Clinical trial results:
Evaluation of Response Rate to Pre-operative Docetaxel + Herceptin study part A and Docetaxel study part B In Locally Advanced Breast Cancer Patients, Stratified by HER2-Status, Trial Phase II

Summary

EudraCT number	2005-000967-24
Trial protocol	DE
Global end of trial date	07 May 2014

Results information

Result version number	v1 (current)
This version publication date	09 February 2021
First version publication date	09 February 2021

Trial information

Trial identification

Sponsor protocol code	HED-324-PAE-0090-I

Additional study identifiers

ISRCTN number	-
ClinicalTrials.gov id (NCT number)	NCT00398489
WHO universal trial number (UTN)	-

Notes:

Sponsors

Sponsor organisation name	Technische Universität München, Fakultät für Medizin
Sponsor organisation address	Ismaninger Str. 22, München, Germany, 81675
Public contact	Dr. Stefan Paepke, Klinikum rechts der Isar der TU München, Klinik und Poliklinik für Frauenheilkunde , +49 89 4140 2419, Stefan.Paepke@mri.tum.de
Scientific contact	Dr. Stefan Paepke, Klinikum rechts der Isar der TU München, Klinik und Poliklinik für Frauenheilkunde , +49 89 4140 2419, Stefan.Paepke@mri.tum.de

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	06 May 2015
Is this the analysis of the primary completion data?	Yes
Primary completion date	07 May 2014
Global end of trial reached?	Yes
Global end of trial date	07 May 2014
Was the trial ended prematurely?	No

Notes:

General information about the trial

Main objective of the trial:

The evaluation of the efficacy of primary systemic therapy with:
- Study part A: Herceptin® + docetaxel (HER2 positive)
- Study part B: docetaxel monotherapy (HER2 negative).

Comparison: rate of pathologic complete remission following neo adjuvant therapy arm A (HER2+): with docetaxel and Herceptin vs rate of pathologic complete remission following neo adjuvant therapy arm B (HER2-) with docetaxel and correlation with predictive factors
Tolerability:
Documentation of nature and frequency of adverse events (AEs/SAEs)

Protection of trial subjects:

The conduct of this clinical study met the local legal and regulatory requirements. The study was conducted in accordance the ethical principles of Good Clinical Practice (GCP).
Participating subjects signed informed consent form and could withdraw from the study at any time without any disadvantage and without having to provide a reason for this decision.
The study was regularly monitored by the Sponsor and the investigators connected to the study were GCP trained.

Background therapy:

Medical treatment will be given according to the clinical trial centers' Routine.

Adjuvant Therapy:
Part A:
4 x epirubicin 90 mg/m² + cyclophosphamide 600 mg/m² (q21) +
Herceptin® 2 mg/kg weekly (visit 3–13), 6 mg/kg (visit 14–20), (visit 2 front loading) 4 mg/kg
Part B:
4 x epirubicin 90 mg/m² + cyclophosphamide 600 mg/m² (q21)

Endocrine therapy:
ER/PR positive patients:
pre-menopausal ≤ 40 years :
Zoladex ® (2–3 years) + tamoxifen (5 years)
> 40 years tamoxifen (5 years)
postmenopausal anastrozol (5 years)

Evidence for comparator:

n.a.

Actual start date of recruitment	06 February 2006
Long term follow-up planned	Yes
Long term follow-up rationale	Safety, Efficacy, Scientific research
Long term follow-up duration	5 Years
Independent data monitoring committee (IDMC) involvement?	Yes

Notes:

Population of trial subjects

Subjects enrolled per country

Country: Number of subjects enrolled	Germany: 94
Worldwide total number of subjects	94
EEA total number of subjects	94

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)	90
From 65 to 84 years	4
85 years and over	0

Subject disposition

Recruitment

Recruitment details:

Pre-screening processes were in place. The study was conducted multicentric in Germany between 06.02.2006 (first patient
recruited) and 17.07.2008 (last patient included).

