Sponsor

Novartis

Generic Drug Name

AUY922

Therapeutic Area of Trial

Advanced or metastatic breast cancer

Approved Indication

Investigational

Protocol Number

CAUY922A2101

Title

A phase I dose escalation, multi-center, open-label study of AUY922 administered IV on a once-weekly schedule in adult patients with advanced solid malignancies including phase II expansion arms in patients with either Human epidermal growth factor receptor 2 (HER2) positive or estrogen receptor (ER) positive locally advanced or metastatic breast cancer.

Phase of Development

Phase I/II

Study Start/End Dates

Phase I: 23–Jul–2007 to 19–Nov–2010

Phase II: 01-Mar-2010 to 20-April-2012 (the study was terminated early on 18-Jul-2011)

Study Design/Methodology

The study was planned as a phase I trial with a phase II expansion arm. In phase I (dose escalation component), patients with advanced solid malignancies were enrolled into cohorts to establish the maximum tolerated dose (MTD), using an adaptive Bayesian logistic regression model (BLRM) with overdose control to guide the dose-escalation. The phase I part was also to include an expansion arm at the MTD which was designed to enroll additional advanced cancer patients (other than those with breast carcinoma) to assess safety events and tolerability. The MTD was not established and the highest dose tested, 70 mg/m^2, was selected as the recommended dose of AUY922 for phase II (open-label, dose expansion component). Data from this 70 mg/m^2 dose expansion cohort is reported together with the phase I dose escalation part of the study. The phase II component was permitted to commence enrolling, in parallel, patients with locally advanced or metastatic breast cancer only for treatment with AUY922 70 mg/m^2. The phase II part had two treatment arms: Patients with HER2 positive locally advanced or metastatic breast cancer who must have had progression of the disease on treatment with at least 8 weeks of a trastuzumab-containing regimen; and patients with ER positive locally advanced or metastatic breast cancer patients whose disease had progressed on at least one and up to three lines of standard sequence endocrine therapy. All breast cancer patients must have had progression of the disease with up to two lines of cytotoxic therapy. Both arms utilized a two-stage multinomial design. According to the number of patients with complete or partial response and the number of patients without stable disease ≥ 6 months (i.e. progressive disease or 'other') observed in this first stage, the statistical boundaries of the multinomial design were to be used to determine whether recruitment into stage 2 could commence (in which a further 20 patients were to be enrolled into each treatment arm), or whether one or both treatment arms were to be closed to recruitment. The phase II portion of the study was terminated during stage 1 because the recruitment target was unlikely to be met.

Centres

Phase I: Nine centres in three countries: Switzerland (1), United Kingdom (1), United States (7)

Phase II: Two centres in two countries: Netherlands (1), United Kingdom (1).

Publication

None.

Test Product (s), Dose(s), and Mode(s) of Administration

AUY922 was administered once weekly as a 1-hour i.v. infusion in 5% glucose/dextrose at a dose of 70 mg/m^2.

Statistical Methods

Data was analyzed by Novartis using statistical analysis software (SAS) version 9.2. Data from both trial centers was combined for the analysis, and data from the dose expansion parts was pooled with the dose escalation data for the same dose. Data was summarized with respect to demographic and baseline characteristics, efficacy observations and measurements, safety observations and measurements, and all relevant pharmacokinetic and pharmacodynamic measurements using descriptive statistics e.g. mean, median, standard deviation (SD), min, max for continuous data and frequency count and percentage for categorical data. Medical history was summarized by Medical Dictionary for Regulatory Activities (MedDRA) primary system organ class (SOC) and preferred term (PT). Prior and concomitant medications, significant non-drug therapies, and antineoplastic medications since discontinuation of study drug were summarized by World Health Organization Anatomical Therapeutic Chemical (WHO ATC) class. Adverse events were summarized by MedDRA primary SOC, and PT, and severity was assessed using common toxicity criteria for adverse events (CTCAE) version 3.0. Pharmacokinetic parameters of AUY922 and its metabolite BJP762 in blood were estimated by non-compartmental methods using WinNonlin® Pro (Version 5.2 - Pharsight, Mountain View, CA). Descriptive statistics (n, geometric and arithmetic means, SD, CV%, median and ranges) were presented for all primary (AUC_{inf}, AUC_{last}, C_{max}) and other ($t_{1/2}$, C_{trough}, t_{max}, CL, V_z) PK parameters. CL, and V_z were assessed for AUY922 only. The ratio of mean AUC and C_{max} of BJP762 to AUY922 were assessed.

Study Population: Inclusion/Exclusion Criteria and Demographics

Inclusion criteria

- **Dose-escalation and MTD dose expansion arm**: Patients with histologically confirmed, advanced malignant solid tumors whose disease had progressed on standard therapy or for whom no standard therapy existed
- **Breast cancer Phase II expansion arm only:**

a. **Female patients with HER2 positive** inoperable locally advanced or metastatic breast cancer must have:

- History of trastuzumab resistance, defined as either local or systemic disease progression on treatment with at least 8 weeks of a trastuzumab containing regimen
- Received up to 3 prior anti HER2 based regimens (i.e. trastuzumab and/or lapatinib in combination with other agents) for advanced disease
- Received up to 2 lines of cytotoxic therapy for advanced disease
- Patients who had developed metastases while receiving adjuvant or neo-adjuvant trastuzumab were eligible.

HER2 positive patients, tumor/s must demonstrate HER2 over-expression based on either:

- Immunohistochemistry (IHC) at the 3+ level, or
- IHC 2+ confirmed by fluorescence in-situ hybridization (FISH). Tumors tested by FISH must have been positive by the specific FISH assay for the amplification of HER2:

b. **Female patients with ER positive** inoperable locally advanced or metastatic breast cancer:

  - Whose disease had progressed on at least one and up to three lines of standard sequence endocrine therapy
  - Who had received up to two lines of cytotoxic therapy for advanced disease.

- All patients must have had at least one measurable lesion as defined by response evaluation in solid tumors (RECIST). Irradiated lesions are only evaluable for disease progression
- All patients must have had progressive disease before entering the study
- Patients who fulfilled the following criteria were eligible for Positron emission tomography (PET) assessments:

  Indications: tumor types expected to have a high [18F]- Fluorodeoxyglucose (FDG) uptake, such as breast, lung, Gastrointestinal stromal tumor (GIST), melanoma, and colorectal cancer

  - At least one lesion must have been measurable (> 2 cm)
  - To be eligible for follow-up scans, patients should have had uptake of the tracer in at least one lesion with a tumor-muscle ratio ≥ 2
  - Able to lie still and flat on the PET table
- Age ≥ 18 years
- World Health Organization (WHO) Performance Status of ≤ 2
- Life expectancy of ≥ 12 weeks
- Patients must have had the following laboratory values:
  - Absolute Neutrophil Count (ANC) ≥ 1.5 x 10^9/L
  - Hemoglobin (Hgb) ≥ 9 g/dL
  - Platelets ≥ 100 x 10^9/L
  - Potassium within normal limits or correctable with supplements
  - Total calcium (corrected for serum albumin) within normal limits or correctable with supplements

- Magnesium within normal limits or correctable with supplements
- Phosphorus within normal limits or correctable with supplements
- Aspartate aminotransferase (AST)/SGOT and alanine aminotransferase (ALT)/SGPT ≤ 2.5 x upper limit of normal (ULN) or ≤ 5.0 x ULN if liver metastases were present
- Serum bilirubin ≤ 1.5 x ULN
- Serum albumin ≥ 2.5g/dL
- Serum creatinine ≤ 1.5 x ULN or 24-hour clearance ≥ 50 mL/min
- Negative serum pregnancy test

- Able to sign informed consent and to comply with the protocol

Exclusion criteria

- Patients with known central nervous system (CNS) metastasis. Note: patients without clinical signs or symptoms of CNS involvement were not required to have a computed tomography (CT)/magnetic resonance imaging (MRI) of the brain
- Prior treatment with any HSP90 or histone deacetylase inhibitor compound with the following exception:
  - Patients with a diagnosis of GIST who had previously received and benefited from treatment with retaspimycin were eligible for the study (not applicable in the UK)
- Patients who received systemic anticancer treatment prior to the first dose of AUY922 within the following time frames:
  - Chemotherapy within 4 weeks
  - Wide-field radiotherapy within 4 weeks
  - Localized palliative radiotherapy within 2 weeks
  - Trastuzumab treatment within 4 weeks
  - Nitrosoureas, mitomycin, and monoclonal antibodies (except trastuzumab) within 6 weeks
  - Any continuous dosing (i.e., daily dosing, every-other-day dosing, Monday- Wednesday-Friday dosing, weekly etc.) of systemic anticancer treatment for which the recovery period is not known, or investigational drugs (i.e., targeted agents) within a duration of ≤ 5 half lives of the agent and their active metabolites (if any)
- Patients who had recovered from side effects of previous systemic anticancer therapy to less than Grade 2 CTCAE prior to the first dose of study treatment

- Treatment with therapeutic doses of sodium warfarin (Coumadin). Low doses of Coumadin (e.g., ≤ 2 mg/day for line patency) were permitted
- Unresolved diarrhea ≥ CTCAE Grade 2
- Patients who did not have an archival tumor sample available or were unwilling to have a fresh tumor sample collected at baseline
- Pregnant or lactating women
- Fertile women of childbearing potential (WCBP) not using adequate contraception (abstinence, oral contraceptives, intrauterine device, or barrier method of contraception in conjunction with spermicidal jelly) or surgically sterile. Male patients whose partners were WCBP, not using adequate contraception
- Acute or chronic liver disease
- Acute or chronic renal disease
- Other concurrent severe and/or uncontrolled medical conditions (e.g., uncontrolled diabetes, active or uncontrolled infection) that could cause unacceptable safety risks or compromise compliance with the protocol
- Cardiac exclusion criteria:
  - History (or family history) of long QT syndrome
  - Mean QTc ≥ 450 msec on screening ECG
  - History of clinically manifest ischemic heart disease including myocardial infarction, stable or unstable angina, coronary arteriography, or cardiac stress testing/imaging with findings consistent with coronary occlusion or infarction ≤ 6 months prior to study start
  - History of heart failure or left ventricular dysfunction (left ventricular ejection fraction [LVEF] ≤ 45%) by Multiple Gated Acquisition Scan (MUGA) or echocardiogram (ECHO)
  - Clinically significant ECG abnormalities including one or more of the following: left bundle branch block, right bundle branch block with left anterior hemiblock, ST segment elevations or depressions > 1 mm, or 2nd (Mobitz II) or 3rd degree atrioventricular block
  - History of atrial fibrillation, atrial flutter, or ventricular arrhythmias including ventricular tachycardia or Torsades de Pointes
  - Other clinically significant heart disease (e.g., congestive heart failure, uncontrolled hypertension, history of labile hypertension, or history of poor compliance with an antihypertensive regimen)
  - Clinically significant resting bradycardia (< 50 beats per minute)
  - Patients who are currently receiving treatment with any medication which has a relative risk of prolonging the QTcF interval or in-

ducing Torsades de Pointes and could not be switched or discontinued to an alternative drug prior to commencing AUY922 dosing
  - Obligate use of a cardiac pacemaker
- Known diagnosis of human immunodeficiency virus (HIV) infection (HIV testing is not mandatory)
- Patients with known disorders due to a deficiency in bilirubin glucuronidation (e.g., Gilbert's syndrome)
- Patients with a history of another primary malignancy that was clinically significant or required active intervention
- Patients unwilling or unable to comply with the protocol
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Participant Flow

Phase I

Patient disposition by treatment group (All patients) - Dose escalation and MTD expansion arm

	2 mg/m^2 N=3 n (%)	4 mg/m^2 N=4 n (%)	8 mg/m^2 N=4 n (%)	16 mg/m^2 N=7 n (%)	22 mg/m^2 N=12 n (%)	28 mg/m^2 N=8 n (%)	40 mg/m^2 N=16 n (%)	54 mg/m^2 N=19 n (%)	70 mg/m^2 N=28 n (%)	All patients N=101 n (%)
Patients Treated										
Treatment ended	3 (100.0)	4 (100.0)	4 (100.0)	7 (100.0)	12 (100.0)	8 (100.0)	16 (100.0)	19 (100.0)	28 (100.0)	101 (100.0)
Treatment ongoing	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
Primary reason for end of treatment										
Disease progression	2 (66.7)	2 (50.0)	4 (100.0)	7 (100.0)	9 (75.0)	7 (87.5)	13 (81.3)	15 (78.9)	22 (78.6)	81 (80.2)
Subject withdrew consent	1 (33.3)	1 (25.0)	0 (0.0)	0 (0.0)	1 (8.3)	0 (0.0)	1 (6.3)	2 (10.5)	4 (14.3)	10 (9.9)
Adverse event (s)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	1 (8.3)	1 (12.5)	2 (12.5)	2 (10.5)	1 (3.6)	7 (6.9)
Abnormal test procedure result (s)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	1 (8.3)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	1 (1.0)
Lost to follow-up	0 (0.0)	1 (25.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	1 (1.0)
New cancer therapy	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	1 (3.6)	1 (1.0)

Phase II

Patient disposition by treatment group (FAS)

Disposition Reason	**HER2 positive N=10 n (%)**	**ER positive N=6 n (%)**	**All Patients N=16 n (%)**
Patients treated			
Treatment ended	10 (100)	6 (100)	16 (100)
Primary reason for end of treatment			
Adverse Event (s)	0	1 (16.7)	1 (6.3)
Disease progression	10 (100)	5 (83.3)	15 (93.8)

Baseline Characteristics

Phase I

Demographic summary by treatment group (FAS) – Dose escalation and MTD expansion arm

