Clinical trial results:
A Randomized, Double-Blind, Multi-Center Study to Evaluate the Efficacy and Safety of Oral Solithromycin (CEM-101) Compared to Oral Moxifloxacin in the Treatment of Adult Patients with Community-Acquired Bacterial Pneumonia

Summary

EudraCT number	2012-003971-20
Trial protocol	HU CZ ES PL LV EE BG RO
Global end of trial date	23 October 2014

Results information

Result version number	v1 (current)
This version publication date	23 April 2016
First version publication date	23 April 2016

Trial information

Trial identification

Sponsor protocol code	CE01-300

Additional study identifiers

ISRCTN number	-
ClinicalTrials.gov id (NCT number)	NCT01756339
WHO universal trial number (UTN)	-
Other trial identifiers	IND: 101317

Notes:

Sponsors

Sponsor organisation name	Cempra Pharmaceuticals, Inc.
Sponsor organisation address	6320 Quadrangle Drive, Suite 360, Chapel Hill, United States, NC 27517
Public contact	Clinical Trials Info, Cempra Pharmaceuticals, Inc, clinicaltrials@cempra.com
Scientific contact	Clinical Trials Info, Cempra Pharmaceuticals, Inc, clinicaltrials@cempra.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	05 February 2016
Is this the analysis of the primary completion data?	Yes
Primary completion date	23 October 2014
Global end of trial reached?	Yes
Global end of trial date	23 October 2014
Was the trial ended prematurely?	No

Notes:

General information about the trial

Main objective of the trial:

To determine the noninferiority (NI) oral solithromycin compared with oral moxifloxacin with respect to the following EMA co-primary endpoints: clinical response assessed at Test of Cure (TOC), also called Short-term Follow-Up Visit (SFU), 5-10 days after the last dose of study drug, in the Intent to Treat (ITT) population and clinically evaluable (CE-SFU) population.

Protection of trial subjects:

This study was conducted in compliance with the protocol and all regulatory requirements, in accordance with GCP, including International Conference on Harmonisation (ICH) guidelines, and in general conformity with the most recent version of the Declaration of Helsinki.

Background therapy:

A single dose of a short-acting antibiotic (penicillins, cephalosporins [not ceftriaxone], tetracyclines, or trimethoprim-sulfamethoxazole) in the 7 days prior to enrolment was permitted (number of patient limited to 25% of the population).

Evidence for comparator:

Moxifloxacin was chosen as the active comparator for multiple reasons.
It has established efficacy in the treatment of CABP, with potent activity against key pathogens associated with CABP. Moxifloxacin is recommended empiric therapy for moderately severe CABP in the EU and USA. Additionally, moxifloxacin is available in IV and oral formulations, and thus is an appropriate comparator for both this study and Study CE01-301, the Phase 3 solithromycin IV-to-Oral CABP trial. It was also possible to define a common moxifloxacin regimen for all countries in which the study was conducted.

Actual start date of recruitment	03 January 2013
Long term follow-up planned	No
Independent data monitoring committee (IDMC) involvement?	Yes

Notes:

Population of trial subjects

Subjects enrolled per country

Country: Number of subjects enrolled	South Africa: 102
Country: Number of subjects enrolled	Spain: 16
Country: Number of subjects enrolled	United States: 190
Country: Number of subjects enrolled	Argentina: 58
Country: Number of subjects enrolled	Bulgaria: 67
Country: Number of subjects enrolled	Canada: 14
Country: Number of subjects enrolled	Czech Republic: 11
Country: Number of subjects enrolled	Dominican Republic: 14
Country: Number of subjects enrolled	Ecuador: 34
Country: Number of subjects enrolled	Estonia: 2

Country: Number of subjects enrolled	Germany: 2
Country: Number of subjects enrolled	Hungary: 60
Country: Number of subjects enrolled	Latvia: 9
Country: Number of subjects enrolled	Poland: 29
Country: Number of subjects enrolled	Romania: 106
Country: Number of subjects enrolled	Russian Federation: 146
Worldwide total number of subjects	860
EEA total number of subjects	302

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)	568
From 65 to 84 years	281
85 years and over	11

Subject disposition

Recruitment

Recruitment details:

A total of 860 patients were enrolled from 114 centers in Europe (448 patients), North America (224 patients), Latin America (106 patients), and South Africa (102 patients). The first patient was enrolled 03 January 2013, the last patient was enrolled 25 September 2014, and the final study visit was conducted 23 October 2014.

