean increase of 9 absolute percentage units of LVEF, and changes reached their maximum increase at day 28 (Figure 3) and were sustained throughout

the duration of the safety measurements. Additionally, at the 90-day time point there was a nonsignificant trend toward a reduction in LVESV, especially at the higher doses (-23.2 ml compared with baseline). The AUC for absolute changes in LVEF during the 90 days of observation by dose groups is shown in Figures 4A and 4B; the high-dose group (0.189-mg/kg,



0.378-mg/kg, 0.756-mg/kg, and 1.512-mg/kg cohorts) was significantly increased compared with placebo and low-dose (0.007-mg/kg, 0.021-mg/kg, and 0.063-mg/kg cohorts) treated patients ($p < 0.01$). Even when censoring the data from the highest dose cohort with the DLT (cohort 7, 1.512 mg/kg), the sustained increases in LVEF persist over 90 days ([Figures 3 and 4A](#)). When mean changes in LVEF over 90 days are plotted for each individual dose cohort ([Figure 4B](#)), there is a significant correlation between dose and LVEF change ($R^2 = 0.6735$; $p = 0.0012$).

DISCUSSION

In this first-in-human study of cimaglermin, a dose range for future studies was identified. There were no discontinuations based on AEs. Overall, the most commonly experienced TEAEs were nausea (7 of 27, 26%) and headache (9 of 27, 33%) that were temporally associated with study drug exposure. Nausea occurred in some patients who received a placebo infusion (2 of 13, 15%). A DLT of transient liver transaminase elevation and hyperbilirubinemia

was observed in 1 patient at the highest planned dose. Some liver enzyme changes were anticipated at higher doses based on preclinical toxicology studies. The liver transaminase elevation and hyperbilirubinemia observed, although it met criteria for Hy's law, was temporary and not associated with any long-term sequelae for the subject.

In addition to these safety findings, the results of the study appear to indicate that a single infusion of

cimaglermin may lead to an increase in LVEF, and this effect seemed to persist for up to 90 days in the high-dose group. The dose levels of cimaglermin examined in this study are within the range of doses used in animal studies and shown to enhance cardiac function (11,13). Preclinical studies indicate that repeated dosing is necessary for sustained improvement in heart function. Further clinical studies are required to determine the optimal dose and dosing interval for this agent, as well as the effect of repeated dosing on LVEF.

The exact mechanism for such a potentially enduring effect of cimaglermin on LV systolic function is not known, but certainly enhancement of cardiac repair processes is one hypothesis that is plausible given the known actions of NRG-1 β stimulation in cardiac cells (31). The preclinical work leading up to this study used multiple doses of intravenous cimaglermin over weeks in animals not on background neurohormonal blockade. There may be marked species differences in the duration of effect. Alternatively, the combined effects of cimaglermin on myocyte survival, fibrosis, and inflammation, in the context of optimal medical therapy with neurohormonal blockade, may provide a possible explanation for this difference between preclinical and clinical data (32).

The most frequent side effects, headache and nausea, are similar to what has been reported with Neucardin, a recombinant protein based upon only the epidermal growth factor domain fragment of NRG-1 β (30). Vomiting was observed in preclinical study of cimaglermin in swine (11), and thus it appears that gastrointestinal side effects might be a class effect. These symptoms were easily managed with standard antiemetics, but the mechanism for this is not clear at this time. Although infrequent compared with other AEs, transient liver transaminase elevation and hyperbilirubinemia is the most concerning AE of a single infusion. It will be important to understand the nature of this potential toxicity so the relative risks and benefits of cimaglermin for the treatment of HF can be determined.

A theoretical concern for the clinical development of neuregulins as therapeutic agents is the potential for growth effects on pre-existing ERBB-driven cancers. In this initial study, we screened patients in an attempt to exclude anyone with a pre-existing tumor. However, 1 patient with multiple risk factors for bladder cancer and pre-existing microscopic hematuria developed gross hematuria 3 months after receiving cimaglermin. This patient was found to have superficial bladder carcinoma that has since

been successfully treated with cystoscopy-based therapy with no evidence of disease recurrence after more than 1 year. An expert urogenital oncologist adjudicated this event to be unrelated to study drug based on the pre-existing hematuria and the expected growth rates of bladder carcinomas following toxin exposure.

The safety, tolerability, and cardiac activity of a range of doses identified in this study support further work with cimaglermin in chronic HF. At the time of this submission, a second trial is under way to assess further the safety, tolerability, drug-drug interactions, and potential efficacy of cimaglermin (NCT01944683). Although the etiology of HF was not part of the inclusion criteria for the current study, we were careful to make sure that this was a relatively homogeneous HF population with respect to other diseases that might impact safety, such as renal insufficiency, liver function abnormalities, and insulin-dependent diabetes mellitus. The study subjects were all symptomatic with NYHA functional class II to III, American Heart Association stage C patients, and despite being on stable optimal medical therapy for a minimum of 3 months (Table 1), showed increases in LVEF following a single infusion of cimaglermin.

STUDY LIMITATIONS. The limitations of this study, by the nature of the design, is that it is a small study intended to document safety. Because it was a first-in-man dose-escalating study, the initial doses in humans were known to be subtherapeutic in animal studies. Similarly, there was only a single infusion as opposed to multiple doses for the same reason to maximize patient safety. Lastly, the relatively short time for follow-up is sufficient to detect potential changes in cardiodynamics but not long enough to establish a difference in major clinical events.

CONCLUSIONS

A single intravenous dose of cimaglermin was tolerated in the majority of patients with systolic LV dysfunction and HF in a first-in-human safety study. The most common AEs, occurring more frequently at the higher doses, were headache (33%) followed by nausea (27%). Serious TEAEs were uncommon, and the DLT at the highest planned dose (1.5 mg/kg) was a case of transient liver transaminase elevation and hyperbilirubinemia meeting U.S. Food and Drug Administration guidance for drug-induced liver injury (Hy's law) that resolved completely within 2 weeks. There was a suggestion of improvement in LV function based on a

sustained increase in LVEF over 90 days at the higher doses of cimaglermin. These findings support continued clinical development of the investigational drug cimaglermin, including further safety evaluations and detailing the potential improvement on clinical HF outcome measures.

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PERSPECTIVES

COMPETENCY IN MEDICAL KNOWLEDGE: In patients with symptomatic HF due to LVSD on optimal medical therapy, a single intravenous dose of cimaglermin appears to result in a dose-dependent improvement in LVEF for up to 90 days. This therapy was associated with nausea and headache, and at a higher dose there was transient liver transaminase elevation and hyperbilirubinemia. The implications of toxicity must be balanced with potential therapeutic benefit.

TRANSLATIONAL OUTLOOK: Larger prospective randomized studies are needed with carefully selected doses, as well as repeat dosing, to establish patient safety and improvement in ventricular remodeling, functional status, and other measures of cardiac function.

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APPENDIX For a supplemental figure, please see the online version of this article.