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Journal

European Heart Journal, 38(30)

ISSN

0195-668X

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Publication Date

2017-08-07

DOI

10.1093/eurheartj/ehx196

Peer reviewed

ESC European Society of Cardiology

European Heart Journal (2017) **38**, 2364–2373
doi:10.1093/eurheartj/ehx196

CLINICAL RESEARCH
Heart failure/cardiomyopathy

Biased ligand of the angiotensin II type 1 receptor in patients with acute heart failure: a randomized, double-blind, placebo-controlled, phase IIB, dose ranging trial (BLAST-AHF)

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Received 15 November 2016; revised 6 February 2017; editorial decision 24 March 2017; accepted 25 March 2017; online publish-ahead-of-print 27 April 2017

See page 2374 for the editorial comment on this article (doi: 10.1093/eurheartj/ehx276)

Aims Currently, no acute heart failure (AHF) therapy definitively improves outcomes. Reducing morbidity and mortality from acute heart failure (AHF) remains an unmet need. TRV027 is a novel 'biased' ligand of the angiotensin II type 1 receptor (AT1R), selectively antagonizing the negative effects of angiotensin II, while preserving the potential pro-contractility effects of AT1R stimulation. BLAST-AHF was designed to determine the safety, efficacy, and optimal dose of TRV027 to advance into future studies.

Methods and results BLAST-AHF was a multi-centre, international, randomized, double-blind, placebo-controlled, parallel group, phase IIb dose-ranging study, enrolling patients with AHF into 4 groups: placebo, 1, 5, or 25 mg/h of TRV027. Treatment was by IV infusion for 48–96 h. The primary composite endpoint was comprised of the following: (i) time from baseline to death through day 30, (ii) time from baseline to heart failure re-hospitalization through day 30, (iii) the first assessment time point following worsening heart failure through day 5, (iv) change in dyspnea visual analogue scale (VAS) score calculated as the area under the curve (AUC) representing the change from baseline over time from baseline through day 5, and (v) length of initial hospital stay (in days) from baseline. Analyses were by modified intention-to-treat. Overall, 621 patients were enrolled. After 254 patients, a pre-specified interim analysis resulted in several protocol changes, including a lower blood pressure inclusion criterion as well as a new allocation scheme of 2:1:2:1, overweighting both placebo, and the 5 mg/h dose. TRV027 did not confer any benefit over placebo at any dose with regards to the primary composite endpoint or any of the individual components. There were no significant safety issues with TRV027.

Conclusion In this phase IIb dose-ranging AHF study, TRV027 did not improve clinical status through 30-day follow-up compared with placebo.

Keywords Acute heart failure • Biased ligand • Angiotensin-II • Clinical trials

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Introduction

Acute heart failure (AHF) impacts millions of patients worldwide.[1–3] Once hospitalized, over 25% are re-hospitalized or die within 30 days.[3,4] To date, no current AHF therapy definitively improves the in-hospital and post-discharge event rate.[1,5] There is a clear unmet need for novel therapies to reduce morbidity and mortality in AHF.[6,7]

TRV027 is a biased ligand of the angiotensin II type 1 receptor (AT1R). In chronic HF, use of angiotensin receptor blockers improves outcomes in patients with chronic systolic HF. However, angiotensin receptor blockade in acute heart failure has not been well studied.[8] TRV027 blocks AT1R-mediated effects including vasoconstriction and reduced renal perfusion. By stimulating β-arrestin signalling, it avoids the adverse contractility effects of classic angiotensin receptor blockers (ARB). Pre-clinical data demonstrated haemodynamic benefits, including balanced vasodilation, improved cardiac performance, preserved glomerular filtration, and improved renal blood flow.[9] Human studies in healthy volunteers and in chronic HF demonstrated dose-dependent reductions in left ventricular filling pressures and mean arterial pressure, particularly among patients with higher renin-angiotensin aldosterone system (RAAS) activation as measured by plasma renin activity (PRA).[10,11] Building upon the pre-clinical and early human data, the Phase 2b Biased Ligand of the Angiotensin receptor STudy in Acute Heart Failure (BLAST-AHF) dose-finding trial was undertaken to evaluate the safety and efficacy of three doses of TRV027 in patients hospitalized with AHF.

Methods

Study design and participants

The design and rationale of BLAST-AHF (NCT01966601) has been previously described.[8] Briefly, this was an international multi-centre, randomized, placebo-controlled, double-blind, parallel group, Phase IIb dose-finding clinical study. Enrolment began in December 2013, was paused between November 2014 and May 2015 for a planned interim analysis, and concluded in February 2016. Institutional review board and/or ethics committee approval was obtained from every site. Only patients who met all eligibility criteria and who provided written, informed consent were enrolled. An independent data safety monitoring board (DSMB) monitored trial conduct and patient safety.

Patients with a history of heart failure (HF) who presented to the hospital with AHF, as evidenced by elevated natriuretic peptides [BNP >400 pg/mL or NTproBNP >1600 pg/mL (For patients with BMI >30 kg/m^2: BNP > 200 pg/mL or NT-proBNP > 800 pg/mL and for patients with rate-controlled persistent or permanent atrial fibrillation: BNP > 600 pg/mL or NT-proBNP > 2400 pg/mL)] and at least two physical HF signs including congestion on chest radiograph, rales, oedema, and/or elevated jugular venous pressure, were eligible. Other key inclusion criteria were a systolic blood pressure (SBP) ≥120 and ≤ 200 mmHg and eGFR (sMDRD) 20–75 mL/min/1.73 m^2. Use of ARBs within 7 days prior, IV inotropes or vasopressors within 2 h prior, or IV nitrates within 1 h prior to randomization were criteria for exclusion (patients receiving nitroglycerin ≤ 0.1 mg/kg/h for screening SBP ≥ 150 mmHg were eligible).[8] (Detailed inclusion and exclusion are provided in Supplementary material online, *Table S1*.)

Study procedures

Patients were randomly assigned to one of the following four (1:1:1:1) parallel dose groups using a web based interactive randomization system: (i) Placebo; (ii) TRV027 1 mg/h; (iii) TRV027 5 mg/h; (iv) TRV027 25 mg/h. Randomization occurred at least 1 h after an initial 40 mg (minimum) dose of IV furosemide (or equivalent dose of another loop diuretic) and no more than 16 h after the first recorded blood pressure assessment was performed in the hospital. Recruitment of eligible patients within 6 h of first hospital blood pressure measurement was encouraged. To remain eligible, patients had to report ongoing dyspnea at rest or with minimal exertion at least 1 h after receiving the most recent dose of IV diuretic. Otherwise, they were deemed a screen failure. Treatment was limited to 96 h of study drug, with a minimum of 48 h. Study drug was to be discontinued if the SBP was <95 mmHg, and the infusion rate was to be halved if the SBP decreased by ≥ 40 mmHg from baseline (recorded within 2 h before initiation of study medication) any time during study drug administration after being confirmed with a second measure 10 min later. The infusion rate was halved 3 h prior to anticipated completion.

