



Clinical trial results:

A Phase II Study of Lapatinib for Brain Metastases in Subjects with ErbB2-Positive Breast Cancer Following Trastuzumab-based Systemic Therapy and Cranial Radiotherapy

Summary

EudraCT number	2005-003944-68
Trial protocol	SE AT DE GB BE ES GR IT
Global end of trial date	15 March 2018

Results information

Result version number	v1 (current)
This version publication date	30 March 2019
First version publication date	30 March 2019

Trial information

Trial identification

Sponsor protocol code	EGF105084
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Additional study identifiers

ISRCTN number	-
ClinicalTrials.gov id (NCT number)	NCT00263588
WHO universal trial number (UTN)	-
Other trial identifiers	Novartis: CLAP016A2202

Notes:

Sponsors

Sponsor organisation name	Novartis Pharma AG
Sponsor organisation address	CH-4002, Basel, Switzerland,
Public contact	Study Lead, Novartis Pharma AG, 41 +613241111, novartis.email@novartis.com
Scientific contact	Study Director, Novartis Pharma AG, 41 +613241111, novartis.email@novartis.com

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	11 March 2019
Is this the analysis of the primary completion data?	No
Global end of trial reached?	Yes
Global end of trial date	15 March 2018
Was the trial ended prematurely?	No

Notes:

General information about the trial

Main objective of the trial:

Determine central nervous system (CNS) objective response rate to lapatinib monotherapy in subjects with progressive brain metastases from human epidermal growth factor receptor 2 (HER2/ErbB2)-overexpressing breast cancer

Protection of trial subjects:

The study was in compliance with the ethical principles derived from the Declaration of Helsinki and the International Conference on Harmonization (ICH) Good Clinical Practice (GCP) guidelines. All the local regulatory requirements pertinent to safety of trial subjects were also followed during the conduct of the trial.

Background therapy: -

Evidence for comparator: -

Actual start date of recruitment	02 December 2005
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	Austria: 8
Country: Number of subjects enrolled	Belgium: 10
Country: Number of subjects enrolled	Canada: 7
Country: Number of subjects enrolled	France: 26
Country: Number of subjects enrolled	Germany: 18
Country: Number of subjects enrolled	Greece: 10
Country: Number of subjects enrolled	Australia: 18
Country: Number of subjects enrolled	India: 2
Country: Number of subjects enrolled	Italy: 9
Country: Number of subjects enrolled	Japan: 6
Country: Number of subjects enrolled	Poland: 4
Country: Number of subjects enrolled	Spain: 8
Country: Number of subjects enrolled	Sweden: 4
Country: Number of subjects enrolled	Switzerland: 5
Country: Number of subjects enrolled	Taiwan: 5
Country: Number of subjects enrolled	United Kingdom: 10
Country: Number of subjects enrolled	United States: 92
Worldwide total number of subjects	242
EEA total number of subjects	107

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)	220
From 65 to 84 years	21
85 years and over	1

Subject disposition

Recruitment

Recruitment details:

The Intent-to-Treat (ITT) Population: all subjects who received at least one dose of study medication

Modified ITT (MITT) Population: all subjects who received at least four doses (750 mg lapatinib twice daily for two days) of study medication and who had measurable brain metastases (≥ 1 cm in diameter) at baseline assessment

Pre-assignment

Screening details:

Main phase: ITT 95 in Cohort A, 147 in Cohort B. MITT, 94 in Cohort A, and 143 subjects in Cohort B
Optional open-label extension phase: 51 subjects. Long-term follow up (LTFU) Protocol amendment added on 15-Apr-2013

Period 1

Period 1 title	Overall Study (overall period)
Is this the baseline period?	Yes
Allocation method	Not applicable
Blinding used	Not blinded

Arms

Are arms mutually exclusive?	Yes
Arm title	Cohort A

Arm description:

750mg lapatinib administered orally twice daily. Cohort A subjects had Eastern Cooperative Oncology Group (ECOG) performance status 0-1, and one or two prior trastuzumab-containing regimens, in total, for treatment of breast cancer in adjuvant and/or metastatic settings

Arm type	Experimental
Investigational medicinal product name	lapatinib
Investigational medicinal product code	EGF105
Other name	
Pharmaceutical forms	Tablet
Routes of administration	Oral use

Dosage and administration details:

Cohort A subjects had Eastern Cooperative Oncology Group (ECOG) performance status 0-1

Arm title	Cohort B
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Arm description:

750mg lapatinib administered orally twice daily. Cohort B subjects had ECOG performance status 2 or more than 2 prior trastuzumab-containing regimens for treatment of breast cancer in the adjuvant and/or metastatic settings.

Arm type	Experimental
Investigational medicinal product name	lapatinib
Investigational medicinal product code	EGF105
Other name	
Pharmaceutical forms	Tablet
Routes of administration	Oral use

Dosage and administration details:

750mg lapatinib administered orally twice daily. Cohort B subjects had ECOG performance status 2 or more than 2 prior trastuzumab-containing regimens

Number of subjects in period 1	Cohort A	Cohort B
Started	95	147
Completed	14	15
Not completed	81	132
Adverse event, serious fatal	54	90
sponsor terminated study	-	1
Consent withdrawn by subject	3	4
coma; disease progression; unknown	10	11
Investigator decision	7	15
Lost to follow-up	7	10
Protocol deviation	-	1

Baseline characteristics

Reporting groups

Reporting group title	Overall Study
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Reporting group description: -

Reporting group values	Overall Study	Total	
Number of subjects	242	242	
Age, Customized			
Units: Subjects			
<18 242	0	0	
18-64 years 242	220	220	
65-84 years 242	21	21	
>85 years 242	1	1	
Age continuous			
Units: years			
arithmetic mean	49.7		
standard deviation	± 10.56	-	
Sex: Female, Male			
Units: Subjects			
Female	241	241	
Male	1	1	
Race/Ethnicity, Customized			
Units: Subjects			
African American/African	7	7	
American Indian/Alaskan Native	1	1	
Asian - Central/South	3	3	
Asian - Japanese	6	6	
Asian - South-East Asian	3	3	
Asia - East	5	5	
Native Hawaiian or other Pacific Islander	1	1	
White - Arabic/North African	2	2	
White - White/ Caucasian/European	212	212	
Mixed race	1	1	
Other	1	1	

Subject analysis sets

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

The Intent-to-Treat (ITT) Population: all subjects who received at least one dose of study medication

Subject analysis set title	MITT
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Subject analysis set type	Modified intention-to-treat
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Subject analysis set description:

Modified ITT (MITT) Population: all subjects who received at least four doses (750 mg lapatinib twice daily for two days) of study medication and who had measurable brain metastases (≥1 cm in diameter) at baseline assessment

Reporting group values	ITT	MITT	
Number of subjects	242	241	
Age, Customized Units: Subjects			
<18 242	0		
18-64 years 242	220		
65-84 years 242	21		
>85 years 242	1		
Age continuous Units: years			
arithmetic mean	49.7	0	
standard deviation	± 10.56	± 0	
Sex: Female, Male Units: Subjects			
Female	241		
Male	1		
Race/Ethnicity, Customized Units: Subjects			
African American/African	7		
American Indian/Alaskan Native	1		
Asian – Central/South	3		
Asian – Japanese	6		
Asian - South-East Asian	3		
Asia - East	5		
Native Hawaiian or other Pacific Islander	1		
White - Arabic/North African	2		
White - White/ Caucasian/European	212		
Mixed race	1		
Other	1		

End points

End points reporting groups

Reporting group title	Cohort A
Reporting group description: 750mg lapatinib administered orally twice daily. Cohort A subjects had Eastern Cooperative Oncology Group (ECOG) performance status 0-1, and one or two prior trastuzumab-containing regimens, in total, for treatment of breast cancer in adjuvant and/or metastatic settings	
Reporting group title	Cohort B
Reporting group description: 750mg lapatinib administered orally twice daily. Cohort B subjects had ECOG performance status 2 or more than 2 prior trastuzumab-containing regimens for treatment of breast cancer in the adjuvant and/or metastatic settings.	
Subject analysis set title	ITT
Subject analysis set type	Intention-to-treat
Subject analysis set description: The Intent-to-Treat (ITT) Population: all subjects who received at least one dose of study medication	
Subject analysis set title	MITT
Subject analysis set type	Modified intention-to-treat
Subject analysis set description: Modified ITT (MITT) Population: all subjects who received at least four doses (750 mg lapatinib twice daily for two days) of study medication and who had measurable brain metastases (≥ 1 cm in diameter) at baseline assessment	

Primary: Central nervous system (CNS) objective response rate

End point title	Central nervous system (CNS) objective response rate ^[1]
End point description: Summary of CNS Objective Response (Lapatinib Monotherapy - MITT Population) Response to lapatinib in patients with progressive brain metastases from ErbB2-overexpressing breast cancer. The primary indicator of drug efficacy was CNS objective response rate. A CNS objective response was defined as either a Complete response (CR) or Partial response (PR), as assessed by volumetric analysis of brain Magnetic resonance imaging (MRI), provided there was no progression of systemic disease outside of the CNS, increasing steroid requirements, or worsening of Neurological signs and symptoms (NSS) A CNS objective response rate was defined as a 50% volumetric reduction in sum of CNS target lesions, with no new or progressive CNS or non-CNS lesions, no increases in tumor-related steroid requirements and no worsening of neurological signs or symptoms	
End point type	Primary
End point timeframe: time from baseline to data cutoff (25 Sept 2007); approximately 2 years	

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: No statistical analyses were planned for primary endpoint

End point values	Cohort A	Cohort B		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	94	143		
Units: participants				
Complete response (CR)	0	0		
Partial response (PR)	6	9		
Stable disease (SD)	40	46		
Progressive disease (PD)	40	70		
Unknown	8	18		

Statistical analyses

No statistical analyses for this end point

Primary: Central nervous system (CNS) objective response rate - Response Rate (CR + PR), a percentage

End point title	Central nervous system (CNS) objective response rate - Response Rate (CR + PR), a percentage ^[2]
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End point description:

Summary of CNS Objective Response (the Complete Response + Partial Response)

End point type	Primary
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End point timeframe:

baseline to time of best response to treatment

Notes:

[2] - 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: No statistical analyses were planned for End Point: Central nervous system (CNS) objective response rate

End point values	Cohort A	Cohort B		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	94	143		
Units: percentage				
number (confidence interval 95%)	6 (2.4 to 13.4)	6 (2.9 to 11.6)		

Statistical analyses

No statistical analyses for this end point

Secondary: Percentage of Participants with Improvement in neurological signs and symptoms (NSS) measured using the Neurological Examination Worksheet

End point title	Percentage of Participants with Improvement in neurological signs and symptoms (NSS) measured using the Neurological Examination Worksheet
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End point description:

Physician-reported NSS worksheet is derived from 13 AEs and measured by NCI CTCAE v3.0 grouped into 7 categories: level of consciousness, neurological symptoms, cranial nerves, language, strength, sensation, and ataxia. Improvement of NSS required all of the following: Decrease by 1 or more grades from baseline of any tumor-related NSS, with confirmation at least 4 wks later, No development or worsening in any tumor-related NSS during interval, No radiographic evidence of CNS progression (assessed by volumetric MRI) or systemic (non-CNS) progression (assessed by RECIST) during interval, Stable or decreasing steroids during interval as defined by GSK equivalent doses of an alternative corticosteroid or a dose increase for non-tumor related reasons (e.g., asthma) didn't constitute a steroid increase. Improvement in any non-tumor associated NSS didn't constitute improvement in NSS. Neurological exam, using Neurological Examination Worksheet was assessed at baseline and each 4 weeks

End point type	Secondary
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End point timeframe:

time from baseline to data cutoff (25 Sept 2007); approximately 2 years

End point values	ITT			
Subject group type	Subject analysis set			
Number of subjects analysed	237			
Units: percentage of participants				
number (confidence interval 95%)				
% with NSS at Baseline	12.1 (7.9 to 17.5)			
% with NSS at Baseline with 20% volume reduction	23.5 (10.7 to 41.2)			
% w NSS at Baseline & any volume reduction	23.7 (13.6 to 36.6)			
% with NSS at Baseline & volume increase of w/drew	7.2 (3.3 to 13.2)			

Statistical analyses

No statistical analyses for this end point

Secondary: Percentage of Subjects with a CNS Objective Response or Improvement in Baseline neurological signs and symptoms (NSS)

End point title	Percentage of Subjects with a CNS Objective Response or Improvement in Baseline neurological signs and symptoms (NSS)
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End point description:

Summary of Proportion of Subjects with a CNS Objective Response or Improvement in Baseline NSS

End point type	Secondary
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End point timeframe:

baseline and weeks 8, 16, 24, 32, 40, 48

End point values	Cohort A	Cohort B		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	94	143		
Units: percentage of participants				
number (confidence interval 95%)				
week 8	23 (14.1 to 33.6)	14 (7.8 to 21.5)		
week 16	2 (0.1 to 12.3)	8 (2.2 to 19.2)		
week 24	8 (0.2 to 38.5)	11 (1.3 to 33.1)		
week 32	17 (0.4 to 64.1)	0.0 (0.0 to 0.0)		
week 40	0.0 (0.0 to 0.0)	0.0 (0.0 to 0.0)		

week 48	0.0 (0.0 to 0.0)	0.0 (0.0 to 0.0)		
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Statistical analyses

No statistical analyses for this end point

Secondary: Duration of Central Nervous System (CNS) objective response

End point title	Duration of Central Nervous System (CNS) objective response
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End point description:

The duration of CNS objective response, defined as the time from first CNS

Objective response until tumor progression at any site or death due to any cause.

A CNS objective response was defined as either a Complete Response (CR) or Partial Response (PR), as assessed by volumetric analysis of magnetic resonance imaging (MRI), provided there was no progression of systemic disease outside of the CNS, increasing steroid requirements, or worsening of tumor-related neurological signs or symptoms.

