



Clinical trial results:

Efficacy and Safety of Bone Marrow-Derived Mesenchymal Cardiopoietic Cells (C3BS-CQR-1) for the Treatment of Chronic Advanced Ischemic Heart Failure

Summary

EudraCT number	2011-001117-13
Trial protocol	BE GB HU PL SE ES IE BG LT EE HR
Global end of trial date	10 August 2017

Results information

Result version number	v1 (current)
This version publication date	07 October 2020
First version publication date	07 October 2020
Summary attachment (see zip file)	Results of CHART-1 primary endpoint in the European Journal of Heart Failure (CHART-1 9 months article EHJ March 2017.pdf)

Trial information

Trial identification

Sponsor protocol code	C3BS-C-11-01
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Additional study identifiers

ISRCTN number	-
ClinicalTrials.gov id (NCT number)	NCT01768702
WHO universal trial number (UTN)	-

Notes:

Sponsors

Sponsor organisation name	Celyad Oncology SA
Sponsor organisation address	2 rue Edouard Belin, Mont Saint Guibert, Belgium, 1435
Public contact	Clinical Trial Information, Celyad Oncology SA, 2472192739 +32472192739, shalleux@celyad.com
Scientific contact	Clinical Trial Information, Celyad Oncology SA, 2472192739 +32472192739, shalleux@celyad.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	15 January 2018
Is this the analysis of the primary completion data?	No
Global end of trial reached?	Yes
Global end of trial date	10 August 2017
Was the trial ended prematurely?	No

Notes:

General information about the trial

Main objective of the trial:

The primary objective is to evaluate the efficacy of C3BS-CQR-1 by comparing the overall response to C3BS-CQR-1 relative to a sham procedure using a composite outcome of mortality, morbidity, changes in quality of life , six-minute walk distance, and left ventricular structure and function at 39 weeks (9 months) post-procedure.

Protection of trial subjects:

The study was conducted in compliance with the requirements of governmental regulatory bodies and ethics committees of each participating centre

Background therapy:

Standard of care

Evidence for comparator: -

Actual start date of recruitment	18 December 2012
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	Poland: 42
Country: Number of subjects enrolled	Spain: 4
Country: Number of subjects enrolled	Belgium: 17
Country: Number of subjects enrolled	Bulgaria: 13
Country: Number of subjects enrolled	Hungary: 97
Country: Number of subjects enrolled	Italy: 2
Country: Number of subjects enrolled	Israel: 18
Country: Number of subjects enrolled	Serbia: 95
Country: Number of subjects enrolled	Switzerland: 2
Worldwide total number of subjects	290
EEA total number of subjects	175

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)	158
From 65 to 84 years	132
85 years and over	0

Subject disposition

Recruitment

Recruitment details:

Eligible patients gave written informed consent prior to any study-related procedures. Patients were not compensated for participation except for travel expenses. Patients were >18 to < 80 years with left ventricular ejection fraction (LVEF) <35%, NYHA 2 and 3 and ischaemic heart failure.

Pre-assignment

Screening details:

Patients were randomized 1:1 to cardiopoietic cell injection or a sham control procedure after confirmation by the central production facility that > 24 million MSCs were achieved according to pre-specified release criteria. An Interactive Web Randomization Service was used according to a central randomization scheme stratified by study centre.

Pre-assignment period milestones

Number of subjects started	315 ^[1]
Intermediate milestone: Number of subjects	Had one intervention: 290
Number of subjects completed	271

Pre-assignment subject non-completion reasons

Reason: Number of subjects	Deaths: 16
Reason: Number of subjects	manufacturing failure: 18
Reason: Number of subjects	Physician decision: 7
Reason: Number of subjects	Consent withdrawn by subject: 3

Notes:

[1] - The number of subjects reported to have started the pre-assignment period are not the same as the worldwide number enrolled in the trial. It is expected that these numbers will be the same.

Justification: As explained 315 were randomized but 19 could not get one of the procedure, as 16 died and 3 withdrew consent. Therefore, the number of patients enrolled in the trial were finally 290.