Endpoints

BLAST-AHF was a phase IIb study designed to identify a safe and efficacious dose to carry forward into future development. As such, multiple clinical endpoints of interest were simultaneously explored to ascertain the potential benefits of TRV027. The primary outcome was a composite z-score, computed from the following outcomes: (i) time from baseline to death through day 30, (ii) time from baseline to heart failure re-hospitalization through day 30, (iii) the first assessment time point following worsening heart failure through day 5, (iv) change in dyspnea visual analogue scale (VAS) score calculated as the area under the curve (AUC) representing the change from baseline over time from baseline through day 5, and (v) length of initial hospital stay (in days) from baseline. Patients reported their dyspnea on a 100-mm VAS, where 0 was the worst and 100 the best their patient's breathing had ever felt, at baseline; 3, 6, and 24 h; then daily through day 4 while hospitalized; and at day 5. Worsening signs and symptoms of heart failure requiring intensification of intravenous or mechanical treatment while hospitalized were classified as worsening heart failure (WHF). Dyspnea VAS scores for assessments following death or the onset of WHF were replaced for analysis with the worst observed score over all patients and time points. Missing dyspnea VAS scores were imputed by linear interpolation or the last observation was carried forward if no following non-missing value was available. Each component of the composite outcome was transformed to a z-score by subtracting the overall mean and dividing by the standard deviation; log-rank scores for time-to-event outcomes were thus transformed.[12] Individual z-scores were then multiplied by -1 as needed so that smaller scores represented worse outcomes for all endpoints. The z-scores averaged over the 5 components then constituted the primary outcome for an individual patient.[13] Vital status and the occurrence of re-hospitalization were determined by in-person visit at day 30 and phone call between day 31 and day 180. The database was locked, and main analyses conducted, when the last patient enrolled reached day 30; interim vital status and re-hospitalization data were obtained for patients who had not yet completed day 180. Day 180 follow-up was completed on all remaining patients following database lock.

The main secondary endpoints were: (i) VAS AUC to day 5, and (ii) the change in core laboratory-measured NTproBNP from baseline to 48 h.

Pre-specified safety endpoints included: (i) all-cause mortality through day 180, (ii) the incidence of treatment-emergent adverse events and serious adverse events, (iii) changes in vital signs including the incidences of asymptomatic and symptomatic hypotension, and (iv) significant changes in laboratory values.

Interim analysis

Using an adaptive design, a pre-specified interim analysis was planned to allow for discontinuing enrolment into one or two dose groups and/or increasing the total number of patients enrolled. Enrolment was paused and an interim analysis conducted when 254 patients had been enrolled. Following independent reviews by the DSMB and Steering Committee suggesting greater efficacy of the 1.0 and 5.0 mg/h TRV027 groups in patients with higher PRA values and lack of adverse BP effects, the protocol was amended to increase the total sample size to 620 patients from 500; revise the allocation ratio to 2:1:2:1, over-weighting both placebo and the 5 mg/h TRV027 dose groups; lower the SBP threshold for terminating the study drug infusion from 95 to 90 mmHg; and modify other eligibility criteria (see Supplementary material online, *Table S1*). Evidence of radiographic congestion became mandatory for inclusion; the SBP entry criterion was lowered from a range of 120 to 180 mmHg to a range of 105 to 160 mmHg inclusive; and patients with serum sodium > 145 mEq/L were excluded. These changes were made to increase the likelihood of higher plasma renin activity.

The main secondary endpoints were also modified: the change in NTproBNP was replaced with a new main secondary endpoint: a modified primary endpoint incorporating changes in high sensitivity troponin-T (hsTnT) and cystatin-C through 48 h to assess for end-organ protection or prevention of injury.

Statistical analysis plan

Sample size calculation

Each TRV027 group was compared with placebo with respect to the primary outcome—the average z-score—using a Wilcoxon rank sum test. Using 1000 simulated trials, power for the comparison between placebo and one TRV027 group ($n = 175$ per group) was estimated at 79% at the 0.05 significance level assuming treatment effects as follows: risk reductions of 43% for 30-day mortality, 7% for 30-day HF rehospitalization, and 43% for 5-day WHF; and mean differences of 0.21 standard deviations (SD) in dyspnea VAS AUC and 0.26 SD in length of stay, as previously described.[7] As noted, the initial sample size of 500 (with equal representation amongst groups) was adjusted during the interim analysis to yield a final sample size of 620, with 185 patients in each of the placebo and TRV027 5.0 mg/h groups, and 125 patients in each of the TRV027 1.0 and 25.0 mg/h groups projected. The final sample sizes were estimated to provide approximately 79 and 73% power at the two-sided 0.05 significance level for the placebo-to-TRV027 5.0 mg/h comparison and the placebo-to-TRV027 1.0 or 25.0 mg/h comparisons, respectively.[7]

Analyses were conducted in a modified intention-to-treat set, excluding patients randomized but not treated with study drug. Two-sided *P*-values < 0.05 were considered statistically significant, with no adjustment for multiplicity in this exploratory trial. No adjustments were made for the interim analysis. Statistical analyses were conducted using SAS® version 9.3 (SAS Institute, Cary, NC, USA).

Role of the funding source

A steering committee, together with the sponsor (Trevena, Inc) designed the trial. All authors had full access to the final data. Authors who were not employed by the sponsor had final editorial authority.

Results

Patient characteristics

A total of 621 patients were randomized from 72 sites within the following countries: Argentina, Bulgaria, Canada, the Czech Republic, Germany, Hungary, Israel, Poland, Romania, Russia, Slovakia, and the United States. Three misrandomized patients not treated with study drug were excluded from the analyses (*Figure 1*). Of the 618 treated patients, 594 survived to day 30; 540 patients completed day 180 follow-up and 78 died prior to day 180. The mean follow-up was 170.0 days.

The mean age across all groups was 70 ± 9.5 years; 62% were male, 98% self-identified as white and 10% as Hispanic or Latino ethnicity. The median ejection fraction (EF) at baseline was 35% (IQR 27–43%) and 70% of patients had a reduced EF (≤40%). At baseline, the median PRA overall was 0.905 ng/mL/h and the median NT-proBNP was 5106 pg/mL. Median time from presentation to randomization was 5.7 (IQR 4.2–8.5) h with median infusion duration of 95.9 (IQR 90.3–96) h. Overall, treatment groups were similar and well balanced (*Table 1*).

Primary endpoint

As seen in *Figure 2*, no significant differences were observed between any of the dose groups compared with placebo with regard to the primary endpoint. Results for the individual components of the composite outcome, without transformation to z-scores, are shown in *Table 2*. None of the studied doses of TRV027 improved any of the individual components of the primary endpoint compared with placebo.

Secondary endpoints

As seen in *Figure 3*, on average, dyspnea improved through day 5 in all treatment groups. Although dyspnea improved somewhat less in the TRV027 groups than in the placebo group, reflected by lower mean baseline-adjusted dyspnea VAS AUCs (*Table 2*), the differences were not statistically significant. When changes in cystatin C and hsTnT at 48 h were added to the primary composite endpoint, no significant differences were observed between any of the treatment groups and placebo (Supplementary material online, *Figure S1*). Individual component outcomes, without transformation to z-scores, are shown in *Table 3*.

NT-proBNP decreased from baseline to 48 h, in all treatment groups (*Figure 4*), with greater decreases in placebo than in active treatment groups. Baseline-adjusted treatment ratios (ratio of change in active to change in placebo) were 1.135, 1.222, and 1.168 with associated *P*-values of 0.0864, 0.0026, and 0.0371 in the 1.0, 5.0, and 25.0 mg/h TRV027 groups, respectively.

Systolic blood pressure and heart rate

No significant differences in SBP or heart rate (HR) compared with placebo were observed, irrespective of TRV027 dose (*Figures 5A* and *B*).

Subgroups

Pre-specified subgroup analyses of the primary composite outcome and its components were performed to identify potential responders

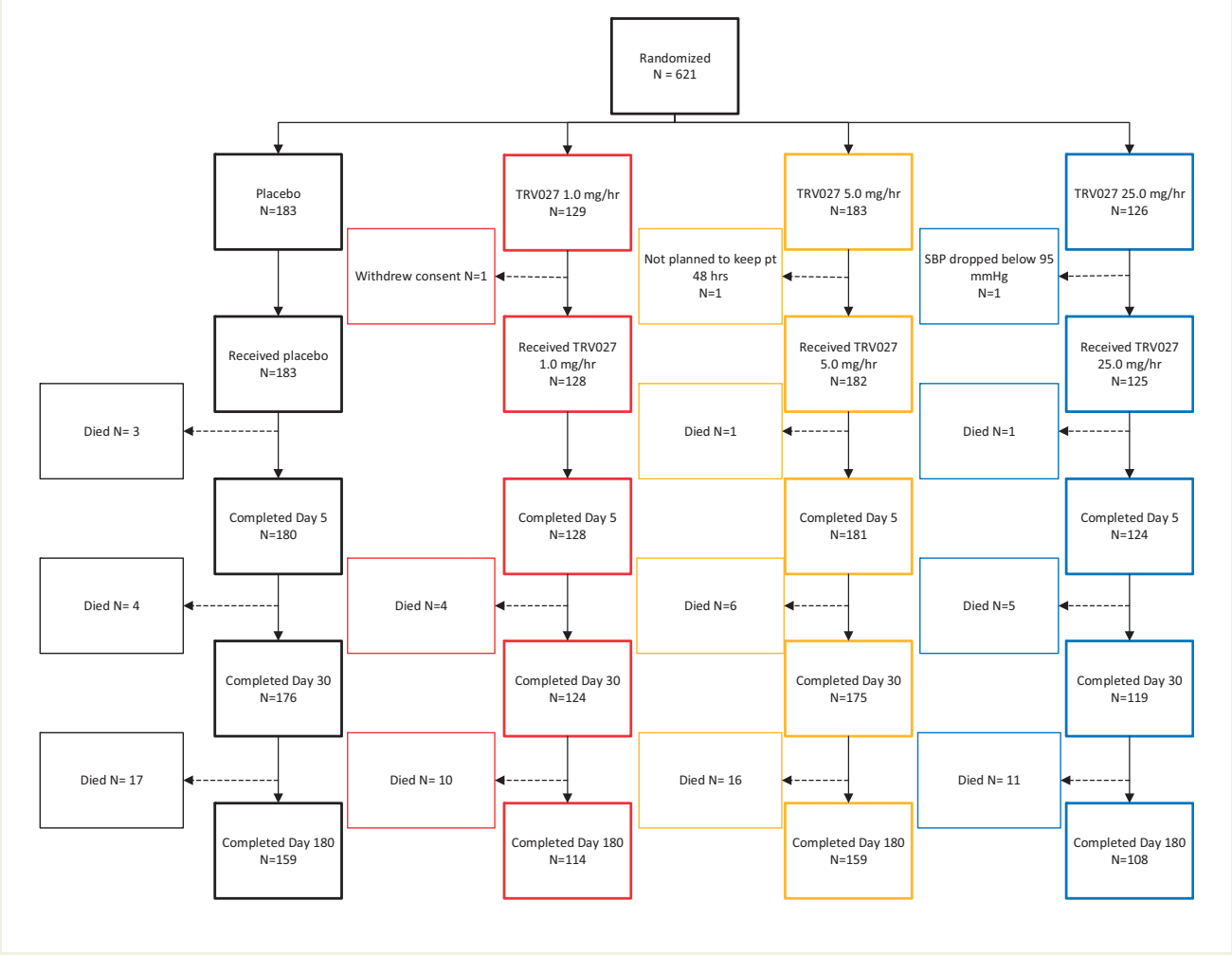

Figure 1 Patient allocation by study arm.

to TRV027. Supplementary material online, *Figure S2* presents results of these subgroup analyses for the primary composite outcome. After pre-specified interim analysis, the 5 mg/h dose was over-weighted in regards to enrolment. However, irrespective of dose, treatment effects were neutral following the interim analysis. Although prior pre-clinical and haemodynamic data supported a greater effect of TRV027 in patients with elevated PRA levels, no significant differences with respect to the primary composite endpoint (average z-score across the five components) in patients above and below the median PRA were observed.

Safety—180 day follow-up

For the 540 patients with 180 day follow-up, estimated rates of all-cause mortality did not differ between placebo and any TRV027 group: 13.1, 11.0, 12.6, and 13.6% in the placebo, and TRV027 1.0, 5.0, and 25.0 mg/h groups, respectively. Rates of occurrence of adverse events were similar among the groups (*Table 4*). Proportions of patients with blood pressure decreases necessitating decreasing the dose or discontinuing study drug were similar in the dose groups: 13.1, 15.6, 11.0, and 12.8% in the placebo and TRV027 1.0, 5.0, and 25.0 mg/h groups, respectively.

Discussion

In the BLAST-AHF study, none of the 3 tested doses of TRV027, a novel biased ligand of the AT1R receptor, resulted in clinically important improvements over placebo with respect to the primary and secondary endpoints. Specifically, no efficacy signals were observed in any of the 5 components of the primary composite endpoint: (i) death through day 30, (ii) heart failure re-hospitalization through day 30, (iii) WHF through day 5, (iv) dyspnea through day 5, or (v) length of hospital stay. Similarly, there was no evidence of efficacy compared with placebo with regard to key secondary endpoints, including dyspnea VAS AUC and change in NT-proBNP, or the composite endpoint with hsTnT and cystatin C changes included. Overall, TRV027 was well tolerated with similar adverse event rates as placebo.

