Clinical trial results:
CD19-targeting 3rd generation CAR T cells for refractory B cell malignancy - a phase I/IIa trial.

Summary

EudraCT number	2013-001393-19
Trial protocol	SE
Global end of trial date	31 May 2017

Results information

Result version number	v1 (current)
This version publication date	20 June 2018
First version publication date	20 June 2018

Trial information

Trial identification

Sponsor protocol code	003:TCELL

Additional study identifiers

ISRCTN number	-
ClinicalTrials.gov id (NCT number)	NCT02132624
WHO universal trial number (UTN)	-

Notes:

Sponsors

Sponsor organisation name	Uppsala university
Sponsor organisation address	Dag Hammarskjöldsväg 20, Uppsala, Sweden, 75185
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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	20 May 2018
Is this the analysis of the primary completion data?	No

Global end of trial reached?	Yes
Global end of trial date	31 May 2017
Was the trial ended prematurely?	No

Notes:

General information about the trial

Main objective of the trial:

To evaluate the feasibility of a single administration of CAR T cells to patients with disseminated B cell lymphoma or leukemia by studying the tolerance and toxicity.

Protection of trial subjects:

The main serious risks for patients treated with CAR T cells are cytokine release syndrome, brain edema and risk of infection due to low immunoglobulin level. The patients have been closely monitored and tocilizumab (anti-IL6R) was successfully used to limit cytokine release syndrome. We had no brain edemas in our study. Treating physician was monitoring immunoglobulin levels to enable displacement therapy when needed.

Background therapy:

In this trial third generation CAR T cells were used to treat adult patients with B cell malignancy (including both NHL and ALL). The CAR construct contained not only two signaling domains (commonly zeta chain and CD28 or 41BB in other clinically used CARs) but three domains. Those are zeta chain of the TcR complex, intracellular CD28 and 41BB. The CAR used was targeted to CD19 expressed on B cells. Patients were pretreated with their standard chemotherapy during weeks of CAR T cell manufacture in an attempt to control tumor growth until CARs were ready to use. The days prior CAR infusion, most patients recieved "preconditioning" with fludarabine and cyclophosphamide (low dose). The patients did not need intensive CAR during preconditioning in this study and it was given as "out patient" treatment.

Evidence for comparator:

No comparator was used.

Actual start date of recruitment	02 September 2013
Long term follow-up planned	No
Independent data monitoring committee (IDMC) involvement?	No

Notes:

Population of trial subjects

Subjects enrolled per country

Country: Number of subjects enrolled	Sweden: 15
Worldwide total number of subjects	15
EEA total number of subjects	15

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)	9
From 65 to 84 years	6
85 years and over	0

Subject disposition

Recruitment

Recruitment details:

Patients were recruited 2014-2016 in Sweden. The trial site was in Uppsala but some patients were referred to by other hospitals.

Pre-assignment

Screening details:

Main reason for failing screening was too short expected survival that would result in patients not surviving long enough for the CAR T cells to be manufactured. Three of enrolled patients did not receive CAR T cells for this reason. Too poor blood status compromized ability to manufacture CARs from patient blood in one patient.

Period 1

Period 1 title	overall trial (overall period)
Is this the baseline period?	Yes
Allocation method	Not applicable
Blinding used	Not blinded

Arms

Arm title	CAR T cells

Arm description:

CAR T cell infusion in patients pretreated/preconditioned

Arm type	Experimental
Investigational medicinal product name	CAR T cells
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Infusion
Routes of administration	Intravenous use

Dosage and administration details:

2x10e7 - 2x10e8 cells/m2

Number of subjects in period 1	CAR T cells
Started	15
Completed	15

Baseline characteristics

Reporting groups	
Reporting group title	overall trial

Reporting group description: -

Reporting group values	overall trial	Total	
Number of subjects	15	15	
Age categorical Units: Subjects			
In utero		0	
Preterm newborn infants (gestational age < 37 wks)		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)		0	
From 65-84 years		0	
85 years and over		0	
Age continuous Units: years			
median	61		
full range (min-max)	24 to 72	-	
Gender categorical Units: Subjects			
Female	7	7	
Male	8	8	

End points

End points reporting groups

Reporting group title	CAR T cells

Reporting group description:

CAR T cell infusion in patients pretreated/preconditioned

Primary: Dose limiting toxicity from treatment to end of study participation

End point title	Dose limiting toxicity from treatment to end of study participation[1]

End point description:

Adverse events leading to decision to reduce CAR T cell dose in the study

End point type	Primary

End point timeframe:

From injection of CAR T cells to end of study participation.

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: This study did not have any dose limiting toxicities. No statistical calculations were done.

End point values	CAR T cells			
Subject group type	Reporting group			
Number of subjects analysed	15			
Units: number of events				
number (not applicable)	0			

Statistical analyses

No statistical analyses for this end point

Secondary: Persistance of CAR T cells

End point title	Persistance of CAR T cells

End point description:

PCR detection of CAR T cells in blood post treatment confirmed or not confirmed

End point type	Secondary

End point timeframe:

From treatment to maximum 24 months post treatment

End point values	CAR T cells			
Subject group type	Reporting group			
Number of subjects analysed	15			
Units: Presence				
number (not applicable)	15			

Statistical analyses

No statistical analyses for this end point

Secondary: Responding patients (at least PR)

End point title	Responding patients (at least PR)

End point description:

Treatment response (at least partial response; PR) post CAR infusion

End point type	Secondary

End point timeframe:

From treatment to maximum 24 months post treatment

End point values	CAR T cells			
Subject group type	Reporting group			
Number of subjects analysed	15			
Units: Number	6			

Statistical analyses

No statistical analyses for this end point

Adverse events

Adverse events information

Timeframe for reporting adverse events:

Enrollment to last visit (maximum 24 months post CAR T cell infusion)

Assessment type	Systematic

Dictionary used

Dictionary name	CTCAE
Dictionary version	4

Reporting groups

Reporting group title	Overall trial

Reporting group description: -

Serious adverse events	Overall trial		
Total subjects affected by serious adverse events			
subjects affected / exposed	5 / 15 (33.33%)		
number of deaths (all causes)	13		
number of deaths resulting from adverse events	0		
Investigations			
Elevated Lactase dehydrogenase			
subjects affected / exposed	1 / 15 (6.67%)		
occurrences causally related to treatment / all	1 / 1		
deaths causally related to treatment / all	0 / 0		
Elevated c-reactive protein			
subjects affected / exposed	2 / 15 (13.33%)		
occurrences causally related to treatment / all	3 / 3		
deaths causally related to treatment / all	0 / 0		
Neoplasms benign, malignant and unspecified (incl cysts and polyps)			
Malignant melanoma in situ			
subjects affected / exposed	1 / 15 (6.67%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Vascular disorders			
Hypertension			
subjects affected / exposed	1 / 15 (6.67%)		
occurrences causally related to treatment / all	1 / 1		
deaths causally related to treatment / all	0 / 0		

Hypotension				
subjects affected / exposed	1 / 15 (6.67%)			
occurrences causally related to treatment / all	1 / 1			
deaths causally related to treatment / all	0 / 0			
Cardiac disorders				
Atrial fibrillation				
subjects affected / exposed	1 / 15 (6.67%)			
occurrences causally related to treatment / all	1 / 1			
deaths causally related to treatment / all	0 / 0			
Atrial tachycardia				
subjects affected / exposed	1 / 15 (6.67%)			
occurrences causally related to treatment / all	1 / 1			
deaths causally related to treatment / all	0 / 0			
Fainting				
subjects affected / exposed	1 / 15 (6.67%)			
occurrences causally related to treatment / all	1 / 1			
deaths causally related to treatment / all	0 / 0			
Syncope				
subjects affected / exposed	1 / 15 (6.67%)			
occurrences causally related to treatment / all	1 / 1			
deaths causally related to treatment / all	0 / 0			
Nervous system disorders				
Ataxia				
subjects affected / exposed	1 / 15 (6.67%)			
occurrences causally related to treatment / all	1 / 1			
deaths causally related to treatment / all	0 / 0			
Cognitive disorder				
subjects affected / exposed	1 / 15 (6.67%)			
occurrences causally related to treatment / all	1 / 1			
deaths causally related to treatment / all	0 / 0			
Dizziness				
subjects affected / exposed	1 / 15 (6.67%)			
occurrences causally related to treatment / all	1 / 1			
deaths causally related to treatment / all	0 / 0			

Dysarthria				
subjects affected / exposed	1 / 15 (6.67%)			
occurrences causally related to treatment / all	1 / 1			
deaths causally related to treatment / all	0 / 0			
Headache				
subjects affected / exposed	1 / 15 (6.67%)			
occurrences causally related to treatment / all	1 / 1			
deaths causally related to treatment / all	0 / 0			
Seizure				
subjects affected / exposed	1 / 15 (6.67%)			
occurrences causally related to treatment / all	1 / 1			
deaths causally related to treatment / all	0 / 0			
Weakness in legs				
subjects affected / exposed	1 / 15 (6.67%)			
occurrences causally related to treatment / all	1 / 1			
deaths causally related to treatment / all	0 / 0			
CNS disturbance				
subjects affected / exposed	1 / 15 (6.67%)			
occurrences causally related to treatment / all	1 / 1			
deaths causally related to treatment / all	0 / 0			
General disorders and administration site conditions				
Chills				
subjects affected / exposed	3 / 15 (20.00%)			
occurrences causally related to treatment / all	3 / 3			
deaths causally related to treatment / all	0 / 0			
Fatigue				
subjects affected / exposed	1 / 15 (6.67%)			
occurrences causally related to treatment / all	1 / 1			
deaths causally related to treatment / all	0 / 0			
Fever				
subjects affected / exposed	4 / 15 (26.67%)			
occurrences causally related to treatment / all	4 / 4			
deaths causally related to treatment / all	0 / 0			

Flu like symtom			
subjects affected / exposed	1 / 15 (6.67%)		
occurrences causally related to treatment / all	1 / 1		
deaths causally related to treatment / all	0 / 0		
Skeletal pain			
subjects affected / exposed	1 / 15 (6.67%)		
occurrences causally related to treatment / all	1 / 1		
deaths causally related to treatment / all	0 / 0		
Immune system disorders			
Cytokine release syndrome			
subjects affected / exposed	2 / 15 (13.33%)		
occurrences causally related to treatment / all	2 / 2		
deaths causally related to treatment / all	0 / 0		
Gastrointestinal disorders			
Dysphagia			
subjects affected / exposed	1 / 15 (6.67%)		
occurrences causally related to treatment / all	1 / 1		
deaths causally related to treatment / all	0 / 0		
Respiratory, thoracic and mediastinal disorders			
Hypoxia			
subjects affected / exposed	1 / 15 (6.67%)		
occurrences causally related to treatment / all	1 / 1		
deaths causally related to treatment / all	0 / 0		
Psychiatric disorders			
Confusional state			
subjects affected / exposed	1 / 15 (6.67%)		
occurrences causally related to treatment / all	1 / 1		
deaths causally related to treatment / all	0 / 0		
Musculoskeletal and connective tissue disorders			
Back pain			
subjects affected / exposed	1 / 15 (6.67%)		
occurrences causally related to treatment / all	1 / 1		
deaths causally related to treatment / all	0 / 0		
Chest wall pain			

subjects affected / exposed	1 / 15 (6.67%)		
occurrences causally related to treatment / all	1 / 1		
deaths causally related to treatment / all	0 / 0		
Infections and infestations			
Septicemia			
subjects affected / exposed	1 / 15 (6.67%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Sore throat			
subjects affected / exposed	1 / 15 (6.67%)		
occurrences causally related to treatment / all	1 / 1		
deaths causally related to treatment / all	0 / 0		

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

Non-serious adverse events	Overall trial		
Total subjects affected by non-serious adverse events			
subjects affected / exposed	15 / 15 (100.00%)		
Vascular disorders			
Ruddiness			
subjects affected / exposed	1 / 15 (6.67%)		
occurrences (all)	1		
hypertension diastolic			
subjects affected / exposed	1 / 15 (6.67%)		
occurrences (all)	1		
General disorders and administration site conditions			
Cold like symptoms			
subjects affected / exposed	1 / 15 (6.67%)		
occurrences (all)	1		
common cold			
subjects affected / exposed	6 / 15 (40.00%)		
occurrences (all)	10		
Enlarged abdomen			
subjects affected / exposed	2 / 15 (13.33%)		
occurrences (all)	2		

Flushing				
subjects affected / exposed	5 / 15 (33.33%)			
occurrences (all)	7			
Mucositis				
subjects affected / exposed	2 / 15 (13.33%)			
occurrences (all)	2			
Pain shoulder blades				
subjects affected / exposed	1 / 15 (6.67%)			
occurrences (all)	1			
Pain lymph node				
subjects affected / exposed	1 / 15 (6.67%)			
occurrences (all)	1			
pain in arm				
subjects affected / exposed	1 / 15 (6.67%)			
occurrences (all)	1			
Sweating				
subjects affected / exposed	1 / 15 (6.67%)			
occurrences (all)	1			
Swollen fingers				
subjects affected / exposed	1 / 15 (6.67%)			
occurrences (all)	1			
Pain in abdomen	Additional description: Due to tumor location			
subjects affected / exposed	1 / 15 (6.67%)			
occurrences (all)	1			
weight gain				
subjects affected / exposed	2 / 15 (13.33%)			
occurrences (all)	2			
pain in legs				
subjects affected / exposed	1 / 15 (6.67%)			
occurrences (all)	1			
swollen feet				
subjects affected / exposed	1 / 15 (6.67%)			
occurrences (all)	1			
inguinal pain				
subjects affected / exposed	1 / 15 (6.67%)			
occurrences (all)	1			

Reproductive system and breast disorders			
gynecological bleeding			
subjects affected / exposed	1 / 15 (6.67%)		
occurrences (all)	1		
Respiratory, thoracic and mediastinal disorders			
Cough			
subjects affected / exposed	4 / 15 (26.67%)		
occurrences (all)	4		
dry cough			
subjects affected / exposed	1 / 15 (6.67%)		
occurrences (all)	1		
Dyspnea			
subjects affected / exposed	1 / 15 (6.67%)		
occurrences (all)	1		
shortness of breath			
subjects affected / exposed	2 / 15 (13.33%)		
occurrences (all)	2		
Shivering			
subjects affected / exposed	1 / 15 (6.67%)		
occurrences (all)	1		
Psychiatric disorders			
Anxiety			
subjects affected / exposed	1 / 15 (6.67%)		
occurrences (all)	1		
Insomnia			
subjects affected / exposed	1 / 15 (6.67%)		
occurrences (all)	1		
Lethargic			
subjects affected / exposed	1 / 15 (6.67%)		
occurrences (all)	1		
Investigations			
Elevated ALT			
subjects affected / exposed	3 / 15 (20.00%)		
occurrences (all)	3		
Elevated bilirubin			

subjects affected / exposed	1 / 15 (6.67%)			
occurrences (all)	1			
Elevated IL-6				
subjects affected / exposed	5 / 15 (33.33%)			
occurrences (all)	5			
Elevated INR				
subjects affected / exposed	2 / 15 (13.33%)			
occurrences (all)	2			
Hypoalbuminemia				
subjects affected / exposed	6 / 15 (40.00%)			
occurrences (all)	8			
Hypocalcemia				
subjects affected / exposed	3 / 15 (20.00%)			
occurrences (all)	3			
hyponatremia				
subjects affected / exposed	3 / 15 (20.00%)			
occurrences (all)	3			
Hypokalemia				
subjects affected / exposed	3 / 15 (20.00%)			
occurrences (all)	3			
Leukopenia				
subjects affected / exposed	8 / 15 (53.33%)			
occurrences (all)	8			
Neutropenia				
subjects affected / exposed	8 / 15 (53.33%)			
occurrences (all)	10			
Trombocytopenia				
subjects affected / exposed	5 / 15 (33.33%)			
occurrences (all)	6			
Increased calcium				
subjects affected / exposed	1 / 15 (6.67%)			
occurrences (all)	3			
Decreased bilirubin				
subjects affected / exposed	1 / 15 (6.67%)			
occurrences (all)	1			
Decreased TPK				

subjects affected / exposed	1 / 15 (6.67%)		
occurrences (all)	1		
Hypernatraemia			
subjects affected / exposed	1 / 15 (6.67%)		
occurrences (all)	1		
decreased lymphocytes			
subjects affected / exposed	4 / 15 (26.67%)		
occurrences (all)	5		
Elevated ALP			
subjects affected / exposed	2 / 15 (13.33%)		
occurrences (all)	3		
Elevated AST			
subjects affected / exposed	3 / 15 (20.00%)		
occurrences (all)	3		
Decreased creatinine			
subjects affected / exposed	2 / 15 (13.33%)		
occurrences (all)	2		
Decreased erythrocytes			
subjects affected / exposed	1 / 15 (6.67%)		
occurrences (all)	1		
Elevated uric acid			
subjects affected / exposed	2 / 15 (13.33%)		
occurrences (all)	2		
Decreased ALT			
subjects affected / exposed	1 / 15 (6.67%)		
occurrences (all)	1		
Elevated thrombocytes			
subjects affected / exposed	1 / 15 (6.67%)		
occurrences (all)	1		
Injury, poisoning and procedural complications			
Fracture	Additional description: lumbar vertebrae		
subjects affected / exposed	1 / 15 (6.67%)		
occurrences (all)	1		
Skin wound			

subjects affected / exposed	1 / 15 (6.67%)		
occurrences (all)	1		
Cardiac disorders			
Fainting symptoms			
subjects affected / exposed	1 / 15 (6.67%)		
occurrences (all)	1		
Tachycardia			
subjects affected / exposed	5 / 15 (33.33%)		
occurrences (all)	6		
Ventricular extrasystoles			
subjects affected / exposed	1 / 15 (6.67%)		
occurrences (all)	1		
atrial septal defect			
subjects affected / exposed	1 / 15 (6.67%)		
occurrences (all)	1		
Nervous system disorders			
Amnesia			
subjects affected / exposed	1 / 15 (6.67%)		
occurrences (all)	1		
balance disturbance			
subjects affected / exposed	1 / 15 (6.67%)		
occurrences (all)	1		
Genital sensory loss			
subjects affected / exposed	1 / 15 (6.67%)		
occurrences (all)	1		
Hallucination			
subjects affected / exposed	2 / 15 (13.33%)		
occurrences (all)	2		
Sensory loss			
subjects affected / exposed	3 / 15 (20.00%)		
occurrences (all)	4		
Blood and lymphatic system disorders			
Anemia			
subjects affected / exposed	11 / 15 (73.33%)		
occurrences (all)	19		
Nose bleeding			

subjects affected / exposed	2 / 15 (13.33%)		
occurrences (all)	4		
Pancytopenia			
subjects affected / exposed	1 / 15 (6.67%)		
occurrences (all)	1		
lymph node bilateral fossa supraclavicula			
subjects affected / exposed	1 / 15 (6.67%)		
occurrences (all)	1		
Lymph node left axilla			
subjects affected / exposed	1 / 15 (6.67%)		
occurrences (all)	1		
Lymph node right axilla			
subjects affected / exposed	1 / 15 (6.67%)		
occurrences (all)	1		
Ear and labyrinth disorders			
Tinnitus			
subjects affected / exposed	1 / 15 (6.67%)		
occurrences (all)	1		
Eye disorders			
Diplopia			
subjects affected / exposed	2 / 15 (13.33%)		
occurrences (all)	2		
Gastrointestinal disorders			
Abdominal pain			
subjects affected / exposed	5 / 15 (33.33%)		
occurrences (all)	5		
Blisters	Additional description: tounge		
subjects affected / exposed	1 / 15 (6.67%)		
occurrences (all)	2		
Constipation			
subjects affected / exposed	4 / 15 (26.67%)		
occurrences (all)	4		
diarrhea			
subjects affected / exposed	3 / 15 (20.00%)		
occurrences (all)	3		
Dry mouth			

subjects affected / exposed	1 / 15 (6.67%)		
occurrences (all)	1		
Esophageal reflux			
subjects affected / exposed	1 / 15 (6.67%)		
occurrences (all)	1		
Flatulence			
subjects affected / exposed	1 / 15 (6.67%)		
occurrences (all)	1		
Nausea			
subjects affected / exposed	7 / 15 (46.67%)		
occurrences (all)	11		
Rectal bleeding			
subjects affected / exposed	1 / 15 (6.67%)		
occurrences (all)	1		
Taste alteration			
subjects affected / exposed	5 / 15 (33.33%)		
occurrences (all)	6		
Vomiting			
subjects affected / exposed	4 / 15 (26.67%)		
occurrences (all)	5		
improved digestion			
subjects affected / exposed	1 / 15 (6.67%)		
occurrences (all)	1		
Stool analysis	Additional description: yellowish		
subjects affected / exposed	1 / 15 (6.67%)		
occurrences (all)	1		
esophageal pain			
subjects affected / exposed	1 / 15 (6.67%)		
occurrences (all)	1		
Smelly stool			
subjects affected / exposed	1 / 15 (6.67%)		
occurrences (all)	1		
Hiccups			
subjects affected / exposed	1 / 15 (6.67%)		
occurrences (all)	1		
Dysphagia			

subjects affected / exposed	2 / 15 (13.33%)		
occurrences (all)	2		
Skin and subcutaneous tissue disorders			
Bruises			
subjects affected / exposed	1 / 15 (6.67%)		
occurrences (all)	2		
Dry skin			
subjects affected / exposed	1 / 15 (6.67%)		
occurrences (all)	2		
Petechiae arms and abdomen			
subjects affected / exposed	1 / 15 (6.67%)		
occurrences (all)	1		
Petechiae, hematoma			
subjects affected / exposed	1 / 15 (6.67%)		
occurrences (all)	2		
Skin rash			
subjects affected / exposed	1 / 15 (6.67%)		
occurrences (all)	1		
turgidity	Additional description: right eye		
subjects affected / exposed	1 / 15 (6.67%)		
occurrences (all)	1		
rash maculopapular			
subjects affected / exposed	1 / 15 (6.67%)		
occurrences (all)	1		
Renal and urinary disorders			
Urine retention			
subjects affected / exposed	2 / 15 (13.33%)		
occurrences (all)	2		
Endocrine disorders			
hyperglycemia			
subjects affected / exposed	2 / 15 (13.33%)		
occurrences (all)	2		
Musculoskeletal and connective tissue disorders			
Difficulties to move			
subjects affected / exposed	1 / 15 (6.67%)		
occurrences (all)	1		

Muscle pain subjects affected / exposed occurrences (all)	1 / 15 (6.67%) 1		
Myalgia subjects affected / exposed occurrences (all)	1 / 15 (6.67%) 1		
Neck pain subjects affected / exposed occurrences (all)	2 / 15 (13.33%) 2		
Osteoporosis subjects affected / exposed occurrences (all)	1 / 15 (6.67%) 1		
arthrosis subjects affected / exposed occurrences (all)	1 / 15 (6.67%) 1		
Infections and infestations Shingles subjects affected / exposed occurrences (all)	1 / 15 (6.67%) 1		
Skin infection subjects affected / exposed occurrences (all)	1 / 15 (6.67%) 1		
Soft tissue infection subjects affected / exposed occurrences (all)	1 / 15 (6.67%) 1		
Pneumonia subjects affected / exposed occurrences (all)	1 / 15 (6.67%) 1		
Metabolism and nutrition disorders Loss of apetite subjects affected / exposed occurrences (all)	3 / 15 (20.00%) 3		
anorexia subjects affected / exposed occurrences (all)	1 / 15 (6.67%) 1		

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