Pre-assignment

Screening details:

First, the screening procedure which includes e.g. examinations, imagings, hematology, biochemistry values such as core biopsy values and also predictive marker analysis, had to be completed.
Patients must have all screening evaluations performed prior to the first dose of study drug and must meet all inclusion and none of the exclusion criteria.

Period 1

Period 1 title	Treatment period (overall period)
Is this the baseline period?	Yes
Allocation method	Non-randomised - controlled
Blinding used	Not blinded

Arms

Are arms mutually exclusive?	Yes
Arm title	Study part A (HER2+)

Arm description:

This study part contains HER2+ (overexpression) patients.

Arm type	Experimental
Investigational medicinal product name	Taxotere
Investigational medicinal product code	L01CD02
Other name	Docetaxel
Pharmaceutical forms	Powder and solvent for solution for infusion
Routes of administration	Intravenous use

Dosage and administration details:

Total: 600 mg/m2 milligram(s)/square meter

Investigational medicinal product name	Trastuzumab
Investigational medicinal product code	ATC L01XC03
Other name	Herceptin, CAS number 180288-69-1
Pharmaceutical forms	Powder and solvent for solution for infusion
Routes of administration	Intravenous use

Dosage and administration details:

Total: 106 mg/kg milligram(s)/kilogram

Arm title	Study part B (HER2-)

Arm description:

This study part contains HER2- patients.

Arm type	Experimental
Investigational medicinal product name	Taxotere
Investigational medicinal product code	L01CD02
Other name	Docetaxel
Pharmaceutical forms	Powder and solvent for solution for infusion
Routes of administration	Intravenous use

Dosage and administration details:

Total: 600 mg/m2 milligram(s)/square meter

Number of subjects in period 1	Study part A (HER2+)	Study part B (HER2-)
Started	33	61
Completed	29	60
Not completed	4	1
Adverse event, serious fatal	-	1
Consent withdrawn by subject	1	-
Lack of compliance	3	-

Baseline characteristics

Reporting groups

Reporting group title	Treatment period

Reporting group description: -

Reporting group values	Treatment period	Total	
Number of subjects	94	94	
Age categorical Units: Subjects			
Adults (18-64 years)	90	90	
From 65-84 years	4	4	
85 years and over	0	0	
Gender categorical Units: Subjects			
Female	94	94	
Male	0	0	
cT			
Tumor stage (clinical)			
Units: Subjects			
cT1	2	2	
cT1c	1	1	
cT2	67	67	
cT3	13	13	
cT4	7	7	
cT4b	1	1	
cT4d	3	3	
cN Units: Subjects			
N0	32	32	
N1	48	48	
N2	13	13	
N3	1	1	

Subject analysis sets

Subject analysis set title	EAP
Subject analysis set type	Per protocol

Subject analysis set description:

Efficacy Analysable Population includes all from the ITT except for patients with protocol deviations concerning inclusion and exclusion criteria and patients without surgery at the end of study treatment.

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

Subject analysis set description:

Includes all patients who received at least one dose of study medication

Reporting group values	EAP	ITT	
Number of subjects	89	94	
Age categorical Units: Subjects			
Adults (18-64 years)	89	94	
From 65-84 years	0	4	
85 years and over	0	0	
Gender categorical Units: Subjects			
Female	89	94	
Male	0	0	
cT			
Tumor stage (clinical)			
Units: Subjects			
cT1		2	
cT1c		1	
cT2		67	
cT3		13	
cT4		7	
cT4b		1	
cT4d		3	
cN Units: Subjects			
N0		32	
N1		48	
N2		13	
N3		1	

End points

End points reporting groups

Reporting group title	Study part A (HER2+)
Reporting group description:	
This study part contains HER2+ (overexpression) patients.	
Reporting group title	Study part B (HER2-)
Reporting group description:	
This study part contains HER2- patients.	
Subject analysis set title	EAP
Subject analysis set type	Per protocol
Subject analysis set description:	
Efficacy Analysable Population includes all from the ITT except for patients with protocol deviations concerning inclusion and exclusion criteria and patients without surgery at the end of study treatment.	
Subject analysis set title	ITT
Subject analysis set type	Intention-to-treat
Subject analysis set description:	
Includes all patients who received at least one dose of study medication	

