Clinical trial results:
A phase Ib/II, multi-center, open-label study to evaluate the efficacy of AUY922 in combination with trastuzumab in patients with locally advanced or metastatic HER2-positive breast cancer that has progressed after or during at least one Trastuzumab-containing regimen

Summary

EudraCT number	2009-015628-27
Trial protocol	SE FR GB DE NL
Global end of trial date	11 September 2013

Results information

Result version number	v1 (current)
This version publication date	13 July 2016
First version publication date	26 July 2015

Trial information

Trial identification

Sponsor protocol code	CAUY922A2109

Additional study identifiers

ISRCTN number	-
ClinicalTrials.gov id (NCT number)	NCT01271920
WHO universal trial number (UTN)	-

Notes:

Sponsors

Sponsor organisation name	Novartis Pharma AG
Sponsor organisation address	CH-4002, Basel, Switzerland,
Public contact	Clinical Disclosure Office, Novartis Pharma AG, +41 613241111,
Scientific contact	Clinical Disclosure Office, Novartis Pharma AG, +41 613241111,

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 September 2013
Is this the analysis of the primary completion data?	No

Global end of trial reached?	Yes
Global end of trial date	11 September 2013
Was the trial ended prematurely?	No

Notes:

General information about the trial

Main objective of the trial:

Primary objective of phase Ib: To define the Maximum Tolerated Dose (MTD) and/or the Recommended Phase Two Dose (RPTD) of AUY922 in combination with Trastuzumab when administered intravenously (i.v.) on a once weekly schedule to adult patients with advanced or metastatic human epidermal growth factor receptor 2 (HER2)-positive breast cancers.

Primary objective of phase II: To evaluate preliminary anti-tumor activity of AUY922 in combination with trastuzumab in adult patients with advanced or metastatic HER2- positive breast cancers.

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	01 September 2010
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: 6
Country: Number of subjects enrolled	United Kingdom: 20
Country: Number of subjects enrolled	France: 3
Country: Number of subjects enrolled	Germany: 2
Country: Number of subjects enrolled	Italy: 4
Country: Number of subjects enrolled	Singapore: 7
Country: Number of subjects enrolled	United States: 3
Worldwide total number of subjects	45
EEA total number of subjects	35

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)	40
From 65 to 84 years	5
85 years and over	0

Subject disposition

Recruitment

Recruitment details: -

Pre-assignment

Screening details:

Subjects were screened over a period of 2 weeks.

Period 1

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

Arms

Are arms mutually exclusive?	Yes
Arm title	55 mg/m2 AUY922 + 2 mg/kg trastuzumab

Arm description:

AUY922 was to be administered in combination with trastuzumab. In the Phase Ib component, patients received escalating doses of AUY922 combined with a standard dose of trastuzumab until the Maximum Tolerated Dose (MTD) and/or Recommended Phase Two Dose (RP2D) had been determined. For the Phase Ib part of the study, the starting dose of AUY922 was 55 mg/m2.

Arm type	Experimental
Investigational medicinal product name	AUY922
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Solution for injection/infusion
Routes of administration	Intravenous use

Dosage and administration details:

AUY922 was diluted to the appropriate concentration (according to patient body surface area [BSA]) in a 500 mL infusion bag containing 5% dextrose or glucose (with a maximum infusion volume of 500 mL) prior to administration. The drug could be administered using a central line or via peripheral vein. For the Phase Ib part of the study, the starting dose of AUY922 was 55 mg/m2, administered i.v. once weekly (Days 1, 8, 15, and 22 of each treatment cycle) in combination with the standard trastuzumab therapy (2 mg/kg once weekly or a loading dose of 4 mg/kg at Cycle 1, Day 1 if felt necessary by the investigator). It was possible for some dose levels to be skipped or additional, intermediate doses added during the course of the study. Dose escalation was not to exceed a 100% increase from the current dose being studied. In no case was the AUY922 infusion to start later than 24 hours after trastuzumab infusion.

Investigational medicinal product name	Trastuzumab
Investigational medicinal product code	
Other name	Herceptin
Pharmaceutical forms	Powder for solution for injection/infusion
Routes of administration	Intravenous use

Dosage and administration details:

Trastuzumab was dosed on a mg/kg basis, using the patient weight at the beginning of each cycle. Administered dose was 2 mg/kg.

