Sponsor

Novartis

Generic Drug Name

AUY922

Trial Indication(s)

Locally advanced or metastatic human epidermal growth factor (HER)2-positive breast cancer that has progressed after or during at least one Trastuzumab-containing regimen.

Protocol Number

CAUY922A2109

Protocol Title

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 positive breast cancer that has progressed after or during one Trastuzumab-containing regimen.

Clinical Trial Phase

Phase Ib/II

Phase of Drug Development

Phase II

Study Start/End Dates

Study initiation date: 01-Sep-2010 (first patient first visit)

Study completion date: 11-Oct-2013 (last patient last visit)

Reason for Termination (If applicable)

Not applicable.

Study Design/Methodology

This open-label, multicenter, Phase Ib/II trial evaluated the efficacy, safety, tolerability, biologic activity, and PK profile of AUY922 in combination with trastuzumab in patients with locally advanced or metastatic HER2 over-expressing breast cancer that had progressed after or during at least one trastuzumab-containing regimen. The study was composed of a dose-escalation part with AUY922 administered in combination with trastuzumab (Phase Ib), followed by a dose expansion part (Phase II) using the same regimen. A two-parameter

Bayesian logistic regression model (BLRM) employing the escalation with overdose control (EWOC) principle (Babb et al 1998, Neuenschwander et al 2008) was used during the dose-escalation phase to guide dose level selection and determination of the MTD/RP2D. Cohorts of patients received escalating doses of AUY922 in combination with the standard trastuzumab therapy until the MTD was reached. Each cohort consisted of newly enrolled patients. No randomization was performed, and the allocation of patients to dose levels was performed by the Sponsor.

Centers

France (1), Germany (2), Italy (2), Spain (3), Singapore (1), UK (4), USA (1).

Publication

None

Objectives:

Primary:

Phase Ib: To define the maximum tolerated dose (MTD) and/or recommended phase two dose (RP2D) of AUY922 in combination with trastuzumab when administered i.v. on a once weekly schedule to adult patients with advanced or metastatic human epidermal growth factor receptor (HER)2-positive breast cancers.

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.

Secondary:

Phase Ib:

• To characterize the safety and tolerability of AUY922 when administered in combination with trastuzumab;

• To characterize the pharmacokinetic (PK) profile of AUY922 and its metabolite BJP762 when given in combination with trastuzumab;

• To evaluate preliminary anti-tumor activity (tumor response, response rate), as defined in Response Evaluation Criteria In Solid Tumors (RECIST) Version 1.0 guidelines;

• To assess the pharmacodynamic (PD) effect of AUY922 in combination with trastuzumab by determining heat shock protein (HSP)70 levels as a measure of HSP90 target inhibition in a surrogate tissue (peripheral blood mononuclear cells [PBMCs]).

Phase II:

• To characterize the safety and tolerability of the combination at the RP2D;

• To characterize the PK profile of AUY922 and its metabolite BJP762 when given in combination with trastuzumab; to assess the efficacy at the RP2D (e.g. Progression Free Survival [PFS] and Overall Survival [OS]);

• To investigate the PD effect of AUY922 in combination with trastuzumab on HSP90 client protein HER 2 in pre and post-therapy tumor tissue pairs, pre vs. post treatment.

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

AUY922 was to be administered in combination with trastuzumab.

AUY922 liquid in ampoule (LIAM): administered as once weekly intravenous infusion (over 1 hour) at a starting dose of 55 mg/m2 in Phase Ib and 70 mg/m2 in Phase II using a central line or via peripheral vein.

Trastuzumab (Herceptin®): administered once weekly at the standard dose of 2 mg/kg over 30 minutes (or 4 mg/kg over 90 minutes if a loading dose was necessary at Cycle 1 Day 1).

Statistical Methods

Analysis of primary variables:

Phase Ib: Estimation of the MTD in the dose-escalation phase of the study was based upon the estimation of the probability of DLT in Cycle 1 for patients in the Dose-Determining Set. A DLT was defined as an 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.

An adaptive BLRM guided by the EWOC principle was used in the dose-escalation. An adaptive two parameter BLRM was used for dose escalation of AUY922 in combination with the standard trastuzumab treatment (2 mg/kg once weekly), since the assumption held that a zero dose of AUY922 corresponded to a zero probability of DLT.

Phase II: The primary analysis was based on tumor response assessed by the investigators according to RECIST Version 1.0, using the FAS.

A Bayesian approach was used to estimate the ORR and to provide inferential statements based on the uncertainty of this quantity. The ORR estimate depended on number of patients with a confirmed best overall response of complete response (CR) or partial response (PR).

PFS and OS were presented in summary tables using a Kaplan-Meier curve. Summary statistics from the Kaplan-Meier distribution were determined, including the median and estimates at 4 and 6 months for PFS and at 8 months for OS. These statistics were provided as point estimates with 95% confidence intervals.

Analysis of secondary variables:

Efficacy (Phase II): For the Phase II part, investigator assessments of PFS using the FAS and PPS, as well as central reads using FAS, were presented in a Kaplan-Meier curve and summary statistics, including the median and estimates at 4 and 6 months for PFS, each with

the corresponding 95% CIs. Overall survival was presented in a Kaplan-Meier curve and summary statistics, including the median and estimate at 8 months for OS, each with the corresponding 95% CIs.

Safety (Phase Ib): All safety analyses were presented by treatment group and based on the Safety Set except for summaries of dose limiting toxicities (DLTs) for which the MTD Determining Analysis Set was used.

(Phase II): Safety assessments consisted of monitoring by investigators and recording all AEs, SAEs, and the regular monitoring of laboratory evaluations, physical examination, vital signs, weight, performance status evaluation, ECGs and repeat cardiac assessments, cardiac enzymes, echocardiogram and or MUGA scan (if clinically indicated).

Adverse events were collected after start of treatment (on or after study Day 1) and starting no later than 28 days after study treatment discontinuation. Any AEs collected before start of treatment were recorded separately under Relevant Medical History/Current Medical Conditions.

Adverse events were assessed according to the CTCAE version 4.0. If CTCAE grading did not exist for an AE, the severity of mild, moderate, severe, and life-threatening, or Grades 1 to 4, was used. CTCAE Grade 5 (death) was not used in this study; rather, this information was collected in the EOT or Survival Information eCRF page. Adverse event monitoring was to be continued for at least 4 weeks following the last dose of study treatment. AEs were summarized in hierarchical tables, presenting the number and percentage of patients having at least one AE, and having at least one AE in each primary SOC and for each PT using MedDRA coding.

