Clinical trial results:
A prospective, multicenter, single-arm, phase II study to evaluate the safety of neoadjuvant liposomal doxorubicin (Myocet®) plus paclitaxel, trastuzumab, and pertuzumab in patients with operable HER2-positive breast cancer

Summary

EudraCT number	2012-001201-24
Trial protocol	ES
Global end of trial date	18 January 2016

Results information

Result version number	v1 (current)
This version publication date	27 April 2022
First version publication date	27 April 2022

Trial information

Trial identification

Sponsor protocol code	SOLTI-1002

Additional study identifiers

ISRCTN number	-
ClinicalTrials.gov id (NCT number)	NCT01669239
WHO universal trial number (UTN)	-

Notes:

Sponsors

Sponsor organisation name	SOLTI
Sponsor organisation address	C/ Balmes 89 3-7, Barcelona, Spain, 08008
Public contact	Investigación Clinica, SOLTI, +34 933436302, regsolti@gruposolti.org
Scientific contact	Investigación Clinica, SOLTI, +34 933436302, regsolti@gruposolti.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	05 April 2017
Is this the analysis of the primary completion data?	Yes
Primary completion date	18 January 2016
Global end of trial reached?	Yes
Global end of trial date	18 January 2016
Was the trial ended prematurely?	No

Notes:

General information about the trial

Main objective of the trial:

To assess cardiac safety, measured by the incidence of type A (symptomatic cardiac failure) and type B (asymptomatic left ventricular ejection fraction [LVEF] decline) cardiac events, of the combination regimen of liposomal doxorubicin, paclitaxel, trastuzumab, and pertuzumab when given as neoadjuvant therapy for patients with operable HER2-positive BC

Protection of trial subjects:

The screening period included the 28 days prior to the start of the treatment under study to perform the scheduled procedures.
During neoadjuvant treatment also assessment procedures were carried out during Visits 2 to 7
A preoperative visit was scheduled within 7 days prior to surgery.
Peri-Surgery Visit: Surgery was planned for patients whose tumor was considered operable based on standard local practice within 4 to 6 weeks after completion of treatment or discontinuation of neoadjuvant treatment due to unacceptable toxicity or unacceptable or withdrawal of consent. Tumor tissue was collected from the surgical specimen for pathologic response analysis and the type of breast surgery was recorded.
The operated patients returned to the clinic two weeks (± 7 days) after the surgery.
Thereafter, patients were followed every 3 months until completing 12 months from the start of neoadjuvant treatment.
Approximately 28 days after the last study visit, a final safety assessment was performed. Patients were followed up every 3 months until 1 year after initiation of study treatment to collect cardiac safety data (follow-up period).

Background therapy: -	
Evidence for comparator: -	
Actual start date of recruitment	10 September 2012
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	Spain: 83
Worldwide total number of subjects	83
EEA total number of subjects	83

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)	75
From 65 to 84 years	8
85 years and over	0

Subject disposition

Recruitment

Recruitment details:

Between June 2013 and January 2015, 93 patients were proposed for study, of which 10 were screening failures, so 83 patients were finally assigned to treatment. A total of 20 spanish hospitals participated.

Pre-assignment

Screening details:

Female patients (18 and 74 years old) with untreated HER2 positive histologically confirmed invasive breast carcinoma (stages II to IIIB) and ECOG 0-1 and with no clinical or radiological evidence of metastasis (stage IV), no previous chemotherapy, RT or CM surgery (except tumor excision on the contralateral breast) or concurrent secondary cancer.

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	Assigned to study treatment

Arm description: -

Arm type	Experimental
Investigational medicinal product name	Myocet®
Investigational medicinal product code	
Other name	Doxorubicin HCL Liposome
Pharmaceutical forms	Powder, dispersion and solvent for concentrate for dispersion for infusion
Routes of administration	Injection , Infusion , Intravenous use

Dosage and administration details:

Myocet® was administered at a dose of 50 mg/m2 as a 1-hour intravenous infusion on Day 1 of each 3-week cycle. Treatment with Myocet® was administered every 3 weeks for 6 cycles.

Investigational medicinal product name	Herceptin®
Investigational medicinal product code	
Other name	Trastuzumab
Pharmaceutical forms	Powder for concentrate for solution for infusion
Routes of administration	Infusion

Dosage and administration details:

One vial contains 150 mg of trastuzumab. Trastuzumab reconstituted solution contains 21 mg/mL of trastuzumab. Trastuzumab was administered weekly, with a loading dose of 4 mg/kg in the first infusion and 2 mg/kg in subsequent infusions.
During neoadjuvant treatment, trastuzumab was administered weekly for 6 cycles (18 weeks). The administration of adjuvant trastuzumab was recommended for at least 12 months from the first administration, based on currently acceptable practice.
Trastuzumab administrations during the adjuvant period should be given at one-week intervals or or 3-week intervals. However, adjuvant treatment with trastuzumab was outside the scope of this protocol.

Investigational medicinal product name	Perjeta®
Investigational medicinal product code	
Other name	Pertuzumab
Pharmaceutical forms	Concentrate for solution for infusion
Routes of administration	Infusion , Intravenous use

Dosage and administration details:

Pertuzumab is supplied as a single-use formulation containing 30 mg/mL of pertuzumab in 20 mM L-histidine-acetate (pH 6.0), 120 mM sucrose and 0.02% polysorbate 20 at 0.02%. Each 20 cc vial (14.0 mL of solution per vial) contains approximately 420 mg of pertuzumab. The entire volume of the bag should be administered as a continuous IV infusion. During neoadjuvant treatment, pertuzumab was administered every 3 weeks for 6 cycles. Pertuzumab was administered on Day 1 of Cycle 1 at the required loading dose of 840 mg as an IV infusion. Three weeks (21 days) after the first dose of pertuzumab, and then every 3 weeks thereafter, pertuzumab was administered at a dose of 420 mg as an IV infusion.

Investigational medicinal product name	Taxol®
Investigational medicinal product code	
Other name	Paclitaxel
Pharmaceutical forms	Concentrate for solution for infusion
Routes of administration	Intravenous use

Dosage and administration details:

The ingredients per milliliter are: l6 mg paclitaxel, 527 mg polyoxyethylated castor oil and 49.7% dehydrated alcohol. Paclitaxel should be diluted before infusion with sodium chloride 0.9% for injection, USP; 5% dextrose for injection, USP; dextrose 5% and sodium chloride 0.9% for Ringer's injection to a final concentration of 0.3 to 1.2 mg/mL.
Paclitaxel treatment was administered weekly for 6 cycles (18 weeks). Paclitaxel was administered at a dose of 80 mg/m2 intravenously for 1 hour every week.

Number of subjects in period 1	Assigned to study treatment
Started	83
Completed	72
Not completed	11
Adverse event, serious fatal	1
did not complete the 6 treatment cycles	6
Consent withdrawn by subject	2
Adverse event, non-fatal	1
Disease progresion	1

Baseline characteristics

Reporting groups	
Reporting group title	Overall trial

Reporting group description: -

Reporting group values	Overall trial	Total	
Number of subjects	83	83	
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	49		
full range (min-max)	22 to 78	-	
Gender categorical Units: Subjects			
Female	83	83	
Male	0	0	
Ethnic group Units: Subjects			
Caucasian	78	78	
Other	5	5	
Body mass index (BMI) Units: Subjects			
<25	38	38	
25-30	24	24	
>30	21	21	
Menopause Units: Subjects			
YES	29	29	
NO	54	54	
ECOG Units: Subjects			
Zero	77	77	
One	6	6	
N stage Units: Subjects			
N0	40	40	