Our primary mechanistic hypothesis—informed by pre-clinical data and prior clinical studies—was that TRV027 would have

Table 1 Baseline characteristics

Parameter	Placebo (*N* = 183)	TRV027 1.0 mg/h (*N* = 128)	TRV027 5.0 mg/h (*N* = 182)	TRV027 25.0 mg/h (*N* = 125)
Age (years), mean ± SD	71.1 ± 9.39	70.1 ± 10.48	69.8 ± 9.03	70.8 ± 9.31
Male, *n* (%)	115 (62.8)	78 (60.9)	113 (62.1)	78 (62.4)
BMI (kg/m^2), mean ± SD	30.8 ± 5.88	31.1 ± 6.68	29.8 ± 6.05	30.5 ± 6.68
Ejection fraction (%), mean ± SD	36 ± 12.2	37 ± 11.6	35 ± 11.9	35 ± 11.9
Time from presentation to randomization (h), median [Q1, Q3]	5.6 [4.1, 8.4]	5.8 [4.5, 8.3]	6.1 [4.2, 9.0]	5.7 [4.0, 8.5]
Race				
White, *n* (%)	180 (98.4)	125 (97.7)	180 (98.9)	123 (98.4)
Black or African American, *n* (%)	3 (1.6)	2 (1.6)	1 (0.5)	1 (0.8)
Ethnicity				
Hispanic or Latino, *n* (%)	19 (10.4)	13 (10.2)	19 (10.4)	10 (8.0)
Not Hispanic or Latino, *n* (%)	164 (89.6)	115 (89.8)	163 (89.6)	115 (92.0)
Medical history				
Heart failure, *n* (%)	178 (97.3)	128 (100)	178 (97.8)	123 (98.4)
Hospitalization for heart failure in past year, *n* (%)	102 (55.7)	64 (50.0)	97 (53.3)	77 (61.6)
Hypertension, *n* (%)	167 (91.3)	116 (90.6)	167 (91.8)	115 (92.0)
Ischaemic heart disease, *n* (%)	120 (65.6)	80 (62.5)	126 (69.2)	82 (65.6)
MI/ACS, *n* (%)	82 (44.8)	50 (39.1)	91 (50.0)	60 (48.0)
History of atrial fibrillation/flutter, *n* (%)	105 (57.4)	73 (57.0)	87 (47.8)	74 (59.2)
Stroke or cerebrovascular event, *n* (%)	28 (15.3)	18 (14.1)	28 (15.4)	19 (15.2)
Peripheral vascular disease, *n* (%)	22 (12.0)	20 (15.6)	26 (14.3)	14 (11.2)
Asthma or COPD, *n* (%)	29 (15.8)	20 (15.6)	27 (14.8)	27 (21.6)
Pulmonary hypertension, *n* (%)	55 (30.1)	31 (24.2)	56 (30.8)	38 (30.4)
Diabetes mellitus, *n* (%)	85 (46.4)	53 (41.4)	78 (42.9)	59 (47.2)
Insulin use for diabetes mellitus, *n* (%)	37 (20.2)	14 (10.9)	30 (16.5)	24 (19.2)
Medications (30 days prior to screening)/device history				
ACE inhibitor, *n* (%)	146 (79.8)	105 (82.0)	139 (76.4)	99 (79.2)
Aldosterone antagonist, *n* (%)	72 (39.3)	44 (34.4)	57 (31.3)	47 (37.6)
Beta-blocker	159 (86.9)	104 (81.3)	158 (86.8)	108 (86.4)
Calcium channel blocker	39 (21.3)	28 (21.9)	35 (19.2)	25 (20.0)
Pacemaker, biventricular pacer, or ICD, *n* (%)	33 (18.0)	25 (19.5)	48 (26.4)	25 (20.0)
Symptoms				
Dyspnea VAS (mm), mean ± SD	37.1 ± 16.56	36.5 ± 17.00	35.1 ± 17.71	36.3 ± 17.59
Vital signs				
Systolic blood pressure (mmHg), mean ± SD	134.5 ± 15.28	134.5 ± 15.20	131.8 ± 15.69	134.6 ± 15.41
Heart rate (b.p.m.), mean ± SD	78.3 ± 15.38	79.9 ± 15.78	77.8 ± 14.39	78.8 ± 15.04
Respiratory rate (breaths/min), mean ± SD	23.3 ± 4.14	24.0 ± 4.22	23.3 ± 3.88	23.6 ± 4.44
Lab values				
Sodium (mmol/L), mean ± SD	140.5 ± 3.43	140.9 ± 3.49	140.5 ± 4.11	140.7 ± 3.89
Creatinine (mg/dL), mean ± SD	1.31 ± 0.460	1.26 ± 0.426	1.32 ± 0.458	1.31 ± 0.449
eGFR (mL/min/1.73 m^2), median [Q1, Q3]	53.37 [42.24, 67.39]	53.79 [41.18, 69.50]	53.96 [40.16, 63.44]	53.62 [41.90, 64.50]
Hematocrit (%), mean ± SD	39.5 ± 6.13	40.7 ± 5.13	40.8 ± 5.99	40.4 ± 5.27
NT-proBNP (pg/mL), median [Q1, Q3]	4404 [2706, 9015]	5062 [2956, 9932]	5741 [2805, 10951]	5280 [3043, 9507]
PRA (ng/mL/h), median [Q1, Q3]	0.965 [0.245, 4.910]	0.630 [0.180, 2.905]	1.045 [0.235, 4.630]	0.820 [0.210, 4.470]

ACE, angiotensin-converting enzyme; ACS, acute coronary syndrome; BMI, body mass index; COPD, chronic obstructive pulmonary disease; eGFR, estimated glomerular filtration rate; ICD, internal cardiac defibrillator; MI, myocardial infarction; NT-proBNP, N-terminal ProB-type natriuretic peptide; PRA, plasma renin activity; Q1, 25-percentile; Q3, 75-percentile; SD, standard deviation; VAS, visual analogue scale.