Arm title	70 mg/m2 AUY922 + 2 mg/kg trastuzumab

Arm description:

AUY922 was to be administered in combination with trastuzumab. Once the MTD and/or RP2D was confirmed, this MTD and/or RP2D cohort was to be
expanded to a total of 40 patients as the Phase 2 part. In the Phase 2 part of the trial, the starting dose for AUY922 was 70 mg/m2.

Arm type	Experimental

Investigational medicinal product name	AUY922
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Solution for injection/infusion
Routes of administration	Intravenous use

Dosage and administration details:

AUY922 was diluted to the appropriate concentration (according to patient body surface area [BSA]) in a 500 mL infusion bag containing 5% dextrose or glucose (with a maximum infusion volume of 500 mL) prior to administration. The drug could be administered using a central line or via peripheral vein. In the Phase 2 part of the trial, the starting dose for AUY922 was 70 mg/m2 administered i.v. once weekly (Days 1, 8, 15, and 22 of each treatment cycle) in combination with the standard trastuzumab therapy (2 mg/kg once weekly or a loading dose of 4 mg/kg at Cycle 1, Day 1 if felt necessary by the investigator). In no case was the AUY922 infusion to start later than 24 hours after trastuzumab infusion.

Investigational medicinal product name	Trastuzumab
Investigational medicinal product code	
Other name	Herceptin
Pharmaceutical forms	Powder for solution for injection/infusion
Routes of administration	Intravenous use

Dosage and administration details:

Trastuzumab was dosed on a mg/kg basis, using the patient weight at the beginning of each cycle. Administered dose was 2 mg/kg.

Number of subjects in period 1	55 mg/m2 AUY922 + 2 mg/kg trastuzumab	70 mg/m2 AUY922 + 2 mg/kg trastuzumab
Started	4	41
Completed	0	0
Not completed	4	41
Consent withdrawn by subject	-	4
Adverse event, non-fatal	1	9
Disease Progression	3	28

Baseline characteristics

Reporting groups	
Reporting group title	55 mg/m2 AUY922 + 2 mg/kg trastuzumab

Reporting group description:

AUY922 was to be administered in combination with trastuzumab. In the Phase Ib component, patients received escalating doses of AUY922 combined with a standard dose of trastuzumab until the Maximum Tolerated Dose (MTD) and/or Recommended Phase Two Dose (RP2D) had been determined. For the Phase Ib part of the study, the starting dose of AUY922 was 55 mg/m2.

Reporting group title	70 mg/m2 AUY922 + 2 mg/kg trastuzumab

Reporting group description:

AUY922 was to be administered in combination with trastuzumab. Once the MTD and/or RP2D was confirmed, this MTD and/or RP2D cohort was to be
expanded to a total of 40 patients as the Phase 2 part. In the Phase 2 part of the trial, the starting dose for AUY922 was 70 mg/m2.

Reporting group values	55 mg/m2 AUY922 + 2 mg/kg trastuzumab	70 mg/m2 AUY922 + 2 mg/kg trastuzumab	Total
Number of subjects	4	41	45
Age categorical Units: Subjects			
< 65 years	4	36	40
≥ 65 years	0	5	5
Age continuous Units: years			
arithmetic mean	53.5	51.8	
standard deviation	± 9.68	± 10.68	-
Gender categorical Units: Subjects			
Female	4	41	45
Male	0	0	0

End points

End points reporting groups

Reporting group title	55 mg/m2 AUY922 + 2 mg/kg trastuzumab

Reporting group description:

AUY922 was to be administered in combination with trastuzumab. In the Phase Ib component, patients received escalating doses of AUY922 combined with a standard dose of trastuzumab until the Maximum Tolerated Dose (MTD) and/or Recommended Phase Two Dose (RP2D) had been determined. For the Phase Ib part of the study, the starting dose of AUY922 was 55 mg/m2.

Reporting group title	70 mg/m2 AUY922 + 2 mg/kg trastuzumab

Reporting group description:

AUY922 was to be administered in combination with trastuzumab. Once the MTD and/or RP2D was confirmed, this MTD and/or RP2D cohort was to be
expanded to a total of 40 patients as the Phase 2 part. In the Phase 2 part of the trial, the starting dose for AUY922 was 70 mg/m2.