N1	30	30	
N2	8	8	
N3	1	1	
Nx	4	4	
Grade			
Units: Subjects			
Gx	18	18	
G1	5	5	
G2	28	28	
G3	32	32	
Stage II			
Units: Subjects			
II	65	65	
Other	18	18	
Estrogen receptor			
Units: Subjects			
Positive	57	57	
Negative	26	26	
Ki67 >14			
Units: Subjects			
>14	78	78	
<14	5	5	
KI67 >20			
Units: Subjects			
Ki67 >20	74	74	
Ki67 <20	9	9	
Stage III			
Units: Subjects			
Stage III	18	18	
Other	65	65	
Tumor size			
Units: millimeter(s)			
median	32		
full range (min-max)	9 to 80	-	
KI67 median			
Units: percent			
median	40		
full range (min-max)	2 to 95	-	

End points

End points reporting groups

Reporting group title	Assigned to study treatment
Reporting group description: -	
Subject analysis set title	intent–to-treat population
Subject analysis set type	Intention-to-treat
Subject analysis set description:	
All recruited patients were included in the intention-to-treat population.	
Subject analysis set title	Per Protocol (PP) population
Subject analysis set type	Per protocol
Subject analysis set description:	
Per-protocol analysis population: Patients were included in the per-protocol analysis population if they met ALL of the following criteria: - Have received ≥ 3 cycles of the study medication (in neoadjuvant format) and - Had not received any other antineoplastic treatment (drugs not included in the study or radiotherapy) and - Have undergone surgery. This analysis was only performed if this population differed from the IDT ≥ 10%.	

Subject analysis set title	Safety population
Subject analysis set type	Safety analysis
Subject analysis set description:	
The safety population includes patients who have received at least one dose of the study treatmentand have completed the safety assessment at the time of enrollment.	

Primary: Cardiac adverse events

End point title	Cardiac adverse events[1]
End point description:	
The main objective of the study is to evaluate cardiac safety, as measured by the incidence of type A (symptomatic heart failure) and type B (asymptomatic reduction in left ventricular ejection fraction [LVEF]), of the combination regimen of liposomal doxorubicin, paclitaxel, trastuzumab and pertuzumab neoadjuvant therapy in patients with non-metastatic HER2-positive CM. The safety population includes patients who have received at least one dose of the study treatment and have completed the safety assessment at the time of inclusion. With 83 patients enrolled, no episode of symptomatic heart failure was observed and only 3 patients had a type B cardiac event.	
End point type	Primary
End point timeframe:	
Overall study	

Notes:

[1] - No statistical analyses have been specified for this primary end point. It is expected there is at least one statistical analysis for each primary end point.
Justification: This non-inferiority study was designed to have 80% statistical power in testing the null hypothesis that the combination would result in a higher rate of cardiac events than the historical value (18%) vs. a non-inferior rate of cardiac events, with a one-sided significance level of 5%. All safety parameters will be summarized and presented in tables based on the safety population. population.

End point values	Safety population			
Subject group type	Subject analysis set			
Number of subjects analysed	81			
Units: Subjects				
Type A	0			
Type B	7			

Statistical analyses

No statistical analyses for this end point

Secondary: Complete Pathological Response

End point title	Complete Pathological Response

End point description:

The pathologic complete response rate determined the primary efficacy endpoint of the study and was assessed at the local level after surgery.
Complete Pathologic Breast Response (CPBR) was defined as the complete absence of invasive breast cancer according to the NSABP algorithm, regardless of axillary status and the presence of carcinoma in situ, assessed after the 6 cycles of treatment and surgery, or after withdrawal from the study, whichever comes first.

End point type	Secondary

End point timeframe:

After surgery

End point values	Assigned to study treatment			
Subject group type	Reporting group			
Number of subjects analysed	82			
Units: Subjects				
Yes	54			

Statistical analyses

No statistical analyses for this end point

Secondary: Complete Pathologic Response in Breast and Axilla (PCRMA)

End point title	Complete Pathologic Response in Breast and Axilla (PCRMA)

End point description:

Complete Pathologic Response in Breast and Axilla (PCRMA) was defined as the absence of invasive tumor cells in the breast and in all axillary lymph nodes removed, assessed after 6 cycles of treatment and surgery, or after withdrawal from the study, whichever comes first.
Nodal stages pN0(i-), pN0(i+), pN0(mol-) and pN0(mol+) were considered pN0.
The rate of RPCMA is summarized as the percentage (%) of patients meeting the criterion, with the exact 95% confidence interval.