Primary: pCR Tis

End point title	pCR Tis
End point description:	
Pathological complete response pCR Tis is defined as the absence of infiltrating tumor cells from breast and lymph node (ypT0, Tis, ypN0). The incidence of pCR Tis in study group A was 44.8% with bootstrap 95%CI (27.6%, 62.1%). The incidence of pCR Tis in study group B was 23.3% with bootstrap 95%CI (13.3%, 35.0%).	
End point type	Primary
End point timeframe:	
After surgery	

End point values	Study part A (HER2+)	Study part B (HER2-)		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	29[1]	60[2]		
Units: Patients				
yes	16	14		
no	13	46		

Notes:

[1] - Analysis on the EAP set.

[2] - Analysis on the EAP set.

Statistical analyses

Statistical analysis title	Difference in incidence of pCR Tis
Statistical analysis description:	
Difference in incidence rates of pCR Tis between study groups A and B.	
Comparison groups	Study part B (HER2-) v Study part A (HER2+)

Number of subjects included in analysis	89
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.039
Method	Chi-squared

Primary: pCR lite

End point title	pCR lite

End point description:

Pathological complete response pCR Tis is defined as the absence of infiltrating tumor cells from breast and lymph node (ypT0, Tis, ypN0).
The incidence of pCR lite in study group A was 55.2% with bootstrap 95%CI (37.9%, 72.4%).
The incidence of pCR lite in study group B was 30.0% with bootstrap 95%CI (20.0%, 41.7%).

End point type	Primary

End point timeframe:

After surgery

End point values	Study part A (HER2+)	Study part B (HER2-)		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	29[3]	60[4]		
Units: Patients				
yes	16	18		
no	13	42		

Notes:

[3] - Analyzed on EAP

[4] - Analyzed on EAP

Statistical analyses

Statistical analysis title	Difference in incidence rates of pCR lite

Statistical analysis description:

Difference in incidence rates of pCR lite between study groups A and B.

Comparison groups	Study part A (HER2+) v Study part B (HER2-)
Number of subjects included in analysis	89
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.022
Method	Chi-squared

Secondary: Overall survial

End point title	Overall survial

End point description:

The mean 60 months survival was 86.6% with a 2-sided 95%CI of (81.5, 91.7).

End point type	Secondary

End point timeframe:
60 months

End point values	EAP			
Subject group type	Subject analysis set			
Number of subjects analysed	88[5]			
Units: Patients				
event	17			
censored	71			

Notes:
[5] - Only 88 patients delivered values for the Kaplan-Meier analysis

Statistical analyses

No statistical analyses for this end point

Secondary: Mastectomy rate

End point title	Mastectomy rate

End point description:
Rate of patients undergoing mastectomy vs. breast conserving therapy.

End point type	Secondary

End point timeframe:
after surgery

End point values	EAP			
Subject group type	Subject analysis set			
Number of subjects analysed	89			
Units: Patients				
mastectomy	30			
breast-conserving therapy	59			

Statistical analyses

No statistical analyses for this end point

Secondary: Concordance between cCR and pCR Tis

End point title	Concordance between cCR and pCR Tis

End point description:
Number of patients with concordant results from the clinical and pathological evaluation.

End point type	Secondary

End point timeframe:
after surgery

End point values	EAP			
Subject group type	Subject analysis set			
Number of subjects analysed	68[6]			
Units: Patients				
concordant	36			
not concordant	32			

Notes:

[6] - Clinical response was available for 68 patients.

Statistical analyses

No statistical analyses for this end point

Secondary: Concordance between sCR and pCR Tis

End point title	Concordance between sCR and pCR Tis

End point description:

Number of patients with concordant results from the sonographical and pathological evaluation.

End point type	Secondary

End point timeframe:

after surgery

End point values	EAP			
Subject group type	Subject analysis set			
Number of subjects analysed	78[7]			
Units: Patients				
concordant	39			
not concordant	39			

Notes:

[7] - Sonographic response was available for 78 patients.

Statistical analyses

No statistical analyses for this end point

Adverse events

Adverse events information	
Timeframe for reporting adverse events:	
Entire study duration	
Assessment type	Systematic

Dictionary used	
Dictionary name	MedDRA
Dictionary version	14.0

Reporting groups	
Reporting group title	All patients
Reporting group description:	
All patients who received at least one dose of study medication.	

Serious adverse events	All patients		
Total subjects affected by serious adverse events			
subjects affected / exposed	38 / 94 (40.43%)		
number of deaths (all causes)	10		
number of deaths resulting from adverse events	10		
Neoplasms benign, malignant and unspecified (incl cysts and polyps)			
Neoplasm malignant			
subjects affected / exposed	1 / 94 (1.06%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Vascular disorders			
Hot flush			
subjects affected / exposed	1 / 94 (1.06%)		
occurrences causally related to treatment / all	1 / 1		
deaths causally related to treatment / all	0 / 0		
Thrombosis			
subjects affected / exposed	1 / 94 (1.06%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Surgical and medical procedures			
Mastectomy			

subjects affected / exposed	1 / 94 (1.06%)			
occurrences causally related to treatment / all	1 / 1			
deaths causally related to treatment / all	0 / 0			
General disorders and administration site conditions				
Death				
subjects affected / exposed	10 / 94 (10.64%)			
occurrences causally related to treatment / all	0 / 10			
deaths causally related to treatment / all	0 / 10			
Fatigue				
subjects affected / exposed	1 / 94 (1.06%)			
occurrences causally related to treatment / all	1 / 1			
deaths causally related to treatment / all	0 / 0			
General physical health deterioration				
subjects affected / exposed	3 / 94 (3.19%)			
occurrences causally related to treatment / all	5 / 5			
deaths causally related to treatment / all	0 / 0			
Generalised oedema				
subjects affected / exposed	1 / 94 (1.06%)			
occurrences causally related to treatment / all	1 / 1			
deaths causally related to treatment / all	0 / 0			
Oedema				
subjects affected / exposed	2 / 94 (2.13%)			
occurrences causally related to treatment / all	1 / 2			
deaths causally related to treatment / all	0 / 0			
Pyrexia				
subjects affected / exposed	12 / 94 (12.77%)			
occurrences causally related to treatment / all	17 / 17			
deaths causally related to treatment / all	0 / 0			
Reproductive system and breast disorders				
Breast disorder				
subjects affected / exposed	1 / 94 (1.06%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			

Respiratory, thoracic and mediastinal disorders			
Cough			
subjects affected / exposed	3 / 94 (3.19%)		
occurrences causally related to treatment / all	3 / 3		
deaths causally related to treatment / all	0 / 0		
Dyspnoea			
subjects affected / exposed	1 / 94 (1.06%)		
occurrences causally related to treatment / all	1 / 1		
deaths causally related to treatment / all	0 / 0		
Psychiatric disorders			
Completed suicide			
subjects affected / exposed	1 / 94 (1.06%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 1		
Investigations			
Liver function test abnormal			
subjects affected / exposed	1 / 94 (1.06%)		
occurrences causally related to treatment / all	1 / 1		
deaths causally related to treatment / all	0 / 0		
Injury, poisoning and procedural complications			
Post procedural complication			
subjects affected / exposed	1 / 94 (1.06%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Cardiac disorders			
Pericardial effusion			
subjects affected / exposed	1 / 94 (1.06%)		
occurrences causally related to treatment / all	1 / 1		
deaths causally related to treatment / all	0 / 0		
Sinus tachycardia			
subjects affected / exposed	1 / 94 (1.06%)		
occurrences causally related to treatment / all	1 / 1		
deaths causally related to treatment / all	0 / 0		
Nervous system disorders			