Subject analysis set title	Dose Determining Set (DDS)
Subject analysis set type	Safety analysis

Subject analysis set description:

The DDS consisted of all patients from the safety set (at least within the dose-escalation part) who either experienced dose-limiting toxicity (DLT) within Cycle 1, or if not experiencing DLT had completed the safety assessments as requested in the protocol during this treatment and observation period of at least 28 days in Cycle 1 and met the following minimum exposure criterion:
• A patient in the Phase Ib part receiving AUY922 and trastuzumab was considered to have met the minimum exposure criterion if they received three of the four planned doses of AUY922 and at least three of the four planned trastuzumab doses within Cycle 1.

Primary: Determination of The Maximum Tolerated Dose (MTD): Number of Subjects Experiencing Dose-limiting Toxicity (DLT) During Phase Ib

End point title	Determination of The Maximum Tolerated Dose (MTD): Number of Subjects Experiencing Dose-limiting Toxicity (DLT) During Phase Ib[1]

End point description:

The number of subjects experiencing a DLT was used to identify the MTD of AUY922 when administered intravenously once a week in combination with the standard trastuzumab therapy. A DLT was defined as an adverse event (AE) or abnormal laboratory value assessed as clinically relevant, occurring ≤ 28 days following the first administration of AUY922 (Cycle 1) in combination with the standard trastuzumab therapy.
The MTD was determined as follows: The distribution of the DLT rate for each AUY922 dose and the starting dose level summarized the probability that the true rate of DLT for each dose lay in the following categories:
1. [0, 16%) under-dosing
2. [16%, 33%) targeted toxicity
3. [33%, 100%] excessive toxicity
The escalation with overdose control (EWOC) principle mandated that any dose of AUY922 in combination with the standard trastuzumab therapy that had more than a 25% chance of being in the excessive toxicity category was not considered for the next dose cohort.

End point type	Primary

End point timeframe:

4 weeks

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 analysis was planned for this outcome measure.

End point values	Dose Determining Set (DDS)			
Subject group type	Subject analysis set			
Number of subjects analysed	11			
Units: subjects	1			

Statistical analyses

No statistical analyses for this end point

Primary: Overall Response Rate: Percentage of Participants With Best Overall Response of Complete Response or Partial Response by Investigator Review Based on Response Evaluation Criteria in Solid Tumors (RECIST)

End point title	Overall Response Rate: Percentage of Participants With Best Overall Response of Complete Response or Partial Response by Investigator Review Based on Response Evaluation Criteria in Solid Tumors (RECIST)[2][3]

End point description:

Overall response rate (ORR) was defined as the percentage of patients with a best overall response of Complete Response (CR) or Partial Response (PR) as defined by the Response Evaluation Criteria In Solid Tumors (RECIST) criteria. CR was defined as the disappearance of target and non-target lesions; at least 2 determinations of CR were required at least 4 weeks apart before progression. PR was defined as at least a 30% decrease in the sum of the longest diameter of all target lesions, taking as reference the baseline sum of the longest diameters; at least 2 determinations of PR or better were required at least 4 weeks apart before progression (and not qualifying for a CR).

End point type	Primary

End point timeframe:

Every 8 weeks for the first 24 weeks and every 12 weeks thereafter

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 analysis was planned for this primary outcome measure.

[3] - The end point is not reporting statistics for all the arms in the baseline period. It is expected all the baseline period arms will be reported on when providing values for an end point on the baseline period.
Justification: No statistical analysis was planned for this outcome measure.

End point values	70 mg/m2 AUY922 + 2 mg/kg trastuzumab			
Subject group type	Reporting group			
Number of subjects analysed	41			
Units: percentage of subjects				
number (confidence interval 95%)	22 (10.6 to 37.6)			

Statistical analyses

No statistical analyses for this end point

Secondary: Plasma Concentration of AUY922 Over Time

End point title	Plasma Concentration of AUY922 Over Time

End point description:

Pharmacokinetic analysis was used to measure the concentration of AUY922 in serum collected at intervals over 8 days post-dose.

End point type	Secondary

End point timeframe:

8 days post-dose

End point values	55 mg/m2 AUY922 + 2 mg/kg trastuzumab	70 mg/m2 AUY922 + 2 mg/kg trastuzumab		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	4	41		
Units: ng/ml				
arithmetic mean (standard deviation)				
0.5 hours post-dose	830.5 (± 237.124)	1038.68 (± 379.662)		
1.0 hours post-dose	500.25 (± 200.144)	680.45 (± 309.032)		
1.5 hours post-dose	115.23 (± 12.728)	242.37 (± 205.976)		
2.0 hours post-dose	99.65 (± 41.537)	144.01 (± 74.058)		
5.0 hours post-dose	26.5 (± 7.65)	47.36 (± 34.791)		
6.0 hours post-dose	17.28 (± 2.878)	41.26 (± 65.554)		
9.0 hours post-dose	15.73 (± 6.033)	19.11 (± 12.646)		
25.0 hours post-dose	5.19 (± 1.196)	12.27 (± 17.474)		
49.0 hours post-dose	2.72 (± 0.64)	5.58 (± 6.104)		
169.0 hours post-dose	0.81 (± 0.558)	1.03 (± 1.404)		

Statistical analyses

No statistical analyses for this end point

Secondary: Plasma Concentration of BJP762 Over Time

End point title	Plasma Concentration of BJP762 Over Time

End point description:

Pharmacokinetic analysis was used to measure the concentration of BJP762 in serum collected at intervals over 8 days post-dose.

End point type	Secondary

End point timeframe:

8 days post-dose

End point values	55 mg/m2 AUY922 + 2 mg/kg trastuzumab	70 mg/m2 AUY922 + 2 mg/kg trastuzumab		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	4	41		
Units: ng/ml				
arithmetic mean (standard deviation)				
0.5 hours post-dose	917 (± 238.386)	1588.73 (± 998.235)		
1.0 hours post-dose	1116.75 (± 378.183)	2279.13 (± 1770.345)		
1.5 hours post-dose	420.25 (± 155.654)	1276.73 (± 1480.698)		
2.0 hours post-dose	397.5 (± 315.765)	766.1 (± 1071.439)		
5.0 hours post-dose	86.18 (± 43.502)	311.9 (± 458.779)		
6.0 hours post-dose	84.3 (± 27.489)	299.29 (± 405.374)		
9.0 hours post-dose	114.05 (± 38.863)	253.63 (± 318.963)		
25.0 hours post-dose	38.48 (± 23.778)	78.32 (± 77.301)		
49.0 hours post-dose	12.5 (± 10.094)	31.04 (± 40.668)		
169.0 hours post-dose	2.43 (± 1.294)	3.08 (± 5.691)		

Statistical analyses

No statistical analyses for this end point

Secondary: Progression Free Survival (PFS) by Investigator Review at The Recommended Phase Two Dose (RPTD)

End point title	Progression Free Survival (PFS) by Investigator Review at The Recommended Phase Two Dose (RPTD)[4]

End point description:

As defined by the RECIST criteria, PFS is the time from date of randomization/start of treatment to the date of event defined as the first documented progression or death due to any cause. Progression was defined as an increase of at least 20% in the sum of the longest diameter of all measured target lesions, taking as reference the smallest sum of longest diameter of all target lesions recorded at or after baseline. If a subject did not have an event, PFS was censored at the date of last adequate tumor assessment. A subject was considered to be censored when data on time to event was missing due to the subject being lost to follow-up before the completion of the trial.

End point type	Secondary

End point timeframe:

Every 3 months until 24 months after the last patient has been enrolled

Notes:

[4] - The end point is not reporting statistics for all the arms in the baseline period. It is expected all the baseline period arms will be reported on when providing values for an end point on the baseline period.
Justification: No statistical analysis was planned for this outcome measure.

End point values	70 mg/m2 AUY922 + 2 mg/kg trastuzumab			
Subject group type	Reporting group			
Number of subjects analysed	41			
Units: months				
median (confidence interval 95%)	3.94 (3.48 to 6.47)			

Statistical analyses

No statistical analyses for this end point

Secondary: Overall Survival (OS) at The RPTD

End point title	Overall Survival (OS) at The RPTD[5]

End point description:

As defined by the RECIST criteria, OS is the time from date of randomization/start of treatment to date of death due to any cause. If a patient was not known to have died, survival was censored at the date of last contact.

End point type	Secondary

End point timeframe:

Every 3 months until 24 months after the last patient has been enrolled

Notes:

[5] - The end point is not reporting statistics for all the arms in the baseline period. It is expected all the baseline period arms will be reported on when providing values for an end point on the baseline period.
Justification: No statistical analysis was planned for this outcome measure.

End point values	70 mg/m2 AUY922 + 2 mg/kg trastuzumab			
Subject group type	Reporting group			
Number of subjects analysed	41			
Units: months				
median (confidence interval 95%)	12.65 (11.7 to 17.22)			

Statistical analyses

No statistical analyses for this end point

Secondary: Number of Subjects With Adverse Events

End point title	Number of Subjects With Adverse Events

End point description:

Adverse events (AEs) were assessed according to the Common Toxicity Criteria for Adverse Events (CTCAE) version 4.0.

End point type	Secondary

End point timeframe:

Average 6 months

End point values	55 mg/m2 AUY922 + 2 mg/kg trastuzumab	70 mg/m2 AUY922 + 2 mg/kg trastuzumab		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	4	41		
Units: participants				
Serious Adverse Event	0	11		
Non-serious Adverse Event	4	41		

Statistical analyses

No statistical analyses for this end point

Adverse events

Adverse events information

Timeframe for reporting adverse events:

Serious Adverse Events are monitored from date of First Patient First Visit (FPFV) until Last Patient Last Visit (LPLV). All other adverse events are monitored from First Patient First Treatment until Last Patient Last Visit.

Assessment type	Systematic

Dictionary used

Dictionary name	MedDRA
Dictionary version	15.0

Reporting groups

Reporting group title	70 mg/m2 AUY922 + 2 mg/kg trastuzumab
Reporting group description:	
70 mg/m2 AUY922 + 2 mg/kg trastuzumab	
Reporting group title	55 mg/m2 AUY922 + 2 mg/kg trastuzumab
Reporting group description:	
55 mg/m2 AUY922 + 2 mg/kg trastuzumab	

Serious adverse events	70 mg/m2 AUY922 + 2 mg/kg trastuzumab	55 mg/m2 AUY922 + 2 mg/kg trastuzumab	
Total subjects affected by serious adverse events			
subjects affected / exposed	11 / 41 (26.83%)	0 / 4 (0.00%)	
number of deaths (all causes)	0	0	
number of deaths resulting from adverse events	0	0	
Investigations			
Electrocardiogram QT prolonged			
subjects affected / exposed	1 / 41 (2.44%)	0 / 4 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Ejection fraction decreased			
subjects affected / exposed	1 / 41 (2.44%)	0 / 4 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Cardiac disorders			
Bundle branch block left			
subjects affected / exposed	1 / 41 (2.44%)	0 / 4 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	

Cardiac failure			
subjects affected / exposed	1 / 41 (2.44%)	0 / 4 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Nervous system disorders			
Headache			
subjects affected / exposed	1 / 41 (2.44%)	0 / 4 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Convulsion			
subjects affected / exposed	1 / 41 (2.44%)	0 / 4 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Hydrocephalus			
subjects affected / exposed	1 / 41 (2.44%)	0 / 4 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Blood and lymphatic system disorders			
Anaemia			
subjects affected / exposed	2 / 41 (4.88%)	0 / 4 (0.00%)	
occurrences causally related to treatment / all	0 / 2	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
General disorders and administration site conditions			
Asthenia			
subjects affected / exposed	1 / 41 (2.44%)	0 / 4 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Eye disorders			
Eye disorder			
subjects affected / exposed	1 / 41 (2.44%)	0 / 4 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Gastrointestinal disorders			
Gastrointestinal haemorrhage			

subjects affected / exposed	1 / 41 (2.44%)	0 / 4 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Melaena			
subjects affected / exposed	1 / 41 (2.44%)	0 / 4 (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	2 / 41 (4.88%)	0 / 4 (0.00%)	
occurrences causally related to treatment / all	1 / 2	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Vomiting			
subjects affected / exposed	2 / 41 (4.88%)	0 / 4 (0.00%)	
occurrences causally related to treatment / all	1 / 2	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Respiratory, thoracic and mediastinal disorders			
Pleural effusion			
subjects affected / exposed	2 / 41 (4.88%)	0 / 4 (0.00%)	
occurrences causally related to treatment / all	1 / 2	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Dyspnoea			
subjects affected / exposed	2 / 41 (4.88%)	0 / 4 (0.00%)	
occurrences causally related to treatment / all	1 / 2	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pneumothorax			
subjects affected / exposed	1 / 41 (2.44%)	0 / 4 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pulmonary embolism			
subjects affected / exposed	1 / 41 (2.44%)	0 / 4 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Infections and infestations			

Application site abscess			
subjects affected / exposed	1 / 41 (2.44%)	0 / 4 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Device related infection			
subjects affected / exposed	1 / 41 (2.44%)	0 / 4 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Mastitis			
subjects affected / exposed	1 / 41 (2.44%)	0 / 4 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	

Frequency threshold for reporting non-serious adverse events: 5 %

Non-serious adverse events	70 mg/m2 AUY922 + 2 mg/kg trastuzumab	55 mg/m2 AUY922 + 2 mg/kg trastuzumab	
Total subjects affected by non-serious adverse events			
subjects affected / exposed	41 / 41 (100.00%)	4 / 4 (100.00%)	
Vascular disorders			
Hypertension			
subjects affected / exposed	1 / 41 (2.44%)	1 / 4 (25.00%)	
occurrences (all)	1	1	
General disorders and administration site conditions			
Asthenia			
subjects affected / exposed	8 / 41 (19.51%)	0 / 4 (0.00%)	
occurrences (all)	12	0	
Fatigue			
subjects affected / exposed	15 / 41 (36.59%)	2 / 4 (50.00%)	
occurrences (all)	16	2	
Oedema peripheral			
subjects affected / exposed	3 / 41 (7.32%)	0 / 4 (0.00%)	
occurrences (all)	3	0	
Pyrexia			

subjects affected / exposed	5 / 41 (12.20%)	0 / 4 (0.00%)	
occurrences (all)	5	0	
Reproductive system and breast disorders			
Breast pain			
subjects affected / exposed	1 / 41 (2.44%)	1 / 4 (25.00%)	
occurrences (all)	1	1	
Respiratory, thoracic and mediastinal disorders			
Rhinorrhoea			
subjects affected / exposed	1 / 41 (2.44%)	2 / 4 (50.00%)	
occurrences (all)	1	2	
Cough			
subjects affected / exposed	5 / 41 (12.20%)	1 / 4 (25.00%)	
occurrences (all)	5	1	
Dyspnoea			
subjects affected / exposed	7 / 41 (17.07%)	0 / 4 (0.00%)	
occurrences (all)	8	0	
Psychiatric disorders			
Insomnia			
subjects affected / exposed	6 / 41 (14.63%)	0 / 4 (0.00%)	
occurrences (all)	6	0	
Investigations			
Alanine aminotransferase increased			
subjects affected / exposed	1 / 41 (2.44%)	1 / 4 (25.00%)	
occurrences (all)	3	1	
Aspartate aminotransferase increased			
subjects affected / exposed	3 / 41 (7.32%)	0 / 4 (0.00%)	
occurrences (all)	4	0	
Blood calcium decreased			
subjects affected / exposed	3 / 41 (7.32%)	0 / 4 (0.00%)	
occurrences (all)	11	0	
Ejection fraction decreased			
subjects affected / exposed	3 / 41 (7.32%)	0 / 4 (0.00%)	
occurrences (all)	3	0	
Transaminases increased			

subjects affected / exposed	0 / 41 (0.00%)	1 / 4 (25.00%)	
occurrences (all)	0	1	
Cardiac disorders			
Tachycardia			
subjects affected / exposed	3 / 41 (7.32%)	0 / 4 (0.00%)	
occurrences (all)	3	0	
Nervous system disorders			
Lethargy			
subjects affected / exposed	3 / 41 (7.32%)	0 / 4 (0.00%)	
occurrences (all)	4	0	
Headache			
subjects affected / exposed	12 / 41 (29.27%)	2 / 4 (50.00%)	
occurrences (all)	19	2	
Dysgeusia			
subjects affected / exposed	3 / 41 (7.32%)	0 / 4 (0.00%)	
occurrences (all)	5	0	
Dizziness			
subjects affected / exposed	4 / 41 (9.76%)	0 / 4 (0.00%)	
occurrences (all)	4	0	
Blood and lymphatic system disorders			
Anaemia			
subjects affected / exposed	11 / 41 (26.83%)	0 / 4 (0.00%)	
occurrences (all)	13	0	
Eye disorders			
Cystoid macular oedema			
subjects affected / exposed	1 / 41 (2.44%)	1 / 4 (25.00%)	
occurrences (all)	1	1	
Accommodation disorder			
subjects affected / exposed	9 / 41 (21.95%)	1 / 4 (25.00%)	
occurrences (all)	11	1	
Eye pain			
subjects affected / exposed	3 / 41 (7.32%)	0 / 4 (0.00%)	
occurrences (all)	4	0	
Maculopathy			
subjects affected / exposed	0 / 41 (0.00%)	1 / 4 (25.00%)	
occurrences (all)	0	1	
Night blindness			

subjects affected / exposed	13 / 41 (31.71%)	1 / 4 (25.00%)	
occurrences (all)	14	1	
Visual acuity reduced			
subjects affected / exposed	5 / 41 (12.20%)	0 / 4 (0.00%)	
occurrences (all)	5	0	
Vision blurred			
subjects affected / exposed	11 / 41 (26.83%)	2 / 4 (50.00%)	
occurrences (all)	17	2	
Photopsia			
subjects affected / exposed	10 / 41 (24.39%)	3 / 4 (75.00%)	
occurrences (all)	16	5	
Photophobia			
subjects affected / exposed	3 / 41 (7.32%)	2 / 4 (50.00%)	
occurrences (all)	3	2	
Visual impairment			
subjects affected / exposed	12 / 41 (29.27%)	2 / 4 (50.00%)	
occurrences (all)	13	2	
Vitreous floaters			
subjects affected / exposed	10 / 41 (24.39%)	1 / 4 (25.00%)	
occurrences (all)	12	1	
Gastrointestinal disorders			
Abdominal pain			
subjects affected / exposed	6 / 41 (14.63%)	0 / 4 (0.00%)	
occurrences (all)	11	0	
Abnormal faeces			
subjects affected / exposed	0 / 41 (0.00%)	1 / 4 (25.00%)	
occurrences (all)	0	1	
Constipation			
subjects affected / exposed	6 / 41 (14.63%)	0 / 4 (0.00%)	
occurrences (all)	7	0	
Diarrhoea			
subjects affected / exposed	38 / 41 (92.68%)	2 / 4 (50.00%)	
occurrences (all)	172	4	
Dyspepsia			
subjects affected / exposed	4 / 41 (9.76%)	0 / 4 (0.00%)	
occurrences (all)	4	0	

Nausea			
subjects affected / exposed	16 / 41 (39.02%)	1 / 4 (25.00%)	
occurrences (all)	22	1	
Stomatitis			
subjects affected / exposed	3 / 41 (7.32%)	1 / 4 (25.00%)	
occurrences (all)	3	1	
Vomiting			
subjects affected / exposed	8 / 41 (19.51%)	1 / 4 (25.00%)	
occurrences (all)	9	1	
Skin and subcutaneous tissue disorders			
Pruritus			
subjects affected / exposed	5 / 41 (12.20%)	1 / 4 (25.00%)	
occurrences (all)	8	1	
Rash			
subjects affected / exposed	3 / 41 (7.32%)	1 / 4 (25.00%)	
occurrences (all)	4	1	
Skin fissures			
subjects affected / exposed	0 / 41 (0.00%)	1 / 4 (25.00%)	
occurrences (all)	0	1	
Musculoskeletal and connective tissue disorders			
Arthralgia			
subjects affected / exposed	6 / 41 (14.63%)	0 / 4 (0.00%)	
occurrences (all)	6	0	
Back pain			
subjects affected / exposed	8 / 41 (19.51%)	0 / 4 (0.00%)	
occurrences (all)	9	0	
Muscle spasms			
subjects affected / exposed	11 / 41 (26.83%)	0 / 4 (0.00%)	
occurrences (all)	18	0	
Musculoskeletal pain			
subjects affected / exposed	5 / 41 (12.20%)	0 / 4 (0.00%)	
occurrences (all)	5	0	
Myalgia			
subjects affected / exposed	4 / 41 (9.76%)	0 / 4 (0.00%)	
occurrences (all)	7	0	
Pain in extremity			

subjects affected / exposed	3 / 41 (7.32%)	0 / 4 (0.00%)	
occurrences (all)	3	0	
Infections and infestations			
Influenza			
subjects affected / exposed	4 / 41 (9.76%)	0 / 4 (0.00%)	
occurrences (all)	9	0	
Nasopharyngitis			
subjects affected / exposed	3 / 41 (7.32%)	0 / 4 (0.00%)	
occurrences (all)	3	0	
Metabolism and nutrition disorders			
Decreased appetite			
subjects affected / exposed	9 / 41 (21.95%)	0 / 4 (0.00%)	
occurrences (all)	11	0	
Hypokalaemia			
subjects affected / exposed	6 / 41 (14.63%)	0 / 4 (0.00%)	
occurrences (all)	6	0	

More information

Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? Yes

Date	Amendment
05 May 2011	This amendment introduced the following changes: * Removal of FDG-PET imaging assessments. Similar data had been obtained in an ongoing phase II study of HER2+ MBC patients [AUY922A2101], and Novartis considered that additional data would not add further scientific value in understanding the efficacy of AUY922 in MBC; * An exploratory objective (effect of AUY922 on the number of circulating tumor cells) was deleted from the Phase II part of the study. Similar data had been obtained in an ongoing phase II study of HER2+ MBC patients [AUY922A2101], and no additional data were needed at this time. Data obtained before the amendment were to be listed. * Post-Text Supplement 2 "Excluded Medications" was made consistent with Section 6.6.7 of the Study Protocol. Namely, drugs known to be metabolized or to interact with CYP3A4 isoenzymes were not excluded medications, but had to be used with caution as this was the case for drugs known to be metabolized or to interact with CYP2C9, CYP2C19 and CYP2C8; * Removal of the request for chest x-ray, as all patients were having a CT of the chest performed as a required radiological assessment in this study; * Clarification that the AUY922 infusion should start as close as possible but no sooner than 10 minutes from the end of the trastuzumab infusion in order to monitor potential allergic reactions to trastuzumab. In no case was the AUY922 infusion to start later than 24 hours from the end of the trastuzumab infusion; * Updating of Table 6-4 of the Study Protocol to align with the National Cancer Institute CTC version 4 grading of diarrhea. (In the original version of the protocol, Table 6-4 of the Study Protocol was still matching the CTC AE version 3.)
14 December 2011	This amendment introduced the following changes: * Reduction of the number of biomarkers to be evaluated. Emerging knowledge in the field indicated that, at this time, there was no strong evidence indicating that several of the parameters initially included in this amendment would bring significant value; * In the already completed Phase Ib part of the trial, the HSP70 biomarker had been analyzed in the blood samples collected to compare the levels of specific biomarkers in pre and post-treatment PBMC samples. Other HSP90 client proteins such as CDK4 had not yet been analyzed in these samples and would not be analyzed in the future as sufficient information had been obtained from the HSP70 analysis; * In the Phase II part of the trial, plasma and serum biomarker samples had not yet been analyzed and would not be analyzed in the future. With this amendment, no further blood collections were to be done for biomarker assessments. so far in pre and post fresh tumor biopsy specimens. The changes in HER2 were analyzed as the only PD marker in pre and post fresh tumor biopsy specimens. Also, the collection of paired pre- and post-treatment fresh tumor biopsies became optional; * In addition, a clarification was made in the imaging Section 7.4.1 of the Study Protocol "Radiological assessment of tumor" for consistency with the Section 5.1 of the Study Protocol (inclusion criteria). Following RECIST, measurable lesions which could not be assessed by CT/MRI (for example skin lesions) were acceptable as target lesions; * Another clarification was made in Table 7-4 of the Study Protocol: Summary of tumor assessment. The word 'scintigraphy' was replaced with 'scan'; * The amendment also updated the information about the starting dose for AUY922 at Cycle 1 Day 1. Based on the Dose Escalation Meeting held at the end of the Phase Ib part of the trial on 25-May,the RP2D for AUY922 in the Phase II part of the trial was 70 mg/m2.

Notes:

Interruptions (globally)

Were there any global interruptions to the trial? No

Limitations and caveats

None reported