Period 1

Period 1 title	Injection to 2y follow up (overall period)
Is this the baseline period?	Yes
Allocation method	Randomised - controlled
Blinding used	Double blind
Roles blinded	Subject, Investigator

Blinding implementation details:

This was a patient- and evaluator-blinded study. To keep the blind, 2 teams were formed at each site, i.e., an Interventional Team that was unblinded to treatment (Team A), and a blinded Evaluator Team (Team B). Members of the unblinded team were clinical site investigators and operators involved in the index procedure (e.g., the reception and unpacking of the drug product and the preparation of the drug product prior to injection; the injection or sham procedure; and the patient's follow-up).

Arms

Are arms mutually exclusive?	Yes
Arm title	C3BS-CQR-1 treated

Arm description:

Injection of the C3BS-CQR-1 using the C-Cath injection catheter.

C3BS-CQR-1 is an autologous stem cell-based bio-therapeutic. The active ingredients of C3BS-CQR-1 are cardiopoietic cells derived from the patient's bone marrow mesenchymal stem cells. A target volume of 65 mL to 85 mL of anti-coagulated bone marrow will be harvested from the iliac crest of the patient at the hospital. The fresh bone marrow sample will be processed and frozen in order to allow its storage until the initiation of the manufacturing process. After thawing, BMMSCs will be isolated, cultured in the presence of a proprietary combination of factors to guide them towards the cardiovascular lineage (thereby called cardiopoietic cells), and expanded. The manufacture process and release of the drug

product takes about 7-15 weeks after thawing of the bone marrow sample. This commitment process of MSCs is based on the cell treatment with a protein-based mixture and excludes genetic manipulation.

Arm type	Experimental
Investigational medicinal product name	C3BS-CQR-1
Investigational medicinal product code	C3BS-CQR-1
Other name	C-CURE
Pharmaceutical forms	Suspension for injection
Routes of administration	Intracardiac use

Dosage and administration details:

Cryopreserved cardiopoietic cell batches meeting release criteria (C3BS-CQR-1 manufactured by Celyad, Mont-Saint-Guibert, Belgium) were shipped frozen to sites and reconstituted within 6 h before injection. Cardiopoietic cells were delivered using standard cardiac catheterization procedures and a cell retention-enhanced injection catheter (C-Cathez TM; Celyad, Mont-Saint-Guibert, Belgium).¹⁷ Intramyocardial injections (0.5mL each, 1 cm apart) were made into left ventricle areas with wall thickness \geq 8mm, avoiding the apex and segments adjacent to the mitral or aortic valves. Target zones were mapped using biplane left ventricular angiography integrating preceding echocardiography information regarding wall thickness.

Arm title	Sham, no injection
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Arm description:

Patients randomized to the control group received sham injection. An introducer sheath was inserted into the right or left femoral artery using standard procedures for percutaneous interventions, and a mock injection procedure was performed over a period of 30 to 60 minutes. No waiting time was required in case the patient was sedated per local practice. The sheath was removed at the end of the mock procedure.

Arm type	Sham procedure
Investigational medicinal product name	Sham
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Injection
Routes of administration	Intracardiac use

Dosage and administration details:

In fact, the operator mimicked intra cardiac injections but did not inject any substances

Investigational medicinal product name	Sham
Investigational medicinal product code	Sham
Other name	
Pharmaceutical forms	Injection
Routes of administration	Intracardiac use

Dosage and administration details:

Patients randomized to the control group received sham injection. An introducer sheath was inserted into the right or left femoral artery using standard procedures for percutaneous interventions, and a mock injection procedure was performed over a period of 30 to 60 minutes. No waiting time was required in case the patient was sedated per local practice. The sheath was removed at the end of the mock procedure.

Number of subjects in period 1^[2]	C3BS-CQR-1 treated	Sham, no injection
Started	120	151
39 weeks efficacy	108	135
52 weeks safety	104	133
Completed	92	109
Not completed	28	42

Deaths	25	38
Lost to follow-up	3	4

Notes:

[2] - The number of subjects reported to be in the baseline period are not the same as the worldwide number enrolled in the trial. It is expected that these numbers will be the same.

Justification: 315 were randomized

However, due to time to get autologous manufacturing (3 weeks) , only 290 were really enrolled to one of the two procedures, and in the end, only 271 received the procedure as planned

This is explained in the CONSORT diagram in the EHJ article.

Out of the 315, 19 could not get one of the procedure, as 16 died and 3 withdrew consent.

Out of the 290, another 19 did not get the CDR-1 procedure as product was out of specs for 18, and 1 was withdrawn by the PI

Baseline characteristics

Reporting groups

Reporting group title	C3BS-CQR-1 treated
Reporting group description:	
<p>Injection of the C3BS-CQR-1 using the C-Cath injection catheter.</p> <p>C3BS-CQR-1 is an autologous stem cell-based bio-therapeutic. The active ingredients of C3BS-CQR-1 are cardiopoietic cells derived from the patient's bone marrow mesenchymal stem cells. A target volume of 65 mL to 85 mL of anti-coagulated bone marrow will be harvested from the iliac crest of the patient at the hospital. The fresh bone marrow sample will be processed and frozen in order to allow its storage until the initiation of the manufacturing process. After thawing, BMMSCs will be isolated, cultured in the presence of a proprietary combination of factors to guide them towards the cardiovascular lineage (thereby called cardiopoietic cells), and expanded. The manufacture process and release of the drug product takes about 7-15 weeks after thawing of the bone marrow sample. This commitment process of MSCs is based on the cell treatment with a protein-based mixture and excludes genetic manipulation.</p>	
Reporting group title	Sham, no injection
Reporting group description:	
<p>Patients randomized to the control group received sham injection. An introducer sheath was inserted into the right or left femoral artery using standard procedures for percutaneous interventions, and a mock injection procedure was performed over a period of 30 to 60 minutes. No waiting time was required in case the patient was sedated per local practice. The sheath was removed at the end of the mock procedure.</p>	

Reporting group values	C3BS-CQR-1 treated	Sham, no injection	Total
Number of subjects	120	151	271
Age categorical			
Patients were selected if they were more than 18 and less than 80			
Units: Subjects			
18 and more, less than 80	120	151	271
Gender categorical			
Units: Subjects			
Female	13	15	28
Male	107	136	243
NYHA Class			
Units: Subjects			
NYHA 1	0	0	0
NYHA 2	23	36	59
NYHA 3	96	114	210
NYHA 4	1	1	2
BMI			
Units: kg/m ²			
arithmetic mean	28.2	28.6	
standard deviation	± 3.7	± 4.4	-
Time from heart failure diagnosis to screening			
Units: months			
median	44.1	46.3	
full range (min-max)	12.3 to 100.1	16 to 97.7	-

Subject analysis sets

Subject analysis set title	Per protocol efficacy
Subject analysis set type	Per protocol

Subject analysis set description:

Subjects randomized according to pre specified arm and administered as randomized

Reporting group values	Per protocol efficacy		
Number of subjects	271		
Age categorical			
Patients were selected if they were more than 18 and less than 80			
Units: Subjects			
18 and more, less than 80	271		
Gender categorical			
Units: Subjects			
Female			
Male			
NYHA Class			
Units: Subjects			
NYHA 1	0		
NYHA 2	59		
NYHA 3	210		
NYHA 4	2		
BMI			
Units: kg/m2			
arithmetic mean			
standard deviation	±		
Time from heart failure diagnosis to screening			
Units: months			
median			
full range (min-max)			

End points

End points reporting groups

Reporting group title	C3BS-CQR-1 treated
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Reporting group description:

Injection of the C3BS-CQR-1 using the C-Cath injection catheter.

C3BS-CQR-1 is an autologous stem cell-based bio-therapeutic. The active ingredients of C3BS-CQR-1 are cardiopoietic cells derived from the patient's bone marrow mesenchymal stem cells. A target volume of 65 mL to 85 mL of anti-coagulated bone marrow will be harvested from the iliac crest of the patient at the hospital. The fresh bone marrow sample will be processed and frozen in order to allow its storage until the initiation of the manufacturing process. After thawing, BMMSCs will be isolated, cultured in the presence of a proprietary combination of factors to guide them towards the cardiovascular lineage (thereby called cardiopoietic cells), and expanded. The manufacture process and release of the drug product takes about 7-15 weeks after thawing of the bone marrow sample. This commitment process of MSCs is based on the cell treatment with a protein-based mixture and excludes genetic manipulation.

Reporting group title	Sham, no injection
-----------------------	--------------------

Reporting group description:

Patients randomized to the control group received sham injection. An introducer sheath was inserted into the right or left femoral artery using standard procedures for percutaneous interventions, and a mock injection procedure was performed over a period of 30 to 60 minutes. No waiting time was required in case the patient was sedated per local practice. The sheath was removed at the end of the mock procedure.

Subject analysis set title	Per protocol efficacy
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Subject analysis set type	Per protocol
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Subject analysis set description:

Subjects randomized according to pre specified arm and administered as randomized

Primary: Efficacy

End point title	Efficacy
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End point description:

It is a hierarchical composite outcome, that was evaluated using a Finkelstein-Schoenfeld's test. This test is an extension of the generalized Wilcoxon rank sum test based on a hierarchy of the endpoints and compared every patient to every other patient in a pairwise manner, thereby assigning +1, 0, or -1 dependent on whether the patient in the pair did better, the same, or worse than the other patient. Each pair of patients was compared with respect to the following endpoints in the order given: (1) Mortality; (2) Number of WHF events: 0, 1, or ≥ 2 ; (3) MLWHFQ ≥ 10 point improvement, ≥ 10 point deterioration, no meaningful change; (4) 6MWT ≥ 40 m improvement, ≥ 40 m deterioration, no meaningful change; (5) LVESV ≥ 15 mL improvement, ≥ 15 mL deterioration, no meaningful change, and (6) LVEF $\geq 4\%$ absolute improvement, $\geq 4\%$ absolute deterioration, no meaningful change. The net scores for each patient were summed and then ranked.

End point type	Primary
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End point timeframe:

39 weeks

End point values	C3BS-CQR-1 treated	Sham, no injection		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	120	151		
Units: 18120	10404	0		

Attachments (see zip file)	Primary endpoint results/Chart-1 Primary endpoint graph
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Statistical analyses

Statistical analysis title	Composite efficacy endpoint in the treated set
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Statistical analysis description:

Treatment arm sample size of 120 patients per group was estimated to provide 87% power to detect a treatment effect corresponding to a Mann–Whitney estimator (the probability of a better response in the active treatment group plus half the probability of a tie) of 0.61 (values > 0.5 favour active treatment).

Comparison groups	C3BS-CQR-1 treated v Sham, no injection
Number of subjects included in analysis	271
Analysis specification	Pre-specified
Analysis type	superiority ^[1]
P-value	> 0.01
Method	Wilcoxon (Mann-Whitney)
Parameter estimate	Hazard ratio (HR)
Point estimate	0.54
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.47
upper limit	0.61
Variability estimate	Standard deviation
Dispersion value	0.24

Notes:

[1] - The treatment arm sample size of 120 patients per group was estimated to provide 87% power to detect a treatment effect corresponding to a Mann–Whitney estimator (the probability of a better response in the active treatment group plus half the probability of a tie) of 0.61 (values > 0.5 favour active treatment).

Adverse events

Adverse events information^[1]

Timeframe for reporting adverse events:

104 weeks, end of study

Adverse event reporting additional description:

Below are the numbers that are part of the Clinical Study Report. The number of patients for which there are non serious events is not specified.

The threshold of 5% was applied to Adverse Events.

Assessment type	Systematic
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Dictionary used

Dictionary name	MedDRA
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Dictionary version	15.0
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Reporting groups

Reporting group title	C3BS-CQR-1 treated
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Reporting group description:

All patients treated with the experimental product

Reporting group title	Sham control group
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Reporting group description:

Group composed of 151 patients that were randomized to receive the Sham procedure and 19 patients that were randomized to receive the experimental product but could not for the following reasons: 18 as the product could not be manufactured within specs and 1 as the procedure was contra indicated by the physician

Notes:

[1] - There are no non-serious adverse events recorded for these results. It is expected that there will be at least one non-serious adverse event reported.

Justification: There are no non-serious AEs with a reporting rate above the 5 % threshold.

Serious adverse events	C3BS-CQR-1 treated	Sham control group	
Total subjects affected by serious adverse events			
subjects affected / exposed	78 / 120 (65.00%)	100 / 170 (58.82%)	
number of deaths (all causes)	26	45	
number of deaths resulting from adverse events	26	45	
Neoplasms benign, malignant and unspecified (incl cysts and polyps)			
Colon cancer			
subjects affected / exposed	2 / 120 (1.67%)	1 / 170 (0.59%)	
occurrences causally related to treatment / all	0 / 2	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Congenital, familial and genetic disorders			
Atrial fibrillation			
subjects affected / exposed	1 / 120 (0.83%)	3 / 170 (1.76%)	
occurrences causally related to treatment / all	0 / 2	0 / 3	
deaths causally related to treatment / all	0 / 0	0 / 0	
Cardiac disorders			

Ventricular fibrillation			
subjects affected / exposed	7 / 120 (5.83%)	5 / 170 (2.94%)	
occurrences causally related to treatment / all	3 / 15	0 / 6	
deaths causally related to treatment / all	0 / 0	0 / 2	
Acute myocardial infarction			
subjects affected / exposed	3 / 120 (2.50%)	2 / 170 (1.18%)	
occurrences causally related to treatment / all	0 / 3	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 1	
Angina unstable			
subjects affected / exposed	1 / 120 (0.83%)	4 / 170 (2.35%)	
occurrences causally related to treatment / all	0 / 1	0 / 7	
deaths causally related to treatment / all	0 / 0	0 / 0	
Angina pectoris			
subjects affected / exposed	4 / 120 (3.33%)	3 / 170 (1.76%)	
occurrences causally related to treatment / all	0 / 4	0 / 3	
deaths causally related to treatment / all	0 / 0	0 / 0	
Atrial flutter			
subjects affected / exposed	2 / 120 (1.67%)	0 / 170 (0.00%)	
occurrences causally related to treatment / all	0 / 2	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Atrioventricular block complete			
subjects affected / exposed	0 / 120 (0.00%)	3 / 170 (1.76%)	
occurrences causally related to treatment / all	0 / 0	0 / 3	
deaths causally related to treatment / all	0 / 0	0 / 0	
Bundle branch block left			
subjects affected / exposed	4 / 120 (3.33%)	0 / 170 (0.00%)	
occurrences causally related to treatment / all	3 / 4	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Cardiac arrest			
subjects affected / exposed	1 / 120 (0.83%)	5 / 170 (2.94%)	
occurrences causally related to treatment / all	0 / 1	1 / 5	
deaths causally related to treatment / all	0 / 1	1 / 4	
Cardiac failure			

subjects affected / exposed	35 / 120 (29.17%)	44 / 170 (25.88%)	
occurrences causally related to treatment / all	2 / 62	0 / 84	
deaths causally related to treatment / all	0 / 8	0 / 14	
Cardiac failure chronic			
subjects affected / exposed	4 / 120 (3.33%)	0 / 170 (0.00%)	
occurrences causally related to treatment / all	0 / 6	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Cardiac failure congestive			
subjects affected / exposed	5 / 120 (4.17%)	2 / 170 (1.18%)	
occurrences causally related to treatment / all	0 / 9	0 / 3	
deaths causally related to treatment / all	0 / 2	0 / 1	
Cardiac tamponade			
subjects affected / exposed	2 / 120 (1.67%)	0 / 170 (0.00%)	
occurrences causally related to treatment / all	2 / 2	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Dyspnoea			
subjects affected / exposed	2 / 120 (1.67%)	0 / 170 (0.00%)	
occurrences causally related to treatment / all	1 / 2	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Intracardiac thrombus			
subjects affected / exposed	0 / 120 (0.00%)	2 / 170 (1.18%)	
occurrences causally related to treatment / all	0 / 0	0 / 3	
deaths causally related to treatment / all	0 / 0	0 / 0	
Ischaemic cardiomyopathy			
subjects affected / exposed	2 / 120 (1.67%)	1 / 170 (0.59%)	
occurrences causally related to treatment / all	0 / 2	0 / 1	
deaths causally related to treatment / all	0 / 1	0 / 1	
Myocardial infarction			
subjects affected / exposed	0 / 120 (0.00%)	3 / 170 (1.76%)	
occurrences causally related to treatment / all	0 / 0	0 / 3	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pericardial effusion			

subjects affected / exposed	2 / 120 (1.67%)	0 / 170 (0.00%)	
occurrences causally related to treatment / all	1 / 2	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Sudden cardiac death			
subjects affected / exposed	2 / 120 (1.67%)	2 / 170 (1.18%)	
occurrences causally related to treatment / all	1 / 2	0 / 2	
deaths causally related to treatment / all	1 / 2	0 / 2	
Supraventricular tachycardia			
subjects affected / exposed	2 / 120 (1.67%)	0 / 170 (0.00%)	
occurrences causally related to treatment / all	0 / 2	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Ventricular tachycardia			
subjects affected / exposed	6 / 120 (5.00%)	15 / 170 (8.82%)	
occurrences causally related to treatment / all	1 / 7	1 / 21	
deaths causally related to treatment / all	0 / 0	0 / 1	
Surgical and medical procedures			
Cardiac pacemaker insertion			
subjects affected / exposed	2 / 120 (1.67%)	2 / 170 (1.18%)	
occurrences causally related to treatment / all	0 / 2	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Implantable defibrillator insertion			
subjects affected / exposed	8 / 120 (6.67%)	5 / 170 (2.94%)	
occurrences causally related to treatment / all	0 / 8	0 / 5	
deaths causally related to treatment / all	0 / 0	0 / 0	
Nervous system disorders			
Ischaemic stroke			
subjects affected / exposed	0 / 120 (0.00%)	2 / 170 (1.18%)	
occurrences causally related to treatment / all	0 / 0	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Multiple sclerosis			
subjects affected / exposed	0 / 120 (0.00%)	2 / 170 (1.18%)	
occurrences causally related to treatment / all	0 / 0	0 / 4	
deaths causally related to treatment / all	0 / 0	0 / 0	
Blood and lymphatic system disorders			

Anaemia			
subjects affected / exposed	2 / 120 (1.67%)	1 / 170 (0.59%)	
occurrences causally related to treatment / all	0 / 2	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
General disorders and administration site conditions			
Death			
subjects affected / exposed	3 / 120 (2.50%)	9 / 170 (5.29%)	
occurrences causally related to treatment / all	0 / 3	0 / 9	
deaths causally related to treatment / all	0 / 3	0 / 9	
Sudden death			
subjects affected / exposed	3 / 120 (2.50%)	0 / 170 (0.00%)	
occurrences causally related to treatment / all	0 / 3	0 / 0	
deaths causally related to treatment / all	0 / 3	0 / 0	
Gastrointestinal disorders			
Gastrointestinal haemorrhage			
subjects affected / exposed	0 / 120 (0.00%)	1 / 170 (0.59%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 1	
Respiratory, thoracic and mediastinal disorders			
Pneumothorax			
subjects affected / exposed	2 / 120 (1.67%)	0 / 170 (0.00%)	
occurrences causally related to treatment / all	0 / 2	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Renal and urinary disorders			
Renal failure			
subjects affected / exposed	5 / 120 (4.17%)	6 / 170 (3.53%)	
occurrences causally related to treatment / all	0 / 6	0 / 7	
deaths causally related to treatment / all	0 / 0	0 / 0	
Infections and infestations			
Pneumonia			
subjects affected / exposed	6 / 120 (5.00%)	5 / 170 (2.94%)	
occurrences causally related to treatment / all	0 / 7	0 / 5	
deaths causally related to treatment / all	0 / 0	0 / 0	
Sepsis			

subjects affected / exposed	0 / 120 (0.00%)	3 / 170 (1.76%)	
occurrences causally related to treatment / all	0 / 0	0 / 3	
deaths causally related to treatment / all	0 / 0	0 / 0	
Septic shock			
subjects affected / exposed	0 / 120 (0.00%)	2 / 170 (1.18%)	
occurrences causally related to treatment / all	0 / 0	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	

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

Non-serious adverse events	C3BS-CQR-1 treated	Sham control group	
Total subjects affected by non-serious adverse events			
subjects affected / exposed	0 / 120 (0.00%)	0 / 170 (0.00%)	

More information

Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? Yes

Date	Amendment
28 April 2014	Extension of shelf-life
19 August 2015	Modification of secondary efficacy endpoint.
03 February 2016	Change of Reference Safety Information in the IB.

Notes:

Interruptions (globally)

Were there any global interruptions to the trial? No

Limitations and caveats

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

Efficacy data shown at 39 weeks, which were not fundamentally changed at 52 weeks. On going analysis at 104 weeks. A sub population of responders was identified in a post hoc analysis, which is explained in the EHJ enclosed paper, to be confirmed.

Notes:

Online references

<http://www.ncbi.nlm.nih.gov/pubmed/28025189>

<http://www.ncbi.nlm.nih.gov/pubmed/28560782>

<http://www.ncbi.nlm.nih.gov/pubmed/26662998>