9.999999999 =upper limit Not evaluable (Due to the low number of CNS responders, a meaningful interpretation of duration of response is not possible). This is only a placeholder

End point type	Secondary
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End point timeframe:

time from baseline to data cutoff (25 Sept 2007); approximately 2 years

End point values	Cohort A	Cohort B		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	94	143		
Units: duration in months				
number (confidence interval 95%)	2.43 (0.99 to 9.9999)	1.58 (0.99 to 3.55)		

Statistical analyses

No statistical analyses for this end point

Secondary: Percentage of patients with CNS disease control (complete response, partial response or stable disease) at 6 months of lapatinib therapy

End point title	Percentage of patients with CNS disease control (complete response, partial response or stable disease) at 6 months of lapatinib therapy
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End point description:

The CNS disease control rate, defined as the percentage of subjects with CR, PR or stable disease at Week 24

End point type	Secondary
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End point timeframe:
from Start of lapatinib to 6 months

End point values	Cohort A	Cohort B		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	94	143		
Units: percentage of participants				
number (confidence interval 95%)	9 (3.7 to 16.1)	2 (0.4 to 6.0)		

Statistical analyses

No statistical analyses for this end point

Secondary: Time to progression (TTP) at any site

End point title	Time to progression (TTP) at any site
End point description:	Summary of Kaplan-Meier Estimates for Progression Free Survival at Any Site
End point type	Secondary
End point timeframe:	time from baseline to data cutoff (25 Sept 2007); approximately 2 years

End point values	Cohort A	Cohort B		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	94	143		
Units: months				
median (confidence interval 95%)	2.60 (1.87 to 3.25)	1.87 (1.84 to 2.63)		

Statistical analyses

No statistical analyses for this end point

Secondary: Overall survival

End point title	Overall survival
End point description:	Overall survival (OS) defined as the time from initiation of investigational product to death due to any cause.
End point type	Secondary
End point timeframe:	time from baseline to data cutoff (25 Sept 2007); approximately 2 years

End point values	Cohort A	Cohort B		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	94	143		
Units: months				
median (confidence interval 95%)	10.78 (7.95 to 12.68)	5.82 (4.78 to 7.89)		

Statistical analyses

No statistical analyses for this end point

Secondary: Summary of site of first progression

End point title	Summary of site of first progression
End point description:	Overall survival (OS) defined as the time from initiation of investigational product to death due to any cause.
End point type	Secondary
End point timeframe:	time from baseline to data cutoff (25 Sept 2007); approximately 2 years

End point values	Cohort A	Cohort B		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	94	143		
Units: participants				
CNS progression	69	72		
Non-CNS progression	1	10		
CNS and Non-CNS progression	12	36		

Statistical analyses

No statistical analyses for this end point

Secondary: Primary cause of death

End point title	Primary cause of death
End point description:	Primary causes of death as reported by investigator
End point type	Secondary
End point timeframe:	time from baseline to data cutoff (25 Sept 2007); approximately 2 years

End point values	Cohort A	Cohort B		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	95	147		
Units: participants				
Disease under study	74	124		
Other	4	4		

Statistical analyses

No statistical analyses for this end point

Adverse events

Adverse events information

Timeframe for reporting adverse events:

Adverse Events are collected from First Patient First Visit (FPFV) until Last Patient Last Visit (LPLV). All Adverse events are reported in this record from First Patient First Treatment until Last Patient Last Visit.

Adverse event reporting additional description:

Consistent with EudraCT disclosure specifications, Novartis has reported under the Serious adverse events field "number of deaths resulting from adverse events" all those deaths, resulting from serious adverse events that are deemed to be causally related to treatment by the investigator.

Assessment type	Systematic
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Dictionary used

Dictionary name	MedDRA
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Dictionary version	20.1
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Reporting groups

Reporting group title	EGF105084/Cohort B
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Reporting group description:

EGF105084/Cohort B

Reporting group title	EGF105084/Cohort A
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Reporting group description:

EGF105084/Cohort A

Serious adverse events	EGF105084/Cohort B	EGF105084/Cohort A	
Total subjects affected by serious adverse events			
subjects affected / exposed	52 / 147 (35.37%)	36 / 95 (37.89%)	
number of deaths (all causes)	48	20	
number of deaths resulting from adverse events	0	1	
Neoplasms benign, malignant and unspecified (incl cysts and polyps)			
Breast cancer			
subjects affected / exposed	1 / 147 (0.68%)	0 / 95 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 1	0 / 0	
Malignant pleural effusion			
subjects affected / exposed	0 / 147 (0.00%)	1 / 95 (1.05%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Vascular disorders			
Deep vein thrombosis			

subjects affected / exposed	2 / 147 (1.36%)	1 / 95 (1.05%)	
occurrences causally related to treatment / all	0 / 2	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Hypotension			
subjects affected / exposed	1 / 147 (0.68%)	0 / 95 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 1	0 / 0	
General disorders and administration site conditions			
Asthenia			
subjects affected / exposed	1 / 147 (0.68%)	0 / 95 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Complication associated with device			
subjects affected / exposed	1 / 147 (0.68%)	0 / 95 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Fatigue			
subjects affected / exposed	1 / 147 (0.68%)	1 / 95 (1.05%)	
occurrences causally related to treatment / all	0 / 1	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
General physical health deterioration			
subjects affected / exposed	1 / 147 (0.68%)	0 / 95 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 1	0 / 0	
Malaise			
subjects affected / exposed	1 / 147 (0.68%)	0 / 95 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Oedema			
subjects affected / exposed	0 / 147 (0.00%)	1 / 95 (1.05%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pain			

