Sponsor

Novartis

Generic Drug Name

AUY922

Therapeutic Area of Trial

Multiple myeloma

Approved Indication

Investigational

Protocol Number

CAUY922A2103

Title

An open-label, multi-center, Phase I-Ib/II study of AUY922 administered as single agent and in combination with bortezomib with or without dexamethasone in adult patients with relapsed or refractory multiple myeloma.

Phase of Development

Phase I-Ib/II

Study Start/End Dates

13 Oct 2008 to 12 Jan 2011 (the study was terminated early on 18 Feb 2011)

Study Design/Methodology

This was an open-label, non-randomized, multicenter study of AUY922 in combination with bortezomib with or without dexamethasone in adult patients with relapsed or refractory multiple myeloma (MM). The study comprised of a dose escalation part with AUY922 administered as a single agent (Phase I), and a dose escalation part (Phase Ib) with AUY922 administered in combination with bortezomib. A dose expansion phase (Phase II) and a triple combination of AUY922 with bortezomib and dexamethasone in Phase Ib were planned but not performed due to early termination of the study.

Centres

8 centres in 5 countries: Germany (2) United States (2), Spain (2), Austria (1), Singapore (1)

Publication

None

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

Phase I (Dose escalation part) - AUY922 was administered as a single agent, at escalating doses from 8 mg/m2 to 70 mg/m2.

Phase Ib AUY922A was administered at a dose of 50 mg/m2 in combination with bortezomib 1.3 mg/m2.

AUY922, was administered as a 1 hour i.v. infusion of AUY922 in 5% glucose/dextran at escalating doses from 8 mg/m^2 to 70 mg/m^2 was administered on Days 1, 8, and 15 of each 21-day treatment cycle

Bortezomib - bolus i.v. injection at 1.3 mg/m^2 twice a week for 2 consecutive weeks (Days 1, 4, 8, and 11) followed by a 10-day rest period (Days 12-21)

Statistical Methods

Data was analyzed by Novartis and/or designated CRO using SAS version 9.2, Rv2.8.1 and WinBUGSv.1.4.1.

An adaptive Bayesian logistic regression model (BLRM) with overdose control (EWOC) was to be used to guide the single agent dose escalation, for dose selection and determination of the MTD of AUY922 as a single agent. The final selection of each MTD (single-, dual- and triple-agent) was to be based on the recommendation of the Bayesian model, but was to also take into account further available safety and tolerability information.

The MTD was defined to be the highest dose of AUY922 given for at least two doses in the first treatment cycle in which it was expected to produce medically unacceptable DLT in < 33% of patients.

Estimation of the MTD during the escalation part of the study was based upon the estimation of the probability of DLT in cycle 1 in patients in the dose-determining set (DDS).

No interim analyses were performed. The final analysis was carried out after the termination of the study. It was based on all patient data of the single agent dose escalation part and the first two cohorts of the combination Phase Ib part with bortezomib enrolled until termination. At the time of the analysis, all enrolled subjects had withdrawn from the study. All data from all patients are presented in this report.

Study Population: Inclusion/Exclusion Criteria and Demographics

Inclusion criteria

The Investigator or his/her designee was to ensure that all patients who were offered enrollment into the study met the following eligibility criteria:

1. Patients must have had a diagnosis of active MM according to the International Myeloma Working Group criteria (IMWG) at the time of diagnosis
   - Presence of an M-component in serum or urine (in patients with no detectable M-component, an abnormal FLC ratio on the serum FLC assay could substitute this criteria),
   - Clonal Plasma cells in the bone marrow (≥ 10% of clonal plasma cells) and/or documented clonal plasmacytoma;

PLUS one or more of the following attributable to plasma cell disorder at the time of diagnosis:

- Calcium elevation (>11.5 mg/dL),
- Renal insufficiency (creatinine > 2 mg/dL),
- Anemia (Hemoglobin < 10g/dL or 2g/dL < normal),
- Bone disease (lytic lesions or osteopenia);

