Clinical trial results:
An Open-Label Multicenter Phase 2 Window of Opportunity Study Evaluating Ganetespib in Women with Breast Cancer

Summary

EudraCT number	2012-000558-71
Trial protocol	GB BE ES
Global end of trial date	31 March 2015

Results information

Result version number	v1 (current)
This version publication date	08 April 2016
First version publication date	08 April 2016

Trial information

Trial identification

Sponsor protocol code	9090-11

Additional study identifiers

ISRCTN number	-
ClinicalTrials.gov id (NCT number)	NCT01677455
WHO universal trial number (UTN)	-

Notes:

Sponsors

Sponsor organisation name	Synta Pharmaceuticals Corp.
Sponsor organisation address	45 Hartwell Avenue, Lexington, MA, United States, 02421
Public contact	VP Clinical Research, Synta Pharmaceuticals Corp., 001 781-541-7261,
Scientific contact	VP Clinical Research, Synta Pharmaceuticals Corp., 001 781-541-7261,

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	16 November 2015
Is this the analysis of the primary completion data?	No

Global end of trial reached?	Yes
Global end of trial date	31 March 2015
Was the trial ended prematurely?	Yes

Notes:

General information about the trial

Main objective of the trial:

Determine the objective response rate of ganetespib monotherapy in patients with these subtypes of breast cancer: human epidermal growth factor receptor 2 (HER2+), triple negative breast cancer (TNBC), and estrogen receptor/progesterone receptor (ER/PR)-positive disease.

Protection of trial subjects:

Prior to the start of any protocol-specific evaluations or screening procedures, the Investigator (or designated staff) explained the nature of the study and its risks and benefits to the patient (or the patient's legal representative). Each patient received an informed consent document with patient information. Patients were given ample time to read the information and the opportunity to ask questions. Informed consent was obtained from each patient prior to performing any protocol-specific evaluations. One copy of the signed informed consent document was given to the patient, and another was retained by the Investigator.

The study design mitigated potential risk to patients treated with an investigational agent in the first line setting by implementing multiple decision points based on clinical and objective evaluations in totality. The Investigator assessment of these evaluations, rather than independent review, determined treatment continuation.

Background therapy: -

Evidence for comparator: -

Actual start date of recruitment	01 October 2012
Long term follow-up planned	No
Independent data monitoring committee (IDMC) involvement?	No

Notes:

Population of trial subjects

Subjects enrolled per country

Country: Number of subjects enrolled	Spain: 5
Country: Number of subjects enrolled	United Kingdom: 8
Country: Number of subjects enrolled	Belgium: 9
Country: Number of subjects enrolled	United States: 16
Country: Number of subjects enrolled	Argentina: 1
Country: Number of subjects enrolled	Brazil: 3
Country: Number of subjects enrolled	Korea, Republic of: 5
Country: Number of subjects enrolled	Peru: 4
Worldwide total number of subjects	51
EEA total number of subjects	22

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)	42
From 65 to 84 years	9
85 years and over	0

Subject disposition

Recruitment

Recruitment details:

A Simon's optimal 2-stage design was planned for each single-agent ganetespib cohort. Up to 15 evaluable patients were enrolled in the first stage, and if at least 1 patient achieved an objective response (OR, defined as CR + PR), enrollment in the cohort was to proceed to Stage 2 for a total of approximately 35 patients per cohort.

Pre-assignment

Screening details:

A total of 68 patients were screened for possible inclusion in the study. Of these, 51 patients were enrolled at 22 study centers.

Period 1

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

Arms

Are arms mutually exclusive?	No
Arm title	Monotherapy: HER2-positive breast cancer

Arm description:

Cohort A includes the subpopulation of breast cancer patients with human epidermal growth factor receptor 2 (HER2). Patients were treated with intravenous ganetespib 150 mg/m^2 twice weekly for 3 consecutive weeks followed by a 1-week rest. Three 4-week cycles were planned.

Arm type	Experimental
Investigational medicinal product name	ganetespib
Investigational medicinal product code	
Other name	STA-9090
Pharmaceutical forms	Concentrate for solution for infusion
Routes of administration	Intravenous use

Dosage and administration details:

Ganetespib administered at a dose of 150 mg/m2 by 1-hour infusion.

Arm title	Monotherapy: TNBC

Arm description:

Cohort B includes the subpopulation of breast cancer patients with triple negative breast cancer (TNBC). Patients were treated with intravenous ganetespib 150 mg/m^2 twice weekly for 3 consecutive weeks followed by a 1-week rest. Three 4-week cycles were planned.

Arm type	Experimental
Investigational medicinal product name	ganetespib
Investigational medicinal product code	
Other name	STA-9090
Pharmaceutical forms	Concentrate for solution for infusion
Routes of administration	Intravenous use

Dosage and administration details:

Ganetespib administered at a dose of 150 mg/m2 by 1-hour infusion.

