Clinical trial results:
A Randomized, Double-Blind, Placebo-Controlled, Dose Ranging Study to Explore the Efficacy of TRV027 in Patients Hospitalized for Acute Decompensated Heart Failure

Summary

EudraCT number	2013-002893-35
Trial protocol	HU DE CZ SK BG
Global end of trial date	26 August 2016

Results information

Result version number	v1 (current)
This version publication date	23 June 2022
First version publication date	23 June 2022

Trial information

Trial identification

Sponsor protocol code	CP027.2002

Additional study identifiers

ISRCTN number	-
ClinicalTrials.gov id (NCT number)	NCT01966601
WHO universal trial number (UTN)	-

Notes:

Sponsors

Sponsor organisation name	Trevena Inc.
Sponsor organisation address	955 Chesterbrook Boulevard, Suite 110, Chesterbrook, United States, PA 19087
Public contact	Mark Demitrack MD, Trevena Inc., +1 6103548840, mdemitrack@trevena.com
Scientific contact	Mark Demitrack MD, Trevena Inc., +1 6103548840, mdemitrack@trevena.com

Notes:

Paediatric regulatory details

Is trial part of an agreed paediatric investigation plan (PIP)	No
Does article 45 of REGULATION (EC) No 1901/2006 apply to this trial?	No
Does article 46 of REGULATION (EC) No 1901/2006 apply to this trial?	No

Notes:

Results analysis stage

Analysis stage	Final
Date of interim/final analysis	18 April 2016
Is this the analysis of the primary completion data?	Yes
Primary completion date	18 April 2016
Global end of trial reached?	Yes
Global end of trial date	26 August 2016
Was the trial ended prematurely?	No

Notes:

General information about the trial

Main objective of the trial:

To evaluate the overall safety and efficacy of TRV027 in addition to standard of care (SOC) on mortality, morbidity, dyspnea, and length of stay, as well as on standard safety measures, in patients hospitalized with Acute Decompensated Heart Failure (ADHF).

Protection of trial subjects:

Vital sign measurements of systolic, diastolic blood pressure and heart rate were collected during study drug infusion, and following study drug infusion for a further six hours.

OR no specific measures required

Background therapy:

Any medical therapy required for patient safety after randomisation could be administered at the discretion of the treating physician. Any patients presribed home high flow oxygen therapy or BiPAP and CPAP devices as part of their medical management of sleep apnoea or heart failure could have these therapies added for the treatment of worsening heart failure during the hospitalization portion of the study and could be considered as part of the worsening heart failure assessment.

Evidence for comparator:

Placebo was used as the reference product to allow for comparisons of the effects of different doses of TRV027 on safety and efficacy in ADHF.

Actual start date of recruitment	24 December 2013
Long term follow-up planned	No
Independent data monitoring committee (IDMC) involvement?	Yes

Notes:

Population of trial subjects

Subjects enrolled per country

Country: Number of subjects enrolled	Israel: 36
Country: Number of subjects enrolled	Romania: 63
Country: Number of subjects enrolled	Russian Federation: 129
Country: Number of subjects enrolled	United States: 8
Country: Number of subjects enrolled	Poland: 89
Country: Number of subjects enrolled	Slovakia: 14
Country: Number of subjects enrolled	Bulgaria: 98
Country: Number of subjects enrolled	Czechia: 27
Country: Number of subjects enrolled	Germany: 12
Country: Number of subjects enrolled	Hungary: 82
Country: Number of subjects enrolled	Canada: 1
Country: Number of subjects enrolled	Argentina: 59

Worldwide total number of subjects	618
EEA total number of subjects	385

Notes:

Subjects enrolled per age group	
In utero	0
Preterm newborn - gestational age < 37 wk	0
Newborns (0-27 days)	0
Infants and toddlers (28 days-23 months)	0
Children (2-11 years)	0
Adolescents (12-17 years)	0
Adults (18-64 years)	160
From 65 to 84 years	458
85 years and over	0

Subject disposition

Recruitment

Recruitment details: -

Pre-assignment

Screening details:

621 patients were randomised and 618 patients were treated. 3 patients were mis-randomised in each of the TRV027 arms and not treated (1 withdrew consent, 1 not expected to be admitted for min 48 hours, and 1 with systolic BP dropped below 95mmHg.

