Clinical trial results:
A randomized, double-blind, placebo-controlled, multicenter, parallel-group,
adaptive group-sequential phase II study, to determine the efficacy and safety of BT086 as an adjunctive treatment in severe community acquired pneumonia (sCAP)

Summary

EudraCT number	2010-022380-35
Trial protocol	DE ES GB BE
Global end of trial date	25 February 2015

Results information

Result version number	v1 (current)
This version publication date	13 December 2021
First version publication date	13 December 2021

Trial information

Trial identification

Sponsor protocol code	982

Additional study identifiers

ISRCTN number	-
ClinicalTrials.gov id (NCT number)	NCT01420744
WHO universal trial number (UTN)	-

Notes:

Sponsors

Sponsor organisation name	Biotest AG
Sponsor organisation address	Landsteinerstraße 5, Dreieich, Germany, 63303
Public contact	Dr. med. Andrea Wartenberg-Demand, Biotest AG, +49 61038010, andrea.wartenberg-demand@biotest.com
Scientific contact	Dr. med. Andrea Wartenberg-Demand, Biotest AG, +49 61038010, andrea.wartenberg-demand@biotest.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	25 May 2016
Is this the analysis of the primary completion data?	Yes
Primary completion date	25 February 2015
Global end of trial reached?	Yes
Global end of trial date	25 February 2015
Was the trial ended prematurely?	No

Notes:

General information about the trial

Main objective of the trial:

The objectives of this study are to evaluate the efficacy and safety of BT086 IgM concentrate in patients with sCAP(severe community acquired pneumonia)

Protection of trial subjects:

To monitor the safety data from adult subjects and to provide advice and recommendations on the enrollment a DSMB consisting of independent experts has been implemented.

Background therapy:

Standard of care

Evidence for comparator: -

Actual start date of recruitment	04 October 2011
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	Spain: 108
Country: Number of subjects enrolled	United Kingdom: 14
Country: Number of subjects enrolled	Germany: 38
Worldwide total number of subjects	160
EEA total number of subjects	160

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)	73
From 65 to 84 years	80

85 years and over	7

Subject disposition

Recruitment

Recruitment details:

The first subject's first visit (date of first enrollment) was on 04-OCT-2011 and the last subject's last visit (date of last completed) was on 25-FEB-2015

Pre-assignment

Screening details:

Major sCAP criterion (IDSA/ATS criteria) need for endotracheal ventilation and patient must have at least one of the minor signs and symptoms of pneumonia following IDSA/ATS criteria.
Treatment of patient with BT086 must start within 12 hours but not earlier than 1 hour after start of endotracheal ventilation

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, Carer, Assessor

Blinding implementation details:

The matching placebo had similar appearance to BT086 which enabled maintaining the treatment blinding. To ensure blinding, vials were covered with transparent colored foils in accordance with study-specific guidance for coating of vials with green foil.

Arms

Are arms mutually exclusive?	Yes
Arm title	BT086

Arm description:

Subjects were treated with BT086, human immunoglobulin (Ig) preparation enriched with IgM/IgA for intravenous administration. The approximate concentration of IgM in BT086 was 18-28% (mean 23%), IgA was 15-27% and IgG was 48-66%.

Arm type	Experimental
Investigational medicinal product name	Trimodulin
Investigational medicinal product code	BT086
Other name	IgM Concentrate
Pharmaceutical forms	Solution for infusion
Routes of administration	Intravenous use

Dosage and administration details:

The dose to be administered was 3.65 mL/kg body weight (bw) administered as intravenous infusion on 5 consecutive days.

Arm title	Placebo

Arm description:

Subjects were treated with placebo containing 1% human albumin solution. The dose to be administered was 3.65 mL/kg body weight (bw) administered as intravenous infusion on 5 consecutive days.

Arm type	Placebo

Investigational medicinal product name	1% human albumin solution
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Solution for infusion
Routes of administration	Intravenous use

Dosage and administration details:

5 days infusion of 1% human albumin solution (Day 1 to 5);3.65 mL/kg bw/day

Number of subjects in period 1	BT086	Placebo
Started	81	79
Completed	81	79

Baseline characteristics

Reporting groups	
Reporting group title	Overall Trial

Reporting group description: -

Reporting group values	Overall Trial	Total	
Number of subjects	160	160	
Age categorical Units: Subjects			
In utero	0	0	
Preterm newborn infants (gestational age < 37 wks)	0	0	
Newborns (0-27 days)	0	0	
Infants and toddlers (28 days-23 months)	0	0	
Children (2-11 years)	0	0	
Adolescents (12-17 years)	0	0	
Adults (18-64 years)	73	73	
From 65-84 years	80	80	
85 years and over	7	7	
Age continuous Units: years			
median	65.5		
standard deviation	± 14.80	-	
Gender categorical Units: Subjects			
Female	47	47	
Male	113	113	

End points

End points reporting groups

Reporting group title	BT086

Reporting group description:

Subjects were treated with BT086, human immunoglobulin (Ig) preparation enriched with IgM/IgA for intravenous administration. The approximate concentration of IgM in BT086 was 18-28% (mean 23%), IgA was 15-27% and IgG was 48-66%.

Reporting group title	Placebo

Reporting group description:

Subjects were treated with placebo containing 1% human albumin solution. The dose to be administered was 3.65 mL/kg body weight (bw) administered as intravenous infusion on 5 consecutive days.

Primary: Ventilator Free Days

End point title	Ventilator Free Days

End point description:

The primary endpoint is the increase of ventilator-free days (VFDs) measured in sCAP patients treated with adjunctive BT086 adjunctive to the appropriate standard-of-care treatment compared to patients treated with placebo and the appropriate standard of care. VFDs were defined as the number of days between successful extubation from endotracheal ventilation and Day 28 after enrollment of the subject into the study. To account for subjects who died during the 28-day period, VFDs were set to 0 if a subject died within this period, even after successful weaning. VFDs of subjects who prematurely discontinued the study were collected and were therefore included in the analysis.

End point type	Primary

End point timeframe:

Day 1-day29

End point values	BT086	Placebo		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	81	79		
Units: Days	81	79		

Statistical analyses

Statistical analysis title	Primary Analysis

Statistical analysis description:

Testing of the null hypothesis using one-sided Wilcoxon-Mann-Whitney tests and inverse normal method, respectively.

Comparison groups	BT086 v Placebo

Number of subjects included in analysis	160
Analysis specification	Pre-specified
Analysis type	superiority[1]
P-value	= 0.139
Method	Wilcoxon (Mann-Whitney)

Notes:

[1] - The primary efficacy analysis will focus on testing the superiority of BT086 versus placebo with regard to the primary efficacy variable, VFDs. BT086 is superior to placebo if more patients treated with BT086 survive and have more VFDs.

Adverse events

Adverse events information	
Timeframe for reporting adverse events:	
Observation period, Day-1 until day 29 (day 43+7 for UK only). All SAEs and related AEs had to be followed up until a final outcome (resolution of the event/recovery of the subject, recovery with sequelae, or death)	
Adverse event reporting additional description:	
Treatment Emergent Adverse Events	
Assessment type	Systematic

Dictionary used	
Dictionary name	MedDRA
Dictionary version	17.1

Reporting groups	
Reporting group title	Safety Analysis Set (SAF)
Reporting group description:	
Full Analysis Set and Safety Analysis Set are identical and include all subjects who received ≥ 1 dose.	

Serious adverse events	Safety Analysis Set (SAF)		
Total subjects affected by serious adverse events			
subjects affected / exposed	124 / 160 (77.50%)		
number of deaths (all causes)	40		
number of deaths resulting from adverse events	40		
Neoplasms benign, malignant and unspecified (incl cysts and polyps)			
Bronchial neoplasm			
subjects affected / exposed	1 / 160 (0.63%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 1		
Laryngeal squamous cell carcinoma			
subjects affected / exposed	1 / 160 (0.63%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Lung neoplasm malignant			
subjects affected / exposed	1 / 160 (0.63%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Squamous cell carcinoma of lung			

subjects affected / exposed	1 / 160 (0.63%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Vascular disorders				
Deep vein thrombosis				
subjects affected / exposed	2 / 160 (1.25%)			
occurrences causally related to treatment / all	0 / 2			
deaths causally related to treatment / all	0 / 0			
Extremity necrosis				
subjects affected / exposed	1 / 160 (0.63%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Hypertension				
subjects affected / exposed	2 / 160 (1.25%)			
occurrences causally related to treatment / all	0 / 2			
deaths causally related to treatment / all	0 / 0			
Jugular vein thrombosis				
subjects affected / exposed	1 / 160 (0.63%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Peripheral ischaemia				
subjects affected / exposed	3 / 160 (1.88%)			
occurrences causally related to treatment / all	0 / 4			
deaths causally related to treatment / all	0 / 1			
Shock haemorrhagic				
subjects affected / exposed	1 / 160 (0.63%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 1			
Subclavian vein thrombosis				
subjects affected / exposed	1 / 160 (0.63%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Vena cava thrombosis				

subjects affected / exposed	2 / 160 (1.25%)		
occurrences causally related to treatment / all	0 / 2		
deaths causally related to treatment / all	0 / 0		
Hypertensive crisis			
subjects affected / exposed	1 / 160 (0.63%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Hypertensive emergency			
subjects affected / exposed	1 / 160 (0.63%)		
occurrences causally related to treatment / all	0 / 2		
deaths causally related to treatment / all	0 / 0		
Hypotension			
subjects affected / exposed	3 / 160 (1.88%)		
occurrences causally related to treatment / all	1 / 3		
deaths causally related to treatment / all	0 / 0		
Surgical and medical procedures			
Tracheostomy			
subjects affected / exposed	1 / 160 (0.63%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
General disorders and administration site conditions			
Brain death			
subjects affected / exposed	1 / 160 (0.63%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 1		
Catheter site haemorrhage			
subjects affected / exposed	1 / 160 (0.63%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Hyperthermia			
subjects affected / exposed	1 / 160 (0.63%)		
occurrences causally related to treatment / all	1 / 1		
deaths causally related to treatment / all	0 / 0		

Medical Device Complication				
subjects affected / exposed	1 / 160 (0.63%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Multi-organ failure				
subjects affected / exposed	5 / 160 (3.13%)			
occurrences causally related to treatment / all	0 / 5			
deaths causally related to treatment / all	0 / 3			
Systemic inflammatory response syndrome				
subjects affected / exposed	1 / 160 (0.63%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Thrombosis in device				
subjects affected / exposed	1 / 160 (0.63%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Respiratory, thoracic and mediastinal disorders				
Acute pulmonary oedema				
subjects affected / exposed	2 / 160 (1.25%)			
occurrences causally related to treatment / all	0 / 2			
deaths causally related to treatment / all	0 / 0			
Acute respiratory distress syndrome				
subjects affected / exposed	8 / 160 (5.00%)			
occurrences causally related to treatment / all	0 / 9			
deaths causally related to treatment / all	0 / 1			
Acute respiratory failure				
subjects affected / exposed	2 / 160 (1.25%)			
occurrences causally related to treatment / all	0 / 2			
deaths causally related to treatment / all	0 / 0			
Bronchospasm				
subjects affected / exposed	1 / 160 (0.63%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			

Chronic obstructive pulmonary disease				
subjects affected / exposed	1 / 160 (0.63%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 1			
Diaphragmatic paralysis				
subjects affected / exposed	1 / 160 (0.63%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Diffuse alveolar damage				
subjects affected / exposed	1 / 160 (0.63%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Dyspnoea exertional				
subjects affected / exposed	1 / 160 (0.63%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Hypoxia				
subjects affected / exposed	4 / 160 (2.50%)			
occurrences causally related to treatment / all	0 / 5			
deaths causally related to treatment / all	0 / 0			
Organising pneumonia				
subjects affected / exposed	1 / 160 (0.63%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Pleural effusion				
subjects affected / exposed	6 / 160 (3.75%)			
occurrences causally related to treatment / all	0 / 6			
deaths causally related to treatment / all	0 / 0			
Pneumonia aspiration				
subjects affected / exposed	1 / 160 (0.63%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Pneumothorax				

subjects affected / exposed	7 / 160 (4.38%)			
occurrences causally related to treatment / all	0 / 7			
deaths causally related to treatment / all	0 / 1			
Pulmonary embolism				
subjects affected / exposed	1 / 160 (0.63%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Pulmonary necrosis				
subjects affected / exposed	1 / 160 (0.63%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Pulmonary oedema				
subjects affected / exposed	2 / 160 (1.25%)			
occurrences causally related to treatment / all	0 / 2			
deaths causally related to treatment / all	0 / 0			
Respiratory acidosis				
subjects affected / exposed	1 / 160 (0.63%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Respiratory failure				
subjects affected / exposed	13 / 160 (8.13%)			
occurrences causally related to treatment / all	0 / 13			
deaths causally related to treatment / all	0 / 3			
Stridor				
subjects affected / exposed	1 / 160 (0.63%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Tracheomalacia				
subjects affected / exposed	1 / 160 (0.63%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 1			
Psychiatric disorders				
Delirium				

subjects affected / exposed	1 / 160 (0.63%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Investigations			
Electrocardiogram QT prolonged			
subjects affected / exposed	2 / 160 (1.25%)		
occurrences causally related to treatment / all	1 / 2		
deaths causally related to treatment / all	0 / 0		
Platelet count decreased			
subjects affected / exposed	2 / 160 (1.25%)		
occurrences causally related to treatment / all	0 / 2		
deaths causally related to treatment / all	0 / 0		
Injury, poisoning and procedural complications			
Endotracheal intubation complication			
subjects affected / exposed	2 / 160 (1.25%)		
occurrences causally related to treatment / all	0 / 2		
deaths causally related to treatment / all	0 / 0		
Mechanical ventilation complication			
subjects affected / exposed	1 / 160 (0.63%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Pneumothorax traumatic			
subjects affected / exposed	1 / 160 (0.63%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Procedural complication			
subjects affected / exposed	1 / 160 (0.63%)		
occurrences causally related to treatment / all	0 / 2		
deaths causally related to treatment / all	0 / 0		
Vascular pseudoaneurysm			
subjects affected / exposed	1 / 160 (0.63%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		

Cardiac disorders			
Acute coronary syndrome			
subjects affected / exposed	1 / 160 (0.63%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Acute myocardial infarction			
subjects affected / exposed	2 / 160 (1.25%)		
occurrences causally related to treatment / all	0 / 2		
deaths causally related to treatment / all	0 / 1		
Atrial fibrillation			
subjects affected / exposed	12 / 160 (7.50%)		
occurrences causally related to treatment / all	0 / 14		
deaths causally related to treatment / all	0 / 0		
Atrial flutter			
subjects affected / exposed	2 / 160 (1.25%)		
occurrences causally related to treatment / all	0 / 2		
deaths causally related to treatment / all	0 / 0		
Atrioventricular block complete			
subjects affected / exposed	1 / 160 (0.63%)		
occurrences causally related to treatment / all	0 / 2		
deaths causally related to treatment / all	0 / 0		
Bradycardia			
subjects affected / exposed	1 / 160 (0.63%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Bundle branch block left			
subjects affected / exposed	1 / 160 (0.63%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Cardiac arrest			
subjects affected / exposed	3 / 160 (1.88%)		
occurrences causally related to treatment / all	0 / 3		
deaths causally related to treatment / all	0 / 2		
Cardiac disorder			

subjects affected / exposed	1 / 160 (0.63%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Cardiac failure				
subjects affected / exposed	3 / 160 (1.88%)			
occurrences causally related to treatment / all	0 / 3			
deaths causally related to treatment / all	0 / 1			
Cardiac failure acute				
subjects affected / exposed	1 / 160 (0.63%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Cardio-respiratory arrest				
subjects affected / exposed	3 / 160 (1.88%)			
occurrences causally related to treatment / all	0 / 3			
deaths causally related to treatment / all	0 / 1			
Cardiogenic shock				
subjects affected / exposed	4 / 160 (2.50%)			
occurrences causally related to treatment / all	0 / 4			
deaths causally related to treatment / all	0 / 3			
Chordae tendinae rupture				
subjects affected / exposed	1 / 160 (0.63%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Left ventricular failure				
subjects affected / exposed	1 / 160 (0.63%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Mitral valve incompetence				
subjects affected / exposed	1 / 160 (0.63%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 1			
Myocardial infarction				

subjects affected / exposed	1 / 160 (0.63%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Right ventricular failure				
subjects affected / exposed	1 / 160 (0.63%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Sinus bradycardia				
subjects affected / exposed	1 / 160 (0.63%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Ventricular fibrillation				
subjects affected / exposed	2 / 160 (1.25%)			
occurrences causally related to treatment / all	0 / 2			
deaths causally related to treatment / all	0 / 1			
Ventricular tachycardia				
subjects affected / exposed	1 / 160 (0.63%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Nervous system disorders				
Brain injury				
subjects affected / exposed	1 / 160 (0.63%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Cerebral haemorrhage				
subjects affected / exposed	1 / 160 (0.63%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Cerebrovascular accident				
subjects affected / exposed	1 / 160 (0.63%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 1			
critical illness polyneuropathy				

subjects affected / exposed	3 / 160 (1.88%)			
occurrences causally related to treatment / all	0 / 3			
deaths causally related to treatment / all	0 / 0			
Epilepsy				
subjects affected / exposed	1 / 160 (0.63%)			
occurrences causally related to treatment / all	0 / 2			
deaths causally related to treatment / all	0 / 0			
Extrapyramidal disorder				
subjects affected / exposed	1 / 160 (0.63%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Hydrocephalus				
subjects affected / exposed	1 / 160 (0.63%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Ischaemic stroke				
subjects affected / exposed	1 / 160 (0.63%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 1			
Partial seizures				
subjects affected / exposed	1 / 160 (0.63%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Polyneuropathy				
subjects affected / exposed	1 / 160 (0.63%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
VIIth nerve paralysis				
subjects affected / exposed	1 / 160 (0.63%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Vocal cord paralysis				

subjects affected / exposed	1 / 160 (0.63%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Blood and lymphatic system disorders			
Anaemia			
subjects affected / exposed	50 / 160 (31.25%)		
occurrences causally related to treatment / all	0 / 59		
deaths causally related to treatment / all	0 / 0		
Thrombocytopenia			
subjects affected / exposed	8 / 160 (5.00%)		
occurrences causally related to treatment / all	1 / 8		
deaths causally related to treatment / all	0 / 0		
Coagulopathy			
subjects affected / exposed	1 / 160 (0.63%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Haemolysis			
subjects affected / exposed	1 / 160 (0.63%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Heparin-induced thrombocytopenia			
subjects affected / exposed	1 / 160 (0.63%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Hypochromic anaemia			
subjects affected / exposed	1 / 160 (0.63%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Normochromic normocytic anaemia			
subjects affected / exposed	1 / 160 (0.63%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Gastrointestinal disorders			

Abdominal compartment syndrome				
subjects affected / exposed	1 / 160 (0.63%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Gastrointestinal haemorrhage				
subjects affected / exposed	1 / 160 (0.63%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Ileus paralytic				
subjects affected / exposed	4 / 160 (2.50%)			
occurrences causally related to treatment / all	0 / 4			
deaths causally related to treatment / all	0 / 0			
Impaired gastric emptying				
subjects affected / exposed	1 / 160 (0.63%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Intestinal ischaemia				
subjects affected / exposed	1 / 160 (0.63%)			
occurrences causally related to treatment / all	1 / 1			
deaths causally related to treatment / all	0 / 0			
Mouth cyst excision				
subjects affected / exposed	2 / 160 (1.25%)			
occurrences causally related to treatment / all	0 / 2			
deaths causally related to treatment / all	0 / 0			
Retroperitoneal haematoma				
subjects affected / exposed	1 / 160 (0.63%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Upper gastrointestinal haemorrhage				
subjects affected / exposed	1 / 160 (0.63%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Hepatobiliary disorders				

Acute hepatic failure				
subjects affected / exposed	1 / 160 (0.63%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 1			
Cholecystitis acute				
subjects affected / exposed	2 / 160 (1.25%)			
occurrences causally related to treatment / all	0 / 2			
deaths causally related to treatment / all	0 / 0			
Hepatic failure				
subjects affected / exposed	1 / 160 (0.63%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Liver disorder				
subjects affected / exposed	1 / 160 (0.63%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 1			
Skin and subcutaneous tissue disorders				
Skin necrosis				
subjects affected / exposed	1 / 160 (0.63%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Subcutaneous emphysema				
subjects affected / exposed	2 / 160 (1.25%)			
occurrences causally related to treatment / all	0 / 2			
deaths causally related to treatment / all	0 / 0			
Renal and urinary disorders				
Renal failure				
subjects affected / exposed	5 / 160 (3.13%)			
occurrences causally related to treatment / all	0 / 5			
deaths causally related to treatment / all	0 / 0			
Renal failure acute				
subjects affected / exposed	11 / 160 (6.88%)			
occurrences causally related to treatment / all	1 / 11			
deaths causally related to treatment / all	0 / 0			

Renal impairment				
subjects affected / exposed	1 / 160 (0.63%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Musculoskeletal and connective tissue disorders				
Critical illness myopathy				
subjects affected / exposed	6 / 160 (3.75%)			
occurrences causally related to treatment / all	0 / 6			
deaths causally related to treatment / all	0 / 0			
Muscular weakness				
subjects affected / exposed	1 / 160 (0.63%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Myopathy				
subjects affected / exposed	4 / 160 (2.50%)			
occurrences causally related to treatment / all	0 / 4			
deaths causally related to treatment / all	0 / 0			
Rhabdomyolysis				
subjects affected / exposed	1 / 160 (0.63%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Infections and infestations				
Arthritis bacterial				
subjects affected / exposed	1 / 160 (0.63%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Bacteraemia				
subjects affected / exposed	1 / 160 (0.63%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Chronic hepatitis C				
subjects affected / exposed	1 / 160 (0.63%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			

Clostridium difficile colitis			
subjects affected / exposed	2 / 160 (1.25%)		
occurrences causally related to treatment / all	0 / 2		
deaths causally related to treatment / all	0 / 0		
Device related infection			
subjects affected / exposed	6 / 160 (3.75%)		
occurrences causally related to treatment / all	0 / 7		
deaths causally related to treatment / all	0 / 0		
Device related sepsis			
subjects affected / exposed	1 / 160 (0.63%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Empyema			
subjects affected / exposed	1 / 160 (0.63%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Endocarditis			
subjects affected / exposed	2 / 160 (1.25%)		
occurrences causally related to treatment / all	0 / 2		
deaths causally related to treatment / all	0 / 0		
Enterococcal sepsis			
subjects affected / exposed	1 / 160 (0.63%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Gastrointestinal infection			
subjects affected / exposed	1 / 160 (0.63%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Infection			
subjects affected / exposed	1 / 160 (0.63%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Lung abscess			

subjects affected / exposed	1 / 160 (0.63%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Pneumonia				
subjects affected / exposed	13 / 160 (8.13%)			
occurrences causally related to treatment / all	0 / 13			
deaths causally related to treatment / all	0 / 2			
Pneumonia necrotising				
subjects affected / exposed	2 / 160 (1.25%)			
occurrences causally related to treatment / all	0 / 2			
deaths causally related to treatment / all	0 / 0			
Postoperative wound infection				
subjects affected / exposed	1 / 160 (0.63%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Pseudomonas infection				
subjects affected / exposed	1 / 160 (0.63%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Pyelonephritis				
subjects affected / exposed	1 / 160 (0.63%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Sepsis				
subjects affected / exposed	5 / 160 (3.13%)			
occurrences causally related to treatment / all	0 / 5			
deaths causally related to treatment / all	0 / 2			
Septic embolus				
subjects affected / exposed	1 / 160 (0.63%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 1			
Septic shock				

subjects affected / exposed	14 / 160 (8.75%)		
occurrences causally related to treatment / all	0 / 14		
deaths causally related to treatment / all	0 / 8		
Systemic candida			
subjects affected / exposed	1 / 160 (0.63%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Metabolism and nutrition disorders			
Fluid imbalance			
subjects affected / exposed	1 / 160 (0.63%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Hyperkalaemia			
subjects affected / exposed	1 / 160 (0.63%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Hyperglycaemia			
subjects affected / exposed	1 / 160 (0.63%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Metabolic acidosis			
subjects affected / exposed	1 / 160 (0.63%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		

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

Non-serious adverse events	Safety Analysis Set (SAF)		
Total subjects affected by non-serious adverse events			
subjects affected / exposed	150 / 160 (93.75%)		
Vascular disorders			
Hypertension			
subjects affected / exposed	20 / 160 (12.50%)		
occurrences (all)	22		

Hypotension subjects affected / exposed occurrences (all) Phlebitis subjects affected / exposed occurrences (all)	11 / 160 (6.88%) 12 13 / 160 (8.13%) 14		
Cardiac disorders Atrial fibrillation subjects affected / exposed occurrences (all)	 10 / 160 (6.25%) 10		
Blood and lymphatic system disorders Thrombocytopenia subjects affected / exposed occurrences (all) Thrombocytosis subjects affected / exposed occurrences (all)	 12 / 160 (7.50%) 15 8 / 160 (5.00%) 8		
General disorders and administration site conditions Generalised oedema subjects affected / exposed occurrences (all) Oedema peripheral subjects affected / exposed occurrences (all) Pyrexia subjects affected / exposed occurrences (all)	 9 / 160 (5.63%) 9 10 / 160 (6.25%) 12 26 / 160 (16.25%) 38		
Gastrointestinal disorders Constipation subjects affected / exposed occurrences (all) Diarrhoea subjects affected / exposed occurrences (all) Impaired gastric emptying	 21 / 160 (13.13%) 24 13 / 160 (8.13%) 13		

subjects affected / exposed	8 / 160 (5.00%)		
occurrences (all)	8		
Vomiting			
subjects affected / exposed	10 / 160 (6.25%)		
occurrences (all)	14		
Hepatobiliary disorders			
Cholestasis			
subjects affected / exposed	10 / 160 (6.25%)		
occurrences (all)	10		
Skin and subcutaneous tissue disorders			
Rash			
subjects affected / exposed	9 / 160 (5.63%)		
occurrences (all)	9		
Psychiatric disorders			
Agitation			
subjects affected / exposed	13 / 160 (8.13%)		
occurrences (all)	13		
Confusional state			
subjects affected / exposed	12 / 160 (7.50%)		
occurrences (all)	12		
Metabolism and nutrition disorders			
Hyperglycaemia			
subjects affected / exposed	10 / 160 (6.25%)		
occurrences (all)	12		
Hyperkalaemia			
subjects affected / exposed	13 / 160 (8.13%)		
occurrences (all)	13		
Hypernatraemia			
subjects affected / exposed	16 / 160 (10.00%)		
occurrences (all)	16		
Hypoglycaemia			
subjects affected / exposed	13 / 160 (8.13%)		
occurrences (all)	17		
Hypokalaemia			
subjects affected / exposed	13 / 160 (8.13%)		
occurrences (all)	14		
Hypophosphataemia			

subjects affected / exposed occurrences (all)	8 / 160 (5.00%) 13		

More information

Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? Yes

Date	Amendment
23 December 2011	Changes were made to add further details and clarifications regarding assessments including addition of the Glasgow Coma score, to detail the constitution of the Data and Safety Monitoring Board (DSMB), and to correct errors and inconsistencies.
16 July 2013	Changes were made to increase the total number of patients to 160, to add additional countries, to change the study timelines, to include a second interim analysis after treatment of 100 patients, to clarify unblinding rules and consequences of emergency unblinding, update risks and precautions, to clarify follow-up of AEs and SAEs, to amend inclusion criterion 4, to clarify recording of SOFA score, to specify laboratory parameters and include immunological testing, to clarify monitoring procedures, to amend staff details, and to correct minor errors and inconsistencies.
11 September 2013	Country-Specific Protocol Amendment for UK only Changes were made to implement a safety follow-up visit after 5 half-lives of trimodulin on study day 43 including safety lab parameters, ECG, physical examination, vital signs and AE reporting

Notes:

Interruptions (globally)

Were there any global interruptions to the trial? No

Limitations and caveats

None reported