Clinical trial results:
Randomized, open-label, parallel-group, multi-centre phase II clinical trial with active cellular immunotherapy DCVAC/PCa in patients with castrate-resistant prostate cancer

Summary

EudraCT number	2011-004735-32
Trial protocol	CZ
Global end of trial date	22 February 2017

Results information

Result version number	v1 (current)
This version publication date	04 March 2018
First version publication date	04 March 2018

Trial information

Trial identification

Sponsor protocol code	SP001

Additional study identifiers

ISRCTN number	-
ClinicalTrials.gov id (NCT number)	NCT02105675
WHO universal trial number (UTN)	-

Notes:

Sponsors

Sponsor organisation name	Sotio a.s.
Sponsor organisation address	Jankovcova 1518/2, Prague, Czech Republic, 170 00
Public contact	Clinical Trials Sotio, SOTIO a.s., +420 224175111, clinicaltrial@sotio.com
Scientific contact	Clinical Trials Sotio, SOTIO a.s., +420 224175111, clinicaltrial@sotio.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	22 February 2017
Is this the analysis of the primary completion data?	Yes
Primary completion date	22 February 2017
Global end of trial reached?	Yes
Global end of trial date	22 February 2017
Was the trial ended prematurely?	No

Notes:

General information about the trial

Main objective of the trial:

The objectives of this clinical trial were to estimate the survival rate of patients 34 months after randomization; to estimate the proportion of patients without disease progression and without PSA progression 34 months after randomization; to evaluate quality of life and pain scale scoring using the standardized European Organization for Research and Treatment of Cancer Quality of Life Questionnaire (EORTC QLQ)-C30, version 3; and to evaluate the incidence of AEs (with the exception of disease progression-related AEs).

Protection of trial subjects:

Not applicable

Background therapy:

Docetaxel 75 mg/m2 at 3-week intervals combined with prednisone 5 mg orally twice daily

Evidence for comparator:

Not applicable

Actual start date of recruitment	24 February 2012
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	Czech Republic: 62
Worldwide total number of subjects	62
EEA total number of subjects	62

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)	20

From 65 to 84 years	42
85 years and over	0

Subject disposition

Recruitment

Recruitment details:

A total of 18 clinical study centers in the Czech Republic participated in the study, and 13 screened at least 1 patient onto the study. Recruitment period started on 24-Feb-2012 (first patient signed the informed consent form) and ended on 28-Feb-2014 (last patient signed the informed consent form).

Pre-assignment

Screening details:

Screened: 87
Randomized: 62
Analyzed for efficacy: 47
Analyzed for safety: 47

Period 1

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

Blinding implementation details:

Not applicable

Arms

Are arms mutually exclusive?	Yes
Arm title	Immunotherapy group

Arm description:

DCVAC/PCa in combination with chemotherapy; patients in the immunotherapy group were treated with 50 mg/day of oral cyclophosphamide for 7 days before the first dose of DCVAC/PCa and applied imiquimod cream to the planned DCVAC/PCa injection sites 24 hours before each DCVAC/PCa administration

Arm type	Experimental
Investigational medicinal product name	DCVAC/PCa
Investigational medicinal product code	Not applicable
Other name	Not applicable
Pharmaceutical forms	Dispersion for injection
Routes of administration	Subcutaneous use

Dosage and administration details:

Subcutaneous injection of approximately 1×10e7 autologous dendritic cells; oral cyclophosphamide 50 mg/day for 7 days before the first dose of DCVAC/PCa; imiquimod cream applied to the planned DCVAC/PCa injection sites 24 hours before each DCVAC/PCa administration

Arm title	Control group

Arm description:

Chemotherapy alone

Arm type	No intervention

No investigational medicinal product assigned in this arm

Number of subjects in period 1	Immunotherapy group	Control group
Started	31	31
Completed	2	4
Not completed	29	27
Physician decision	4	3
Consent withdrawn by subject	5	7
Adverse event, non-fatal	3	2
Death due to underlying disease	6	6
Manufacturing failure	3	-
Progressive disease	6	9
Protocol deviation	2	-

Baseline characteristics

Reporting groups	
Reporting group title	Immunotherapy group
Reporting group description:	
DCVAC/PCa in combination with chemotherapy; patients in the immunotherapy group were treated with 50 mg/day of oral cyclophosphamide for 7 days before the first dose of DCVAC/PCa and applied imiquimod cream to the planned DCVAC/PCa injection sites 24 hours before each DCVAC/PCa administration	
Reporting group title	Control group
Reporting group description:	
Chemotherapy alone	

Reporting group values	Immunotherapy group	Control group	Total
Number of subjects	31	31	62
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	67.0	70.38	
full range (min-max)	51.79 to 82.36	44.87 to 81.25	-
Gender categorical			
Units: Subjects			
Female	0	0	0
Male	31	31	62

End points

End points reporting groups

Reporting group title	Immunotherapy group

Reporting group description:

DCVAC/PCa in combination with chemotherapy; patients in the immunotherapy group were treated with 50 mg/day of oral cyclophosphamide for 7 days before the first dose of DCVAC/PCa and applied imiquimod cream to the planned DCVAC/PCa injection sites 24 hours before each DCVAC/PCa administration

Reporting group title	Control group

Reporting group description:

Chemotherapy alone

Subject analysis set title	mITT
Subject analysis set type	Modified intention-to-treat

Subject analysis set description:

All randomized patients who started chemotherapy except those for whom no data were available following the randomization visit. It was not clinically meaningful to include patients who did not start chemotherapy as the information from these patients did not reflect the real effect of the study treatment. Therefore, the mITT population was the primary population when evaluating the study endpoints.

Subject analysis set title	Safety
Subject analysis set type	Safety analysis

Subject analysis set description:

All randomized patients who received at least 1 dose of chemotherapy (control group) and, at the same time, received at least 1 dose of DCVAC/PCa (immunotherapy group)

Primary: Survival rate of patients 34 months after randomization

End point title	Survival rate of patients 34 months after randomization

End point description:

End point type	Primary

End point timeframe:

34 months after randomization

End point values	Immunotherapy group	Control group		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	25[1]	22[2]		
Units: Proportion of pts alive at 34 months				
number (confidence interval 95%)	0.360 (0.182 to 0.542)	0.500 (0.282 to 0.684)		

Notes:

[1] - mITT

[2] - mITT

Statistical analyses

Statistical analysis title	Primary analysis

Statistical analysis description:

Kaplan-Meier analysis and log-rank test

Comparison groups	Control group v Immunotherapy group
Number of subjects included in analysis	47
Analysis specification	Pre-specified
Analysis type	other
P-value	= 0.2791
Method	Logrank

Secondary: Survival rate of patients without disease progression and without PSA progression 34 months after randomization

End point title	Survival rate of patients without disease progression and without PSA progression 34 months after randomization

End point description:

Disease progression was defined as at least 2 additional lesions on bone scintigraphy and/or a new finding in soft tissues as per Response Evaluation Criteria in Solid Tumors (RECIST) version 1.1; PSA progression was defined as 2 consecutive increases by at least 2 ng/mL at least 2 weeks apart and by >25% above the nadir or baseline value. The main analysis used the start of chemotherapy as baseline.

End point type	Secondary

End point timeframe:

34 months after randomization

End point values	Immunotherapy group	Control group		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	25[3]	22[4]		
Units: Proportion of pts without progression				
number (confidence interval 95%)	0 (0 to 0)	0.051 (0.004 to 0.209)		

Notes:

[3] - mITT

[4] - mITT

Statistical analyses

Statistical analysis title	Secondary analysis

Statistical analysis description:

Kaplan-Meier analysis and log-rank test

Comparison groups	Immunotherapy group v Control group
Number of subjects included in analysis	47
Analysis specification	Pre-specified
Analysis type	other
P-value	= 0.3196
Method	Logrank

Secondary: Survival rate of patients without disease progression 34 months after randomization

End point title	Survival rate of patients without disease progression 34 months after randomization

End point description:

Disease progression was defined as at least 2 additional lesions on bone scintigraphy and/or a new finding in soft tissues as per Response Evaluation Criteria in Solid Tumors (RECIST) version 1.1. The main analysis used the start of chemotherapy as baseline.

End point type	Secondary

End point timeframe:

34 months after randomization

End point values	Immunotherapy group	Control group		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	25[5]	22[6]		
Units: Proportion of pts alive w/o progression				
number (confidence interval 95%)	0.048 (0.004 to 0.196)	0.134 (0.027 to 0.329)		

Notes:

[5] - mITT

[6] - mITT

Statistical analyses

Statistical analysis title	Secondary analysis

Statistical analysis description:

Kaplan-Meier analysis and log-rank test

Comparison groups	Immunotherapy group v Control group
Number of subjects included in analysis	47
Analysis specification	Pre-specified
Analysis type	other
P-value	= 0.1803
Method	Logrank

Secondary: Quality of life (Global health status) as per the standardized EORTC QLQ-C30 version 3 questionnaire

End point title	Quality of life (Global health status) as per the standardized EORTC QLQ-C30 version 3 questionnaire

End point description:

Mean profiles of scales and items of the EORTC QLQ-C30 version 3 questionnaire display for each visit the mean ±1.96× standard error of the mean and the number of patients who completed the questionnaire. These profiles showed that mean scores of all items of the EORTC QLQ-C30 version 3 questionnaire were comparable in both treatment groups.

A repeated measurement analysis was performed to investigate whether treatment, baseline score, time (i.e., visit), or interaction of treatment with time (visit) had an effect on the scores of the Global health status. The baseline score was the only factor having a statistically significant effect on the scores of the Global health status ($p < 0.0001$).

End point type	Secondary

End point timeframe:

34 months after randomization

End point values	Immunotherapy group	Control group		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	25[7]	22[8]		
Units: Not applicable				
number (not applicable)	0	0		

Notes:

[7] - mITT

[8] - mITT

Statistical analyses

Statistical analysis title	Secondary analysis

Statistical analysis description:

A repeated measurement analysis was performed using a marginal model with a robust covariance matrix. As a response variable, the scores for "on-treatment" visits with more than 10 patients with an available score in either treatment group were included. As explanatory variables, terms for treatment, baseline score, time (i.e., visit), and an interaction for treatment and time were included.

Comparison groups	Control group v Immunotherapy group
Number of subjects included in analysis	47
Analysis specification	Pre-specified
Analysis type	other
P-value	= 0.6349 [9]
Method	Marginal model

Notes:

[9] - Effect of treatment on the scores of Global health status

Secondary: Pain scale influence scoring as per the standardized EORTC QLQ-C30 version 3 questionnaire

End point title	Pain scale influence scoring as per the standardized EORTC QLQ-C30 version 3 questionnaire

End point description:

Mean profiles of scales and items of the EORTC QLQ-C30 version 3 questionnaire display for each visit the mean ±1.96× standard error of the mean and the number of patients who completed the questionnaire. These profiles showed that mean scores of all items of the EORTC QLQ-C30 version 3 questionnaire were comparable in both treatment groups.

A repeated measurement analysis was performed to investigate whether treatment, baseline score, time (i.e., visit), or interaction of treatment with time (visit) had an effect on the scores of the Pain scales. The baseline score and visit were the two factors having a statistically significant effect on the scores of the Pain scale (p = 0.0001 and p = 0.0140, respectively).

End point type	Secondary

End point timeframe:

34 months after randomization

End point values	Immunotherapy group	Control group		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	25[10]	22[11]		
Units: Not applicable				
number (not applicable)	0	0		

Notes:

[10] - mITT

[11] - mITT

Statistical analyses

Statistical analysis title	Secondary analysis

Statistical analysis description:

A repeated measurement analysis was performed using a marginal model with a robust covariance matrix. As a response variable, the scores for "on-treatment" visits with more than 10 patients with an available score in either treatment group were included. As explanatory variables, terms for treatment, baseline score, time (i.e., visit), and an interaction for treatment and time were included.

Comparison groups	Immunotherapy group v Control group
Number of subjects included in analysis	47
Analysis specification	Pre-specified
Analysis type	other
P-value	= 0.6089 [12]
Method	Marginal model

Notes:

[12] - Effect of treatment on the scores of Pain scales

Adverse events

Adverse events information

Timeframe for reporting adverse events:

Adverse events, serious adverse events: from the first dose of treatment to 30 days after the last dose of DCVAC/PCa (immunotherapy group) or completion/discontinuation of chemotherapy (control group)
Deaths: from consent signature to trial termination

Adverse event reporting additional description:

The tables include information on treatment-emergent adverse events, treatment-emergent serious adverse events, and all deaths. An event causally related to treatment was one which was assessed by investigators as causally related to DCVAC/PCa administration.

Assessment type	Systematic

Dictionary used

Dictionary name	MedDRA
Dictionary version	20.0

Reporting groups

Reporting group title	Immunotherapy group

Reporting group description:

DCVAC/PCa in combination with chemotherapy

Reporting group title	Control group

Reporting group description:

Chemotherapy alone

Serious adverse events	Immunotherapy group	Control group	
Total subjects affected by serious adverse events			
subjects affected / exposed	10 / 25 (40.00%)	5 / 22 (22.73%)	
number of deaths (all causes)	19	14	
number of deaths resulting from adverse events	1	0	
Injury, poisoning and procedural complications			
Gastroenteritis radiation			
subjects affected / exposed	1 / 25 (4.00%)	0 / 22 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Vascular disorders			
Peripheral artery occlusion			
subjects affected / exposed	0 / 25 (0.00%)	1 / 22 (4.55%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Cardiac disorders			
Cardiac failure			

subjects affected / exposed	1 / 25 (4.00%)	0 / 22 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Blood and lymphatic system disorders			
Febrile neutropenia			
subjects affected / exposed	1 / 25 (4.00%)	0 / 22 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Neutropenia			
subjects affected / exposed	0 / 25 (0.00%)	1 / 22 (4.55%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
General disorders and administration site conditions			
Fatigue			
subjects affected / exposed	1 / 25 (4.00%)	0 / 22 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Sudden death			
subjects affected / exposed	1 / 25 (4.00%)	0 / 22 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 1	0 / 0	
Eye disorders			
Retinal detachment			
subjects affected / exposed	1 / 25 (4.00%)	0 / 22 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Gastrointestinal disorders			
Colitis			
subjects affected / exposed	1 / 25 (4.00%)	0 / 22 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Duodenal ulcer			

subjects affected / exposed	0 / 25 (0.00%)	1 / 22 (4.55%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pancreatitis			
subjects affected / exposed	1 / 25 (4.00%)	0 / 22 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Renal and urinary disorders			
Acute kidney injury			
subjects affected / exposed	1 / 25 (4.00%)	0 / 22 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Bladder obstruction			
subjects affected / exposed	1 / 25 (4.00%)	0 / 22 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Haematuria			
subjects affected / exposed	0 / 25 (0.00%)	1 / 22 (4.55%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Infections and infestations			
Diabetic foot infection			
subjects affected / exposed	1 / 25 (4.00%)	0 / 22 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Phlebitis superficial			
subjects affected / exposed	0 / 25 (0.00%)	1 / 22 (4.55%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pneumonia streptococcal			
subjects affected / exposed	1 / 25 (4.00%)	0 / 22 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Septic shock			

subjects affected / exposed	1 / 25 (4.00%)	0 / 22 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Metabolism and nutrition disorders			
Hyperkalaemia			
subjects affected / exposed	1 / 25 (4.00%)	0 / 22 (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	Immunotherapy group	Control group	
Total subjects affected by non-serious adverse events			
subjects affected / exposed	23 / 25 (92.00%)	21 / 22 (95.45%)	
Nervous system disorders			
Neuropathy peripheral			
subjects affected / exposed	5 / 25 (20.00%)	2 / 22 (9.09%)	
occurrences (all)	5	2	
Paraesthesia			
subjects affected / exposed	6 / 25 (24.00%)	7 / 22 (31.82%)	
occurrences (all)	6	7	
Blood and lymphatic system disorders			
Anaemia			
subjects affected / exposed	3 / 25 (12.00%)	3 / 22 (13.64%)	
occurrences (all)	3	3	
Leukocytosis			
subjects affected / exposed	1 / 25 (4.00%)	3 / 22 (13.64%)	
occurrences (all)	1	3	
Neutropenia			
subjects affected / exposed	3 / 25 (12.00%)	5 / 22 (22.73%)	
occurrences (all)	3	5	
General disorders and administration site conditions			
Asthenia			
subjects affected / exposed	1 / 25 (4.00%)	3 / 22 (13.64%)	
occurrences (all)	1	3	
Fatigue			

subjects affected / exposed	10 / 25 (40.00%)	5 / 22 (22.73%)	
occurrences (all)	10	5	
Pyrexia			
subjects affected / exposed	3 / 25 (12.00%)	0 / 22 (0.00%)	
occurrences (all)	3	0	
Gastrointestinal disorders			
Diarrhoea			
subjects affected / exposed	6 / 25 (24.00%)	7 / 22 (31.82%)	
occurrences (all)	6	7	
Respiratory, thoracic and mediastinal disorders			
Cough			
subjects affected / exposed	3 / 25 (12.00%)	0 / 22 (0.00%)	
occurrences (all)	3	0	
Dyspnoea			
subjects affected / exposed	2 / 25 (8.00%)	3 / 22 (13.64%)	
occurrences (all)	2	3	
Skin and subcutaneous tissue disorders			
Alopecia			
subjects affected / exposed	5 / 25 (20.00%)	3 / 22 (13.64%)	
occurrences (all)	5	3	
Hyperhidrosis			
subjects affected / exposed	3 / 25 (12.00%)	1 / 22 (4.55%)	
occurrences (all)	3	1	
Nail dystrophy			
subjects affected / exposed	4 / 25 (16.00%)	0 / 22 (0.00%)	
occurrences (all)	4	0	
Rash			
subjects affected / exposed	1 / 25 (4.00%)	4 / 22 (18.18%)	
occurrences (all)	1	4	
Psychiatric disorders			
Insomnia			
subjects affected / exposed	5 / 25 (20.00%)	1 / 22 (4.55%)	
occurrences (all)	5	1	
Musculoskeletal and connective tissue disorders			
Back pain			

subjects affected / exposed	3 / 25 (12.00%)	3 / 22 (13.64%)	
occurrences (all)	3	3	
Pain in extremity			
subjects affected / exposed	3 / 25 (12.00%)	2 / 22 (9.09%)	
occurrences (all)	3	2	
Metabolism and nutrition disorders			
Decreased appetite			
subjects affected / exposed	2 / 25 (8.00%)	3 / 22 (13.64%)	
occurrences (all)	2	3	
Hyperglycaemia			
subjects affected / exposed	5 / 25 (20.00%)	3 / 22 (13.64%)	
occurrences (all)	5	3	

More information

Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? Yes

Date	Amendment
14 December 2011	- European Pharminvent Services to be responsible for pharmacovigilance services - Added specifications of the assessments of leukapheresis feasibility (vein access evaluation) prior to the procedure for patients in the immunotherapy group - Specification for HIV tests added (CE-marked kits; accredited laboratory)
11 June 2012	- Prolongation of the time frame for leukapheresis and for leukapheresis feasibility assessment - Clarification of cyclophosphamide dosing - Clarification of ACI dosing - Highlighted synchronization of visits for both groups of patients - Modified exclusion criteria - Updated SAE reporting - Explanation added for not performing leukapheresis in the control group - Reasons for early termination of patient participation in the trial added - inability to perform leukapheresis or failure to manufacture ACI - ACI transport and application description updated - Prolonged sampling time frame for Immunology and Immunomonitoring to 6 months - Explanation added that missed ACI administration is not considered a reason for termination of patients' participation in the trial
11 August 2014	- Detailed description of exploratory objectives, endpoints and analysis - Clearly distinguishing IMP from stimulating medication - Detailed description of laboratory testing performed, including samples for research - Statistical analysis section updated - Information about phase I/II clinical trials conducted by the University Hospital Motol updated per current knowledge - Section on concomitant medication was updated - Updated safety reporting sections - New term introduction: End of the Treatment, End of Study, End of Study Examination visit, Follow-up and Survival Follow-up - Updated trial duration - Updated section Rationale for Prostate Cancer Immunotherapy - Terminology harmonization
23 July 2015	- Updated safety reporting sections to capture transfer of safety monitoring responsibilities from the European PharmInvent Services transferred to SOTIO a.s. as of 03-Jan-2015 - Implementation of the Pregnancy Data Collection Form and minor wording updates in the pharmacovigilance section - Wording for Exploratory Endpoints and Analysis was detailed

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.

None reported

Notes: