



## Clinical trial results:

### A phase I-II study of lapatinib and docetaxel as neoadjuvant treatment for HER-2 positive locally advanced/inflammatory or large operable breast cancer.

#### Summary

EudraCT number	2006-000864-94
Trial protocol	BE FR GB SI
Global end of trial date	22 April 2015

#### Results information

Result version number	v1 (current)
This version publication date	30 July 2016
First version publication date	30 July 2016

#### Trial information

##### Trial identification

Sponsor protocol code	EORTC protocol 10054
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##### Additional study identifiers

ISRCTN number	-
ClinicalTrials.gov id (NCT number)	NCT00450892
WHO universal trial number (UTN)	-

Notes:

##### Sponsors

Sponsor organisation name	European Organisation for Research and Treatment of Cancer
Sponsor organisation address	Avenue E. Mounier 83/11, Brussels, Belgium, 1200
Public contact	Project, Budget and Regulatory Dept, European Organisation for Research and Treatment of Cancer, +32 27441062, regulatory@eortc.be
Scientific contact	Project, Budget and Regulatory Dept, European Organisation for Research and Treatment of Cancer, +32 27441062, regulatory@eortc.be

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:

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## Results analysis stage

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Analysis stage	Final
Date of interim/final analysis	05 May 2014
Is this the analysis of the primary completion data?	Yes
Primary completion date	05 May 2014
Global end of trial reached?	Yes
Global end of trial date	22 April 2015
Was the trial ended prematurely?	No

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Notes:

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## General information about the trial

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Main objective of the trial:

The primary objective of the Phase I stage of the trial was to recommend a dose of lapatinib and docetaxel to be given pre-operatively over 3 cycles to HER-2 positive breast cancer patients, following 3 cycles of FEC. In order to achieve this, the study determined the maximum tolerated dose (MTD) based on the documentation of the acute dose limiting toxicity (DLT).  
=> The phase I results were published in 2013 (see publication in "more information").

The primary objective of the phase II is to assess the activity of the combination docetaxel + anti-HER2 treatment (lapatinib or lapatinib+trastuzumab) followed by FEC. The pathological response rate will be used as a surrogate for activity. The reference arm will be docetaxel+trastuzumab (3 cycles) followed by FEC 100 (3 cycles).  
=> This report contains only the results of the phase II part.

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Protection of trial subjects:

The responsible investigator will ensure that this study is conducted in agreement with either the Declaration of Helsinki (available on the World Medical Association web site (<http://www.wma.net>)) and/or the laws and regulations of the country, whichever provides the greatest protection of the patient.

The protocol has been written, and the study will be conducted according to the ICH Harmonized Tripartite Guideline on Good Clinical Practice (ICH-GCP, available online at <http://www.ema.europa.eu/pdfs/human/ich/013595en.pdf>).

The protocol must be approved by the competent ethics committee(s) as required by the applicable national legislation.

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Background therapy:

3 cycles Docetaxel (100 mg/m<sup>2</sup> on day 1) followed by 3 cycles of FEC 100 (5-FU 500 mg/m<sup>2</sup> i.v., Epirubicin 100 mg/m<sup>2</sup> i.v., Cyclophosphamide 500 mg/m<sup>2</sup> i.v.)

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Evidence for comparator:

The clinical development program of lapatinib in combination with chemotherapy in breast cancer can be summarized as:

1. An understandable focus on advanced breast cancer. An active tyrosine kinase inhibitor is likely to manifest its greatest benefit in early breast cancer, and therefore an obvious further development should be to study this compound in the adjuvant or neoadjuvant setting of early breast cancer. As a consequence, a comprehensive program is under development to explore the activity of lapatinib in the adjuvant and the neo-adjuvant settings of breast cancer, including study designs based on the N9831 model and the HERA model. The neo-adjuvant study that we are proposing is part of this program.
2. To date, little focus (other than a couple of advanced disease studies) on the question as to precisely which tumors benefit most (and least) from this agent. In the proposed study, the EORTC Breast Group has therefore incorporated a comprehensive translational research program based on systematic tumor and blood samples collection at various time points in an attempt to identify biological markers predictive for response to lapatinib.

The use of trastuzumab in combination with taxanes has been shown to result in a significantly higher pCR rate in HER2-positive breast cancer, and docetaxel has been shown in a randomized trial to be more effective than 3-weekly Paclitaxel. Thus, particularly given its possibly superior cardiac safety signal, the combination of docetaxel and lapatinib could be an effective therapy for HER2 breast cancer.

Actual start date of recruitment	26 October 2010
Long term follow-up planned	Yes
Long term follow-up rationale	Efficacy, Scientific research
Long term follow-up duration	3 Years
Independent data monitoring committee (IDMC) involvement?	No

Notes:

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### Population of trial subjects

#### Subjects enrolled per country

Country: Number of subjects enrolled	Slovenia: 4
Country: Number of subjects enrolled	United Kingdom: 5
Country: Number of subjects enrolled	Belgium: 14
Country: Number of subjects enrolled	France: 97
Country: Number of subjects enrolled	Switzerland: 8
Worldwide total number of subjects	128
EEA total number of subjects	120

Notes:

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#### 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)	121
From 65 to 84 years	7
85 years and over	0

## Subject disposition

### Recruitment

Recruitment details:

Registration period from October 2010 to January 2013

14 institutions in 5 countries

### Pre-assignment

Screening details:

Female patients with any large operable T2 or T3 breast cancers, M0 or female patients with locally advanced or inflammatory breast cancer

HER-2 positive (IHC 3+, or IHC 2+ and FISH/CISH +, or FISH, or CISH+ only)

Known hormone receptor status: ER/PR positive or negative.

Informed consent

### 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
<b>Arm title</b>	Lapatinib only

Arm description:

3 cycles of Docetaxel (100 mg/m<sup>2</sup> on day 1) + Lapatinib (1000 mg daily), followed by 3 cycles of FEC 100

Arm type	Experimental
Investigational medicinal product name	Lapatinib
Investigational medicinal product code	
Other name	GW572016
Pharmaceutical forms	Capsule
Routes of administration	Oral use

Dosage and administration details:

1000 mg daily during the 3 cycles of docetaxel.

<b>Arm title</b>	Lapatinib + Trastuzumab
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Arm description:

3 cycles Docetaxel (100 mg/m<sup>2</sup> on day 1) + Lapatinib (1000 mg daily) + Trastuzumab, followed by 3 cycles of FEC 100

Arm type	Experimental
Investigational medicinal product name	Lapatinib
Investigational medicinal product code	
Other name	GW572016
Pharmaceutical forms	Capsule
Routes of administration	Oral use

Dosage and administration details:

1000 mg daily during the 3 cycles of docetaxel.

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

Dosage and administration details:

Trastuzumab is to be given as a loading dose of 4mg/kg IV over 90 minutes on day 1 of cycle 4 followed

by a maintenance dose of 2mg/kg given over 30 minutes on days 8 and 15 of cycle 4 and on days 1, 8, and 15 of each subsequent cycle (cycles 5 and 6).

<b>Arm title</b>	Trastuzumab only
Arm description: 3 cycles Docetaxel (100 mg/m <sup>2</sup> on day 1) + Trastuzumab, followed by 3 cycles of FEC 100	
Arm type	Active comparator
Investigational medicinal product name	Trastuzumab
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Concentrate for solution for infusion
Routes of administration	Intravenous use

Dosage and administration details:

Trastuzumab is to be given as a loading dose of 4mg/kg IV over 90 minutes on day 1 of cycle 4 followed by a maintenance dose of 2mg/kg given over 30 minutes on days 8 and 15 of cycle 4 and on days 1, 8, and 15 of each subsequent cycle (cycles 5 and 6).

<b>Number of subjects in period 1</b>	Lapatinib only	Lapatinib + Trastuzumab	Trastuzumab only
Started	23	52	53
Started allocated treatment	22	50	53
Normal completion of allocated treatment	21	37	48
Completed	21	37	48
Not completed	2	15	5
Consent withdrawn by subject	1	-	1
Physician decision	-	1	-
Adverse event, non-fatal	1	10	3
Protocol deviation	-	4	1

## Baseline characteristics

### Reporting groups

Reporting group title	Lapatinib only
Reporting group description:	3 cycles of Docetaxel (100 mg/m <sup>2</sup> on day 1) + Lapatinib (1000 mg daily), followed by 3 cycles of FEC 100
Reporting group title	Lapatinib + Trastuzumab
Reporting group description:	3 cycles Docetaxel (100 mg/m <sup>2</sup> on day 1) + Lapatinib (1000 mg daily) + Trastuzumab, followed by 3 cycles of FEC 100
Reporting group title	Trastuzumab only
Reporting group description:	3 cycles Docetaxel (100 mg/m <sup>2</sup> on day 1) + Trastuzumab, followed by 3 cycles of FEC 100

