Clinical trial results:
Prospective, phase II/III, randomized clinical study to compare BEGEDINA® versus "conventional treatment" for treating steroid resistant acute graft-versus host disease

Summary

EudraCT number	2015-001360-19
Trial protocol	DE ES GB FR IT
Global end of trial date	31 July 2017

Results information

Result version number	v1 (current)
This version publication date	15 March 2019
First version publication date	15 March 2019

Trial information

Trial identification

Sponsor protocol code	ADN011

Additional study identifiers

ISRCTN number	-
ClinicalTrials.gov id (NCT number)	NCT02411084
WHO universal trial number (UTN)	-
Other trial identifiers	-: -

Notes:

Sponsors

Sponsor organisation name	ADIENNE S.A
Sponsor organisation address	Via Zurigo, 46, Lugano, Switzerland, 6900
Public contact	Clinical Project Manager, ADIENNE S.A, +41 7657305069, renata.palmieri@adienne.com
Scientific contact	Clinical Project Manager, ADIENNE S.A, +41 7657305069, renata.palmieri@adienne.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 June 2018
Is this the analysis of the primary completion data?	Yes
Primary completion date	31 July 2017
Global end of trial reached?	Yes
Global end of trial date	31 July 2017
Was the trial ended prematurely?	Yes

Notes:

General information about the trial

Main objective of the trial:

To determine the efficacy of BEGEDINA® versus conventional therapy in steroid-resistant acute graft-versus-host disease (GvHD) in terms of overall response at 28 days and transplant-related mortality (TRM) up to 180 days.

Protection of trial subjects:

All subjects were free to withdraw from participation in the study at any time, for any reason, specified or unspecified and without prejudice to further treatment.
In case of any intolerable AE or clinically significant laboratory value occurence, which could have compromised the subject's safety, the investigator decided that the subject's treatment should be discontinued for the health and welfare of the subject.
In the situation where subjects needed supportive care, this was administered according to local regulations and standards of care and institutional and international guidelines.
The care included, but was not limited to, the following:
-Oral decontamination and oral hygiene;
-Antibacterial, antiviral, antifungal prophylaxis; notably for: cytomegalovirus (CMV), gram positive (encapsulated) bacteria, Pneumocystis carinii and fungal infections per institutional practice;
-Monitoring and treatment of CMV, Epstein-Barr virus (EBV), human herpesvirus 6 and adenovirus viremia (for "matched unrelated donor" follow specific Epstein-Barr virus monitoring);
-Transfusions of erythrocite and platelet concentrates; all blood products were leukocyte depleted and irradiated;
-Antiemetic prophylaxis and pain therapy.

Background therapy:

During the study period, the subjects were allowed to the following medications and therapies:
-Blood products;
-Steroid therapy and calcineurin inhibitor were allowed as concomitant baseline therapy per protocol;
-Subjects could continue any prior therapy used for prophylaxis at a stable dose from baseline if it has not been discontinued and restarted after initiating steroid treatment for acute GvHD;
-Subjects with stable disease (SD) or progressive disease at Study Day 28 or subjects who cannot tolerate the randomized study treatment received third-line treatment for steroid-resistant acute GvHD;
-Other routine supportive care as per standard practice.

Evidence for comparator:

At the beginning of this clinical trial, there were no approved regimens for the treatment of steroid-refractory acute GvHD in adults. Therefore in the study, the choice of conventional treatment was at the discretion of the investigator (physician's best choice).
The study design was unblinded, because the administration schedule could have varied between the different conventional treatments chosen and also between the conventional treatments and BEGEDINA.

Actual start date of recruitment	19 February 2016
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: 10
Country: Number of subjects enrolled	France: 7
Country: Number of subjects enrolled	Germany: 1
Country: Number of subjects enrolled	Italy: 6
Country: Number of subjects enrolled	United States: 12
Worldwide total number of subjects	36
EEA total number of subjects	24

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)	35
From 65 to 84 years	1
85 years and over	0

Subject disposition

Recruitment

Recruitment details:

Out of the 29 sites selected (USA, France, Italy, Spain, Switzerland, UK, Germany) for participation in this study, 22 of them have activated screening and enrolment procedures, and 15 sites have effectively enrolled and randomized participants in the study. The first site approved was in Spain on 07 October 2015.

Pre-assignment

Screening details:

Out of 184 subjects planned, 37 subjects were screened and 36 subjects were randomized by IVRS in a 1:1 ratio. All subjects signed the informed consent and met all eligibility criteria except one case that had an incomplete screening procedure (some blood tests have not been performed for the screening visit as requested by the protocol).

Period 1

Period 1 title	Baseline
Is this the baseline period?	Yes
Allocation method	Randomised - controlled
Blinding used	Not blinded

Blinding implementation details:

The study team of the Sponsor and CRO (except the on-site monitors, pharmacovigilance and personnel as specified in the study-specific
blinding plan), were blinded regarding the study treatment up to database lock and general unblinding. The same applied for the independent hematologist who evaluated the response.
The DSMB members received unblinded outputs generated by a dedicated unblinded statistician and statistical programmer (both separated from the blinded study team members).

Arms

Are arms mutually exclusive?	Yes
Arm title	BEGEDINA

Arm description: -

Arm type	Experimental
Investigational medicinal product name	BEGEDINA
Investigational medicinal product code	
Other name	Begelomab
Pharmaceutical forms	Concentrate for solution for infusion
Routes of administration	Intravenous use, Parenteral use

Dosage and administration details:

Subjects have received BEGEDINA 2.7 mg/m2/day IV for 5 consecutive days (Study Days 1, 2, 3, 4, 5) and then on Study Days 10, 14, 17, 21, 24 and 28, for a total of 11 doses. A window (+/- 1 day) was permitted for doses from Day 10 to Day 28, however, all efforts have been made to plan these doses with at least 48 hours between doses.
The total volume of BEGEDINA to be administered was diluted in 100 mL of sodium chloride 9 mg/mL (0.9%) solution for injection prior to administration. The infusion lasted for 60 minutes.

Arm title	Conventional Treatment

Arm description: -

Arm type	Active comparator
Investigational medicinal product name	Entanercept
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Solution for injection
Routes of administration	Subcutaneous use

Dosage and administration details:

Dose: 25mg - administered in accordance with SPC

Investigational medicinal product name	Extracorporeal photopheresis
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Capsule
Routes of administration	Extracorporeal use

Dosage and administration details:

The dose was established by the physician for each patient depending on the weight.

