



Clinical trial results:

A phase IIa clinical trial to evaluate the safety and efficacy of osimertinib (AZD9291) in first-line patients with EGFR mutation-positive locally advanced or metastatic non-small cell lung cancer and concomitant EGFR T790M mutation at time of diagnosis (AZENT study)

Summary

EudraCT number	2015-004828-66
Trial protocol	ES
Global end of trial date	

Results information

Result version number	v1 (current)
This version publication date	16 May 2021
First version publication date	16 May 2021

Trial information

Trial identification

Sponsor protocol code	MedOPP112
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Additional study identifiers

ISRCTN number	-
ClinicalTrials.gov id (NCT number)	NCT02841579
WHO universal trial number (UTN)	-

Notes:

Sponsors

Sponsor organisation name	Medica Scientia Innovation Research (MEDSIR)
Sponsor organisation address	Avenida Diagonal, 211, Barcelona, Spain, 08018
Public contact	Alicia Garcia, Medica Scientia Innovation Research (MEDSIR), 0034 932214135, alicia.garcia@medsir.org
Scientific contact	Project Manager, Medica Scientia Innovation Research (MEDSIR), 0034 932214135, margarida.garcia@medsir.org

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	Interim
Date of interim/final analysis	17 December 2018
Is this the analysis of the primary completion data?	Yes
Primary completion date	04 December 2018
Global end of trial reached?	No

Notes:

General information about the trial

Main objective of the trial:

To evaluate the efficacy of osimertinib (AZD9291), in terms of the objective response rate in patients with advanced non-squamous NSCLC with EGFR mutations and the EGFR T790M mutation at diagnosis as defined by RECIST 1.1 criteria.

Protection of trial subjects:

Standard of Care

Background therapy: -

Evidence for comparator: -

Actual start date of recruitment	02 July 2016
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	Spain: 22
Worldwide total number of subjects	22
EEA total number of subjects	22

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	10
85 years and over	3

Subject disposition

Recruitment

Recruitment details:

Between Jul 2016 and Jul 2018, a total of 22 patients with EGFR mutant NSCLC were enrolled at 7 sites.

Pre-assignment

Screening details:

Patient \geq 18 years

ECOG performance \leq 2.

CPNM with activator EGFR mutation and T790 mutation.

M1a or M1b stadium.

Life expectancy \geq 12w

Adequate bone marrow, hepatic, renal and cardiovascular function.

Recovery from all reported toxicities of previous anti-cancer therapies to baseline or grade \leq 1

Must have measurable disease (RECIST v1.1)

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	Experimental arm
Arm description: -	
Arm type	Experimental
Investigational medicinal product name	Osimertinib
Investigational medicinal product code	AZD9291
Other name	Tagrisso
Pharmaceutical forms	Film-coated tablet
Routes of administration	Oral use

Dosage and administration details:

After signing the informed consent form, the patients were treated orally with osimertinib (AZD9291) tablet 80 mg, once daily, with or without food. Tablets was packed in child-resistant high-density polyethylene (HDPE) bottles. The bottles dispensed to patients was specially prepared for the study Treatment with osimertinib (AZD9291) was continuous, and every 21-day period was considered one cycle. The treatment begins on day 1 of the first cycle. Individual bottles were dispensed in accordance with the medication identification numbers provided by the sponsor.

Patients were treated until PD, occurrence of unacceptable side effects, death, withdrawal of consent or the end of the study (EoS), after a maximum of 78 weeks after the first dose administered to the last patient enrolled in the study, whichever occur first.

Follow-up visits will take place every 6 weeks to obtain basic safety data and every 12 weeks to obtain complete efficacy and safety data.

Number of subjects in period 1	Experimental arm
Started	22
Completed	22

Baseline characteristics

Reporting groups

Reporting group title	Overall trial
Reporting group description: -	

Reporting group values	Overall trial	Total	
Number of subjects	22	22	
Age categorical			
Units: Subjects			
In utero	0	0	
Preterm newborn infants (gestational age < 37 wks)	0	0	
Newborns (0-27 days)	0	0	
Infants and toddlers (28 days-23 months)	0	0	
Children (2-11 years)	0	0	
Adolescents (12-17 years)	0	0	
Adults (18-64 years)	9	9	
From 65-84 years	10	10	
85 years and over	3	3	
Age continuous			
Units: years			
median	69.9		
full range (min-max)	59.3 to 77.7	-	
Gender categorical			
Units: Subjects			
Female	13	13	
Male	9	9	

Subject analysis sets

Subject analysis set title	Full Analysis and Safety population
Subject analysis set type	Safety analysis

Subject analysis set description:

Includes all included subjects who have received any study drug, independently of the degree of adherence to the protocol.