subjects affected / exposed	0 / 147 (0.00%)	1 / 95 (1.05%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	1 / 1	
Performance status decreased			
subjects affected / exposed	0 / 147 (0.00%)	1 / 95 (1.05%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pyrexia			
subjects affected / exposed	1 / 147 (0.68%)	1 / 95 (1.05%)	
occurrences causally related to treatment / all	0 / 1	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Respiratory, thoracic and mediastinal disorders			
Acute respiratory distress syndrome			
subjects affected / exposed	1 / 147 (0.68%)	0 / 95 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Dyspnoea			
subjects affected / exposed	2 / 147 (1.36%)	0 / 95 (0.00%)	
occurrences causally related to treatment / all	0 / 2	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Hypoxia			
subjects affected / exposed	1 / 147 (0.68%)	0 / 95 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 1	0 / 0	
Pleural effusion			
subjects affected / exposed	1 / 147 (0.68%)	0 / 95 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pneumonia aspiration			
subjects affected / exposed	1 / 147 (0.68%)	0 / 95 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 1	0 / 0	
Pneumothorax			

subjects affected / exposed	0 / 147 (0.00%)	1 / 95 (1.05%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pulmonary embolism			
subjects affected / exposed	4 / 147 (2.72%)	5 / 95 (5.26%)	
occurrences causally related to treatment / all	0 / 4	0 / 5	
deaths causally related to treatment / all	0 / 1	0 / 1	
Psychiatric disorders			
Completed suicide			
subjects affected / exposed	0 / 147 (0.00%)	1 / 95 (1.05%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 1	
Depression			
subjects affected / exposed	1 / 147 (0.68%)	0 / 95 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Mental status changes			
subjects affected / exposed	0 / 147 (0.00%)	2 / 95 (2.11%)	
occurrences causally related to treatment / all	0 / 0	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Investigations			
Blood phosphorus increased			
subjects affected / exposed	1 / 147 (0.68%)	0 / 95 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Ejection fraction decreased			
subjects affected / exposed	4 / 147 (2.72%)	2 / 95 (2.11%)	
occurrences causally related to treatment / all	4 / 4	2 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Gamma-glutamyltransferase increased			
subjects affected / exposed	1 / 147 (0.68%)	0 / 95 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	

Injury, poisoning and procedural complications			
Fall			
subjects affected / exposed	0 / 147 (0.00%)	1 / 95 (1.05%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Femur fracture			
subjects affected / exposed	1 / 147 (0.68%)	0 / 95 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Head injury			
subjects affected / exposed	0 / 147 (0.00%)	1 / 95 (1.05%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Hip fracture			
subjects affected / exposed	0 / 147 (0.00%)	1 / 95 (1.05%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Spinal compression fracture			
subjects affected / exposed	1 / 147 (0.68%)	0 / 95 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Cardiac disorders			
Atrial fibrillation			
subjects affected / exposed	1 / 147 (0.68%)	0 / 95 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Cardio-respiratory arrest			
subjects affected / exposed	0 / 147 (0.00%)	1 / 95 (1.05%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 1	
Left ventricular dysfunction			
subjects affected / exposed	1 / 147 (0.68%)	0 / 95 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	

Pericardial effusion			
subjects affected / exposed	1 / 147 (0.68%)	0 / 95 (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			
Altered state of consciousness			
subjects affected / exposed	1 / 147 (0.68%)	0 / 95 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Aphasia			
subjects affected / exposed	1 / 147 (0.68%)	1 / 95 (1.05%)	
occurrences causally related to treatment / all	1 / 1	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Cerebral haemorrhage			
subjects affected / exposed	1 / 147 (0.68%)	0 / 95 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 1	0 / 0	
Cerebrovascular accident			
subjects affected / exposed	0 / 147 (0.00%)	1 / 95 (1.05%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Cognitive disorder			
subjects affected / exposed	0 / 147 (0.00%)	1 / 95 (1.05%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Coma			
subjects affected / exposed	0 / 147 (0.00%)	1 / 95 (1.05%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 1	
Dizziness			
subjects affected / exposed	0 / 147 (0.00%)	1 / 95 (1.05%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Epilepsy			

subjects affected / exposed	0 / 147 (0.00%)	2 / 95 (2.11%)	
occurrences causally related to treatment / all	0 / 0	0 / 3	
deaths causally related to treatment / all	0 / 0	0 / 0	
Generalised tonic-clonic seizure			
subjects affected / exposed	1 / 147 (0.68%)	0 / 95 (0.00%)	
occurrences causally related to treatment / all	0 / 2	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Headache			
subjects affected / exposed	1 / 147 (0.68%)	1 / 95 (1.05%)	
occurrences causally related to treatment / all	1 / 1	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Ischaemic stroke			
subjects affected / exposed	1 / 147 (0.68%)	0 / 95 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Leukoencephalopathy			
subjects affected / exposed	1 / 147 (0.68%)	0 / 95 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Migraine			
subjects affected / exposed	0 / 147 (0.00%)	1 / 95 (1.05%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Paraplegia			
subjects affected / exposed	1 / 147 (0.68%)	0 / 95 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Partial seizures			
subjects affected / exposed	0 / 147 (0.00%)	1 / 95 (1.05%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Seizure			

subjects affected / exposed	5 / 147 (3.40%)	3 / 95 (3.16%)	
occurrences causally related to treatment / all	0 / 5	0 / 3	
deaths causally related to treatment / all	0 / 0	0 / 0	
Ear and labyrinth disorders			
Vertigo			
subjects affected / exposed	1 / 147 (0.68%)	0 / 95 (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 / 147 (0.00%)	1 / 95 (1.05%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Diarrhoea			
subjects affected / exposed	4 / 147 (2.72%)	6 / 95 (6.32%)	
occurrences causally related to treatment / all	3 / 4	4 / 6	
deaths causally related to treatment / all	0 / 0	0 / 0	
Duodenal ulcer			
subjects affected / exposed	1 / 147 (0.68%)	0 / 95 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Duodenal ulcer haemorrhage			
subjects affected / exposed	1 / 147 (0.68%)	0 / 95 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Gastrointestinal haemorrhage			
subjects affected / exposed	2 / 147 (1.36%)	0 / 95 (0.00%)	
occurrences causally related to treatment / all	0 / 2	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Haematemesis			
subjects affected / exposed	0 / 147 (0.00%)	1 / 95 (1.05%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Nausea			

subjects affected / exposed	3 / 147 (2.04%)	3 / 95 (3.16%)	
occurrences causally related to treatment / all	2 / 3	2 / 3	
deaths causally related to treatment / all	0 / 0	0 / 0	
Small intestinal perforation			
subjects affected / exposed	1 / 147 (0.68%)	0 / 95 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 1	0 / 0	
Vomiting			
subjects affected / exposed	5 / 147 (3.40%)	3 / 95 (3.16%)	
occurrences causally related to treatment / all	2 / 5	2 / 3	
deaths causally related to treatment / all	0 / 0	0 / 0	
Hepatobiliary disorders			
Bile duct obstruction			
subjects affected / exposed	1 / 147 (0.68%)	0 / 95 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 1	0 / 0	
Hyperbilirubinaemia			
subjects affected / exposed	1 / 147 (0.68%)	0 / 95 (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			
Exfoliative rash			
subjects affected / exposed	1 / 147 (0.68%)	1 / 95 (1.05%)	
occurrences causally related to treatment / all	0 / 1	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Musculoskeletal and connective tissue disorders			
Arthralgia			
subjects affected / exposed	1 / 147 (0.68%)	0 / 95 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Back pain			
subjects affected / exposed	1 / 147 (0.68%)	0 / 95 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	

Myopathy			
subjects affected / exposed	1 / 147 (0.68%)	0 / 95 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Infections and infestations			
Abscess limb			
subjects affected / exposed	1 / 147 (0.68%)	0 / 95 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Acinetobacter infection			
subjects affected / exposed	1 / 147 (0.68%)	0 / 95 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Bronchopulmonary aspergillosis			
subjects affected / exposed	1 / 147 (0.68%)	0 / 95 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Cellulitis			
subjects affected / exposed	1 / 147 (0.68%)	0 / 95 (0.00%)	
occurrences causally related to treatment / all	0 / 2	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Erysipelas			
subjects affected / exposed	3 / 147 (2.04%)	0 / 95 (0.00%)	
occurrences causally related to treatment / all	0 / 3	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Escherichia urinary tract infection			
subjects affected / exposed	1 / 147 (0.68%)	0 / 95 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Febrile infection			
subjects affected / exposed	1 / 147 (0.68%)	0 / 95 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Lower respiratory tract infection			

subjects affected / exposed	1 / 147 (0.68%)	0 / 95 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0
Lung infection		
subjects affected / exposed	0 / 147 (0.00%)	1 / 95 (1.05%)
occurrences causally related to treatment / all	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0
Meningitis bacterial		
subjects affected / exposed	1 / 147 (0.68%)	0 / 95 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0
Necrotising fasciitis		
subjects affected / exposed	0 / 147 (0.00%)	1 / 95 (1.05%)
occurrences causally related to treatment / all	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0
Oesophageal candidiasis		
subjects affected / exposed	0 / 147 (0.00%)	1 / 95 (1.05%)
occurrences causally related to treatment / all	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0
Pneumocystis jirovecii pneumonia		
subjects affected / exposed	1 / 147 (0.68%)	0 / 95 (0.00%)
occurrences causally related to treatment / all	1 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0
Pneumonia		
subjects affected / exposed	1 / 147 (0.68%)	2 / 95 (2.11%)
occurrences causally related to treatment / all	0 / 1	0 / 2
deaths causally related to treatment / all	0 / 0	0 / 1
Pulmonary tuberculosis		
subjects affected / exposed	1 / 147 (0.68%)	0 / 95 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 1	0 / 0
Sepsis		

subjects affected / exposed	1 / 147 (0.68%)	0 / 95 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 1	0 / 0	
Septic shock			
subjects affected / exposed	1 / 147 (0.68%)	0 / 95 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 1	0 / 0	
Staphylococcal sepsis			
subjects affected / exposed	1 / 147 (0.68%)	0 / 95 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 1	0 / 0	
Urinary tract infection			
subjects affected / exposed	4 / 147 (2.72%)	0 / 95 (0.00%)	
occurrences causally related to treatment / all	0 / 6	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Metabolism and nutrition disorders			
Dehydration			
subjects affected / exposed	2 / 147 (1.36%)	4 / 95 (4.21%)	
occurrences causally related to treatment / all	2 / 2	4 / 4	
deaths causally related to treatment / all	0 / 0	0 / 0	
Hypokalaemia			
subjects affected / exposed	0 / 147 (0.00%)	1 / 95 (1.05%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Hyponatraemia			
subjects affected / exposed	1 / 147 (0.68%)	1 / 95 (1.05%)	
occurrences causally related to treatment / all	0 / 1	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Hypovolaemia			
subjects affected / exposed	1 / 147 (0.68%)	0 / 95 (0.00%)	
occurrences causally related to treatment / all	1 / 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	EGF105084/Cohort B	EGF105084/Cohort A	
Total subjects affected by non-serious adverse events			
subjects affected / exposed	131 / 147 (89.12%)	90 / 95 (94.74%)	
Investigations			
Alanine aminotransferase increased			
subjects affected / exposed	13 / 147 (8.84%)	4 / 95 (4.21%)	
occurrences (all)	13	4	
Blood bilirubin increased			
subjects affected / exposed	1 / 147 (0.68%)	7 / 95 (7.37%)	
occurrences (all)	1	9	
Weight decreased			
subjects affected / exposed	11 / 147 (7.48%)	5 / 95 (5.26%)	
occurrences (all)	12	6	
Nervous system disorders			
Dizziness			
subjects affected / exposed	5 / 147 (3.40%)	8 / 95 (8.42%)	
occurrences (all)	5	11	
Dysgeusia			
subjects affected / exposed	5 / 147 (3.40%)	5 / 95 (5.26%)	
occurrences (all)	5	5	
Headache			
subjects affected / exposed	29 / 147 (19.73%)	23 / 95 (24.21%)	
occurrences (all)	40	31	
Blood and lymphatic system disorders			
Anaemia			
subjects affected / exposed	7 / 147 (4.76%)	5 / 95 (5.26%)	
occurrences (all)	8	6	
General disorders and administration site conditions			
Asthenia			
subjects affected / exposed	15 / 147 (10.20%)	9 / 95 (9.47%)	
occurrences (all)	18	9	
Fatigue			
subjects affected / exposed	29 / 147 (19.73%)	30 / 95 (31.58%)	
occurrences (all)	33	31	

Oedema peripheral subjects affected / exposed occurrences (all)	16 / 147 (10.88%) 18	6 / 95 (6.32%) 6	
Pyrexia subjects affected / exposed occurrences (all)	6 / 147 (4.08%) 7	5 / 95 (5.26%) 6	
Gastrointestinal disorders			
Abdominal pain subjects affected / exposed occurrences (all)	4 / 147 (2.72%) 5	5 / 95 (5.26%) 5	
Constipation subjects affected / exposed occurrences (all)	16 / 147 (10.88%) 19	9 / 95 (9.47%) 10	
Diarrhoea subjects affected / exposed occurrences (all)	92 / 147 (62.59%) 153	71 / 95 (74.74%) 113	
Dry mouth subjects affected / exposed occurrences (all)	6 / 147 (4.08%) 7	6 / 95 (6.32%) 7	
Dyspepsia subjects affected / exposed occurrences (all)	9 / 147 (6.12%) 10	3 / 95 (3.16%) 3	
Nausea subjects affected / exposed occurrences (all)	47 / 147 (31.97%) 58	29 / 95 (30.53%) 42	
Vomiting subjects affected / exposed occurrences (all)	39 / 147 (26.53%) 50	24 / 95 (25.26%) 37	
Respiratory, thoracic and mediastinal disorders			
Cough subjects affected / exposed occurrences (all)	8 / 147 (5.44%) 9	5 / 95 (5.26%) 6	
Dyspnoea subjects affected / exposed occurrences (all)	11 / 147 (7.48%) 12	6 / 95 (6.32%) 8	
Skin and subcutaneous tissue disorders			

Acne			
subjects affected / exposed	11 / 147 (7.48%)	6 / 95 (6.32%)	
occurrences (all)	12	8	
Dermatitis acneiform			
subjects affected / exposed	10 / 147 (6.80%)	6 / 95 (6.32%)	
occurrences (all)	10	8	
Dry skin			
subjects affected / exposed	15 / 147 (10.20%)	7 / 95 (7.37%)	
occurrences (all)	16	9	
Palmar-plantar erythrodysesthesia syndrome			
subjects affected / exposed	21 / 147 (14.29%)	16 / 95 (16.84%)	
occurrences (all)	27	16	
Pruritus			
subjects affected / exposed	13 / 147 (8.84%)	8 / 95 (8.42%)	
occurrences (all)	13	9	
Rash			
subjects affected / exposed	37 / 147 (25.17%)	40 / 95 (42.11%)	
occurrences (all)	44	48	
Musculoskeletal and connective tissue disorders			
Arthralgia			
subjects affected / exposed	7 / 147 (4.76%)	5 / 95 (5.26%)	
occurrences (all)	10	6	
Back pain			
subjects affected / exposed	6 / 147 (4.08%)	6 / 95 (6.32%)	
occurrences (all)	6	6	
Bone pain			
subjects affected / exposed	8 / 147 (5.44%)	2 / 95 (2.11%)	
occurrences (all)	8	2	
Pain in extremity			
subjects affected / exposed	7 / 147 (4.76%)	8 / 95 (8.42%)	
occurrences (all)	8	9	
Infections and infestations			
Nasopharyngitis			
subjects affected / exposed	2 / 147 (1.36%)	5 / 95 (5.26%)	
occurrences (all)	2	6	
Urinary tract infection			

subjects affected / exposed occurrences (all)	8 / 147 (5.44%) 9	7 / 95 (7.37%) 8	
Metabolism and nutrition disorders			
Decreased appetite			
subjects affected / exposed occurrences (all)	28 / 147 (19.05%) 29	16 / 95 (16.84%) 17	
Hypokalaemia			
subjects affected / exposed occurrences (all)	11 / 147 (7.48%) 14	5 / 95 (5.26%) 8	

More information

Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? Yes

Date	Amendment
13 October 2005	Amendment 01 (13-Oct-2005) - Country specific amendment for Germany and Poland to remove the requirement for specialized radiological assessments using positron emission tomography (PET).
21 December 2005	Amendment 02 (21-Dec-2005) – Country specific amendment for Japan to (1) add a pharmacokinetic component to the protocol (2) add a Go/No Go decision based on dose limiting toxicities in first 6 Japanese subjects (3) remove option to enroll into an open-label extension phase (lapatinib combination therapy) and (4) elect as an option, on a site basis, the specialized radiological assessments using positron emission tomography (PET)
19 June 2006	Amendment 03 (19-Jun-2006) – Optional protocol extension added for subjects on monotherapy lapatinib who develop disease progression in the CNS, to receive the combination of lapatinib and capecitabine, protocol clarifications added throughout.
22 January 2007	Amendment 04 (22-Jan-2007) – Country specific amendment for Japan, to allow the trial to remain open in Japan beyond the full-enrollment closure globally, in order to allow the participation of at least 6 Japanese subjects and the collection of PK and safety data.
29 May 2008	Amendment 05 (29-May-2008) – Additional safety information and treatment guidelines related to hepatotoxicity added.
29 August 2012	<p>Amendment 06 (29-Aug-2012)</p> <ul style="list-style-type: none"> - Discontinuation of many specific efficacy and safety assessments. The study was stopped for subjects in post treatment follow up. Continued access to study treatment lapatinib was permitted for subject ongoing at the time of implementation of this amendment. - Update to Prohibited Medications was added - Extension phases of the study were removed <p>This amendment was not circulated outside Sponsor (GSK) and later replaced by Protocol Amendment 07 which re-instated the extension phase of the study.</p>
15 April 2013	<p>Protocol Amendment 07 was implemented to discontinue collection of many study-specific assessments while allowing the one subject receiving treatment to have continued access to the treatment until the occurrence of unacceptable toxicity or disease progression (as determined by the investigator).</p> <p>Amendment 07 (15-Apr-2013), introduced the following changes:</p> <ul style="list-style-type: none"> - Re-instated the Extension phase of the study - Continued access to treatment under one of the extension phases permitted. - Reduced the number of study assessments in the extension phases. - Updated information on LAP016A2305/EGF111438 results added to align with Supplement 01 of Lapatinib Investigator’s Brochure version 13 - Updated safety guidelines <ul style="list-style-type: none"> - Addition of the efficacy results of the Study EGF111438 interim analysis (CSR dated 16-Oct-2012) <p>Amendment 08 (03-Oct-2016), introduced the following changes:</p> <ul style="list-style-type: none"> - Deleted or replaced references to GSK or its staff with that of Novartis and its authorized agents. - Administrative changes to align with Novartis processes and procedures.

Notes:

Interruptions (globally)

Were there any global interruptions to the trial? No

Limitations and caveats

Limitations of the trial such as small numbers of subjects analysed or technical problems leading to unreliable data.

3 objectives not in protocol were initially registered in error. There was no analysis of these outcomes and there should not have been 2 participants were counted twice when they moved from one site to another. 1 in Japan and 1 in US. Actual global

Notes: