Clinical trial results:
Prospective, Open-Label, Randomized Study of Combination Therapy of MYOCET® Plus Cyclophosphamide and Trastuzumab Versus Free Doxorubicin Plus Cyclophosphamide Alone, Each Followed by Docetaxel and Trastuzumab, in Neoadjuvant Setting in Treatment-Naïve Patients With HER2-Positive Breast Cancer

Summary

EudraCT number	2008-000709-12
Trial protocol	FR BE ES AT NL GB IT
Global end of trial date	17 September 2015

Results information

Result version number	v1 (current)
This version publication date	17 February 2017
First version publication date	17 February 2017

Trial information

Trial identification

Sponsor protocol code	C19562/2037/BC/EU

Additional study identifiers

ISRCTN number	-
ClinicalTrials.gov id (NCT number)	NCT00712881
WHO universal trial number (UTN)	-
Other trial identifiers	Sponsor short code: C19562/2037

Notes:

Sponsors

Sponsor organisation name	Teva Branded Pharmaceutical Products R&D, Inc
Sponsor organisation address	41 Moores Road, Frazer, Pennsylvania, United States, 19355
Public contact	Director, Clinical Research, Teva Branded Pharmaceutical Products, R&D Inc., 001 215-591-3000, info.era-clinical@teva.de
Scientific contact	Director, Clinical Research, Teva Branded Pharmaceutical Products, R&D Inc., 001 215-591-3000, info.era-clinical@teva.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	17 October 2016
Is this the analysis of the primary completion data?	No

Global end of trial reached?	Yes
Global end of trial date	17 September 2015
Was the trial ended prematurely?	No

Notes:

General information about the trial

Main objective of the trial:

The primary objective of this study was to compare the efficacy of up to 8 cycles (24 weeks) of MYOCET plus cyclophosphamide and trastuzumab for 4 cycles followed by docetaxel plus trastuzumab for 4 cycles (MCHTH) with free doxorubicin plus cyclophosphamide alone for 4 cycles followed by docetaxel plus trastuzumab for 4 cycles (ACTH), each on day 1 of a 21-day cycle, as assessed by the proportion of patients with pathological complete response (pCR) in breast.

Protection of trial subjects:

This study was conducted in full accordance with the International Conference on Harmonization (ICH) Good Clinical Practice (GCP) Consolidated Guideline (E6) and any applicable national and local laws and regulations (eg, Code of Federal Regulations Title 21, Parts 50, 54, 56, 312, and 314; European Union Directive 2001/20/EC on the approximation of the laws, regulations and administrative provisions of the Member States relating to the implementation of good clinical practice in the conduct of clinical trials on medicinal products for human use).
Written and/or oral information about the study was provided to all patients in a language understandable by the patient. The information included an adequate explanation of the aims, methods, anticipated benefits, potential hazards, and insurance arrangements in force. Written informed consent was obtained from each patient before any study procedures or assessments were done. It was explained to the patients that they were free to refuse entry into the study and free to withdraw from the study at any time without prejudice to future treatment.
Each patient’s willingness to participate in the study was documented in writing in an informed consent form that was signed by the patient with the date of that signature indicated. Each investigator kept the original consent forms, and copies were given to the patients.

Background therapy: -
Evidence for comparator: -

Actual start date of recruitment	02 June 2008
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: 39
Country: Number of subjects enrolled	Austria: 7
Country: Number of subjects enrolled	Belgium: 10
Country: Number of subjects enrolled	France: 8
Country: Number of subjects enrolled	Germany: 49
Country: Number of subjects enrolled	Italy: 13
Worldwide total number of subjects	126
EEA total number of subjects	126

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)	112
From 65 to 84 years	14
85 years and over	0

Subject disposition

Recruitment

Recruitment details: -

Pre-assignment

Screening details:

A total of 137 patients with treatment naïve, HER2+ breast cancer were screened for enrollment and 126 patients met entry criteria. Of the 11 patients who were not enrolled, 8 were excluded on the basis of inclusion/exclusion criteria, 1 patient withdrew consent, 1 had an AE, and 1 patient was excluded for a reason of "other."

Period 1

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

Arms

Are arms mutually exclusive?	Yes
Arm title	MCH - TH

Arm description:

- MCH: On day 1 of each of 4 consecutive 21-day cycles, each patient was infused with liposomal doxorubicin hydrochloride (60 mg/m^2), cyclophosphamide (600 mg/m^2), and trastuzumab (8 or 6 mg/kg). For the first cycle, the loading dose of trastuzumab was 8 mg/kg; 6 mg/kg was used for the remaining cycles.
- TH: After 4 cycles of MCH, the treatment changed to 4 consecutive 21 day cycles of docetaxel (100 mg/m^2) and trastuzumab (6 mg/kg).

Arm type	Experimental
Investigational medicinal product name	liposomal doxorubicin hydrochloride
Investigational medicinal product code	
Other name	Myocet®, CEP-19562
Pharmaceutical forms	Infusion
Routes of administration	Intravenous use

Dosage and administration details:

Liposomal doxorubicin hydrochloride, 60 mg/m^2, was infused in 1 hour on day 1 of each of four 21 day cycles.

Investigational medicinal product name	cyclophosphamide
Investigational medicinal product code	
Other name	cytophosphane
Pharmaceutical forms	Infusion
Routes of administration	Intravenous use

Dosage and administration details:

Cyclophosphamide, 600 mg/m^2, was infused on day 1 of each of four 21 day cycles. Marketed formulations of cyclophosphamide were constituted and used as directed in the summary of product characteristics that accompany the study drugs.

Investigational medicinal product name	trastuzumab
Investigational medicinal product code	
Other name	Herceptin ®
Pharmaceutical forms	Infusion
Routes of administration	Intravenous use

Dosage and administration details:

Trastuzumab was infused in 90 minutes (loading dose of 8 mg/kg;), then in 1 hour (dose of 6 mg/kg) every 3 weeks. Marketed formulations of trastuzumab were constituted and used as directed in the summary of product characteristics that accompany the study drugs.

Investigational medicinal product name	docetaxel
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Infusion
Routes of administration	Intravenous use

Dosage and administration details:

100 mg/m^2
Marketed formulations of docetaxel were constituted and used as directed in the summary of product characteristics that accompany the study drugs.

Arm title	AC - TH

Arm description:

- AC: On day 1 of each of 4 consecutive 21-day cycles, each patient was infused with free doxorubicin hydrochloride (60 mg/m^2) and cyclophosphamide (600 mg/m^2).
- TH: After 4 cycles of AC, the treatment changed to 4 consecutive 21-day cycles of docetaxel (100 mg/m^2) and trastuzumab (8 or 6 mg/kg). For the first cycle, the loading dose of trastuzumab was 8 mg/kg; 6 mg/kg was used for the remaining 3 cycles.

Arm type	Active comparator
Investigational medicinal product name	free doxorubicin hydrochloride
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Infusion
Routes of administration	Intravenous use

Dosage and administration details:

Free doxorubicin hydrochloride, 60 mg/m^2, was infused in 1 hour on day 1 of each of four 21 day cycles.

Investigational medicinal product name	cyclophosphamide
Investigational medicinal product code	
Other name	cytophosphane
Pharmaceutical forms	Infusion
Routes of administration	Intravenous use

Dosage and administration details:

Cyclophosphamide, 600 mg/m^2, was infused on day 1 of each of four 21 day cycles. Marketed formulations of cyclophosphamide were constituted and used as directed in the summary of product characteristics that accompany the study drugs.

Investigational medicinal product name	docetaxel
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Infusion
Routes of administration	Intravenous use

Dosage and administration details:

100 mg/m^2
Marketed formulations of docetaxel were constituted and used as directed in the summary of product characteristics that accompany the study drugs.

Investigational medicinal product name	trastuzumab
Investigational medicinal product code	
Other name	Herceptin ®
Pharmaceutical forms	Infusion
Routes of administration	Intravenous use

Dosage and administration details:

Trastuzumab was infused in 90 minutes (loading dose of 8 mg/kg;), then in 1 hour (dose of 6 mg/kg) every 3 weeks. Marketed formulations of trastuzumab were constituted and used as directed in the summary of product characteristics that accompany the study drugs.

Number of subjects in period 1	MCH - TH	AC - TH
Started	63	63
Safety analysis set	62	63
Completed four cycles	60	61
Completed eight cycles	55	56
Completed	55	56
Not completed	8	7
Consent withdrawn by subject	1	-
Disease progression	1	1
Adverse event, non-fatal	4	5
Noncompliance to study procedures	1	-
Protocol deviation	1	1

Baseline characteristics

Reporting groups	
Reporting group title	MCH - TH

Reporting group description:

- MCH: On day 1 of each of 4 consecutive 21-day cycles, each patient was infused with liposomal doxorubicin hydrochloride (60 mg/m^2), cyclophosphamide (600 mg/m^2), and trastuzumab (8 or 6 mg/kg). For the first cycle, the loading dose of trastuzumab was 8 mg/kg; 6 mg/kg was used for the remaining cycles.
- TH: After 4 cycles of MCH, the treatment changed to 4 consecutive 21 day cycles of docetaxel (100 mg/m^2) and trastuzumab (6 mg/kg).

Reporting group title	AC - TH

Reporting group description:

- AC: On day 1 of each of 4 consecutive 21-day cycles, each patient was infused with free doxorubicin hydrochloride (60 mg/m^2) and cyclophosphamide (600 mg/m^2).
- TH: After 4 cycles of AC, the treatment changed to 4 consecutive 21-day cycles of docetaxel (100 mg/m^2) and trastuzumab (8 or 6 mg/kg). For the first cycle, the loading dose of trastuzumab was 8 mg/kg; 6 mg/kg was used for the remaining 3 cycles.

Reporting group values	MCH - TH	AC - TH	Total
Number of subjects	63	63	126
Age categorical Units: Subjects			
Age continuous Units: years			
arithmetic mean	48.8	51.1	
standard deviation	± 11.6	± 11.3	-
Gender categorical Units: Subjects			
Female	63	63	126
Male	0	0	0
Race Units: Subjects			
White	61	59	120
Black	0	1	1
Asian	1	0	1
Other	1	3	4
HER2 asssessment Units: Subjects			
Positive	63	62	125
Missing	0	1	1
Type of invasive carcinoma Units: Subjects			
Ductal	59	60	119
Lobular	2	1	3
Medullary	0	1	1
Micropapillary	1	0	1
Mixte	1	0	1
Mucinous	0	1	1

Histological Elston-Ellis modified SBR grade			
SBR = Scarff-Bloom-Richardson			
Units: Subjects			
Missing	1	0	1
Grade 1	1	2	3
Grade 2	30	20	50
Grade 3	26	35	61
NA	5	6	11
Estrogen receptor Units: Subjects			
Positive	37	37	74
Negative	26	26	52
Progestrone receptor Units: Subjects			
Positive	29	26	55
Negative	34	37	71
Breast cancer stage Units: Subjects			
I: tumor <=2.0, lymph nodes clear, no metastasis	1	1	2
IIa: tumor <=2.0 cm, regional lymph node	20	23	43
IIb: tumor >2.0<5.0cm, regional lymph nodes	22	17	39
IIIa: tumor may be >5.0 cm, regional lymph nodes	14	12	26
IIIb: tumor extending to chest wall or skin	4	5	9
IIIc: tumor with extensive lymph node involvement	2	4	6
IV: distant metastasis	0	1	1
Eastern Cooperative Oncology Group (ECOG) Performance Status			
ECOG criteria: 0: Fully active. 1: Ambulatory, carry out work of a light or sedentary nature. 2: Ambulatory, capable of all selfcare. 3: Capable of limited selfcare, confined to bed or chair more than 50% of waking hours. 4: Completely disabled, no selfcare, totally confined to bed or chair. 5: Dead.			
Units: Subjects			
0: Fully active	60	55	115
1: Ambulatory, carry out light work	2	7	9
Not done	1	1	2
Weight			
n=62, 63			
Units: kg			
arithmetic mean	68.21	70.07	
standard deviation	± 13.69	± 14.1	-
Height			
n=62, 60			
Units: cm			
arithmetic mean	161.82	163.18	
standard deviation	± 7.92	± 7.08	-

End points

End points reporting groups

Reporting group title	MCH - TH

Reporting group description:

- MCH: On day 1 of each of 4 consecutive 21-day cycles, each patient was infused with liposomal doxorubicin hydrochloride (60 mg/m^2), cyclophosphamide (600 mg/m^2), and trastuzumab (8 or 6 mg/kg). For the first cycle, the loading dose of trastuzumab was 8 mg/kg; 6 mg/kg was used for the remaining cycles.
- TH: After 4 cycles of MCH, the treatment changed to 4 consecutive 21 day cycles of docetaxel (100 mg/m^2) and trastuzumab (6 mg/kg).

Reporting group title	AC - TH

Reporting group description:

- AC: On day 1 of each of 4 consecutive 21-day cycles, each patient was infused with free doxorubicin hydrochloride (60 mg/m^2) and cyclophosphamide (600 mg/m^2).
- TH: After 4 cycles of AC, the treatment changed to 4 consecutive 21-day cycles of docetaxel (100 mg/m^2) and trastuzumab (8 or 6 mg/kg). For the first cycle, the loading dose of trastuzumab was 8 mg/kg; 6 mg/kg was used for the remaining 3 cycles.

Primary: Percentage of Participants Who Achieved a Pathological Complete Response (pCR) in Breast Following 8 Cycles of Chemotherapy

End point title	Percentage of Participants Who Achieved a Pathological Complete Response (pCR) in Breast Following 8 Cycles of Chemotherapy

End point description:

Pathological examination of resected tumors retrieved during mastectomy or breast conservative surgery following 8 cycles of chemotherapy was done by central review. If a patient had several responses, only the worst case was taken into account. Patients who dropped out early and had no evidence of pCR were considered non-responders.

End point type	Primary

End point timeframe:

up to 28 weeks (24 weeks treatment, up to 4 additional weeks for surgery)

End point values	MCH - TH	AC - TH		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	63[1]	63[2]		
Units: percentage of participants				
number (not applicable)	41.3	54		

Notes:

[1] - Enrolled patients

[2] - Enrolled patients

Statistical analyses

Statistical analysis title	Percentage of pCR in Breast
Comparison groups	MCH - TH v AC - TH

Number of subjects included in analysis	126
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.154 [3]
Method	t-test, 2-sided
Confidence interval	
level	95 %
sides	2-sided
lower limit	-0.3
upper limit	0.05

Notes:

[3] - Significance at 0.05

Secondary: Percentage of Participants Who Achieved a Pathological Complete Response in Breast and Axillary Lymph Node Following 8 Cycles of Chemotherapy.

End point title	Percentage of Participants Who Achieved a Pathological Complete Response in Breast and Axillary Lymph Node Following 8 Cycles of Chemotherapy.

End point description:

Pathological examination of resected tumors and axillary lymph node retrieved during mastectomy or breast conservative surgery following 8 cycles of chemotherapy was done by central review. If a patient had several responses, only the worst case was taken into account. Patients who dropped out early and had no evidence of pCR were considered non-responders.

End point type	Secondary

End point timeframe:

up to 28 weeks (24 weeks treatment, up to 4 additional weeks for surgery)

End point values	MCH - TH	AC - TH		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	63[4]	63[5]		
Units: percentage of participants				
number (not applicable)	38.1	47.6		

Notes:

[4] - Enrolled patients

[5] - Enrolled patients

Statistical analyses

Statistical analysis title	Percentage of pCR in Breast + Axillary Lymph Node
Comparison groups	MCH - TH v AC - TH
Number of subjects included in analysis	126
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.28 [6]
Method	t-test, 2-sided
Confidence interval	
level	95 %
sides	2-sided
lower limit	-0.27
upper limit	0.08

Notes:

[6] - Significance at 0.05

Secondary: Percentage of Participants Who Achieved an Objective Response As Defined by the World Health Organization

End point title	Percentage of Participants Who Achieved an Objective Response As Defined by the World Health Organization

End point description:

An objective response using WHO criteria includes a complete response or partial response combined. For target lesions, a complete response was defined as the disappearance of all target lesions; a partial response was defined as at least a 30% decrease in the sum of the longest diameter of target lesions, taking as reference the baseline sum longest diameter.

End point type	Secondary

End point timeframe:

up to 28 weeks (24 weeks treatment, up to 4 additional weeks for surgery)

End point values	MCH - TH	AC - TH		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	63[7]	63[8]		
Units: percentage of participants				
number (not applicable)	77.8	84.1		

Notes:

[7] - Enrolled patients

[8] - Enrolled patients

Statistical analyses

Statistical analysis title	Objective Response Using WHO
Comparison groups	MCH - TH v AC - TH
Number of subjects included in analysis	126
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.364 [9]
Method	t-test, 2-sided
Confidence interval	
level	95 %
sides	2-sided
lower limit	-0.2
upper limit	0.07

Notes:

[9] - Significance at 0.05

Secondary: Percentage of Participants Undergoing Breast Conservative Surgery

End point title	Percentage of Participants Undergoing Breast Conservative Surgery

End point description:

End point type	Secondary

End point timeframe:
Weeks 25-28

End point values	MCH - TH	AC - TH		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	63[10]	63[11]		
Units: percentage of participants				
number (not applicable)	58.9	53.4		

Notes:
[10] - Enrolled patients
[11] - Enrolled patients

Statistical analyses

Statistical analysis title	Percentage Undergoing Breast Conservation Surgery
Comparison groups	MCH - TH v AC - TH
Number of subjects included in analysis	126
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.556 [12]
Method	t-test, 2-sided

Notes:
[12] - Significance at 0.05

Secondary: Percentage of Participants With Progression-Free Survival (PFS) within 5 Years of Randomization

End point title	Percentage of Participants With Progression-Free Survival (PFS) within 5 Years of Randomization

End point description:

Progression free survival (PFS) was defined as the time from the randomization date to the date of disease progression or death, whichever was observed first. The disease progression was detected based on at least one of the following methods: physical exam, computed tomography scan, X-ray, ultrasound, magnetic resonance imaging (MRI) and/or pathological examinations. If a patient did not develop an event (disease progression or death), the patient was censored at the last known tumor assessment date (or last follow-up visit without progression documented).

This outcome reports the percentage of patients without a PFS event (ie, patients experiencing either disease progression or death) 5 years after randomization.

End point type	Secondary

End point timeframe:
Up to 5 years after randomization

End point values	MCH - TH	AC - TH		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	63[13]	63[14]		
Units: percentage of participants				
number (not applicable)	11.1	12.7		

Notes:

[13] - Enrolled patients

[14] - Enrolled patients

Statistical analyses

Statistical analysis title	PFS
Comparison groups	MCH - TH v AC - TH
Number of subjects included in analysis	126
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.783 [15]
Method	t-test, 2-sided
Confidence interval	
level	95 %
sides	2-sided
lower limit	-0.13
upper limit	0.1

Notes:

[15] - Significance at 0.05

Secondary: Participants with an Occurrence of New York Heart Association (NYHA) Functional Class 3 or 4 Congestive Heart Failure (CHF) During the Study

End point title	Participants with an Occurrence of New York Heart Association (NYHA) Functional Class 3 or 4 Congestive Heart Failure (CHF) During the Study

End point description:

The New York Heart Association grades heart failure into 4 classes, I - IV. Of interest to this outcome are patients with a functional class III or IV during the study.

Class III: Marked limitation of physical activity. Comfortable at rest. Less than ordinary activity causes fatigue, palpitation, or dyspnea.
Class IV: Unable to carry on any physical activity without discomfort. Symptoms of heart failure at rest. If any physical activity is undertaken, discomfort increases.

End point type	Secondary

End point timeframe:

Screening (approximately Day -21), Baseline (Day -6 to 1), Before each 21-day cycle (8 cycles total), within 1 week before surgery (weeks 25-28), post-surgical follow-up (4 weeks of surgery, approximately week 32)

End point values	MCH - TH	AC - TH		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	62[16]	63[17]		
Units: participants				
Class III	0	0		
Class IV	0	0		

Notes:

[16] - Safety analysis set

[17] - Safety analysis set

Statistical analyses

No statistical analyses for this end point

Secondary: Participants with a Reduction from Baseline in Left Ventricular Ejection Fraction (LVEF) At Any Time During the Study

End point title	Participants with a Reduction from Baseline in Left Ventricular Ejection Fraction (LVEF) At Any Time During the Study

End point description:

Left ventricular ejection fraction (LVEF) "events" were defined in the SAP as either a decrease from baseline of more than 15% or a decrease from baseline of ≤15% (but more than 10%) with an absolute value of ≤50%. Data are offered at Week 4, and cumulatively over the course of the study and follow-up.

End point type	Secondary

End point timeframe:

Baseline (Day -6 to Day 1), after each 4 cycles (Weeks 12 and 24), within 3 weeks before surgery (Weeks 26-28), 4 weeks after surgery (Week 32), annually during the 5-year follow-up

End point values	MCH - TH	AC - TH		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	62[18]	63[19]		
Units: participants				
Week 4	1	1		
Throughout the study and follow-up	6	7		

Notes:

[18] - Safety analysis set

[19] - Safety analysis set

Statistical analyses

No statistical analyses for this end point

Secondary: Participants with Treatment-emergent Adverse Events

End point title	Participants with Treatment-emergent Adverse Events

End point description:

An adverse event was defined as any untoward medical occurrence that develops or worsens in severity during the conduct of a clinical study and does not necessarily have a causal relationship to the study drug. Severity was rated by the investigator on a scale of 1-5; reported are the most severe ratings of 3 (severe AE), 4 (life threatening or disabling AE) and 5 (death due to an AE). Relationship of AE to treatment was determined by the investigator. Serious AEs include death, a life-threatening adverse event, inpatient hospitalization or prolongation of existing hospitalization, persistent or significant disability or incapacity, a congenital anomaly or birth defect, OR an important medical event that jeopardized the patient and required medical intervention to prevent the previously listed serious outcomes.

End point type	Secondary

End point timeframe:
Day 1 to Week 32

End point values	MCH - TH	AC - TH		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	62[20]	63[21]		
Units: participants				
>= 1 adverse event	62	63		
>=1 severe AE (grades 3-5)	51	50		
>=1 treatment-related AE	62	44		
AEs resulting in death	0	0		
Deaths due to any cause	0	4		
Serious AE	18	21		
Withdrawn from the study due to an AE	4	5		

Notes:
[20] - Safety analysis set
[21] - Safety analysis set

Statistical analyses

No statistical analyses for this end point

Adverse events

Adverse events information

Timeframe for reporting adverse events:

Day 1 to Week 32

Assessment type	Systematic

Dictionary used

Dictionary name	MedDRA
Dictionary version	11.1

Reporting groups

Reporting group title	MCH - TH

Reporting group description:

- MCH: On day 1 of each of 4 consecutive 21-day cycles, each patient was infused with liposomal doxorubicin hydrochloride (60 mg/m^2), cyclophosphamide (600 mg/m^2), and trastuzumab (8 or 6 mg/kg). For the first cycle, the loading dose of trastuzumab was 8 mg/kg; 6 mg/kg was used for the remaining cycles.
- TH: After 4 cycles of MCH, the treatment changed to 4 consecutive 21 day cycles of docetaxel (100 mg/m^2) and trastuzumab (6 mg/kg).

Reporting group title	AC - TH

Reporting group description:

- AC: On day 1 of each of 4 consecutive 21-day cycles, each patient was infused with free doxorubicin hydrochloride (60 mg/m^2) and cyclophosphamide (600 mg/m^2).
- TH: After 4 cycles of AC, the treatment changed to 4 consecutive 21-day cycles of docetaxel (100 mg/m^2) and trastuzumab (8 or 6 mg/kg). For the first cycle, the loading dose of trastuzumab was 8 mg/kg; 6 mg/kg was used for the remaining 3 cycles.

Serious adverse events	MCH - TH	AC - TH	
Total subjects affected by serious adverse events			
subjects affected / exposed	18 / 62 (29.03%)	21 / 63 (33.33%)	
number of deaths (all causes)	0	4	
number of deaths resulting from adverse events			
Injury, poisoning and procedural complications			
Whiplash injury			
subjects affected / exposed	0 / 62 (0.00%)	1 / 63 (1.59%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Vascular disorders			
Capillary leak syndrome			
subjects affected / exposed	0 / 62 (0.00%)	1 / 63 (1.59%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Deep vein thrombosis			

subjects affected / exposed	1 / 62 (1.61%)	0 / 63 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Aneurysm			
subjects affected / exposed	1 / 62 (1.61%)	0 / 63 (0.00%)	
occurrences causally related to treatment / all	0 / 2	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Cardiac disorders			
Myocardial infarction			
subjects affected / exposed	0 / 62 (0.00%)	1 / 63 (1.59%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Atrial fibrillation			
subjects affected / exposed	0 / 62 (0.00%)	1 / 63 (1.59%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Cyanosis			
subjects affected / exposed	1 / 62 (1.61%)	0 / 63 (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			
Acute polyneuropathy			
subjects affected / exposed	1 / 62 (1.61%)	0 / 63 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Dizziness			
subjects affected / exposed	1 / 62 (1.61%)	0 / 63 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Blood and lymphatic system disorders			
Febrile neutropenia			
subjects affected / exposed	9 / 62 (14.52%)	7 / 63 (11.11%)	
occurrences causally related to treatment / all	0 / 9	0 / 7	
deaths causally related to treatment / all	0 / 0	0 / 0	

Leukopenia			
subjects affected / exposed	1 / 62 (1.61%)	0 / 63 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
General disorders and administration site conditions			
Pyrexia			
subjects affected / exposed	1 / 62 (1.61%)	2 / 63 (3.17%)	
occurrences causally related to treatment / all	0 / 1	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Fatigue			
subjects affected / exposed	1 / 62 (1.61%)	0 / 63 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Asthenia			
subjects affected / exposed	1 / 62 (1.61%)	0 / 63 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Ear and labyrinth disorders			
Vertigo positional			
subjects affected / exposed	1 / 62 (1.61%)	0 / 63 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Gastrointestinal disorders			
Constipation			
subjects affected / exposed	0 / 62 (0.00%)	2 / 63 (3.17%)	
occurrences causally related to treatment / all	0 / 0	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Abdominal pain			
subjects affected / exposed	0 / 62 (0.00%)	1 / 63 (1.59%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Respiratory, thoracic and mediastinal disorders			
Dyspnoea			

subjects affected / exposed	1 / 62 (1.61%)	0 / 63 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Skin and subcutaneous tissue disorders			
Erythema multiforme			
subjects affected / exposed	0 / 62 (0.00%)	1 / 63 (1.59%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Infections and infestations			
Wound infection			
subjects affected / exposed	0 / 62 (0.00%)	1 / 63 (1.59%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pneumonia			
subjects affected / exposed	0 / 62 (0.00%)	1 / 63 (1.59%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Device related infection			
subjects affected / exposed	0 / 62 (0.00%)	1 / 63 (1.59%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Catheter related infection			
subjects affected / exposed	0 / 62 (0.00%)	1 / 63 (1.59%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Urinary tract infection			
subjects affected / exposed	1 / 62 (1.61%)	0 / 63 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Erysipelas			
subjects affected / exposed	1 / 62 (1.61%)	0 / 63 (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	MCH - TH	AC - TH	
Total subjects affected by non-serious adverse events			
subjects affected / exposed	62 / 62 (100.00%)	63 / 63 (100.00%)	
Vascular disorders			
Hot flush			
subjects affected / exposed	10 / 62 (16.13%)	12 / 63 (19.05%)	
occurrences (all)	12	20	
Hypertension			
subjects affected / exposed	3 / 62 (4.84%)	4 / 63 (6.35%)	
occurrences (all)	5	4	
General disorders and administration site conditions			
Asthenia			
subjects affected / exposed	28 / 62 (45.16%)	36 / 63 (57.14%)	
occurrences (all)	115	116	
Mucosal inflammation			
subjects affected / exposed	32 / 62 (51.61%)	25 / 63 (39.68%)	
occurrences (all)	62	55	
Fatigue			
subjects affected / exposed	19 / 62 (30.65%)	15 / 63 (23.81%)	
occurrences (all)	62	54	
Pyrexia			
subjects affected / exposed	17 / 62 (27.42%)	11 / 63 (17.46%)	
occurrences (all)	21	21	
Oedema peripheral			
subjects affected / exposed	9 / 62 (14.52%)	11 / 63 (17.46%)	
occurrences (all)	10	15	
Oedema			
subjects affected / exposed	10 / 62 (16.13%)	7 / 63 (11.11%)	
occurrences (all)	13	9	
Infusion related reaction			
subjects affected / exposed	3 / 62 (4.84%)	4 / 63 (6.35%)	
occurrences (all)	5	4	
Pain			

subjects affected / exposed	1 / 62 (1.61%)	4 / 63 (6.35%)	
occurrences (all)	2	5	
Respiratory, thoracic and mediastinal disorders			
Epistaxis			
subjects affected / exposed	7 / 62 (11.29%)	6 / 63 (9.52%)	
occurrences (all)	8	6	
Dyspnoea			
subjects affected / exposed	5 / 62 (8.06%)	8 / 63 (12.70%)	
occurrences (all)	9	12	
Oropharyngeal pain			
subjects affected / exposed	7 / 62 (11.29%)	4 / 63 (6.35%)	
occurrences (all)	7	4	
Cough			
subjects affected / exposed	6 / 62 (9.68%)	4 / 63 (6.35%)	
occurrences (all)	6	4	
Nasal mucosal disorder			
subjects affected / exposed	7 / 62 (11.29%)	2 / 63 (3.17%)	
occurrences (all)	8	2	
Psychiatric disorders			
Insomnia			
subjects affected / exposed	7 / 62 (11.29%)	7 / 63 (11.11%)	
occurrences (all)	10	8	
Anxiety			
subjects affected / exposed	3 / 62 (4.84%)	5 / 63 (7.94%)	
occurrences (all)	3	5	
Depression			
subjects affected / exposed	4 / 62 (6.45%)	3 / 63 (4.76%)	
occurrences (all)	4	4	
Investigations			
Alanine aminotransferase increased			
subjects affected / exposed	10 / 62 (16.13%)	4 / 63 (6.35%)	
occurrences (all)	17	6	
Gamma-glutamyltransferase increased			
subjects affected / exposed	10 / 62 (16.13%)	4 / 63 (6.35%)	
occurrences (all)	18	4	
Aspartate aminotransferase			

increased			
subjects affected / exposed	6 / 62 (9.68%)	5 / 63 (7.94%)	
occurrences (all)	8	6	
Blood lactate dehydrogenase increased			
subjects affected / exposed	4 / 62 (6.45%)	1 / 63 (1.59%)	
occurrences (all)	4	1	
Weight increased			
subjects affected / exposed	0 / 62 (0.00%)	4 / 63 (6.35%)	
occurrences (all)	0	5	
Nervous system disorders			
Headache			
subjects affected / exposed	13 / 62 (20.97%)	15 / 63 (23.81%)	
occurrences (all)	20	20	
Dysgeusia			
subjects affected / exposed	14 / 62 (22.58%)	13 / 63 (20.63%)	
occurrences (all)	24	15	
Paraesthesia			
subjects affected / exposed	9 / 62 (14.52%)	15 / 63 (23.81%)	
occurrences (all)	14	31	
Peripheral sensory neuropathy			
subjects affected / exposed	8 / 62 (12.90%)	2 / 63 (3.17%)	
occurrences (all)	14	3	
Neuropathy peripheral			
subjects affected / exposed	1 / 62 (1.61%)	7 / 63 (11.11%)	
occurrences (all)	1	9	
Dizziness			
subjects affected / exposed	4 / 62 (6.45%)	3 / 63 (4.76%)	
occurrences (all)	4	3	
Disturbance in attention			
subjects affected / exposed	4 / 62 (6.45%)	3 / 63 (4.76%)	
occurrences (all)	5	4	
Neurotoxicity			
subjects affected / exposed	1 / 62 (1.61%)	4 / 63 (6.35%)	
occurrences (all)	1	6	
Blood and lymphatic system disorders			

Neutropenia			
subjects affected / exposed	41 / 62 (66.13%)	46 / 63 (73.02%)	
occurrences (all)	145	143	
Leukopenia			
subjects affected / exposed	24 / 62 (38.71%)	34 / 63 (53.97%)	
occurrences (all)	77	111	
Anaemia			
subjects affected / exposed	13 / 62 (20.97%)	21 / 63 (33.33%)	
occurrences (all)	27	60	
Thrombocytopenia			
subjects affected / exposed	5 / 62 (8.06%)	5 / 63 (7.94%)	
occurrences (all)	5	8	
Lymphopenia			
subjects affected / exposed	3 / 62 (4.84%)	6 / 63 (9.52%)	
occurrences (all)	15	17	
Febrile neutropenia			
subjects affected / exposed	2 / 62 (3.23%)	4 / 63 (6.35%)	
occurrences (all)	2	4	
Ear and labyrinth disorders			
Vertigo			
subjects affected / exposed	5 / 62 (8.06%)	5 / 63 (7.94%)	
occurrences (all)	8	6	
Eye disorders			
Conjunctivitis			
subjects affected / exposed	11 / 62 (17.74%)	10 / 63 (15.87%)	
occurrences (all)	12	13	
Lacrimation increased			
subjects affected / exposed	6 / 62 (9.68%)	8 / 63 (12.70%)	
occurrences (all)	7	9	
Gastrointestinal disorders			
Nausea			
subjects affected / exposed	44 / 62 (70.97%)	39 / 63 (61.90%)	
occurrences (all)	95	95	
Stomatitis			
subjects affected / exposed	21 / 62 (33.87%)	21 / 63 (33.33%)	
occurrences (all)	47	45	
Diarrhoea			

subjects affected / exposed	27 / 62 (43.55%)	25 / 63 (39.68%)	
occurrences (all)	57	44	
Vomiting			
subjects affected / exposed	17 / 62 (27.42%)	21 / 63 (33.33%)	
occurrences (all)	29	38	
Constipation			
subjects affected / exposed	19 / 62 (30.65%)	16 / 63 (25.40%)	
occurrences (all)	35	28	
Abdominal pain upper			
subjects affected / exposed	12 / 62 (19.35%)	12 / 63 (19.05%)	
occurrences (all)	19	16	
Dyspepsia			
subjects affected / exposed	8 / 62 (12.90%)	9 / 63 (14.29%)	
occurrences (all)	9	10	
Abdominal pain			
subjects affected / exposed	5 / 62 (8.06%)	4 / 63 (6.35%)	
occurrences (all)	8	5	
Dry mouth			
subjects affected / exposed	1 / 62 (1.61%)	4 / 63 (6.35%)	
occurrences (all)	1	5	
Skin and subcutaneous tissue disorders			
Alopecia			
subjects affected / exposed	37 / 62 (59.68%)	41 / 63 (65.08%)	
occurrences (all)	55	52	
Nail disorder			
subjects affected / exposed	13 / 62 (20.97%)	11 / 63 (17.46%)	
occurrences (all)	19	13	
Dry skin			
subjects affected / exposed	15 / 62 (24.19%)	7 / 63 (11.11%)	
occurrences (all)	17	8	
Rash			
subjects affected / exposed	11 / 62 (17.74%)	8 / 63 (12.70%)	
occurrences (all)	16	14	
Palmar-plantar erythrodysaesthesia syndrome			

subjects affected / exposed	9 / 62 (14.52%)	7 / 63 (11.11%)	
occurrences (all)	13	12	
Skin toxicity			
subjects affected / exposed	10 / 62 (16.13%)	4 / 63 (6.35%)	
occurrences (all)	11	8	
Nail toxicity			
subjects affected / exposed	8 / 62 (12.90%)	6 / 63 (9.52%)	
occurrences (all)	1	7	
Pruritus			
subjects affected / exposed	5 / 62 (8.06%)	4 / 63 (6.35%)	
occurrences (all)	6	4	
Erythema			
subjects affected / exposed	6 / 62 (9.68%)	1 / 63 (1.59%)	
occurrences (all)	8	1	
Musculoskeletal and connective tissue disorders			
Myalgia			
subjects affected / exposed	17 / 62 (27.42%)	17 / 63 (26.98%)	
occurrences (all)	26	23	
Bone pain			
subjects affected / exposed	18 / 62 (29.03%)	15 / 63 (23.81%)	
occurrences (all)	28	33	
Musculoskeletal pain			
subjects affected / exposed	13 / 62 (20.97%)	13 / 63 (20.63%)	
occurrences (all)	35	36	
Arthralgia			
subjects affected / exposed	10 / 62 (16.13%)	10 / 63 (15.87%)	
occurrences (all)	16	15	
Back pain			
subjects affected / exposed	6 / 62 (9.68%)	2 / 63 (3.17%)	
occurrences (all)	6	3	
Pain in extremity			
subjects affected / exposed	4 / 62 (6.45%)	2 / 63 (3.17%)	
occurrences (all)	6	2	
Infections and infestations			