Reporting group values	Lapatinib only	Lapatinib + Trastuzumab	Trastuzumab only
Number of subjects	23	52	53
Age categorical			
Units: Subjects			
In utero	0	0	0
Preterm newborn infants (gestational age < 37 wks)	0	0	0
Newborns (0-27 days)	0	0	0
Infants and toddlers (28 days-23 months)	0	0	0
Children (2-11 years)	0	0	0
Adolescents (12-17 years)	0	0	0
Adults (18-64 years)	21	48	52
From 65-84 years	2	4	1
85 years and over	0	0	0
Age continuous			
Units: years			
median	49	49	47
full range (min-max)	27 to 68	27 to 70	25 to 68
Gender categorical			
Units: Subjects			
Female	23	52	53
Male	0	0	0
Breast cancer stage			
Units: Subjects			
locally advanced or inflammatory	6	11	11
large operable	17	41	42
clinical tumor status			
Units: Subjects			
T0 or Tis	0	1	0
T1	1	0	0
T2	11	28	24
T3	8	13	19
T4	3	9	10
unknown	0	1	0

clinical nodal status			
Units: Subjects			
N0	7	19	17
N1	13	29	32
N2	2	3	3
N3	1	1	1
ER status (local assessment)			
Units: Subjects			
ER+	14	24	26
ER-	9	27	27
unknown	0	1	0

<b>Reporting group values</b>	Total		
Number of subjects	128		
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)	121		
From 65-84 years	7		
85 years and over	0		
Age continuous			
Units: years			
median			
full range (min-max)	-		
Gender categorical			
Units: Subjects			
Female	128		
Male	0		
Breast cancer stage			
Units: Subjects			
locally advanced or inflammatory	28		
large operable	100		
clinical tumor status			
Units: Subjects			
T0 or Tis	1		
T1	1		
T2	63		
T3	40		
T4	22		
unknown	1		
clinical nodal status			
Units: Subjects			
N0	43		
N1	74		
N2	8		

N3	3		
ER status (local assessment) Units: Subjects			
ER+	64		
ER-	63		
unknown	1		

## End points

### End points reporting groups

Reporting group title	Lapatinib only
Reporting group description: 3 cycles of Docetaxel (100 mg/m <sup>2</sup> on day 1) + Lapatinib (1000 mg daily), followed by 3 cycles of FEC 100	
Reporting group title	Lapatinib + Trastuzumab
Reporting group description: 3 cycles Docetaxel (100 mg/m <sup>2</sup> on day 1) + Lapatinib (1000 mg daily) + Trastuzumab, followed by 3 cycles of FEC 100	
Reporting group title	Trastuzumab only
Reporting group description: 3 cycles Docetaxel (100 mg/m <sup>2</sup> on day 1) + Trastuzumab, followed by 3 cycles of FEC 100	
Subject analysis set title	Historical control
Subject analysis set type	Per protocol
Subject analysis set description: Used for primary test based on expected pCR rate in the standard arm (tras only). 1 ARTIFICIAL patient was added to this ARTIFICIAL analysis set, to be able to include the single arm test.	

### Primary: pCR rate in Lapatinib + Trastuzumab arm

End point title	pCR rate in Lapatinib + Trastuzumab arm
End point description: Pathologic Complete response (pCR) is defined as "complete disappearance of invasive cancer with the exception of very few scattered tumor cells". ypT0/is.  Patients will be categorized as having either "pCR" or "no pCR". Patients who progress and come off study, or in whom no definitive surgery is carried out (e.g. at patient's request or in the case of early death) will be deemed to be evaluable for this endpoint and to have not achieved pCR (classified as "no pCR"). The only patients who would be non-evaluable for the primary end-point will be those who do not receive any chemotherapy related to this protocol and who are excluded in the per protocol population.	
End point type	Primary
End point timeframe: pathological assessment based on the surgery specimen (following neo-adjuvant therapy)	

End point values	Lapatinib only	Lapatinib + Trastuzumab	Trastuzumab only	Historical control
Subject group type	Reporting group	Reporting group	Reporting group	Subject analysis set
Number of subjects analysed	22	48	52	1
Units: Number of patients				
pCR	10	29	27	0
no pCR	12	19	25	0

### Statistical analyses

Statistical analysis title	primary test
Statistical analysis description: The study has a one-stage Fleming design for the experimental arm (lapatinib+trastuzumab+docetaxel followed by FEC) with a randomized reference arm (trastuzumab and docetaxel followed by FEC). The	

type I error will be 10%. For a null hypothesis of a 40% pCR rate and an alternative hypothesis of a 60% pCR rate, 50 eligible patients need to be treated in the lapa+tras arm to have a 92.5% power. The trial will be positive if at least 25 pCR's out of 50 treated eligible patients are observed.