2. AUY922 single agent **(Phase I dose escalation)**
   - Patients with relapsed-refractory MM who had received at least two but not more than four prior anti-myeloma regimens and had progressed during or after the last therapy,
   - Prior therapy must have included at least one of the following: bortezomib or lenalidomide or thalidomide,
   - Induction therapy followed by any kind of stem cell transplantation and/or maintenance therapy was considered as one regimen,

   AUY922 in combination **(Phase Ib dose escalation part)**
   - Patients with relapsed-refractory MM who had received no more than two prior anti-myeloma regimens (excluding dexamethasone as single agent),
   - Patients had to be suitable (according to their local product information) for treatment with bortezomib. Note: patients previously treated with lenalidomide or thalidomide were eligible to participate in the trial,
   - Induction therapy followed by any kind of stem cell transplantation and/or maintenance therapy was considered as one regimen;
3. Patient must have had measurable disease defined by at least one of the following four measurements at the time of inclusion in the study:
   - Serum M-protein ≥ 1 g/dL of immunoglobulin (Ig) G myeloma or ≥ 0.5 g/dL of Ig A myeloma or Ig M myeloma,
   - Urinary M-protein ≥ 200 mg/24 hours,
   - Serum FLC assay: Involved FLC level ≥ 10 mg/dL provided serum FLC ratio was abnormal,
   - Bone marrow plasma cells ≥ 30% (for patients with non-secretory MM),
   - Patients with extramedullary disease: measurable lesions should be defined by X-ray, computed tomography (CT) or magnetic resonance imaging (MRI) scanning (or other technique as per site practice);
4. Patients using medications that are substrates, inhibitors, or inducers of CYP3A4, CYP2C8, CYP2C9 and CYP2C19 and could not be switched or discontinued or switched to an alternative drug prior to commencing AUY922 dosing needed special
5. Age ≥ 18 years;
6. Eastern Cooperative Oncology Group (ECOG) Performance Status of ≤ 2;
7. Life expectancy of ≥ 12 weeks;
8. Patients must have had the following laboratory values:
   - Absolute neutrophil count (ANC) ≥ 1.5 x 10^9/L,
   - Platelets ≥ 50 x 10^9/L,

- Total calcium (corrected for serum albumin) ≥ lower limit of normal (LLN),
- Potassium within normal limits or corrected with supplements prior to first administration of AUY922,
- Magnesium above LLN or correctable with supplements prior to first administration of AUY922,
- Phosphorus within normal limits or corrected with supplements prior to first administration of AUY922,
- Aspartate aminotransferase/serum glutamic oxaloacetic transaminase (AST/SGOT) and alanine aminotransferase/serum glutamic pyruvic transaminase (ALT/SGPT) ≤ 2.5 x upper limit of normal (ULN),
- Serum bilirubin ≤ 1.5 x ULN,
- Serum albumin ≥ 2.5 g/dL,
- Calculated creatinine clearance ≥ 30 mL/min (Modification of Diet in Renal Disease formula);

9. Negative serum pregnancy test. The serum pregnancy test had to be conducted prior to the first administration of AUY922 (≤ 72 hours prior to dosing) in all women of childbearing potential (WCBP), all pre-menopausal women and women < 2 years after the onset of menopause;
10. Patients had to be willing and able to undergo bone marrow aspirates as per protocol, with/without bone marrow biopsy according to their center's practice. The bone marrow aspirate/biopsy had to be adequate to allow for comparison for the later efficacy response assessments;
11. Able to sign informed consent.

Exclusion criteria

1. Patients who had received allogenic stem cell transplantation < 12 months prior to entry in the study;
2. Patients who had received allogenic stem cell transplantation and shown evidence of active graft-versus-host disease that required immunosuppressive therapy;
3. Patients with unresolved diarrhea ≥ Common Terminology Criteria for Adverse Events (CTCAE) Grade 2;
4. Patients with acute or chronic liver disease;
5. Peripheral neuropathy > CTCAE Grade 1 (only for patients in the combination part of the study);
6. 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;
7. Pregnant or lactating women;
8. Fertile 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;
9. Impaired cardiac function or clinically significant cardiac diseases, including any of the following:
   - History (or family history) of long QT syndrome,
   - Mean QTcF ≥ 450 msec on screening electrocardiogram (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 function [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 (RBBB) with left anterior hemiblock (LAH). ST segment elevations or depressions > 1 mm, 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 were currently receiving treatment with any medication which had a relative risk or prolonging the QTcF interval or inducing Torsades de and who could not be discontinued or switched to an alternative drug prior to commencing AUY922 dosing,
- Obligate use of a cardiac pacemaker;