Laboratory data were summarized by presenting grade shift tables for those parameters for which CTCAE version 4.0 allowed classification.

Pharmacokinetics (Phase II): Pharmacokinetic parameters were determined by non-compartmental method(s) using WinNonlin® Pro (Version 5.2). Descriptive statistics (n, geometric and arithmetic means, SD, CV%, median and ranges) were presented for AUY922 and BJP762 plasma concentrations at different time points, all primary (AUC(0-∞), AUC(0 - tlast), Cmax) and other (tmax, T1/2, CL, Vz) PK parameters for each treatment group. AUC(0-∞) and T1/2 were estimated for AUY922 and its metabolite BJP762. CL and Vz were assessed for AUY922. Median values and ranges were given for tmax. The ratio of geometric mean AUC and Cmax of BJP762 to AUY922 was assessed.

Study Population: Key Inclusion/Exclusion Criteria

Inclusion criteria:

- Female patients aged ≥ 18 years with confirmed HER2-positive non-operable locally advanced or metastatic breast cancer which demonstrated HER2 overexpression (based on either immunohistochemistry (IHC) at the 3+ level or IHC 2+ confirmed by fluorescence in situ hybridization [FISH])

- At least one but no more than two prior anti-HER2-based regimens including at least one regimen containing trastuzumab
- At least one measurable lesion as defined by RECIST
- Documented progressive disease following the last line of therapy
- Eastern Cooperative Oncology Group (ECOG) Performance Status of ≤ 1
- Able to sign informed consent and to comply with the protocol
- Hematology and biochemistry laboratory values within protocol-specified limits
- Negative serum pregnancy test

Exclusion criteria:

- Known central nervous system metastasis (symptomatic or requiring symptom control and/or growing);
- Prior treatment with any HSP90 or HDAC inhibitor
- Patients who received systemic anti-cancer treatment prior to the first dose of AUY922 within the following time frames:
  - Radiotherapy, chemotherapy, hormonotherapy, investigational drugs and monoclonal antibodies other than Trastuzumab: within 4 weeks
  - Palliative radiotherapy: within 2 weeks
  - Nitrosoureas, mitomycin: within 6 weeks
- Patients with unresolved diarrhea > CTCAE grade 1
- Patients who have not recovered from the reversible side effects of previous systemic anticancer therapy (except for alopecia) to less than CTCAE grade 2 prior to the first dose.
- Treatment with therapeutic doses of sodium warfarin (Coumadin). Low doses of Coumadin (e.g. < 2mg/day for line patency) are permitted.
- 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).
- Patients with acute or chronic liver or renal disease.
- Patients with other concurrent severe and/or uncontrolled medical conditions (e.g. uncontrolled diabetes mellitus, active untreated or uncontrolled infection, chronic obstructive or chronic restrictive pulmonary disease including dyspnea at rest from any cause) that could cause unacceptable safety risks or compromise compliance with the protocol.
- Known hypersensitivity to any study medication.
- Impaired cardiac function, including any one of the following:
  - History (or family history) of long QT syndrome.
  - Mean QTcF ≥ 450 msec on screening ECG.

- History of clinically manifested ischemic heart disease ≤ 6 months prior to study start.
- History of heart failure or left ventricular (LV) dysfunction (LVEF ≤ 45%) by MUGA or ECHO.
- Clinically significant ECG abnormalities including one or more of the following: left bundle branch block (LBBB), right bundle branch block (RBBB) with left anterior hemiblock (LAHB). ST segment elevations or depressions > 1mm, or 2nd (Mobitz II) or 3rd degree AV block.
- History or presence 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 inducing Torsades de Pointes and cannot be switched or discontinued to an alternative drug prior to commencing AUY922.
- Obligate use of a cardiac pacemaker.

- Known diagnosis of HIV infection (HIV testing is not mandatory.)
- Patients with a history of another primary malignancy that is currently clinically significant or currently requires active intervention.
- Patients who do not have either an archival tumor sample (or sections of it) available or readily obtainable in the course of the study or are unwilling to have a fresh tumor sample collected at baseline
- Patients unwilling or unable to comply with the protocol.

Participant Flow Table

Patient disposition by treatment in Phase Ib/II (All patients)

	55 mg/m^2 AUY922 + 2 mg/kg trastuzumab N=4 n (%)	70 mg/m^2 AUY922 + 2 mg/kg trastuzumab N=41 n (%)	All patients N=45 n (%)
Patients enrolled			
Treated	4 (100.0)	41 (100.0)	45 (100.0)
Patients treated			
Treatment discontinued	4 (100.0)	39 (95.1)	43 (95.6)
Treatment ongoing*	0 (0.0)	2 (4.9)	2 (4.4)
Primary reason for end of treatment			

	55 mg/m^2 AUY922 + 2 mg/kg trastuzumab N=4 n (%)	70 mg/m^2 AUY922 + 2 mg/kg trastuzumab N=41 n (%)	All patients N=45 n (%)
Adverse Event (s)	1 (25.0)	7 (17.1)	8 (17.8)
Subject withdrew consent	0 (0.0)	4 (9.8)	4 (8.9)
Disease progression	3 (75.0)	28 (68.3)	31 (68.9)
Primary reason for study evaluation completion			
Subject withdrew consent	0 (0.0)	6 (14.6)	6 (13.3)
Administrative problems	0 (0.0)	1 (2.4)	1 (2.2)
New cancer therapy	1 (25.0)	3 (7.3)	4 (8.9)
Disease progression	0 (0.0)	3 (7.3)	3 (6.7)
Follow-up phase completed as per protocol	3 (75.0)	25 (61.0)	28 (62.2)

* Patients ongoing at the time of data cut-off 29-Jan-2013

Baseline Characteristics

Demographics by treatment group in Phase Ib/II (FAS)