Headache				
subjects affected / exposed	1 / 94 (1.06%)			
occurrences causally related to treatment / all	1 / 1			
deaths causally related to treatment / all	0 / 0			
Hypertonia				
subjects affected / exposed	1 / 94 (1.06%)			
occurrences causally related to treatment / all	1 / 1			
deaths causally related to treatment / all	0 / 0			
Tremor				
subjects affected / exposed	1 / 94 (1.06%)			
occurrences causally related to treatment / all	1 / 1			
deaths causally related to treatment / all	0 / 0			
Blood and lymphatic system disorders				
Febrile neutropenia				
subjects affected / exposed	13 / 94 (13.83%)			
occurrences causally related to treatment / all	14 / 14			
deaths causally related to treatment / all	0 / 0			
Leukopenia				
subjects affected / exposed	3 / 94 (3.19%)			
occurrences causally related to treatment / all	3 / 3			
deaths causally related to treatment / all	0 / 0			
Thrombocytopenia				
subjects affected / exposed	1 / 94 (1.06%)			
occurrences causally related to treatment / all	1 / 1			
deaths causally related to treatment / all	0 / 0			
Eye disorders				
Eye pain				
subjects affected / exposed	1 / 94 (1.06%)			
occurrences causally related to treatment / all	1 / 1			
deaths causally related to treatment / all	0 / 0			
Gastrointestinal disorders				
Abdominal pain				

subjects affected / exposed	1 / 94 (1.06%)			
occurrences causally related to treatment / all	1 / 1			
deaths causally related to treatment / all	0 / 0			
Abdominal symptom				
subjects affected / exposed	1 / 94 (1.06%)			
occurrences causally related to treatment / all	1 / 1			
deaths causally related to treatment / all	0 / 0			
Diarrhoea				
subjects affected / exposed	2 / 94 (2.13%)			
occurrences causally related to treatment / all	2 / 2			
deaths causally related to treatment / all	0 / 0			
Vomiting				
subjects affected / exposed	3 / 94 (3.19%)			
occurrences causally related to treatment / all	3 / 3			
deaths causally related to treatment / all	0 / 0			
Skin and subcutaneous tissue disorders				
Dermatitis allergic				
subjects affected / exposed	1 / 94 (1.06%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Erythema				
subjects affected / exposed	1 / 94 (1.06%)			
occurrences causally related to treatment / all	1 / 1			
deaths causally related to treatment / all	0 / 0			
Hyperhidrosis				
subjects affected / exposed	1 / 94 (1.06%)			
occurrences causally related to treatment / all	1 / 1			
deaths causally related to treatment / all	0 / 0			
Infections and infestations				
Anal abscess				
subjects affected / exposed	1 / 94 (1.06%)			
occurrences causally related to treatment / all	1 / 1			
deaths causally related to treatment / all	0 / 0			
Bacterial infection				

subjects affected / exposed	1 / 94 (1.06%)		
occurrences causally related to treatment / all	1 / 1		
deaths causally related to treatment / all	0 / 0		
Breast infection			
subjects affected / exposed	1 / 94 (1.06%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Infection			
subjects affected / exposed	1 / 94 (1.06%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Nasopharyngitis			
subjects affected / exposed	1 / 94 (1.06%)		
occurrences causally related to treatment / all	1 / 1		
deaths causally related to treatment / all	0 / 0		
Pneumonia			
subjects affected / exposed	2 / 94 (2.13%)		
occurrences causally related to treatment / all	2 / 2		
deaths causally related to treatment / all	0 / 0		
Subcutaneous abscess			
subjects affected / exposed	1 / 94 (1.06%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Wound infection			
subjects affected / exposed	2 / 94 (2.13%)		
occurrences causally related to treatment / all	1 / 2		
deaths causally related to treatment / all	0 / 0		
Metabolism and nutrition disorders			
Hypokalaemia			
subjects affected / exposed	1 / 94 (1.06%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		