10. Known diagnosis of human immunodeficiency virus (HIV) infection (HIV testing was not mandatory);
11. Patients with known disorders due to a deficiency in bilirubin glucuronidation (e.g. Gilbert's syndrome);
12. Patients with a history of another malignancy within the past 5 years except adequately treated basal cell skin cancer or carcinoma in situ of the cervix;
13. Prior treatment with any HSP90 or histone deacetylase inhibitor for the treatment of MM;
14. Prior treatment with bortezomib (only for patients in the combination part of the study);
15. 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 was 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);
16. Patients who had not recovered (≤ CTCAE grade 1) from side effects of previous systemic anticancer therapy prior to the first dose of study treatment;
17. Patients who had received either immunotherapy within ≤ 8 weeks; chemotherapy within ≤ 4 weeks; or radiation therapy to > 30% of marrow-bearing bone within≤2 weeks prior to starting study treatment; or who had not yet recovered from side effects of such therapies (≤ CTCAE grade 1);
18. Treatment with therapeutic doses of coumarin-based anticoagulants (e.g. warfarin sodium, Coumadin®). Low doses of courmarin-based anticoagulants (e.g. ≤ 2 mg/day for line patency) were permitted;
19. Patients who had received steroids (e.g. dexamethasone) ≤ 2 weeks prior to starting study treatment or who had not recovered from side effects of such therapy. Concomitant therapy medica-

tions that included corticosteroids were allowed if patients received < 20 mg of prednisone or equivalent as indicated for other medical conditions (and not as maintenance or an anticancer therapy for MM) or up to 100 mg of hydrocortisone as premedication for administration of certain medications or blood products, while enrolled in this study;

20. Patients who had contraindications to the use of high doses of dexamethasone (only for patients receiving combination treatment during the study);
21. Patients who had undergone major surgery ≤ 4 weeks prior to starting study drug or who had not recovered from side effects of such therapy;
22. Patients who were unwilling or unable to comply with the protocol.

Participant Flow

Patient disposition by treatment in Phase I (All patients) – Dose escalation part

	AUY922 8 mg/m^2 N=3 n (%)	AUY922 16 mg/m^2 N=3 n (%)	AUY922 30 mg/m^2 N=3 n (%)	AUY922 45 mg/m^2 N=5 n (%)	AUY922 60 mg/m^2 N=3 n (%)	AUY922 70 mg/m^2 N=7 n (%)	All patients N=24 n (%)
Patients enrolled							
Untreated	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
Treated	3 (100.0)	3 (100.0)	3 (100.0)	5 (100.0)	3 (100.0)	7 (100.0)	24 (100.0)
Patients treated							
Treatment completed as per protocol	3 (100.0)	2 (66.7)	0 (0.0)	1 (20.0)	3 (100.0)	3 (42.9)	12 (50.0)
Treatment discontinued	0 (0.0)	1 (33.3)	3 (100.0)	4 (80.0)	0 (0.0)	4 (57.1)	12 (50.0)
Treatment ongoing	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							
Adverse Event(s)	0 (0.0)	1 (33.3)	0 (0.0)	3 (60.0)	0 (0.0)	4 (57.1)	8 (33.3)
Patient withdrew consent	0 (0.0)	0 (0.0)	1 (33.3)	1 (20.0)	0 (0.0)	0 (0.0)	2 (8.3)
New cancer therapy	0 (0.0)	0 (0.0)	2 (66.7)	0 (0.0)	0 (0.0)	0 (0.0)	2 (8.3)
Disease progression	3 (100.0)	2 (66.7)	0 (0.0)	1 (20.0)	3 (100.0)	3 (42.9)	12 (50.0)

Patient disposition by treatment in Phase Ib (All patients) – Combination part

	AUY922 50 mg/m^2 + Bort. 1.3 mg/m^2 N=5 n (%)	All patients N=5 n (%)
Patients enrolled		
Untreated	0 (0.0)	0 (0.0)
Treated	5 (100.0)	5 (100.0)
Patients treated		
Treatment completed as per protocol	0 (0.0)	0 (0.0)
Treatment discontinued	5 (100.0)	5 (100.0)
Treatment ongoing	0 (0.0)	0 (0.0)
Primary reason for end of treatment		

Adverse Event(s)	5 (100.0)	5 (100.0)

Baseline Characteristics

Demographic summary by treatment group in Phase I (Full analysis set)

		AUY922 8 mg/m^2 N=3	AUY922 16 mg/m^2 N=3	AUY922 30 mg/m^2 N=3	AUY922 45 mg/m^2 N=5	AUY922 60 mg/m^2 N=3	AUY922 70 mg/m^2 N=7	All patients N=24
Age (years)	Mean	63.3	56.3	60.0	66.8	63.7	60.4	62.0
	SD	3.06	14.15	7.94	8.35	10.41	11.34	9.48
	Median	64.0	64.0	63.0	70.0	67.0	62.0	63.5
	Min	60	40	51	56	52	39	39
	Max	66	65	66	75	72	75	75
Age group (years)	< 65	2 (66.7)	2 (66.7)	2 (66.7)	2 (40.0)	1 (33.3)	5 (71.4)	14 (58.3)
	≥ 65	1 (33.3)	1 (33.3)	1 (33.3)	3 (60.0)	2 (66.7)	2 (28.6)	10 (41.7)
Gender - n (%)	Male	3 (100.0)	2 (66.7)	1 (33.3)	2 (40.0)	3 (100.0)	4 (57.1)	15 (62.5)
	Female	0 (0.0)	1 (33.3)	2 (66.7)	3 (60.0)	0 (0.0)	3 (42.9)	9 (37.5)
Predominant Race - n (%)	Caucasian	3 (100.0)	2 (66.7)	3 (100.0)	4 (80.0)	3 (100.0)	4 (57.1)	19 (79.2)
	Black	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
	Asian	0 (0.0)	1 (33.3)	0 (0.0)	1 (20.0)	0 (0.0)	1 (14.3)	3 (12.5)
	Native American	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
	Pacific Islander	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
	Other	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	2 (28.6)	2 (8.3)
Ethnicity - n (%)	Hispanic /Latino	1 (33.3)	2 (66.7)	0 (0.0)	2 (40.0)	1 (33.3)	2 (28.6)	8 (33.3)
	Chinese	0 (0.0)	1 (33.3)	0 (0.0)	1 (20.0)	0 (0.0)	1 (14.3)	3 (12.5)
	Indian (Indian subcontinent)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
	Japanese	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
	Mixed Ethnicity	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	1 (14.3)	1 (4.2)
	Other	2 (66.7)	0 (0.0)	3 (100.0)	2 (40.0)	2 (66.7)	3 (42.9)	12 (50.0)
Body Mass Index (kg/m^2)	Mean	27.7	26.3	24.3	24.4	27.4	26.7	26.1
	SD	2.98	2.06	3.89	1.87	3.39	3.42	2.98
	Median	27.8	25.3	22.4	24.8	29.1	26.2	25.3
	Min	25	25	22	22	24	23	22
	Max	31	29	29	27	30	33	33
ECOG Performance	Grade 0	0 (0.0)	0 (0.0)	2 (66.7)	1 (20.0)	1 (33.3)	1 (14.3)	5 (20.8)

Status								
	Grade 1	3 (100.0)	3 (100.0)	1 (33.3)	3 (60.0)	2 (66.7)	6 (85.7)	18 (75.0)
	Grade 2	0 (0.0)	0 (0.0)	0 (0.0)	1 (20.0)	0 (0.0)	0 (0.0)	1 (4.2)
	Grade >2	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)

Demographic summary by treatment group in Phase Ib (Full analysis set)

		AUY922 50 mg/m^2 + Bort. 1.3 mg/m^2 N=5	**All patients N=5**
Age (years)	Mean	62.0	62.0
	SD	15.22	15.22
	Median	68.0	68.0
	Min	35	35
	Max	72	72
Age group (years)	< 65	1 (20.0)	1 (20.0)
	≥ 65	4 (80.0)	4 (80.0)
Gender - n (%)	Male	2 (40.0)	2 (40.0)
	Female	3 (60.0)	3 (60.0)
Predominant Race - n (%)	Caucasian	5 (100.0)	5 (100.0)
	Black	0 (0.0)	0 (0.0)
	Asian	0 (0.0)	0 (0.0)
	Native Ameri-can	0 (0.0)	0 (0.0)
	Pacific Islander	0 (0.0)	0 (0.0)
	Other	0 (0.0)	0 (0.0)
Ethnicity - n (%)	Hispanic/Latino	0 (0.0)	0 (0.0)
	Chinese	0 (0.0)	0 (0.0)
	Indian (Indian subcontinent)	0 (0.0)	0 (0.0)
	Japanese	0 (0.0)	0 (0.0)
	Mixed Ethnicity	0 (0.0)	0 (0.0)
	Other	5 (100.0)	5 (100.0)
Body Mass Index (kg/m^2)	Mean	28.9	28.9
	SD	2.41	2.41
	Median	28.9	28.9
	Min	26	26
	Max	32	32
ECOG Performance Sta-tus	Grade 0	2 (40.0)	2 (40.0)
	Grade 1	3 (60.0)	3 (60.0)
	Grade 2	0 (0.0)	0 (0.0)
	Grade >2	0 (0.0)	0 (0.0)

Safety Results

Adverse Events by System Organ Class (Safety Population)

Incidence of AEs regardless of causality (occurring in at least 10% of all patients) by primary system organ class and treatment group in Phase I (Safety set)

Primary system organ class	AUY922 8 mg/m^2 N=3	AUY922 16 mg/m^2 N=3	AUY922 30 mg/m^2 N=3	AUY922 45 mg/m^2 N=5	AUY922 60 mg/m^2 N=3	AUY922 70 mg/m^2 N=7	All patients N=24
Patients with at least one AE	3 (100.0)	3 (100.0)	3 (100.0)	5 (100.0)	3 (100.0)	7 (100.0)	24 (100.0)
Gastrointestinal disorders	0 (0.0)	2 (66.7)	3 (100.0)	5 (100.0)	3 (100.0)	6 (85.7)	19 (79.2)
Blood and lymphatic system disorders	1 (33.3)	3 (100.0)	1 (33.3)	4 (80.0)	0 (0.0)	4 (57.1)	13 (54.2)
Infections and infestations	2 (66.7)	1 (33.3)	1 (33.3)	2 (40.0)	0 (0.0)	6 (85.7)	12 (50.0)
General disorders and administration site conditions	1 (33.3)	1 (33.3)	1 (33.3)	4 (80.0)	1 (33.3)	3 (42.9)	11 (45.8)
Investigations	0 (0.0)	1 (33.3)	1 (33.3)	4 (80.0)	2 (66.7)	2 (28.6)	10 (41.7)
Eye disorders	0 (0.0)	0 (0.0)	0 (0.0)	2 (40.0)	2 (66.7)	5 (71.4)	9 (37.5)
Musculo-skeletal and connective tissue disorders	1 (33.3)	0 (0.0)	0 (0.0)	2 (40.0)	2 (66.7)	4 (57.1)	9 (37.5)
Metabolism and nutrition disorders	0 (0.0)	2 (66.7)	0 (0.0)	1 (20.0)	0 (0.0)	4 (57.1)	7 (29.2)
Respiratory, thoracic and mediastinal disorders	0 (0.0)	0 (0.0)	0 (0.0)	1 (20.0)	0 (0.0)	5 (71.4)	6 (25.0)
Vascular disorders	0 (0.0)	1 (33.3)	0 (0.0)	2 (40.0)	1 (33.3)	2 (28.6)	6 (25.0)
Nervous system disorders	0 (0.0)	0 (0.0)	1 (33.3)	1 (20.0)	0 (0.0)	3 (42.9)	5 (20.8)
Skin and subcutaneous tissue disorders	0 (0.0)	0 (0.0)	0 (0.0)	1 (20.0)	1 (33.3)	3 (42.9)	5 (20.8)
Cardiac disorders	1 (33.3)	0 (0.0)	0 (0.0)	1 (20.0)	0 (0.0)	2 (28.6)	4 (16.7)

