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STUDY DESIGN

Rationale and design for the development of a novel nitroxyl donor in patients with acute heart failure

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Hospitalisation for acute heart failure remains a major public health problem with high prevalence, morbidity, mortality, and cost. Prior attempts to develop new therapies for this condition have not been successful. Nitroxyl (HNO) plays a unique role in cardiovascular physiology by direct post-translational modification of thiol residues on target proteins, specifically SERCA2a, phospholamban, the ryanodine receptor and myofilament proteins in cardiomyocytes. In animal models, these biological effects lead to vasodilatation, increased inotropy and lusitropy, but without tachyphylaxis, pro-arrhythmia or evidence of increased myocardial oxygen demand. BMS-986231 is an HNO donor being developed as a therapy for heart failure, and initial studies in patients with heart failure support the potential clinical value of these physiological effects. In this manuscript, we describe the ongoing phase II development programme for BMS-986231, which consists of three related randomised placebo-controlled clinical trials, StandUP-AHF, StandUP-Imaging and StandUP-Kidney, which are designed to provide evidence of tolerability and efficacy as well as confirm the anticipated physiological effects in patients with heart failure with reduced ejection fraction. These studies will set the stage for the further study of BMS-986231 in future phase III clinical trials.

Keywords Clinical trial design • Heart failure • Inotropy • Nitroxyl • HNO donor • BMS-986231

Introduction

Hospitalisation for worsening heart failure (HF), often termed acute HF (AHF), remains a major public health problem with high prevalence, morbidity, mortality, and cost. To date, attempts to develop effective new therapies for this condition have been unsuccessful. The reasons for the failures of prior AHF drug development programmes have been the subject of intense debate.[1] Proposed explanations include issues around patient selection, trial conduct, appropriate pathophysiological targets, ideal endpoints, possibility of affecting long-term outcomes with short-term treatments, and whether AHF is even a distinct disease entity at all. Even the term 'acute heart failure' is imprecise, because many patients are admitted with increasing fluid retention developing over days or weeks leading to peripheral oedema, orthopnoea and increasing exertional dyspnoea rather than breathlessness at rest.[2] Despite these challenges, it is clear that improving the short- and long-term outcomes for these patients remains an unmet medical need. Accordingly, we report the rationale for a novel therapeutic approach to patients hospitalised with HF using an intravenous (IV) nitroxyl (HNO) donor, and summarise the design of the ongoing phase II development programme for this compound.

Standard of care and goals of therapy for acute heart failure

Because the vast majority of patients hospitalised with AHF present with signs and symptoms of congestion, the current standard of care consists primarily of addressing congestion with loop

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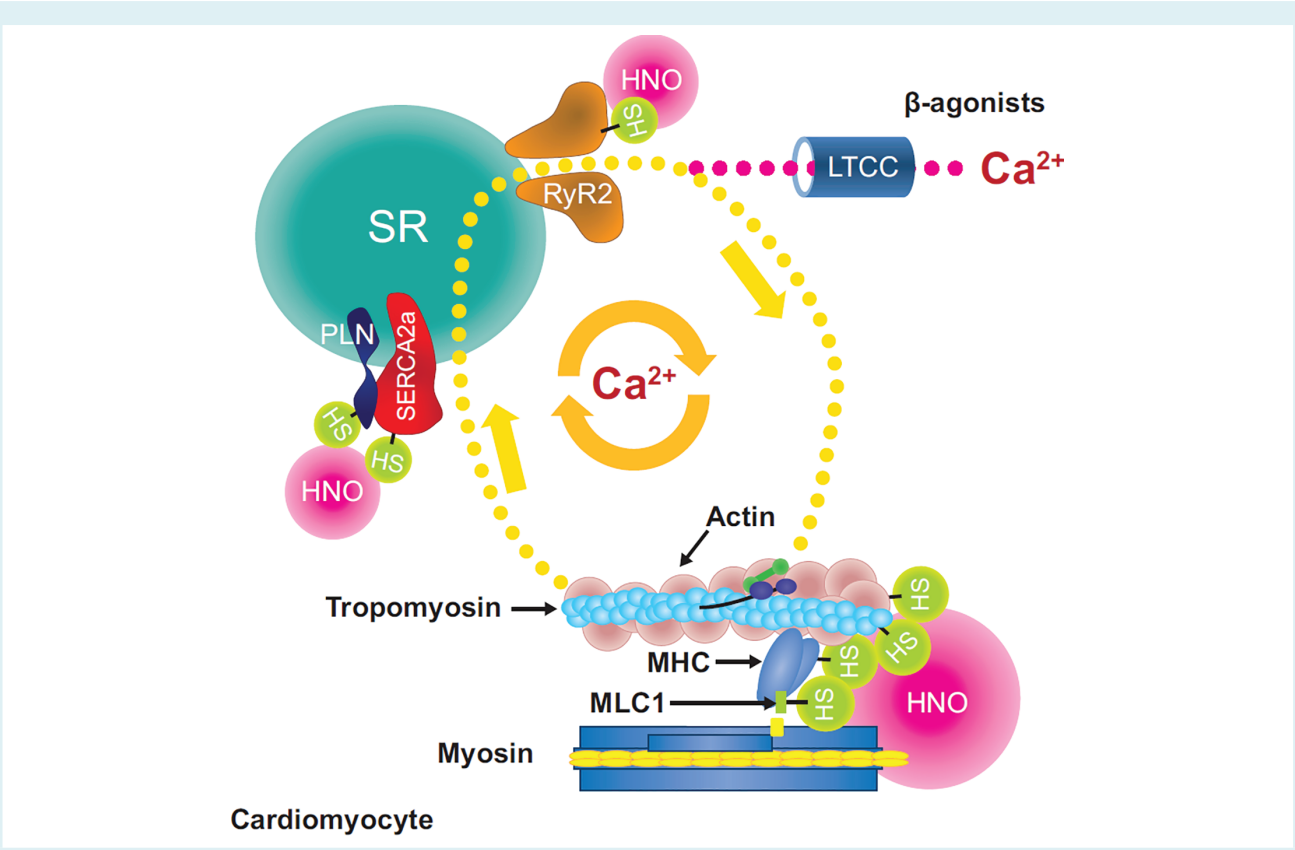

Figure 1 Schematic of putative mechanism of action of nitroxyl (HNO) on the cardiovascular system. HNO exerts its physiological effects by direct post-translational modification of thiol residues (SH) on target proteins, including sarcoplasmic reticulum Ca^{2+} adenosine triphosphatase (SERCA2a), phospholamban (PLN), the ryanodine receptor (RyR2), and myofilament proteins in cardiomyocytes. LTCC, L-type calcium channel; MHC, myosin heavy chain; MLC, myosin light chain; SR, sarcoplasmic reticulum. Adapted with permission from Tocchetti *et al.*[15]

diuretics.[3] In selected patients, additional therapies may be targeted at reducing preload/afterload with vasodilators (generally in patients with elevated blood pressure) or enhancing contractility with inotropic agents (in patients with low cardiac output and/or impaired end-organ perfusion).[4] Remarkably, none of these three AHF treatment classes have a strong evidence base to support their use.[4,5] Diuretics are a mainstay of treatment and provide symptomatic benefit in most patients, but have not been rigorously tested in placebo-controlled trials in patients hospitalised with HF. Placebo controlled trials of vasodilators and inotropes in combination with standard therapy in AHF have generally shown very modest (or absent) clinical benefits, and have sometimes been harmful.[6–8] Broadly speaking, the treatment goals for a patient hospitalised with AHF are straightforward: (i) rapid and complete relief of symptoms; (ii) prevention of in-hospital mortality or clinical deterioration; (iii) safely minimising length of hospital stay and resource utilisation (e.g. intensive care unit stay); (iv) reducing the likelihood of readmission after discharge; and (v) reducing long-term mortality. As management becomes increasingly complex, efforts to streamline and simplify care are also important. Any novel therapy directed at this problem needs to have a clinically relevant impact on at least one or more of the above goals to be considered an important advance.

Rationale for nitroxyl therapy in heart failure

Nitroxyl gas is a chemical sibling of nitric oxide (NO); although NO and HNO appear to be closely related chemically, HNO exists only in the protonated form in physiological settings and does not readily interconvert with NO. Importantly, the physiological effects and biological mechanisms of HNO and NO action are highly distinct.[9] The biological effects of HNO are reversible and mediated by direct post-translational modification of thiol residues in target proteins, specifically SERCA2a, phospholamban, the ryanodine receptor and myofilament proteins in cardiomyocytes.[10–14] *In vitro*, HNO increases the efficiency of calcium cycling, improves myofilament sensitivity to calcium and enhances cardiac contractility and lusitropy via the above proteins.[15] HNO also mediates peripheral vasodilatation in a manner dependent on soluble guanylate cyclase in the endothelium. Importantly, unlike the activity of NO, tachyphylaxis does not appear to impact the effects of HNO in the peripheral vasculature.[16] The effects of HNO do not appear to be mediated by adrenergic receptors, which may be important given the nearly ubiquitous use of beta-blockers in HF.[17] A

schematic of the putative mechanisms of action of HNO on the heart is shown in *Figure 1*.

Nitroxyl donors release HNO via chemical breakdown upon exposure to the physiological aqueous environment. In large animal models of HF, HNO donors directly enhance both contractility and relaxation and reduce both preload and afterload.[18,19] Despite reliable augmentation of inotropy and lusitropy in these models, HNO donors do not increase heart rate or myocardial oxygen consumption, nor do they result in QT prolongation.[18,19] This combination of physiological effects makes HNO donors potentially attractive therapeutic candidates in HF.

BMS-986231 is an HNO donor in development for HF. In early clinical studies, BMS-986231 exhibited a short plasma elimination half-life of approximately 1 h, with a mean time to steady state of approximately 3 h. Less than 1% of prodrug is eliminated in urine, the majority of dose was excreted in urine as metabolites that are not expected to exert significant physiological effects. It has low potential for drug–drug interactions at anticipated plasma concentrations. In euvolemic healthy volunteers, BMS-986231 reduced blood pressure at escalating doses but did not cause symptomatic hypotension.[20] BMS-986231 was generally well tolerated, with the emergence of headache as a likely drug-related adverse event at higher doses. In a study of patients with HF and hypervolaemia, BMS-986231 reduced blood pressure to a much lesser extent and headaches were infrequent during the infusion.[21] In this early proof of concept study, a 6 h infusion of BMS-986231 produced rapid and sustained decreases in intracardiac filling pressures and suggested improvements in non-invasively measured cardiac index (by thermodilution but not by Fick) in 46 patients with advanced HF with reduced ejection fraction (HFrEF). There was also no increase in tachycardia, arrhythmia or symptomatic hypotension with BMS-986231 compared with placebo.[21] However, BMS-986231 was administered for a short duration and vasoactive medications, including IV or oral diuretics, were prohibited for ≥ 4 h prior to baseline haemodynamic assessment until completion of the 6 h infusion.

In summary, data from large animal models and initial human studies suggest that BMS-986231 has multiple and potentially beneficial haemodynamic effects in patients with HF. These include peripheral vasodilatation as well as improvements in contractility (inotropy) and ventricular relaxation (lusitropy), all without evidence of the adverse effects seen with existing inotropes, such as pro-arrhythmia or myocardial ischaemia.

Challenges in phase II studies in acute heart failure

Broadly speaking, phase II studies in cardiovascular disease are intended to show target engagement, assess for signals of efficacy and safety in the target patient population, allow for selection of appropriate dose or doses for future study and refine estimates of treatment effect for the planning of larger more definitive trials. In AHF, all of these goals have been persistently challenging. There is no accepted and validated surrogate endpoint that might be used in phase II studies in AHF to predict clinically important treatment effects in larger trials.[22] The absence of validated surrogate endpoints for efficacy presents challenges in terms of making a decision to proceed to phase III trials as well as for decisions about dose selection. Although adaptive designs are increasingly used in early phase studies in other areas of medicine, the lack of a reliable surrogate endpoint has limited the ability to utilise this approach in HF.[23] In this context, the goals of the phase II development programme for the HNO donor BMS-986231 are as follows:

1. Establish tolerability of one or more doses of BMS-986231 in patients hospitalised with HFrEF (ejection fraction $\leq 40\%$), specifically with regard to the incidence of symptomatic hypotension.
2. Identify signals of efficacy and/or safety in these patients, specifically effects on symptoms, evidence of congestion, natriuretic peptides, length of stay, the incidence of worsening HF, rehospitalisation for HF, and mortality.
3. Evaluate whether BMS-986231 improves systolic and diastolic function in patients with stable HF through an echocardiographic cross-over study.
4. Evaluate whether BMS-986231 alters the excretion of water and salt or enhances the effects of diuretic agents in patients with stable HF.

These goals are being pursued through three separate, randomised, double-blind controlled trials, each described briefly below.

The StandUP-AHF study

StandUP-AHF (STudy Assessing Nitroxyl Donor Upon Presentation with Acute Heart Failure) is a multicentre, randomised, double-blind, placebo-controlled, ascending dose trial of continuous 48 h IV infusions of BMS-986231 vs. placebo in hospitalised patients with AHF and impaired ejection fraction ($\leq 40\%$). The primary objective of the study is to evaluate the effects of various doses of BMS-986231 compared with placebo on clinically relevant hypotension [defined as systolic blood pressure (SBP) < 90 mmHg or symptoms of hypotension]. The study consists of two parts, each with a unique cohort of patients.

In Part I (Cohort 1), approximately 100 patients are randomised in a 1:1 ratio to escalating doses of BMS-986231 (3 μg/kg/min for 4 h, then 6 μg/kg/min for another 4 h, followed by 12 μg/kg/min for the remaining 40 h) or escalating doses of placebo. In Part II (Cohort 2) of the study, the two highest-tolerated doses of BMS-986231 in Cohort 1 (BMS-986231 6 μg/kg/min and 12 μg/kg/min) are administered. Approximately 210 patients are randomised in a 1:1:1 ratio to one of the two active doses of BMS-986231 or placebo. A schematic for the overall design of the StandUP-AHF study is shown in *Figure 2*.

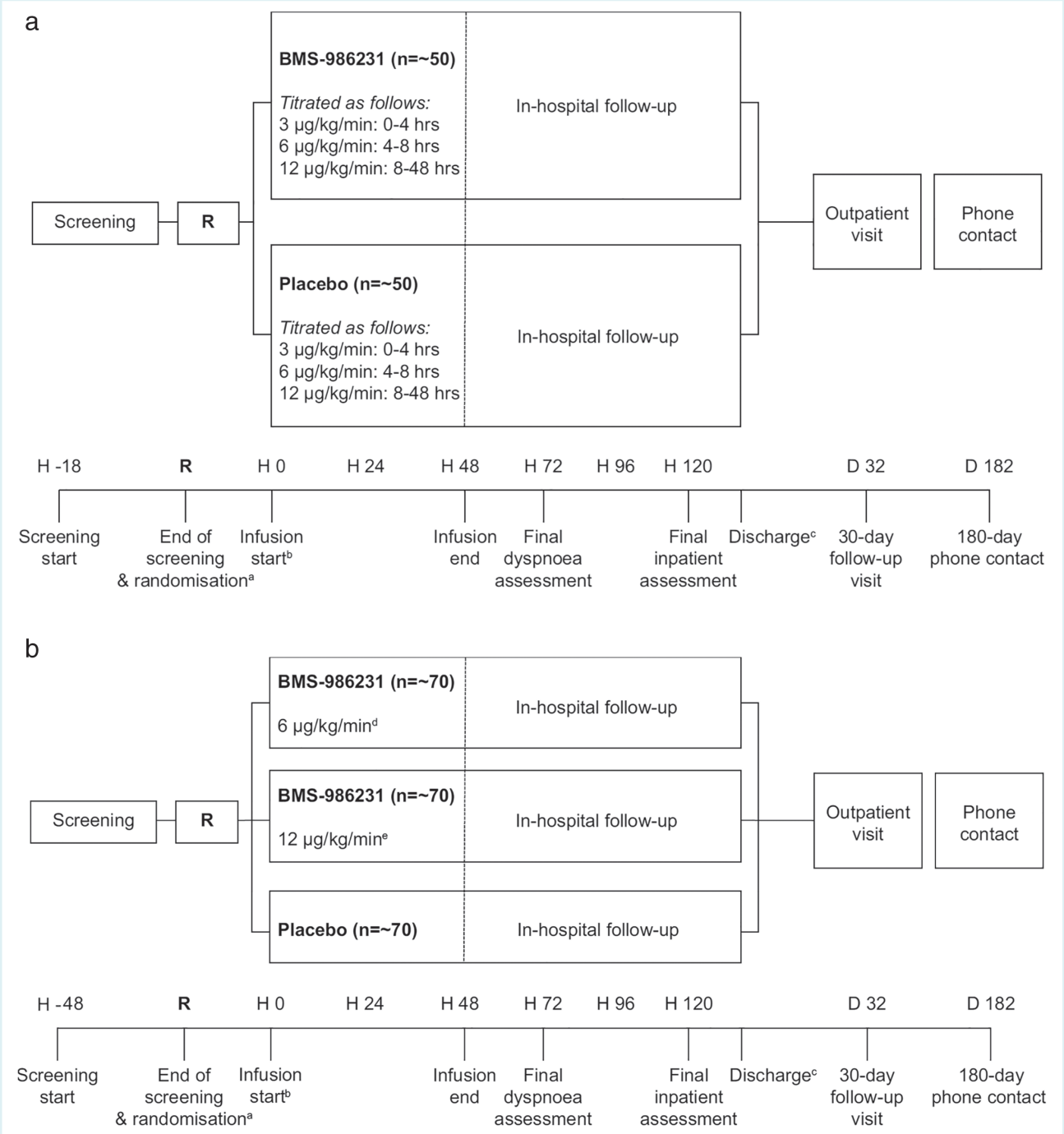

Figure 2 Schematic of (*A*) Part I (Cohort 1) and (*B*) Part II (Cohort 2) of the StandUP-AHF study. [a]Every effort should be made to initiate study drug administration promptly after randomisation. [b]Study drug infusion must start within 18 h of presentation, defined as the first dose of diuretic for current episode, but not within 2 h of an intravenous bolus dose of diuretics, or within 2 h of the initiation or an increase in the dose of an intravenous diuretic administered by continuous infusion. [c]Discharge may occur as per standard medical practice. It is recommended that subjects remain in the hospital for safety monitoring for at least 24 h after the completion of the 48 h infusion of the study drug. [d]3 µg/kg/min if 12 µg/kg/min is not tolerated in Part I. [e]6 µg/kg/min if 12 µg/kg/min is not tolerated in Part I. H, hour; D, day; R, randomisation.

Table 1 Key inclusion and exclusion criteria for the StandUP-AHF study

Inclusion criteria

- Hospitalised for AHF.
- Must have received at least 40 mg IV furosemide or equivalent for the current HF episode.
- Must be randomised and treated within 18 h of first dose of IV diuretic for Part I Cohort 1 (or within 48 h of first dose for Part II Cohort 2).
- Dyspnoea at rest or with minimal exertion after administration of at least one dose of IV diuretics.
- Must not be randomised within 2 h after an IV bolus dose of diuretics, or within 2 h after the initiation or a dose increase of an IV diuretic administered by continuous infusion.
- History of HF and a LVEF ≤ 40%.
- Evidence of congestion manifested by at least two of the following at time of screening:
  - Evidence of pulmonary congestion on chest X-ray.
  - Rales by chest auscultation.
  - Oedema ≥ 2+ on a 0–3+ scale (easily identifiable indentation, skin rebounds in 15–30 s).
  - Presence of jugular venous distention.
- Elevated NT-proBNP ≥ 1600 pg/mL (189 pmol/L) or BNP ≥ 400 pg/mL (116 pmol/L) as determined at the local laboratory within 18 h prior to the start of study drug infusion for Part I Cohort 1 (or 48 h for Part II Cohort 2). For patients with atrial fibrillation: NT-proBNP ≥ 2400 pg/mL or BNP ≥ 600 pg/mL.
- Body weight ≥ 50 kg and ≤ 140 kg at screening.

Exclusion criteria

- SBP < 105 mmHg or > 160 mmHg at screening and just prior to randomisation.
- Heart rate < 50 b.p.m. or > 130 b.p.m. at screening and just prior to randomisation.
- Primary HF aetiology attributable to either restrictive/obstructive cardiomyopathy, idiopathic hypertrophic or uncorrected severe valvular disease.
- Suspected acute lung disease (e.g. pneumonia or asthma) or severe chronic lung disease.
- History of sudden cardiac death with resuscitation within the past 6 months.
- Hospitalisation for acute coronary syndrome, coronary revascularisation or acute myocardial infarction during the previous 90 days.
- History of CVA, stroke or TIA during the previous 90 days.
- eGFR < 30 mL/min/1.73 m^2 (based on any standard limit and equation employed by the local lab, e.g. MDRD equation).
- Haemoglobin < 9 g/dL (< 5.59 mmol/L).
- Administered IV or transdermal nitrate therapy prior to randomisation, except if all three of the following criteria are met:
  - SBP at screening or just prior to randomisation is > 120 mmHg.
  - The IV nitroglycerin dose is < 100 μg/min (or isosorbide dinitrate < 3 mg/h).
  - The infusion rate and dose have been unchanged for > 2 h.
- History of chronic or intermittent renal support therapy (haemodialysis, ultrafiltration, or peritoneal dialysis).
- Treated during the current hospitalisation with IV vasoactive drugs or has an anticipated need to be treated with such agents during the study drug infusion.
- Treated with oral PDE5 inhibitor sildenafil, vardenafil or avanafil within 24 h of screening or treated with tadalafil within 4 days of screening.
- Receiving any mechanical ventilation at the time of screening.
- Receiving non-invasive ventilation (CPAP/BiPAP) < 2 h prior to randomisation.

AHF, acute heart failure; BiPAP, bilevel positive airway pressure; BNP, B-type natriuretic peptide; CPAP, continuous positive airway pressure; CVA, cerebrovascular accident; eGFR, estimated glomerular filtration rate; HF, heart failure; IV, intravenous; LVEF, left ventricular ejection fraction; MDRD, Modification of Diet in Renal Disease; NT-proBNP, N-terminal pro-B-type natriuretic peptide; PDE5, phosphodiesterase type 5; SBP, systolic blood pressure; TIA, transient ischaemic attack.

Study population

The key inclusion and exclusion criteria for StandUP-AHF are provided in *Table 1*. Briefly, patients must be hospitalised for HF with signs and symptoms of congestion requiring treatment with IV loop diuretics. Patients must have a history of chronic HF and documented ejection fraction ≤ 40% within the prior 18 months. Patients with SBP < 105 mmHg or > 160 mmHg are excluded. Patients receiving IV vasodilators or IV inotropic agents are also excluded, except for those receiving IV or transdermal nitrate therapy with SBP > 120 mmHg and receiving a stable dose of nitrates with a dose < 100 μg/min. For Cohort 1, patients had to be randomised within 18 h of their initial dose of IV loop diuretics. This time window has been expanded to 48 h for Cohort 2 to better capture the spectrum of patients that might be targeted in potential phase III trials.

Treatment and strategies to mitigate hypotension

In StandUP-AHF, patients are treated with IV BMS-986231 or matching placebo in a double-blind fashion for 48 h. In Cohort 1, doses were escalated every 4 h for the first 8 h. In Cohort 2, patients are treated with their assigned dose throughout the 48 h

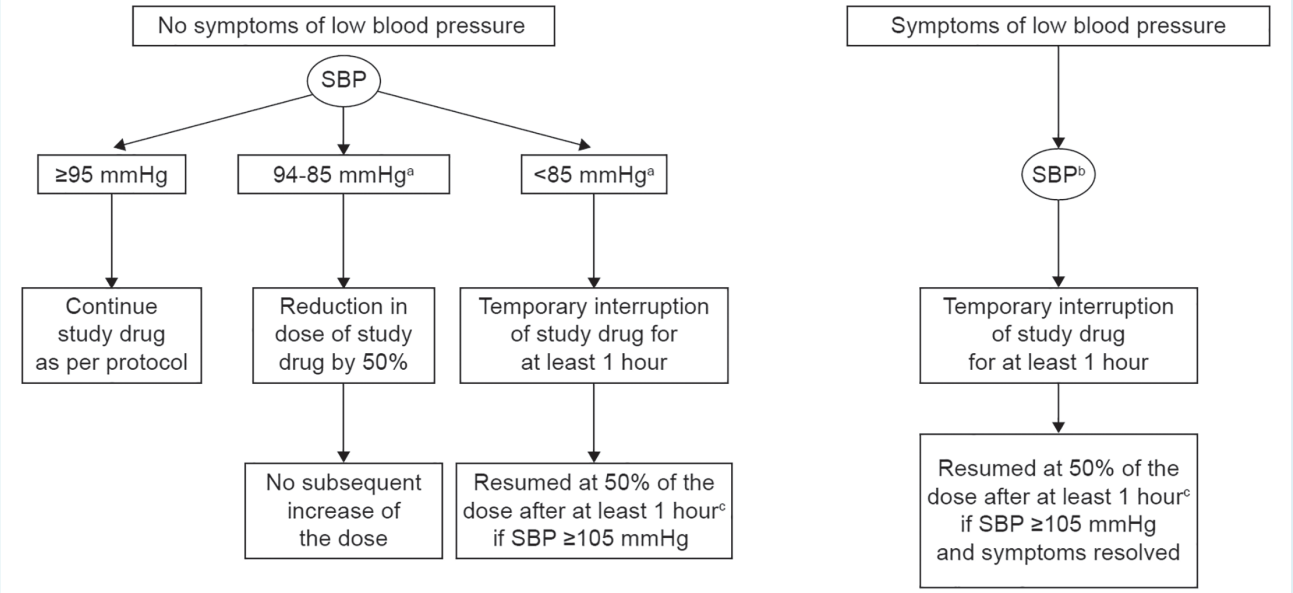

Figure 3 Protocol for dose adjustment based on systolic blood pressure (SBP) in StandUP-AHF. [a]Confirmed by a second measurement within 15 min. [b]No need for a confirmatory blood pressure measurement if symptomatic hypotension. [c]But no more than 4 h.

treatment period. Background therapy for HF is standard of care based on the patient's clinical status.

Avoiding hypotension is an important safety goal during the treatment of AHF, particularly when treating with IV vasodilators. In the StandUP-AHF study, a protocol for adjusting the BMS-986231 dose based on SBP and potential symptoms of hypotension is used (*Figure 3*). Briefly, if a patient experiences SBP 94–85 mmHg without symptoms of hypotension, the blood pressure measurement must be repeated within 15 min. If SBP remains within this range, the dose is reduced by 50%. If SBP falls below < 85 mmHg (and remains < 85 mmHg following a repeated measurement within 15 min), or if the patient experiences symptoms of hypotension (regardless of blood pressure), the study drug must be interrupted for at least 1 h and then resumed at 50% of the prior dose, provided that SBP is now ≥ 105 mmHg and symptoms of hypotension have resolved. After dose reductions, the dose is not increased further. BMS-986231 must be permanently discontinued after it has been down-titrated once and criteria for dose reduction or interruption have been met again.

Endpoints and assessments

The primary endpoint for StandUP-AHF is the incidence of clinically relevant hypotension, defined as SBP < 90 mmHg (confirmed by repeat measurement) or symptoms of hypotension up to 6 h after the end of study infusion. Secondary endpoints are change in N-terminal pro-B-type natriuretic peptide from baseline at various time points and change in patient-reported resting dyspnoea using the area under the curve of an 11-point numerical rating scale (dyspnoea assessed on a scale of 0–10) from baseline to 72 h. Other endpoints of interest are the incidence of worsening HF (defined as worsening signs or symptoms of HF and the need to escalate therapy) through Day 5 (or discharge), changes in renal function, changes in signs and symptoms of congestion, length of stay, patient global assessment, physical activity tracked using wearable accelerometry, and post-discharge death or rehospitalisation through Day 32. Patients will be followed through Day 182 for mortality as a safety endpoint. Adverse events will be captured through Day 32.

Interim analysis and statistical considerations

For Part I (Cohort 1), approximately 50 patients per group are randomised to placebo or an incremental dose of BMS-986231 (3 to 6 to 12 μg/kg/min). Under a sample decision rule (e.g. observed doubling with a difference of more than 4%) and assuming clinically relevant hypotension incidences of 5% or 10% in the placebo group, the posterior probabilities of detecting a four- or three-fold increase in these respective incidences are 86% and 80%, respectively. If there is no increase in clinically relevant hypotension, the posterior probabilities of falsely detecting an increase are 11–12%.

Upon completion of Part I, an interim analysis was conducted to select the BMS-986231 doses for use in Part II. This was conducted in an unblinded fashion by the study executive committee and the study sponsor, with input from the data safety monitoring committee. As noted previously, the doses selected for Part II (based on the overall totality of the available safety and efficacy data) were the two highest doses administered in Part I; specifically, BMS-986231 6 μg/kg/min and 12 μg/kg/min.

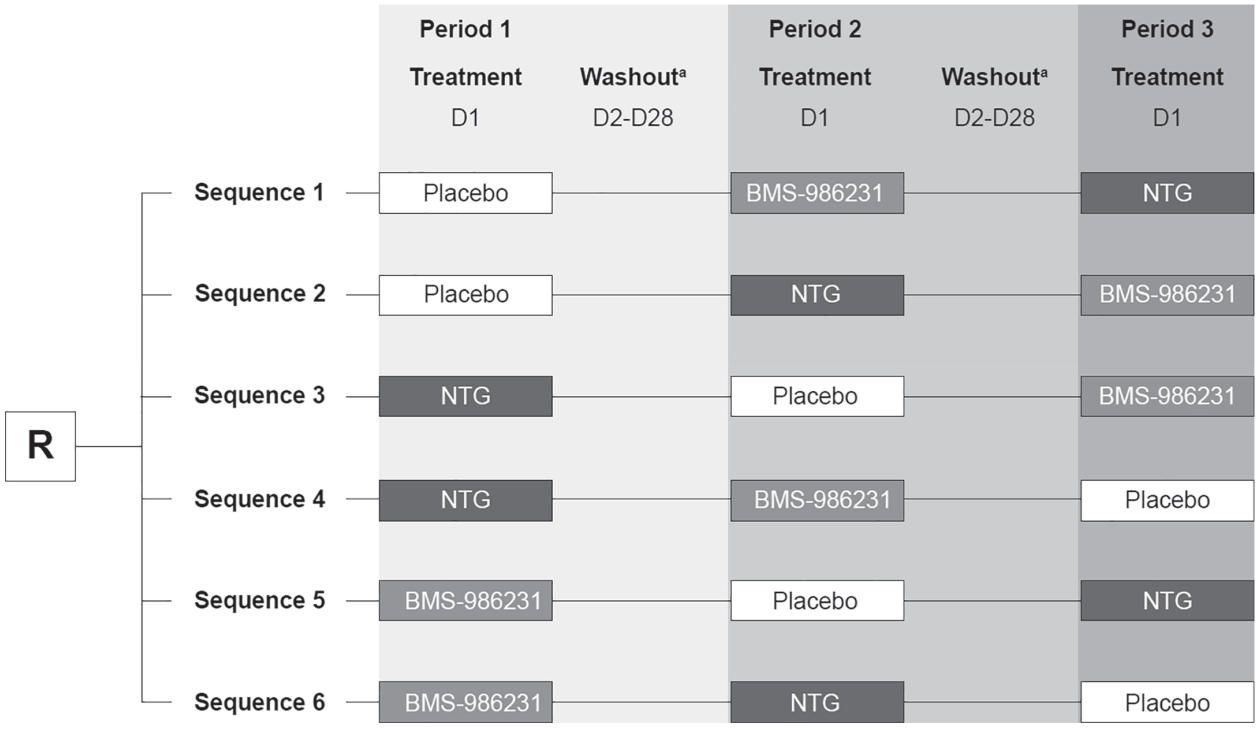

Figure 4 Schematic for design of the StandUP-Imaging study. [a]Washout period is at least 5 days and no more than 4 weeks. D, day; NTG, nitroglycerin; R, randomisation.

For Part II (Cohort 2), approximately 70 patients per group are randomised to placebo or one of the two BMS-986231 doses. Under a sample decision rule (e.g. observed 1.8-fold increase with a difference of more than 3%) and assuming clinically relevant hypotension incidences of 5% or 10% in the placebo group, the posterior probabilities of detecting a 3- or 2.5-fold respective increase in hypotension incidence are 82% and 80%, respectively. If there is no increase in clinically relevant hypotension, then the posterior probabilities of falsely detecting an increase are 13–15%. These probabilities do not reflect multiple comparisons.

The StandUP-Imaging study

Studies of drugs whose primary physiological effect is acute vasodilatation have generally not demonstrated substantial clinical benefit in AHF. Given that the mechanism of action for HNO donors suggests they would have potentially clinically important effects on inotropy and lusitropy, the StandUP-Imaging study is designed to evaluate the effects of BMS-986231 compared with those of nitrates or placebo in patients with HF. Detecting such physiological effects in the context of AHF is challenging, as background therapy changes over time and loading conditions change dramatically with decongestive therapies. Therefore, the StandUP-Imaging study uses a crossover design to evaluate the physiological effects of BMS-986231 in patients with chronic stable HF with ejection fraction $\leq$ 40% and who are in sinus rhythm (see *Figure 4* for study design and the online supplementary *Table S1* for inclusion and exclusion criteria). StandUP-Imaging is a multicentre, randomised, crossover, placebo and active-controlled double-blind study of continuous 5 h IV infusions of BMS-986231 designed to evaluate the drug's effect on systolic and diastolic parameters, as measured by echocardiography using a central core laboratory. Each patient receives the three interventions [BMS-986231, nitroglycerin (NTG) and placebo] across three treatment periods, with one intervention occurring during each period. Each of these periods includes a 5 h infusion of BMS-986231, NTG or placebo, followed by a washout period. Forty-two study participants are being randomised to receive BMS-986231, NTG and placebo in one of the six possible sequences (*Figure 4*). In the event of a decrease in SBP, an algorithm is used to down-titrate, interrupt or discontinue the study drug infusion, similar to that described for the StandUP-AHF study (*Figure 3*).

Assessments and endpoints

A core lab performs all echocardiographic analyses in the StandUP-Imaging study. Prior to enrolment, participants undergo a screening echocardiography that is submitted to the core lab for review to confirm eligibility. At least two echo examinations are performed on the first day of each period (prior to infusion and near the end of the infusion between Hour 4 and Hour 5).

The primary endpoint is stroke volume index derived from the left ventricular (LV) outflow tract. Comparisons between placebo and BMS-986231 are performed using a mixed model repeated

measures analysis, controlling for treatment sequence, treatment period, specific treatment (i.e. BMS-986231 or placebo) and the difference in the treatment period baselines. Secondary comparisons of interest include that between BMS-986231 and NTG, as well as comparison to placebo and NTG on selected other LV systolic and diastolic indices (LV ejection fraction, tissue Doppler, LV diastolic function, including indices that have been shown to be less load-dependent such as LV power index, LV global longitudinal and circumferential strain with speckle tracking echocardiography, LV end-systolic elastance and LV myocardial performance index). In addition, other parameters are part of the echo examination protocol and will be assessed: LV structure, dimensions, mitral inflow, left atrial size and function, right ventricular size and function, pulmonary vascular assessment and valvular assessment.

The StandUP-Kidney study

Decongestion is a major therapeutic goal in patients with decompensated HF.[24,25] Given its mechanism of action, BMS-986231 might alter water- and salt-handling by direct renal actions or by its haemodynamic effects, and could also alter the activity of loop diuretics. However, it is difficult to study the effects of diuretics in patients with unstable, worsening HF, especially if the patient is to act as their own control in a crossover trial. Accordingly, a double-blind, randomised, placebo-controlled two-way crossover study to evaluate the effects of BMS-986231 on 4 h urine output in patients after administration of 40 mg of IV furosemide is being undertaken. Enrolled patients have chronic HF with an ejection fraction $<45\%$, are on stable, guideline-directed medical therapy for HF, including at least 40 mg oral furosemide (or equivalent) daily, and have elevated natriuretic peptides. The StandUP-Kidney study consists of two 1-day treatment periods (BMS-986231 or placebo) separated by a washout period. Approximately 20 patients will be studied (see the online supplementary *Table S2* for key inclusion and exclusion criteria). BMS-986231 or placebo is administered in a blinded manner for 8 h as continuous IV infusion. At Hour 4 after infusion start, a 40 mg IV bolus of furosemide is administered to both treatment groups through a separate IV line, given slowly over 1–2 min. If blood pressure drops or symptomatic hypotension occurs, the infusion may be slowed or stopped, similar to that described for the StandUP-AHF study (*Figure 3*). As mentioned previously, the primary objective is to evaluate the effects of BMS-986231 on 4 h urine output against a background of administration of 40 mg of IV furosemide. Secondary endpoints include the effect of BMS-986231 on fractional excretion of sodium and potassium, as well as urinary and plasma concentrations of furosemide.

Discussion

Given the lack of success in developing new therapies for patients hospitalised with AHF, the ideal design for phase II development programmes remains uncertain. Suggested reasons for the failure of prior programmes include a lack of understanding of the drug's mechanism of action in the target population, inappropriate patient selection or endpoints, or issues of trial conduct. In this paper, we have reviewed the design and rationale for the ongoing development of a novel HNO donor for patients hospitalised with AHF. BMS-986231 has displayed a variety of potentially favourable haemodynamic effects in patients with HF, including vasodilatation, increased contractility (inotropy) and improved ventricular relaxation (lusitropy), without evidence of adverse effects such as pro-arrhythmia or increases in myocardial oxygen demand.

The BMS-986231 development programme has several important objectives. First, it will assess how well various doses of BMS-986231 are tolerated in the target population of patients hospitalised with AHF. Although vasodilator drugs can be targeted primarily at HF patients with elevated blood pressure at presentation, such patients are known to have a relatively good prognosis and are therefore in less need of novel therapies.[26] StandUP-AHF is enrolling patients across a spectrum of blood pressure values (from SBP 105–160 mmHg) that represent a broad cohort of patients hospitalised with AHF (approximately 70% of patients, based on data from the OPTIMIZE-HF registry).[26] The primary endpoint of StandUP-AHF is tolerability with regard to hypotension. Additionally, this study is enrolling patients across a relatively wide time window from hospitalisation, with Cohort 1 enrolled within 18 h and Cohort 2 enrolled within 48 h (with time zero being defined as the initial dose of IV loop diuretic). This recognises that a paradigm of emphasising rapid 'time to treatment' has generally not been successful in prior studies, and that it may be patients who do not respond well to initial therapy with diuretics who have the largest unmet medical need. Such patients are more likely to have a higher burden of co-morbidities, greater diuretic resistance, more complicated in-hospital course, longer length of hospital stay, and greater post-discharge morbidity and mortality.

An important criticism of prior programmes in AHF has been that the mechanism of action and physiological effects of the drug candidate were incompletely understood. In that light, a second major goal of the development programme is to understand the effects of BMS-986231 on relevant physiology in patients with HF. In particular, this programme will investigate the effects of BMS-986231 on physiological effects beyond vasodilatation alone. Using a crossover design, the StandUP-Imaging study is comparing the haemodynamic effects of BMS-986231 with those of nitrates and placebo to determine whether the targeted dose range has demonstrable effects on inotropy and lusitropy beyond those induced by changes in loading conditions alone. The StandUP-Kidney study will assess whether BMS-986231 has additive effects on top of loop diuretics in improving decongestion in patients with HF. To minimise other sources of variability over time, both StandUP-Imaging and StandUP-Kidney will enrol patients with stable chronic HF. While this approach will limit other sources of variability, one potential limitation is the need to extrapolate findings from patients with stable heart failure to those with acute decompensation.

In summary, the results of the three described studies should provide information on the safety and tolerability of BMS-986231 as well as signals of efficacy across a broad spectrum of the potential target population. They should also provide

an understanding of relevant physiology with regard to haemodynamics and decongestion. The results of these studies will inform the continued development of BMS-986231 for patients with HF.

Supplementary Information

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

Table S1. Key inclusion and exclusion criteria for the StandUP-Imaging study.

Table S2. Key inclusion and exclusion criteria for the StandUP-Kidney study.

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References

1. Vaduganathan M, Greene SJ, Ambrosy AP, Gheorghiade M, Butler J. The disconnect between phase II and phase III trials of drugs for heart failure. *Nat Rev Cardiol* 2013;**10**:85–97.
2. Shoaib A, Waleed M, Khan S, Raza A, Zuhair M, Kassianides X, Djahit A, Goode K, Wong K, Rigby A, Clark A, Cleland J. Breathlessness at rest is not the dominant presentation of patients admitted with heart failure. *Eur J Heart Fail* 2014;**16**:1283–1291.
3. Felker GM, Lee KL, Bull DA, Redfield MM, Stevenson LW, Goldsmith SR, LeWinter MM, Deswal A, Rouleau JL, Ofili EO, Anstrom KJ, Hernandez AF, McNulty SE, Velazquez EJ, Kfoury AG, Chen HH, Givertz MM, Semigran MJ, Bart BA, Mascette AM, Braunwald E, O'Connor CM. Diuretic strategies in patients with acute decompensated heart failure. *N Engl J Med* 2011;**364**:797–805.
4. Yancy CW, Jessup M, Bozkurt B, Butler J, Casey DE Jr, Colvin MM, Drazner MH, Filippatos GS, Fonarow GC, Givertz MM, Hollenberg SM, Lindenfeld J, Masoudi FA, McBride PE, Peterson PN, Stevenson LW, Westlake C. 2017 ACC/AHA/HFSA Focused update of the 2013 ACCF/AHA guideline for the management of heart failure: a report of the American College of Cardiology/American Heart Association Task Force on Clinical Practice Guidelines and the Heart Failure Society of America. *J Am Coll Cardiol* 2017;**70**:776–803.
5. 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. 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 J Heart Fail* 2016;**18**:891–975.
6. O'Connor CM, Starling RC, Hernandez AF, Armstrong PW, Dickstein K, Hasselblad V, Heizer GM, Komajda M, Massie BM, McMurray JJ, Nieminen MS, Reist CJ, Rouleau JL, Swedberg K, Adams KF Jr, Anker SD, Atar D, Battler A, Botero R, Bohidar NR, Butler J, Clausell N, Corbalan R, Costanzo MR, Dahlstrom U, Deckelbaum LI, Diaz R, Dunlap ME, Ezekowitz JA, Feldman D, Felker GM, Fonarow GC, Gennevois D, Gottlieb SS, Hill JA, Hollander JE, Howlett JG, Hudson MP, Kociol RD, Krum H, Laucevicius A, Levy WC, Mendez GF, Metra M, Mittal S, Oh BH, Pereira NL, Ponikowski P, Tang WH, Tanomsup S, Teerlink JR, Triposkiadis F, Troughton RW, Voors AA, Whellan DJ, Zannad F, Califf RM. Effect of nesiritide in patients with acute decompensated heart failure. *N Engl J Med* 2011;**365**:32–43.
7. Packer M, O'Connor C, McMurray JJV, Wittes J, Abraham WT, Anker SD, Dickstein K, Filippatos G, Holcomb R, Krum H, Maggioni AP, Mebazaa A, Peacock WF, Petrie MC, Ponikowski P, Ruschitzka F, van Veldhuisen DJ, Kowarski LS, Schactman M, Holzmeister J; TRUE-AHF Investigators. Effect of ularitide on cardiovascular mortality in acute heart failure. *N Engl J Med* 2017;**376**:1956–1964.
8. Cuffe MS, Califf RM, Adams KF Jr, Benza R, Bourge R, Colucci WS, Massie BM, O'Connor CM, Pina I, Quigg R, Silver MA, Gheorghiade M. Short-term intravenous milrinone for acute exacerbation of chronic heart failure: a randomized controlled trial. *JAMA* 2002;**287**:1541–1547.
9. Paolocci N, Jackson MI, Lopez BE, Miranda K, Tocchetti CG, Wink DA, Hobbs AJ, Fukuto JM. The pharmacology of nitroxyl (HNO) and its therapeutic potential: not just the Janus face of NO. *Pharmacol Ther* 2007;**113**:442–458.
10. Tocchetti CG, Wang W, Froehlich JP, Huke S, Aon MA, Wilson GM, Di Benedetto G, O'Rourke B, Gao WD, Wink DA, Toscano JP, Zaccolo M, Bers DM, Valdivia HH, Cheng H, Kass DA, Paolocci N. Nitroxyl improves cellular heart function by directly enhancing cardiac sarcoplasmic reticulum Ca^{2+} cycling. *Circ Res* 2007;**100**:96–104.
11. Dai T, Tian Y, Tocchetti CG, Katori T, Murphy AM, Kass DA, Paolocci N, Gao WD. Nitroxyl increases force development in rat cardiac muscle. *J Physiol* 2007;**580**(Pt 3:951–960.
12. Lancel S, Zhang J, Evangelista A, Trucillo MP, Tong X, Siwik DA, Cohen RA, Colucci WS. Nitroxyl activates SERCA in cardiac myocytes via glutathiolation of cysteine 674. *Circ Res* 2009;**104**:720–723.
13. Kohr MJ, Kaludercic N, Tocchetti CG, Dong Gao W, Kass DA, Janssen PM, Paolocci N, Ziolo MT. Nitroxyl enhances myocyte Ca^{2+} transients by exclusively targeting SR Ca^{2+}-cycling. *Front Biosci (Elite Ed)* 2010:614–626.
14. Keceli G, Majumdar A, Thorpe CN, Jun S, Tocchetti CG, Lee DI, Mahaney JE, Paolocci N, Toscano JP. Nitroxyl (HNO) targets phospholamban cysteines 41 and 46 to enhance cardiac function. *J Gen Physiol* 2019;**151**:758–770.
15. Tocchetti CG, Stanley BA, Murray CI, Sivakumaran V, Donzelli S, Mancardi D, Pagliaro P, Gao WD, van Eyk J, Kass DA, Wink DA, Paolocci N. Playing with cardiac "redox switches": the "HNO way" to modulate cardiac function. *Antioxid Redox Signal* 2011;**14**:1687–1698.
16. Irvine JC, Ravi RM, Kemp-Harper BK, Widdop RE. Nitroxyl donors retain their depressor effects in hypertension. *Am J Physiol Heart Circ Physiol* 2013;**305**:H939–H945.
17. Paolocci N, Katori T, Champion HC, St John ME, Miranda KM, Fukuto JM, Wink DA, Kass DA. Positive inotropic and lusitropic effects of HNO/NO in

failing hearts: independence from β-adrenergic signaling. *Proc Natl Acad Sci U S A* 2003;**100**:5537–5542.
18. Sabbah HN, Tocchetti CG, Wang M, Daya S, Gupta RC, Tunin RS, Mazhari R, Takimoto E, Paolocci N, Cowart D, Colucci WS, Kass DA. Nitroxyl (HNO): a novel approach for the acute treatment of heart failure. *Circ Heart Fail* 2013;**6**:1250–1258.
19. Hartman JC, del Rio CL, Reardon JE, Zhang K, Sabbah HN. Intravenous infusion of the novel HNO donor BMS-986231 is associated with beneficial inotropic, lusitropic, and vasodilatory properties in 2 canine models of heart failure. *JACC Basic Transl Sci* 2018;**3**:625–638.
20. Cowart D, Venuti R, Guptill J, Noveck R, Foo S. A phase 1 study of the safety and pharmacokinetics of the intravenous nitroxyl prodrug, CXL-1427. *J Am Coll Cardiol* 2015;**65**:A876 (abstr).
21. Tita C, Gilbert EM, Van Bakel AB, Grzybowski J, Haas GJ, Jarrah M, Dunlap SH, Gottlieb SS, Klapholz M, Patel PC, Pfister R, Seidler T, Shah KB, Zielinski T, Venuti RP, Cowart D, Foo SY, Vishnevsky A, Mitrovic V. A phase 2a dose-escalation study of the safety, tolerability, pharmacokinetics and haemodynamic effects of BMS-986231 in hospitalized patients with heart failure with reduced ejection fraction. *Eur J Heart Fail* 2017;**19**:1321–1332.
22. Greene SJ, Mentz RJ, Fiuzat M, Butler J, Solomon SD, Ambrosy AP, Mehta C, Teerlink JR, Zannad F, O'Connor CM. Reassessing the role of surrogate end points in drug development for heart failure. *Circulation* 2018;**138**:1039–1053.
23. Pang PS, Butler J, Collins SP, Cotter G, Davison BA, Ezekowitz JA, Filippatos G, Levy PD, Metra M, Ponikowski P, Teerlink JR, Voors AA, Bharucha D, Goin K, Soergel DG, Felker GM. 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). *Eur Heart J* 2017;**38**:2354–2373.
24. Mullens W, Damman K, Harjola VP, Mebazaa A, Brunner-La Rocca HP, Martens P, Testani JM, Tang WH, Orso F, Rossignol P, Metra M, Filippatos G, Seferovic PM, Ruschitzka F, Coats AJ. The use of diuretics in heart failure with congestion – a position statement from the Heart Failure Association of the European Society of Cardiology. *Eur J Heart Fail* 2019;**21**:137–155.
25. Mentz RJ, Kjeldsen K, Rossi GP, Voors AA, Cleland JG, Anker SD, Gheorghiade M, Fiuzat M, Rossignol P, Zannad F, Pitt B, O'Connor C, Felker GM. Decongestion in acute heart failure. *Eur J Heart Fail* 2014;**16**:471–482.
26. Gheorghiade M, Abraham WT, Albert NM, Greenberg BH, O'Connor CM, She L, Stough WG, Yancy CW, Young JB, Fonarow GC; OPTIMIZE-HF Investigators and Coordinators. Systolic blood pressure at admission, clinical characteristics, and outcomes in patients hospitalized with acute heart failure. *JAMA* 2006;**296**:2217–2226.