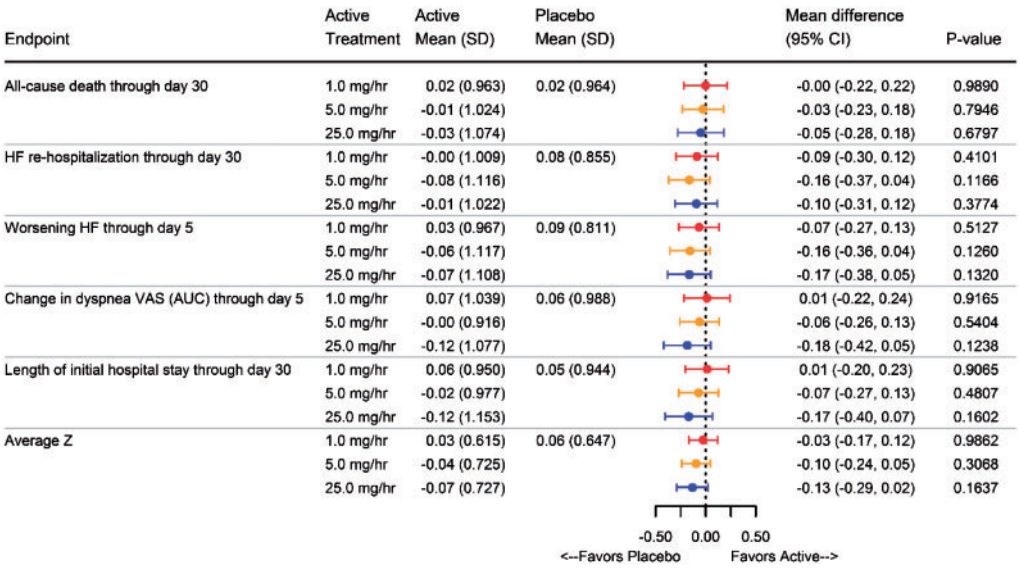

Figure 2 Forest plot of primary composite endpoint average Z and components. Mean difference and 95% confidence interval for the difference of each active arm to placebo. *P*-value according to *t*-test for components and according to Wilcoxon rank sum test for average Z.

beneficial haemodynamic effects, especially in patients with elevated PRA levels.[8–11] However, we did not observe significant decrease in SBP with TRV027 compared with placebo. Further stratification by PRA levels above the median value (data not shown) did not alter this finding. This lack of effect on blood pressure contrasts with the haemodynamic activity of TRV027 observed in prior studies.[9] While reductions in blood pressure were consistently noted in preclinical and early clinical trials in patients with chronic, stable HF, BLAST-AHF was the first study in which patients with AHF were enrolled. It is possible that the pharmacological activities of TRV027 may manifest differently in the setting of AHF, for example the procontractility or antiapoptotic effects observed with TRV027 may produce effects unrelated to reductions in blood pressure.[9]

Neurohormonal blockade of the renin-angiotensin-aldosterone-system (RAAS) is the cornerstone of chronic HF management in patients with reduced systolic function. ACEI/ARBs, mineralocorticoid receptor antagonists (MRAs), and the angiotensin receptor blocker/neprilysin inhibitor (ARB/NEPI), significantly reduce morbidity and mortality.[4,5] The prevailing paradigm posits RAAS activation in HF as a result of inadequate tissue perfusion. Specifically, RAAS activation and consequent increase in circulating angiotensin II (AngII) results in vasoconstriction, fibrosis, sodium and water retention, and decreased renal perfusion. We hypothesized RAAS blockade in AHF would lead to improved symptoms, less worsening heart failure, and less death/re-hospitalization through 30 days.

RAAS blockade in AHF has not been previously well studied. CONSENSUS-2, published in 1992, targeted acute myocardial infarction patients with IV enalprilat.[14] Subgroup analysis of patients with HF demonstrated no benefits, along with signals of harm (i.e. hypotension and worsening renal function). Other studies have been small, physiologic studies demonstrating haemodynamic effects.[8,15]

The concept of neurohormonal activation in AHF derives from studies conducted prior to the modern era of RAAS inhibition.[16] Contrary to a widely held belief based on studies conducted prior to the use of ace inhibitors and beta blockers in clinical practice, a recent study by Mentz *et al.*[17] suggested high dose IV loop diuretic therapy did not cause greater neurohormonal activation than low dose. Intriguingly, the baseline mean PRA levels reported by Mentz *et al.* were 13.3 ng/mL/h (SD 23.1) in DOSE-AHF vs. 3.99 ng/mL/h (SD 6.7, placebo arm, see Supplementary material online) in BLAST-AHF. These differences in PRA levels raises the possibility of distinct patient populations within the spectrum of AHF. However, the PRA assays used in these two trials were not the same and the acquisition of samples may be significant confounders. Unlike animal models, background RAAS modulation in chronic HF patients who decompensate may have also contributed either to lower PRA levels or influenced the RAAS modulatory effects of TRV027. Regardless, no differences were seen by median PRA split in BLAST-AHF. Whether this relatively low PRA contributed to the lack of efficacy signals is unknown. Another potential explanation: our underlying assumptions regarding greater efficacy in elevated PRA patients based on pre-clinical and *chronic* HF data simply may not apply to our targeted AHF population.

Although not statistically significant, improvements in dyspnea, changes in NTproBNP, and haemodynamic effect as measured by SBP appear to favour placebo, especially when contrasted with the highest dose. Whether this suggests a potential adverse effect at the highest dose is speculative, as no significant differences in pre-defined safety events were observed.

Changes to the protocol during the interim analysis and subsequent results are important to highlight. These changes were primarily designed to increase enrolment of patients with higher RAAS activation. While the lack of significant SBP lowering or NT-proBNP

Table 2 Results for components of the primary composite endpoint

Component	Placebo (*N* = 183)	TRV027 1.0 mg/h (*N* = 128)	TRV027 5.0 mg/h (*N* = 182)	TRV027 25.0 mg/h (*N* = 125)
Death through day 30, *n* (%)	7 (3.8)	5 (3.9)	8 (4.4)	6 (4.8)
Hazard ratio		1.01	1.14	1.26
(95% CI)		(0.32, 3.18)	(0.42, 3.16)	(0.42, 3.74)
P-value[a]		0.9879	0.7929	0.6787
HF Rehospitalization through day 30 day, *n* (%)	10 (5.5)	10 (7.8)	18 (9.9)	10 (8.0)
Hazard ratio		1.44	1.84	1.48
(95% CI)		(0.60, 3.47)	(0.85, 3.99)	(0.62, 3.56)
P-value[a]		0.4095	0.1163	0.3745
WHF through day 5, *n* (%)				
Hour 3	0 (0.0)	0 (0.0)	0 (0.0)	1 (0.8)
Hour 6	1 (0.5)	0 (0.0)	1 (0.5)	1 (0.8)
Hour 24	1 (0.5)	4 (3.1)	6 (3.3)	3 (2.4)
Hour 48	6 (3.3)	4 (3.1)	9 (4.9)	7 (5.6)
Day 3	7 (3.8)	7 (5.5)	13 (7.1)	9 (7.2)
Day 4	9 (4.9)	8 (6.3)	17 (9.3)	10 (8.0)
Day 5	11 (6.0)	10 (7.8)	18 (9.9)	15 (12.0)
P-value[b]		0.5284	0.1623	0.0661
Dyspnea VAS AUC through day 5, mean (mean mm-h)	2779.8	2807.7	2639.9	2359.6
SD	2260.71	2377.59	2096.67	2465.77
LS Mean difference		-9.8	-283.1	-465.0
(95% CI)		(-469.1, 449.6)	(-701.0, 134.8)	(-927.6, -2.3)
P-value[c]		0.9667	0.1839	0.0489
Length of Initial Hospital Stay, mean (days)	8.8	8.7	9.2	9.7
SD	5.25	5.28	5.43	6.40
Median	7.0	7.0	7.0	8.0
Q1, Q3	6.0, 10.0	6.0, 10.0	6.0, 11.0	6.0, 11.0
P-value[d]		0.9114	0.4980	0.1462

[a]From log-rank test.
[b]From Wilcoxon rank-sum test.
[c]From ANCOVA with baseline dyspnea VAS as the covariate and treatment as factor.
[d]From ANOVA with treatment.