		2 mg/m^2 N=3	**4 mg/m^2 N=4**	**8 mg/m^2 N=4**	**16 mg/m^2 N=7**	**22 mg/m^2 N=12**	**28 mg/m^2 N=8**	**40 mg/m^2 N=16**	**54 mg/m^2 N=19**	**70 mg/m^2 N=28**	**All patients N=101**
Age (years)	n	3	4	4	7	12	8	16	19	28	101
	Mean	58.33	57.75	58.75	54.14	61.17	54.38	52.81	59.37	57.25	57.08
	SD	3.786	15.650	13.426	10.854	8.397	16.561	10.938	13.259	10.076	11.461
	Median	60.00	58.50	61.50	50.00	61.00	60.00	52.50	63.00	55.00	57.00
	Min	54.0	41.0	41.0	42.0	48.0	25.0	28.0	23.0	35.0	23.0
	Max	61.0	73.0	71.0	70.0	80.0	72.0	73.0	79.0	73.0	80.0
Age group (years)	< 65	3 (100.0)	2 (50.0)	2 (50.0)	5 (71.4)	10 (83.3)	6 (75.0)	14 (87.5)	10 (52.6)	19 (67.9)	71 (70.3)
	≥ 65	0	2 (50.0)	2 (50.0)	2 (28.6)	2 (16.7)	2 (25.0)	2 (12.5)	9 (47.4)	9 (32.1)	30 (29.7)
Gender – n (%)	Male	0	2 (50.0)	3 (75.0)	3 (42.9)	8 (66.7)	4 (50.0)	6 (37.5)	6 (31.6)	9 (32.1)	41 (40.6)
	Female	3 (100.0)	2 (50.0)	1 (25.0)	4 (57.1)	4 (33.3)	4 (50.0)	10 (62.5)	13 (68.4)	19 (67.9)	60 (59.4)
Predominant Race – n (%)	Caucasian	3 (100.0)	2 (50.0)	4 (100.0)	6 (85.7)	9 (75.0)	7 (87.5)	14 (87.5)	15 (78.9)	22 (78.6)	82 (81.2)
	Black	0	0	0	0	3 (25.0)	1 (12.5)	2 (12.5)	2 (10.5)	4 (14.3)	12 (11.9)
	Asian	0	1 (25.0)	0	1 (14.3)	0	0	0	2 (10.5)	1 (3.6)	5 (5.0)

	Other	0	1 (25.0)	0	0	0	0	0	0	1 (3.6)	2 (2.0)
Ethnicity – n (%)	Hispanic/ Latino	0	1 (25.0)	1 (25.0)	1 (14.3)	3 (25.0)	2 (25.0)	5 (31.3)	8 (42.1)	7 (25.0)	28 (27.7)
	Chinese	0	0	0	0	0	0	0	0	1 (3.6)	1 (1.0)
	Japanese	0	0	0	1 (14.3)	0	0	0	1 (5.3)	0	2 (2.0)
	Mixed ethnicity	0	0	0	0	1 (8.3)	0	0	0	0	1 (1.0)
	Other	3 (100.0)	3 (75.0)	3 (75.0)	5 (71.4)	8 (66.7)	6 (75.0)	11 (68.8)	10 (52.6)	20 (71.4)	69 (68.3)
BMI (kg/m^2)	n	3	4	4	7	12	8	16	19	28	101
	Mean	37.47	27.50	22.25	21.91	24.13	26.59	25.66	25.72	26.63	25.86
	SD	14.511	8.828	2.473	3.159	2.970	6.171	3.178	6.523	6.110	6.046
	Median	44.30	25.35	22.70	21.90	23.90	24.20	25.65	25.60	26.10	24.70
	Min	20.8	19.5	18.9	18.0	19.6	21.5	19.6	14.8	17.9	14.8
	Max	47.3	39.8	24.7	27.2	30.1	39.6	31.1	41.9	45.7	47.3
BMI Group (kg/m^2)	≤ 25	1 (33.3)	2 (50.0)	4 (100.0)	6 (85.7)	9 (75.0)	5 (62.5)	7 (43.8)	9 (47.4)	11 (39.3)	54 (53.5)
	> 25 and < 30	0	1 (25.0)	0	1 (14.3)	2 (16.7)	1 (12.5)	7 (43.8)	7 (36.8)	12 (42.9)	31 (30.7)
	≥ 30	2 (66.7)	1 (25.0)	0	0	1 (8.3)	2 (25.0)	2 (12.5)	3 (15.8)	5 (17.9)	16 (15.8)
Body Surface Area (m^2)	N	3	4	4	7	12	8	16	19	28	101
	Mean	2.13	1.93	1.73	1.67	1.83	1.90	1.83	1.82	1.85	1.84
	SD	0.473	0.275	0.171	0.236	0.215	0.256	0.185	0.271	0.230	0.243
	Median	2.30	1.95	1.75	1.70	1.80	1.90	1.80	1.80	1.80	1.80
	Min	1.6	1.6	1.5	1.3	1.5	1.5	1.6	1.3	1.4	1.3
	Max	2.5	2.2	1.9	2.0	2.1	2.4	2.2	2.3	2.4	2.5
LVEF (%) at Baseline	n	3	4	4	7	12	8	16	19	28	101
	Mean	60.67	71.00	56.75	62.00	60.42	63.56	58.69	59.73	62.02	61.10
	SD	2.309	2.944	3.304	6.083	5.054	6.161	7.171	6.204	7.905	6.834
	Median	62.00	70.50	57.00	60.00	61.00	61.50	55.00	60.00	63.50	60.00
	Min	58.0	68.0	53.0	55.0	50.0	55.5	50.0	49.4	50.0	49.4
	Max	62.0	75.0	60.0	71.0	65.0	74.0	73.0	70.0	78.0	78.0
WHO Perfor-	0	0	0	3 (75.0)	4 (57.1)	4	3 (37.5)	8 (50.0)	7 (36.8)	11 (39.3)	40 (39.6)

mance Status					(3.3)					
	1	3 (100.0)	4 (100.0)	1 (25.0)	3 (42.9)	7 (58.3)	5 (62.5)	8 (50.0)	11 (57.9)	17 (60.7)	59 (58.4)
	2	0	0	0	0	1 (8.3)	0	0	1 (5.3)	0	2 (2.0)

Body Mass Index: BMI (kg/m^2) = weight (kg) / (height [m] **2)

Body Surface Area: BSA (m^2) = 234.94* (height [cm]**0.422)* (weight [kg] **0.515) / 10000

LVEF: left ventricular ejection fraction

WHO Performance Scale: 0 = no restrictions, 1 = only light work, 2 = only self care, 3 = limited self care, 4 = completely disabled, 5 = dead

Phase II

Demographic summary by treatment group (FAS)

	HER2 positive N=10	ER positive N=6	All patients N=16
Age (years)			
N	10	6	16
Mean	54.6	56.2	55.2
SD	10.54	9.04	9.72
Median	55.5	53.5	54.5
Min	39.0	45.0	39.0
Max	72.0	69.0	72.0
Age group (years)			
< 65	8 (80.0%)	4 (66.7%)	12 (75.0%)
>= 65	2 (20.0%)	2 (33.3%)	4 (25.0%)
Gender - n (%)			
Female	10 (100.0%)	6 (100.0%)	16 (100.0%)
Predominant Race - n(%)			
Caucasian	8 (80.0%)	6 (100.0%)	14 (87.5%)
Black	1 (10.0%)	0 (0.0%)	1 (6.3%)
Other	1 (10.0%)	0 (0.0%)	1 (6.3%)
Ethnicity – n (%)			
Other	10 (100.0%)	6 (100.0%)	16 (100.0%)

Body mass index (kg/m^2)			
N	10	6	16
Mean	28.1	25.5	27.1
SD	5.32	5.61	5.39
Median	27.4	24.1	26.6
Min	20.3	19.6	19.6
Max	38.4	35.1	38.4
BMI group (kg/m^2)			
<=25	3 (30.0%)	4 (66.7%)	7 (43.8%)
>25 - <30	5 (50.0%)	1 (16.7%)	6 (37.5%)
>=30	2 (20.0%)	1 (16.7%)	3 (18.8%)
Body surface area (m^2)			
N	10	6	16
Mean	1.9	1.8	1.8
SD	0.25	0.29	0.26
Median	1.8	1.8	1.8
Min	1.5	1.5	1.5
Max	2.3	2.3	2.3
LVEF (%) at baseline			
N	10	6	16
Mean	64.7	62.3	63.8
SD	11.07	6.80	9.50
Median	63.0	65.0	64.5
Min	52.0	49.0	49.0
Max	94.0	68.0	94.0
WHO Performance Status			
0	7 (70.0%)	5 (83.3%)	12 (75.0%)
1	3 (30.0%)	1 (16.7%)	4 (25.0%)
Body Mass Index: BMI [kg/m^2] = weight[kg] / (height[m]**^{2})			