Period 1

Period 1 title	overall trial (overall period)
Is this the baseline period?	Yes
Allocation method	Randomised - controlled
Blinding used	Double blind
Roles blinded	Subject, Investigator, Monitor, Data analyst, Assessor

Blinding implementation details:

The study was conducted in a double-blind manner. Study patients, Investigators/site personnel and Sponsor representatives were blinded to study drug assignments. Both TRV027 and the placebo were presented as colourless solutions in matching clear vials. Treatment was assigned through the IVRS/IWRS based on the randomisation plan.

Arms

Are arms mutually exclusive?	Yes
Arm title	TRV027 1.0mg/hr

Arm description:

Subjects received TRV027 1.0mg/hr

Arm type	Experimental
Investigational medicinal product name	TRV027 1.0mg/hr
Investigational medicinal product code	TRV027
Other name	
Pharmaceutical forms	Injection/infusion
Routes of administration	Infusion

Dosage and administration details:

TRV027 supplied as 100mg at 10mg/ml concentration. TRV027 was administered as a continuous IV infusion (diluted at the clinical site in 0.9% NaCl) for at least 48 hours and up to 96 hours. The intravenous infusion rate was reduced by 50% for 3 hours before terminating the study drug infusion, except in the case of where the study drug is being discontinued for a safety reason (down-titration step not needed).

Arm title	TRV027 5.0 mg/hr

Arm description:

Subjects received TRV027 5.0 mg/hr

Arm type	Experimental
Investigational medicinal product name	TRV027 5.0mg/hr
Investigational medicinal product code	TRV027
Other name	
Pharmaceutical forms	Injection/infusion
Routes of administration	Infusion

Dosage and administration details:

TRV027 supplied as 100mg at 10mg/ml concentration. TRV027 was administered as a continuous IV infusion (diluted at the clinical site in 0.9% NaCl) for at least 48 hours and up to 96 hours. The intravenous infusion rate was reduced by 50% for 3 hours before terminating the study drug infusion, except in the case of where the study drug is being discontinued for a safety reason (down-titration step not needed).

Arm title	TRV027 25.0 mg/hr

Arm description:

Subjects receoved TRV027 25.0 mg/hr

Arm type	Experimental
Investigational medicinal product name	TRV027 25.0mg/hr
Investigational medicinal product code	TRV027
Other name	
Pharmaceutical forms	Injection/infusion
Routes of administration	Infusion

Dosage and administration details:

TRV027 supplied as 100mg at 10mg/ml concentration. TRV027 was administered as a continuous IV infusion (diluted at the clinical site in 0.9% NaCl) for at least 48 hours and up to 96 hours. The intravenous infusion rate was reduced by 50% for 3 hours before terminating the study drug infusion, except in the case of where the study drug is being discontinued for a safety reason (down-titration step not needed).

Arm title	Placebo

Arm description:

Subject received placebo

Arm type	Placebo
Investigational medicinal product name	Placebo
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Injection/infusion
Routes of administration	Infusion

Dosage and administration details:

Placebo vial provided to match IMP. Placebo was administered as a continuous IV infusion (diluted at the clinical site in 0.9% NaCl) for at least 48 hours and up to 96 hours. The intravenous infusion rate was reduced by 50% for 3 hours before terminating the study drug infusion, except in the case of where the study drug is being discontinued for a safety reason (down-titration step not needed).

Number of subjects in period 1	TRV027 1.0mg/hr	TRV027 5.0 mg/hr	TRV027 25.0 mg/hr
Started	128	182	125
Completed	90	111	83
Not completed	38	71	42
Adverse event, serious fatal	14	23	16
Day 180 follow up status undetermined	24	48	26

Number of subjects in period 1	Placebo
Started	183
Completed	107
Not completed	76
Adverse event, serious fatal	22
Day 180 follow up status undetermined	54

Baseline characteristics

Reporting groups	
Reporting group title	TRV027 1.0mg/hr
Reporting group description: Subjects received TRV027 1.0mg/hr	
Reporting group title	TRV027 5.0 mg/hr
Reporting group description: Subjects received TRV027 5.0 mg/hr	
Reporting group title	TRV027 25.0 mg/hr
Reporting group description: Subjects receoved TRV027 25.0 mg/hr	
Reporting group title	Placebo
Reporting group description: Subject received placebo	

Reporting group values	TRV027 1.0mg/hr	TRV027 5.0 mg/hr	TRV027 25.0 mg/hr
Number of subjects	128	182	125
Age categorical Units: Subjects			
Adults (18-64 years)	36	49	32
From 65-84 years	92	133	93
Gender categorical Units: Subjects			
Female	50	69	47
Male	78	113	78

Reporting group values	Placebo	Total	
Number of subjects	183	618	
Age categorical Units: Subjects			
Adults (18-64 years)	43	160	
From 65-84 years	140	458	
Gender categorical Units: Subjects			
Female	68	234	
Male	115	384	

End points

End points reporting groups	
Reporting group title	TRV027 1.0mg/hr
Reporting group description: Subjects received TRV027 1.0mg/hr	
Reporting group title	TRV027 5.0 mg/hr
Reporting group description: Subjects received TRV027 5.0 mg/hr	
Reporting group title	TRV027 25.0 mg/hr
Reporting group description: Subjects receoved TRV027 25.0 mg/hr	
Reporting group title	Placebo
Reporting group description: Subject received placebo	

Primary: Mean Z score	
End point title	Mean Z score
End point description: The primary clinical endpoint will be a composite of the following outcomes, representing potential treatment targets in ADHF: • Time from baseline reference date to death through day 30 • Time from baseline reference date to heart failure re-hospitalization through day 30 • Study day of worsening heart failure (WHF) through day 5 • Change in dyspnea visual analog scale (VAS) score (calculated area under the curve (AUC)) from baseline through day 5 • Length of initial hospital stay (in days) from randomization through day 30 Each of the above five component endpoints of the primary composite outcome will be derived, and an average z score derived for each patient.	
End point type	Primary
End point timeframe: Day 30	

End point values	TRV027 1.0mg/hr	TRV027 5.0 mg/hr	TRV027 25.0 mg/hr	Placebo
Subject group type	Reporting group	Reporting group	Reporting group	Reporting group
Number of subjects analysed	128	182	125	183
Units: mean				
arithmetic mean (standard deviation)	0.034 (± 0.6146)	-0.036 (± 0.7253)	-0.072 (± 0.7274)	0.060 (± 0.6475)

Statistical analyses

Statistical analysis title	Mean z score
Comparison groups	TRV027 25.0 mg/hr v Placebo v TRV027 1.0mg/hr v TRV027 5.0 mg/hr

Number of subjects included in analysis	618
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.05
Method	Wilcoxon rank sum
Parameter estimate	Mean difference (final values)

Adverse events

Adverse events information

Timeframe for reporting adverse events:

To Day 30

Adverse event reporting additional description:

All adverse events that occur from the time the subject signs informed consent through the study Day 30 visit will be recorded. At each contact with the patient during the study period, the Investigator queried the patient with regard to adverse events.

Assessment type	Systematic

Dictionary used

Dictionary name	MedDRA
Dictionary version	18.1

Reporting groups

Reporting group title	TRV027 1.0mg/hr

Reporting group description:

Subjects received TRV027 1.0mg/hr

Reporting group title	TRV027 5.0 mg/hr

Reporting group description:

Subjects received TRV027 5.0 mg/hr

Reporting group title	TRV027 25.0 mg/hr

Reporting group description:

Subjects receoved TRV027 25.0 mg/hr

Reporting group title	Placebo

Reporting group description:

Subject received placebo

Serious adverse events	TRV027 1.0mg/hr	TRV027 5.0 mg/hr	TRV027 25.0 mg/hr
Total subjects affected by serious adverse events			
subjects affected / exposed	16 / 128 (12.50%)	36 / 182 (19.78%)	22 / 125 (17.60%)
number of deaths (all causes)	6	9	8
number of deaths resulting from adverse events			
Neoplasms benign, malignant and unspecified (incl cysts and polyps)			
plasmocytoma			
subjects affected / exposed	0 / 128 (0.00%)	1 / 182 (0.55%)	0 / 125 (0.00%)
occurrences causally related to treatment / all	0 / 0	1 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Adenocarcinoma of colon			
subjects affected / exposed	0 / 128 (0.00%)	0 / 182 (0.00%)	0 / 125 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0

Bladder neoplasm			
subjects affected / exposed	1 / 128 (0.78%)	0 / 182 (0.00%)	0 / 125 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Vascular disorders			
Peripheral ischaemia			
subjects affected / exposed	0 / 128 (0.00%)	0 / 182 (0.00%)	0 / 125 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Peripheral artery thrombosis			
subjects affected / exposed	0 / 128 (0.00%)	0 / 182 (0.00%)	0 / 125 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
General disorders and administration site conditions			
Death			
subjects affected / exposed	0 / 128 (0.00%)	0 / 182 (0.00%)	0 / 125 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Sudden death			
subjects affected / exposed	1 / 128 (0.78%)	0 / 182 (0.00%)	1 / 125 (0.80%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 1	0 / 0	0 / 1
Non-cardiac chest pain			
subjects affected / exposed	0 / 128 (0.00%)	0 / 182 (0.00%)	1 / 125 (0.80%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Localised oedema			
subjects affected / exposed	0 / 128 (0.00%)	1 / 182 (0.55%)	0 / 125 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Respiratory, thoracic and mediastinal disorders			
Acute respiratory distress syndrome			

subjects affected / exposed	1 / 128 (0.78%)	0 / 182 (0.00%)	0 / 125 (0.00%)
occurrences causally related to treatment / all	1 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Pneumonia aspiration			
subjects affected / exposed	0 / 128 (0.00%)	0 / 182 (0.00%)	0 / 125 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Pulmonary embolism			
subjects affected / exposed	0 / 128 (0.00%)	1 / 182 (0.55%)	0 / 125 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 1	0 / 0
Pulmonary oedema			
subjects affected / exposed	1 / 128 (0.78%)	0 / 182 (0.00%)	0 / 125 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 1	0 / 0	0 / 0
Chronic obstructive pulmonary disease			
subjects affected / exposed	0 / 128 (0.00%)	1 / 182 (0.55%)	0 / 125 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Acute pulmonary oedema			
subjects affected / exposed	0 / 128 (0.00%)	1 / 182 (0.55%)	0 / 125 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Cardiac disorders			
Acute myocardial infarction			
subjects affected / exposed	1 / 128 (0.78%)	0 / 182 (0.00%)	1 / 125 (0.80%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 1
Cardiac arrest			
subjects affected / exposed	0 / 128 (0.00%)	0 / 182 (0.00%)	0 / 125 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Cardiac failure			

subjects affected / exposed	5 / 128 (3.91%)	13 / 182 (7.14%)	4 / 125 (3.20%)
occurrences causally related to treatment / all	0 / 5	0 / 14	0 / 4
deaths causally related to treatment / all	0 / 1	0 / 4	0 / 1
Cardiac failure congestive			
subjects affected / exposed	2 / 128 (1.56%)	1 / 182 (0.55%)	1 / 125 (0.80%)
occurrences causally related to treatment / all	0 / 3	0 / 1	0 / 2
deaths causally related to treatment / all	0 / 1	0 / 0	0 / 0
Cardio-respiratory arrest			
subjects affected / exposed	0 / 128 (0.00%)	0 / 182 (0.00%)	1 / 125 (0.80%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Cardiogenic shock			
subjects affected / exposed	1 / 128 (0.78%)	0 / 182 (0.00%)	0 / 125 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 1	0 / 0	0 / 0
Left ventricular failure			
subjects affected / exposed	0 / 128 (0.00%)	0 / 182 (0.00%)	0 / 125 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Ventricular fibrillation			
subjects affected / exposed	0 / 128 (0.00%)	0 / 182 (0.00%)	0 / 125 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Ventricular tachycardia			
subjects affected / exposed	0 / 128 (0.00%)	1 / 182 (0.55%)	2 / 125 (1.60%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 2
deaths causally related to treatment / all	0 / 0	0 / 1	0 / 1
Atrial fibrillation			
subjects affected / exposed	0 / 128 (0.00%)	0 / 182 (0.00%)	0 / 125 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Atrioventricular block complete			

subjects affected / exposed	0 / 128 (0.00%)	0 / 182 (0.00%)	0 / 125 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Cardiac failure acute			
subjects affected / exposed	0 / 128 (0.00%)	2 / 182 (1.10%)	1 / 125 (0.80%)
occurrences causally related to treatment / all	0 / 0	0 / 2	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Myocardial infarction			
subjects affected / exposed	1 / 128 (0.78%)	1 / 182 (0.55%)	0 / 125 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Cardiac failure chronic			
subjects affected / exposed	0 / 128 (0.00%)	0 / 182 (0.00%)	1 / 125 (0.80%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Sinus node dysfunction			
subjects affected / exposed	0 / 128 (0.00%)	0 / 182 (0.00%)	1 / 125 (0.80%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Bradycardia			
subjects affected / exposed	0 / 128 (0.00%)	1 / 182 (0.55%)	0 / 125 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Coronary artery disease			
subjects affected / exposed	0 / 128 (0.00%)	2 / 182 (1.10%)	0 / 125 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 2	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Nervous system disorders			
Ischaemic stroke			
subjects affected / exposed	0 / 128 (0.00%)	2 / 182 (1.10%)	0 / 125 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 2	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 2	0 / 0
Cerebrovascular accident			

subjects affected / exposed	0 / 128 (0.00%)	0 / 182 (0.00%)	1 / 125 (0.80%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 1
Metabolic encephalopathy			
subjects affected / exposed	0 / 128 (0.00%)	1 / 182 (0.55%)	0 / 125 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 1	0 / 0
Syncope			
subjects affected / exposed	0 / 128 (0.00%)	0 / 182 (0.00%)	1 / 125 (0.80%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Transient ischaemic attack			
subjects affected / exposed	0 / 128 (0.00%)	1 / 182 (0.55%)	0 / 125 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Blood and lymphatic system disorders			
Anaemia			
subjects affected / exposed	0 / 128 (0.00%)	1 / 182 (0.55%)	0 / 125 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Gastrointestinal disorders			
Gastrointestinal haemorrhage			
subjects affected / exposed	0 / 128 (0.00%)	0 / 182 (0.00%)	0 / 125 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Rectal haemorrhage			
subjects affected / exposed	0 / 128 (0.00%)	0 / 182 (0.00%)	0 / 125 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Abdominal mass			
subjects affected / exposed	1 / 128 (0.78%)	0 / 182 (0.00%)	0 / 125 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Abdominal wall haematoma			

subjects affected / exposed	0 / 128 (0.00%)	0 / 182 (0.00%)	1 / 125 (0.80%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Abdominal pain upper			
subjects affected / exposed	0 / 128 (0.00%)	1 / 182 (0.55%)	0 / 125 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Gastroenteritis			
subjects affected / exposed	0 / 128 (0.00%)	1 / 182 (0.55%)	0 / 125 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Hepatobiliary disorders			
Hepatic failure			
subjects affected / exposed	0 / 128 (0.00%)	0 / 182 (0.00%)	1 / 125 (0.80%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 1
Skin and subcutaneous tissue disorders			
Stasis dermatitis			
subjects affected / exposed	0 / 128 (0.00%)	1 / 182 (0.55%)	0 / 125 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Renal and urinary disorders			
Renal failure			
subjects affected / exposed	0 / 128 (0.00%)	1 / 182 (0.55%)	0 / 125 (0.00%)
occurrences causally related to treatment / all	0 / 0	1 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
renal failure chronic			
subjects affected / exposed	0 / 128 (0.00%)	0 / 182 (0.00%)	1 / 125 (0.80%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 1
Acute kidney injury			
subjects affected / exposed	0 / 128 (0.00%)	1 / 182 (0.55%)	0 / 125 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0

Musculoskeletal and connective tissue disorders			
Back pain			
subjects affected / exposed	1 / 128 (0.78%)	0 / 182 (0.00%)	0 / 125 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Osteoarthritis			
subjects affected / exposed	0 / 128 (0.00%)	0 / 182 (0.00%)	1 / 125 (0.80%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Intervertebral disc protrusion			
subjects affected / exposed	0 / 128 (0.00%)	1 / 182 (0.55%)	0 / 125 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Infections and infestations			
Pneumonia			
subjects affected / exposed	0 / 128 (0.00%)	2 / 182 (1.10%)	2 / 125 (1.60%)
occurrences causally related to treatment / all	0 / 0	0 / 2	0 / 2
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Septic shock			
subjects affected / exposed	1 / 128 (0.78%)	0 / 182 (0.00%)	0 / 125 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 1	0 / 0	0 / 0
Gangrene			
subjects affected / exposed	0 / 128 (0.00%)	0 / 182 (0.00%)	0 / 125 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Urinary tract infection			
subjects affected / exposed	0 / 128 (0.00%)	0 / 182 (0.00%)	0 / 125 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Pseudomembranous colitis			
subjects affected / exposed	1 / 128 (0.78%)	0 / 182 (0.00%)	0 / 125 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0

Urosepsis			
subjects affected / exposed	1 / 128 (0.78%)	1 / 182 (0.55%)	0 / 125 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Bronchitis			
subjects affected / exposed	0 / 128 (0.00%)	0 / 182 (0.00%)	1 / 125 (0.80%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Erysipelas			
subjects affected / exposed	0 / 128 (0.00%)	0 / 182 (0.00%)	1 / 125 (0.80%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Sepsis			
subjects affected / exposed	0 / 128 (0.00%)	0 / 182 (0.00%)	1 / 125 (0.80%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Viral infection			
subjects affected / exposed	0 / 128 (0.00%)	1 / 182 (0.55%)	0 / 125 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Bronchopneumopathy			
subjects affected / exposed	0 / 128 (0.00%)	1 / 182 (0.55%)	1 / 125 (0.80%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 1
Metabolism and nutrition disorders			
Hypokalaemia			
subjects affected / exposed	0 / 128 (0.00%)	0 / 182 (0.00%)	0 / 125 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Electrolyte imbalance			
subjects affected / exposed	0 / 128 (0.00%)	1 / 182 (0.55%)	0 / 125 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Hypoglycaemia			

subjects affected / exposed	0 / 128 (0.00%)	1 / 182 (0.55%)	0 / 125 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0

Serious adverse events	Placebo		
Total subjects affected by serious adverse events			
subjects affected / exposed	24 / 183 (13.11%)		
number of deaths (all causes)	9		
number of deaths resulting from adverse events			
Neoplasms benign, malignant and unspecified (incl cysts and polyps)			
plasmocytoma			
subjects affected / exposed	0 / 183 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Adenocarcinoma of colon			
subjects affected / exposed	1 / 183 (0.55%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Bladder neoplasm			
subjects affected / exposed	0 / 183 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Vascular disorders			
Peripheral ischaemia			
subjects affected / exposed	1 / 183 (0.55%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 1		
Peripheral artery thrombosis			
subjects affected / exposed	1 / 183 (0.55%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
General disorders and administration site conditions			
Death			

subjects affected / exposed	1 / 183 (0.55%)			
occurrences causally related to treatment / all	1 / 1			
deaths causally related to treatment / all	1 / 1			
Sudden death				
subjects affected / exposed	0 / 183 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
Non-cardiac chest pain				
subjects affected / exposed	0 / 183 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
Localised oedema				
subjects affected / exposed	0 / 183 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
Respiratory, thoracic and mediastinal disorders				
Acute respiratory distress syndrome				
subjects affected / exposed	0 / 183 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
Pneumonia aspiration				
subjects affected / exposed	1 / 183 (0.55%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Pulmonary embolism				
subjects affected / exposed	0 / 183 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
Pulmonary oedema				
subjects affected / exposed	0 / 183 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
Chronic obstructive pulmonary disease				

subjects affected / exposed	1 / 183 (0.55%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Acute pulmonary oedema				
subjects affected / exposed	0 / 183 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
Cardiac disorders				
Acute myocardial infarction				
subjects affected / exposed	1 / 183 (0.55%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 1			
Cardiac arrest				
subjects affected / exposed	1 / 183 (0.55%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 1			
Cardiac failure				
subjects affected / exposed	6 / 183 (3.28%)			
occurrences causally related to treatment / all	0 / 6			
deaths causally related to treatment / all	0 / 3			
Cardiac failure congestive				
subjects affected / exposed	0 / 183 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
Cardio-respiratory arrest				
subjects affected / exposed	0 / 183 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
Cardiogenic shock				
subjects affected / exposed	0 / 183 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
Left ventricular failure				

subjects affected / exposed	1 / 183 (0.55%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 1			
Ventricular fibrillation				
subjects affected / exposed	1 / 183 (0.55%)			
occurrences causally related to treatment / all	1 / 1			
deaths causally related to treatment / all	0 / 0			
Ventricular tachycardia				
subjects affected / exposed	0 / 183 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
Atrial fibrillation				
subjects affected / exposed	1 / 183 (0.55%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Atrioventricular block complete				
subjects affected / exposed	1 / 183 (0.55%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Cardiac failure acute				
subjects affected / exposed	1 / 183 (0.55%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Myocardial infarction				
subjects affected / exposed	0 / 183 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
Cardiac failure chronic				
subjects affected / exposed	0 / 183 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
Sinus node dysfunction				

subjects affected / exposed	0 / 183 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Bradycardia			
subjects affected / exposed	0 / 183 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Coronary artery disease			
subjects affected / exposed	0 / 183 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Nervous system disorders			
Ischaemic stroke			
subjects affected / exposed	0 / 183 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Cerebrovascular accident			
subjects affected / exposed	0 / 183 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Metabolic encephalopathy			
subjects affected / exposed	0 / 183 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Syncope			
subjects affected / exposed	0 / 183 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Transient ischaemic attack			
subjects affected / exposed	0 / 183 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Blood and lymphatic system disorders			

Anaemia			
subjects affected / exposed	0 / 183 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Gastrointestinal disorders			
Gastrointestinal haemorrhage			
subjects affected / exposed	3 / 183 (1.64%)		
occurrences causally related to treatment / all	0 / 3		
deaths causally related to treatment / all	0 / 0		
Rectal haemorrhage			
subjects affected / exposed	1 / 183 (0.55%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Abdominal mass			
subjects affected / exposed	0 / 183 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Abdominal wall haematoma			
subjects affected / exposed	0 / 183 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Abdominal pain upper			
subjects affected / exposed	0 / 183 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Gastroenteritis			
subjects affected / exposed	0 / 183 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Hepatobiliary disorders			
Hepatic failure			
subjects affected / exposed	0 / 183 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		

Skin and subcutaneous tissue disorders			
Stasis dermatitis			
subjects affected / exposed	0 / 183 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Renal and urinary disorders			
Renal failure			
subjects affected / exposed	0 / 183 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
renal failure chronic			
subjects affected / exposed	1 / 183 (0.55%)		
occurrences causally related to treatment / all	1 / 1		
deaths causally related to treatment / all	0 / 0		
Acute kidney injury			
subjects affected / exposed	0 / 183 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Musculoskeletal and connective tissue disorders			
Back pain			
subjects affected / exposed	0 / 183 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Osteoarthritis			
subjects affected / exposed	0 / 183 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Intervertebral disc protrusion			
subjects affected / exposed	0 / 183 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Infections and infestations			
Pneumonia			

subjects affected / exposed	3 / 183 (1.64%)			
occurrences causally related to treatment / all	0 / 3			
deaths causally related to treatment / all	0 / 1			
Septic shock				
subjects affected / exposed	0 / 183 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
Gangrene				
subjects affected / exposed	1 / 183 (0.55%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Urinary tract infection				
subjects affected / exposed	1 / 183 (0.55%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Pseudomembranous colitis				
subjects affected / exposed	0 / 183 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
Urosepsis				
subjects affected / exposed	0 / 183 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
Bronchitis				
subjects affected / exposed	0 / 183 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
Erysipelas				
subjects affected / exposed	0 / 183 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
Sepsis				

subjects affected / exposed	0 / 183 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Viral infection			
subjects affected / exposed	0 / 183 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Bronchopneumopathy			
subjects affected / exposed	0 / 183 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Metabolism and nutrition disorders			
Hypokalaemia			
subjects affected / exposed	1 / 183 (0.55%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Electrolyte imbalance			
subjects affected / exposed	0 / 183 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Hypoglycaemia			
subjects affected / exposed	0 / 183 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		

Frequency threshold for reporting non-serious adverse events: 5 %

Non-serious adverse events	TRV027 1.0mg/hr	TRV027 5.0 mg/hr	TRV027 25.0 mg/hr
Total subjects affected by non-serious adverse events			
subjects affected / exposed	30 / 128 (23.44%)	41 / 182 (22.53%)	31 / 125 (24.80%)
Cardiac disorders			
Cardiac failure			
subjects affected / exposed	12 / 128 (9.38%)	22 / 182 (12.09%)	14 / 125 (11.20%)
occurrences (all)	12	26	14
Nervous system disorders			

Headache			
subjects affected / exposed	7 / 128 (5.47%)	6 / 182 (3.30%)	6 / 125 (4.80%)
occurrences (all)	7	7	7
Metabolism and nutrition disorders			
Hypokalaemia			
subjects affected / exposed	11 / 128 (8.59%)	13 / 182 (7.14%)	11 / 125 (8.80%)
occurrences (all)	16	14	14

Non-serious adverse events	Placebo		
Total subjects affected by non-serious adverse events			
subjects affected / exposed	33 / 183 (18.03%)		
Cardiac disorders			
Cardiac failure			
subjects affected / exposed	11 / 183 (6.01%)		
occurrences (all)	11		
Nervous system disorders			
Headache			
subjects affected / exposed	11 / 183 (6.01%)		
occurrences (all)	12		
Metabolism and nutrition disorders			
Hypokalaemia			
subjects affected / exposed	11 / 183 (6.01%)		
occurrences (all)	11		

More information

Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? Yes

Date	Amendment
23 July 2014	-added instruction about stopping study drug if infusion is discontinued multiple times within a 24 hour period -removed instruction to discontinue study drug after 48 hours -removed exclusion criteria of pulmonary hypotension -added exclusion criteria for significant pulmonary disease
04 March 2015	-revised randomization scheme following interim analysis from 1:1:1:1 to 2:1:1:1 (placebo:TRV027 1.0 mg/hr:TRV027 5.0 mg/hr:TRV027 25 mg/hr) -included additional secondary efficacy measure: average Z comprising the components of the primary endpoint and incorporating changes in troponin-T and cystanin-C baseline to 48 hours -amended enrollment to be approx. 620 patients -revised inclusion criteria so that the definition of ADHF must include radiographic evidence of chest congestion -revised safety systolic blood pressure measurement between 105 mmHg and 160 mmHg, inclusive -refined inclusion criteria that pre-existing HF diagnosis may be reported but must include treatment for at least the last 30 days with daily oral loop diuretics plus an ACE inhibitor and/or beta-adrenergic blocker for all patients for whom ACE inhibitors and beta blockers are not documented as contraindicated -clarified that current suspicion of ACS, coronary revascularization within the 3 months prior to screening are exclusions -added exclusion criteria that clinical presentation may not include a serum sodium >145 mEq/L (145 mmol/L) -clarified that current or planned thoracentesis is an exclusion criteria -clarified exclusion criteria for history of current use of left ventricular assist devices or use within the last year prior to screening of intra-aortic balloon pumps

Notes:

Interruptions (globally)

Were there any global interruptions to the trial? No

Limitations and caveats

None reported