Frequency threshold for reporting non-serious adverse events: 5 %

Non-serious adverse events	All patients		
Total subjects affected by non-serious adverse events			
subjects affected / exposed	92 / 94 (97.87%)		
Vascular disorders			
Hot flush			
subjects affected / exposed	10 / 94 (10.64%)		
occurrences (all)	19		
Thrombosis			
subjects affected / exposed	4 / 94 (4.26%)		
occurrences (all)	6		
General disorders and administration site conditions			
Oedema			
subjects affected / exposed	46 / 94 (48.94%)		
occurrences (all)	118		
Asthenia			
subjects affected / exposed	62 / 94 (65.96%)		
occurrences (all)	289		
Pyrexia			
subjects affected / exposed	3 / 94 (3.19%)		
occurrences (all)	5		
Mucosal inflammation			
subjects affected / exposed	13 / 94 (13.83%)		
occurrences (all)	29		
Pain			
subjects affected / exposed	12 / 94 (12.77%)		
occurrences (all)	16		
Immune system disorders			
Hypersensitivity			
subjects affected / exposed	30 / 94 (31.91%)		
occurrences (all)	59		
Respiratory, thoracic and mediastinal disorders			
Dyspnoea			
subjects affected / exposed	45 / 94 (47.87%)		
occurrences (all)	126		

Psychiatric disorders Insomnia subjects affected / exposed occurrences (all)	 2 / 94 (2.13%) 5		
Nervous system disorders Peripheral sensory neuropathy subjects affected / exposed occurrences (all) Hypertonia subjects affected / exposed occurrences (all)	 65 / 94 (69.15%) 114 10 / 94 (10.64%) 21		
Blood and lymphatic system disorders Febrile neutropenia subjects affected / exposed occurrences (all) Anaemia subjects affected / exposed occurrences (all) Leukopenia subjects affected / exposed occurrences (all) Neutropenia subjects affected / exposed occurrences (all)	 8 / 94 (8.51%) 9 16 / 94 (17.02%) 40 8 / 94 (8.51%) 13 4 / 94 (4.26%) 8		
Eye disorders Conjunctivitis subjects affected / exposed occurrences (all) Lacrimation increased subjects affected / exposed occurrences (all)	 54 / 94 (57.45%) 156 2 / 94 (2.13%) 5		
Gastrointestinal disorders Diarrhoea subjects affected / exposed occurrences (all) Dysphagia	 42 / 94 (44.68%) 86 		

subjects affected / exposed	18 / 94 (19.15%)		
occurrences (all)	37		
Nausea			
subjects affected / exposed	39 / 94 (41.49%)		
occurrences (all)	91		
Vomiting			
subjects affected / exposed	13 / 94 (13.83%)		
occurrences (all)	19		
Stomatitis			
subjects affected / exposed	54 / 94 (57.45%)		
occurrences (all)	158		
Skin and subcutaneous tissue disorders			
Alopecia			
subjects affected / exposed	86 / 94 (91.49%)		
occurrences (all)	431		
Palmar-plantar erythrodysaesthesia syndrome			
subjects affected / exposed	29 / 94 (30.85%)		
occurrences (all)	62		
Nail disorder			
subjects affected / exposed	56 / 94 (59.57%)		
occurrences (all)	126		
Musculoskeletal and connective tissue disorders			
Arthralgia			
subjects affected / exposed	52 / 94 (55.32%)		
occurrences (all)	181		
Myalgia			
subjects affected / exposed	41 / 94 (43.62%)		
occurrences (all)	155		
Infections and infestations			
Infection			
subjects affected / exposed	26 / 94 (27.66%)		
occurrences (all)	37		
Metabolism and nutrition disorders			
Fluid retention			
subjects affected / exposed	33 / 94 (35.11%)		
occurrences (all)	76		

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