Body Surface Area: BSA [m^2] = 234.94* (height[cm]**0.422)* (weight[kg]**0.515)/10000
LVEF = Left Ventricular Ejection Fraction

Outcome measures

Primary Outcome Result

Phase I

Prior and posterior probabilities of DLT (MTD Determining Analysis Set)

	2 mg/m^2	4 mg/m^2	8 mg/m^2	16 mg/m^2	22 mg/m^2	28 mg/m^2	40 mg/m^2	54 mg/m^2	70 mg/m^2	80 mg/m^2	90 mg/m^2	100 mg/m^2
Prior												
Probability of DLT												
0 – 0.16	0.879	0.834	0.757	0.603	0.473	0.376	0.295	0.260	0.243	0.236	0.231	0.227
0.16 – 0.33	0.048	0.061	0.087	0.128	0.146	0.132	0.097	0.072	0.054	0.047	0.043	0.039
0.33 - 1	0.073	0.104	0.156	0.270	0.381	0.491	0.608	0.668	0.703	0.717	0.726	0.734
Mean	0.071	0.096	0.139	0.226	0.306	0.389	0.496	0.564	0.608	0.627	0.642	0.654
SD	0.172	0.199	0.235	0.281	0.308	0.337	0.368	0.381	0.386	0.388	0.389	0.390
2.5 percentile	0.000	0.000	0.000	0.001	0.002	0.003	0.003	0.003	0.003	0.003	0.003	0.003
Median	0.005	0.010	0.023	0.084	0.186	0.318	0.526	0.675	0.771	0.811	0.840	0.862
97.5 percentile	0.709	0.795	0.868	0.926	0.951	0.976	0.997	1.000	1.000	1.000	1.000	1.000
Posterior following dose-escalation arm												
Probability of DLT												
0 – 0.16	1.000	1.000	1.000	1.000	0.999	0.995	0.950	0.696	0.421	0.326	0.268	0.230
0.16 – 0.33	0.000	0.000	0.000	0.000	0.001	0.005	0.050	0.302	0.518	0.530	0.499	0.456
0.33 - 1	0.000	0.000	0.000	0.000	0.000	0.000	0.000	0.002	0.061	0.144	0.233	0.315
Mean	0.011	0.014	0.021	0.036	0.048	0.063	0.094	0.135	0.185	0.216	0.246	0.273
SD	0.021	0.021	0.022	0.025	0.026	0.028	0.036	0.055	0.086	0.107	0.128	0.146
2.5 percentile	0.000	0.000	0.001	0.005	0.011	0.020	0.036	0.042	0.043	0.044	0.044	0.044
Median	0.002	0.005	0.013	0.030	0.044	0.058	0.090	0.131	0.176	0.204	0.230	0.255
97.5 percentile	0.078	0.080	0.084	0.097	0.111	0.129	0.176	0.257	0.381	0.460	0.537	0.606
Posterior following dose-escalation and MTD expansion arms												
Probability of DLT												

0 – 0.16	1.000	1.000	1.000	1.000	0.999	0.998	0.985	0.865	0.594	0.461	0.374	0.314
0.16 – 0.33	0.000	0.000	0.000	0.000	0.001	0.002	0.015	0.135	0.400	0.511	0.552	0.550
0.33 - 1	0.000	0.000	0.000	0.000	0.000	0.000	0.000	0.000	0.006	0.028	0.074	0.135
Mean	0.013	0.017	0.024	0.038	0.049	0.060	0.085	0.115	0.151	0.173	0.195	0.216
SD	0.023	0.024	0.024	0.025	0.025	0.026	0.030	0.040	0.059	0.073	0.088	0.103
2.5 percentile	0.000	0.000	0.001	0.005	0.011	0.019	0.036	0.046	0.049	0.049	0.050	0.050
Median	0.003	0.007	0.016	0.033	0.045	0.057	0.082	0.112	0.147	0.167	0.186	0.204
97.5 percentile	0.087	0.087	0.090	0.099	0.108	0.120	0.151	0.202	0.280	0.334	0.392	0.451

DLTs are as identified by the investigator on the end of Cycle 1 CRF

Phase II

Response assessment as per central radiological review (FAS)

	HER2 positive N=10 n (%)	ER positive N=6 n (%)
Clinical responders (CR or PR)	1 (10.0)	0 (0.0)
Non-responders with stable disease for at least 6 months (SD >= 6 months)	0 (0.0)	1 (16.7)
Progressive disease (PD) within 6 months from study start, or other	9 (90.0)	5 (83.3)

Best overall response on RECIST as per central radiological review, by treatment group (FAS)

	HER2 positive (N=10)	ER positive (N=6)	All patients (N=16)
Best overall response			
Complete response (CR)	0	0	0
Partial response (PR)	1 (10.0)	0	1 (6.3)
Stable disease (SD)	3 (30.0)	4 (66.7)	7 (43.8)
Progressive disease (PD)	5 (50.0)	1 (16.7)	6 (37.5)
Unknown	1 (10.0)	1 (16.7)	2 (12.5)
Overall response rate (CR or PR)	1 (10.0%)	0	1 (6.3%)
95% confidence interval *	[0.3%, 44.5%]	[0%, 45.9%]	[0.2%, 30.2%]
Disease Control (CR, PR or SD)	4 (40.0%)	4 (66.7%)	8 (50.0%)
95% confidence interval *	[12.2%, 73.8%]	[22.3%, 95.7%]	[24.7%, 75.3%]

* Exact binomial confidence intervals

Secondary Outcome Results

Phase I

Summary of primary PK parameters for blood AUY922 by treatment group (PK analysis subset) - Dose escalation and MTD expansion arms

Analyte: AUY922

Profile Day: Cycle 1 Day 1

Treatment group	Statistics	AUCinf (h.ng/mL)	AUClast (h.ng/mL)	C_{max} (ng/mL)
2 mg/m^2 (N=3)	n	3	3	3
	Mean (SD)	1755.7 (31.5)	1633.1 (34.3)	73.8 (9.9)
	CV% mean	1.8	2.1	13.4
	Geo-mean	1755.5	1632.9	73.4
	CV% geo-mean	1.8	2.1	13.6
	Median	1756.4	1626.9	74.0
	[Min; Max]	[1723.8; 1786.9]	[1602.4; 1670.1]	[63.8; 83.6]
4 mg/m^2 (N=4)	n	3	3	3
	Mean (SD)	2074.5 (834.1)	1958.2 (804.6)	116.8 (40.3)
	CV% mean	40.2	41.1	34.5
	Geo-mean	1938.0	1823.5	112.0
	CV% geo-mean	50.5	51.9	37.4
	Median	2438.6	2289.9	117.0
`	[Min; Max]	[1120.2; 2664.6]	[1040.8; 2544.0]	[76.5; 157.0]
8 mg/m^2 (N=4)	n	3	3	3
	Mean (SD)	4577.5 (1444.8)	3904.1 (1206.8)	162.3 (27.4)
	CV% mean	31.6	30.9	16.9
	Geo-mean	4437.8	3789.7	160.7

	CV% geo-mean	30.6	29.9	18.0
	Median	3979.6	3398.1	174.0
	[Min; Max]	[3527.7; 6225.3]	[3032.7; 5281.6]	[131.0; 182.0]
16 mg/m^2 (N=7)	n	7	7	7
	Mean (SD)	5381.9 (1690.1)	4333.3 (1254.5)	267.3 (49.9)
	CV% mean	31.4	29.0	18.7
	Geo-mean	5179.7	4194.1	263.0
	CV% geo-mean	29.9	27.5	19.9
	Median	4881.3	3882.1	264.0
	[Min; Max]	[3792.7; 8580.6]	[3258.5; 6578.6]	[194.0; 322.0]
22 mg/m^2 (N=12)	n	12	12	12
	Mean (SD)	8274.7 (2147.9)	6305.1 (1217.4)	349.7 (51.8)
	CV% mean	26.0	19.3	14.8
	Geo-mean	8029.1	6202.6	346.2
	CV% geo-mean	25.9	18.9	15.0
	Median	7887.9	6132.2	349.0
	[Min; Max]	[5570.6;11976.3]	[4808.0;8663.2]	[275.0;425.0]
28 mg/m^2 (N=8)	n	8	8	8
	Mean (SD)	7967.7 (1862.7)	6125.2 (1092.6)	523.3 (272.5)
	CV% mean	23.4	17.8	52.1
	Geo-mean	7778.3	6040.4	479.1
	CV% geo-mean	23.9	18.0	43.7
	Median	8183.0	5887.5	415.0
	[Min; Max]	[5480.8;11168.4]	[4915.5;7418.5]	[305.0;1150.0]
40 mg/m^2 (N=16)	n	16	16	16
	Mean (SD)	9261.5 (2199.2)	6739.1 (1952.6)	714.4 (249.7)
	CV% mean	23.7	29.0	35.0
	Geo-mean	9014.1	6326.7	683.8
	CV% geo-mean	24.6	44.3	29.6
	Median	9186.6	6823.2	685.5

	[Min; Max]	[6038.8;12820.9]	[1579.1;9426.5]	[454.0;1520.0]
54 mg/m^2 (N=18)	n	18	18	18
	Mean (SD)	14020.2 (5983.2)	9276.4 (2465.9)	922.8 (213.8)
	CV% mean	42.7	26.6	23.2
	Geo-mean	12986.0	8960.9	902.5
	CV% geo-mean	41.2	27.9	21.3
	Median	13755.1	9416.2	873.5
	[Min; Max]	[7775.2;30193.1]	[5768.8;14016.2]	[667.0;1440.0]
70 mg/m^2 (N=28)	n	28	28	28
	Mean (SD)	13456.7 (6200.1)	8386.1 (1653.0)	1277.9 (506.1)
	CV% mean	46.1	19.7	39.6
	Geo-mean	12555.1	8218.6	1193.6
	CV% geo-mean	36.6	21.2	38.3
	Median	12406.1	8622.5	1100.0
	[Min; Max]	[6417.5;40140.3]	[4586.9;11792.4]	[621.0;2510.0]

CV% = coefficient of variation (%) = sd/mean*100
CV% geo-mean = sqrt (exp [variance for log transformed data] -1) *100

Summary of primary PK parameters for blood BJP762 by treatment group (PK analysis subset) - Dose escalation and MTD expansion arms

Analyte: BJP762

Profile Day: Cycle 1 Day 1

Treatment group	Statistics	AUCinf (h.ng/mL)	AUClast (h.ng/mL)	C_{max} (ng/mL)
2 mg/m^2 (N=3)	n	3	3	3
	Mean (SD)	189.9 (145.2)	154.5 (108.8)	26.9 (7.1)
	CV% mean	76.5	70.4	26.3
	Geo-mean	159.0	133.1	26.3
	CV% geo-mean	79.9	71.8	26.6
	Median	110.4	92.2	25.7

	[Min; Max]	[101.9;357.6]	[91.2;280.1]	[20.5;34.5]
4 mg/m^2 (N=4)	n	3	3	3
	Mean (SD)	290.5 (170.1)	247.6 (155.9)	66.0 (31.2)
	CV% mean	58.6	62.9	47.3
	Geo-mean	242.6	200.3	59.8
	CV% geo-mean	97.1	109.8	63.5
	Median	375.1	300.6	77.5
	[Min; Max]	[94.7;401.8]	[72.2;370.1]	[30.7;89.9]
8 mg/m^2 (N=4)	n	3	3	3
	Mean (SD)	579.6 (210.3)	525.3 (202.1)	102.2 (28.2)
	CV% mean	36.3	38.5	27.6
	Geo-mean	549.7	496.0	99.3
	CV% geo-mean	43.5	45.1	31.4
	Median	658.0	562.6	117.0
	[Min; Max]	[341.5;739.5]	[307.2;706.2]	[69.7;120.0]
16 mg/m^2 (N=7)	n	7	7	7
	Mean (SD)	1245.3 (908.1)	1128.4 (809.8)	245.7 (167.5)
	CV% mean	72.9	71.8	68.2
	Geo-mean	984.7	905.7	198.6
	CV% geo-mean	85.6	81.3	83.1
	Median	774.3	714.9	161.0
	[Min; Max]	[412.7;2573.6]	[391.4;2393.1]	[67.0;539.0]
22 mg/m^2 (N=12)	n	12	12	12
	Mean (SD)	3017.7 (2606.4)	2830.7 (2395.1)	542.1 (454.7)
	CV% mean	86.4	84.6	83.9
	Geo-mean	2234.9	2099.7	422.2
	CV% geo-mean	97.1	98.1	85.4
	Median	2017.0	1888.3	461.0
	[Min; Max]	[523.0;9877.7]	[459.5;9019.6]	[99.7;1860.0]

28 mg/m^2 (N=8)	n	8	8	8
	Mean (SD)	3054.6 (3623.8)	2984.9 (3609.1)	523.6 (352.0)
	CV% mean	118.6	120.9	67.2
	Geo-mean	2002.3	1924.7	450.8
	CV% geo-mean	110.5	113.4	59.2
	Median	1281.1	1165.6	371.0
	[Min; Max]	[918.3;11533.2]	[887.5;11431.1]	[246.0;1310.0]
40 mg/m^2 (N=16)	n	16	16	16
	Mean (SD)	6061.9 (4655.3)	5809.8 (4527.8)	946.5 (619.2)
	CV% mean	76.8	77.9	65.4
	Geo-mean	4710.1	4395.3	799.1
	CV% geo-mean	83.2	91.9	63.6
	Median	3934.3	3786.9	700.5
	[Min; Max]	[1522.6;17643.4]	[1106.0;16609.5]	[313.0;2520.0]
54 mg/m^2 (N=18)	n	18	18	18
	Mean (SD)	6295.9 (4129.9)	6074.7 (4011.6)	1308.1 (734.4)
	CV% mean	65.6	66.0	56.1
	Geo-mean	5273.1	5067.9	1122.1
	CV% geo-mean	65.8	66.9	62.9
	Median	4973.9	4719.4	1120.0
	[Min; Max]	[2237.0;15266.8]	[2032.7;14791.2]	[500.0;2820.0]
70 mg/m^2 (N=28)	n	28	28	28
	Mean (SD)	7979.6 (8238.4)	7768.6 (8075.2)	1466.9 (1000.3)
	CV% mean	103.2	103.9	68.2
	Geo-mean	5262.3	5110.8	1192.2
	CV% geo-mean	110.4	110.5	71.5
	Median	4275.9	4008.5	1005.0
	[Min; Max]	[1556.4;28968.1]	[1482.6;28645.8]	[505.0;3710.0]

CV% = coefficient of variation (%) = sd/mean*100
CV% geo-mean = sqrt (exp [variance for log transformed data] -1) *100

PK-QT analysis and QT prolongation assessment: Following end of infusion, QTcF tended to decrease, followed by a large increase at 24 hours post-infusion. This pattern was observed repeatedly in the higher dose groups and on three profile days. The 24-hour increase in QTcF showed dose dependancy. No direct concentration-QT effect was demonstrated.