End point type	Secondary

End point timeframe:

After surgery

End point values	Assigned to study treatment			
Subject group type	Reporting group			
Number of subjects analysed	83			
Units: Subjects				
YES	47			

Statistical analyses

No statistical analyses for this end point

Secondary: Overall response rate (ORR)

End point title	Overall response rate (ORR)

End point description:

The clinical tumor response evaluates efficacy before surgery (pre-surgery), and is classified according to the RECIST 1.1 criteria.

End point type	Secondary

End point timeframe:

Before surgery

End point values	Assigned to study treatment			
Subject group type	Reporting group			
Number of subjects analysed	81			
Units: RECIST 1.1				
CR	35			
PR	39			
SD	6			
PD	1			

Statistical analyses

No statistical analyses for this end point

Secondary: Objective Clinical Response Rate

End point title	Objective Clinical Response Rate

End point description:

The Objective Clinical Response Rate (ORR) was defined as the overall response before surgery equal to complete response (CR) or partial response (PR).
The ORR is summarized as the percentage (%) of patients meeting the definition, with the confidence

interval (%) of patients meeting the definition, with the exact 95% confidence interval.

End point type	Secondary

End point timeframe:

Before surgery

End point values	Assigned to study treatment			
Subject group type	Reporting group			
Number of subjects analysed	81			
Units: Subjects				
YES	74			

Statistical analyses

No statistical analyses for this end point

Secondary: Clinical Benefit

End point title	Clinical Benefit

End point description:

Clinical Benefit (CB) was defined as the overall response before surgery equal to complete response (CR) or partial response (PR) or stable disease (SD).
The CB is summarized with the percentage (%) of patients meeting the definition, with the exact confidence interval of 95%

End point type	Secondary

End point timeframe:

Before surgery

End point values	Assigned to study treatment			
Subject group type	Reporting group			
Number of subjects analysed	81			
Units: Subjects				
YES	80			

Statistical analyses

No statistical analyses for this end point

Adverse events

Adverse events information

Timeframe for reporting adverse events:

Overall study

Assessment type	Systematic

Dictionary used

Dictionary name	MedDRA
Dictionary version	18.0

Reporting groups

Reporting group title	Safety Population

Reporting group description: -

Serious adverse events	Safety Population		
Total subjects affected by serious adverse events			
subjects affected / exposed	21 / 83 (25.30%)		
number of deaths (all causes)	1		
number of deaths resulting from adverse events	1		
Investigations			
Ejection fraction decreased			
subjects affected / exposed	1 / 83 (1.20%)		
occurrences causally related to treatment / all	1 / 1		
deaths causally related to treatment / all	0 / 0		
Injury, poisoning and procedural complications			
Infusion related reaction			
subjects affected / exposed	1 / 83 (1.20%)		
occurrences causally related to treatment / all	1 / 1		
deaths causally related to treatment / all	0 / 0		
Lumbar vertebral fracture			
subjects affected / exposed	1 / 83 (1.20%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Blood and lymphatic system disorders			
Febrile neutropenia			
subjects affected / exposed	5 / 83 (6.02%)		
occurrences causally related to treatment / all	4 / 5		
deaths causally related to treatment / all	0 / 0		

Neutropenia				
subjects affected / exposed	2 / 83 (2.41%)			
occurrences causally related to treatment / all	2 / 2			
deaths causally related to treatment / all	0 / 0			
General disorders and administration site conditions				
Asthenia				
subjects affected / exposed	1 / 83 (1.20%)			
occurrences causally related to treatment / all	1 / 1			
deaths causally related to treatment / all	0 / 0			
Gastrointestinal disorders				
Diarrhoea				
subjects affected / exposed	3 / 83 (3.61%)			
occurrences causally related to treatment / all	3 / 3			
deaths causally related to treatment / all	0 / 0			
Vomiting				
subjects affected / exposed	2 / 83 (2.41%)			
occurrences causally related to treatment / all	2 / 2			
deaths causally related to treatment / all	0 / 0			
Nausea				
subjects affected / exposed	1 / 83 (1.20%)			
occurrences causally related to treatment / all	1 / 1			
deaths causally related to treatment / all	0 / 0			
Respiratory, thoracic and mediastinal disorders				
Acute respiratory failure				
subjects affected / exposed	1 / 83 (1.20%)			
occurrences causally related to treatment / all	1 / 1			
deaths causally related to treatment / all	1 / 1			
Pulmonary embolism				
subjects affected / exposed	1 / 83 (1.20%)			
occurrences causally related to treatment / all	1 / 1			
deaths causally related to treatment / all	0 / 0			
Acute interstitial pneumonitis				

subjects affected / exposed	1 / 83 (1.20%)			
occurrences causally related to treatment / all	1 / 1			
deaths causally related to treatment / all	0 / 0			
Bronchitis				
subjects affected / exposed	2 / 83 (2.41%)			
occurrences causally related to treatment / all	1 / 2			
deaths causally related to treatment / all	0 / 0			
Infections and infestations				
Sepsis				
subjects affected / exposed	2 / 83 (2.41%)			
occurrences causally related to treatment / all	0 / 2			
deaths causally related to treatment / all	0 / 0			
Pneumonia				
subjects affected / exposed	4 / 83 (4.82%)			
occurrences causally related to treatment / all	0 / 4			
deaths causally related to treatment / all	0 / 0			
Urinary tract infection				
subjects affected / exposed	2 / 83 (2.41%)			
occurrences causally related to treatment / all	0 / 2			
deaths causally related to treatment / all	0 / 0			
Upper respiratory tract infection				
subjects affected / exposed	1 / 83 (1.20%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Respiratory tract infection				
subjects affected / exposed	1 / 83 (1.20%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Appendicitis				
subjects affected / exposed	2 / 83 (2.41%)			
occurrences causally related to treatment / all	1 / 2			
deaths causally related to treatment / all	0 / 0			
Device related infection				

subjects affected / exposed	1 / 83 (1.20%)		
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	Safety Population		
Total subjects affected by non-serious adverse events			
subjects affected / exposed	83 / 83 (100.00%)		
Neoplasms benign, malignant and unspecified (incl cysts and polyps)			
Neuropathy peripheral			
subjects affected / exposed	16 / 83 (19.28%)		
occurrences (all)	16		
General disorders and administration site conditions			
Asthenia			
subjects affected / exposed	67 / 83 (80.72%)		
occurrences (all)	67		
Mucosal inflammation			
subjects affected / exposed	52 / 83 (62.65%)		
occurrences (all)	52		
Pyrexia			
subjects affected / exposed	36 / 83 (43.37%)		
occurrences (all)	36		
Immune system disorders			
Hypersensitivity			
subjects affected / exposed	6 / 83 (7.23%)		
occurrences (all)	6		
Respiratory, thoracic and mediastinal disorders			
Epistaxis			
subjects affected / exposed	13 / 83 (15.66%)		
occurrences (all)	13		
Cough			
subjects affected / exposed	12 / 83 (14.46%)		
occurrences (all)	12		
Dysphonia			

subjects affected / exposed	5 / 83 (6.02%)		
occurrences (all)	5		
Dyspnoea			
subjects affected / exposed	5 / 83 (6.02%)		
occurrences (all)	5		
Investigations			
Laboratory test abnormal			
subjects affected / exposed	13 / 83 (15.66%)		
occurrences (all)	13		
Weight decreased			
subjects affected / exposed	5 / 83 (6.02%)		
occurrences (all)	5		
Injury, poisoning and procedural complications			
Neurotoxicity			
subjects affected / exposed	21 / 83 (25.30%)		
occurrences (all)	21		
Nail toxicity			
subjects affected / exposed	7 / 83 (8.43%)		
occurrences (all)	7		
Nervous system disorders			
Dysgeusia			
subjects affected / exposed	15 / 83 (18.07%)		
occurrences (all)	15		
Headache			
subjects affected / exposed	13 / 83 (15.66%)		
occurrences (all)	13		
Dizziness			
subjects affected / exposed	6 / 83 (7.23%)		
occurrences (all)	6		
Blood and lymphatic system disorders			
Neutropenia			
subjects affected / exposed	36 / 83 (43.37%)		
occurrences (all)	36		
Anaemia			
subjects affected / exposed	28 / 83 (33.73%)		
occurrences (all)	28		