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

Subject analysis set description:

The Per Protocol set includes all patients included in the FAS who did not violate the protocol in a way that might affect the evaluation of the effect of the study drug on the primary endpoint, i.e., without a major protocol violation.

Subject analysis set title	ITT
Subject analysis set type	Intention-to-treat

Subject analysis set description:

All patients who received at least one dose of study medication and were evaluable for primary endpoints (overall response rate), was considered the primary population for the analysis.

Subject analysis set title	Biomarker analysis set
Subject analysis set type	Sub-group analysis

Subject analysis set description:

Consisted of all patients included in the full analysis set with evaluable samples for exploratory analyses. Further analysis sets might be defined if considered appropriate, e.g., subjects without valid determinations in all biomarker endpoints.

Reporting group values	Full Analysis and Safety population	Per protocol	ITT
Number of subjects	22	20	22
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)	9	9	6
From 65-84 years	10	8	13
85 years and over	3	3	3
Age continuous Units: years			
median	69,9	69,9	69,9
full range (min-max)	59,3 to 77,7	59,3 to 77,7	59,3 to 77,7
Gender categorical Units: Subjects			
Female	13	12	13
Male	9	8	9

Reporting group values	Biomarker analysis set		
Number of subjects	22		
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)	6		
From 65-84 years	13		
85 years and over	3		
Age continuous Units: years			
median	69,9		
full range (min-max)	59,3 to 77,7		
Gender categorical Units: Subjects			
Female	13		
Male	9		

End points

End points reporting groups

Reporting group title	Experimental arm
Reporting group description: -	
Subject analysis set title	Full Analysis and Safety population
Subject analysis set type	Safety analysis
Subject analysis set description: Includes all included subjects who have received any study drug, independently of the degree of adherence to the protocol.	
Subject analysis set title	Per protocol
Subject analysis set type	Per protocol
Subject analysis set description: The Per Protocol set includes all patients included in the FAS who did not violate the protocol in a way that might affect the evaluation of the effect of the study drug on the primary endpoint, i.e., without a major protocol violation.	
Subject analysis set title	ITT
Subject analysis set type	Intention-to-treat
Subject analysis set description: All patients who received at least one dose of study medication and were evaluable for primary endpoints (overall response rate), was considered the primary population for the analysis.	
Subject analysis set title	Biomarker analysis set
Subject analysis set type	Sub-group analysis
Subject analysis set description: Consisted of all patients included in the full analysis set with evaluable samples for exploratory analyses. Further analysis sets might be defined if considered appropriate, e.g., subjects without valid determinations in all biomarker endpoints.	

Primary: Objective response rate

End point title	Objective response rate
End point description: The primary endpoint was the objective response rate (ORR) which is defined as the Complete Responses (CR) or Partial Responses (PR) to treatment in accordance with the guidelines of RECIST version 1.1 criteria.	
End point type	Primary
End point timeframe: An objective response should be confirmed at least 4-6 weeks after the initial response.	

End point values	Full Analysis and Safety population	ITT		
Subject group type	Subject analysis set	Subject analysis set		
Number of subjects analysed	22	22		
Units: CR or PR	22	22		

Statistical analyses

Statistical analysis title	Analysis of cORR
Statistical analysis description:	
In accordance with preplanned sample size: in the first stage, 22 patients will be accrued. If there are 11 or fewer responses in these 22 patients, the study will be stopped. We report 17 patients with confirmed overall response. Therefore, based on cORR the criterion to continue the study has been achieved.	
Comparison groups	Full Analysis and Safety population v ITT
Number of subjects included in analysis	44
Analysis specification	Pre-specified
Analysis type	equivalence
P-value	< 0.025
Method	UMVUE
Parameter estimate	cORR
Point estimate	77.3
Confidence interval	
level	95 %
sides	2-sided
lower limit	54.6
upper limit	92.2

Secondary: Safety endpoint

End point title	Safety endpoint
End point description:	
Assess adverse events was evaluated using the Common Terminology Criteria for Adverse Events (CTCAE) of the US National Cancer Institute (NCI), version 4. Grade 3 or 4 adverse events and serious adverse events was assessed to determine the safety and tolerability of the various combinations of drugs.	
End point type	Secondary
End point timeframe:	
During the treatment and the follow-up period.	

