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STATE-OF-THE-ART PAPER

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)

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ABSTRACT

The BLAST-AHF (Biased Ligand of the Angiotensin Receptor Study in Acute Heart Failure) study is designed to test the efficacy and safety of TRV027, a novel biased ligand of the angiotensin-2 type 1 receptor, in patients with acute heart failure (AHF). AHF remains a major public health problem, and no currently-available therapies have been shown to favorably affect outcomes. TRV027 is a novel biased ligand of the angiotensin-2 type 1 receptor that antagonizes angiotensin-stimulated G-protein activation while stimulating β-arrestin. In animal models, these effects reduce afterload while increasing cardiac performance and maintaining stroke volume. In initial human studies, TRV027 appears to be hemodynamically active primarily in patients with activation of the renin-angiotensin-aldosterone system, a potentially attractive profile for an AHF therapeutic. BLAST-AHF is an international prospective, randomized, phase IIb, dose-ranging study that will randomize up to 500 AHF patients with systolic blood pressure ≥120 mm Hg and ≤200 mm Hg within 24 h of initial presentation to 1 of 3 doses of intravenous TRV027 (1, 5, or 25 mg/h) or matching placebo (1:1:1:1) for at least 48 h and up to 96 h. The primary endpoint is a composite of 5 clinical endpoints (dyspnea, worsening heart failure, length of hospital stay, 30-day rehospitalization, and 30-day mortality) combined using an average z-score. Secondary endpoints will include the assessment of dyspnea and change in amino-terminal pro-B-type natriuretic peptide. The BLAST-AHF study will assess the efficacy and safety of a novel biased ligand of the angiotensin-2 type 1 receptor in AHF. (J Am Coll Cardiol HF 2015;3:193–201) © 2015 by the American College of Cardiology Foundation.

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ABBREVIATIONS AND ACRONYMS

AHF = acute heart failure

AngII = angiotensin II

ARB = angiotensin receptor blocker

AT1R = angiotensin II type 1 receptor

GPCR = G-protein-coupled receptor

HF = heart failure

HR = heart rate

RAAS = renin angiotensin aldosterone system

VAS = visual analog scale

Acute heart failure (AHF) remains a major public health problem, with more than 1 million hospitalizations occurring annually in the United States and over 4 million worldwide (1,2). Nearly 35% of patients will die or be rehospitalized within 90 days after discharge. Despite over 2 decades of efforts, no new therapies for this syndrome have conclusively demonstrated symptom relief or improved hospital course or post-discharge morbidity or mortality (3). None of the currently-available therapies, including diuretic agents, vasodilators such as nitrates or nesiritide, or inotropic agents such as milrinone or dobutamine, have been shown to favorably alter the natural history of AHF. Indeed, convincing evidence for even clinically-important symptomatic benefits with any of the currently-available AHF treatments is lacking (4). Thus, there remains a major unmet need to develop new therapies for AHF.

AHF is associated with acute symptoms (primarily dyspnea), an unpredictable in-hospital course characterized by events such as worsening heart failure (HF), and a high rate of post-discharge adverse events such as recurrent hospitalizations and death. Ideally, an effective AHF therapy would provide rapid and durable improvement in symptoms as well as improve both in-hospital course and post-discharge outcomes (5).

Fully capturing the effect of a therapy on each of these treatment goals in the context of a clinical trial has been a major challenge in trial design, and there remains no consensus about the ideal endpoint for clinical trials in AHF. Past clinical trials have generally focused on short-term symptom relief in the belief that short-term intravenous (IV) therapy was unlikely to substantially alter the long-term course of AHF (6–8). The recent results of the RELAX-AHF study, in which serelaxin showed reductions in 6-month cardiovascular morality, have challenged this belief, and these results are now being tested in the larger ongoing RELAX-AHF2 study (9). Trial design is even more challenging for early-phase studies, as there is no reliable surrogate for clinical efficacy and safety for AHF that can provide clear guidance for dose selection or reliably predict outcomes in phase III studies (10).

RENIN-ANGIOTENSIN-ALDOSTERONE SYSTEM MODULATION IN AHF

Activation of the renin-angiotensin-aldosterone system (RAAS) is one of the fundamental aspects of HF pathophysiology. Through angiotensin II (AngII), RAAS increases vascular tone and stimulates the kidney to retain both sodium and water. In the setting of normal cardiac function and fluid depletion, these effects help to maintain cardiac output; however, when cardiac function is impaired, the increase in pre-load and afterload produced by AngII becomes maladaptive, chronically increasing hemodynamic strain on the failing heart. AngII also has direct effects on the myocardium and interstitium, leading to myocyte hypertrophy, interstitial collagen deposition, and adverse remodeling. Inhibition of the RAAS system, either through inhibiting the conversion of angiotensin 1 to AngII (through inhibition of the angiotensin-converting-enzyme [11]) or direct blockade of the angiotensin receptor (using angiotensin-receptor blockers [ARBs] [12]), has proven long-term beneficial effects in patients with chronic systolic HF as well as post-myocardial infarction left ventricular dysfunction. RAAS activation is greater in patients during HF decompensation (13); however, there are minimal data on the acute

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use of drugs that target RAAS activation. In the CONSENSUS-2 (Cooperative New Scandinavian Enalapril Survival Study-2), which studied IV enalaprilat in acute myocardial infarction with subgroup analysis for patients with pulmonary edema and HF after admission, no benefits were observed in the overall study population or in the pre-specified subgroups. Substantially higher rates of hypotension and worsening renal function were seen in the enalaprilat-treated patients (14). Other smaller studies in patients with AHF without myocardial infarction have suggested potential therapeutic benefits (15,16). A small, randomized, double-blind, placebo-controlled trial tested the efficacy and safety of IV enalaprilat in 20 patients with acute pulmonary edema unrelated to acute myocardial infarction (15). Compared with placebo, enalaprilat led to greater reduction in pulmonary capillary wedge pressure (37% vs. 10%) as well as improved renal blood flow, without excessive hypotension or adverse effects. A recent trial of subacute RAAS inhibition with the direct renin inhibitor aliskiren in patients after initial stabilization for AHF did not show benefit in post-discharge outcomes (17). Overall, it remains unknown whether the hemodynamic and neurohormonal blocking effects of acute RAAS inhibition would be beneficial in AHF, although such an approach has theoretical appeal given the role of RAAS activation in HF in general.

BIASED LIGANDS OF G-PROTEIN-COUPLED RECEPTORS

G-protein-coupled receptors (GPCRs) have been targets for drug discovery in diverse therapeutic areas. GPCRs activate a broad network of downstream effects comprised of parallel signal transduction pathways. The angiotensin II type I receptor (AT1R), a GPCR, mediates the biological effects of AngII. Although traditionally thought to mediate all of their biological effects through G-protein signaling pathways, it is now apparent that other signaling pathways mediated by β-arrestins play a role in downstream signaling of GPCRs, including AT1R. The 2 β-arrestin isoforms (β-arrestin-1 and -2), both of which desensitize G-protein signals, promote receptor internalization (18) and can activate a range of downstream signaling pathways, including mitogen-activated protein kinase and phosphoinositide 3-kinase pathways (19). The discovery that these pathways can independently modulate ligand effects was a major advance, but more recent work uncovered activation of a subset of receptor signaling pathways that can be selected at the level of the ligand. This opened the door for the development of a new class of functionally selective drugs, "biased ligands," which aim to preserve beneficial effects while reducing unwanted effects (20).

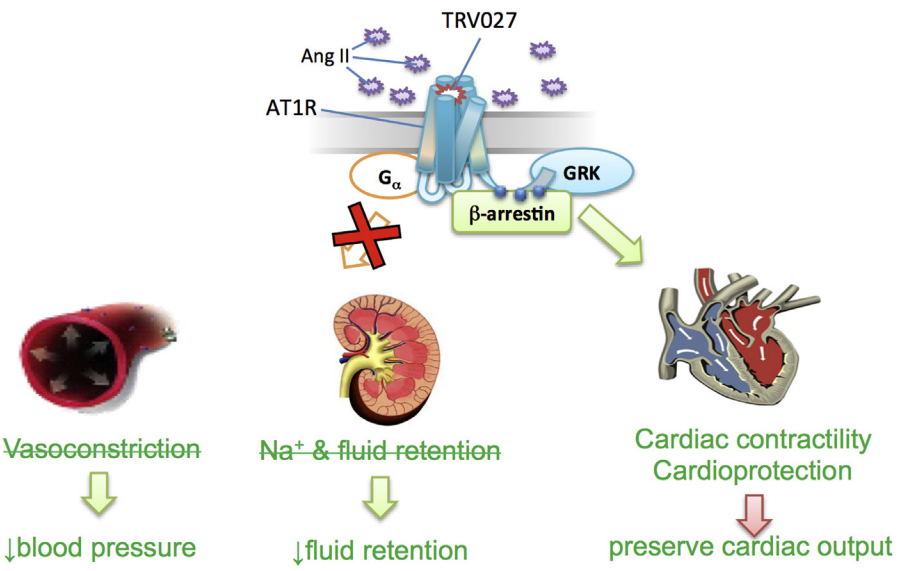
For the AT1R, signaling mediated by Gq, 1 of the family of heterotrimeric G proteins, has been shown to mediate vasoconstriction (21) and cardiac hypertrophy (22), whereas β-arrestin-2 recruitment to the receptor results in modest positive inotropy, receptor desensitization and internalization, and activation of antiapoptotic signals. ARBs block both of these pathways equally, with the net effect being a beneficial reduction in vascular tone, but at the expense of blocking potential positive effects on cardiac contractility and cardioprotective signals. It has been reported that β-arrestin biased ligands at the AT1R can stimulate cardiomyocyte proliferation (23), activate the pro-survival kinase Akt (24), reduce cardiac apoptosis caused by mechanical stretch or ischemia/reperfusion injury in mice (25), and promote contractility in vitro in a β-arrestin-dependent manner (26). In addition, these ligands promote AT1R and β-arrestin-dependent cardiomyocyte contractility in mice (25), likely by increasing calcium sensitivity of cardiac myofilaments (27). Therefore, a β-arrestin biased ligand at the AT1R could produce vasodilation by blocking the Gq pathway while simultaneously promoting beneficial cardiac effects through β-arrestin signaling.

TRV027: A NOVEL "BIASED" RAAS MODULATOR

TRV027 is a biased ligand of AT1R, antagonizing angiotensin-stimulated G-protein activation while stimulating β-arrestin (**Figure 1**). In normal rats, TRV027 reduces afterload while increasing cardiac performance and maintaining stroke volume. This contrasts with classical ARBs, which in normal animals, decrease cardiac contractility, cardiac output, and stroke volume (28). In large animal models of HF, TRV027 has been shown to be a potent, balanced vasodilator that enhances cardiac output and preserves glomerular filtration rate while decreasing renal vascular resistance and increasing renal blood flow (29,30). In theory, TRV027 would allow the beneficial effects of RAAS blockade while avoiding potentially negative effects on cardiac performance, a profile of hemodynamic effects that is inherently attractive for the treatment of AHF.

Prior human studies of TRV027 have included small, early phase studies in normal volunteers (31) as well as a phase IIa study in patients with New York Heart Association functional class III to IV HF and

FIGURE 1 Mechanistic Hypothesis of TRV027 at Angiotensin Receptor



TRV027 antagonizes G-protein-mediated signaling (vasoconstriction, fluid retention) but agonizes beta-arrestin mediated signaling (increased cardiac contractility and cardioprotection). Ang = angiotensin; AT1R = angiotensin II type 1 receptor; GRK = G-protein-coupled receptor kinase.

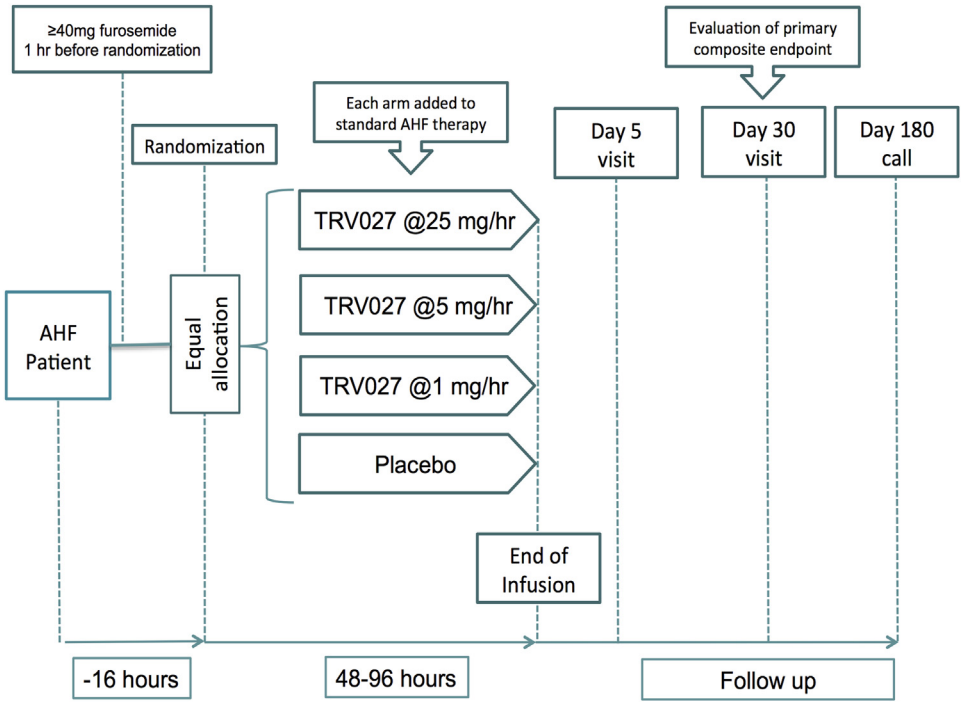
elevated filling pressures (pulmonary capillary wedge pressure ≥20 mm Hg) (32). These early data demonstrate that TRV027 was well tolerated, had a predictable pharmacokinetic profile, and produced a rapidly reversible, dose-related decrease in mean arterial pressure without any adverse safety signals. Effects on pulmonary capillary wedge pressure were noted primarily in patients with RAAS activation (based on measured plasma renin activity). Loop diuretic agents may further activate RAAS, potentially worsening this core pathophysiologic characteristic of AHF. The differential effects of TRV027 based on RAAS activation are potentially appealing for both safety and efficacy reasons, because only those patients with the targeted pathophysiology will likely respond to the drug, unlike existing vasodilators. Consistent with this hypothesis, normal human and chronic HF studies demonstrated attenuated hemodynamic effects in patients with low plasma renin activity. Its rapid onset of action and reversibility (approximately 2-min half-life) both support the potential titratability of this agent, unlike classical ARBs, which have a much longer half-life. Taken together, these data support the ongoing development of TRV027 as a treatment for patients with AHF. The efficacy and safety of this approach is currently being tested in an international phase IIb randomized clinical trial, BLAST-AHF (Biased Ligand of the Angiotensin Receptor Study in Acute Heart Failure).

DESIGN OF THE BLAST-AHF STUDY

BLAST-AHF is an international, randomized, double-blind, placebo-controlled, dose-ranging phase IIB study designed to evaluate the overall safety and efficacy of TRV027, when administered in addition to standard of care, on morbidity and mortality, acute symptoms, and in-hospital clinical course in patients hospitalized with AHF. The overall study design is described in **Figure 2**. A total of up to 500 patients are planned for enrollment at over 70 sites in 12 countries, with the first patient enrolled in December 2013 (NCT01966601). All study sites will have approval from their local ethics committee or institutional review board, as well as applicable country and local regulatory approval. The BLAST-AHF study is being conducted under the International Committee on Harmonization Good Clinical Practice Consolidated Guideline. All patients enrolled in the BLAST-AHF study will provide written informed consent. The study will be led by an academic steering committee composed of experts in AHF.

STUDY POPULATION. Inclusion and exclusion criteria for the BLAST-AHF study are summarized in

FIGURE 2 Schematic of Study Design for the BLAST-AHF Study



AHF = acute heart failure; BLAST-AHF = Biased Ligand of the Angiotensin Receptor Study in Acute Heart Failure.

Table 1. Patients must present with dyspnea at rest or with minimal exertion, have elevated natriuretic peptide levels (with distinct natriuretic peptide criteria for those with atrial fibrillation or obesity), and at least one of the following additional signs or symptoms: radiographic evidence of pulmonary congestion, rales, elevated jugular venous pressure, or peripheral edema. All enrolled subjects must, in the opinion of the investigator, have a high likelihood of requiring at least 48 h of hospital-based AHF treatment. Randomization will occur no sooner than 1 h after at least 40 mg of IV furosemide (or equivalent loop diuretic) to ensure patients remain symptomatic (e.g., dyspnea at rest or with minimal exertion) after initial presentation, and no later than 16 h after the first recorded systolic blood pressure measurement. Systolic blood pressure at entry must be between 120 and 200 mm Hg. Enrollment as early as possible in the clinical course is strongly emphasized, and ideally, patients will be enrolled within 6 h of presentation. Of note, ejection fraction is not an inclusion criterion; however, patients must have a history of chronic HF treated for at least 30 days. Given the hypothesis that TRV027 may provide renal protection, study subjects must have estimated glomerular filtration rate between 20 and 75 ml/min/1.73 m^2.

Given the mechanism of TRV027, any patient on ARBs within 7 days of randomization will be excluded, although the angiotensin-converting enzyme inhibitors are permitted. Although concomitant ARB use is not anticipated to be a contraindication to the use of TRV027, ARBs were excluded in this study to avoid confounding the dose response to TRV027. Concomitant IV nitroprusside, nesiritide, or vasopressor within 2 h of randomization is an exclusion criterion. For inotropes, use for at least 4 h before randomization or planned use within 48 h of randomization is an exclusion criterion. However, use of dopamine <2.5 μg/kg/min is allowed for any duration of time before or planned after randomization, as long as it was not used within 2 h of randomization. Intravenous nitrates (nitroglycerin at a dose >0.1 mg/kg/h or equivalent) or any IV nitrates if the patient's screening systolic blood pressure is <150 mm Hg within 1 h before randomization, is an exclusion criterion. In patients with systolic blood pressure >150 mm Hg, doses of IV nitrates ≤0.1 mg/kg/h are permitted.

TABLE 1 Inclusion Criteria

Inclusion criteria—patients may be included in the study if **all** of the following criteria are met:

- Men or women age ≥21 and ≤85 yrs
- Women of non-child-bearing potential must have:
  - Documentation of surgical sterilization (hysterectomy and/or bilateral oophorectomy) OR
  - Experienced menopause: no menses for >12 months
- Women of child bearing potential must have:
  A negative pregnancy test, AND
  Had their most recent menstrual period ≥2 weeks before presentation
- Able to provide written informed consent
- Pre-existing diagnosis of HF (treated by stable, HF therapy consistent with American College of Cardiology/American Heart Association and European Society of Cardiology practice guidelines for the treatment of chronic heart failure for at least 30 days before screening including any of the following classes of medications: diuretic agents, ACE inhibitors, beta-adrenergic blockers)
- Systolic blood pressure ≥120 and ≤200 mm Hg within 30 min of randomization
- Ventricular rate ≤125 beats/min. Patients with rate-controlled persistent or permanent AF at screening are permitted.
- Presence of ADHF defined by:
  - BNP >400 pg/ml or NT-proBNP >1,600 pg/ml
  - For patients with BMI >30 kg/m^2: BNP >200 pg/ml or NT-proBNP >800 pg/ml
  - For patients with rate-controlled persistent or permanent AF: BNP >600 pg/ml or NT-proBNP >2,400 pg/ml
  - AND at least 2 of the following:
    Congestion on chest radiograph
    Rales by chest auscultation
    Edema ≥+1 on a 0 to 3+ scale, indicating indentation of skin with mild digital pressure that requires 10 s or more to resolve in any dependent area including extremities or sacral region.
    Elevated jugular venous pressure (≥8 cm H_2O)
- Receipt of an IV loop diuretic agent at a minimal dose of 40 mg furosemide (or equivalent loop diuretic agent) for the treatment of dyspnea due to ADHF at least 1 h before anticipated randomization and the initiation of study medication
- Patient report of dyspnea at rest or upon minimal exertion during screening at least 1 h after administration of IV loop diuretic agent

ACE = angiotensin-converting enzyme; ADHF = acute decompensated heart failure; AF = atrial fibrillation; BMI = body mass index; BNP = B-type natriuretic peptide; HF = heart failure; IV = intravenous; NT-proBNP = amino-terminal pro-B-type natriuretic peptide.

STUDY TREATMENT. Patients will be randomly assigned in a double-blind fashion to either placebo or to 1 of 3 dose levels (1, 5, 25 mg/h) of TRV027 (1:1:1:1 randomization). Study drug will be given as a continuous infusion for at least 48 h and up to 96 h (precise duration at investigator's discretion). Three hours before termination of study drug infusion, the infusion rate will be reduced by 50%. Patients will be evaluated throughout the infusion period, with formal assessments at day 5, hospital discharge, and day 30. Patients will be followed up to 180 days for vital status.

Excessive hypotension during AHF treatment has been identified as a major safety concern and has limited the development of other potentially promising AHF therapies (33). To reduce the risk of hypotension, careful blood pressure monitoring and study drug dose adjustment criteria have been implemented in the BLAST-AHF study. Blood pressure will be measured hourly through the first 6 h of study drug infusion, then every 3 h through hour 12, every 6 h through hour 72, and every 8 h through the end of infusion. The actions listed in the following text will be taken if a patient experiences a decrease in blood pressure at any time during study drug infusion:

- Patients that experience symptomatic hypotension will have study drug permanently discontinued.
- Patients who experience a systolic blood pressure ≤95 mm Hg (confirmed by a second reading within 10 min) at any time during study drug infusion will have study drug permanently discontinued.
- Patients who experience a decrease of more than 40 mm Hg (confirmed by a second reading within 10 min) in systolic blood pressure from their pre-dose baseline but remain asymptomatic will have the study drug infusion rate decreased by 50%.

For patients experiencing an episode of decreased blood pressure requiring study drug dose reduction or discontinuation, additional blood pressure monitoring will be performed every one-half hour through 2 h and hourly through 5 h following the study drug dose change. If a reduction in study drug is required, the dosage of study drug cannot be increased at any time thereafter.

ENDPOINTS. Designing endpoints for phase II studies in AHF that can capture the various clinical domains of potential interest has been a significant challenge in drug development (3). For the BLAST-AHF study, the primary endpoint will be a composite of 5 clinical outcomes: 1) time from randomization to death through day 30; 2) time from randomization to HF re-hospitalization through day 30; 3) time from randomization to worsening HF through day 5; 4) change in dyspnea visual analog scale (VAS) score (calculated area under the change from baseline curve) from baseline through day 5; and 5) length of initial hospital stay (in days) from randomization. These component outcomes will be combined by deriving an average z-score (34) for each patient as further described in the following text.

Lack of standardized assessment of dyspnea has been a methodological limitation in some prior AHF studies (35). In the BLAST-AHF study, dyspnea assessments will be performed under standardized conditions, with the patients' physical position at each dyspnea assessment documented in their source records and assessed with the same procedure throughout the study. The assessment will be done after the patient has rested without supplemental oxygen for 3 to 5 min lying in bed with legs level and the head of the bed raised to 30°. If the patient does not tolerate removal of supplemental oxygen and/or

the bed position, oxygen will be replaced and/or the bed raised and the patient asked to report the dyspnea severity at the point when the oxygen was off and the bed was reclined. Dyspnea by VAS will be assessed at baseline as well as at 3, 6, 24, 48, 72, and 96 h/end of study drug infusion. Secondary efficacy endpoints are: 1) the change in dyspnea VAS scores (calculated area under the curve representing the change from baseline over time) from baseline through day 5; and 2) the change in amino-terminal pro-B-type natriuretic peptide (measured at a central core laboratory) from baseline to 48 h. Other exploratory analyses will be undertaken to evaluate the efficacy, safety, and tolerability of TRV027 in predefined subgroups of patients with AHF. A detailed list of efficacy assessments is provided in Table 2.

SAFETY MEASURES. Safety endpoints will include: 1) all-cause mortality through day 180; 2) the incidence of treatment-emergent adverse events and serious adverse events; 3) changes in vital signs including the incidences of asymptomatic and symptomatic hypotension; and 4) changes in laboratory values from baseline. Asymptomatic reduction in systolic blood pressure is defined as a drop to <95 mm Hg or a decrease from baseline of >40 mm Hg without symptoms; symptomatic reduction in systolic blood pressure is defined as <95 mm Hg or by a decrease from baseline of >40 mm Hg along with symptoms such as lightheadedness or dizziness. Clinical safety data from adverse event reporting, clinical observations, 12-lead electrocardiograms, findings from cardiac telemetry monitoring, vital signs (blood pressure, heart rate, respiratory rate, and oral temperature), oxygen saturation, and safety laboratory tests will be summarized, and any clinically-significant abnormalities will be described. An independent data safety and monitoring board will oversee the safety of patients throughout the trial.

STATISTICAL ANALYSIS AND POWER. The primary efficacy measure is a composite of 5 clinical endpoints described in the previous text, combined using an average z-score. This framework allows the combination of multiple clinical endpoints into a single statistical assessment, without assigning a rank of relative importance to each domain as is required with other related methods (36,37). O'Brien (38) had proposed that simple or weighted summation of single endpoints with standard procedures leads to asymptotically normal statistics. The average z extends this approach to include continuous, ordinal, dichotomous, and time-to-event endpoints. Specifically, continuous, ordinal, and dichotomous variables are converted to z-scores by subtracting an individual's value from the overall mean and dividing by the SD of the pooled group; time-to-event variables are first transformed to log-rank scores (39) and then converted to z-scores by subtracting the mean

TABLE 2 Exclusion Criteria

Exclusion criteria—patients will be excluded if any of the following apply:

Women who are pregnant or breast-feeding

Clinical presentation
- Suspected ACS on the basis of clinical judgment or coronary revascularization in the 3 months before screening or planned during current admission. NOTE: the presence of elevated troponin concentrations in the absence of other clinical findings is not sufficient for a diagnosis of ACS
- Temperature >38.5°C (oral or equivalent) or suspected sepsis or active infection requiring IV antimicrobial treatment
- Clinically-significant anemia (hematocrit <25%)
- Current or planned ultrafiltration, paracentesis, hemofiltration, or dialysis at time of screening
- Any mechanical ventilation requiring tracheal intubation and sedation at the time of screening or during the current hospitalization
- CPAP/BiPAP discontinued <1 h before randomization, unless prescribed for treatment of sleep apnea and used for >3 months
- History or current use of left ventricular assist devices or intra-aortic balloon pumps
- Administration of intravenous radiographic contrast agent within 72 h before screening or presence of acute contrast induced nephropathy at the time of screening
- Presence of clinically-significant arrhythmia that, in the investigator's opinion, is the primary cause of WHF symptoms, including ventricular tachycardia or bradyarrhythmia with ventricular rate <45 beats/min
- Uncertainty about ability to complete follow-up including (but not limited to) alcoholism, severe drug abuse, homelessness, unknown or uncertain residency status, and so on.

Medications
- Use of intravenous nitroprusside or nesiritide within 2 h before randomization
- IV nitrates (nitroglycerin at a dose >0.1 mg/kg/h or equivalent) or any IV nitrates if the patient's screening systolic blood pressure is <150 mm Hg within 1 h before randomization
- Use for at least 4 h or planned use of inotropes (milrinone, levosimendan, dobutamine, or >2.5 μg/kg/min dopamine), within 48 h before randomization or any use of IV inotropes or vasopressors within 2 h before randomization
- Use of ARBs within 7 days before randomization. ACE inhibitors are permitted.
- Use of any investigational medication within 30 days or 5 terminal elimination half-lives (whichever is longer) before randomization
- As determined by the investigator, clinically significant hypersensitivity, allergy to, or intolerance of ARBs

Medical history
- Any significant pulmonary disease that requires steroid IV or inhalation therapy, is known to significantly affect pulmonary function tests, or led in the past to respiratory failure.
- Major surgery within 8 weeks before screening
- Stroke within 3 months before screening
- eGFR (sMDRD) <20 ml/min/1.73 m^2 or >75 ml/min/1.73 m^2 between presentation and randomization
- Post-cardiac or renal transplant
- Listed for renal transplant or cardiac transplant with anticipated transplant time to transplant <6 months
- History of severe left ventricular outlet obstruction (either valvular or subvalvular), severe mitral valve stenosis, or any other surgically-correctable valvular disease as the primary cause of AHF, with the exception of mitral regurgitations secondary to left ventricular dilation
- Complex congenital heart disease
- Diagnosis of hypertrophic or restrictive cardiomyopathy
- In the opinion of the investigator, significant pulmonary or hepatic disease that could interfere with the evaluation of safety or efficacy of TRV027
- In the opinion of the investigator, has a life expectancy of <6 months including significant malignant or premalignant conditions known to substantially limit prognosis

ACS = acute coronary syndrome; AHF = acute heart failure; ARB = angiotensin-receptor blocker; BiPAP = bilevel positive airway pressure; CPAP = continuous positive airway pressure; eGFR = estimated glomerular filtration rate; sMDRD = simplified Modification of Diet in Renal Disease formula; WHF = worsening heart failure; other abbreviations as in Table 1.

TABLE 3 Estimated Treatment Effects Used for Power Calculations

Endpoint	Placebo	Active
Death 30 days post-randomization (event rate)	7%	4%
Heart failure rehospitalization at 30 days (event rate)	14%	13%
Worsening heart failure at 5 days (event rate)	20%	11.5%
Visual analog scale area under the curve through day 5 (mean mm-h)	1,680	2,250
Length of initial hospital stay (mean days)	10	8.2

and dividing by the SD of the pooled data. The z-scores are then aligned to the same direction so that worse outcomes have smaller scores. The z-scores are then averaged across endpoints for each patient. Treatment groups will be compared with respect to this average z-score, the primary efficacy outcome, using the Wilcoxon rank-sum test. An interim analysis of the efficacy and safety data will take place after approximately 300 patients have been exposed to the study drug. Using a combination of qualitative and quantitative methods, the best TRV027 dose will then be selected to continue in the remaining 200 patients (TRV027 or placebo in a 1:1 randomization scheme). This will result in a total of approximately 175 placebo patients and 175 active patients treated with the selected TRV027 dose. Based on simulations and assuming a modest correlation among the endpoints, a total of 175 placebo and 175 active patients provides approximately 79% power at the 2-sided 0.05 significance level to detect the following treatment effects across the 5 components of the primary clinical composite endpoint (Table 3).

CONCLUSIONS

The BLAST-AHF study will test a novel, biased ligand pharmacologic intervention based on evolving understanding of the biology of GPCRs. The overall clinical course of subjects in the trial will be assessed using an innovative endpoint framework, evaluating the response to therapy across multiple domains of interest, including acute symptoms, in-hospital clinical course, and post-discharge outcomes. The results of the BLAST-AHF study will inform decisions about dose selection and study design for further development of TRV027 as a novel therapeutic agent for AHF.

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