Leukopenia			
subjects affected / exposed	5 / 83 (6.02%)		
occurrences (all)	5		
Eye disorders			
Conjunctivitis			
subjects affected / exposed	7 / 83 (8.43%)		
occurrences (all)	7		
Gastrointestinal disorders			
Diarrhoea			
subjects affected / exposed	66 / 83 (79.52%)		
occurrences (all)	66		
Nausea			
subjects affected / exposed	49 / 83 (59.04%)		
occurrences (all)	49		
Vomiting			
subjects affected / exposed	27 / 83 (32.53%)		
occurrences (all)	27		
Abdominal pain upper			
subjects affected / exposed	24 / 83 (28.92%)		
occurrences (all)	24		
Dyspepsia			
subjects affected / exposed	14 / 83 (16.87%)		
occurrences (all)	14		
Constipation			
subjects affected / exposed	12 / 83 (14.46%)		
occurrences (all)	12		
Abdominal pain			
subjects affected / exposed	10 / 83 (12.05%)		
occurrences (all)	10		
Odynophagia			
subjects affected / exposed	6 / 83 (7.23%)		
occurrences (all)	6		
Haemorrhoids			
subjects affected / exposed	5 / 83 (6.02%)		
occurrences (all)	5		
Stomatitis			

subjects affected / exposed occurrences (all)	5 / 83 (6.02%) 5		
Skin and subcutaneous tissue disorders Alopecia subjects affected / exposed occurrences (all) Rash subjects affected / exposed occurrences (all) Skin toxicity subjects affected / exposed occurrences (all) Dry skin subjects affected / exposed occurrences (all) Onycholysis subjects affected / exposed occurrences (all) Dermatitis acneiform subjects affected / exposed occurrences (all) Palmar-plantar erythrodysaesthesia syndrome subjects affected / exposed occurrences (all) Dermatitis subjects affected / exposed occurrences (all) Pruritus subjects affected / exposed occurrences (all)	 33 / 83 (39.76%) 33 19 / 83 (22.89%) 19 14 / 83 (16.87%) 14 11 / 83 (13.25%) 11 11 / 83 (13.25%) 11 10 / 83 (12.05%) 10 9 / 83 (10.84%) 9 6 / 83 (7.23%) 6 6 / 83 (7.23%) 6		
Endocrine disorders Hot flush subjects affected / exposed occurrences (all)	 6 / 83 (7.23%) 6		
Musculoskeletal and connective tissue disorders			

Myalgia subjects affected / exposed occurrences (all) Arthralgia subjects affected / exposed occurrences (all) Bone pain subjects affected / exposed occurrences (all) Back pain subjects affected / exposed occurrences (all)	 16 / 83 (19.28%) 16 15 / 83 (18.07%) 15 7 / 83 (8.43%) 7 5 / 83 (6.02%) 5		
Infections and infestations Respiratory tract infection subjects affected / exposed occurrences (all) Urinary tract infection subjects affected / exposed occurrences (all) Folliculitis subjects affected / exposed occurrences (all)	 10 / 83 (12.05%) 10 8 / 83 (9.64%) 8 5 / 83 (6.02%) 5		
Metabolism and nutrition disorders Decreased appetite subjects affected / exposed occurrences (all)	 23 / 83 (27.71%) 23		

More information

Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? Yes

Date	Amendment
05 December 2012	Protocol v.2.0_19-Jul-2012
18 December 2013	Protocol v.3.0_17-oct-2013
22 July 2015	Protocol v.4.0_20-may-2015

Notes:

Interruptions (globally)

Were there any global interruptions to the trial? No

Limitations and caveats

None reported