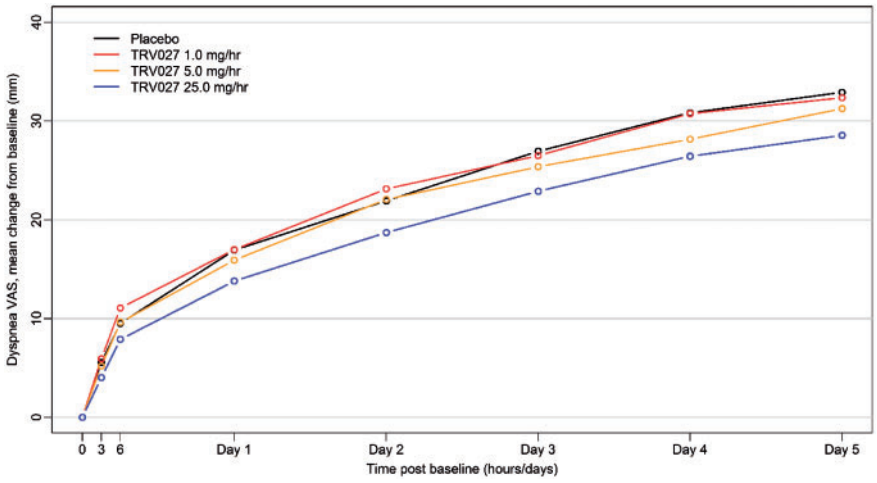

Figure 3 Dyspnea VAS: Change from baseline through day 5 (in mm).

Table 3 Results for additional components to the primary composite endpoint

Component	Placebo (*N* = 183)	TRV027 1.0 mg/h (*N* = 128)	TRV027 5.0 mg/h (*N* = 182)	TRV027 25.0 mg/h (*N* = 125)
Cystatin C change from baseline to Hour 48, geometric mean (GM)	1.07	1.09	1.04	1.07
95% CI on GM	(1.02, 1.11)	(1.05, 1.13)	(1.00, 1.08)	(1.04, 1.11)
Treatment difference[a]		1.013	0.981	1.013
P-value[a]		0.6160	0.4095	0.6070
Troponin T change from baseline to Hour 48, geometric mean (GM)	1.03	1.09	0.99	1.01
95% CI on GM	(0.98, 1.08)	(1.01, 1.17)	(0.94, 1.04)	(0.95, 1.07)
Treatment difference[a]		1.052	0.968	0.979
P-value[a]		0.2079	0.3843	0.5951

Linear interpolation and last observation carried forward for missing values.
[a]Model-adjusted treatment difference and *P*-value are from ANCOVA fitted differences between log results at time point and baseline with log baseline biomarker result as the covariate and treatment as factor. Treatment difference is the geometric LS mean difference. GM of change from baseline represents the ratio of the post-baseline value over the baseline value.

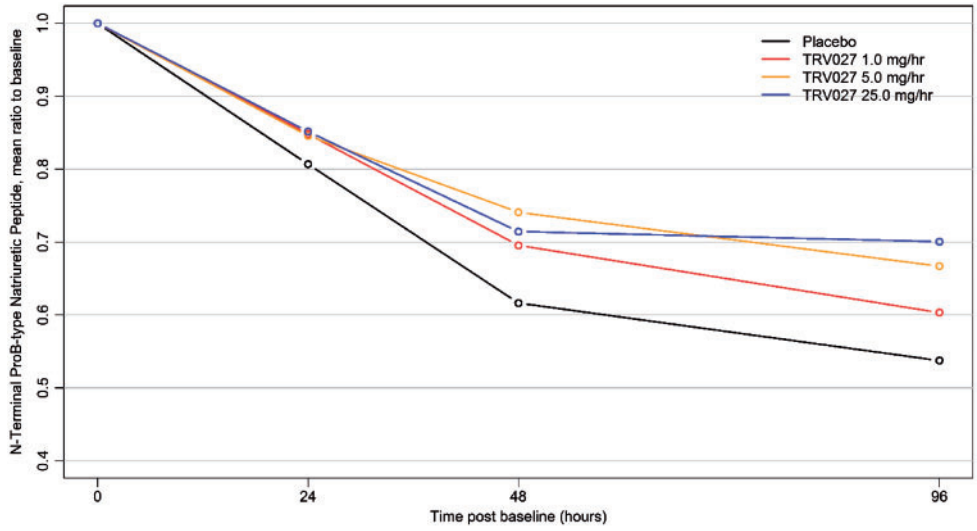

Figure 4 NT-proBNP: Ratio to baseline through 96 h.

change at the interim analysis raised questions as to dose-effect, they also allowed for a lower SBP entry criterion, which was expected to select a population with greater RAAS elevation. However, despite lowering the SBP entry criteria (from 120 to 105 mmHg) to a maximum of 160 mmHg (from 200 mmHg), mandating radiographic pulmonary congestion, and excluding higher baseline serum sodium patients, baseline PRA levels were not appreciably higher in the post-IA population (data not shown).

Finally, BLAST-AHF utilized a composite analysis of five clinically important endpoints, combined using an average Z score. The components of the primary analysis were chosen because of their importance to patient care and their use in previous AHF trials, and this combination was expected to enhance the trial's power compared with use of a single clinical endpoint. However, because of the low observed rates of the 30-day events and WHF in the placebo arm, the primary endpoint was driven by effects on dyspnea and hospital length of stay. There was no effect of TRV027 observed on these components of the primary endpoint. Evaluation of longer term outcomes, beyond 30 days, may be required in future trials in order to ensure a robust event rate.

Conclusions

In this Phase IIb dose-ranging AHF study of TRV027, a biased ligand of the AT1R, no benefit over placebo was observed in the primary or pre-specified secondary endpoints.