Demography data	55 mg/m^2 AUY922 + 2 mg/kg trastuzumab N=4	70 mg/m^2 AUY922 + 2 mg/kg trastuzumab N=41	All patients N=45
Age (year)			
n	4	41	45
Mean	53.5	51.8	52.0
SD	9.68	10.68	10.51
Median	53.5	51.0	51.0
Min	43.0	29.0	29.0
Max	64.0	71.0	71.0
Age category (year)			
< 65	4 (100.0%)	36 (87.8%)	40 (88.9%)
≥ 65	0 (0.0%)	5 (12.2%)	5 (11.1%)
Predominant Race			
Caucasian	2 (50.0%)	34 (82.9%)	36 (80.0%)
Black	0 (0.0%)	1 (2.4%)	1 (2.2%)
Asian	2 (50.0%)	6 (14.6%)	8 (17.8%)
Ethnicity			
Hispanic/Latino	0 (0.0%)	3 (7.3%)	3 (6.7%)
Chinese	1 (25.0%)	3 (7.3%)	4 (8.9%)
Indian (Indian subcontinent)	0 (0.0%)	1 (2.4%)	1 (2.2%)
Mixed ethnicity	1 (25.0%)	0 (0.0%)	1 (2.2%)
Other	2 (50.0%)	34 (82.9%)	36 (80.0%)
Body surface area (m^2)			

Demography data	55 mg/m^2 AUY922 + 2 mg/kg trastuzumab N=4	70 mg/m^2 AUY922 + 2 mg/kg trastuzumab N=41	All patients N=45
n	4	41	45
Mean	1.8	1.8	1.8
SD	0.31	0.25	0.25
Median	1.7	1.8	1.8
Min	1.5	1.3	1.3
Max	2.2	2.3	2.3
ECOG Performance Status			
0	2 (50.0%)	29 (70.7%)	31 (68.9%)
1	2 (50.0%)	12 (29.3%)	14 (31.1%)

Body mass index (BMI) [kg/m^2] = weight [kg] / height[m]^2
Body surface area: BSA[m^2] = ([Height (cm) x weight (kg)] /3600)^1/2
LVEF = Left ventricular ejection fraction
ECOG Performance Status Scale: Grade 0 = Fully active, able to carry on all pre-disease performance without restriction; Grade 1= Restricted in physically strenuous activity but ambulatory and able to carry out work of a light or sedentary nature, e.g. light housework, office work; Grade 2=Ambulatory and capable of all self-care but unable to carry out any work activities. Up and about more than 50% of waking hours; Grade 3=Capable of only limited self-care, confined to bed or chair more than 50% of waking hours; Grade 4=Completely disabled. Cannot carry on any self-care. Totally confined to bed or chair; Grade 5=Dead.

Summary of Efficacy:

Primary Outcome Result(s):

Phase Ib: The primary objective of the Phase Ib component of this study was to determine the MTD and the RP2D of AUY922 in combination with trastuzumab. ***Please refer to Safety Result section for the primary outcome result of the Phase Ib component.***

Phase II: Efficacy analysis was the primary objective of the Phase. The results are given below:

Best overall response in Phase II based on RECIST as per investigator (FAS)

Best overall response	70 mg/m^2 AUY922 + 2 mg/kg trastuzumab (N=41)
Complete Response (CR)	1 (2.4)
Partial Response (PR)	8 (19.5)
Stable Disease (SD)	20 (48.8)
Progressive Disease (PD)	11 (26.8)
Unknown	1 (2.4)
Objective response (CR or PR)	9 (22.0)
95% Confidence interval	[10.6; 37.6]

Secondary Outcome Result(s)

Phase II: A secondary objective of Phase II of the study was to assess the efficacy at the RP2D, in terms of PFS and OS. The results are given below:

Progression free survival (PFS) as per investigator in Phase II (FAS)

	70 mg/m^2 AUY922 + 2 mg/kg trastuzumab (N=41)
Number of PFS events	
Progression	32 (78.0)
Number censored	9 (22.0)
Kaplan-Meier estimates (%) PFS rate [95% CI] at:	
4 months	47.9 [31.4; 62.7]
6 months	38.7 [23.1; 54.1]
Median PFS (months) [95% CI]	3.94 [3.48; 6.47]

Overall survival (OS) in phase II (FAS)

	70 mg/m^2 AUY922 + 2 mg/kg trastuzumab (N=41)
Number of OS events	
Death	15 (36.6)
Number censored	26 (63.4)
Kaplan-Meier estimates (%) OS rate [95% CI] at:	
8 months	91.6 [76.0; 97.2]
Median OS (months) [95% CI]	12.65 [11.70;17.22]

Summary of Safety

Safety Results

Phase Ib:

Prior and posterior probabilities of DLT by time point (Dose determining set)

AUY922 (mg/m2)	0-0.16	0.16–0.33	0.33-1	Mean	SD	2.5%	50%	97.5%
Prior								
20	0.956	0.041	0.003	0.054	0.051	0.007	0.039	0.195
25	0.866	0.083	0.051	0.103	0.161	0.010	0.056	0.730
30	0.800	0.104	0.096	0.141	0.216	0.011	0.066	0.990
35	0.754	0.116	0.130	0.170	0.248	0.012	0.074	1.000
40	0.718	0.125	0.157	0.193	0.270	0.012	0.081	1.000