Vulvovaginal mycotic infection			
subjects affected / exposed	4 / 62 (6.45%)	0 / 63 (0.00%)	
occurrences (all)	7	0	
Nasopharyngitis			
subjects affected / exposed	4 / 62 (6.45%)	16 / 63 (25.40%)	
occurrences (all)	6	21	
Respiratory tract infection			
subjects affected / exposed	4 / 62 (6.45%)	4 / 63 (6.35%)	
occurrences (all)	4	5	
Bronchitis			
subjects affected / exposed	3 / 62 (4.84%)	4 / 63 (6.35%)	
occurrences (all)	4	7	
Urinary tract infection			
subjects affected / exposed	4 / 62 (6.45%)	1 / 63 (1.59%)	
occurrences (all)	4	2	
Metabolism and nutrition disorders			
Anorexia			
subjects affected / exposed	12 / 62 (19.35%)	12 / 63 (19.05%)	
occurrences (all)	16	23	

More information

Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? Yes

Date	Amendment
12 May 2008	Amendment 1 was issued before any patients were enrolled into the study. • An Independent Safety Data Monitoring Committee was set-up to review the patients safety events including: - suspected unexpected serious adverse reactions, - All grade 3, 4 or 5 non-hematologic AEs (grading according to NCI CTCAE version 3.0), - Febrile neutropenia, - Thrombocytopenia with hemorrhage, - Events of interest, such as symptomatic cardiac function failure (NYHA Class 3 or 4) or asymptomatic decrease in LVEF. • The Steering Committee reviewed and implemented the recommendation issued by the Independent Safety Data Monitoring Committee.
07 July 2008	Amendment 2 was issued before any patients were enrolled into the study. • In the primary objective, the primary efficacy variable was clarified to indicate the proportion of patients who achieve pCR in breast. • The secondary objectives were updated and 2 additional secondary objectives were to be evaluated: - The proportion of patients who achieve pCR in breast and axillary lymph node. - The proportion of patients with conservative surgery. • SISH and CISH tests, in addition to the FISH test, were allowed to check the amplification of the HER2 gene. These 2 tests were the reference tests in some European centers. • Additional information concerning diagnosis biopsy and SLN procedure have been included as follows: - Introduction of a tumor clip at the time of the diagnosis biopsy is highly recommended. - Pre-treatment SLN is not a standard procedure but is acceptable for clinical stage T2, N0 patients. • The following statement was deleted concerning anti estrogen or anti aromatase hormonal treatment: - Patients with ER positive tumors will be allowed to receive anti estrogen or anti aromatase hormonal treatment at the discretion of the investigator. • The timing of the postsurgical visit was clarified from Postsurgical follow-up to end of cycle 8/Postsurgical visit. • The number and timing of mammography/MRI procedures to be performed was changed to avoid unnecessary repetition of these procedures. • Clarification concerning the breast surgery and axillary dissection as follows: The patient will then undergo surgery: mastectomy or breast conservative surgery that must remove all residual tumor providing clear margins (>2 mm). Axillary dissection is mandatory in the absence of pre-treatment negative SLN. • The timing for platelet and absolute neutrophil counts was modified to avoid unnecessary repetition of procedures; the number of blood tests was reduced from a weekly schedule at each cycle to a weekly schedule for selected cycles.

15 September 2010	Amendment 3 was issued after 122 patients were enrolled. • The planned study end date and the duration of the study were changed to the last patient last visit by third quarter 2012 including the 2-year follow-up period, with a duration of 48 months. The expected study end date and duration were updated according to currently available information on patients' inclusion and accrual rates and a clarification was added indicating that the end of the study was after the 2-year follow-up period. • A sentence was added in order to clarify that all patients who received treatment should still be monitored after they stopped receiving study treatment for up to 2 years from randomization. • In Appendix D of the protocol (NYHA Functional Classification of Cardiac Disease), the presentation of the NYHA classification was modified in order to clarify that patients with no cardiac disease should not be classified according the Functional Capacity Class and to avoid any confusion between the Functional Capacity Class and the Objective Assessment. • In Appendix F (WHO criteria of tumor response) of the protocol, the table for the determination of overall response was simplified.
23 February 2011	Amendment 4 (dated 23 February 2011) to the protocol was issued after 125 patients were enrolled. Administrative changes in study personnel (sponsor's medical expert and contact person for medical issues) were made to the protocol.
29 February 2012	Amendment 5 (dated 29 February 2012) to the protocol was issued after 125 patients were enrolled. • The duration of follow-up for PFS and cardiac insufficiency was changed from 2 to 5 years so that data on PFS and cardiac insufficiency were collected for 3 more years. • The duration of the study and the expected completion date were changed (last patient last visit by third quarter 2015 including the 5-year follow-up period, with a duration of 84 months) so that data on PFS and cardiac insufficiency were collected for 3 more years. • The number of study visits was updated to include additional visits during the extended posttreatment follow-up period and the study flowchart was updated accordingly. • The description of study periods requiring AEs and SAEs reporting was clarified. • The description of study periods requiring SAEs reporting was clarified. • The duration of follow-up for LVEF was changed from 2 to 5 years.
29 November 2012	Amendment 6 (dated 29 November 2012) to the protocol was issued after 125 patients were enrolled. • The sponsor was changed from Cephalon to Teva. • Administrative changes in personnel were made.

Notes:

Interruptions (globally)

Were there any global interruptions to the trial? No

Limitations and caveats

None reported