Pre-assignment

Screening details:

Eligible patients were males or females ≥18 years of age with an acute onset or worsening of at least 3 of the following signs and symptoms of CABP: cough, production of purulent sputum, shortness of breath (dyspnea), chest pain.
And at least 1 of the following: fever, hypothermia, presence of pulmonary rales and/or pulmonary consolidation.

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, Monitor, Data analyst, Carer, Assessor

Blinding implementation details:

A double-dummy design was utilized, with solithromycin placebo capsules identical in appearance to solithromycin capsules and moxifloxacin placebo over-encapsulated tablets identical in appearance to moxifloxacin overencapsulated tablets.All personnel involved with the evaluation of patient efficacy and safety were blind with the exception of an unblinded statistician who was responsible for generating tables for the Data Monitoring Committee (DMC) and the bioanalytical personnel.

Arms

Are arms mutually exclusive?	Yes
Arm title	Solithromycin

Arm description:

Solithromycin treatment group

Arm type	Experimental
Investigational medicinal product name	Solithromycin
Investigational medicinal product code	CEM-101
Other name	
Pharmaceutical forms	Capsule, hard
Routes of administration	Oral use

Dosage and administration details:

Day 1: Oral solithromycin 800 mg (4×200 mg capsules) and 1 oral moxifloxacin placebo capsule.
Days 2-5: Oral solithromycin 400 mg (2×200 mg capsules) and 1 oral moxifloxacin placebo capsule daily
Days 6-7:2 Oral solithromycin placebo capsules and 1 oral moxifloxacin placebo capsule daily

Arm title	Moxifloxacin

Arm description:

Moxifloxacin treatment group

Arm type	Active comparator
Investigational medicinal product name	Moxifloxacin
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Tablet
Routes of administration	Oral use

Dosage and administration details:

Day 1: Oral moxifloxacin 400 mg (1×400 mg over-encapsulated tablet) and 4 oral solithromycin placebo capsules
Days 2-7: Oral moxifloxacin 400 mg (1×400 mg over-encapsulated tablet) and 2 oral solithromycin placebo capsules daily

Number of subjects in period 1	Solithromycin	Moxifloxacin
Started	426	434
Completed	406	413
Not completed	20	21
Adverse event, serious fatal	6	6
Consent withdrawn by subject	11	6
Physician decision	-	1
Adverse event, non-fatal	1	2
randomised in error	-	1
Lost to follow-up	2	5

Baseline characteristics

Reporting groups	
Reporting group title	Solithromycin
Reporting group description: Solithromycin treatment group	
Reporting group title	Moxifloxacin
Reporting group description: Moxifloxacin treatment group	

Reporting group values	Solithromycin	Moxifloxacin	Total
Number of subjects	426	434	860
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)	271	297	568
From 65-84 years	150	131	281
85 years and over	5	6	11
Age continuous Units: years			
arithmetic mean	58.5	56.7	
standard deviation	± 14.7	± 15.5	-
Gender categorical Units: Subjects			
Female	199	205	404
Male	227	229	456
PORT risk class			
PORT core reported in the eCRF			
Units: Subjects			
Port I	1	0	1
Port II	209	223	432
Port IIII	168	173	341
Port IV	48	38	86