Investigational medicinal product name	Antithymocyte globulin
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Solution for infusion
Routes of administration	Intravenous use

Dosage and administration details:

Dose: 100mg once per day

Investigational medicinal product name	Mycophenolate Mofetil
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Tablet
Routes of administration	Oral use

Dosage and administration details:

Dose: 1000mg/8 hours or 1000mg/12 hours

Investigational medicinal product name	Tacrolimus
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Capsule
Routes of administration	Oral use

Dosage and administration details:

Dose: 0.5 mg twice per day

Investigational medicinal product name	Ruxolitinib
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Tablet
Routes of administration	Oral use

Dosage and administration details:

Dose: 5mg twice per day, or 10 mg twice per day

Investigational medicinal product name	Methoxsalen
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Injection
Routes of administration	Parenteral use

Dosage and administration details:

Dose: 200mcg according to SPC

Investigational medicinal product name	Tocilizumab
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Solution for infusion
Routes of administration	Intravenous use

Dosage and administration details:

Dose 500mg

Number of subjects in period 1	BEGEDINA	Conventional Treatment
Started	18	18
Completed	18	18

Period 2	
Period 2 title	End of treatment (Day 28)
Is this the baseline period?	No
Allocation method	Randomised - controlled
Blinding used	Not blinded

Arms	
Are arms mutually exclusive?	Yes
Arm title	BEGEDINA

Arm description: -

Arm type	Experimental
Investigational medicinal product name	BEGEDINA
Investigational medicinal product code	
Other name	Begelomab
Pharmaceutical forms	Concentrate for solution for infusion
Routes of administration	Intravenous use, Parenteral use

Dosage and administration details:

Subjects have received BEGEDINA 2.7 mg/m2/day IV for 5 consecutive days (Study Days 1, 2, 3, 4, 5) and then on Study Days 10, 14, 17, 21, 24 and 28, for a total of 11 doses. A window (+/- 1 day) was permitted for doses from Day 10 to Day 28, however, all efforts have been made to plan these doses with at least 48 hours between doses.
The total volume of BEGEDINA to be administered was diluted in 100 mL of sodium chloride 9 mg/mL (0.9%) solution for injection prior to administration. The infusion lasted for 60 minutes.

Arm title	Conventional Treatment

Arm description: -

Arm type	Active comparator
Investigational medicinal product name	Entanercept
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Solution for injection
Routes of administration	Subcutaneous use

Dosage and administration details:

Dose: 25mg - administered in accordance with PCR

Investigational medicinal product name	Extracorporeal photopheresis
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Capsule
Routes of administration	Parenteral use

Dosage and administration details:

The dose was established by the physician for each patient, depending on the weight.

Investigational medicinal product name	Antithymocyte globulin
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Solution for infusion
Routes of administration	Intravenous use
Dosage and administration details: Dose: 100mg QOD	
Investigational medicinal product name	Mycophenolate Mofetil
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Tablet
Routes of administration	Oral use
Dosage and administration details: Dose: 1000mg/8 hours or 1000mg/12 hours	
Investigational medicinal product name	Tacrolimus
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Capsule
Routes of administration	Oral use
Dosage and administration details: Dose: 0.5 mg twice a day	
Investigational medicinal product name	Ruxolitinib
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Tablet
Routes of administration	Oral use
Dosage and administration details: Dose: 5mg twice per day, or 10 mg twice per day	
Investigational medicinal product name	Methoxsalen
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Injection
Routes of administration	Parenteral use
Dosage and administration details: Dose: 200mcg according to PCR	

Number of subjects in period 2	BEGEDINA	Conventional Treatment
Started	18	18
Completed	5	5
Not completed	13	13
Adverse event, serious fatal	5	4
Adverse event, non-fatal	2	1
Other reasons	-	5
Lack of efficacy	6	3

Period 3

Period 3 title	End of Study (Day 180)
Is this the baseline period?	No
Allocation method	Randomised - controlled
Blinding used	Not blinded

Arms

Are arms mutually exclusive?	Yes
Arm title	BEGEDINA

Arm description: -

Arm type	Experimental
Investigational medicinal product name	BEGEDINA
Investigational medicinal product code	
Other name	Begelomab
Pharmaceutical forms	Concentrate for solution for infusion
Routes of administration	Intravenous use, Parenteral use

Dosage and administration details:

Subjects have received BEGEDINA 2.7 mg/m2/day IV for 5 consecutive days (Study Days 1, 2, 3, 4, 5) and then on Study Days 10, 14, 17, 21, 24 and 28, for a total of 11 doses. A window (+/- 1 day) was permitted for doses from Day 10 to Day 28, however, all efforts have been made to plan these doses with at least 48 hours between doses.
The total volume of BEGEDINA to be administered was diluted in 100 mL of sodium chloride 9 mg/mL (0.9%) solution for injection prior to administration. The infusion lasted for 60 minutes.

Arm title	Conventional Treatment

Arm description: -

Arm type	Active comparator
Investigational medicinal product name	Entanercept
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Solution for injection
Routes of administration	Subcutaneous use

Dosage and administration details:

Dose: 25mg - administered in accordance with PCR

Investigational medicinal product name	Extracorporeal photopheresis
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Capsule
Routes of administration	Parenteral use

Dosage and administration details:

The dose was established by the physician for each patient, depending on the weight.

Investigational medicinal product name	Antithymocyte globulin
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Solution for infusion
Routes of administration	Intravenous use

Dosage and administration details:

Dose: 100mg QOD

Investigational medicinal product name	Mycophenolate Mofetil
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Tablet
Routes of administration	Oral use

Dosage and administration details:

Dose: 1000mg/8 hours or 1000mg/12 hours

Investigational medicinal product name	Tacrolimus
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Capsule
Routes of administration	Oral use

Dosage and administration details:

Dose: 0.5 mg twice a day

Investigational medicinal product name	Ruxolitinib
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Tablet
Routes of administration	Oral use

Dosage and administration details:

Dose: 5mg twice per day, or 10 mg twice per day

Investigational medicinal product name	Methoxsalen
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Injection
Routes of administration	Parenteral use

Dosage and administration details:

Dose: 200mcg according to PCR

Number of subjects in period 3	BEGEDINA	Conventional Treatment
Started	5	5
Completed	2	4
Not completed	3	1
Adverse event, serious fatal	2	1
Adverse event, non-fatal	1	-

Baseline characteristics

Reporting groups	
Reporting group title	BEGEDINA
Reporting group description: -	
Reporting group title	Conventional Treatment
Reporting group description: -	

Reporting group values	BEGEDINA	Conventional Treatment	Total
Number of subjects	18	18	36
Age categorical Units: Subjects			
In utero	0	0	0
Preterm newborn infants (gestational age < 37 wks)	0	0	0
Newborns (0-27 days)	0	0	0
Infants and toddlers (28 days-23 months)	0	0	0
Children (2-11 years)	0	0	0
Adolescents (12-17 years)	0	0	0
Adults (18-64 years)	17	18	35
From 65-84 years	1	0	1
85 years and over	0	0	0
Gender categorical Units: Subjects			
Female	5	7	12
Male	13	11	24

End points

End points reporting groups

Reporting group title	BEGEDINA
Reporting group description: -	
Reporting group title	Conventional Treatment
Reporting group description: -	
Reporting group title	BEGEDINA
Reporting group description: -	
Reporting group title	Conventional Treatment
Reporting group description: -	
Reporting group title	BEGEDINA
Reporting group description: -	
Reporting group title	Conventional Treatment
Reporting group description: -	

Primary: Efficacy

End point title	Efficacy[1]

End point description:

Analysis of primary efficacy endpoints could not be perfomed because of the premature discontinuation of the study.

End point type	Primary

End point timeframe:

Day 180

Notes:

[1] - No statistical analyses have been specified for this primary end point. It is expected there is at least one statistical analysis for each primary end point.
Justification: The statistical analysis of primary efficacy endpoints could not be performed because of the premature discontinuation of the study.

End point values	BEGEDINA	Conventional Treatment	BEGEDINA	Conventional Treatment
Subject group type	Reporting group	Reporting group	Reporting group	Reporting group
Number of subjects analysed	18	18	5	5
Units: percentage	18	18	5	5

End point values	BEGEDINA	Conventional Treatment		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	2	4		
Units: percentage	2	4		

Statistical analyses

No statistical analyses for this end point

Secondary: Safety

End point title	Safety

End point description:

The secondary safety objectives were:
-to compare the safety and tolerability of BEGEDINA and conventional therapy.
-to gather additional information on the safety of BEGEDINA in subjects with Grades II-IV acute GvHD, who have failed to respond to steroid treatment.
-to evaluate the immunogenicity of BEGEDINA
- to evaluate the effect of BEGEDINA on glucose metabolism.
-to compare the incidence of second malignancies at the end of the follow-up between BEGEDINA and convetional therapy

End point type	Secondary

End point timeframe:

Day 0 until Day 180.

End point values	BEGEDINA	Conventional Treatment	BEGEDINA	Conventional Treatment
Subject group type	Reporting group	Reporting group	Reporting group	Reporting group
Number of subjects analysed	18	18	5	5
Units: percentage	18	18	5	5

End point values	BEGEDINA	Conventional Treatment		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	2	4		
Units: percentage	2	4		

Statistical analyses

No statistical analyses for this end point

Adverse events

Adverse events information

Timeframe for reporting adverse events:

A total of 650 adverse events were recorded during the study, almost similar distributed in both groups: 326 cases in BEGEDINA® group (301 non–serious AEs and 25 serious AEs) vs 324 cases in Conventional treatment group (295 non-serious and 29 serious)

Adverse event reporting additional description:

Information about all AEs, whether volunteered by the subjects, discovered by investigator questioning, or detected through physical examination, laboratory test or other means, were collected and recorded on the eCRF AE section.

Assessment type	Systematic

Dictionary used

Dictionary name	MedDRA
Dictionary version	19.0

Reporting groups

Reporting group title	BEGEDINA group

Reporting group description:

The most frequent adverse events recorded after administration of BEGEDINA® were platelet count decreased (19.4% cases), anemia (16.7% cases), leukocytes count decreased (11.1% cases). Cytomegalovirus infection was found in 16.7% cases and peripheral edema in 13.9% cases.
There were recorded 25 serious adverse events. At the end of the study rate of serious adverse events which determined early discontinuation in BEGEDINA® group was 22.2 % (4 subjects). At the end of the study (approx. day 180), death occurred in 36.1 % (13 subjects) in BEGEDINA® group.

Reporting group title	Conventional treatment

Reporting group description:

The most frequent adverse events recorded in the conventional treatment arm were peripheral edema(22.2% cases), pyrexia (19.4% cases). Cytomegalovirus infection was found in 13.9% cases. There were recorded 29 serious adverse events.
At Day 28, death occurred in 11.1% cases in this treatment group. At the end of the study rate of serious adverse events which determined early discontinuation in conventional treatment arm was 5.6 % (one subject). Mortality (approx. day 180) was 22.2 % (8 subjects) in the conventional treatment group.

Serious adverse events	BEGEDINA group	Conventional treatment	
Total subjects affected by serious adverse events			
subjects affected / exposed	16 / 18 (88.89%)	13 / 18 (72.22%)	
number of deaths (all causes)	13	8	
number of deaths resulting from adverse events	13	8	
Neoplasms benign, malignant and unspecified (incl cysts and polyps)			
Chronic myeloid leukaemia			
subjects affected / exposed	0 / 18 (0.00%)	1 / 18 (5.56%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 1	
Vascular disorders			
Shock haemorrhagic			

subjects affected / exposed	0 / 18 (0.00%)	1 / 18 (5.56%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 1	
General disorders and administration site conditions			
Pyrexia			
subjects affected / exposed	0 / 18 (0.00%)	1 / 18 (5.56%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Multiple organ dysfunction syndrome			
subjects affected / exposed	1 / 18 (5.56%)	0 / 18 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 1	0 / 0	
Immune system disorders			
Graft versus host disease			
subjects affected / exposed	2 / 18 (11.11%)	1 / 18 (5.56%)	
occurrences causally related to treatment / all	0 / 2	0 / 1	
deaths causally related to treatment / all	0 / 1	0 / 1	
Graft versus host disease in liver			
subjects affected / exposed	0 / 18 (0.00%)	1 / 18 (5.56%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 1	
Acute graft versus host disease			
subjects affected / exposed	2 / 18 (11.11%)	0 / 18 (0.00%)	
occurrences causally related to treatment / all	0 / 2	0 / 0	
deaths causally related to treatment / all	0 / 2	0 / 0	
Acute graft versus host disease in skin			
subjects affected / exposed	0 / 18 (0.00%)	1 / 18 (5.56%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Respiratory, thoracic and mediastinal disorders			
Dyspnoea			

subjects affected / exposed	0 / 18 (0.00%)	1 / 18 (5.56%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Lung disorder			
subjects affected / exposed	1 / 18 (5.56%)	1 / 18 (5.56%)	
occurrences causally related to treatment / all	1 / 1	0 / 1	
deaths causally related to treatment / all	1 / 1	0 / 0	
Obliterative bronchiolitis			
subjects affected / exposed	0 / 18 (0.00%)	1 / 18 (5.56%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 1	
Pulmonary embolism			
subjects affected / exposed	0 / 18 (0.00%)	1 / 18 (5.56%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Respiratory distress			
subjects affected / exposed	1 / 18 (5.56%)	0 / 18 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Respiratory failure			
subjects affected / exposed	1 / 18 (5.56%)	0 / 18 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 1	0 / 0	
Injury, poisoning and procedural complications			
Rib fracture			
subjects affected / exposed	0 / 18 (0.00%)	1 / 18 (5.56%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Cardiac disorders			
Cardiac arrest			
subjects affected / exposed	1 / 18 (5.56%)	0 / 18 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 1	0 / 0	

Nervous system disorders			
Cerebral haemorrhage			
subjects affected / exposed	1 / 18 (5.56%)	1 / 18 (5.56%)	
occurrences causally related to treatment / all	0 / 1	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 1	
Blood and lymphatic system disorders			
Febrile neutropenia			
subjects affected / exposed	1 / 18 (5.56%)	1 / 18 (5.56%)	
occurrences causally related to treatment / all	0 / 1	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Gastrointestinal disorders			
Gastrointestinal haemorrhage			
subjects affected / exposed	0 / 18 (0.00%)	1 / 18 (5.56%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pneumoperitoneum			
subjects affected / exposed	0 / 18 (0.00%)	1 / 18 (5.56%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Hepatobiliary disorders			
Hepatic failure			
subjects affected / exposed	1 / 18 (5.56%)	0 / 18 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 1	0 / 0	
Cholecystitis			
subjects affected / exposed	0 / 18 (0.00%)	1 / 18 (5.56%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Skin and subcutaneous tissue disorders			
Rash maculo-papular			
subjects affected / exposed	1 / 18 (5.56%)	0 / 18 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Renal and urinary disorders			
Haematuria			

subjects affected / exposed	0 / 18 (0.00%)	1 / 18 (5.56%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Acute kidney injury			
subjects affected / exposed	1 / 18 (5.56%)	0 / 18 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Infections and infestations			
Cytomegalovirus infection			
subjects affected / exposed	0 / 18 (0.00%)	2 / 18 (11.11%)	
occurrences causally related to treatment / all	0 / 0	4 / 4	
deaths causally related to treatment / all	0 / 0	0 / 0	
Diverticulitis			
subjects affected / exposed	0 / 18 (0.00%)	1 / 18 (5.56%)	
occurrences causally related to treatment / all	0 / 0	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Fungal infection			
subjects affected / exposed	1 / 18 (5.56%)	0 / 18 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pneumonia			
subjects affected / exposed	1 / 18 (5.56%)	1 / 18 (5.56%)	
occurrences causally related to treatment / all	0 / 1	0 / 1	
deaths causally related to treatment / all	0 / 1	0 / 1	
Sepsis			
subjects affected / exposed	2 / 18 (11.11%)	1 / 18 (5.56%)	
occurrences causally related to treatment / all	0 / 2	0 / 1	
deaths causally related to treatment / all	0 / 1	0 / 0	
Septic shock			
subjects affected / exposed	3 / 18 (16.67%)	1 / 18 (5.56%)	
occurrences causally related to treatment / all	1 / 3	0 / 1	
deaths causally related to treatment / all	0 / 1	0 / 0	
Cytomegalovirus enteritis			

subjects affected / exposed	1 / 18 (5.56%)	1 / 18 (5.56%)	
occurrences causally related to treatment / all	1 / 1	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Bacterial sepsis			
subjects affected / exposed	1 / 18 (5.56%)	0 / 18 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 1	0 / 0	
Phlebitis infective			
subjects affected / exposed	1 / 18 (5.56%)	0 / 18 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pneumonia bacterial			
subjects affected / exposed	0 / 18 (0.00%)	1 / 18 (5.56%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 1	
Device related infection			
subjects affected / exposed	0 / 18 (0.00%)	1 / 18 (5.56%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Metabolism and nutrition disorders			
Hypokalaemia			
subjects affected / exposed	1 / 18 (5.56%)	0 / 18 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	

Frequency threshold for reporting non-serious adverse events: 0 %

Non-serious adverse events	BEGEDINA group	Conventional treatment	
Total subjects affected by non-serious adverse events			
subjects affected / exposed	18 / 18 (100.00%)	18 / 18 (100.00%)	
Vascular disorders			
Flushing			
subjects affected / exposed	0 / 18 (0.00%)	1 / 18 (5.56%)	
occurrences (all)	0	1	

Hypertension			
subjects affected / exposed	2 / 18 (11.11%)	5 / 18 (27.78%)	
occurrences (all)	2	5	
Hypotension			
subjects affected / exposed	3 / 18 (16.67%)	4 / 18 (22.22%)	
occurrences (all)	3	4	
Shock			
subjects affected / exposed	1 / 18 (5.56%)	0 / 18 (0.00%)	
occurrences (all)	1	0	
Deep vein thrombosis			
subjects affected / exposed	1 / 18 (5.56%)	1 / 18 (5.56%)	
occurrences (all)	1	1	
Superior vena cava occlusion			
subjects affected / exposed	1 / 18 (5.56%)	0 / 18 (0.00%)	
occurrences (all)	1	0	
Surgical and medical procedures			
Transurethral bladder resection			
subjects affected / exposed	0 / 18 (0.00%)	1 / 18 (5.56%)	
occurrences (all)	0	1	
General disorders and administration site conditions			
Asthenia			
subjects affected / exposed	0 / 18 (0.00%)	2 / 18 (11.11%)	
occurrences (all)	0	2	
Chest pain			
subjects affected / exposed	0 / 18 (0.00%)	1 / 18 (5.56%)	
occurrences (all)	0	1	
Face oedema			
subjects affected / exposed	0 / 18 (0.00%)	1 / 18 (5.56%)	
occurrences (all)	0	2	
Fatigue			
subjects affected / exposed	3 / 18 (16.67%)	3 / 18 (16.67%)	
occurrences (all)	4	6	
Gait disturbance			
subjects affected / exposed	0 / 18 (0.00%)	1 / 18 (5.56%)	
occurrences (all)	0	1	
Hypothermia			

subjects affected / exposed	1 / 18 (5.56%)	0 / 18 (0.00%)	
occurrences (all)	1	0	
Malaise			
subjects affected / exposed	0 / 18 (0.00%)	1 / 18 (5.56%)	
occurrences (all)	0	1	
Oedema peripheral			
subjects affected / exposed	5 / 18 (27.78%)	8 / 18 (44.44%)	
occurrences (all)	7	9	
Non-cardiac chest pain			
subjects affected / exposed	0 / 18 (0.00%)	1 / 18 (5.56%)	
occurrences (all)	0	1	
Localised oedema			
subjects affected / exposed	1 / 18 (5.56%)	0 / 18 (0.00%)	
occurrences (all)	1	0	
Pyrexia			
subjects affected / exposed	3 / 18 (16.67%)	6 / 18 (33.33%)	
occurrences (all)	4	7	
Immune system disorders			
Hypogammaglobulinaemia			
subjects affected / exposed	1 / 18 (5.56%)	1 / 18 (5.56%)	
occurrences (all)	1	1	
Graft versus host disease in gastrointestinal tract			
subjects affected / exposed	2 / 18 (11.11%)	0 / 18 (0.00%)	
occurrences (all)	2	0	
Graft versus host disease in liver			
subjects affected / exposed	2 / 18 (11.11%)	0 / 18 (0.00%)	
occurrences (all)	2	0	
Acute graft versus host disease			
subjects affected / exposed	0 / 18 (0.00%)	1 / 18 (5.56%)	
occurrences (all)	0	1	
Reproductive system and breast disorders			
Menorrhagia			
subjects affected / exposed	0 / 18 (0.00%)	1 / 18 (5.56%)	
occurrences (all)	0	1	
Oedema genital			

