Clinical trial results:
Multicenter, Randomized Phase 2B Study to Evaluate the Efficacy, Safety and Tolerability of OCR-002 (ornithine phenylacetate) in Hospitalized Patients with Cirrhosis and Associated Hyperammonemia with an Episode of Hepatic Encephalopathy

Summary

EudraCT number	2013-005412-10
Trial protocol	EE CZ AT HU IT DE NL BE DK BG
Global end of trial date	29 December 2016

Results information

Result version number	v1 (current)
This version publication date	22 November 2020
First version publication date	22 November 2020

Trial information

Trial identification

Sponsor protocol code	OCR002-HE209

Additional study identifiers

ISRCTN number	-
ClinicalTrials.gov id (NCT number)	NCT01966419
WHO universal trial number (UTN)	-
Other trial identifiers	Acronym: STOP-HE

Notes:

Sponsors

Sponsor organisation name	Ocera Therapeutics, Inc.
Sponsor organisation address	1425 U.S. Route 206, Bedminster, NJ, United States, 07921
Public contact	Mallinckrodt Medical Information Call Center, Ocera Therapeutics, Inc., +1 800-556-3314 Ext. 5, clinicaltrials@mnk.com
Scientific contact	Mallinckrodt Medical Information Call Center, Ocera Therapeutics, Inc., +1 800-556-3314 Ext. 5, clinicaltrials@mnk.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	23 August 2017
Is this the analysis of the primary completion data?	No

Global end of trial reached?	Yes
Global end of trial date	29 December 2016
Was the trial ended prematurely?	No

Notes:

General information about the trial

Main objective of the trial:

The purpose of this study is to determine whether ornithine phenylacetate can speed recovery from an acute hepatic encephalopathy episode requiring hospitalization in cirrhotic patients.

The primary objectives of the study were to evaluate the efficacy of OCR-002 for treatment of an acute hepatic encephalopathy (HE) episode in cirrhotic patients requiring hospitalization and the safety and tolerability of OCR-002 in hospitalized cirrhotic patients with an acute episode of HE.

Protection of trial subjects:

The investigator ensured that this study was conducted in accordance with the principles of the Declaration of Helsinki (as amended in Tokyo, Venice, Hong Kong, South Africa, and Edinburgh), International Council for Harmonisation guidelines, or with the laws and regulations of the country in which the research was conducted, whichever afforded the greater protection to the study patient. Further, protection of trial participants was ensured by an Independent Data Monitoring Committee (IDMC).

Background therapy: -

Evidence for comparator: -

Actual start date of recruitment	07 January 2014
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	Netherlands: 1
Country: Number of subjects enrolled	Spain: 13
Country: Number of subjects enrolled	Austria: 7
Country: Number of subjects enrolled	Belgium: 7
Country: Number of subjects enrolled	Bulgaria: 3
Country: Number of subjects enrolled	Czech Republic: 5
Country: Number of subjects enrolled	Denmark: 2
Country: Number of subjects enrolled	France: 21
Country: Number of subjects enrolled	Hungary: 5
Country: Number of subjects enrolled	Italy: 2
Country: Number of subjects enrolled	United States: 128
Country: Number of subjects enrolled	Russian Federation: 12
Country: Number of subjects enrolled	Israel: 22
Country: Number of subjects enrolled	Australia: 1
Country: Number of subjects enrolled	Canada: 2

Worldwide total number of subjects	231
EEA total number of subjects	66

Notes:

Subjects enrolled per age group	
In utero	0
Preterm newborn - gestational age < 37 wk	0
Newborns (0-27 days)	0
Infants and toddlers (28 days-23 months)	0
Children (2-11 years)	0
Adolescents (12-17 years)	0
Adults (18-64 years)	160
From 65 to 84 years	71
85 years and over	0

Subject disposition

Recruitment

Recruitment details:

A total of 231 participants were enrolled (randomized) into the trial at multiple (68) sites in 15 countries, including the United States, Australia and Europe.

Pre-assignment

Screening details:

Of all potential patients screened, 231 patients were randomized in a 1:1 ratio.

Period 1

Period 1 title	Overall Study (overall period)
Is this the baseline period?	Yes
Allocation method	Randomised - controlled
Blinding used	Double blind
Roles blinded	Subject, Investigator

Blinding implementation details:

While the study was double-blind (participant and investigator blinded), the care provider and outcomes assessor were also blinded.

Arms

Are arms mutually exclusive?	Yes
Arm title	Placebo

Arm description:

Patients receive matching placebo via continuous IV infusion for up to 5 days, in addition to standard of care (SOC)

Arm type	Placebo
Investigational medicinal product name	Placebo
Investigational medicinal product code	
Other name	Matching placebo
Pharmaceutical forms	Solution for infusion
Routes of administration	Intravenous use

Dosage and administration details:

Placebo for continuous IV infusion that is visually identical to the experimental product

Arm title	OCR-002

Arm description:

Patients receive ornithine phenylacetate by continuous IV infusion for up to 5 days in addition to SOC

Arm type	Experimental
Investigational medicinal product name	Ornithine phenylacetate
Investigational medicinal product code	
Other name	OCR-002
Pharmaceutical forms	Solution for infusion
Routes of administration	Intravenous use

Dosage and administration details:

Ornithine phenylacetate for continuous IV infusion at dose levels predicated on level of hepatic decompensation

Number of subjects in period 1	Placebo	OCR-002
Started	115	116
Intention to Treat (ITT) Population	115	116
Safety Population	112	114
Completed	74	80
Not completed	41	36
Voluntary withdrawal by patient or representative	8	4
Adverse event, non-fatal	2	3
Death	14	8
Investigator decision	-	1
Patient had liver transplant	7	4
Lost to follow-up	2	2
Reason not specified	7	14
Missing	1	-

Baseline characteristics

Reporting groups	
Reporting group title	Placebo
Reporting group description:	
Patients receive matching placebo via continuous IV infusion for up to 5 days, in addition to standard of care (SOC)	
Reporting group title	OCR-002
Reporting group description:	
Patients receive ornithine phenylacetate by continuous IV infusion for up to 5 days in addition to SOC	

Reporting group values	Placebo	OCR-002	Total
Number of subjects	115	116	231
Age categorical			
Units: Subjects			
Adults (18-64 years)	81	79	160
From 65-84 years	34	37	71
Age continuous			
The aggregate mean and standard deviation of patient age (in years) is reported for the Intent to Treat (ITT) population.			
Units: years			
arithmetic mean	60	50	
standard deviation	± 9.5	± 9.8	-
Gender categorical			
Units: Subjects			
Female	37	44	81
Male	78	72	150

End points

End points reporting groups

Reporting group title	Placebo
Reporting group description:	
Patients receive matching placebo via continuous IV infusion for up to 5 days, in addition to standard of care (SOC)	
Reporting group title	OCR-002
Reporting group description:	
Patients receive ornithine phenylacetate by continuous IV infusion for up to 5 days in addition to SOC	

Primary: Percentage of Participants in each HE Stage

End point title	Percentage of Participants in each HE Stage[1]
End point description:	
To support the primary endpoint of confirmed clinical response, the investigator rated patients twice daily to determine the percentage of patients in each HE stage on a 4-point scale (from 4=coma to 0/1=no disorientation), where a lower score is better. Percentages less than 1 are entered as 0 due to database constraints. Not all patients were assessed at all post-baseline time points.	
End point type	Primary
End point timeframe:	
Baseline to End of Study (at 3 hours Post End-of-Infusion or Early Hospital Discharge or Early Termination)	
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: No statistical analyses were performed to arrive at these summary aggregate data values.	

End point values	Placebo	OCR-002		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	115[2]	116[3]		
Units: percentage of patients				
number (not applicable)				
Baseline, Stage 4	10	5		
Baseline, Stage 3	26	34		
Baseline, Stage 2	62	59		
Baseline, Stage 0/1	0	0		
Baseline, Missing	3	2		
Day 1- 7 am, Stage 4	0	0		
Day 1- 7 am, Stage 3	0	3		
Day 1- 7 am, Stage 2	2	3		
Day 1- 7 am, Stage 0/1	0	0		
Day 1- 7 am, Missing	0	0		
Day 1- 5 pm, Stage 4	0	5		
Day 1- 5 pm, Stage 3	7	14		
Day 1- 5 pm, Stage 2	32	36		
Day 1- 5 pm, Stage 0/1	0	1		
Day 1- 5 pm, Missing	0	0		
Day 2- 7 am, Stage 4	3	4		

Day 2 - 7 am, Stage 3	21	15		
Day 2 - 7 am, Stage 2	61	69		
Day 2 - 7 am, Stage 0/1	10	10		
Day 2 - 7 am, Missing	0	0		
Day 2 - 5 pm, Stage 4	3	4		
Day 2 - 5 pm, Stage 3	14	9		
Day 2 - 5 pm, Stage 2	57	61		
Day 2 - 5 pm, Stage 0/1	16	16		
Day 2 - 5 pm, Missing	0	0		
Day 3 - 7 am, Stage 4	3	2		
Day 3 - 7 am, Stage 3	15	10		
Day 3 - 7 am, Stage 2	50	55		
Day 3 - 7 am, Stage 0/1	21	25		
Day 3 - 7 am, Missing	0	0		
Day 3 - 5 pm, Stage 4	3	3		
Day 3 - 5 pm, Stage 3	7	9		
Day 3 - 5 pm, Stage 2	46	45		
Day 3 - 5 pm, Stage 0/1	20	27		
Day 3 - 5 pm, Missing	0	0		
Day 4 - 7 am, Stage 4	2	0		
Day 4 - 7 am, Stage 3	5	9		
Day 4 - 7 am, Stage 2	42	40		
Day 4 - 7 am, Stage 0/1	28	30		
Day 4 - 7 am, Missing	0	0		
Day 4 - 5 pm, Stage 4	2	0		
Day 4 - 5 pm, Stage 3	7	7		
Day 4 - 5 pm, Stage 2	29	34		
Day 4 - 5 pm, Stage 0/1	25	28		
Day 4 - 5 pm, Missing	0	0		
Day 5 - 7 am, Stage 4	0	0		
Day 5 - 7 am, Stage 3	9	7		
Day 5 - 7 am, Stage 2	29	28		
Day 5 - 7 am, Stage 0/1	23	32		
Day 5 - 7 am, Missing	0	0		
Day 5 - 5 pm, Stage 4	0	0		
Day 5 - 5 pm, Stage 3	8	3		
Day 5 - 5 pm, Stage 2	24	22		
Day 5 - 5 pm, Stage 0/1	23	28		
Day 5 - 5 pm, Missing	0	0		
Day 6 - 7 am, Stage 4	0	0		
Day 6 - 7 am, Stage 3	10	3		
Day 6 - 7 am, Stage 2	21	24		
Day 6 - 7 am, Stage 0/1	23	27		
Day 6 - 7 am, Missing	0	0		
Day 6 - 5 pm, Stage 4	0	0		
Day 6 - 5 pm, Stage 3	3	3		
Day 6 - 5 pm, Stage 2	5	7		
Day 6 - 5 pm, Stage 0/1	6	5		
Day 6 - 5 pm, Missing	0	0		
End of Study, Stage 4	5	3		
End of Study, Stage 3	10	7		
End of Study, Stage 2	31	28		

End of Study, Stage 0/1	45	55		
End of Study, Missing	0	0		

Notes:

[2] - ITT patients with data at the given time point - patients did not all start at the same time

[3] - ITT patients with data at the given time point - patients did not all start at the same time

Statistical analyses

No statistical analyses for this end point

Adverse events

Adverse events information	
Timeframe for reporting adverse events:	
20 days	
Adverse event reporting additional description:	
Adverse events are reported in the safety population	
Assessment type	Systematic

Dictionary used	
Dictionary name	MedDRA
Dictionary version	14.1

Reporting groups	
Reporting group title	Placebo
Reporting group description:	
Matching placebo up to 5 days continuous IV infusion in addition to standard of care (SOC)	
Reporting group title	OCR-002
Reporting group description:	
Continuous intravenous infusion of ornithine phenylacetate for up to 5 days on top of standard of care at dose levels predicated on level of hepatic decompensation	

Serious adverse events	Placebo	OCR-002	
Total subjects affected by serious adverse events			
subjects affected / exposed	34 / 112 (30.36%)	29 / 114 (25.44%)	
number of deaths (all causes)	15	11	
number of deaths resulting from adverse events	15	11	
Neoplasms benign, malignant and unspecified (incl cysts and polyps)			
Hepatocellular carcinoma			
subjects affected / exposed	1 / 112 (0.89%)	0 / 114 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 1	0 / 0	
Vascular disorders			
Hypotension			
subjects affected / exposed	1 / 112 (0.89%)	0 / 114 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Shock haemorrhagic			
subjects affected / exposed	1 / 112 (0.89%)	1 / 114 (0.88%)	
occurrences causally related to treatment / all	0 / 1	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	

General disorders and administration site conditions			
General physical health deterioration			
subjects affected / exposed	0 / 112 (0.00%)	1 / 114 (0.88%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Generalised oedema			
subjects affected / exposed	1 / 112 (0.89%)	0 / 114 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Multi-organ failure			
subjects affected / exposed	4 / 112 (3.57%)	1 / 114 (0.88%)	
occurrences causally related to treatment / all	1 / 4	0 / 1	
deaths causally related to treatment / all	1 / 4	0 / 0	
Oedema peripheral			
subjects affected / exposed	0 / 112 (0.00%)	1 / 114 (0.88%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pyrexia			
subjects affected / exposed	1 / 112 (0.89%)	0 / 114 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Reproductive system and breast disorders			
Pelvic haemorrhage			
subjects affected / exposed	1 / 112 (0.89%)	0 / 114 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 1	0 / 0	
Respiratory, thoracic and mediastinal disorders			
Acute respiratory distress syndrome			
subjects affected / exposed	2 / 112 (1.79%)	0 / 114 (0.00%)	
occurrences causally related to treatment / all	0 / 2	0 / 0	
deaths causally related to treatment / all	0 / 1	0 / 0	
Hepatic hydrothorax			

subjects affected / exposed	0 / 112 (0.00%)	1 / 114 (0.88%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Hypoxia			
subjects affected / exposed	1 / 112 (0.89%)	0 / 114 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pulmonary oedema			
subjects affected / exposed	0 / 112 (0.00%)	1 / 114 (0.88%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 1	
Respiratory distress			
subjects affected / exposed	1 / 112 (0.89%)	1 / 114 (0.88%)	
occurrences causally related to treatment / all	0 / 1	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Respiratory failure			
subjects affected / exposed	1 / 112 (0.89%)	0 / 114 (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			
Fall			
subjects affected / exposed	0 / 112 (0.00%)	1 / 114 (0.88%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Cardiac disorders			
Cardio-respiratory arrest			
subjects affected / exposed	0 / 112 (0.00%)	1 / 114 (0.88%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 1	
Ventricular tachycardia			
subjects affected / exposed	0 / 112 (0.00%)	1 / 114 (0.88%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	1 / 1	

Nervous system disorders			
Encephalopathy			
subjects affected / exposed	2 / 112 (1.79%)	1 / 114 (0.88%)	
occurrences causally related to treatment / all	0 / 2	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Epilepsy			
subjects affected / exposed	1 / 112 (0.89%)	0 / 114 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Hepatic encephalopathy			
subjects affected / exposed	9 / 112 (8.04%)	9 / 114 (7.89%)	
occurrences causally related to treatment / all	0 / 9	0 / 9	
deaths causally related to treatment / all	0 / 1	0 / 1	
Intracranial pressure increased			
subjects affected / exposed	1 / 112 (0.89%)	0 / 114 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Thalamus haemorrhage			
subjects affected / exposed	0 / 112 (0.00%)	1 / 114 (0.88%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Blood and lymphatic system disorders			
Anaemia			
subjects affected / exposed	0 / 112 (0.00%)	1 / 114 (0.88%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Gastrointestinal disorders			
Ascites			
subjects affected / exposed	2 / 112 (1.79%)	0 / 114 (0.00%)	
occurrences causally related to treatment / all	0 / 2	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Gastrointestinal haemorrhage			

subjects affected / exposed	1 / 112 (0.89%)	1 / 114 (0.88%)	
occurrences causally related to treatment / all	0 / 1	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Localised intraabdominal fluid collection			
subjects affected / exposed	1 / 112 (0.89%)	0 / 114 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Upper gastrointestinal haemorrhage			
subjects affected / exposed	1 / 112 (0.89%)	1 / 114 (0.88%)	
occurrences causally related to treatment / all	0 / 1	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Hepatobiliary disorders			
Chronic hepatic failure			
subjects affected / exposed	1 / 112 (0.89%)	2 / 114 (1.75%)	
occurrences causally related to treatment / all	0 / 1	0 / 2	
deaths causally related to treatment / all	0 / 1	0 / 2	
Hepatic cirrhosis			
subjects affected / exposed	1 / 112 (0.89%)	0 / 114 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 1	0 / 0	
Hepatic failure			
subjects affected / exposed	2 / 112 (1.79%)	2 / 114 (1.75%)	
occurrences causally related to treatment / all	0 / 2	0 / 2	
deaths causally related to treatment / all	0 / 2	0 / 2	
Hepatic function abnormal			
subjects affected / exposed	0 / 112 (0.00%)	1 / 114 (0.88%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 1	
Renal and urinary disorders			
Anuria			
subjects affected / exposed	0 / 112 (0.00%)	1 / 114 (0.88%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	

Renal failure			
subjects affected / exposed	1 / 112 (0.89%)	1 / 114 (0.88%)	
occurrences causally related to treatment / all	0 / 1	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Renal failure acute			
subjects affected / exposed	3 / 112 (2.68%)	1 / 114 (0.88%)	
occurrences causally related to treatment / all	0 / 3	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Infections and infestations			
Erysipelas			
subjects affected / exposed	0 / 112 (0.00%)	1 / 114 (0.88%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Lobar pneumonia			
subjects affected / exposed	0 / 112 (0.00%)	1 / 114 (0.88%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Peritonitis bacterial			
subjects affected / exposed	1 / 112 (0.89%)	0 / 114 (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 / 112 (0.89%)	3 / 114 (2.63%)	
occurrences causally related to treatment / all	0 / 1	0 / 3	
deaths causally related to treatment / all	0 / 0	0 / 0	
Sepsis			
subjects affected / exposed	2 / 112 (1.79%)	2 / 114 (1.75%)	
occurrences causally related to treatment / all	0 / 3	0 / 2	
deaths causally related to treatment / all	0 / 1	0 / 1	
Septic shock			
subjects affected / exposed	1 / 112 (0.89%)	1 / 114 (0.88%)	
occurrences causally related to treatment / all	0 / 1	0 / 1	
deaths causally related to treatment / all	0 / 1	0 / 1	
Metabolism and nutrition disorders			

Hypovolaemia			
subjects affected / exposed	1 / 112 (0.89%)	0 / 114 (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: 5 %

Non-serious adverse events	Placebo	OCR-002	
Total subjects affected by non-serious adverse events			
subjects affected / exposed	31 / 112 (27.68%)	30 / 114 (26.32%)	
Blood and lymphatic system disorders			
Anaemia			
subjects affected / exposed	8 / 112 (7.14%)	13 / 114 (11.40%)	
occurrences (all)	11	14	
General disorders and administration site conditions			
Pyrexia			
subjects affected / exposed	7 / 112 (6.25%)	6 / 114 (5.26%)	
occurrences (all)	7	6	
Infections and infestations			
Urinary tract infection			
subjects affected / exposed	4 / 112 (3.57%)	8 / 114 (7.02%)	
occurrences (all)	4	8	
Metabolism and nutrition disorders			
Hypokalaemia			
subjects affected / exposed	8 / 112 (7.14%)	9 / 114 (7.89%)	
occurrences (all)	10	9	
Hypophosphataemia			
subjects affected / exposed	9 / 112 (8.04%)	5 / 114 (4.39%)	
occurrences (all)	9	5	

More information

Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? Yes

Date	Amendment
25 February 2014	The protocol was updated to facilitate participation of countries outside of North America and to improve recruitment rates.
19 March 2014	The protocol was modified to optimize the dosing paradigm.
24 October 2014	The protocol was updated to improve recruitment rate.
01 July 2015	The protocol was updated to incorporate recommendations from the Independent Data Monitoring Committee (IDMC).

Notes:

Interruptions (globally)

Were there any global interruptions to the trial? No

Limitations and caveats

None reported