End points

End points reporting groups

Reporting group title	Solithromycin
Reporting group description: Solithromycin treatment group	
Reporting group title	Moxifloxacin
Reporting group description: Moxifloxacin treatment group	
Subject analysis set title	Solithromycin -ITT Set
Subject analysis set type	Intention-to-treat
Subject analysis set description: The analysis set consists of all randomized patients regardless of whether or not the patient received study drug. A patient is considered randomized when the Investigator or Investigator's designee receives the IWRS-generated randomization number.	
Subject analysis set title	Moxifloxacin - ITT Set
Subject analysis set type	Intention-to-treat
Subject analysis set description: The ITT set consists of all randomized patients regardless of whether or not the patient received study drug. A patient is considered randomized when the Investigator or Investigator's designee receives the IWRS-generated randomization number.	
Subject analysis set title	Solithromycin - Clinically Evaluable Set
Subject analysis set type	Per protocol
Subject analysis set description: The Clinically Evaluable (CE) populations will consist of all patients in the ITT population who also meet the criteria listed in the SAP, among them: met key inclusion criteria, did not met the exclusion criteria, completed the TOC Visit 5-10 days after the last dose of study drug, Received ≥2 doses of study drug during the first 48 hours if the patient is a clinical failure, received ≥3 doses of study drug during the first 72 hours if the patient is a clinical success, did not receive another systemic antibacterial from the first dose of study drug through EOT (end of treatment) or through TOC with likely or documented activity against confirmed or potential CABP pathogens, received the correct study drug based on randomization assignment.	
Subject analysis set title	Moxifloxacin- Clinically Evaluable Set
Subject analysis set type	Per protocol
Subject analysis set description: The Clinically Evaluable (CE) populations will consist of all patients in the ITT population who also meet the criteria listed in the SAP, among them: met key inclusion criteria, did not met the exclusion criteria, completed the TOC Visit 5-10 days after the last dose of study drug, Received ≥2 doses of study drug during the first 48 hours if the patient is a clinical failure, received ≥3 doses of study drug during the first 72 hours if the patient is a clinical success, did not receive another systemic antibacterial from the first dose of study drug through EOT (end of treatment) or through TOC with likely or documented activity against confirmed or potential CABP pathogens, received the correct study drug based on randomization assignment.	

Primary: Clinical response-ITT at TOC: non-inferiority hypothesis

End point title	Clinical response-ITT at TOC: non-inferiority hypothesis
End point description: Proportion of patients with clinical success of CABP symptoms. Clinical response rates at the TOC visit (or SFU visit) for the ITT Population is a co-primary endpoint of the study. Clinical response (Investigator assessment) is classified as success, failure, or indeterminate according to the definitions in the SAP.	
End point type	Primary
End point timeframe: At Test of Cure (TOC) , i.e. 5-10 days after last dose of study drug.	

End point values	Solithromycin	Moxifloxacin		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	426[1]	434[2]		
Units: number of patients (%)				
success	360	376		
failure	49	38		
indeterminate	17	20		

Notes:

[1] - ITT Population

[2] - ITT Population

Statistical analyses

Statistical analysis title	Non-inferiority hypothesis test (success)-ITT

Statistical analysis description:

H0: Difference (Solithromycin treatment group minus Moxifloxacin treatment group) of clinical success rates ≤ -10%

Comparison groups	Solithromycin v Moxifloxacin
Number of subjects included in analysis	860
Analysis specification	Pre-specified
Analysis type	non-inferiority[3]
Parameter estimate	Difference of clinical success rates
Point estimate	-2.13
Confidence interval	
level	95 %
sides	2-sided
lower limit	-6.9
upper limit	2.6

Notes:

[3] - A non-inferiority margin of 10% was used.

Primary: Clinical response- CE at TOC: non-inferiority hypothesis

End point title	Clinical response- CE at TOC: non-inferiority hypothesis

End point description:

Proportion of patients with clinical success of CABP symptoms at TOC for the Clinically Evaluable (CE) Population is a co-primary endpoint.
Clinical response (Investigator assessment) is classified as success, failure or indeterminate according to the definition in the SAP.

End point type	Primary

End point timeframe:

At TOC

End point values	Solithromycin	Moxifloxacin		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	388[4]	390[5]		
Units: number of patients (%)				
Success	342	356		
Failure	46	33		
Indeterminate	0	1		

Notes:

[4] - Clinically Evaluable Population

[5] - Clinically Evaluable Population

Statistical analyses

Statistical analysis title	Non-inferiority hypotesis test (success) - CE

Statistical analysis description:

H0: Difference (solithromycin minus Moxifloxacin treatment group) of clinical success rates ≤ -10%.

Comparison groups	Solithromycin v Moxifloxacin
Number of subjects included in analysis	778
Analysis specification	Pre-specified
Analysis type	non-inferiority[6]
Parameter estimate	Difference in clinical success rates
Point estimate	-3.14
Confidence interval	
level	95 %
sides	2-sided
lower limit	-7.6
upper limit	1.1

Notes:

[6] - A non-inferiority margin of 10% was used.

Adverse events

Adverse events information

Timeframe for reporting adverse events:

From first study drug administration to late follow-up visit (Day 28-35 after first dose of study drug).

Assessment type	Systematic

Dictionary used

Dictionary name	MedDRA
Dictionary version	17.1

Reporting groups

Reporting group title	Solithromycin
Reporting group description: -	
Reporting group title	Moxifloxacin

Reporting group description: -

Serious adverse events	Solithromycin	Moxifloxacin	
Total subjects affected by serious adverse events			
subjects affected / exposed	28 / 424 (6.60%)	27 / 432 (6.25%)	
number of deaths (all causes)	6	6	
number of deaths resulting from adverse events	0	0	
Neoplasms benign, malignant and unspecified (incl cysts and polyps)			
Leukaemia			
subjects affected / exposed	0 / 424 (0.00%)	1 / 432 (0.23%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Lung cancer metastatic			
subjects affected / exposed	1 / 424 (0.24%)	0 / 432 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Lung carcinoma cell type unspecified stage IV			
subjects affected / exposed	0 / 424 (0.00%)	1 / 432 (0.23%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Lung neoplasm malignant			

subjects affected / exposed	0 / 424 (0.00%)	2 / 432 (0.46%)	
occurrences causally related to treatment / all	0 / 0	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Vascular disorders			
Deep vein thrombosis			
subjects affected / exposed	1 / 424 (0.24%)	1 / 432 (0.23%)	
occurrences causally related to treatment / all	0 / 1	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pregnancy, puerperium and perinatal conditions			
Pregnancy			
subjects affected / exposed	1 / 424 (0.24%)	0 / 432 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
General disorders and administration site conditions			
Multi-organ failure			
subjects affected / exposed	1 / 424 (0.24%)	0 / 432 (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	0 / 424 (0.00%)	1 / 432 (0.23%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 1	
Acute respiratory failure			
subjects affected / exposed	1 / 424 (0.24%)	2 / 432 (0.46%)	
occurrences causally related to treatment / all	0 / 1	0 / 2	
deaths causally related to treatment / all	0 / 1	0 / 0	
Asthma			
subjects affected / exposed	1 / 424 (0.24%)	0 / 432 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Bronchitis chronic			

subjects affected / exposed	1 / 424 (0.24%)	0 / 432 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Bronchospasm			
subjects affected / exposed	1 / 424 (0.24%)	0 / 432 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 1	0 / 0	
Chronic obstructive pulmonary disease			
subjects affected / exposed	1 / 424 (0.24%)	0 / 432 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Hypoxia			
subjects affected / exposed	1 / 424 (0.24%)	0 / 432 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pleural effusion			
subjects affected / exposed	1 / 424 (0.24%)	1 / 432 (0.23%)	
occurrences causally related to treatment / all	0 / 1	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pulmonary embolism			
subjects affected / exposed	1 / 424 (0.24%)	1 / 432 (0.23%)	
occurrences causally related to treatment / all	0 / 1	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 1	
Respiratory failure			
subjects affected / exposed	2 / 424 (0.47%)	2 / 432 (0.46%)	
occurrences causally related to treatment / all	0 / 2	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 2	
Injury, poisoning and procedural complications			
Femur fracture			
subjects affected / exposed	0 / 424 (0.00%)	1 / 432 (0.23%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Cardiac disorders			

Acute myocardial infarction			
subjects affected / exposed	1 / 424 (0.24%)	0 / 432 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 1	0 / 0	
Atrial fibrillation			
subjects affected / exposed	1 / 424 (0.24%)	1 / 432 (0.23%)	
occurrences causally related to treatment / all	0 / 1	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
cardiac failure			
subjects affected / exposed	1 / 424 (0.24%)	1 / 432 (0.23%)	
occurrences causally related to treatment / all	0 / 1	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 1	
Cardiac failure congestive			
subjects affected / exposed	0 / 424 (0.00%)	2 / 432 (0.46%)	
occurrences causally related to treatment / all	0 / 0	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 1	
Ventricular failure			
subjects affected / exposed	0 / 424 (0.00%)	1 / 432 (0.23%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Nervous system disorders			
Cerebrovascular accident			
subjects affected / exposed	2 / 424 (0.47%)	0 / 432 (0.00%)	
occurrences causally related to treatment / all	0 / 2	0 / 0	
deaths causally related to treatment / all	0 / 2	0 / 0	
Gastrointestinal disorders			
Gastritis erosive			
subjects affected / exposed	0 / 424 (0.00%)	1 / 432 (0.23%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Oesophageal obstruction			
subjects affected / exposed	1 / 424 (0.24%)	0 / 432 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	

Hepatobiliary disorders			
Hepatorenal syndrome			
subjects affected / exposed	0 / 424 (0.00%)	1 / 432 (0.23%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 1	
Renal and urinary disorders			
Renal failure			
subjects affected / exposed	1 / 424 (0.24%)	0 / 432 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Endocrine disorders			
Thyroiditis subacute			
subjects affected / exposed	0 / 424 (0.00%)	1 / 432 (0.23%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Infections and infestations			
Empyema			
subjects affected / exposed	1 / 424 (0.24%)	1 / 432 (0.23%)	
occurrences causally related to treatment / all	0 / 1	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Infectious pleural effusion			
subjects affected / exposed	1 / 424 (0.24%)	1 / 432 (0.23%)	
occurrences causally related to treatment / all	0 / 1	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Lung abscess			
subjects affected / exposed	0 / 424 (0.00%)	1 / 432 (0.23%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pneumonia			
subjects affected / exposed	6 / 424 (1.42%)	3 / 432 (0.69%)	
occurrences causally related to treatment / all	0 / 6	0 / 3	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pneumonia influenzal			

subjects affected / exposed	1 / 424 (0.24%)	0 / 432 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pneumonia pseudomonal			
subjects affected / exposed	1 / 424 (0.24%)	0 / 432 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pulmonary tuberculosis			
subjects affected / exposed	1 / 424 (0.24%)	1 / 432 (0.23%)	
occurrences causally related to treatment / all	0 / 1	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Septic shock			
subjects affected / exposed	1 / 424 (0.24%)	0 / 432 (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: 2 %

Non-serious adverse events	Solithromycin	Moxifloxacin	
Total subjects affected by non-serious adverse events			
subjects affected / exposed	65 / 424 (15.33%)	62 / 432 (14.35%)	
Nervous system disorders			
Dizziness			
subjects affected / exposed	9 / 424 (2.12%)	7 / 432 (1.62%)	
occurrences (all)	9	7	
Headache			
subjects affected / exposed	19 / 424 (4.48%)	10 / 432 (2.31%)	
occurrences (all)	19	10	
Gastrointestinal disorders			
Diarrhoea			
subjects affected / exposed	15 / 424 (3.54%)	27 / 432 (6.25%)	
occurrences (all)	15	28	
Nausea			
subjects affected / exposed	13 / 424 (3.07%)	16 / 432 (3.70%)	
occurrences (all)	13	16	

Vomiting subjects affected / exposed occurrences (all)	9 / 424 (2.12%) 9	9 / 432 (2.08%) 11	

More information

Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? No

Interruptions (globally)

Were there any global interruptions to the trial? No

Limitations and caveats

None reported