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.

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

Primary system organ class	AUY 922 50 mg/m^2+ Bort.1.3 mg/m^2 (N=5)	All patients (N=5)
Patients with at least one AE	5 (100.0)	5 (100.0)
Gastrointestinal disorders	4 (80.0)	4 (80.0)
General disorders and administration site conditions	4 (80.0)	4 (80.0)
Blood and lymphatic system disorders	3 (60.0)	3 (60.0)
Eye disorders	3 (60.0)	3 (60.0)
Infections and infestations	3 (60.0)	3 (60.0)
Metabolism and nutrition disorders	3 (60.0)	3 (60.0)
Musculoskeletal and connective tissue disorders	3 (60.0)	3 (60.0)
Nervous system disorders	3 (60.0)	3 (60.0)
Skin and subcutaneous tissue disorders	3 (60.0)	3 (60.0)
Cardiac disorders	2 (40.0)	2 (40.0)
Investigations	2 (40.0)	2 (40.0)
Psychiatric disorders	2 (40.0)	2 (40.0)
Respiratory, thoracic and mediastinal disorders	2 (40.0)	2 (40.0)
Reproductive system and breast disorders	1 (20.0)	1 (20.0)
Vascular disorders	1 (20.0)	1 (20.0)

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.

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

Incidence of AEs regardless of causality (occurring in at least 10% of all patients) by preferred term and treatment group in Phase I (Safety set)

Preferred term	AUY922 8 mg/m^2 N=3	AUY922 16 mg/m^2 N=3	AUY922 30 mg/m^2 N=3	AUY922 45 mg/m^2 N=5	AUY922 60 mg/m^2 N=3	AUY922 70 mg/m^2 N=7	All patients N=24
Patients with at least one AE	3 (100.0)	3 (100.0)	3 (100.0)	5 (100.0)	3 (100.0)	7 (100.0)	24 (100.0)
Diarrhoea	0 (0.0)	1 (33.3)	2 (66.7)	4 (80.0)	3 (100.0)	6 (85.7)	16 (66.7)
Pyrexia	1 (33.3)	1 (33.3)	0 (0.0)	4 (80.0)	0 (0.0)	3 (42.9)	9 (37.5)
Anaemia	1 (33.3)	2 (66.7)	1 (33.3)	1 (20.0)	0 (0.0)	2 (28.6)	7 (29.2)
Nausea	0 (0.0)	0 (0.0)	2 (66.7)	1 (20.0)	0 (0.0)	4 (57.1)	7 (29.2)
Thrombocytopenia	1 (33.3)	0 (0.0)	0 (0.0)	3 (60.0)	0 (0.0)	2 (28.6)	6 (25.0)
Fatigue	1 (33.3)	1 (33.3)	0 (0.0)	2 (40.0)	1 (33.3)	0 (0.0)	5 (20.8)
Electrocardiogram QT prolonged	0 (0.0)	0 (0.0)	0 (0.0)	1 (20.0)	2 (66.7)	1 (14.3)	4 (16.7)
Hypertension	0 (0.0)	0 (0.0)	0 (0.0)	1 (20.0)	1 (33.3)	2 (28.6)	4 (16.7)

Night blindness	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	2 (66.7)	2 (28.6)	4 (16.7)
Photopsia	0 (0.0)	0 (0.0)	0 (0.0)	1 (20.0)	1 (33.3)	2 (28.6)	4 (16.7)
Upper respiratory tract infection	0 (0.0)	1 (33.3)	1 (33.3)	1 (20.0)	0 (0.0)	1 (14.3)	4 (16.7)
Visual impairment	0 (0.0)	0 (0.0)	0 (0.0)	1 (20.0)	0 (0.0)	3 (42.9)	4 (16.7)
Vomiting	0 (0.0)	0 (0.0)	0 (0.0)	2 (40.0)	0 (0.0)	2 (28.6)	4 (16.7)
Abdominal pain	0 (0.0)	1 (33.3)	1 (33.3)	1 (20.0)	0 (0.0)	0 (0.0)	3 (12.5)
Cough	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	3 (42.9)	3 (12.5)
Nasopharyngitis	2 (66.7)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	1 (14.3)	3 (12.5)
Rash	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	1 (33.3)	2 (28.6)	3 (12.5)

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.

Incidence of AEs (occurring in atleast 40% of all patients) regardless of causality by preferred term and treatment group in Phase Ib (Safety set)

Preferred term	AUY 922 50 mg/m^2 + Bort. 1.3 mg/m^2 (N=5)	All patients (N=5)
Patients with at least one AE	5 (100.0)	5 (100.0)
Diarrhoea	4 (80.0)	4 (80.0)
Musculoskeletal pain	3 (60.0)	3 (60.0)
Nasopharyngitis	3 (60.0)	3 (60.0)
Thrombocytopenia	3 (60.0)	3 (60.0)
Abdominal pain	2 (40.0)	2 (40.0)
C-reactive protein increased	2 (40.0)	2 (40.0)
Fatigue	2 (40.0)	2 (40.0)
Leukopenia	2 (40.0)	2 (40.0)
Nausea	2 (40.0)	2 (40.0)
Neutropenia	2 (40.0)	2 (40.0)
Night blindness	2 (40.0)	2 (40.0)
Night sweats	2 (40.0)	2 (40.0)
Photopsia	2 (40.0)	2 (40.0)
Pyrexia	2 (40.0)	2 (40.0)
Visual impairment	2 (40.0)	2 (40.0)
Vomiting	2 (40.0)	2 (40.0)

Serious Adverse Events and Deaths

Number of patients who died or experienced other serious or clinically significant adverse events in Phase I (Safety set)

Patients with serious or significant AEs	AUY922 8 mg/m^2 N=3	AUY922 16 mg/m^2 N=3	AUY922 30 mg/m^2 N=3	AUY922 45 mg/m^2 N=5	AUY922 60 mg/m^2 N=3	AUY922 70 mg/m^2 N=7	All patients N=24
Death on study	0 (0.0)	1 (33.3)	0 (0.0)	1 (20.0)	0 (0.0)	0 (0.0)	2 (8.3)*
SAEs	0 (0.0)	1 (33.3)	0 (0.0)	3 (60.0)	0 (0.0)	3 (42.9)	7 (29.2)
Discontinued due to AEs	0 (0.0)	1 (33.3)	0 (0.0)	3 (60.0)	0 (0.0)	4 (57.1)	8 (33.3)
Discontinued due to SAEs	0 (0.0)	0 (0.0)	0 (0.0)	2 (40.0)	0 (0.0)	1 (14.3)	3 (12.5)

* One further death occurred > 28 days after last dose and is not counted in this table.

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

Patients with serious or significant AEs	AUY 922 50 mg/m^2 + Bort. 1.3 mg/m^2 (N=5)	All patients (N=5)
Death on study	0 (0.0)	0 (0.0)
SAEs	3 (60.0)	3 (60.0)
Discontinued due to AEs	5 (100.0)	5 (100.0)
Discontinued due to SAEs	2 (40.0)	2 (40.0)

Other Relevant Findings

None

Date of Clinical Trial Report

24-May-2012

Date Inclusion on Novartis Clinical Trial Results Database

21-Aug-2012

Date of Latest Update