AUY922 (mg/m2)	0-0.16	0.16–0.33	0.33-1	Mean	SD	2.5%	50%	97.5%
45	0.691	0.129	0.180	0.212	0.286	0.013	0.087	1.000
50	0.669	0.133	0.199	0.227	0.299	0.013	0.092	1.000
55	0.650	0.136	0.215	0.241	0.308	0.014	0.097	1.000
60	0.634	0.137	0.229	0.252	0.316	0.014	0.102	1.000
65	0.621	0.139	0.240	0.262	0.323	0.015	0.106	1.000
70	0.608	0.140	0.251	0.272	0.328	0.015	0.110	1.000
75	0.598	0.141	0.262	0.280	0.333	0.015	0.114	1.000
80	0.588	0.142	0.271	0.287	0.337	0.015	0.118	1.000
Posterior: Cohort 1, 3 patients								
20	0.972	0.028	0.001	0.048	0.042	0.007	0.036	0.167
25	0.966	0.033	0.001	0.053	0.044	0.008	0.040	0.174
30	0.959	0.040	0.001	0.058	0.046	0.009	0.045	0.185
35	0.947	0.052	0.002	0.063	0.050	0.010	0.049	0.198
40	0.931	0.066	0.003	0.068	0.055	0.010	0.053	0.216
45	0.913	0.081	0.006	0.074	0.062	0.011	0.056	0.242
50	0.893	0.095	0.012	0.079	0.069	0.011	0.059	0.269
55	0.875	0.107	0.018	0.085	0.078	0.011	0.061	0.300
60	0.861	0.114	0.026	0.090	0.087	0.012	0.063	0.333
65	0.845	0.122	0.033	0.095	0.096	0.012	0.065	0.368
70	0.832	0.127	0.041	0.101	0.105	0.012	0.067	0.405
75	0.818	0.133	0.049	0.106	0.113	0.012	0.069	0.445
80	0.807	0.137	0.056	0.110	0.121	0.013	0.071	0.480
Posterior: Cohort 1, 4 patients								
20	0.978	0.022	0.000	0.047	0.040	0.006	0.035	0.154
25	0.974	0.026	0.000	0.051	0.041	0.008	0.039	0.163
30	0.967	0.032	0.001	0.055	0.043	0.009	0.043	0.173
35	0.958	0.041	0.001	0.060	0.046	0.009	0.047	0.183
40	0.945	0.054	0.002	0.065	0.051	0.010	0.050	0.199
45	0.928	0.068	0.004	0.069	0.056	0.010	0.053	0.218
50	0.911	0.081	0.008	0.074	0.063	0.011	0.056	0.242
55	0.895	0.092	0.012	0.079	0.070	0.011	0.058	0.270
60	0.880	0.102	0.018	0.084	0.077	0.011	0.060	0.298
65	0.866	0.109	0.025	0.089	0.085	0.011	0.062	0.328
70	0.854	0.113	0.032	0.093	0.093	0.012	0.064	0.361
75	0.845	0.116	0.039	0.098	0.101	0.012	0.066	0.394
80	0.834	0.121	0.045	0.102	0.108	0.012	0.067	0.425
Posterior: Cohort 2								
20	0.960	0.039	0.001	0.058	0.046	0.008	0.046	0.182
25	0.953	0.046	0.001	0.064	0.047	0.011	0.052	0.189
30	0.944	0.055	0.001	0.070	0.048	0.014	0.058	0.198
35	0.931	0.067	0.002	0.077	0.050	0.016	0.065	0.207
40	0.914	0.083	0.002	0.083	0.053	0.017	0.070	0.221

AUY922 (mg/m2)	0-0.16	0.16–0.33	0.33-1	Mean	SD	2.5%	50%	97.5%
45	0.888	0.108	0.004	0.089	0.057	0.018	0.076	0.236
50	0.860	0.134	0.007	0.096	0.063	0.019	0.081	0.257
55	0.832	0.156	0.012	0.102	0.069	0.019	0.085	0.280
60	0.803	0.179	0.018	0.109	0.076	0.020	0.089	0.305
65	0.776	0.198	0.027	0.115	0.083	0.020	0.093	0.338
70	0.754	0.208	0.037	0.122	0.091	0.021	0.097	0.366
75	0.736	0.217	0.048	0.128	0.099	0.021	0.100	0.396
80	0.719	0.220	0.060	0.134	0.107	0.021	0.103	0.430
Posterior: Phase Ib end								
20	0.975	0.025	0.000	0.053	0.040	0.008	0.043	0.161
25	0.971	0.028	0.000	0.058	0.041	0.011	0.048	0.165
30	0.967	0.033	0.000	0.063	0.042	0.013	0.052	0.171
35	0.960	0.039	0.000	0.067	0.043	0.014	0.057	0.177
40	0.950	0.049	0.001	0.072	0.045	0.015	0.062	0.185
45	0.938	0.061	0.001	0.076	0.047	0.016	0.065	0.195
50	0.923	0.076	0.001	0.081	0.050	0.017	0.069	0.208
55	0.903	0.095	0.002	0.085	0.054	0.018	0.073	0.223
60	0.884	0.112	0.004	0.089	0.058	0.018	0.075	0.239
65	0.864	0.129	0.007	0.094	0.063	0.018	0.078	0.256
70	0.847	0.142	0.010	0.098	0.068	0.019	0.081	0.275
75	0.831	0.153	0.016	0.103	0.074	0.019	0.083	0.295
80	0.816	0.163	0.021	0.107	0.079	0.019	0.085	0.318

Phase II:

Incidence of AEs by primary system organ class and treatment group in Phase Ib/II (Safety set)

Primary system organ class	55 mg/m^2 AUY922 + 2 mg/kg trastuzumab N=4 n (%)	70 mg/m^2 AUY922 + 2 mg/kg trastuzumab N=41 n (%)	All patients N=45 n (%)
Patients with at least one AE	4 (100.0)	41 (100.0)	45 (100.0)
Eye disorders	4 (100.0)	37 (90.2)	41 (91.1)
Gastrointestinal disorders	3 (75.0)	38 (92.7)	41 (91.1)
General disorders and administration	2 (50.0)	26 (63.4)	28 (62.2)

Primary system organ class	55 mg/m^2 AUY922 + 2 mg/kg trastuzumab N=4 n (%)	70 mg/m^2 AUY922 + 2 mg/kg trastuzumab N=41 n (%)	All patients N=45 n (%)
site conditions			
Nervous system disorders	2 (50.0)	20 (48.8)	22 (48.9)
Musculoskeletal and connective tissue	0 (0.0)	21 (51.2)	21 (46.7)
disorders			
Infections and infestations	0 (0.0)	19 (46.3)	19 (42.2)
Investigations	2 (50.0)	17 (41.5)	19 (42.2)
Respiratory, thoracic and mediastinal	2 (50.0)	17 (41.5)	19 (42.2)
disorders			
Skin and subcutaneous tissue disorders	3 (75.0)	13 (31.7)	16 (35.6)
Metabolism and nutrition disorders	0 (0.0)	15 (36.6)	15 (33.3)
Blood and lymphatic system disorders	0 (0.0)	11 (26.8)	11 (24.4)
Psychiatric disorders	0 (0.0)	9 (22.0)	9 (20.0)
Cardiac disorders	0 (0.0)	5 (12.2)	5 (11.1)
Vascular disorders	1 (25.0)	4 (9.8)	5 (11.1)
Ear and labyrinth disorders	0 (0.0)	3 (7.3)	3 (6.7)
Endocrine disorders	0 (0.0)	3 (7.3)	3 (6.7)
Injury, poisoning and procedural	0 (0.0)	3 (7.3)	3 (6.7)
complications			
Reproductive system and breast disorders	1 (25.0)	2 (4.9)	3 (6.7)
Congenital, familial and genetic	0 (0.0)	1 (2.4)	1 (2.2)
disorders			
Hepatobiliary disorders	0 (0.0)	1 (2.4)	1 (2.2)
Neoplasms benign, malignant and unspecified (incl cysts and polyps)	0 (0.0)	1 (2.4)	1 (2.2)
Renal and urinary disorders	0 (0.0)	1 (2.4)	1 (2.2)

AEs by SOC are presented in descending order of frequency in 'All patients' group.
A patient with multiple occurrences of an AE under one treatment is counted only once in the AE.
Only AEs occurring during treatment or within 28 days of the last study medication are reported.

Incidence of AEs by preferred term and treatment group in Phase Ib/II (at least 5% incidence in any group) (Safety set)

Preferred term	55 mg/m^2 AUY922 + 2 mg/kg trastuzumab N=4 n (%)	70 mg/m^2 AUY922 + 2 mg/kg trastuzumab N=41 n (%)	All patients N=45 n (%)
Patients with at least one AE	4 (100.0)	41 (100.0)	45 (100.0)
Diarrhoea	2 (50.0)	38 (92.7)	40 (88.9)
Fatigue	2 (50.0)	15 (36.6)	17 (37.8)

Preferred term	55 mg/m^2 AUY922 + 2 mg/kg trastuzumab N=4 n (%)	70 mg/m^2 AUY922 + 2 mg/kg trastuzumab N=41 n (%)	All patients N=45 n (%)
Nausea	1 (25.0)	16 (39.0)	17 (37.8)
Headache	2 (50.0)	12 (29.3)	14 (31.1)
Night blindness	1 (25.0)	13 (31.7)	14 (31.1)
Visual impairment	2 (50.0)	12 (29.3)	14 (31.1)
Photopsia	3 (75.0)	10 (24.4)	13 (28.9)
Vision blurred	2 (50.0)	11 (26.8)	13 (28.9)
Anaemia	0 (0.0)	11 (26.8)	11 (24.4)
Vitreous floaters	1 (25.0)	10 (24.4)	11 (24.4)
Accommodation disorder	1 (25.0)	9 (22.0)	10 (22.2)
Muscle spasms	0 (0.0)	10 (24.4)	10 (22.2)
Vomiting	1 (25.0)	9 (22.0)	10 (22.2)
Asthenia	0 (0.0)	9 (22.0)	9 (20.0)
Decreased appetite	0 (0.0)	9 (22.0)	9 (20.0)
Back pain	0 (0.0)	8 (19.5)	8 (17.8)
Dyspnoea	0 (0.0)	8 (19.5)	8 (17.8)
Abdominal pain	0 (0.0)	6 (14.6)	6 (13.3)
Arthralgia	0 (0.0)	6 (14.6)	6 (13.3)
Constipation	0 (0.0)	6 (14.6)	6 (13.3)
Cough	1 (25.0)	5 (12.2)	6 (13.3)
Hypokalaemia	0 (0.0)	6 (14.6)	6 (13.3)
Insomnia	0 (0.0)	6 (14.6)	6 (13.3)
Pruritus	1 (25.0)	5 (12.2)	6 (13.3)
Dyspepsia	0 (0.0)	5 (12.2)	5 (11.1)
Musculoskeletal pain	0 (0.0)	5 (12.2)	5 (11.1)
Photophobia	2 (50.0)	3 (7.3)	5 (11.1)
Pyrexia	0 (0.0)	5 (12.2)	5 (11.1)
Visual acuity reduced	0 (0.0)	5 (12.2)	5 (11.1)
Dizziness	0 (0.0)	4 (9.8)	4 (8.9)
Ejection fraction decreased	0 (0.0)	4 (9.8)	4 (8.9)
Influenza	0 (0.0)	4 (9.8)	4 (8.9)
Myalgia	0 (0.0)	4 (9.8)	4 (8.9)
Rash	1 (25.0)	3 (7.3)	4 (8.9)
Stomatitis	1 (25.0)	3 (7.3)	4 (8.9)
Aspartate aminotransferase increased	0 (0.0)	3 (7.3)	3 (6.7)
Blood calcium decreased	0 (0.0)	3 (7.3)	3 (6.7)
Dysgeusia	0 (0.0)	3 (7.3)	3 (6.7)
Eye pain	0 (0.0)	3 (7.3)	3 (6.7)
Nasopharyngitis	0 (0.0)	3 (7.3)	3 (6.7)
Oedema peripheral	0 (0.0)	3 (7.3)	3 (6.7)

Preferred term	55 mg/m^2 AUY922 + 2 mg/kg trastuzumab N=4 n (%)	70 mg/m^2 AUY922 + 2 mg/kg trastuzumab N=41 n (%)	All patients N=45 n (%)
Pain in extremity	0 (0.0)	3 (7.3)	3 (6.7)
Rhinorrhoea	2 (50.0)	1 (2.4)	3 (6.7)
Tachycardia	0 (0.0)	3 (7.3)	3 (6.7)
Alanine aminotransferase increased	1 (25.0)	1 (2.4)	2 (4.4)
Breast pain	1 (25.0)	1 (2.4)	2 (4.4)
Cystoid macular oedema	1 (25.0)	1 (2.4)	2 (4.4)
Hypertension	1 (25.0)	1 (2.4)	2 (4.4)
Abnormal faeces	1 (25.0)	0 (0.0)	1 (2.2)
Maculopathy	1 (25.0)	0 (0.0)	1 (2.2)
Skin fissures	1 (25.0)	0 (0.0)	1 (2.2)
Transaminases increased	1 (25.0)	0 (0.0)	1 (2.2)

Preferred terms are sorted in descending frequency, as reported in the 'All patient' column.
A patient with multiple occurrences of an AE under one treatment is counted only once in the AE category for that treatment.
A patient with multiple AEs is counted only once in the total row.
Only AEs occurring during treatment or within 28 days of the last study medication are reported.

The three patients those were ongoing after the previous cut-off of 07-Nov-2012, one patient was reported to suffer from a serious adverse event (fatigue) which was not related to the study medication and the remaining two patients discontinued the study due to adverse events of lethargy and blurred vision.

Study treatment related adverse events (at least 5% incidence in any group) by preferred term and treatment group in Phase Ib/II (Safety set)

Preferred term	55 mg/m^2 AUY922 + 2 mg/kg trastuzumab N=4 n (%)	70 mg/m^2 AUY922 + 2 mg/kg trastuzumab N=41 n (%)	All patients N=45 n (%)
Patient with at least one study drug related AE	4 (100.0)	40 (97.6)	44 (97.8)
Diarrhoea	2 (50.0)	38 (92.7)	40 (88.9)
Fatigue	2 (50.0)	13 (31.7)	15 (33.3)
Nausea	1 (25.0)	14 (34.1)	15 (33.3)
Visual impairment	2 (50.0)	12 (29.3)	14 (31.1)
Night blindness	1 (25.0)	12 (29.3)	13 (28.9)
Photopsia	3 (75.0)	10 (24.4)	13 (28.9)
Vision blurred	2 (50.0)	11 (26.8)	13 (28.9)
Vitreous floaters	1 (25.0)	10 (24.4)	11 (24.4)
Accommodation disorder	1 (25.0)	9 (22.0)	10 (22.2)
Asthenia	0 (0.0)	8 (19.5)	8 (17.8)

Preferred term	55 mg/m^2 AUY922 + 2 mg/kg trastuzumab N=4 n (%)	70 mg/m^2 AUY922 + 2 mg/kg trastuzumab N=41 n (%)	All patients N=45 n (%)
Decreased appetite	0 (0.0)	7 (17.1)	7 (15.6)
Headache	1 (25.0)	6 (14.6)	7 (15.6)
Vomiting	1 (25.0)	6 (14.6)	7 (15.6)
Abdominal pain	0 (0.0)	6 (14.6)	6 (13.3)
Muscle spasms	0 (0.0)	6 (14.6)	6 (13.3)
Pruritus	1 (25.0)	5 (12.2)	6 (13.3)
Anaemia	0 (0.0)	5 (12.2)	5 (11.1)
Hypokalaemia	0 (0.0)	5 (12.2)	5 (11.1)
Photophobia	2 (50.0)	3 (7.3)	5 (11.1)
Visual acuity reduced	0 (0.0)	5 (12.2)	5 (11.1)
Ejection fraction decreased	0 (0.0)	4 (9.8)	4 (8.9)
Dizziness	0 (0.0)	3 (7.3)	3 (6.7)
Dyspepsia	0 (0.0)	3 (7.3)	3 (6.7)
Eye pain	0 (0.0)	3 (7.3)	3 (6.7)
Rash	0 (0.0)	3 (7.3)	3 (6.7)
Stomatitis	0 (0.0)	3 (7.3)	3 (6.7)
Cystoid macular oedema	1 (25.0)	1 (2.4)	2 (4.4)
Abnormal faeces	1 (25.0)	0 (0.0)	1 (2.2)
Alanine aminotransferase increased	1 (25.0)	0 (0.0)	1 (2.2)
Maculopathy	1 (25.0)	0 (0.0)	1 (2.2)
Transaminases increased	1 (25.0)	0 (0.0)	1 (2.2)

AEs by PT are presented in descending order of frequency in 'All patients' group.
A patient with multiple occurrences of an AE under one treatment is counted only once in the AE category for that treatment.
Only AEs occurring during treatment or within 28 days of the last study medication are reported.

Adverse events with CTC grades 3 and 4, regardless of causality, by preferred term and treatment group in Phase Ib/II (Safety set)

Preferred term	55 mg/m^2 AUY922 + 2 mg/kg trastuzumab N=4 n (%)	70 mg/m^2 AUY922 + 2 mg/kg trastuzumab N=41 n (%)	All patients N=45 n (%)
Patients with at least one grade 3 or 4 AE	1 (25.0)	20 (48.8)	21 (46.7)
Dyspnoea	0 (0.0)	3 (7.3)	3 (6.7)
Accommodation disorder	0 (0.0)	2 (4.9)	2 (4.4)
Anaemia	0 (0.0)	2 (4.9)	2 (4.4)
Arthralgia	0 (0.0)	2 (4.9)	2 (4.4)
Diarrhoea	0 (0.0)	2 (4.9)	2 (4.4)

Preferred term	55 mg/m^2 AUY922 + 2 mg/kg trastuzumab N=4 n (%)	70 mg/m^2 AUY922 + 2 mg/kg trastuzumab N=41 n (%)	All patients N=45 n (%)
Ejection fraction decreased	0 (0.0)	2 (4.9)	2 (4.4)
Fatigue	0 (0.0)	2 (4.9)	2 (4.4)
Nausea	0 (0.0)	2 (4.9)	2 (4.4)
Alanine aminotransferase increased	1 (25.0)	0 (0.0)	1 (2.2)
Aspartate aminotransferase increased	0 (0.0)	1 (2.4)	1 (2.2)
Asthenia	0 (0.0)	1 (2.4)	1 (2.2)
Back pain	0 (0.0)	1 (2.4)	1 (2.2)
Blood calcium decreased	0 (0.0)	1 (2.4)	1 (2.2)
Breast cancer	0 (0.0)	1 (2.4)	1 (2.2)
Bundle branch block left	0 (0.0)	1 (2.4)	1 (2.2)
Cardiac failure	0 (0.0)	1 (2.4)	1 (2.2)
Convulsion	0 (0.0)	1 (2.4)	1 (2.2)
Cystoid macular oedema	1 (25.0)	0 (0.0)	1 (2.2)
Device related infection	0 (0.0)	1 (2.4)	1 (2.2)
Gastrointestinal haemorrhage	0 (0.0)	1 (2.4)	1 (2.2)
Herpes simplex	0 (0.0)	1 (2.4)	1 (2.2)
Hydrocephalus	0 (0.0)	1 (2.4)	1 (2.2)
Hyperkalaemia	0 (0.0)	1 (2.4)	1 (2.2)
Hypertension	0 (0.0)	1 (2.4)	1 (2.2)
Hypokalaemia	0 (0.0)	1 (2.4)	1 (2.2)
Jaundice	0 (0.0)	1 (2.4)	1 (2.2)
Mastitis	0 (0.0)	1 (2.4)	1 (2.2)
Melaena	0 (0.0)	1 (2.4)	1 (2.2)
Muscle spasms	0 (0.0)	1 (2.4)	1 (2.2)
Myalgia	0 (0.0)	1 (2.4)	1 (2.2)
Optic nerve disorder	0 (0.0)	1 (2.4)	1 (2.2)
Photopsia	0 (0.0)	1 (2.4)	1 (2.2)
Pleural effusion	0 (0.0)	1 (2.4)	1 (2.2)
Pneumothorax	0 (0.0)	1 (2.4)	1 (2.2)
Pulmonary embolism	0 (0.0)	1 (2.4)	1 (2.2)
Visual impairment	1 (25.0)	0 (0.0)	1 (2.2)
Vomiting	0 (0.0)	1 (2.4)	1 (2.2)

AEs by PT are presented in descending order of frequency in 'All patients' group.
A patient with multiple occurrences of an AE under one treatment is counted only once in the AE category for that treatment.
Only AEs occurring during treatment or within 28 days of the last study medication are reported.

Number of patients who died or experienced other serious or clinically significant adverse events, regardless of causality, in Phase Ib/II (Safety set)

Patients with serious or significant AEs	55 mg/m^2 AUY922 + 2 mg/kg trastuzumab (N=4) n (%)	70 mg/m^2 AUY922 + 2 mg/kg trastuzumab (N=41) n (%)	All patients (N=45) n (%)
Deaths on study	0 (0.0)	0 (0.0)	0 (0.0)
SAEs	0 (0.0)	11 (26.8)	11 (24.4)
Discontinued due to AEs	1 (25.0)	7 (17.1)	8 (17.8)
Discontinued due to SAEs	0 (0.0)	0 (0.0)	0 (0.0)

Patients discontinuing due to SAEs are not also counted in the category of discontinuing due to AEs
Only AEs, SAEs and deaths occurring during treatment or within 28 days of the last study medication are reported.

Serious adverse events, regardless of causality, by primary system organ class, preferred term and treatment group in Phase Ib/II (Safety set)

Primary system organ class Preferred term	70 mg/m^2 AUY922 + 2 mg/kg trastuzumab N=41 n (%)	All patients N=45 n (%)
-Any primary system organ class		
-Total	11 (26.8)	11 (24.4)
Blood and lymphatic system disorders		
-Total	2 (4.9)	2 (4.4)
Anaemia	2 (4.9)	2 (4.4)
Cardiac disorders		
-Total	1 (2.4)	1 (2.2)
Bundle branch block left	1 (2.4)	1 (2.2)
Cardiac failure	1 (2.4)	1 (2.2)
Eye disorders		
-Total	1 (2.4)	1 (2.2)
Eye disorder	1 (2.4)	1 (2.2)
Gastrointestinal disorders		
-Total	3 (7.3)	3 (6.7)
Nausea	2 (4.9)	2 (4.4)
Vomiting	2 (4.9)	2 (4.4)
Gastrointestinal haemorrhage	1 (2.4)	1 (2.2)
Melaena	1 (2.4)	1 (2.2)
General disorders and administration site conditions		
-Total	1 (2.4)	1 (2.2)
Asthenia	1 (2.4)	1 (2.2)
Infections and infestations		
-Total	3 (7.3)	3 (6.7)
Application site abscess	1 (2.4)	1 (2.2)
Device related infection	1 (2.4)	1 (2.2)
Mastitis	1 (2.4)	1 (2.2)
Investigations		

Primary system organ class Preferred term	70 mg/m^2 AUY922 + 2 mg/kg trastuzumab N=41 n (%)	All patients N=45 n (%)
-Total	1 (2.4)	1 (2.2)
Ejection fraction decreased	1 (2.4)	1 (2.2)
Electrocardiogram QT prolonged	1 (2.4)	1 (2.2)
Nervous system disorders		
-Total	2 (4.9)	2 (4.4)
Convulsion	1 (2.4)	1 (2.2)
Headache	1 (2.4)	1 (2.2)
Hydrocephalus	1 (2.4)	1 (2.2)
Respiratory, thoracic and mediastinal disorders		
-Total	3 (7.3)	3 (6.7)
Dyspnoea	2 (4.9)	2 (4.4)
Pleural effusion	2 (4.9)	2 (4.4)
Pneumothorax	1 (2.4)	1 (2.2)
Pulmonary embolism	1 (2.4)	1 (2.2)

Primary system organ classes are presented alphabetically; preferred terms are sorted within primary system organ class in descending frequency, as reported in the 'all patients' column.
A patient with multiple occurrences of an AE under one treatment is counted only once in the AE category for that treatment.
A patient with multiple AEs within a primary system organ class is counted only once in the total row.
Only AEs occurring during treatment or within 28 days of the last study medication are reported.

AEs leading to study treatment discontinuation, regardless of causality, by primary system organ class, preferred term and treatment group in Phase Ib/II (Safety set)

Primary system organ class Preferred term	55 mg/m^2 AUY922 + 2 mg/kg trastuzumab N=4 n (%)	70 mg/m^2 AUY922 + 2 mg/kg trastuzumab N=41 n (%)	All patients N=45 n (%)
-Any primary system organ class			
-Total	1 (25.0)	7 (17.1)	8 (17.8)
Eye disorders			
-Total	0 (0.0)	2 (4.9)	2 (4.4)
Accommodation disorder	0 (0.0)	1 (2.4)	1 (2.2)
Optic nerve disorder	0 (0.0)	1 (2.4)	1 (2.2)
Infections and infestations			
-Total	0 (0.0)	1 (2.4)	1 (2.2)
Lower respiratory tract infection	0 (0.0)	1 (2.4)	1 (2.2)
Investigations			
-Total	1 (25.0)	2 (4.9)	3 (6.7)
Ejection fraction decreased	0 (0.0)	2 (4.9)	2 (4.4)
Alanine aminotransferase increased	1 (25.0)	0 (0.0)	1 (2.2)
Metabolism and nutrition disorders			

Primary system organ class Preferred term	55 mg/m^2 AUY922 + 2 mg/kg trastuzumab N=4 n (%)	70 mg/m^2 AUY922 + 2 mg/kg trastuzumab N=41 n (%)	All patients N=45 n (%)
-Total	0 (0.0)	2 (4.9)	2 (4.4)
Decreased appetite	0 (0.0)	1 (2.4)	1 (2.2)
Hyperkalaemia	0 (0.0)	1 (2.4)	1 (2.2)
Musculoskeletal and connective tissue disorders			
-Total	0 (0.0)	1 (2.4)	1 (2.2)
Back pain	0 (0.0)	1 (2.4)	1 (2.2)
Neoplasms benign, malignant and unspecified (incl cysts and polyps)			
-Total	0 (0.0)	1 (2.4)	1 (2.2)
Breast cancer	0 (0.0)	1 (2.4)	1 (2.2)

AEs by SOC are presented in descending order of frequency in 'all patients' group.
A patient with multiple occurrences of an AE under one treatment is counted only once in the AE category for that treatment.
Only AEs occurring during treatment or within 28 days of the last study medication are reported.

Time (days) to first adverse event with primary system organ class of eye disorders (regardless of causality) by preferred term and treatment group in Phase Ib/II (Safety set)

	55 mg/m^2 AUY922 + 2 mg/kg trastuzumab N=4	70 mg/m^2 AUY922 + 2 mg/kg trastuzumab N=41	All Patients N=45
All patients			
Censored - n (%)	0	4 (9.8)	4 (8.9)
With event - n (%)	4 (100)	37 (90.2)	41 (91.1)
Median	12.5	16.0	15.0
Patients experiencing the event			
With event - n (%)	4 (100)	37 (90.2)	41 (91.1)
Median	12.5	15.0	15.0
Min	3.0	0.0	0.0
Max	39.0	79.0	79.0

Time to first adverse event is the time between the date of the first occurrence of the event of interest and the start date of study drug.

Summary of Pharmacokinetics

Phase II:

Summary of primary PK parameters for plasma AUY922 and BJP762 by treatment group (PK analysis set)

Analyte	Statistics	AUC (0-inf) (h.ng/mL)	AUC (0-tlast) (h.ng/mL)	Cmax (ng/mL)

Analyte	Statistics	AUC (0-inf) (h.ng/mL)	AUC (0-tlast) (h.ng/mL)	Cmax (ng/mL)
Treatment group: 55 mg/m^2 AUY922 + 2 mg/kg trastuzumab (N=4)				
AUY922	**n**	**4**	**4**	**4**
	Mean (SD)	1608 (436)	1523 (408)	831 (237)
	CV% mean	27.1	26.8	28.6
	Geo-mean	1563	1482	807
	CV% geo-mean	27.9	27.3	28.0
	Median	1573	1467	782
	[Min; Max]	[1197;2088]	[1161;1996]	[598;1160]
BJP762	**n**	**4**	**4**	**4**
	Mean (SD)	5328 (1625)	5194(1573)	1118 (377)
	CV% mean	30.5	30.3	33.7
	Geo-mean	5106	4978	1067
	CV% geo-mean	36.5	36.6	37.0
	Median	5698	5594	1158
	[Min; Max]	[3072;6843]	[2980;6607]	[696;1460]
Treatment group: 70 mg/m^2 AUY922 + 2 mg/kg trastuzumab (N=41)				
AUY922	**n**	**41**	**41**	**41**
	Mean (SD)	2429 (1445)	2307 (1390)	1064 (375)
	CV% mean	59.5	60.3	35.2
	Geo-mean	2187	2077	1005
	CV% geo-mean	44.5	44.4	35.7
	Median	2030	1920	962
	[Min; Max]	[1053;9735]	[995;9513]	[313;2240]
BJP762	**n**	**41**	**41**	**41**
	Mean (SD)	11804 (11836)	11559 (11474)	2295 (1741)
	CV% mean	100	99.3	75.9
	Geo-mean	9058	8888	1853
	CV% geo-mean	78.8	78.9	73.4
	Median	8250	8185	1710
	[Min; Max]	[1282;75400]	[1220;73136]	[283;9070]

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

Conclusion:

- Established in previous studies, Phase II doses of AUY922 and trastuzumab were recommended as the RP2D for the AUY922 and trastuzumab combination;
- One patient (in the 70 mg/m2 cohort) experienced a dose limiting toxicities (Grade 3 diarrhea). Further escalations were possible based on the BRLM, but did not take place since other studies had already declared 70 mg/m2 as the RP2D, thus prohibiting further dose escalations. The dose 70 mg/m2 was taken as the RP2D;

- Plasma concentration-time profiles were biphasic with terminal phase half-lives of 45.2 hours and 33.4 hours for AUY922 and BJP762, respectively. The metabolite BJP762 had higher exposures than the parent AUY922 in plasma, with metabolite to parent ratios of ~3.5 in AUC(0-tlast) and ~1.5 in Cmax. AUY922 had a mean CL value of 60 L/h and a Vz value of 3850 L in plasma. Overall, the PK profiles of AUY922 in the current study (in which AUY922 was co-administered with trastuzumab) were consistent with those observed in other single agent studies, suggesting no drug interactions effects on AUY922 by trastuzumab;
- The ORR (CR or PR) at the RP2D was 22.0% (95% credible interval: 11.1; 35.5), based on Bayesian posterior distribution. One patient (2.4%) showed CR. A further eight patients (19.5%) showed PR and 20 patients (48.8%) showed SD;
- Thirty-two patients (78.0%) had a PFS event. Kaplan-Meier estimates of PFS rate at 4 and 6 months were 47.9% (95% CI: 31.4; 62.7), and 38.7% (95% CI: 23.1; 54.1), respectively. The median PFS was 3.94 months (95% CI: 3.48; 6.47). Fifteen patients (36.6%) had an OS event. The median OS was 12.65 months (95% CI: 11.70; 17.22);
- All patients reported at least one AE, regardless of causality. The most common AE was diarrhea; other common AEs were fatigue, nausea, headache, night blindness, and visual impairment. Study drug related AEs occurred in 97.8% of patients. The most common was diarrhea; other common causally-related AEs were fatigue, nausea, and visual impairment;
- Grade 3 or 4 events, regardless of causality, occurred in 46.7% of patients. The most common were dyspnea, accommodation disorder, anemia, arthralgia, diarrhea, ejection fraction decreased, fatigue, and nausea;
- Causally-related Grade 3 or 4 AEs occurred in 31.1% of patients. The most common causally related events were diarrhea, fatigue, accommodation disorder, and ejection fraction decreased.
- There were no deaths within 28 days of last dose of study medication;
- Overall, 11 patients (24.4%) experienced SAEs, regardless of causality. All were in the 70 mg cohort. The most common were anemia, nausea, vomiting, dyspnea, and pleural effusion, occurring in two patients each. Causally-related SAEs (occurring in three patients) were eye disorder, nausea, vomiting, dyspnea, pleural effusion, left bundle branch block, ECG QT prolonged, cardiac failure, ejection fraction decreased, and pulmonary embolism. None resulted in permanent discontinuation;
- Eight patients (17.8%) discontinued due to AEs, regardless of causality. All events were non-serious.

Date of Clinical Trial Report

Interim CSR: 07-Oct-2013

Close-out CSR: 28-May-2014

Date of Initial Inclusion on Novartis Clinical Trial Results website

24-Sep-2014

Date of Latest Update

Reason for Update