End point values	Full Analysis and Safety population			
Subject group type	Subject analysis set			
Number of subjects analysed	22			
Units: Presence of AE	22			

Statistical analyses

No statistical analyses for this end point

Secondary: Efficacy endpoint

End point title	Efficacy endpoint
End point description:	
The progression-free survival (PFS) is defined as the time from the start of the treatment to death or	

progressive disease (PD), assessed by the investigator in accordance with Response Evaluation Criteria in Solid Tumors (RECIST) version 1.1, regardless of whether the patient has discontinued the study treatment or is receiving treatment with another drug.

End point type	Secondary
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End point timeframe:

From the start of the treatment to death or progressive disease.

End point values	Full Analysis and Safety population	Per protocol		
Subject group type	Subject analysis set	Subject analysis set		
Number of subjects analysed	22	22		
Units: PFS	22	22		

Statistical analyses

No statistical analyses for this end point

Adverse events

Adverse events information

Timeframe for reporting adverse events:

Until the last patient completes the 78 weeks of treatment, shows a progression or until his death. The event that occurs first.

Assessment type	Systematic
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Dictionary used

Dictionary name	CTCAE
Dictionary version	4

Reporting groups

Reporting group title	Reporting group
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Reporting group description: -

Reporting group			
Serious adverse events			
Total subjects affected by serious adverse events			
subjects affected / exposed	6 / 22 (27.27%)		
number of deaths (all causes)	0		
number of deaths resulting from adverse events	0		
Cardiac disorders			
Ventricular aortic block			
subjects affected / exposed	1 / 22 (4.55%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Blood and lymphatic system disorders			
Pulmonary thrombosis			
subjects affected / exposed	1 / 22 (4.55%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Respiratory, thoracic and mediastinal disorders			
Respiratory failure			
subjects affected / exposed	2 / 22 (9.09%)		
occurrences causally related to treatment / all	0 / 2		
deaths causally related to treatment / all	0 / 0		
Pulmonary infection			

subjects affected / exposed	1 / 22 (4.55%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Musculoskeletal and connective tissue disorders			
Femur fracture			
subjects affected / exposed	1 / 22 (4.55%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Metabolism and nutrition disorders			
Hyperkalaemia			
subjects affected / exposed	1 / 22 (4.55%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		

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

Non-serious adverse events	Reporting group		
Total subjects affected by non-serious adverse events			
subjects affected / exposed	21 / 22 (95.45%)		
Vascular disorders			
Oedema bimaleolar			
subjects affected / exposed	1 / 22 (4.55%)		
occurrences (all)	1		
Hypotension			
subjects affected / exposed	1 / 22 (4.55%)		
occurrences (all)	1		
Surgical and medical procedures			
Postoperative wound			
subjects affected / exposed	1 / 22 (4.55%)		
occurrences (all)	1		
General disorders and administration site conditions			
Abdominal pain			
subjects affected / exposed	1 / 22 (4.55%)		
occurrences (all)	1		
Headache			

subjects affected / exposed	2 / 22 (9.09%)		
occurrences (all)	3		
Lower limb weakness			
subjects affected / exposed	1 / 22 (4.55%)		
occurrences (all)	1		
Flu			
subjects affected / exposed	1 / 22 (4.55%)		
occurrences (all)	1		
Hip pain			
subjects affected / exposed	1 / 22 (4.55%)		
occurrences (all)	1		
Costal pain			
subjects affected / exposed	1 / 22 (4.55%)		
occurrences (all)	1		
Operated extremity pain			
subjects affected / exposed	1 / 22 (4.55%)		
occurrences (all)	3		
General pain			
subjects affected / exposed	1 / 22 (4.55%)		
occurrences (all)	1		
lumbar pain			
subjects affected / exposed	1 / 22 (4.55%)		
occurrences (all)	1		
Pleural pain			
subjects affected / exposed	1 / 22 (4.55%)		
occurrences (all)	2		
Chest pain			
subjects affected / exposed	1 / 22 (4.55%)		
occurrences (all)	1		
Fatigue			
subjects affected / exposed	1 / 22 (4.55%)		
occurrences (all)	1		
Cephalic instability			
subjects affected / exposed	1 / 22 (4.55%)		
occurrences (all)	1		
Insomnia			

subjects affected / exposed occurrences (all)	1 / 22 (4.55%) 1		
Reproductive system and breast disorders Erectile dysfunction subjects affected / exposed occurrences (all)	1 / 22 (4.55%) 1		
Respiratory, thoracic and mediastinal disorders Bronchitis subjects affected / exposed occurrences (all) Cold upper respiratory tract subjects affected / exposed occurrences (all) Nasal congestion subjects affected / exposed occurrences (all) Cold subjects affected / exposed occurrences (all) Dyspnoea subjects affected / exposed occurrences (all) Pharyngitis subjects affected / exposed occurrences (all)	1 / 22 (4.55%) 1 2 / 22 (9.09%) 2 2 / 22 (9.09%) 2 1 / 22 (4.55%) 1 10 / 22 (45.45%) 11 1 / 22 (4.55%) 1		
Psychiatric disorders Depression subjects affected / exposed occurrences (all) Anxiety subjects affected / exposed occurrences (all)	1 / 22 (4.55%) 1 1 / 22 (4.55%) 1		
Investigations Gait disturbance subjects affected / exposed occurrences (all)	1 / 22 (4.55%) 1		