Arm title	Monotherapy: ER/PR+

Arm description:

Cohort D includes the subpopulation of breast cancer patients with estrogen receptor/progesterone receptor positive (ER/PR+). Patients were treated with intravenous ganetespib 150 mg/m^2 twice weekly for 3 consecutive weeks followed by a 1-week rest. Three 4-week cycles were planned.

Arm type	Experimental

Investigational medicinal product name	ganetespib
Investigational medicinal product code	
Other name	STA-9090
Pharmaceutical forms	Concentrate for solution for infusion
Routes of administration	Intravenous use

Dosage and administration details:

Ganetespib administered at a dose of 150 mg/m2 by 1-hour infusion.

Arm title	Combination Therapy

Arm description:

Patients with disease progression while on Monotherapy (i.e. treated only with ganetespib) had the option of entering combination therapy (Cohort C) in which patients were treated with intravenous ganetespib 150 mg/m^2 in a weekly 1-hour infusion for 3 out of 4 weeks, ie, Days 1, 8, and 15 every 28 days. After an
hour rest, patients were then given paclitaxel administered at a dose of 80 mg/m^2 by a 1-hour infusion on the same treatment days. Combination therapy continued until disease progression, unacceptable toxicity, or withdrawal from the study.

Arm type	Experimental
Investigational medicinal product name	ganetespib
Investigational medicinal product code	
Other name	STA-9090
Pharmaceutical forms	Concentrate for solution for infusion
Routes of administration	Intravenous use

Dosage and administration details:

Ganetespib administered at a dose of 150 mg/m2 by 1-hour infusion.

Investigational medicinal product name	paclitaxel
Investigational medicinal product code	
Other name	taxol
Pharmaceutical forms	Solution for infusion
Routes of administration	Intravenous use

Dosage and administration details:

Paclitaxel administered at a dose of 80 mg/m^2 by a 1-hour infusion weekly for 3 out of 4 weeks, eg, Days 1, 8, and 15 every 28 days (the most commonly used paclitaxel
schedule).

Number of subjects in period 1	Monotherapy: HER2-positive breast cancer	Monotherapy: TNBC	Monotherapy: ER/PR+
Started	12	38	1
Completed	0	1	0
Not completed	12	37	1
Clinical progression	1	3	-
Rollover to Combination Therapy	1	5	-
Adverse event, serious fatal	-	1	-
Consent withdrawn by subject	3	2	-
Adverse event, non-fatal	1	1	-
Progressive disease	5	24	1
Sponsor decision	1	-	-
Protocol deviation	-	1	-

Number of subjects in period 1	Combination Therapy
Started	6
Completed	0
Not completed	6
Clinical progression	1
Rollover to Combination Therapy	-
Adverse event, serious fatal	-
Consent withdrawn by subject	-
Adverse event, non-fatal	-
Progressive disease	5
Sponsor decision	-
Protocol deviation	-

Baseline characteristics

Reporting groups	
Reporting group title	Overall Trial
Reporting group description:	
Group combines Cohorts A+B+D and includes all patients who were treated with intravenous ganetespib 150 mg/m^2 twice weekly for 3 consecutive weeks followed by a 1-week rest.	

Reporting group values	Overall Trial	Total	
Number of subjects	51	51	
Age categorical Units: Subjects			
Adults (18-64 years)	42	42	
From 65-84 years	9	9	
Age continuous Units: years			
arithmetic mean	53.5		
standard deviation	± 10.56	-	
Gender categorical Units: Subjects			
Female	51	51	
Male	0	0	
Eastern Cooperative Oncology Group Performance Status Units: Subjects			
0=fully active	30	30	
1=restrictive but ambulatory	21	21	
2=ambulatory, unable to work	0	0	
3=limited self-care	0	0	
4=completely disabled	0	0	
Breast Cancer Stage			
Stage I: tumor <=2.0 cm, lymph nodes clear, no metastasis Stage IIa: tumor <=2.0 cm, regional lymph node Stage IIb: tumor >2.0<5.0 cm, regional lymph nodes Stage IIIa: tumor >5.0 cm, regional lymph nodes Stage IIIb: tumor extending to chest wall or skin Stage IIIc: tumor with extensive lymph node involvement Stage IV: distant metastasis Not recorded			
Units: Subjects			
Stage I	0	0	
Stage IIa	0	0	
Stage IIb	0	0	
Stage IIIa	0	0	
Stage IIIb	1	1	
Stage IIIc	1	1	
Stage IV	16	16	
Not recorded	33	33	

Weight Units: kg arithmetic mean standard deviation	 70.27 ± 15.1	 -	
Body Surface Area (BSA) Units: m^2 arithmetic mean standard deviation	 1.743 ± 0.1749	 -	

End points

End points reporting groups

Reporting group title	Monotherapy: HER2-positive breast cancer

Reporting group description:

Cohort A includes the subpopulation of breast cancer patients with human epidermal growth factor receptor 2 (HER2). Patients were treated with intravenous ganetespib 150 mg/m^2 twice weekly for 3 consecutive weeks followed by a 1-week rest. Three 4-week cycles were planned.

Reporting group title	Monotherapy: TNBC

Reporting group description:

Cohort B includes the subpopulation of breast cancer patients with triple negative breast cancer (TNBC). Patients were treated with intravenous ganetespib 150 mg/m^2 twice weekly for 3 consecutive weeks followed by a 1-week rest. Three 4-week cycles were planned.

Reporting group title	Monotherapy: ER/PR+

Reporting group description:

Cohort D includes the subpopulation of breast cancer patients with estrogen receptor/progesterone receptor positive (ER/PR+). Patients were treated with intravenous ganetespib 150 mg/m^2 twice weekly for 3 consecutive weeks followed by a 1-week rest. Three 4-week cycles were planned.

Reporting group title	Combination Therapy

Reporting group description:

Patients with disease progression while on Monotherapy (i.e. treated only with ganetespib) had the option of entering combination therapy (Cohort C) in which patients were treated with intravenous ganetespib 150 mg/m^2 in a weekly 1-hour infusion for 3 out of 4 weeks, ie, Days 1, 8, and 15 every 28 days. After an
hour rest, patients were then given paclitaxel administered at a dose of 80 mg/m^2 by a 1-hour infusion on the same treatment days. Combination therapy continued until disease progression, unacceptable toxicity, or withdrawal from the study.

Subject analysis set title	Ganetespib Monotherapy
Subject analysis set type	Safety analysis

Subject analysis set description:

Group combines Cohorts A+B+D and includes all patients who were treated with intravenous ganetespib 150 mg/m^2 twice weekly for 3 consecutive weeks followed by a 1-week rest.

Subject analysis set title	Ganetespib Combination Therapy
Subject analysis set type	Safety analysis

Subject analysis set description:

Patients with disease progression while in the Monotherapy Period had the option of entering the combination therapy period (Cohort C) in which patients were treated with intravenous ganetespib 150 mg/m^2 in a weekly 1-hour infusion for 3 out of 4 weeks, ie, Days 1, 8, and 15 every 28 days. After an hour rest, patients were then given paclitaxel administered at a dose of 80 mg/m^2 by a 1-hour infusion on the same treatment days. Combination therapy continued until disease progression, unacceptable toxicity, or withdrawal from the study.

Primary: Objective Response Rate (ORR)

End point title	Objective Response Rate (ORR)[1]

End point description:

The ORR (defined as the percentage of patients with complete response + the percentage with partial response, according to modified RECIST 1.1 according to the investigator's assessment) was the primary efficacy endpoint.

- Complete Response (CR): Disappearance (or normalization) of all target lesions. Any pathological lymph nodes (whether target or non-target) must have had reduction in short axis to <10 mm.
- Partial Response (PR): ≥30% decrease in the sum of diameters of target lesions compared to the baseline sum.

Disease assessments in patients with locally advanced disease could be submitted with ultrasound, MRI, mammogram, or physical examination. Digital photographs to detect skin lesions, if present, were taken at baseline. The same method of assessment used at baseline were used for all subsequent assessments.

End point type	Primary

End point timeframe:

Baseline (within one week of first dose of treatment), Weeks 3, 6, 12 after the first dose and repeated every 6 weeks thereafter until drug is discontinued.

Notes:

[1] - No statistical analyses have been specified for this primary end point. It is expected there is at least one statistical analysis for each primary end point.
Justification: This was a two-stage design where success is determined by achieving a minimum number of required responders.

End point values	Monotherapy: HER2-positive breast cancer	Monotherapy: TNBC	Monotherapy: ER/PR+	Combination Therapy
Subject group type	Reporting group	Reporting group	Reporting group	Reporting group
Number of subjects analysed	12[2]	38[3]	1[4]	6[5]
Units: percentage of participants				
number (confidence interval 95%)	41.7 (15.2 to 72.3)	5.3 (0.6 to 17.7)	0 (0 to 0)	16.7 (0.4 to 65.1)

Notes:

[2] - All patients

[3] - All patients

[4] - All patients

[5] - Rollover patients

Statistical analyses

No statistical analyses for this end point

Secondary: Best Overall Response

End point title	Best Overall Response

End point description:

Best overall response was the % of patients who obtained the most positive response per RECIST 1.1 according to the investigator's assessment.

- Complete Response: Disappearance of all target lesions. Any pathological lymph nodes must have had reduction in short axis to <10 mm.
- Partial Response (PR): ≥30% decrease in the sum of diameters of target lesions compared to the baseline sum.
- Stable Disease: Neither sufficient shrinkage to qualify for PR nor sufficient increase to qualify for PD
- Progressive Disease (PD): ≥20% increase in the sum of diameters of target lesions. The sum must also have an absolute increase >=5 mm.
- Non-evaluable: inadequate or missing images, including the inability to visualize >25% of target disease.

Disease assessments in patients with locally advanced disease used ultrasound, MRI, mammogram, or physical exams. Digital photographs were used
to detect skin lesions.

End point type	Secondary

End point timeframe:

Baseline (within one week of first dose of treatment) Weeks 3, 6, 12 after the first dose and repeated every 6 weeks thereafter until drug is discontinued.

End point values	Monotherapy: HER2-positive breast cancer	Monotherapy: TNBC	Monotherapy: ER/PR+	Combination Therapy
Subject group type	Reporting group	Reporting group	Reporting group	Reporting group
Number of subjects analysed	12[6]	38[7]	1[8]	6[9]
Units: percentage of patients				
number (confidence interval 95%)				
Complete Response	16.7 (2.1 to 48.4)	0 (0 to 0)	0 (0 to 0)	0 (0 to 0)
Partial Response	25 (5.5 to 57.2)	5.3 (0.6 to 17.7)	0 (0 to 0)	16.7 (0.4 to 64.11)
Stable Disease	41.7 (15.2 to 72.3)	26.3 (13.4 to 43.1)	0 (0 to 0)	16.7 (0.4 to 64.7)
Progressive Disease	8.3 (0.2 to 38.5)	42.1 (26.3 to 59.2)	100 (2.5 to 100)	50 (11.8 to 88.2)
Non-evaluable	8.3 (8.3 to 8.3)	26.3 (26.3 to 26.3)	0 (0 to 0)	16.7 (16.7 to 16.7)

Notes:

[6] - All patients

[7] - All patients

[8] - All patients

[9] - Rollover patients

Statistical analyses

No statistical analyses for this end point

Secondary: Metabolic Response Rate

End point title	Metabolic Response Rate

End point description:

Investigators assessed F-18-fluorodeoxyglucose (FDG)-PET for metabolic response and identification of metabolic progressive disease. The European Organization for Research and Treatment of Cancer (EORTC) PET study group general quantitative parameters was used [Young, Eur J Cancer, 1999]. The exception was that Metabolic Progressive Disease (mPD) was defined as the identification of new lesions and/or >25% increase in maximum standard uptake value >=1 target lesion, to more accurately assess responses.
FDG-PET Patient-based Response Classification:

- Class 1=All lesions showed a metabolic progressive response (mPR) or metabolic complete response (mCR)
- Class 2=Mixed response: dominant part of tumor load showed metabolic response - without any progressive lesions
- Class 3=Mixed response: dominant part of tumor load showed non-response - without any progressive lesions
- Class 4=No lesions showed a response, or presence of =>1 progressive new lesion

End point type	Secondary

End point timeframe:

Baseline (within one week prior to first treatment), Week 3

End point values	Monotherapy: HER2-positive breast cancer	Monotherapy: TNBC	Monotherapy: ER/PR+	Combination Therapy
Subject group type	Reporting group	Reporting group	Reporting group	Reporting group
Number of subjects analysed	12[10]	38[11]	1[12]	0[13]
Units: percentage of patients				
number (not applicable)				

Class 1	75	21.1	0	
Class 2	16.7	28.9	0	
Class 3	8.3	2.6	100	
Class 4	0	31.6	0	
Not applicable	0	15.8	0	

Notes:

[10] - All patients

[11] - All patients

[12] - All patients

[13] - Reporting timeframe is during monotherapy only

Statistical analyses

No statistical analyses for this end point

Secondary: Clinical Benefit Rate (CBR)

End point title	Clinical Benefit Rate (CBR)

End point description:

Clinical benefit rate is an established clinical endpoint in breast cancer trials in the metastatic setting. It provides a more comprehensive assessment of response to treatment. CBR is defined as the percentage of patients with best response, according to modified RECIST 1.1, of CR, PR, or SD.

- Complete Response (CR): Disappearance (or normalization) of all target lesions. Any pathological lymph nodes (whether target or non-target) must have had reduction in SA to <10 mm.
- Partial Response (PR): ≥30% decrease in the sum of diameters of target lesions compared to the baseline sum.
- Stable Disease (SD): Neither sufficient shrinkage to qualify for PR nor sufficient increase to qualify for PD, taking as reference the smallest sum of diameters while on study. For patients with a best response of SD, duration of SD must be for at least 18 weeks.

End point type	Secondary

End point timeframe:

Baseline (within one week of first treatment), Weeks 5, 9, 13 and repeated every 6 weeks thereafter until drug is discontinued.

End point values	Monotherapy: HER2-positive breast cancer	Monotherapy: TNBC	Monotherapy: ER/PR+	Combination Therapy
Subject group type	Reporting group	Reporting group	Reporting group	Reporting group
Number of subjects analysed	0[14]	0[15]	0[16]	0[17]
Units: percentage of patients				
number (not applicable)				

Notes:

[14] - No data was summarized due to early study termination

[15] - No data was summarized due to early study termination

[16] - No data was summarized due to early study termination

[17] - No data was summarized due to early study termination

Statistical analyses

No statistical analyses for this end point

Secondary: Progression-Free Survival (PFS)

End point title	Progression-Free Survival (PFS)

End point description:

PFS is the interval from the date of Day 1 until objective tumor progression or death from any cause, whichever occurs first. Patients who discontinue from the study for other reasons than disease progression were censored at the time of the last radiological scans. Patients who started an alternative anticancer therapy were treated as censored at that time.

End point type	Secondary

End point timeframe:

Day 1 up to Day 625 (maximum treatment days)

End point values	Monotherapy: HER2-positive breast cancer	Monotherapy: TNBC	Monotherapy: ER/PR+	Combination Therapy
Subject group type	Reporting group	Reporting group	Reporting group	Reporting group
Number of subjects analysed	0[18]	0[19]	0[20]	0[21]
Units: months				
median (standard error)	()	()	()	()

Notes:

[18] - No data was summarized due to early study termination

[19] - No data was summarized due to early study termination

[20] - No data was summarized due to early study termination

[21] - No data was summarized due to early study termination

Statistical analyses

No statistical analyses for this end point

Secondary: Patients with Treatment-Emergent Adverse Events

End point title	Patients with Treatment-Emergent Adverse Events

End point description:

An adverse event was defined in the protocol 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=mild, 2=moderate, 3=severe, 4=life-threatening and 5=death. 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 up to Day 625 (maximum treatment days)

End point values	Ganetespib Monotherapy	Ganetespib Combination Therapy		
Subject group type	Subject analysis set	Subject analysis set		
Number of subjects analysed	51	6		
Units: patients				
=>1 adverse event (AE)	51	6		
=>1 AE severity grade 3 or 4	34	4		
=>1 serious AE (SAE)	13	3		
=>1 AE leading to dose reduction	14	0		

=>1 AE leading to dose delay	24	4		
=>1 AE leading to study drug discontinuation	3	1		
=>1 SAE leading to study drug discontinuation	1	1		
=>1 SAE leading to hospitalization	12	3		
=>1 AE with outcome of death	4	1		

Statistical analyses

No statistical analyses for this end point

Adverse events

Adverse events information

Timeframe for reporting adverse events:

Day 1 up to Day 625 (maximum treatment days)

Assessment type	Systematic

Dictionary used

Dictionary name	MedDRA
Dictionary version	16.1

Reporting groups

Reporting group title	Ganetespib Monotherapy

Reporting group description:

Group combines Cohorts A+B+D and includes all patients who were treated with intravenous ganetespib 150 mg/m^2 twice weekly for 3 consecutive weeks followed by a 1-week rest.

Reporting group title	Ganetespib Combination Therapy

Reporting group description:

Patients with disease progression while in the Monotherapy Period had the option of entering the combination therapy period (Cohort C) in which patients were treated with intravenous ganetespib 150 mg/m^2 in a weekly 1-hour infusion for 3 out of 4 weeks, ie, Days 1, 8, and 15 every 28 days. After an hour rest, patients were then given paclitaxel administered at a dose of 80 mg/m^2 by a 1-hour infusion on the same treatment days. Combination therapy continued until disease progression, unacceptable toxicity, or withdrawal from the study.

Serious adverse events	Ganetespib Monotherapy	Ganetespib Combination Therapy	
Total subjects affected by serious adverse events			
subjects affected / exposed	13 / 51 (25.49%)	3 / 6 (50.00%)	
number of deaths (all causes)	4	1	
number of deaths resulting from adverse events			
Neoplasms benign, malignant and unspecified (incl cysts and polyps)			
Neoplasm progression			
subjects affected / exposed	3 / 51 (5.88%)	1 / 6 (16.67%)	
occurrences causally related to treatment / all	0 / 3	0 / 1	
deaths causally related to treatment / all	0 / 3	0 / 1	
Injury, poisoning and procedural complications			
Fall			
subjects affected / exposed	1 / 51 (1.96%)	0 / 6 (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			
Dizziness			

subjects affected / exposed	2 / 51 (3.92%)	0 / 6 (0.00%)	
occurrences causally related to treatment / all	1 / 2	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Headache			
subjects affected / exposed	1 / 51 (1.96%)	0 / 6 (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			
Asthenia			
subjects affected / exposed	0 / 51 (0.00%)	1 / 6 (16.67%)	
occurrences causally related to treatment / all	0 / 0	3 / 3	
deaths causally related to treatment / all	0 / 0	0 / 0	
Fatigue			
subjects affected / exposed	1 / 51 (1.96%)	0 / 6 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
General physical health deterioration			
subjects affected / exposed	1 / 51 (1.96%)	0 / 6 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 1	0 / 0	
Pain			
subjects affected / exposed	1 / 51 (1.96%)	0 / 6 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Gastrointestinal disorders			
Abdominal pain			
subjects affected / exposed	1 / 51 (1.96%)	0 / 6 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Diarrhoea			
subjects affected / exposed	2 / 51 (3.92%)	0 / 6 (0.00%)	
occurrences causally related to treatment / all	2 / 2	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	

Gastrointestinal haemorrhage			
subjects affected / exposed	1 / 51 (1.96%)	0 / 6 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Large intestinal ulcer			
subjects affected / exposed	1 / 51 (1.96%)	0 / 6 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Nausea			
subjects affected / exposed	1 / 51 (1.96%)	1 / 6 (16.67%)	
occurrences causally related to treatment / all	1 / 1	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Hepatobiliary disorders			
Cholecystitis acute			
subjects affected / exposed	1 / 51 (1.96%)	0 / 6 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Gallbladder perforation			
subjects affected / exposed	1 / 51 (1.96%)	0 / 6 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Respiratory, thoracic and mediastinal disorders			
Dyspnoea			
subjects affected / exposed	1 / 51 (1.96%)	0 / 6 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Epistaxis			
subjects affected / exposed	1 / 51 (1.96%)	0 / 6 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pleural effusion			
subjects affected / exposed	0 / 51 (0.00%)	1 / 6 (16.67%)	
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	1 / 51 (1.96%)	0 / 6 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Musculoskeletal and connective tissue disorders			
Musculoskeletal chest pain			
subjects affected / exposed	1 / 51 (1.96%)	0 / 6 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Musculoskeletal pain			
subjects affected / exposed	1 / 51 (1.96%)	0 / 6 (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			
Lower respiratory tract infection			
subjects affected / exposed	1 / 51 (1.96%)	0 / 6 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pneumonia			
subjects affected / exposed	1 / 51 (1.96%)	0 / 6 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Urinary tract infection			
subjects affected / exposed	1 / 51 (1.96%)	0 / 6 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Urosepsis			
subjects affected / exposed	0 / 51 (0.00%)	1 / 6 (16.67%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Metabolism and nutrition disorders			
Hyponatraemia			

subjects affected / exposed	2 / 51 (3.92%)	0 / 6 (0.00%)	
occurrences causally related to treatment / all	1 / 2	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	Ganetespib Monotherapy	Ganetespib Combination Therapy	
Total subjects affected by non-serious adverse events			
subjects affected / exposed	51 / 51 (100.00%)	6 / 6 (100.00%)	
Investigations			
Alanine aminotransferase increased			
subjects affected / exposed	13 / 51 (25.49%)	2 / 6 (33.33%)	
occurrences (all)	18	2	
Amylase increased			
subjects affected / exposed	3 / 51 (5.88%)	1 / 6 (16.67%)	
occurrences (all)	8	1	
Aspartate aminotransferase increased			
subjects affected / exposed	12 / 51 (23.53%)	1 / 6 (16.67%)	
occurrences (all)	18	1	
Blood alkaline phosphatase increased			
subjects affected / exposed	5 / 51 (9.80%)	0 / 6 (0.00%)	
occurrences (all)	9	0	
Blood magnesium decreased			
subjects affected / exposed	0 / 51 (0.00%)	1 / 6 (16.67%)	
occurrences (all)	0	1	
Lipase increased			
subjects affected / exposed	3 / 51 (5.88%)	0 / 6 (0.00%)	
occurrences (all)	3	0	
Lymphocyte count decreased			
subjects affected / exposed	3 / 51 (5.88%)	0 / 6 (0.00%)	
occurrences (all)	7	0	
Platelet count decreased			
subjects affected / exposed	1 / 51 (1.96%)	1 / 6 (16.67%)	
occurrences (all)	1	2	

Weight decreased			
subjects affected / exposed	7 / 51 (13.73%)	1 / 6 (16.67%)	
occurrences (all)	7	1	
Vascular disorders			
Hypertension			
subjects affected / exposed	5 / 51 (9.80%)	0 / 6 (0.00%)	
occurrences (all)	10	0	
Nervous system disorders			
Headache			
subjects affected / exposed	11 / 51 (21.57%)	1 / 6 (16.67%)	
occurrences (all)	23	2	
Neuropathy peripheral			
subjects affected / exposed	2 / 51 (3.92%)	1 / 6 (16.67%)	
occurrences (all)	2	1	
Paraesthesia			
subjects affected / exposed	3 / 51 (5.88%)	0 / 6 (0.00%)	
occurrences (all)	5	0	
Peripheral sensory neuropathy			
subjects affected / exposed	4 / 51 (7.84%)	2 / 6 (33.33%)	
occurrences (all)	5	3	
Blood and lymphatic system disorders			
Anaemia			
subjects affected / exposed	4 / 51 (7.84%)	1 / 6 (16.67%)	
occurrences (all)	5	2	
General disorders and administration site conditions			
Asthenia			
subjects affected / exposed	9 / 51 (17.65%)	1 / 6 (16.67%)	
occurrences (all)	16	1	
Fatigue			
subjects affected / exposed	21 / 51 (41.18%)	2 / 6 (33.33%)	
occurrences (all)	44	8	
Oedema peripheral			
subjects affected / exposed	8 / 51 (15.69%)	0 / 6 (0.00%)	
occurrences (all)	8	0	
Pain			

subjects affected / exposed	1 / 51 (1.96%)	1 / 6 (16.67%)	
occurrences (all)	1	1	
Pyrexia			
subjects affected / exposed	4 / 51 (7.84%)	0 / 6 (0.00%)	
occurrences (all)	4	0	
Gastrointestinal disorders			
Abdominal pain			
subjects affected / exposed	11 / 51 (21.57%)	0 / 6 (0.00%)	
occurrences (all)	14	0	
Abdominal pain upper			
subjects affected / exposed	3 / 51 (5.88%)	0 / 6 (0.00%)	
occurrences (all)	4	0	
Constipation			
subjects affected / exposed	10 / 51 (19.61%)	1 / 6 (16.67%)	
occurrences (all)	14	1	
Diarrhoea			
subjects affected / exposed	43 / 51 (84.31%)	3 / 6 (50.00%)	
occurrences (all)	193	6	
Dry mouth			
subjects affected / exposed	3 / 51 (5.88%)	0 / 6 (0.00%)	
occurrences (all)	5	0	
Dyspepsia			
subjects affected / exposed	3 / 51 (5.88%)	0 / 6 (0.00%)	
occurrences (all)	3	0	
Haemorrhoids			
subjects affected / exposed	4 / 51 (7.84%)	0 / 6 (0.00%)	
occurrences (all)	4	0	
Nausea			
subjects affected / exposed	30 / 51 (58.82%)	4 / 6 (66.67%)	
occurrences (all)	66	10	
Proctalgia			
subjects affected / exposed	3 / 51 (5.88%)	0 / 6 (0.00%)	
occurrences (all)	3	0	
Rectal haemorrhage			
subjects affected / exposed	3 / 51 (5.88%)	0 / 6 (0.00%)	
occurrences (all)	3	0	

Vomiting			
subjects affected / exposed	16 / 51 (31.37%)	2 / 6 (33.33%)	
occurrences (all)	29	2	
Respiratory, thoracic and mediastinal disorders			
Cough			
subjects affected / exposed	4 / 51 (7.84%)	0 / 6 (0.00%)	
occurrences (all)	6	0	
Dyspnoea			
subjects affected / exposed	5 / 51 (9.80%)	1 / 6 (16.67%)	
occurrences (all)	6	1	
Productive cough			
subjects affected / exposed	2 / 51 (3.92%)	1 / 6 (16.67%)	
occurrences (all)	3	1	
Skin and subcutaneous tissue disorders			
Alopecia			
subjects affected / exposed	3 / 51 (5.88%)	2 / 6 (33.33%)	
occurrences (all)	3	3	
Dermatitis acneiform			
subjects affected / exposed	2 / 51 (3.92%)	1 / 6 (16.67%)	
occurrences (all)	2	1	
Pruritus			
subjects affected / exposed	5 / 51 (9.80%)	1 / 6 (16.67%)	
occurrences (all)	5	1	
Rash			
subjects affected / exposed	4 / 51 (7.84%)	0 / 6 (0.00%)	
occurrences (all)	4	0	
Psychiatric disorders			
Anxiety			
subjects affected / exposed	4 / 51 (7.84%)	0 / 6 (0.00%)	
occurrences (all)	4	0	
Depression			
subjects affected / exposed	4 / 51 (7.84%)	0 / 6 (0.00%)	
occurrences (all)	4	0	
Insomnia			
subjects affected / exposed	17 / 51 (33.33%)	1 / 6 (16.67%)	
occurrences (all)	25	2	

Musculoskeletal and connective tissue disorders			
Arthralgia			
subjects affected / exposed	4 / 51 (7.84%)	0 / 6 (0.00%)	
occurrences (all)	5	0	
Back pain			
subjects affected / exposed	6 / 51 (11.76%)	0 / 6 (0.00%)	
occurrences (all)	7	0	
Muscle spasms			
subjects affected / exposed	3 / 51 (5.88%)	0 / 6 (0.00%)	
occurrences (all)	3	0	
Musculoskeletal chest pain			
subjects affected / exposed	4 / 51 (7.84%)	0 / 6 (0.00%)	
occurrences (all)	4	0	
Musculoskeletal pain			
subjects affected / exposed	4 / 51 (7.84%)	0 / 6 (0.00%)	
occurrences (all)	4	0	
Myalgia			
subjects affected / exposed	3 / 51 (5.88%)	1 / 6 (16.67%)	
occurrences (all)	3	1	
Neck pain			
subjects affected / exposed	3 / 51 (5.88%)	0 / 6 (0.00%)	
occurrences (all)	5	0	
Infections and infestations			
Acarodermatitis			
subjects affected / exposed	0 / 51 (0.00%)	1 / 6 (16.67%)	
occurrences (all)	0	1	
Herpes zoster			
subjects affected / exposed	0 / 51 (0.00%)	1 / 6 (16.67%)	
occurrences (all)	0	1	
Oral candidiasis			
subjects affected / exposed	3 / 51 (5.88%)	0 / 6 (0.00%)	
occurrences (all)	6	0	
Urinary tract infection			
subjects affected / exposed	3 / 51 (5.88%)	1 / 6 (16.67%)	
occurrences (all)	5	2	
Metabolism and nutrition disorders			

Decreased appetite			
subjects affected / exposed	16 / 51 (31.37%)	1 / 6 (16.67%)	
occurrences (all)	24	1	
Hyperglycaemia			
subjects affected / exposed	5 / 51 (9.80%)	1 / 6 (16.67%)	
occurrences (all)	6	1	
Hyperuricaemia			
subjects affected / exposed	0 / 51 (0.00%)	1 / 6 (16.67%)	
occurrences (all)	0	1	

More information

Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? Yes

Date	Amendment
05 April 2012	Deleted that patients with OR or SD at the end of the 12-week treatment phase might be offered the opportunity to enroll in a companion study of ganetespib in combination with standard treatment. Modified the inclusion criteria as follows: HER2+ patients must have relapsed following prior trastuzumab or other approved anti-HER2 agent in the adjuvant setting, and at least 6 months must have elapsed since the discontinuation of prior adjuvant therapy. Required a biopsy at study entry for patients with accessible tumors, and patients with inaccessible tumors could substitute an archived tissue with prior Sponsor approval. The original protocol required archived tissue and a fresh biopsy (or recent biopsy, with Sponsor approval) at study entry. Modified the exclusion criteria as follows: Clarified that exclusion criteria regarding prior systemic therapy for metastatic breast cancer applied to such therapy received in the first line setting. All patients with de novo diagnosed HER2+ disease were excluded. Clarified that patients with "active" coronary artery disease were excluded (rather than "current" coronary artery disease, as worded in the original protocol). Specified that during the extended treatment phase, bone scans would be repeated only if clinically indicated and that CT would be repeated every 12 weeks post Week 12. Specified that vital signs would be measured prior to each dose of ganetespib, rather than at Week 1 Day 1 and Week 2 Day 8 only. Added the definition of an evaluable patient, ie, a patient who received at least 1 dose of ganetespib and had a subsequent follow-up scan.
29 January 2013	Protocol Amendment 2 was prepared and submitted but not implemented; therefore, no patients were enrolled under this amendment.
06 March 2013	Protocol Amendment 3 was prepared and submitted but not implemented; therefore, no patients were enrolled under this amendment.

11 September 2013	A total of 11 patients were enrolled under Protocol Amendment 4. The primary changes specified in this amendment were as follows: Revised the study design to encompass all types of breast cancer; therefore, specific types of breast cancer (HER2+ and TNBC) were removed from the description of the study population and the study title. Expanded Cohorts A and B and added Cohort D was added based on the results of the formal interim analysis, which showed that ganetespib monotherapy on a twice-weekly schedule was well tolerated with a safety profile similar to the overall experience in the ganetespib program and Cohorts A and B exceeded the protocol specified criteria for proceeding to Stage 2: Cohort A - 2 of the first 4 patients achieved OR and the other 2 patients achieved SD; Cohort B - 2 of the first 10 patients achieved OR and 3 achieved SD. Enrollment in Cohorts A and B were continued to approximately 35 patients (previously approximately 33 evaluable patients per cohort). Cohort D, which evaluated ganetespib monotherapy activity in patients with hormone receptor (ER/PR)-positive disease) was added, with a planned enrollment of approximately 35 patients. Specified that patients with OR or SD in any cohort could continue ganetespib monotherapy beyond the initial 12-week treatment period. Added treatment with ganetespib once weekly in combination with weekly paclitaxel for patients with disease progression after ganetespib monotherapy (optional for Cohort A, mandatory for Cohorts B and D). The secondary study objectives were expanded as follows: Added the evaluation of the clinical benefit rate (CBR), duration of response (DOR), and progression free survival (PFS) with ganetespib monotherapy Added the evaluation of the ORR, CBR, DOR, and PFS with ganetespib in combination with weekly paclitaxel in patients whose disease progressed on ganetespib monotherapy Other....

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.

The study was terminated early since the objective of determining the level of activity in the patient populations was met. There was no impact on the study data due to early termination.

Notes: