Clinical trial results:
A randomized phase III trial of Exemestane versus Anastrozole in postmenopausal women with receptor-positive primary breast cancer.

Summary

EudraCT number	2005-001893-28
Trial protocol	HU BE IT
Global end of trial date	31 October 2013

Results information

Result version number	v1 (current)
This version publication date	07 February 2020
First version publication date	07 February 2020
Summary attachment (see zip file)	Publication_Stearns_JCO_2015_DOI: 10.1200/JCO.2014.57.2461 (305_Stearns_IBCSG30-

Trial information

Trial identification

Sponsor protocol code	IBCSG 30-04

Additional study identifiers

ISRCTN number	-
ClinicalTrials.gov id (NCT number)	NCT00066573
WHO universal trial number (UTN)	-

Notes:

Sponsors

Sponsor organisation name	IBCSG
Sponsor organisation address	Effingerstrasse 40, Bern, Switzerland, 3008
Public contact	IBCSG Coordinating Center, IBCSG, +41 31 389 93 91, regulatoryoffice@ibcsg.org
Scientific contact	IBCSG Coordinating Center, IBCSG, +41 31 389 93 91, regulatoryoffice@ibcsg.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	Final
Date of interim/final analysis	15 April 2010
Is this the analysis of the primary completion data?	Yes
Primary completion date	15 April 2010
Global end of trial reached?	Yes
Global end of trial date	31 October 2013
Was the trial ended prematurely?	No

Notes:

General information about the trial

Main objective of the trial:

This randomized phase III trial is studying exemestane to see how well it works compared to anastrozole in preventing cancer recurrence in postmenopausal women who have undergone surgery for primary breast cancer.

Protection of trial subjects:

Permitted concomitant therapy:
Osteoporosis:
- Calcium intake
- Biphosphonates for prevention or treatment of osteoporosis

Therapies considered necessary for the subject's well-being which do not interfere with study endpoints:
- Lipid lowering agents
- NSAIDs and Cox-2 inhibitors (e.g. celecoxib, rofecoxib)
- Herceptin prior to or concurrently with protocol therapy .

Management of toxicity:
- Hot Flashes
Measures taken: Vitamin E; Low dose Clonidine; Venlafaxine; etc (no SERMs or hormones)

- Vaginal Atrophy
Measures taken: If refractory to local measures, may be treated with intermittent vaginal estrogens (maximum 3X/week) with lowest dose necessary to control symptoms. Use Estring only in patients who continue to have symptoms after 3X/week cream use.

- Any other type of toxicities:
Measures taken: A break from study medication of up to 4 weeks at one time is allowed to ascertain the source of patient’s intolerable symptoms. Similar breaks may be repeated until a total of 8 weeks off treatment have accumulated. Management of patients who need to stay off treatment for more than 4 weeks consecutively or more than 8 weeks in total will be at the discretion of the Investigator.

Background therapy: -

Evidence for comparator: -

Actual start date of recruitment	02 June 2003
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	Australia: 114
Country: Number of subjects enrolled	Chile: 29
Country: Number of subjects enrolled	Peru: 3
Country: Number of subjects enrolled	Romania: 39

Country: Number of subjects enrolled	Switzerland: 92
Country: Number of subjects enrolled	South Africa: 44
Country: Number of subjects enrolled	Canada: 1301
Country: Number of subjects enrolled	United States: 5526
Country: Number of subjects enrolled	Belgium: 45
Country: Number of subjects enrolled	Hungary: 213
Country: Number of subjects enrolled	Italy: 170
Worldwide total number of subjects	7576
EEA total number of subjects	467

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)	4049
From 65 to 84 years	3449
85 years and over	78

Subject disposition

Recruitment

Recruitment details:

The first patient was randomized on 6 June 2003. The trial was closed for accrual on 31 July 2008 (IBCSG: 15 December 2006).

Pre-assignment

Screening details:

Not available.

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, Carer, Assessor

Arms

Are arms mutually exclusive?	Yes
Arm title	Exemestane

Arm description:

Patients receive oral exemestane (25 mg) once daily for 5 years.

Arm type	Experimental
Investigational medicinal product name	Exemestane
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Tablet
Routes of administration	Oral use

Dosage and administration details:

Patients receive oral exemestane (25 mg) once daily for 5 years. Treatment is be continued for five years unless unacceptable toxicity occurs or the subject has recurrent tumour or concurrent illness necessitates withdrawal or the patient decides to withdraw from participation for any reason.

Arm title	Anastrozole

Arm description:

Patients receive oral anastrozole (1 mg) once daily for 5 years.

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

Dosage and administration details:

Patients receive oral anastrozole (1 mg) once daily for 5 years. Treatment is continued for five years unless unacceptable toxicity occurs or the subject has recurrent tumour or concurrent illness necessitates withdrawal or the patient decides to withdraw from participation for any reason.

Number of subjects in period 1	Exemestane	Anastrozole
Started	3789	3787
Completed	3761	3759
Not completed	28	28
Protocol deviation	28	28

Baseline characteristics

Reporting groups	
Reporting group title	Exemestane
Reporting group description:	
Patients receive oral exemestane (25 mg) once daily for 5 years.	
Reporting group title	Anastrozole
Reporting group description:	
Patients receive oral anastrozole (1 mg) once daily for 5 years.	

Reporting group values	Exemestane	Anastrozole	Total
Number of subjects	3789	3787	7576
Age categorical			
Age as continuous characteristic only			
Units: Subjects			
Age continuous			
Units: years			
median	63.9	64.3	
full range (min-max)	35.9 to 93.6	32.3 to 95.1	-
Gender categorical			
Units: Subjects			
Female	3789	3787	7576
Male	0	0	0

End points

End points reporting groups

Reporting group title	Exemestane
Reporting group description:	
Patients receive oral exemestane (25 mg) once daily for 5 years.	
Reporting group title	Anastrozole
Reporting group description:	
Patients receive oral anastrozole (1 mg) once daily for 5 years.	

Primary: Event-free Survival

End point title	Event-free Survival
End point description:	
Event-free survival, the primary endpoint of this study, is defined as the time from randomization to the time of documented locoregional or distant recurrence, new primary breast cancer, or death from any cause.	
End point type	Primary
End point timeframe:	
5 years	

End point values	Exemestane	Anastrozole		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	3789	3787		
Units: Percentage of participants				
number (confidence interval 95%)	88 (87 to 89)	89 (88 to 90)		

Statistical analyses

Statistical analysis title	Statistical analysis EFS
Statistical analysis description:	
To detect a hazard ratio (HR) of 0.80 between exemestane and anastrozole (ie, an improvement in 5-year EFS from 87.5% to 89.9%, with a two-sided 5% level test and 80% power, 6,840 patients and 630 events were needed for final analysis.	
Comparison groups	Exemestane v Anastrozole
Number of subjects included in analysis	7576
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.85
Method	Logrank
Parameter estimate	Hazard ratio (HR)
Point estimate	1.02

Confidence interval	
level	95 %
sides	2-sided
lower limit	0.87
upper limit	1.18

Secondary: Overall Survival: Percentage of Participants Alive at 5 Years

End point title	Overall Survival: Percentage of Participants Alive at 5 Years

End point description:

Overall survival is defined as the time from randomization to the time of death from any cause.

End point type	Secondary

End point timeframe:

5 years

End point values	Exemestane	Anastrozole		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	3789	3787		
Units: Percentage of participants				
number (confidence interval 95%)	92 (91 to 93)	92 (91 to 93)		

Statistical analyses

Statistical analysis title	Statistical analysis OS
Comparison groups	Exemestane v Anastrozole
Number of subjects included in analysis	7576
Analysis specification	Pre-specified
Analysis type	superiority[1]
P-value	= 0.46
Method	Logrank
Parameter estimate	Hazard ratio (HR)
Point estimate	0.93
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.77
upper limit	1.13

Notes:

[1] - No power calculation for secondary analysis

Secondary: Distant Disease-free Survival: Number of Participants Without Documented Distant Recurrence

End point title	Distant Disease-free Survival: Number of Participants Without Documented Distant Recurrence

End point description:

Time to distant disease-free survival (DDFS) is defined as the time from randomization to the time of documented distant recurrence. Distant recurrence is the cancer coming back in a part of the body away from the breast, such as the bones or liver.

End point type	Secondary

End point timeframe:

5 years

End point values	Exemestane	Anastrozole		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	3789	3787		
Units: Participants	157	164		

Statistical analyses

No statistical analyses for this end point

Secondary: Clinical Fracture Rate: Number of Participants With Bone Fractures

End point title	Clinical Fracture Rate: Number of Participants With Bone Fractures

End point description:

Clinical fracture at any time, including hip, spine, wrist fractures and other bone fractures.

End point type	Secondary

End point timeframe:

8 years

End point values	Exemestane	Anastrozole		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	3789	3787		
Units: Participants	358	354		

Statistical analyses

No statistical analyses for this end point

Adverse events

Adverse events information

Timeframe for reporting adverse events:

8 years

Adverse event reporting additional description:

Participants at Risk of Adverse Event or SAE were those who received at least one dose of protocol therapy.

Assessment type	Systematic

Dictionary used

Dictionary name	NCI CTCAE
Dictionary version	3.0

Reporting groups

Reporting group title	Exemestane

Reporting group description:

Patients receive oral exemestane (25 mg) once daily for 5 years.

exemestane: Given orally

Reporting group title	Anastrozole

Reporting group description:

Patients receive oral anastrozole (1 mg) once daily for 5 years.

anastrozole: Given orally

Serious adverse events	Exemestane	Anastrozole	
Total subjects affected by serious adverse events			
subjects affected / exposed	19 / 3761 (0.51%)	7 / 3759 (0.19%)	
number of deaths (all causes)	0	0	
number of deaths resulting from adverse events			
Investigations			
Bilirubin			
subjects affected / exposed	1 / 3761 (0.03%)	0 / 3759 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Creatinine			
subjects affected / exposed	1 / 3761 (0.03%)	0 / 3759 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
cTnI			

subjects affected / exposed	1 / 3761 (0.03%)	0 / 3759 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Vascular disorders			
Thrombosis/thrombus/embolism			
subjects affected / exposed	1 / 3761 (0.03%)	1 / 3759 (0.03%)	
occurrences causally related to treatment / all	0 / 3	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Cardiac disorders			
Cardiac ischemia/infarction			
subjects affected / exposed	1 / 3761 (0.03%)	0 / 3759 (0.00%)	
occurrences causally related to treatment / all	0 / 3	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Left ventricular systolic dysfunction			
subjects affected / exposed	1 / 3761 (0.03%)	0 / 3759 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Restrictive cardiomyopathy			
subjects affected / exposed	1 / 3761 (0.03%)	0 / 3759 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Supraven.arrhyth. Atrial flutter			
subjects affected / exposed	1 / 3761 (0.03%)	0 / 3759 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Ventric.arrhyth. Trigeminy			
subjects affected / exposed	1 / 3761 (0.03%)	0 / 3759 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Nervous system disorders			
CNS ischemia			
subjects affected / exposed	1 / 3761 (0.03%)	1 / 3759 (0.03%)	
occurrences causally related to treatment / all	0 / 3	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	

Neurology - Other			
subjects affected / exposed	1 / 3761 (0.03%)	0 / 3759 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Neuropathy-motor			
subjects affected / exposed	0 / 3761 (0.00%)	1 / 3759 (0.03%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Neuropathy: cranial CN VIII			
subjects affected / exposed	1 / 3761 (0.03%)	0 / 3759 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Speech impairment			
subjects affected / exposed	0 / 3761 (0.00%)	1 / 3759 (0.03%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Syncope			
subjects affected / exposed	0 / 3761 (0.00%)	1 / 3759 (0.03%)	
occurrences causally related to treatment / all	0 / 0	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
General disorders and administration site conditions			
Fatigue			
subjects affected / exposed	1 / 3761 (0.03%)	0 / 3759 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Immune system disorders			
Allergic reaction			
subjects affected / exposed	1 / 3761 (0.03%)	0 / 3759 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Eye disorders			
Blurred vision			

subjects affected / exposed	1 / 3761 (0.03%)	0 / 3759 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Nyctalopia			
subjects affected / exposed	0 / 3761 (0.00%)	1 / 3759 (0.03%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Ocular - Other			
subjects affected / exposed	1 / 3761 (0.03%)	0 / 3759 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Retinopathy			
subjects affected / exposed	1 / 3761 (0.03%)	0 / 3759 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Psychiatric disorders			
Confusion			
subjects affected / exposed	1 / 3761 (0.03%)	0 / 3759 (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			
Incontinence, urinary			
subjects affected / exposed	0 / 3761 (0.00%)	1 / 3759 (0.03%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Renal failure			
subjects affected / exposed	1 / 3761 (0.03%)	0 / 3759 (0.00%)	
occurrences causally related to treatment / all	0 / 2	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Endocrine disorders			
Hypothyroidism			
subjects affected / exposed	0 / 3761 (0.00%)	1 / 3759 (0.03%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	

Musculoskeletal and connective tissue disorders			
Osteonecrosis			
subjects affected / exposed	1 / 3761 (0.03%)	0 / 3759 (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	Exemestane	Anastrozole	
Total subjects affected by non-serious adverse events			
subjects affected / exposed	3556 / 3761 (94.55%)	3543 / 3759 (94.25%)	
Investigations			
Cholesterol			
subjects affected / exposed	591 / 3761 (15.71%)	677 / 3759 (18.01%)	
occurrences (all)	909	1143	
Weight gain			
subjects affected / exposed	257 / 3761 (6.83%)	286 / 3759 (7.61%)	
occurrences (all)	400	420	
Weight loss			
subjects affected / exposed	229 / 3761 (6.09%)	218 / 3759 (5.80%)	
occurrences (all)	309	280	
Injury, poisoning and procedural complications			
Fracture			
subjects affected / exposed	290 / 3761 (7.71%)	292 / 3759 (7.77%)	
occurrences (all)	326	337	
Vascular disorders			
Hot flashes			
subjects affected / exposed	2086 / 3761 (55.46%)	2138 / 3759 (56.88%)	
occurrences (all)	6532	6435	
Hypertension			
subjects affected / exposed	300 / 3761 (7.98%)	326 / 3759 (8.67%)	
occurrences (all)	462	503	
Nervous system disorders			
Dizziness			

subjects affected / exposed	526 / 3761 (13.99%)	504 / 3759 (13.41%)	
occurrences (all)	872	923	
Neuropathy-sensory			
subjects affected / exposed	576 / 3761 (15.32%)	528 / 3759 (14.05%)	
occurrences (all)	1247	1096	
Pain Head/headache			
subjects affected / exposed	414 / 3761 (11.01%)	399 / 3759 (10.61%)	
occurrences (all)	780	742	
General disorders and administration site conditions			
Edema: limb			
subjects affected / exposed	749 / 3761 (19.91%)	760 / 3759 (20.22%)	
occurrences (all)	1531	1590	
Fatigue			
subjects affected / exposed	1697 / 3761 (45.12%)	1749 / 3759 (46.53%)	
occurrences (all)	4458	4378	
Gastrointestinal disorders			
Constipation			
subjects affected / exposed	614 / 3761 (16.33%)	606 / 3759 (16.12%)	
occurrences (all)	1234	1219	
Diarrhea			
subjects affected / exposed	464 / 3761 (12.34%)	414 / 3759 (11.01%)	
occurrences (all)	781	665	
Flatulence			
subjects affected / exposed	399 / 3761 (10.61%)	363 / 3759 (9.66%)	
occurrences (all)	818	808	
Heartburn			
subjects affected / exposed	574 / 3761 (15.26%)	556 / 3759 (14.79%)	
occurrences (all)	1128	1084	
Nausea			
subjects affected / exposed	436 / 3761 (11.59%)	442 / 3759 (11.76%)	
occurrences (all)	630	661	
Pain Abdomen NOS			

subjects affected / exposed	202 / 3761 (5.37%)	220 / 3759 (5.85%)	
occurrences (all)	293	294	
Reproductive system and breast disorders			
Pain Breast			
subjects affected / exposed	288 / 3761 (7.66%)	312 / 3759 (8.30%)	
occurrences (all)	453	516	
Vaginal dryness			
subjects affected / exposed	248 / 3761 (6.59%)	260 / 3759 (6.92%)	
occurrences (all)	526	586	
Respiratory, thoracic and mediastinal disorders			
Cough			
subjects affected / exposed	671 / 3761 (17.84%)	666 / 3759 (17.72%)	
occurrences (all)	1323	1267	
Dyspnea			
subjects affected / exposed	656 / 3761 (17.44%)	652 / 3759 (17.35%)	
occurrences (all)	1359	1428	
Skin and subcutaneous tissue disorders			
Alopecia			
subjects affected / exposed	235 / 3761 (6.25%)	212 / 3759 (5.64%)	
occurrences (all)	418	371	
Rash			
subjects affected / exposed	474 / 3761 (12.60%)	437 / 3759 (11.63%)	
occurrences (all)	721	626	
Sweating			
subjects affected / exposed	626 / 3761 (16.64%)	603 / 3759 (16.04%)	
occurrences (all)	1486	1324	
Psychiatric disorders			
Insomnia			
subjects affected / exposed	574 / 3761 (15.26%)	521 / 3759 (13.86%)	
occurrences (all)	1285	1072	
Mood alteration Anxiety			
subjects affected / exposed	258 / 3761 (6.86%)	229 / 3759 (6.09%)	
occurrences (all)	481	418	
Mood alteration Depression			

subjects affected / exposed	374 / 3761 (9.94%)	377 / 3759 (10.03%)	
occurrences (all)	707	659	
Musculoskeletal and connective tissue disorders			
Arthritis			
subjects affected / exposed	264 / 3761 (7.02%)	242 / 3759 (6.44%)	
occurrences (all)	481	468	
Osteoporosis			
subjects affected / exposed	1243 / 3761 (33.05%)	1369 / 3759 (36.42%)	
occurrences (all)	1916	2134	
Pain Back			
subjects affected / exposed	480 / 3761 (12.76%)	504 / 3759 (13.41%)	
occurrences (all)	835	824	
Pain Bone			
subjects affected / exposed	381 / 3761 (10.13%)	410 / 3759 (10.91%)	
occurrences (all)	586	678	
Pain Extremity-limb			
subjects affected / exposed	468 / 3761 (12.44%)	511 / 3759 (13.59%)	
occurrences (all)	750	796	
Pain Joint			
subjects affected / exposed	2085 / 3761 (55.44%)	2086 / 3759 (55.49%)	
occurrences (all)	5539	5467	
Pain Muscle			
subjects affected / exposed	667 / 3761 (17.73%)	629 / 3759 (16.73%)	
occurrences (all)	1150	1110	
Metabolism and nutrition disorders			
Anorexia			
subjects affected / exposed	238 / 3761 (6.33%)	249 / 3759 (6.62%)	
occurrences (all)	360	387	
Hyperglycemia			
subjects affected / exposed	347 / 3761 (9.23%)	373 / 3759 (9.92%)	
occurrences (all)	608	673	

More information

Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? Yes

Date	Amendment
24 November 2005	- Increase in sample size from 5800 to 6840 - Allowed use of Herceptin (see also prior memo dated June 06, 2005) - Inclusion of patients with LCIS only at the surgical margin - Additional clarifications and updates according to newer scientific literature - Adaptation of the CRFs to the amended protocol
03 November 2006	This amendment primarily involves an update of each study drug's safety information and removal of the details describing the dispensation frequency of the study treatment. The case report forms have not been revised.
02 May 2007	This amendment involves mainly a reduction in reporting to AdEERS for patients on Anastrozole following the classification of Anastrozole as commercial agent.
09 March 2009	This amendment involves primarily changes to the statistical section to add a futility analysis to the statistical analysis plan. It does not involve any changes to the patient information/informed consent.

Notes:

Interruptions (globally)

Were there any global interruptions to the trial? No

Limitations and caveats

None reported