Sensitive altered subjects affected / exposed occurrences (all)	2 / 22 (9.09%) 2		
Cramps subjects affected / exposed occurrences (all)	3 / 22 (13.64%) 3		
Basocelular carcinoma subjects affected / exposed occurrences (all)	1 / 22 (4.55%) 1		
Dysgeusia subjects affected / exposed occurrences (all)	1 / 22 (4.55%) 1		
Right hypochondrium pain subjects affected / exposed occurrences (all)	1 / 22 (4.55%) 1		
Stomatitis subjects affected / exposed occurrences (all)	1 / 22 (4.55%) 1		
Nervous system disorders Dysaesthesia hands subjects affected / exposed occurrences (all)	1 / 22 (4.55%) 1		
Blood and lymphatic system disorders Anaemia subjects affected / exposed occurrences (all)	2 / 22 (9.09%) 7		
Oedema subjects affected / exposed occurrences (all)	2 / 22 (9.09%) 2		
Epistaxis subjects affected / exposed occurrences (all)	1 / 22 (4.55%) 1		
Hyperaemia pharingea subjects affected / exposed occurrences (all)	1 / 22 (4.55%) 1		
Ear and labyrinth disorders			

Hypoacusis subjects affected / exposed occurrences (all)	1 / 22 (4.55%) 2		
Hypophonesis subjects affected / exposed occurrences (all)	1 / 22 (4.55%) 1		
Eye disorders Conjunctivitis subjects affected / exposed occurrences (all)	1 / 22 (4.55%) 1		
Visual acuity reduced subjects affected / exposed occurrences (all)	1 / 22 (4.55%) 1		
Gastrointestinal disorders stomach burn subjects affected / exposed occurrences (all)	1 / 22 (4.55%) 1		
Diarrhoea subjects affected / exposed occurrences (all)	16 / 22 (72.73%) 49		
Dyspepsia subjects affected / exposed occurrences (all)	2 / 22 (9.09%) 3		
Epigastralgia subjects affected / exposed occurrences (all)	3 / 22 (13.64%) 4		
Constipation subjects affected / exposed occurrences (all)	7 / 22 (31.82%) 9		
Hyporeflexia subjects affected / exposed occurrences (all)	2 / 22 (9.09%) 4		
Skin and subcutaneous tissue disorders Alopecia subjects affected / exposed occurrences (all)	3 / 22 (13.64%) 3		
Nasolabial furrow dermatitis			

subjects affected / exposed occurrences (all)	1 / 22 (4.55%) 1		
erythema plantar subjects affected / exposed occurrences (all)	1 / 22 (4.55%) 1		
Cutaneous eruption subjects affected / exposed occurrences (all)	1 / 22 (4.55%) 1		
Phototoxicity subjects affected / exposed occurrences (all)	1 / 22 (4.55%) 1		
Capillary fragility subjects affected / exposed occurrences (all)	1 / 22 (4.55%) 2		
Ungueal fragillity subjects affected / exposed occurrences (all)	1 / 22 (4.55%) 1		
Musculoskeletal and connective tissue disorders			
thumb stiffness subjects affected / exposed occurrences (all)	1 / 22 (4.55%) 1		
Artralgia left ankle subjects affected / exposed occurrences (all)	1 / 22 (4.55%) 1		
Artralgia subjects affected / exposed occurrences (all)	1 / 22 (4.55%) 1		
Asthenia subjects affected / exposed occurrences (all)	10 / 22 (45.45%) 16		
Right coxalgia subjects affected / exposed occurrences (all)	1 / 22 (4.55%) 1		
Articular pain			

subjects affected / exposed occurrences (all)	1 / 22 (4.55%) 1		
Musculoskeletal pain subjects affected / exposed occurrences (all)	2 / 22 (9.09%) 2		
Sprain left ankle subjects affected / exposed occurrences (all)	1 / 22 (4.55%) 1		
Infections and infestations			
Ear infection subjects affected / exposed occurrences (all)	1 / 22 (4.55%) 1		
Belly button infection subjects affected / exposed occurrences (all)	1 / 22 (4.55%) 1		
Upper respiratory tract infection subjects affected / exposed occurrences (all)	7 / 22 (31.82%) 12		
Urinary infection subjects affected / exposed occurrences (all)	6 / 22 (27.27%) 6		
Metabolism and nutrition disorders			
Alanine aminotransferase increased subjects affected / exposed occurrences (all)	1 / 22 (4.55%) 1		
Amylase increased subjects affected / exposed occurrences (all)	1 / 22 (4.55%) 1		
Anorexia nervosa subjects affected / exposed occurrences (all)	5 / 22 (22.73%) 8		
Aspartate aminotransferase increased subjects affected / exposed occurrences (all)	1 / 22 (4.55%) 1		
creatinine kinase increased			

subjects affected / exposed	3 / 22 (13.64%)		
occurrences (all)	4		
Gastroenteritis			
subjects affected / exposed	2 / 22 (9.09%)		
occurrences (all)	2		
Hyperglycaemia			
subjects affected / exposed	2 / 22 (9.09%)		
occurrences (all)	4		
Hypertransaminasaemia			
subjects affected / exposed	1 / 22 (4.55%)		
occurrences (all)	1		
Hyperuricaemia			
subjects affected / exposed	1 / 22 (4.55%)		
occurrences (all)	1		

More information

Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? Yes

Date	Amendment
20 December 2016	<p>-Revision of background information to include recent published data on palbociclib and fulvestrant on the treatment of ER+/HER2- metastatic breast cancer patients.</p> <p>-Revision of statistical assumptions leading to:</p> <ul style="list-style-type: none">• Modification of statistical assumptions regarding expected median PFS and Hazard Ratio for control vs. interventional arm.• Modification of primary variable from Progression free Survival at 1 year (1y-PFS) to overall PFS.• Change in sample size from 304 patients to 486 as result of updating the assumptions for its calculation. <p>-Switch of analysis of primary end-point from superiority only to non-inferiority analyses, if the superiority criteria cannot be met.</p> <p>-Re-definition of interim analysis. Interim analysis was initially planned to occur after half of all expected patients have completed one-year follow-up period or have discontinued. Re-defined interim analysis will occur at 22 months after 35% of the total PFS events (89 events) have been observed.</p> <p>-Addition of new secondary end-points: Duration of Response and time to response.</p> <p>-Update on the definition of End of Study, EoS will occur one year after randomization of the last patient or when trial efficacy decision criteria are met, whichever is earlier.</p> <p>-Extend the justification of translational sub-studies analysis in the statistical section.</p> <p>-Addition of patient derived xenograft (PDX) models as potential studies to be performed from tumor samples obtained from patients enrolled in the study.</p>

12 November 2018	<ul style="list-style-type: none"> -Inclusion criteria # 7 is modified to no longer limit the time to take biopsy sample within 60 days prior to patient entry in the study. The limitation for accepting a tumor sample as valid is restricted to the absence of systemic treatment for advanced or metastatic non-small cell lung cancer between tumor sample collection to study start. -Exclusion criteria #8 to modify that the corrected QT value > 470 msec, it calculated based on ECG data at rest removing the requirement for triplicate ECGs -Exclusion criteria #14 modified to remove restriction for anticoagulant therapy. -Exclusion criteria #16 and #17 modified to add radiation therapy as exclusionary anti-cancer treatments within 6 months prior to study start. -Primary End-Point is modified removing the requirement for confirmation of response -Evaluations and procedures of the study. Clarification on the expected parameters to be included in the Hemogram, Biochemistry and coagulation lab results. -It has also been specified that the radiological assessments with CT, PET-CT or MRI should include at least thorax and abdomen. -Clarification on the definition of end of study (EoS). EoS should occur at the latest 78 weeks after the first dose administered to last patient included in the study. -Clarification of the patient treatment period: Patient treatment should continue up to progression disease, death, unacceptable toxicities or until the end of study. -Modification on the follow-up period until interim analysis. -Minimum follow-up period to conduct interim analysis has been corrected from 42 to 24 weeks according to primary end-point and time frequency for tumor assessments defined in the study protocol. -Removal of multivariate analysis of baseline data vs safety data. -Update estimated recruitment period from 10 months to 26 months. -Clarification on the definitions of population analysis
17 July 2019	<p>The Adverse Events listing has been updated with the following information: addition in the rare section (less than 0,1%, less than 1 in 1000 cases) the following adverse event: Blisters formation or severe skin peeling (suggests a Stevens-Johnson Syndrome).</p>

Notes:

Interruptions (globally)

Were there any global interruptions to the trial? No

Limitations and caveats

None reported