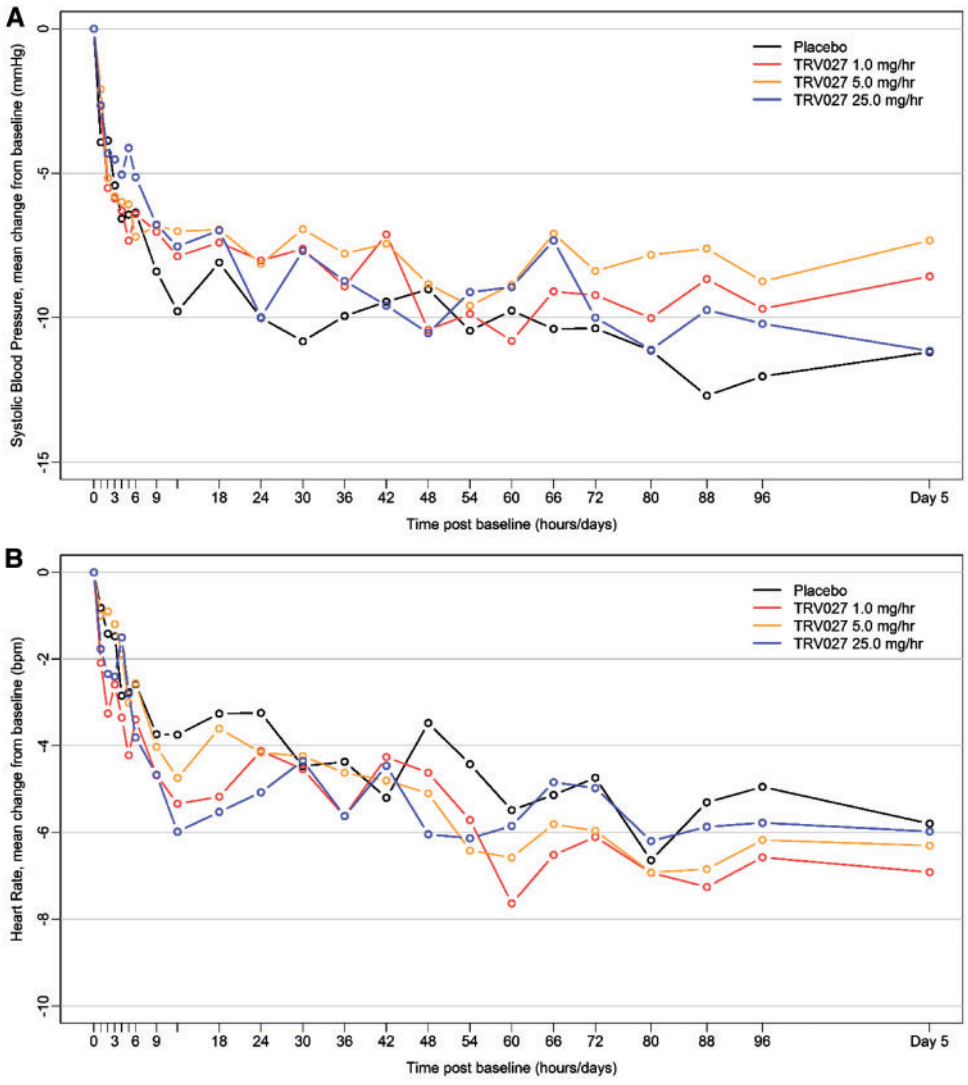

Figure 5 Changes in (*A*) systolic blood pressure (mmHg) and (*B*) heart rate (b.p.m.): from baseline through day 5.

Table 4 **Adverse events**

Number of patients with	Placebo (*N* = 183)	TRV027 1.0 mg/h (*N* = 128)	TRV027 5.0 mg/h (*N* = 182)	TRV027 25.0 mg/h (*N* = 125)
Any treatment-emergent adverse event, *n* (%)	116 (63.4%)	82 (64.1%)	120 (65.9%)	88 (70.4%)
Any serious treatment-emergent adverse event, *n* (%)	24 (13.1%)	16 (12.5%)	36 (19.8%)	22 (17.6%)
Any study drug related[a] treatment-emergent adverse event, *n* (%)	22 (12.0%)	8 (6.3%)	8 (4.4%)	10 (8.0%)
Any study drug related[a] serious treatment-emergent adverse event, *n* (%)	3 (1.6%)	1 (0.8%)	1 (0.5%)	0 (0.0%)
Any treatment-emergent adverse event leading to treatment discontinuation, *n* (%)	9 (4.9%)	6 (4.7%)	9 (4.9%)	7 (5.6%)
Any treatment-emergent adverse event leading to death[b], *n* (%)	9 (4.9%)	6 (4.7%)	9 (4.9%)	8 (6.4%)

[a]Relatedness to study drug determined by site investigator.
[b]Fatal adverse event with an onset through day 30.

Acknowledgements

We would like to thank the patients, investigators, and research staff for their participation and dedication.

Funding

This work was supported by Trevena, Inc.

Conflict of interest: Peter S. Pang is or has been in the last one year a Consultant for: BMS, Novartis, Trevena, scPharmaceuticals, Roche Diagnostics, Relypsa, Research Support: Roche, Novartis, PCORI, Dr. Collins' reports grants and personal fees from Novartis, personal fees from Roche, grants from NIH, grants from PCORI, personal fees from Trevena, grants and personal fees from Intersection Medical, grants and personal fees from Cardiorentis, outside the submitted work; Dr. Cotter and Davison reports grants from Trevena, Inc., during the conduct of the study; grants and personal fees from Novartis, grants from Celyad, grants from Singulex, grants from ChanRx, grants from Laguna Pharmaceuticals, grants from Sorbent Therapeutics, grants from Amgen, outside the submitted work; Bharucha is an employee of Allergan plc (Forest Labs), a sponsor of this trial. Dr. Butler reports personal fees from Trevena, during the conduct of the study; other from Amgen, other from Bayer, other from Boehringer Ingelheim, other from CardioCell, other from Merck, other from Novartis, other from Relypsa, other from ZS Pharma, other from Janssen, other from Astra Zeneca, outside the submitted work; Dr Ezekowitz reports grants from Trevena, during the conduct of the study. Dr. Levy reports grants from Trevena Inc, during the conduct of the study; along with consultant fees from Trevena, Inc, outside the submitted work; and is a consultant for Novartis Pharmaceuticals, Cardiorentis, and the Medicines Company. He has (through his institution) also received research contract payments from Cardiorentis, Bristol Meyers Squibb, and the Medicines Company. Dr. Metra reports personal fees from Trevena, during the conduct of the study; personal fees from Bayer, personal fees from Novartis, personal fees from Servier, outside the submitted work; Dr. Ponikowski reports other from Trevena, during the conduct of the study; grants, personal fees and other from Servier, personal fees and other from Novartis, personal fees and other from Bayer, personal fees from Pfizer, personal fees and other from Cardiorentis, grants from Singulex, outside the submitted work; consulting from Bayer, Boehringer-Ingelheim, Novartis. Dr. Filippatos reports he was Committee member of trials and registries sponsored from Bayer, Novartis, outside the submitted work; Teerlink: Consulting from: Amgen, Bayer, BMS, Cytokinetics, Gilead, Merck, Novartis, Relypsa, Stealth Bio-therapeutics, ZS Pharma; Research funding from: Amgen, Bayer, BMS, Cardio3Biosciences, Medtronic, Novartis, St. Jude, Trevena. Goins was an employee of Trevena Inc. Soergel is an employee of Trevena, the primary sponsor of this trial. Voors: reports personal fees from Trevena, during the conduct of the study; personal fees from Novartis, personal fees from Servier, personal fees from Boehringer, personal fees from GSK, personal fees from Stealth, personal fees from Amgen, personal fees from Merck, outside the submitted work; Dr. Felker reports personal fees from Trevena, during the conduct of the study; grants and personal fees from Novartis, grants and personal fees from Amgen, personal fees from BMS, personal fees from GSK, personal fees from Myokardia, grants from Merck, grants from Roche Diagnostics, outside the submitted work.

References

1. Ponikowski P, Voors AA, Anker SD, Bueno H, Cleland JG, Coats AJ, Falk V, Gonzalez-Juanatey JR, Harjola VP, Jankowska EA, Jessup M, Linde C, Nihoyannopoulos P, Parissis JT, Pieske B, Riley JP, Rosano GM, Ruilope LM, Ruschitzka F, Rutten FH, van der Meer P. Authors/Task Force M, Document R. 2016 ESC Guidelines for the diagnosis and treatment of acute and chronic heart failure: The Task Force for the diagnosis and treatment of acute and chronic heart failure of the European Society of Cardiology (ESC)Developed with the special contribution of the Heart Failure Association (HFA) of the ESC. *Eur Heart J* 2016;**37**:2129–2200.
2. Cook C, Cole G, Asaria P, Jabbour R, Francis DP. The annual global economic burden of heart failure. *Int J Cardiol* 2014;**171**:368–376.
3. Maggioni AP, Dahlstrom U, Filippatos G, Chioncel O, Crespo Leiro M, Drozdz J, Fruhwald F, Gullestad L, Logeart D, Fabbri G, Urso R, Metra M, Parissis J, Persson H, Ponikowski P, Rauchhaus M, Voors AA, Nielsen OW, Zannad F, Tavazzi L. Heart Failure Association of the European Society of C. EURObservational Research Programme: regional differences and 1-year follow-up results of the Heart Failure Pilot Survey (ESC-HF Pilot). *Eur J Heart Fail* 2013;**15**:808–817.
4. Eapen ZJ, Liang L, Fonarow GC, Heidenreich PA, Curtis LH, Peterson ED, Hernandez AF. Validated, electronic health record deployable prediction models for assessing patient risk of 30-day rehospitalization and mortality in older heart failure patients. *JACC Heart Fail* 2013;**1**:245–251.
5. Yancy CW, Jessup M, Bozkurt B, Masoudi FA, Butler J, McBride PE, Casey DE, Jr., McMurray JJ, Drazner MH, Mitchell JE, Fonarow GC, Peterson PN, Geraci SA, Horwich T, Januzzi JL, Johnson MR, Kasper EK, Levy WC, Riegel B, Sam F, Stevenson LW, Tang WH, Tsai EJ, Wilkoff BL, Members AATF. 2013 ACCF/AHA Guideline for the Management of Heart Failure: a Report of the American College of Cardiology Foundation/American Heart Association Task Force on Practice Guidelines. *J Am Coll Cardiol* 2013;**62**:e147–0239.
6. Pang PS, Givertz MM. The challenge of drug development in acute heart failure: balancing mechanisms, targeting patients, and gambling on outcomes. *JACC Heart Fail* 2013;**1**:442–444.
7. Pang PS, Komajda M, Gheorghiade M. The current and future management of acute heart failure syndromes. *Eur Heart J* 2010;**31**:784–793.
8. Felker GM, Butler J, Collins SP, Cotter G, Davison BA, Ezekowitz JA, Filippatos G, Levy PD, Metra M, Ponikowski P, Soergel DG, Teerlink JR, Violin JD, Voors AA, Pang PS. Heart failure therapeutics on the basis of a biased ligand of the angiotensin-2 type 1 receptor: rationale and design of the BLAST-AHF Study (Biased Ligand of the Angiotensin Receptor Study in Acute Heart Failure). *JACC Heart Fail* 2015;**3**:193–201.
9. Violin JD, Soergel DG, Boerrigter G, Burnett JC, Jr, Lark MW. GPCR biased ligands as novel heart failure therapeutics. *Trends Cardiovasc Med* 2013;**23**:242–249.
10. Soergel DG, Subach RA, Cowan CL, Violin JD, Lark MW. First clinical experience with TRV027: pharmacokinetics and pharmacodynamics in healthy volunteers. *J Clin Pharmacol* 2013;**53**:892–899.
11. Soergel D, Subach RA, James IE, Cowan CL, Gowan M, Lark M. TRV027, a beta-arrestin biased ligand at the angiotensin 2 type 1 receptor, produces rapid, reversible changes in hemodynamics in patients with stable systolic heart failure (abstract). *J Am Coll Cardiol* 2013;**61**(Suppl 10):e683.
12. Saville BR, Herring AH, Koch GG. A robust method for comparing two treatments in a confirmatory clinical trial via multivariate time-to-event methods that jointly incorporate information from longitudinal and time-to-event data. *Stat Med* 2010;**29**:75–85.
13. Sun H, Davison BA, Cotter G, Pencina MJ, Koch GG. Evaluating treatment efficacy by multiple end points in phase II acute heart failure clinical trials: analyzing data using a global method. *Circ Heart Fail* 2012;**5**:742–749.
14. Swedberg K, Held P, Kjekshus J, Rasmussen K, Ryden L, Wedel H. Effects of the early administration of enalapril on mortality in patients with acute myocardial infarction. Results of the Cooperative New Scandinavian Enalapril Survival Study II (CONSENSUS II). *N Engl J Med* 1992;**327**:678–684.
15. Annane D, Bellissant E, Pussard E, Asmar R, Lacombe F, Lanata E, Madonna O, Safar M, Giudicelli JF, Gajdos P. Placebo-controlled, randomized, double-blind study of intravenous enalaprilat efficacy and safety in acute cardiogenic pulmonary edema. *Circulation* 1996;**94**:1316–1324.
16. Francis GS, Goldsmith SR, Levine TB, Olivari MT, Cohn JN. The neurohumoral axis in congestive heart failure. *Ann Internal Med* 1984;**101**:370–377.
17. Mentz RJ, Stevens SR, DeVore AD, Lala A, Vader JM, AbouEzzeddine OF, Khazanie P, Redfield MM, Stevenson LW, O'connor CM, Goldsmith SR, Bart BA, Anstrom KJ, Hernandez AF, Braunwald E, Felker GM. Decongestion strategies and renin-angiotensin-aldosterone system activation in acute heart failure. *JACC Heart Fail* 2015;**3**:97–107.