Comparison groups	Lapatinib + Trastuzumab v Historical control
Number of subjects included in analysis	49
Analysis specification	Pre-specified
Analysis type	superiority <sup>[1]</sup>
P-value	= 0.003 <sup>[2]</sup>
Method	Pearson Clopper
Parameter estimate	Rate
Point estimate	0.6
Confidence interval	
level	Other: 80 %
sides	2-sided
lower limit	0.5
upper limit	0.7

Notes:

[1] - The 80% 2-sided confidence intervals for the pCR rate is reported. More than 25 pCR cases were observed for the 48 patients in the Lapatinib+Trastuzumab arm, leading to a rejection of the null hypothesis. The value of lower limit of confidence interval (< 0.40 vs. > 0.40) and the p-value (compared to the 10% level) can be considered an adaptation of the decision rule, adjusted to the actual sample size.

[2] - p-value in the lapatinib+trastuzumab arm for null hypothesis: pCR rate=0.40 versus alternative hypothesis: pCR rate>0.40. The test is done only in the lapatinib+trastuzumab arm (n=48), the "historical control" group has been artificially added.

### Secondary: Best overall response

End point title	Best overall response
End point description:	
Best overall response to neo-adjuvant treatment according to RECIST v1.0	
Endpoint evaluated in the response population (all eligible patients who have started their allocated treatment and had measurable disease at baseline)	
End point type	Secondary
End point timeframe:	
During neo-adjuvant therapy.	

End point values	Lapatinib only	Lapatinib + Trastuzumab	Trastuzumab only	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	21	47	52	
Units: Number of patients				
CR	12	24	28	
PR	5	12	18	
SD	0	5	3	
PD	0	0	0	
Early Death	0	0	0	
not assessable	4	6	3	

### Statistical analyses

No statistical analyses for this end point

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**Secondary: Type of surgery**

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End point title	Type of surgery
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End point description:

The type of surgery was evaluated in the safety population (ie all patients who have started their allocated treatment).

End point type	Secondary
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End point timeframe:

After neo-adjuvant therapy, at surgery.

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<b>End point values</b>	Lapatinib only	Lapatinib + Trastuzumab	Trastuzumab only	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	22	50	53	
Units: Number of patients				
Mastectomy	8	20	26	
Lumpectomy/quadrantectomy	14	28	26	
Biopsy only	0	1	0	
Surgery done, type unknown	0	1	0	
No surgery	0	0	1	

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**Statistical analyses**

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No statistical analyses for this end point

## Adverse events

### Adverse events information

Timeframe for reporting adverse events:

AEs were collected on a CRF to be submitted at baseline, during each protocol treatment cycle, at end of treatment and during follow-up if clinically needed in case of toxicity. Only clinical AEs after treatment start (excl. lab data) are reported.

Adverse event reporting additional description:

CRF for AEs contain pre-specified items + additional boxes for all "other" AEs. 5 patients had grade3 AEs reported under "other": 4 vascular AEs, 1 myositis. These cases are not reported since they were not pre-specified on the CRF.

Non-SAEs has not been collected specifically; ALL AEs of grade 3 or higher are reported in non-SAE section.

Assessment type	Non-systematic
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### Dictionary used

Dictionary name	MedDRA
Dictionary version	18.1

### Reporting groups

Reporting group title	Lapatinib Only (Safety)
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Reporting group description:

3 cycles of Docetaxel (100 mg/m<sup>2</sup> on day 1) + Lapatinib (1000 mg daily), followed by 3 cycles of FEC 100. Only patients that started the allocated treatment (safety population).

Reporting group title	Trastuzumab only (Safety)
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Reporting group description:

3 cycles Docetaxel (100 mg/m<sup>2</sup> on day 1) + Trastuzumab, followed by 3 cycles of FEC 100. Only patients that started the allocated treatment (safety population).

Reporting group title	Lapatinib + Trastuzumab (Safety)
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Reporting group description:

3 cycles Docetaxel (100 mg/m<sup>2</sup> on day 1) + Lapatinib (1000 mg daily) + Trastuzumab, followed by 3 cycles of FEC 100. Only patients that started the allocated treatment (safety population).

Serious adverse events	Lapatinib Only (Safety)	Trastuzumab only (Safety)	Lapatinib + Trastuzumab (Safety)
Total subjects affected by serious adverse events			
subjects affected / exposed	6 / 22 (27.27%)	12 / 53 (22.64%)	5 / 50 (10.00%)
number of deaths (all causes)	0	0	0
number of deaths resulting from adverse events	0	0	0
Vascular disorders			
Embolism	Additional description: From pharmacovigilance database.		
subjects affected / exposed	0 / 22 (0.00%)	1 / 53 (1.89%)	0 / 50 (0.00%)
occurrences causally related to treatment / all	0 / 0	1 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Thrombophlebitis	Additional description: From pharmacovigilance database.		

subjects affected / exposed	1 / 22 (4.55%)	0 / 53 (0.00%)	0 / 50 (0.00%)
occurrences causally related to treatment / all	1 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
<b>Blood and lymphatic system disorders</b>			
Febrile bone marrow aplasia	Additional description: From pharmacovigilance database.		
subjects affected / exposed	0 / 22 (0.00%)	1 / 53 (1.89%)	0 / 50 (0.00%)
occurrences causally related to treatment / all	0 / 0	1 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Febrile neutropenia	Additional description: From pharmacovigilance database.		
subjects affected / exposed	2 / 22 (9.09%)	4 / 53 (7.55%)	1 / 50 (2.00%)
occurrences causally related to treatment / all	2 / 2	5 / 5	2 / 2
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Neutropenia	Additional description: From pharmacovigilance database.		
subjects affected / exposed	1 / 22 (4.55%)	0 / 53 (0.00%)	1 / 50 (2.00%)
occurrences causally related to treatment / all	2 / 2	0 / 0	1 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
<b>General disorders and administration site conditions</b>			
Pyrexia	Additional description: From pharmacovigilance database.		
subjects affected / exposed	1 / 22 (4.55%)	3 / 53 (5.66%)	0 / 50 (0.00%)
occurrences causally related to treatment / all	1 / 1	2 / 3	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
<b>Immune system disorders</b>			
Hypersensitivity	Additional description: From pharmacovigilance database.		
subjects affected / exposed	1 / 22 (4.55%)	0 / 53 (0.00%)	0 / 50 (0.00%)
occurrences causally related to treatment / all	1 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
<b>Gastrointestinal disorders</b>			
Abdominal pain	Additional description: From pharmacovigilance database.		
subjects affected / exposed	0 / 22 (0.00%)	0 / 53 (0.00%)	1 / 50 (2.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	1 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Diarrhoea	Additional description: From pharmacovigilance database.		

subjects affected / exposed	0 / 22 (0.00%)	1 / 53 (1.89%)	2 / 50 (4.00%)
occurrences causally related to treatment / all	0 / 0	1 / 1	2 / 2
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Nausea	Additional description: From pharmacovigilance database.		
subjects affected / exposed	0 / 22 (0.00%)	0 / 53 (0.00%)	1 / 50 (2.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	1 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Vomiting	Additional description: From pharmacovigilance database.		
subjects affected / exposed	0 / 22 (0.00%)	1 / 53 (1.89%)	1 / 50 (2.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	1 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Respiratory, thoracic and mediastinal disorders			
Dyspnoea	Additional description: From pharmacovigilance database.		
subjects affected / exposed	1 / 22 (4.55%)	0 / 53 (0.00%)	0 / 50 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Skin and subcutaneous tissue disorders			
Erythema	Additional description: From pharmacovigilance database.		
subjects affected / exposed	0 / 22 (0.00%)	1 / 53 (1.89%)	0 / 50 (0.00%)
occurrences causally related to treatment / all	0 / 0	1 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Psychiatric disorders			
Anxiety	Additional description: From pharmacovigilance database.		
subjects affected / exposed	0 / 22 (0.00%)	1 / 53 (1.89%)	0 / 50 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Musculoskeletal and connective tissue disorders			
Myositis	Additional description: From pharmacovigilance database.		
subjects affected / exposed	0 / 22 (0.00%)	1 / 53 (1.89%)	0 / 50 (0.00%)
occurrences causally related to treatment / all	0 / 0	1 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Infections and infestations			
Escherichia infection	Additional description: From pharmacovigilance database.		

subjects affected / exposed	0 / 22 (0.00%)	0 / 53 (0.00%)	1 / 50 (2.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	1 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Paronychia	Additional description: From pharmacovigilance database.		
subjects affected / exposed	0 / 22 (0.00%)	1 / 53 (1.89%)	0 / 50 (0.00%)
occurrences causally related to treatment / all	0 / 0	1 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Staphylococcal infection	Additional description: From pharmacovigilance database.		
subjects affected / exposed	1 / 22 (4.55%)	0 / 53 (0.00%)	0 / 50 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Streptococcal infection	Additional description: From pharmacovigilance database.		
subjects affected / exposed	0 / 22 (0.00%)	0 / 53 (0.00%)	1 / 50 (2.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	1 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Tonsillitis	Additional description: From pharmacovigilance database.		
subjects affected / exposed	1 / 22 (4.55%)	0 / 53 (0.00%)	1 / 50 (2.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	1 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Upper respiratory tract infection	Additional description: From pharmacovigilance database.		
subjects affected / exposed	0 / 22 (0.00%)	1 / 53 (1.89%)	0 / 50 (0.00%)
occurrences causally related to treatment / all	0 / 0	1 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0

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

<b>Non-serious adverse events</b>	Lapatinib Only (Safety)	Trastuzumab only (Safety)	Lapatinib + Trastuzumab (Safety)
Total subjects affected by non-serious adverse events			
subjects affected / exposed	9 / 22 (40.91%)	18 / 53 (33.96%)	22 / 50 (44.00%)
Nervous system disorders			
Neurology other	Additional description: From clinical database, All AEs grade3 and above: NEUROLOGY for CTC v3.0		
alternative dictionary used: CTC 3			

subjects affected / exposed occurrences (all)	0 / 22 (0.00%) 0	1 / 53 (1.89%) 2	0 / 50 (0.00%) 0
General disorders and administration site conditions			
Fatigue	Additional description: From clinical database, All AEs grade3 and above: CONSTITUTIONAL SYMPTOMS and PAIN for CTC v3.0		
alternative dictionary used: CTC 3 subjects affected / exposed occurrences (all)	2 / 22 (9.09%) 3	2 / 53 (3.77%) 2	0 / 50 (0.00%) 0
Pain Abdomen NOS	Additional description: From clinical database, All AEs grade3 and above: CONSTITUTIONAL SYMPTOMS and PAIN for CTC v3.0		
alternative dictionary used: CTC 3 subjects affected / exposed occurrences (all)	0 / 22 (0.00%) 0	0 / 53 (0.00%) 0	1 / 50 (2.00%) 1
Pain muscle	Additional description: From clinical database, All AEs grade3 and above: CONSTITUTIONAL SYMPTOMS and PAIN for CTC v3.0		
alternative dictionary used: CTC 3 subjects affected / exposed occurrences (all)	0 / 22 (0.00%) 0	1 / 53 (1.89%) 1	0 / 50 (0.00%) 0
Pain other	Additional description: From clinical database, All AEs grade3 and above: CONSTITUTIONAL SYMPTOMS and PAIN for CTC v3.0		
alternative dictionary used: CTC 3 subjects affected / exposed occurrences (all)	0 / 22 (0.00%) 0	0 / 53 (0.00%) 0	1 / 50 (2.00%) 1
Immune system disorders			
Allergic reaction	Additional description: From clinical database, All AEs grade3 and above: ALLERGY/IMMUNOLOGY and LYMPHATICS for CTC v3.0		
alternative dictionary used: CTC 3 subjects affected / exposed occurrences (all)	0 / 22 (0.00%) 0	1 / 53 (1.89%) 1	1 / 50 (2.00%) 1
Gastrointestinal disorders			
Anorexia	Additional description: From clinical database, All AEs grade3 and above: GASTROINTESTINAL for CTC v3.0		
alternative dictionary used: CTC 3 subjects affected / exposed occurrences (all)	0 / 22 (0.00%) 0	1 / 53 (1.89%) 1	0 / 50 (0.00%) 0
Constipation	Additional description: From clinical database, All AEs grade3 and above: GASTROINTESTINAL for CTC v3.0		
alternative dictionary used: CTC 3 subjects affected / exposed occurrences (all)	0 / 22 (0.00%) 0	0 / 53 (0.00%) 0	1 / 50 (2.00%) 1
Dehydration	Additional description: From clinical database, All AEs grade3 and above: GASTROINTESTINAL for CTC v3.0		

alternative dictionary used: CTC 3			
subjects affected / exposed	1 / 22 (4.55%)	0 / 53 (0.00%)	0 / 50 (0.00%)
occurrences (all)	1	0	0
Diarrhea	Additional description: From clinical database, All AEs grade3 and above: GASTROINTESTINAL for CTC v3.0		
alternative dictionary used: CTC 3			
subjects affected / exposed	2 / 22 (9.09%)	1 / 53 (1.89%)	9 / 50 (18.00%)
occurrences (all)	2	1	9
Gastrointestinal other	Additional description: From clinical database, All AEs grade3 and above: GASTROINTESTINAL for CTC v3.0		
alternative dictionary used: CTC 3			
subjects affected / exposed	0 / 22 (0.00%)	0 / 53 (0.00%)	1 / 50 (2.00%)
occurrences (all)	0	0	1
Mucositis	Additional description: From clinical database, All AEs grade3 and above: GASTROINTESTINAL for CTC v3.0		
alternative dictionary used: CTC 3			
subjects affected / exposed	0 / 22 (0.00%)	0 / 53 (0.00%)	1 / 50 (2.00%)
occurrences (all)	0	0	1
Nausea	Additional description: From clinical database, All AEs grade3 and above: GASTROINTESTINAL for CTC v3.0		
alternative dictionary used: CTC 3			
subjects affected / exposed	2 / 22 (9.09%)	2 / 53 (3.77%)	0 / 50 (0.00%)
occurrences (all)	2	3	0
Vomiting	Additional description: From clinical database, All AEs grade3 and above: GASTROINTESTINAL for CTC v3.0		
alternative dictionary used: CTC 3			
subjects affected / exposed	0 / 22 (0.00%)	0 / 53 (0.00%)	1 / 50 (2.00%)
occurrences (all)	0	0	1
Respiratory, thoracic and mediastinal disorders			
Dyspnea	Additional description: From clinical database, All AEs grade3 and above: PULMONARY/UPPER RESPIRATORY for CTC v3.0		
alternative dictionary used: CTC 3			
subjects affected / exposed	1 / 22 (4.55%)	0 / 53 (0.00%)	0 / 50 (0.00%)
occurrences (all)	1	0	0
Skin and subcutaneous tissue disorders			
Dermatology other	Additional description: From clinical database, All AEs grade3 and above: DERMATOLOGY/SKIN for CTC v3.0		
alternative dictionary used: CTC 3			
subjects affected / exposed	0 / 22 (0.00%)	0 / 53 (0.00%)	2 / 50 (4.00%)
occurrences (all)	0	0	2
Dry skin	Additional description: From clinical database, All AEs grade3 and above: DERMATOLOGY/SKIN for CTC v3.0		

alternative dictionary used: CTC 3			
subjects affected / exposed	0 / 22 (0.00%)	0 / 53 (0.00%)	1 / 50 (2.00%)
occurrences (all)	0	0	1
Rash	Additional description: From clinical database, All AEs grade3 and above: DERMATOLOGY/SKIN for CTC v3.0		
alternative dictionary used: CTC 3			
subjects affected / exposed	0 / 22 (0.00%)	2 / 53 (3.77%)	0 / 50 (0.00%)
occurrences (all)	0	2	0
Infections and infestations			
Febrile neutropenia	Additional description: From clinical database, All AEs grade3 and above: INFECTION for CTC v3.0		
alternative dictionary used: CTC 3			
subjects affected / exposed	5 / 22 (22.73%)	8 / 53 (15.09%)	5 / 50 (10.00%)
occurrences (all)	6	10	6
Infection other	Additional description: From clinical database, All AEs grade3 and above: INFECTION for CTC v3.0		
alternative dictionary used: CTC 3			
subjects affected / exposed	2 / 22 (9.09%)	2 / 53 (3.77%)	4 / 50 (8.00%)
occurrences (all)	2	2	5

## More information

### Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? Yes

Date	Amendment
14 May 2007	<p>Protocol version 2.0 dd 14MAY2007.</p> <p>The main reason for this amendment is to extend the patient population to a subpopulation of large operable tumor with a worse prognosis than the global population of patients with large operable breast cancer (this worse prognosis is mainly due to the HER2 overexpression of these tumours). This subpopulation will consist of cT3cN0,1 any ER or cT2cN1 any ER or cT2cN0 ER negative.</p> <p>The dose levels have been amended by increasing alternatively the dose of Lapatinib and Docetaxel in order to properly document the relationship dose - safety profile and to understand whether we will obtain more anti-HER1/2 activity from a daily dose of 1250 mg than 1000 mg of Lapatinib.</p> <p>Please note that the content of Patient Information Sheet/Informed Consent and the summary of the protocol have not been modified by this substantial amendment, only the version has been updated according to the last version of the protocol.</p>
20 February 2008	<p>Protocol version 3.0 , 20 February 2008</p> <ul style="list-style-type: none"><li>• The addition of a third treatment arm in order to assess the pathological complete response rate after the combination of trastuzumab + Lapatinib which implies the increase of patient population to 180 patients (30 patients for the phase I and 150 patients for the phase II)</li><li>• The continuation of the adjuvant setting with the same anti-HER2 treatment used in the neo-adjuvant setting in combination with Docetaxel.</li><li>• The Update of toxicity profile of Lapatinib due to the edition of a new Investigator's Brochure</li></ul>
09 July 2008	<p>Protocol version 4.0, 9 July 2008</p> <ul style="list-style-type: none"><li>• The Update of the Investigator's Brochure, Protocol and the PIS/IC according to new data provided by GSK provided on the risk of hepatotoxicity of Lapatinib and it's management.</li><li>• New Phase II secondary endpoints defined: In the context of the comparison between different neoadjuvant treatment regimens the possibility of the breast conservation measured by the rate of breast conserving surgery was added as secondary endpoint.</li><li>• The recommendations regarding the Locoregional therapy after the chemotherapy had to be added in a tentative to make it uniform, improving the possibility to analyse the rate of breast conserving surgery as a secondary endpoint.</li><li>• The removal of bridge step.</li></ul>
09 March 2009	<p>Protocol Version 5, March 09, 2009</p> <ul style="list-style-type: none"><li>• The escalation of dose to dose level 6: the addition of a test of the original dose level 6 (Docetaxel 100 mg/m2 and Lapatinib 1250 mg/day) with primary prophylactic GCSF.</li><li>• The implementation of the Trastuzumab (Q3 Weeks) for one year as adjuvant treatment after surgery for all patients in the 3 arms.</li></ul>

26 May 2010	<p>Protocol version 6.0 , 26 may 2010</p> <p>The main reasons for this substantial amendment to the protocol are the following:</p> <ul style="list-style-type: none"> <li>• The protocol and the patient information sheet have been updated according to new data gathered during the phase I part of the trial. For information, the intermediate Phase I report is already available and is appended</li> <li>• The Eligibility criteria have been reviewed.</li> <li>• New data emerging from two other published large trials using the same investigational medicinal products have identified diarrhea as a major safety issue. As a consequence, it has been decided to de-escalate the recommended dose of lapatinib from 1250mg to 1000mg daily and to modify the sequence of administration starting first by the combination with anti-HER-2 treatment followed by FEC.</li> <li>• To implement also guidelines for management of cardiac toxicity, diarrhea and interstitial lung disease.</li> </ul>
14 October 2010	<p>Protocol version 7.0 dated 14OCT2010</p> <ul style="list-style-type: none"> <li>• The protocol chapter (5.7) for concomitant medications has been updated regarding the drug interactions with lapatinib and the use with caution of the following medications: telithromycin, posaconazole, quinidine, cisapride, pimozide, repaglinide, digoxin.</li> <li>• A new protocol chapter (5.7.2.3) on overdose management has been added</li> <li>• The patient information sheet has been updated regarding the risk of acute renal failure in case of severe dehydration and the risk of hypersensitivity reactions.</li> </ul>
19 December 2011	<p>Protocol version 8.0 dated 19DEC2011</p>
30 October 2012	<p>Protocol version 9.0 dated 30OCT2012</p> <p>Rationale for the amendment and its classification:</p> <p>Initial plan Phase I: depending on the toxicity profile, the phase I part of the study would enroll 12 to 30 patients</p> <p>Phase II: 150 patients randomized Arm 1:50 on docetaxel+lapatinib, Arm 2:50 on docetaxel+trastuzumab Arm 3:50 on docetaxel+lapatinib+trastuzumab</p> <p>Data conducted in different settings are all pointing in the same direction: that lapatinib monotherapy plus chemotherapy is either less effective, or not inferior to but more toxic, than chemotherapy plus Trastuzumab.</p> <p>As a consequence the following was decided in June 2012:</p> <ul style="list-style-type: none"> <li>- To close arm 1 for futility based on new information external to the trial.</li> <li>- To pursue the randomized Phase II study with 2 arms (arm 2 with docetaxel plus weekly trastuzumab and arm 3 with docetaxel plus weekly trastuzumab and lapatinib</li> </ul> <p>All centers have been informed accordingly in June 2012. Patients were allowed to be randomized only in the two remaining arms since then and until the enrollment of the last patient which took place on 29 January 2013. Therefore we declare the end of recruitment date to be the 29th of January 2013. Patients enrolled into the original first randomized arm that was discontinued, will be analyzed as a separate group in the final analysis. This arm will be too small for conclusions. So this can be called an exploratory analysis.</p> <p>Also, the preliminary analysis of the Phase I Pharmacokinetics samples have led to the conclusion that new PK analysis during the phase II will not give any new information. As a consequence, it has been decided to stop collecting PK samples in February 2012. The centers have been informed accordingly at that time.</p>

Notes:

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## **Interruptions (globally)**

Were there any global interruptions to the trial? No

## **Limitations and caveats**

None reported

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## **Online references**

<http://www.ncbi.nlm.nih.gov/pubmed/22999386>

<http://www.ncbi.nlm.nih.gov/pubmed/25467016>