Phase II

Summary statistics for sSUVmax as per central radiological review, by imaging method and treatment group (FAS)

sSUVmax		HER2 Positive N=10	HER2 Positive N=6	All Patients N=16
% change from Baseline at Cycle 2 Day 1	n	6	3	9
	Mean	-14.4	-9.4	-12.7
	SD	21.32	16.02	18.83
	Median	-11.6	-13.8	-13.1
	Minimum	-45.4	-22.7	-45.4
	Maximum	14.4	8.4	14.4
	90% CI – LCL	-32.0	-36.4	-24.4
	90% CI – UCL	3.1	17.6	-1.1
% change from Baseline at Cycle 3 Day 1	N	5	4	9
	Mean	-17.0	-20.4	-18.5
	SD	35.35	12.68	26.24
	Median	-35.6	-17.0	-19.5
	Minimum	-46.9	-38.3	-46.9
	Maximum	39.5	-9.2	39.5
	90% CI – LCL	-50.7	-35.3	-34.8
	90% CI – UCL	16.7	-5.4	-2.2

Summary of primary PK parameters for blood AUY922 and BJP762 by treatment group (PK analysis subset)

Treatment group	Statistics	AUCinf (h.ng/mL)	AUClast (h.ng/mL)	Cmax (ng/mL)
Analyte: AUY922 Profile day: Cycle 1 Day 1				

HER2 positive (N=10)	n	10	10	10
	Mean (SD)	10853 (3732)	7698 (2507)	903 (223)
	CV% mean	34.4	32.6	24.7
	Geo-mean	10349	7359	870
	CV% geo-mean	32.5	32.2	32.7
	Median	9948	7135	939
	[Min; Max]	[7197;18078]	[4251;12800]	[380;1190]
ER positive (N=6)	n	6	6	6
	Mean (SD)	19940 (15995)	9874 (2553)	1306(521)
	CV% mean	80.2	25.9	39.9
	Geo-mean	16713	9635	1238
	CV% geo-mean	63.3	23.8	35.2
	Median	13535	8627	1205
	[Min; Max]	[11106;52286]	[8089;14506]	[864;2320]
Analyte: BJP762 **Profile day: Cycle 1 Day 1**				
HER2 positive (N=10)	n	10	10	10
	Mean (SD)	4584 (1952)	4514 (1955)	1090 (518)
	CV% mean	42.6	43.3	47.5
	Geo-mean	4177	4098	986
	CV% geo-mean	49.9	51.1	50.8
	Median	4352	4317	1063
	[Min; Max]	[1836;7245]	[1818;7204]	[415;2200]
ER positive (N=6)	n	6	6	6
	Mean (SD)	13848 (21757)	13387 (20979)	1620(1786)
	CV% mean	157	157	110
	Geo-mean	7156	6954	1167
	CV% geo-mean	149	148	92.0
	Median	4862	4756	964

	[Min; Max]	[2963;58107]	[2885;56069]	[610;5230]

CV% = coefficient of variation (%) = sd/mean*100
CV% geo-mean = sqrt (exp (variance for log transformed data)-1)*100

Blood biomarkers: (HSP70 levels in PMMCs): the mean maximum % change from baseline for HSP70 in Cycle 1, Week 1 was 493.0% in the HER2+ arm and 518.5% in the ER+ arm.

Safety Results

Adverse Events by System Organ Class

Phase I

Incidence of AEs regardless of causality by primary system organ class and treatment group (Safety set) – Dose escalation and MTD expansion arm

Primary system organ class	2 mg/m^2 N=3 n (%)	4 mg/m^2 N=4 n (%)	8 mg/m^2 N=4 n (%)	16 mg/m^2 N=7 n (%)	22 mg/m^2 N=12 n (%)	28 mg/m^2 N=8 n (%)	40 mg/m^2 N=16 n (%)	54 mg/m^2 N=19 n (%)	70 mg/m^2 N=28 n (%)	All patients N=101 n (%)
Any primary system organ class	2 (66.7)	4 (100.0)	4 (100.0)	7 (100.0)	12 (100.0)	8 (100.0)	15 (93.8)	19 (100.0)	28 (100.0)	99 (98.0)
Gastrointestinal disorders	2 (66.7)	1 (25.0)	3 (75.0)	5 (71.4)	8 (66.7)	8 (100.0)	15 (93.8)	17 (89.5)	27 (96.4)	86 (85.1)
General disorders and administration site conditions	1 (33.3)	4 (100.0)	3 (75.0)	6 (85.7)	8 (66.7)	8 (100.0)	11 (68.8)	15 (78.9)	19 (67.9)	75 (74.3)
Metabolism and nutrition disorders	1 (33.3)	2 (50.0)	1 (25.0)	4 (57.1)	9 (75.0)	2 (25.0)	11 (68.8)	14 (73.7)	11 (39.3)	55 (54.5)
Musculoskeletal and connective tissue disorders	1 (33.3)	1 (25.0)	3 (75.0)	2 (28.6)	5 (41.7)	3 (37.5)	6 (37.5)	10 (52.6)	16 (57.1)	47 (46.5)
Eye disorders	0 (0.0)	0 (0.0)	0 (0.0)	1 (14.3)	0 (0.0)	0 (0.0)	4 (25.0)	15 (78.9)	24 (85.7)	44 (43.6)
Nervous system disorders	0 (0.0)	2 (50.0)	2 (50.0)	4 (57.1)	4 (33.3)	3 (37.5)	4 (25.0)	7 (36.8)	14 (50.0)	40 (39.6)
Respiratory, thoracic and mediastinal disorders	2 (66.7)	2 (50.0)	2 (50.0)	4 (57.1)	3 (25.0)	3 (37.5)	3 (18.8)	9 (47.4)	10 (35.7)	38 (37.6)
Investigations	1 (33.3)	0 (0.0)	2 (50.0)	1 (14.3)	4 (33.3)	2 (25.0)	5 (31.3)	9 (47.4)	9 (32.1)	33 (32.7)
Blood and lymphatic	0 (0.0)	0 (0.0)	1 (25.0)	2 (28.6)	1 (8.3)	2 (25.0)	7 (43.8)	7 (36.8)	9 (32.1)	29 (28.7)

system disorders										
Psychiatric disorders	0 (0.0)	1 (25.0)	0 (0.0)	3 (42.9)	2 (16.7)	3 (37.5)	4 (25.0)	4 (21.1)	8 (28.6)	25 (24.8)
Infections and infestations	1 (33.3)	0 (0.0)	0 (0.0)	1 (14.3)	0 (0.0)	5 (62.5)	4 (25.0)	4 (21.1)	6 (21.4)	21 (20.8)
Skin and subcutaneous tissue disorders	0 (0.0)	1 (25.0)	1 (25.0)	3 (42.9)	1 (8.3)	2 (25.0)	3 (18.8)	4 (21.1)	4 (14.3)	19 (18.8)
Cardiac disorders	0 (0.0)	0 (0.0)	0 (0.0)	1 (14.3)	2 (16.7)	2 (25.0)	4 (25.0)	3 (15.8)	4 (14.3)	16 (15.8)
Vascular disorders	0 (0.0)	1 (25.0)	0 (0.0)	2 (28.6)	1 (8.3)	1 (12.5)	1 (6.3)	5 (26.3)	2 (7.1)	13 (12.9)
Neoplasms benign, malignant and unspecified (incl cysts and polyps)	0 (0.0)	0 (0.0)	0 (0.0)	1 (14.3)	2 (16.7)	0 (0.0)	2 (12.5)	1 (5.3)	4 (14.3)	10 (9.9)
Injury, poisoning and procedural complications	0 (0.0)	1 (25.0)	0 (0.0)	1 (14.3)	1 (8.3)	0 (0.0)	1 (6.3)	1 (5.3)	2 (7.1)	7 (6.9)
Renal and urinary disorders	0 (0.0)	0 (0.0)	0 (0.0)	3 (42.9)	1 (8.3)	1 (12.5)	1 (6.3)	0 (0.0)	0 (0.0)	6 (5.9)
Hepatobiliary disorders	0 (0.0)	0 (0.0)	0 (0.0)	1 (14.3)	2 (16.7)	0 (0.0)	0 (0.0)	0 (0.0)	2 (7.1)	5 (5.0)
Reproductive system and breast disorders	0 (0.0)	1 (25.0)	0 (0.0)	0 (0.0)	0 (0.0)	1 (12.5)	1 (6.3)	0 (0.0)	1 (3.6)	4 (4.0)
Ear and labyrinth disorders	1 (33.3)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	1 (12.5)	1 (6.3)	0 (0.0)	0 (0.0)	3 (3.0)
Immune system disorders	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	1 (5.3)	0 (0.0)	1 (1.0)

AEs by SOC are presented in descending order of frequency in 'All patients' group.

Phase II

Incidence of AEs by primary system organ class and treatment group regardless of causality (Safety set)

Primary system organ class	HER2 positive N=10 n (%)	ER positive N=6 n (%)	All patients N=16 n (%)
Patients with at least one AE	10 (100.0)	6 (100.0)	16 (100.0)

Gastrointestinal disorders	10 (100.0)	6 (100.0)	16 (100.0)
Eye disorders	8 (80.0)	6 (100.0)	14 (87.5)
General disorders and administration	7 (70.0)	6 (100.0)	13 (81.3)
site conditions			
Musculoskeletal and connective tissue	6 (60.0)	3 (50.0)	9 (56.3)
disorders			
Nervous system disorders	5 (50.0)	4 (66.7)	9 (56.3)
Infections and infestations	5 (50.0)	2 (33.3)	7 (43.8)
Investigations	6 (60.0)	1 (16.7)	7 (43.8)
Metabolism and nutrition disorders	3 (30.0)	2 (33.3)	5 (31.3)
Neoplasms benign, malignant and	4 (40.0)	1 (16.7)	5 (31.3)
unspecified (incl cysts and polyps)			
Skin and subcutaneous tissue disorders	2 (20.0)	3 (50.0)	5 (31.3)
Blood and lymphatic system disorders	3 (30.0)	1 (16.7)	4 (25.0)
Respiratory, thoracic and mediastinal	3 (30.0)	1 (16.7)	4 (25.0)
disorders			
Injury, poisoning and procedural	2 (20.0)	1 (16.7)	3 (18.8)
complications			
Psychiatric disorders	0 (0.0)	2 (33.3)	2 (12.5)
Vascular disorders	1 (10.0)	1 (16.7)	2 (12.5)
Ear and labyrinth disorders	0 (0.0)	1 (16.7)	1 (6.3)
Hepatobiliary disorders	0 (0.0)	1 (16.7)	1 (6.3)
Renal and urinary disorders	0 (0.0)	1 (16.7)	1 (6.3)
AEs by SOC are presented in descending order of frequency in ‘All patients’ group.			

Most Frequently Reported AEs Overall by Preferred Term n (%)

Phase I

Incidence of AEs regardless of causality (occurring in at least 10 percent of patients overall) by preferred term and treatment group (Safety set) – Dose escalation and MTD expansion arm

Primary system organ class	2 mg/m^2 N=3 n (%)	4 mg/m^2 N=4 n (%)	8 mg/m^2 N=4 n (%)	16 mg/m^2 N=7 n (%)	22 mg/m^2 N=12 n (%)	28 mg/m^2 N=8 n (%)	40 mg/m^2 N=16 n (%)	54 mg/m^2 N=19 n (%)	70 mg/m^2 N=28 n (%)	All patients N=101 n (%)
Any preferred term	2 (66.7)	4 (100.0)	4 (100.0)	7 (100.0)	12 (100.0)	8 (100.0)	15 (93.8)	19 (100.0)	28 (100.0)	99 (98.0)
Diarrhoea	2 (66.7)	0 (0.0)	3 (75.0)	3 (42.9)	4 (33.3)	5 (62.5)	13 (81.3)	15 (78.9)	24 (85.7)	69 (68.3)
Nausea	1 (33.3)	1 (25.0)	2 (50.0)	5 (71.4)	4 (33.3)	7 (87.5)	10 (62.5)	10 (52.6)	14 (50.0)	54 (53.5)
Fatigue	0 (0.0)	2 (50.0)	2 (50.0)	3 (42.9)	4 (33.3)	4 (50.0)	6 (37.5)	8 (42.1)	13 (46.4)	42 (41.6)
Vomiting	2 (66.7)	1 (25.0)	1 (25.0)	2 (28.6)	3 (25.0)	2 (25.0)	7 (43.8)	7 (36.8)	9 (32.1)	34 (33.7)
Decreased appetite	0 (0.0)	1 (25.0)	1 (25.0)	3 (42.9)	3 (25.0)	2 (25.0)	6 (37.5)	8 (42.1)	8 (28.6)	32 (31.7)
Asthenia	0 (0.0)	0 (0.0)	1 (25.0)	1 (14.3)	6 (50.0)	4 (50.0)	4 (25.0)	8 (42.1)	7 (25.0)	31 (30.7)
Abdominal pain	1 (33.3)	0 (0.0)	1 (25.0)	0 (0.0)	1 (8.3)	3 (37.5)	2 (12.5)	8 (42.1)	8 (28.6)	24 (23.8)
Anaemia	0 (0.0)	0 (0.0)	1 (25.0)	2 (28.6)	1 (8.3)	2 (25.0)	5 (31.3)	5 (26.3)	8 (28.6)	24 (23.8)
Night blindness	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	2 (12.5)	9 (47.4)	12 (42.9)	23 (22.8)
Dyspnoea	0 (0.0)	1 (25.0)	1 (25.0)	2 (28.6)	2 (16.7)	3 (37.5)	3 (18.8)	4 (21.1)	3 (10.7)	19 (18.8)
Pyrexia	0 (0.0)	1 (25.0)	1 (25.0)	2 (28.6)	1 (8.3)	1 (12.5)	2 (12.5)	4 (21.1)	7 (25.0)	19 (18.8)
Constipation	0 (0.0)	0 (0.0)	0 (0.0)	1 (14.3)	1 (8.3)	0 (0.0)	5 (31.3)	5 (26.3)	6 (21.4)	18 (17.8)
Headache	0 (0.0)	0 (0.0)	1 (25.0)	2 (28.6)	2 (16.7)	1 (12.5)	2 (12.5)	3 (15.8)	7 (25.0)	18 (17.8)
Hypokalaemia	0 (0.0)	1 (25.0)	0 (0.0)	2 (28.6)	2 (16.7)	0 (0.0)	1 (6.3)	7 (36.8)	5 (17.9)	18 (17.8)
Weight decreased	1 (33.3)	0 (0.0)	1 (25.0)	0 (0.0)	2 (16.7)	1 (12.5)	3 (18.8)	6 (31.6)	4 (14.3)	18 (17.8)
Back pain	0 (0.0)	0 (0.0)	2 (50.0)	0 (0.0)	2 (16.7)	0 (0.0)	3 (18.8)	4 (21.1)	4 (14.3)	15 (14.9)
Cough	1 (33.3)	1 (25.0)	0 (0.0)	3 (42.9)	1 (8.3)	1 (12.5)	1 (6.3)	2 (10.5)	5 (17.9)	15 (14.9)
Photopsia	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	1 (6.3)	5 (26.3)	8 (28.6)	14 (13.9)
Vision blurred	0 (0.0)	0 (0.0)	0 (0.0)	1 (14.3)	0 (0.0)	0 (0.0)	2 (12.5)	3 (15.8)	8 (28.6)	14 (13.9)
Arthralgia	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	1 (8.3)	1 (12.5)	1 (6.3)	1 (5.3)	8 (28.6)	12 (11.9)
Hypomagnesaemia	0 (0.0)	1 (25.0)	0 (0.0)	1 (14.3)	4 (33.3)	1 (12.5)	2 (12.5)	1 (5.3)	2 (7.1)	12 (11.9)

Visual impairment	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	2 (10.5)	10 (35.7)	12 (11.9)

Preferred terms are sorted by descending frequency in the 'All patients' column. Includes all adverse events on study and up to 28 days after last dose.

Phase II

Incidence of AEs (occurring in at least 10 percent of patients overall) by preferred term and treatment group regardless of causality (Safety set)

Preferred term	HER2 positive N=10 n (%)	ER positive N=6 n (%)	All patients N=16 n (%)
Patients with at least one AE	10 (100.0)	6 (100.0)	16 (100.0)
Diarrhoea	10 (100.0)	6 (100.0)	16 (100.0)
Fatigue	7 (70.0)	6 (100.0)	13 (81.3)
Night blindness	6 (60.0)	5 (83.3)	11 (68.8)
Nausea	6 (60.0)	4 (66.7)	10 (62.5)
Vision blurred	3 (30.0)	5 (83.3)	8 (50.0)
Headache	3 (30.0)	4 (66.7)	7 (43.8)
Photopsia	3 (30.0)	4 (66.7)	7 (43.8)
Decreased appetite	3 (30.0)	2 (33.3)	5 (31.3)
Vomiting	4 (40.0)	1 (16.7)	5 (31.3)
Back pain	1 (10.0)	3 (50.0)	4 (25.0)
Rash	2 (20.0)	2 (33.3)	4 (25.0)
Abdominal pain	3 (30.0)	0 (0.0)	3 (18.8)
Anaemia	3 (30.0)	0 (0.0)	3 (18.8)
Dry mouth	2 (20.0)	1 (16.7)	3 (18.8)
Metastases to central nervous system	2 (20.0)	1 (16.7)	3 (18.8)
Non-cardiac chest pain	1 (10.0)	2 (33.3)	3 (18.8)
Pain in extremity	3 (30.0)	0 (0.0)	3 (18.8)
Alanine aminotransferase increased	2 (20.0)	0 (0.0)	2 (12.5)
Constipation	0 (0.0)	2 (33.3)	2 (12.5)
Cough	1 (10.0)	1 (16.7)	2 (12.5)

Halo vision	2 (20.0)	0 (0.0)	2 (12.5)
Muscle spasms	1 (10.0)	1 (16.7)	2 (12.5)
Pain of skin	0 (0.0)	2 (33.3)	2 (12.5)
Photophobia	1 (10.0)	1 (16.7)	2 (12.5)
Retinogram abnormal	2 (20.0)	0 (0.0)	2 (12.5)
Urinary tract infection	1 (10.0)	1 (16.7)	2 (12.5)
Weight decreased	1 (10.0)	1 (16.7)	2 (12.5)

Preferred term are sorted by descending frequency in the 'All patients' column
Includes all adverse events on study and up to 28 days after last dose

Serious Adverse Events and Deaths

Phase I

Number of patients who died or experienced other serious or clinically significant adverse events (Safety set) – Dose escalation and MTD expansion arm

	4 mg/m^2 (N=4) n (%)	16 mg/m^2 (N=7) n (%)	22 mg/m^2 (N=12) n (%)	28 mg/m^2 (N=8) n (%)	40 mg/m^2 (N=16) n (%)	54 mg/m^2 (N=19) n (%)	70 mg/m^2 (N=28) n (%)	All patients (N=101) n (%)
Patients with serious or significant AEs								
Deaths on study	1 (25.0)	0 (0.0)	2 (16.7)	0 (0.0)	1 (6.3)	1 (5.3)	1 (3.6)	6 (5.9)
SAEs	1 (25.0)	2 (28.6)	6 (50.0)	2 (25.0)	5 (31.3)	5 (26.3)	11 (39.3)	32 (31.7)
Discontinued due to AEs	0 (0.0)	0 (0.0)	2 (16.7)	1 (12.5)	1 (6.3)	2 (10.5)	2 (7.1)	8 (7.9)
Discontinued due to SAEs	0 (0.0)	0 (0.0)	2 (16.7)	1 (12.5)	1 (6.3)	1 (5.3)	0 (0.0)	5 (5.0)

Subjects discontinuing due to SAEs are also counted in the category of discontinuing due to AEs. Includes adverse events on study and up to 28 days after last dose

Phase II

Number of patients who died or experienced other serious or clinically significant adverse events regardless of causality (Safety set)

Patients with serious or significant AEs	HER2 positive N=10 n (%)	ER positive N=6 n (%)	All patients N=16 n (%)
Deaths on study	0 (0.0)	0 (0.0)	0 (0.0)
SAEs	4 (40.0)	2 (33.3)	6 (37.5)
Discontinued due to AEs	0 (0.0)	1 (16.7)	1 (6.3)
Discontinued due to SAEs	0 (0.0)	0 (0.0)	0 (0.0)
Subjects discontinuing due to SAEs are not also counted in the category of discontinuing due to AEs			

Other Relevant Findings

None

Date of Clinical Trial Report

Phase I: 23-Feb-2012

Phase II: 18-Dec-2012

Date of amendment :10-Apr-2013

Date Inclusion on Novartis Clinical Trial Results Database

25-Mar-2013

Date of Latest Update

17-Apr-2013 (change in aLPLV date form 26-Mar-2012 to 20-Apr-2012)