subjects affected / exposed	1 / 18 (5.56%)	0 / 18 (0.00%)	
occurrences (all)	1	0	
Pelvic pain			
subjects affected / exposed	0 / 18 (0.00%)	1 / 18 (5.56%)	
occurrences (all)	0	1	
Penile pain			
subjects affected / exposed	0 / 18 (0.00%)	1 / 18 (5.56%)	
occurrences (all)	0	1	
Respiratory, thoracic and mediastinal disorders			
Acute pulmonary oedema			
subjects affected / exposed	1 / 18 (5.56%)	0 / 18 (0.00%)	
occurrences (all)	1	0	
Acute respiratory failure			
subjects affected / exposed	1 / 18 (5.56%)	0 / 18 (0.00%)	
occurrences (all)	1	0	
Aspiration			
subjects affected / exposed	0 / 18 (0.00%)	1 / 18 (5.56%)	
occurrences (all)	0	1	
Epistaxis			
subjects affected / exposed	1 / 18 (5.56%)	1 / 18 (5.56%)	
occurrences (all)	1	1	
Hiccups			
subjects affected / exposed	2 / 18 (11.11%)	0 / 18 (0.00%)	
occurrences (all)	2	0	
Hypoxia			
subjects affected / exposed	1 / 18 (5.56%)	0 / 18 (0.00%)	
occurrences (all)	1	0	
Pleural effusion			
subjects affected / exposed	2 / 18 (11.11%)	0 / 18 (0.00%)	
occurrences (all)	2	0	
Pneumonia aspiration			
subjects affected / exposed	1 / 18 (5.56%)	0 / 18 (0.00%)	
occurrences (all)	1	0	
Pneumonitis			

subjects affected / exposed	0 / 18 (0.00%)	1 / 18 (5.56%)	
occurrences (all)	0	1	
Pulmonary oedema			
subjects affected / exposed	1 / 18 (5.56%)	0 / 18 (0.00%)	
occurrences (all)	1	0	
Dyspnoea			
subjects affected / exposed	1 / 18 (5.56%)	1 / 18 (5.56%)	
occurrences (all)	1	1	
Pulmonary embolism			
subjects affected / exposed	0 / 18 (0.00%)	1 / 18 (5.56%)	
occurrences (all)	0	1	
Psychiatric disorders			
Adjustment disorder with depressed mood			
subjects affected / exposed	0 / 18 (0.00%)	1 / 18 (5.56%)	
occurrences (all)	0	1	
Anxiety			
subjects affected / exposed	4 / 18 (22.22%)	2 / 18 (11.11%)	
occurrences (all)	5	3	
Apathy			
subjects affected / exposed	0 / 18 (0.00%)	1 / 18 (5.56%)	
occurrences (all)	0	1	
Confusional state			
subjects affected / exposed	3 / 18 (16.67%)	0 / 18 (0.00%)	
occurrences (all)	4	0	
Delirium			
subjects affected / exposed	1 / 18 (5.56%)	0 / 18 (0.00%)	
occurrences (all)	1	0	
Depressed mood			
subjects affected / exposed	0 / 18 (0.00%)	1 / 18 (5.56%)	
occurrences (all)	0	1	
Depression			
subjects affected / exposed	2 / 18 (11.11%)	2 / 18 (11.11%)	
occurrences (all)	2	2	
Disorientation			

subjects affected / exposed	0 / 18 (0.00%)	1 / 18 (5.56%)	
occurrences (all)	0	1	
Hallucination			
subjects affected / exposed	1 / 18 (5.56%)	0 / 18 (0.00%)	
occurrences (all)	1	0	
Hallucination, auditory			
subjects affected / exposed	1 / 18 (5.56%)	0 / 18 (0.00%)	
occurrences (all)	1	0	
Insomnia			
subjects affected / exposed	1 / 18 (5.56%)	1 / 18 (5.56%)	
occurrences (all)	1	1	
Mental status changes			
subjects affected / exposed	0 / 18 (0.00%)	1 / 18 (5.56%)	
occurrences (all)	0	1	
Bradyphrenia			
subjects affected / exposed	0 / 18 (0.00%)	1 / 18 (5.56%)	
occurrences (all)	0	1	
Investigations			
Alanine aminotransferase increased			
subjects affected / exposed	2 / 18 (11.11%)	1 / 18 (5.56%)	
occurrences (all)	7	1	
Aspartate aminotransferase increased			
subjects affected / exposed	1 / 18 (5.56%)	1 / 18 (5.56%)	
occurrences (all)	1	2	
Blood bilirubin increased			
subjects affected / exposed	5 / 18 (27.78%)	1 / 18 (5.56%)	
occurrences (all)	10	1	
Blood creatine increased			
subjects affected / exposed	2 / 18 (11.11%)	0 / 18 (0.00%)	
occurrences (all)	2	0	
Blood lactate dehydrogenase increased			
subjects affected / exposed	1 / 18 (5.56%)	1 / 18 (5.56%)	
occurrences (all)	1	1	
Blood magnesium decreased			

subjects affected / exposed	1 / 18 (5.56%)	0 / 18 (0.00%)	
occurrences (all)	1	0	
Blood potassium decreased			
subjects affected / exposed	1 / 18 (5.56%)	0 / 18 (0.00%)	
occurrences (all)	1	0	
Blood triglycerides increased			
subjects affected / exposed	0 / 18 (0.00%)	1 / 18 (5.56%)	
occurrences (all)	0	1	
Gamma-glutamyltransferase increased			
subjects affected / exposed	2 / 18 (11.11%)	0 / 18 (0.00%)	
occurrences (all)	2	0	
Haptoglobin decreased			
subjects affected / exposed	1 / 18 (5.56%)	0 / 18 (0.00%)	
occurrences (all)	1	0	
International normalised ratio increased			
subjects affected / exposed	1 / 18 (5.56%)	0 / 18 (0.00%)	
occurrences (all)	3	0	
Low density lipoprotein increased			
subjects affected / exposed	1 / 18 (5.56%)	0 / 18 (0.00%)	
occurrences (all)	1	0	
Lymphocyte count decreased			
subjects affected / exposed	3 / 18 (16.67%)	2 / 18 (11.11%)	
occurrences (all)	7	5	
Neutrophil count decreased			
subjects affected / exposed	2 / 18 (11.11%)	2 / 18 (11.11%)	
occurrences (all)	5	2	
Platelet count decreased			
subjects affected / exposed	7 / 18 (38.89%)	1 / 18 (5.56%)	
occurrences (all)	24	6	
Weight decreased			
subjects affected / exposed	2 / 18 (11.11%)	0 / 18 (0.00%)	
occurrences (all)	2	0	
Weight increased			

subjects affected / exposed	1 / 18 (5.56%)	1 / 18 (5.56%)	
occurrences (all)	1	1	
White blood cell count decreased			
subjects affected / exposed	4 / 18 (22.22%)	2 / 18 (11.11%)	
occurrences (all)	8	2	
Transaminases increased			
subjects affected / exposed	0 / 18 (0.00%)	2 / 18 (11.11%)	
occurrences (all)	0	2	
Troponin increased			
subjects affected / exposed	0 / 18 (0.00%)	1 / 18 (5.56%)	
occurrences (all)	0	1	
Blood alkaline phosphatase increased			
subjects affected / exposed	1 / 18 (5.56%)	0 / 18 (0.00%)	
occurrences (all)	2	0	
Staphylococcus test positive			
subjects affected / exposed	0 / 18 (0.00%)	1 / 18 (5.56%)	
occurrences (all)	0	2	
Klebsiella test positive			
subjects affected / exposed	0 / 18 (0.00%)	1 / 18 (5.56%)	
occurrences (all)	0	1	
Liver function test increased			
subjects affected / exposed	1 / 18 (5.56%)	0 / 18 (0.00%)	
occurrences (all)	1	0	
Injury, poisoning and procedural complications			
Fall			
subjects affected / exposed	1 / 18 (5.56%)	4 / 18 (22.22%)	
occurrences (all)	1	5	
Excoriation			
subjects affected / exposed	0 / 18 (0.00%)	1 / 18 (5.56%)	
occurrences (all)	0	1	
Rib fracture			
subjects affected / exposed	0 / 18 (0.00%)	1 / 18 (5.56%)	
occurrences (all)	0	1	
Cardiac disorders			

Palpitations			
subjects affected / exposed	0 / 18 (0.00%)	1 / 18 (5.56%)	
occurrences (all)	0	1	
Sinus tachycardia			
subjects affected / exposed	1 / 18 (5.56%)	0 / 18 (0.00%)	
occurrences (all)	1	0	
Tachycardia			
subjects affected / exposed	2 / 18 (11.11%)	0 / 18 (0.00%)	
occurrences (all)	2	0	
Left ventricular hypertrophy			
subjects affected / exposed	0 / 18 (0.00%)	1 / 18 (5.56%)	
occurrences (all)	0	1	
Cardiac disorder			
subjects affected / exposed	0 / 18 (0.00%)	1 / 18 (5.56%)	
occurrences (all)	0	1	
Mitral valve disease			
subjects affected / exposed	0 / 18 (0.00%)	1 / 18 (5.56%)	
occurrences (all)	0	1	
Nervous system disorders			
Dizziness			
subjects affected / exposed	0 / 18 (0.00%)	2 / 18 (11.11%)	
occurrences (all)	0	2	
Dysgeusia			
subjects affected / exposed	1 / 18 (5.56%)	0 / 18 (0.00%)	
occurrences (all)	1	0	
Encephalopathy			
subjects affected / exposed	1 / 18 (5.56%)	0 / 18 (0.00%)	
occurrences (all)	1	0	
Haemorrhage intracranial			
subjects affected / exposed	1 / 18 (5.56%)	0 / 18 (0.00%)	
occurrences (all)	1	0	
Headache			
subjects affected / exposed	1 / 18 (5.56%)	0 / 18 (0.00%)	
occurrences (all)	2	0	
Hemiparesis			

subjects affected / exposed	0 / 18 (0.00%)	1 / 18 (5.56%)	
occurrences (all)	0	1	
Intention tremor			
subjects affected / exposed	0 / 18 (0.00%)	1 / 18 (5.56%)	
occurrences (all)	0	1	
Memory impairment			
subjects affected / exposed	0 / 18 (0.00%)	1 / 18 (5.56%)	
occurrences (all)	0	1	
Neuropathy peripheral			
subjects affected / exposed	0 / 18 (0.00%)	1 / 18 (5.56%)	
occurrences (all)	0	1	
Palmar-plantar erythrodysaesthesia syndrome			
subjects affected / exposed	0 / 18 (0.00%)	1 / 18 (5.56%)	
occurrences (all)	0	1	
Paraesthesia			
subjects affected / exposed	0 / 18 (0.00%)	1 / 18 (5.56%)	
occurrences (all)	0	1	
Somnolence			
subjects affected / exposed	1 / 18 (5.56%)	1 / 18 (5.56%)	
occurrences (all)	1	1	
Spinal cord compression			
subjects affected / exposed	0 / 18 (0.00%)	1 / 18 (5.56%)	
occurrences (all)	0	1	
Syncope			
subjects affected / exposed	0 / 18 (0.00%)	1 / 18 (5.56%)	
occurrences (all)	0	1	
Tremor			
subjects affected / exposed	1 / 18 (5.56%)	3 / 18 (16.67%)	
occurrences (all)	1	3	
Blood and lymphatic system disorders			
Anaemia			
subjects affected / exposed	6 / 18 (33.33%)	4 / 18 (22.22%)	
occurrences (all)	11	6	
Leukopenia			

subjects affected / exposed	0 / 18 (0.00%)	1 / 18 (5.56%)	
occurrences (all)	0	1	
Neutropenia			
subjects affected / exposed	2 / 18 (11.11%)	2 / 18 (11.11%)	
occurrences (all)	3	2	
Neutrophilia			
subjects affected / exposed	0 / 18 (0.00%)	1 / 18 (5.56%)	
occurrences (all)	0	1	
Thrombocytopenia			
subjects affected / exposed	0 / 18 (0.00%)	3 / 18 (16.67%)	
occurrences (all)	0	3	
Ear and labyrinth disorders			
Vertigo			
subjects affected / exposed	1 / 18 (5.56%)	1 / 18 (5.56%)	
occurrences (all)	1	1	
Eustachian tube disorder			
subjects affected / exposed	1 / 18 (5.56%)	0 / 18 (0.00%)	
occurrences (all)	1	0	
Eye disorders			
Dry eye			
subjects affected / exposed	1 / 18 (5.56%)	2 / 18 (11.11%)	
occurrences (all)	1	2	
Visual impairment			
subjects affected / exposed	0 / 18 (0.00%)	1 / 18 (5.56%)	
occurrences (all)	0	2	
Gastrointestinal disorders			
Abdominal distension			
subjects affected / exposed	2 / 18 (11.11%)	0 / 18 (0.00%)	
occurrences (all)	2	0	
Abdominal pain			
subjects affected / exposed	3 / 18 (16.67%)	4 / 18 (22.22%)	
occurrences (all)	5	10	
Abdominal pain lower			
subjects affected / exposed	0 / 18 (0.00%)	1 / 18 (5.56%)	
occurrences (all)	0	1	
Abdominal pain upper			

subjects affected / exposed	0 / 18 (0.00%)	2 / 18 (11.11%)	
occurrences (all)	0	2	
Diarrhoea			
subjects affected / exposed	2 / 18 (11.11%)	2 / 18 (11.11%)	
occurrences (all)	3	2	
Dry mouth			
subjects affected / exposed	1 / 18 (5.56%)	1 / 18 (5.56%)	
occurrences (all)	1	1	
Dyspepsia			
subjects affected / exposed	0 / 18 (0.00%)	1 / 18 (5.56%)	
occurrences (all)	0	1	
Enterocolitis			
subjects affected / exposed	1 / 18 (5.56%)	0 / 18 (0.00%)	
occurrences (all)	1	0	
Gastric dilatation			
subjects affected / exposed	0 / 18 (0.00%)	1 / 18 (5.56%)	
occurrences (all)	0	1	
Gastrooesophageal reflux disease			
subjects affected / exposed	1 / 18 (5.56%)	0 / 18 (0.00%)	
occurrences (all)	1	0	
Gastrointestinal pain			
subjects affected / exposed	0 / 18 (0.00%)	1 / 18 (5.56%)	
occurrences (all)	0	1	
Haematemesis			
subjects affected / exposed	1 / 18 (5.56%)	1 / 18 (5.56%)	
occurrences (all)	1	1	
Haemorrhoids			
subjects affected / exposed	0 / 18 (0.00%)	1 / 18 (5.56%)	
occurrences (all)	0	1	
Ileus			
subjects affected / exposed	2 / 18 (11.11%)	0 / 18 (0.00%)	
occurrences (all)	3	0	
Nausea			
subjects affected / exposed	0 / 18 (0.00%)	2 / 18 (11.11%)	
occurrences (all)	0	2	
Pancreatitis			

subjects affected / exposed	0 / 18 (0.00%)	1 / 18 (5.56%)	
occurrences (all)	0	1	
Rectal haemorrhage			
subjects affected / exposed	0 / 18 (0.00%)	1 / 18 (5.56%)	
occurrences (all)	0	4	
Vomiting			
subjects affected / exposed	3 / 18 (16.67%)	2 / 18 (11.11%)	
occurrences (all)	3	2	
Anal haemorrhage			
subjects affected / exposed	1 / 18 (5.56%)	1 / 18 (5.56%)	
occurrences (all)	1	1	
Lower gastrointestinal haemorrhage			
subjects affected / exposed	1 / 18 (5.56%)	0 / 18 (0.00%)	
occurrences (all)	1	0	
Gastrointestinal haemorrhage			
subjects affected / exposed	1 / 18 (5.56%)	0 / 18 (0.00%)	
occurrences (all)	1	0	
Hepatobiliary disorders			
Hepatocellular injury			
subjects affected / exposed	0 / 18 (0.00%)	1 / 18 (5.56%)	
occurrences (all)	0	1	
Hyperbilirubinaemia			
subjects affected / exposed	0 / 18 (0.00%)	1 / 18 (5.56%)	
occurrences (all)	0	1	
Bile duct stenosis			
subjects affected / exposed	0 / 18 (0.00%)	1 / 18 (5.56%)	
occurrences (all)	0	1	
Hepatobiliary disease			
subjects affected / exposed	1 / 18 (5.56%)	1 / 18 (5.56%)	
occurrences (all)	1	1	
Skin and subcutaneous tissue disorders			
Acne			
subjects affected / exposed	0 / 18 (0.00%)	1 / 18 (5.56%)	
occurrences (all)	0	1	
Decubitus ulcer			

subjects affected / exposed	3 / 18 (16.67%)	0 / 18 (0.00%)	
occurrences (all)	3	0	
Dermatitis bullous			
subjects affected / exposed	1 / 18 (5.56%)	0 / 18 (0.00%)	
occurrences (all)	1	0	
Dry skin			
subjects affected / exposed	0 / 18 (0.00%)	2 / 18 (11.11%)	
occurrences (all)	0	2	
Ecchymosis			
subjects affected / exposed	0 / 18 (0.00%)	1 / 18 (5.56%)	
occurrences (all)	0	1	
Nail dystrophy			
subjects affected / exposed	1 / 18 (5.56%)	0 / 18 (0.00%)	
occurrences (all)	1	0	
Petechiae			
subjects affected / exposed	0 / 18 (0.00%)	1 / 18 (5.56%)	
occurrences (all)	0	1	
Pruritus			
subjects affected / exposed	0 / 18 (0.00%)	2 / 18 (11.11%)	
occurrences (all)	0	3	
Skin atrophy			
subjects affected / exposed	0 / 18 (0.00%)	1 / 18 (5.56%)	
occurrences (all)	0	1	
Skin ulcer			
subjects affected / exposed	1 / 18 (5.56%)	0 / 18 (0.00%)	
occurrences (all)	1	0	
Rash maculo-papular			
subjects affected / exposed	1 / 18 (5.56%)	0 / 18 (0.00%)	
occurrences (all)	1	0	
Renal and urinary disorders			
Dysuria			
subjects affected / exposed	1 / 18 (5.56%)	0 / 18 (0.00%)	
occurrences (all)	1	0	
Oliguria			
subjects affected / exposed	0 / 18 (0.00%)	1 / 18 (5.56%)	
occurrences (all)	0	1	

Pollakiuria			
subjects affected / exposed	1 / 18 (5.56%)	2 / 18 (11.11%)	
occurrences (all)	2	2	
Proteinuria			
subjects affected / exposed	2 / 18 (11.11%)	0 / 18 (0.00%)	
occurrences (all)	4	0	
Renal failure			
subjects affected / exposed	0 / 18 (0.00%)	2 / 18 (11.11%)	
occurrences (all)	0	2	
Urethral pain			
subjects affected / exposed	0 / 18 (0.00%)	1 / 18 (5.56%)	
occurrences (all)	0	1	
Urinary incontinence			
subjects affected / exposed	1 / 18 (5.56%)	0 / 18 (0.00%)	
occurrences (all)	1	0	
Bladder disorder			
subjects affected / exposed	0 / 18 (0.00%)	1 / 18 (5.56%)	
occurrences (all)	0	1	
Renal impairment			
subjects affected / exposed	0 / 18 (0.00%)	1 / 18 (5.56%)	
occurrences (all)	0	1	
Haematuria			
subjects affected / exposed	2 / 18 (11.11%)	3 / 18 (16.67%)	
occurrences (all)	2	4	
Acute kidney injury			
subjects affected / exposed	4 / 18 (22.22%)	1 / 18 (5.56%)	
occurrences (all)	4	1	
Endocrine disorders			
Hyperparathyroidism			
subjects affected / exposed	1 / 18 (5.56%)	0 / 18 (0.00%)	
occurrences (all)	1	0	
Infections and infestations			
Bacterial disease carrier			
subjects affected / exposed	1 / 18 (5.56%)	0 / 18 (0.00%)	
occurrences (all)	1	0	
Cellulitis			

subjects affected / exposed	1 / 18 (5.56%)	0 / 18 (0.00%)	
occurrences (all)	1	0	
Clostridium difficile colitis			
subjects affected / exposed	1 / 18 (5.56%)	0 / 18 (0.00%)	
occurrences (all)	1	0	
Cystitis			
subjects affected / exposed	1 / 18 (5.56%)	1 / 18 (5.56%)	
occurrences (all)	1	1	
Enterococcal bacteraemia			
subjects affected / exposed	0 / 18 (0.00%)	1 / 18 (5.56%)	
occurrences (all)	0	1	
Epstein-Barr virus infection			
subjects affected / exposed	3 / 18 (16.67%)	1 / 18 (5.56%)	
occurrences (all)	3	1	
Liver abscess			
subjects affected / exposed	0 / 18 (0.00%)	1 / 18 (5.56%)	
occurrences (all)	0	1	
Urinary tract infection			
subjects affected / exposed	4 / 18 (22.22%)	2 / 18 (11.11%)	
occurrences (all)	4	2	
Wound infection			
subjects affected / exposed	0 / 18 (0.00%)	1 / 18 (5.56%)	
occurrences (all)	0	1	
Staphylococcal bacteraemia			
subjects affected / exposed	1 / 18 (5.56%)	0 / 18 (0.00%)	
occurrences (all)	1	0	
Stenotrophomonas infection			
subjects affected / exposed	1 / 18 (5.56%)	0 / 18 (0.00%)	
occurrences (all)	1	0	
Escherichia bacteraemia			
subjects affected / exposed	1 / 18 (5.56%)	1 / 18 (5.56%)	
occurrences (all)	1	1	
Staphylococcal sepsis			
subjects affected / exposed	0 / 18 (0.00%)	1 / 18 (5.56%)	
occurrences (all)	0	1	
Parvovirus infection			

subjects affected / exposed	0 / 18 (0.00%)	1 / 18 (5.56%)	
occurrences (all)	0	1	
Oesophageal infection			
subjects affected / exposed	0 / 18 (0.00%)	1 / 18 (5.56%)	
occurrences (all)	0	1	
Adenovirus infection			
subjects affected / exposed	0 / 18 (0.00%)	1 / 18 (5.56%)	
occurrences (all)	0	2	
Enterococcal infection			
subjects affected / exposed	2 / 18 (11.11%)	0 / 18 (0.00%)	
occurrences (all)	2	0	
Escherichia infection			
subjects affected / exposed	1 / 18 (5.56%)	0 / 18 (0.00%)	
occurrences (all)	1	0	
Candida infection			
subjects affected / exposed	2 / 18 (11.11%)	0 / 18 (0.00%)	
occurrences (all)	2	0	
Cytomegalovirus infection			
subjects affected / exposed	6 / 18 (33.33%)	4 / 18 (22.22%)	
occurrences (all)	8	6	
Fungal infection			
subjects affected / exposed	1 / 18 (5.56%)	0 / 18 (0.00%)	
occurrences (all)	1	0	
Pneumonia			
subjects affected / exposed	1 / 18 (5.56%)	2 / 18 (11.11%)	
occurrences (all)	1	2	
Sepsis			
subjects affected / exposed	1 / 18 (5.56%)	2 / 18 (11.11%)	
occurrences (all)	1	2	
Bacterial sepsis			
subjects affected / exposed	1 / 18 (5.56%)	0 / 18 (0.00%)	
occurrences (all)	1	0	
Device related infection			
subjects affected / exposed	2 / 18 (11.11%)	3 / 18 (16.67%)	
occurrences (all)	2	3	
Metabolism and nutrition disorders			

Cachexia			
subjects affected / exposed	0 / 18 (0.00%)	1 / 18 (5.56%)	
occurrences (all)	0	1	
Dehydration			
subjects affected / exposed	1 / 18 (5.56%)	1 / 18 (5.56%)	
occurrences (all)	1	1	
Diabetes mellitus			
subjects affected / exposed	2 / 18 (11.11%)	0 / 18 (0.00%)	
occurrences (all)	2	0	
Haemochromatosis			
subjects affected / exposed	0 / 18 (0.00%)	1 / 18 (5.56%)	
occurrences (all)	0	1	
Hyperglycaemia			
subjects affected / exposed	7 / 18 (38.89%)	3 / 18 (16.67%)	
occurrences (all)	11	3	
Hyperkalaemia			
subjects affected / exposed	1 / 18 (5.56%)	0 / 18 (0.00%)	
occurrences (all)	2	0	
Hypernatraemia			
subjects affected / exposed	0 / 18 (0.00%)	1 / 18 (5.56%)	
occurrences (all)	0	1	
Hypertriglyceridaemia			
subjects affected / exposed	2 / 18 (11.11%)	0 / 18 (0.00%)	
occurrences (all)	6	0	
Hypoalbuminaemia			
subjects affected / exposed	3 / 18 (16.67%)	4 / 18 (22.22%)	
occurrences (all)	3	5	
Hypocalcaemia			
subjects affected / exposed	3 / 18 (16.67%)	2 / 18 (11.11%)	
occurrences (all)	3	3	
Hypomagnesaemia			
subjects affected / exposed	2 / 18 (11.11%)	3 / 18 (16.67%)	
occurrences (all)	2	5	
Hyponatraemia			
subjects affected / exposed	1 / 18 (5.56%)	1 / 18 (5.56%)	
occurrences (all)	1	2	

Hypophosphataemia				
subjects affected / exposed	2 / 18 (11.11%)	1 / 18 (5.56%)		
occurrences (all)	8	1		
Hypovolaemia				
subjects affected / exposed	0 / 18 (0.00%)	1 / 18 (5.56%)		
occurrences (all)	0	1		
Tetany				
subjects affected / exposed	0 / 18 (0.00%)	1 / 18 (5.56%)		
occurrences (all)	0	1		
Malnutrition				
subjects affected / exposed	2 / 18 (11.11%)	1 / 18 (5.56%)		
occurrences (all)	2	1		
Decreased appetite				
subjects affected / exposed	2 / 18 (11.11%)	0 / 18 (0.00%)		
occurrences (all)	2	0		
Arthralgia				
subjects affected / exposed	0 / 18 (0.00%)	1 / 18 (5.56%)		
occurrences (all)	0	2		
Back pain				
subjects affected / exposed	1 / 18 (5.56%)	3 / 18 (16.67%)		
occurrences (all)	1	6		
Bone pain				
subjects affected / exposed	0 / 18 (0.00%)	1 / 18 (5.56%)		
occurrences (all)	0	1		
Flank pain				
subjects affected / exposed	0 / 18 (0.00%)	1 / 18 (5.56%)		
occurrences (all)	0	1		
Muscular weakness				
subjects affected / exposed	0 / 18 (0.00%)	1 / 18 (5.56%)		
occurrences (all)	0	1		
Pain in extremity				
subjects affected / exposed	0 / 18 (0.00%)	1 / 18 (5.56%)		
occurrences (all)	0	1		
Sarcopenia				
subjects affected / exposed	0 / 18 (0.00%)	1 / 18 (5.56%)		
occurrences (all)	0	1		

Hypokalaemia subjects affected / exposed occurrences (all)	4 / 18 (22.22%) 13	3 / 18 (16.67%) 8	

More information

Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? Yes

Date	Amendment
09 April 2015	Protocol version 1.0 was submitted in US only and have received comments from US authorities
12 May 2015	Protocol version 2.0 (12-May-2015) of the protocol was never submitted to the authorities and was only for internal use.
25 June 2015	Protocol version 3.0, was submitted to FDA, FR, DE, IT, ES, UK and Switzerland. In addition, modifications that have been requested by the health authorities in the United Kingdom and Spain (and issued in these countries, specific versions 3.1) regarding acceptable methods of birth control have been incorporated here. Protocol version 3.1 was approved in UK on 01-SEP-2015 ans in Spain on 22-OCT-2015.
14 October 2016	Protocol Version 4.0 has never been implemented.
13 March 2017	Protocol version 5.0 Protocol version 5.0 has been amended to reduce follow-up time in line with endpoints of the protocol, from 365 days to 180 days. Also, from Version 3.0 to 5.0, a number of changes have been made regarding the: study enrolment period, Inclusion and exclusion criteria, laboratory assessments, blinding methods, a list of secondary efficacy objectives was added, changes in protocol background and protocol references.

Notes:

Interruptions (globally)

Were there any global interruptions to the trial? Yes

Date	Interruption	Restart date
06 March 2017	The study was prematurely terminated because of the lack of enrollment	-

Notes:

Limitations and caveats

Limitations of the trial such as small numbers of subjects analysed or technical problems leading to unreliable data.

Lack of enrollment

Notes: