Sponsor

Novartis

Generic Drug Name

Alpelisib/BYL719 and AUY922

Trial Indication(s)

Advanced or metastatic gastric cancer (GC) carrying a molecular alteration of PIK3CA or an amplification of HER2

Protocol Number

CBYL719X2103

Protocol Title

A phase IB, multicenter, open-label dose escalation study of the PI3K inhibitor BYL719 in combination with the HSP90 inhibitor AUY922 in patients with advanced or metastatic gastric cancer carrying a molecular alteration of PIK3CA or an amplification of HER2

Clinical Trial Phase

Phase Ib

Phase of Drug Development

Phase I

Study Start/End Dates

27-Dec-2012 to 24-Mar-2014

Reason for Termination (If applicable)

The study was terminated early due to slow enrollment of the targeted population.

Study Design/Methodology

This was a multi-center, open-label, dose finding, Phase Ib study to estimate the MTDs and/or recommended dose(s) for safety expansion (RDE) for the combination of alpelisib and AUY922, followed by an expansion phase to further assess the safety and preliminary activity of the combination in a selected population with advanced or metastatic GC carrying molecular alterations (mutation/amplification) of PIK3CA or amplification of HER2. The starting dose for alpelisib was 270 mg/day orally and for AUY922 28 mg/m^2/week by intravenous infusion.

Centers

10 centers in 6 countries: Germany (2), Japan (1), South Korea (2), Switzerland (1), Taiwan (1), United States of America (3)

Publication

None

Objectives:

The primary objective of the study was to determine the maximum tolerated dose (MTD) and/or recommended dose expansion (RDE) and schedule of alpelisib and AUY922 when used as a combination in patients with advanced or metastatic gastric cancer carrying a molecular alteration of PIK3CA and/or an amplification of HER2.

The secondary objectives were

- To characterize the safety and tolerability of alpelisib and AUY922 in combination
- To assess the preliminary anti-tumor activity of alpelisib/AUY922 combination, and
- To determine the single dose PK of alpelisib single agent and multiple doses PK of alpelisib and AUY922 in combination.

Since the study was discontinued, the MTD and/or RDE were not determined and the dose expansion phase of the study was not initiated.

Test Products, Doses, and Modes of Administration

Alpelisib was supplied as oral tablets of dosage strengths of 10, 50 and 200 mg. The tablets were differentiated through different tablet sizes and/or colors. AUY922 was supplied as 50 mg/20 mL concentrate vials for intravenous infusion.

The starting dose for alpelisib was 270 mg/day orally and for AUY922 28 mg/m^2/week by intravenous infusion.

Statistical Methods

An adaptive Bayesian logistic regression model (BLRM) guided by the dose escalation with escalation with overdose control (EWOC) principle was used in the dose-escalation. A 5-parameter BLRM for combination treatment was fitted on the Cycle 1 dose-limiting toxicity(DLT) data (i.e. absence or presence of DLT) accumulated throughout the dose escalation to model the dose toxicity relationship of alpelisib and AUY922 when given in combination. Information available from single agent studies was used to derive prior distributions for the BLRM model parameters.

Data from participating centers were combined. The data were summarized with respect to demographic and baseline characteristics, efficacy observations and measurements, safety observations and measurements, and pharmacokinetic and biomarker measurements.

The following analysis sets were used:

The full analysis set (FAS) included all patients who received at least one dose of alpelisib or AUY922. Patients were classified according to the planned treatment combination. The FAS was used for all listings of raw data. Unless otherwise specified, the FAS was the default analysis set used for all analyses.

The safety set (SS) included all patients who received at least one dose of alpelisib or AUY922, and had at least one valid post-baseline safety assessment. The statement that a patient had no adverse events (on the Adverse Event eCRF) constituted a valid safety assessment.

Patients were classified according to treatment received, where treatment received was defined as: The treatment assigned if it was received at least once or the first treatment received when starting therapy with study treatment if the assigned treatment was never received.

The dose-determining set (DDS) consisted of all patients from the safety set who either met the following minimum exposure criterion and had sufficient safety evaluations during Cycle 1, or discontinued earlier due to DLT during Cycle 1.

A patient was considered to have met the minimum exposure criterion in Cycle 1, if having received at least 21 out of 28 planned daily doses of alpelisib (qd/bid) and at least 3 of the 4 planned doses of AUY922. To complete the minimum safety evaluations a patient must have been observed for at least 1 cycle (28 days following the dose on Cycle 1 Day 1) and considered to have had sufficient safety data by both the Sponsor and Investigators to conclude that a DLT did not occur in Cycle 1. Patients who did not meet these minimum exposure and safety evaluation requirements were regarded as ineligible for the dose-determining set.

The pharmacokinetic analysis set (PAS) consisted of all patients who had at least one blood sample providing evaluable PK data. The PAS was used for summaries of PK data (Tables and Figures) as well as for listings of derived parameters. Patients were removed from the estimation of certain PK parameters on an individual basis depending on the number of available blood samples. These patients were identified at the time of the analyses.

Study Population: Key Inclusion/Exclusion Criteria

Inclusion criteria

- Written informed consent obtained prior to any screening procedures (including molecular pre-screening, if applicable).
- Patients aged ≥ 18 years (male or female).
- Patients with cytologically or histologically confirmed advanced or metastatic adenocarcinoma of stomach or gastroesophageal junction. Patients must not have had a complete gastrectomy.

- Patients with documented gastric tumors carrying PIK3CA mutation or amplification, or HER2-overexpression (IHC3+ or IHC2+ with positive fluorescence in situ hybridization), or both.
- A representative tumor sample was available for molecular testing, unless agreed upon between Novartis and the Investigator. An archival tumor sample may have been submitted; however, if not available, a newly obtained tumor biopsy may have been submitted instead.
- Patients progressing after at least 1 but no more than 3 previous lines of treatment for advanced or metastatic disease.
- Patients with PIK3CA mutated or amplified tumors must have failed at least 1 line but no more than 3 lines of standard chemotherapy and/or targeted agents.
- Patients with HER2 amplified tumor must have failed at least 1 line, but no more than 3 lines, with or without anti-HER2 therapy (e.g. trastuzumab or lapatinib containing regimens) as part of their previous treatments. All HER2 positive patients were expected to have received trastuzumab unless contraindications were present or trastuzumab was unavailable.
- Measurable disease as determined by the Response Evaluation Criteria In Solid Tumors (RECIST) v1.1. Lesions in previously irradiated areas should not have been considered measurable unless they had progressed since the radiotherapy.
- Patients were expected to tolerate a combination therapy with World Health Organization (WHO) Performance Status (PS) ≤ 1.
- Adequate bone marrow, liver and other organ functions and laboratory parameters
- Recovery from all AEs of previous anti-cancer therapies, including surgery and radiotherapy, to baseline or to CTCAE Grade ≤ 1, except for alopecia.
- Negative serum pregnancy (β-hCG) test within 72 hrs before starting study treatment in all pre-menopausal women and women <12 months after the onset of menopause.

Exclusion criteria

- Progressive disease (PD) during or after prior combination treatment with PI3K-inhibitors and HSP90- inhibitors.
- Patients with a history of prior significant toxicity from another PI3K- or HSP90- inhibitor requiring discontinuation of treatment.
- Patients with primary central nervous system (CNS) tumor or uncontrolled CNS metastatic involvement.
- Patients who had received prior systemic anti-cancer treatment within the following time frames:
- Cyclical chemotherapy within a period of time that was shorter than the cycle length used for that treatment (e.g. 6 weeks for nitrosourea, mitomycin-C) prior to starting study treatment

- Biologic therapy (e.g. antibodies), continuous or intermittent small molecule therapeutics, or any other investigational agents within a period of time which is ≤ 5 $t_{1/2}$ or ≤ 4 weeks (whichever was shorter) prior to starting study treatment
- Patients who received radiotherapy ≤ 4 weeks prior to starting study drug, who had not recovered from side effects of such therapy to baseline or grade ≤ 1 and/or from whom ≥ 30% of the bone marrow was irradiated.
- Patients who had undergone major surgery ≤ 4 weeks prior to starting study treatment or who had not recovered from side effects of such procedure.
- Patients who were currently receiving medication with a known risk of prolonging the QT interval or inducing Torsades de Pointes and the treatment could not either be discontinued or switched to a different medication prior to starting study drug treatment. For a list of prohibited drugs with a known risk of Torsades de Pointes.
- Clinically significant cardiac disease or impaired cardiac function.
- Patients with diabetes mellitus requiring insulin treatment and/or with clinical signs or with fasting glucose ≥ 140 mg/dL/7.8 mmol/L, history of clinically significant gestational diabetes mellitus or documented steroid-induced diabetes mellitus; patients with diarrhea CTCAE grade ≥ 2.
- Patients with acute or chronic pancreatitis; history or current evidence of central serous retinopathy, retinal vein occlusion or ophthalmopathy as assessed by ophthalmologic examination at baseline that would have been considered a risk factor for central serous retinopathy/ retinal vein occlusion.
- Impaired gastrointestinal (GI) function or GI disease that may significantly alter the absorption of oral alpelisib.
- Patients receiving chronic slow-release formulation of Proton Pump Inhibitors (PPI), H2-antagonists or other gastric pH elevating agents.
- Treatment with therapeutic doses of coumarin-based anticoagulants (e.g., warfarin sodium, Coumadin®). Low doses of coumarin-based anticoagulants (e.g. ≤ 2 mg/day for line patency) are permitted.
- Patients receiving chronic or high dose corticosteroids therapy (inhaled steroids and short courses of oral steroids for anti-emesis or as an appetite stimulant are allowed)

Other protocol-defined inclusion/exclusion criteria may apply.

Participant Flow Table

Patient Disposition by Treatment (Full Analysis Set)

Disposition reason	Alpelisib 270 mg + AUY922 28 mg/m2 N=10 n (%)	Alpelisib 270 mg + AUY922 35 mg/m2 N=3 n (%)	Alpelisib 270 mg + AUY922 40 mg/m2 N=5 n (%)	All patients N=18 n (%)
Patients treated				
Treatment discontinued	10 (100.0)	3 (100.0)	5 (100.0)	18 (100.0)
Primary reason for end of treatment				
Progressive disease	6 (60.0)	3 (100.0)	5 (100.0)	14 (77.8)
Patient/guardian decision	2 (20.0)	0	0	2 (11.1)
Physician decision	1 (10.0)	0	0	1 (5.6)
Adverse event	1 (10.0)	0	0	1 (5.6)

Baseline Characteristics

Demographics and Other Baseline Characteristics (Full Analysis Set)

Demographic variable	Alpelisib 270 mg + AUY922 28 mg/m2 N=10 n (%)	Alpelisib 270 mg + AUY922 35 mg/m2 N=3 n (%)	Alpelisib 270 mg + AUY922 40 mg/m2 N=5 n (%)	All patients N=18 n (%)
Age (years)				
Mean (SD)	57.1 (9.64)	60.0 (17.09)	58.0 (14.88)	57.8 (11.70)
Median	54.5	62.0	60.0	59.5
Min; max	44; 73	42; 76	34; 75	34; 76
Age category (years) – n (%)				
<65	7 (70.0)	2 (66.7)	4 (80.0)	13 (72.2)
≥ 65	3 (30.0)	1 (33.3)	1 (20.0)	5 (27.8)
Sex – n (%)				
Male	8 (80.0)	3 (100)	5 (100)	16 (88.9)
Female	2 (20.0)	0	0	2 (11.1)
Race – n (%)				
Caucasian	10 (100)	1 (33.3)	3 (60.0)	14 (77.8)
Asian	0	2 (66.7)	2 (40.0)	4 (22.2)
Ethnicity – n (%)				
East Asian	0	2 (66.7)	2 (40.0)	4 (22.2)
Not reported	1 (10.0)	0	1 (20.0)	2 (11.1)
Unknown	1 (10.0)	0	1 (20.0)	2 (11.1)

Demographic variable	Alpelisib 270 mg + AUY922 28 mg/m2 N=10 n (%)	Alpelisib 270 mg + AUY922 35 mg/m2 N=3 n (%)	Alpelisib 270 mg + AUY922 40 mg/m2 N=5 n (%)	All patients N=18 n (%)
Other	8 (80.0)	1 (33.3)	1 (20.0)	10 (55.6)
Height (cm)				
Mean (SD)	174.5 (7.35)	167.8 (9.93)	172.6 (6.80)	172.9 (7.56)
Median	173.3	172.0	170.0	172.5
Min; max	162; 189	157; 175	165; 182	157; 189
Weight (kg)[1]				
Mean (SD)	90.41 (22.576)	63.43 (8.864)	79.76 (12.067)	82.96 (20.404)
Median	94.00	64.00	74.40	77.70
Min; max	60.0; 133.5	54.3; 72.0	69.0; 98.2	54.3; 133.5
Weight (kg) – n (%)[1]				
<55	0	1 (33.3)	0	1 (5.6)
≥ 55 to <75	3 (30.0)	2 (66.7)	3 (60.0)	8 (44.4)
≥ 75	7 (70.0)	0	2 (40.0)	9 (50.0)
Body mass index (kg/m^2)				
Mean (SD)	29.655 (7.2830)	22.438 (0.9666)	26.647 (2.2045)	27.616 (6.0652)
Median	29.006	22.170	27.291	27.309
Min; max	20.34; 45.39	21.63; 23.51	24.16; 29.65	20.34; 45.39
Body surface area (m^2)				
Mean (SD)	2.069 (0.2642)	1.720 (0.1670)	1.924 (0.1747)	1.971 (0.2546)
Median	2.090	1.750	1.850	1.885
Min; max	1.70; 2.52	1.54; 1.87	1.80; 2.23	1.54; 2.52
ECOG performance status (WHO) n (%)				
0	6 (60.0)	1 (33.3)	2 (40.0)	9 (50.0)
1	4 (40.0)	2 (66.7)	3 (60.0)	9 (50.0)
HER2 positive expression; n (%)				
Missing	1 (10.0)	0	1 (20.0)	2 (11.1)
Negative	1 (10.0)	0	0	1 (5.6)
Positive	8 (80.0)	3 (100)	4 (80.0)	15 (83.3)
HER2 amplification; n (%)				
Missing	3 (30.0)	2 (66.7)	2 (40.0)	7 (38.9)
Positive	7 (70.0)	1 (33.3)	3 (60.0)	11 (61.1)
PIK3CA mutation; n (%)				

Demographic variable	Alpelisib 270 mg + AUY922 28 mg/m2 N=10 n (%)	Alpelisib 270 mg + AUY922 35 mg/m2 N=3 n (%)	Alpelisib 270 mg + AUY922 40 mg/m2 N=5 n (%)	All patients N=18 n (%)
Missing	7 (70.0)	3 (100)	5 (100)	15 (83.3)
Mutant	1 (10.0)	0	0	1 (5.6)
Wild type	2 (20.0)	0	0	2 (11.1)
PIK3CA amplification; n(%)				
Missing	10 (100)	3 (100)	5 (100)	18 (100)

[1]At baseline
Body Mass Index: BMI [kg/m^2] = weight[kg] / (height[m]**2)
Body Surface Area (Gehan and George):
BSA[m2]=234.94*(height[cm]**0.422)*(weight[kg]**0.515)/10000
ECOG Performance status (WHO) 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, light house work, office work.

Summary of Efficacy

Primary Outcome Results

Summary of Primary Pharmacokinetic (PK) Parameters for Alpelisib in Plasma by Treatment Group at Cycle 1 Day 1 (PK Analysis Set)

Treatment group	Statistics	AUClast (hr*ng/mL)	AUCinf (hr*ng/mL)	Cmax (ng/mL)	Tmax (hr)
Alpelisib 270 mg + AUY922 28 mg/m^2, N=10	n	10	5	10	10
	Mean (SD)	13500 (5760)	14300 (5860)	1220 (532)	
	CV% mean	42.8	41.1	43.5	
	Geo-mean	12300	13400	1110	
	CV% Geo-mean	50.1	42.1	52.6	
	Median	14300	14900	1310	2.5
	Min; Max	5920; 21200	8480; 23200	529; 1900	1.25; 22.4
Alpelisib 270 mg + AUY922 35 mg/m^2, N=3	n	3		3	3
	Mean (SD)	18800 (798)		1680 (185)	
	CV% mean	4.2		11.0	
	Geo-mean	18800		1670	
	CV% Geo-mean	4.2		10.8	
	Median	18400		1580	6

Treatment group	Statistics	AUClast (hr*ng/mL)	AUCinf (hr*ng/mL)	Cmax (ng/mL)	Tmax (hr)
	Min; Max	18200; 19700		1560; 1890	3.08; 7.5
Alpelisib 270 mg + AUY922 40 mg/m^2, N=5	n	5	2	5	5
	Mean (SD)	11900 (5060)	15300 (176)	991 (489)	
	CV% mean	42.6	1.1	49.4	
	Geo-mean	10800	15300	878	
	CV% Geo-mean	54.0	1.1	63.2	
	Median	12500	15300	991	3.08
	Min; Max	4870; 18400	15200; 15400	381; 1510	3; 7.58

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 Plasma Alpelisib by Treatment Group at Cycle 1 Day 8 and Cycle 2 Day 1(PK Analysis Set)

Treatment group	Statistics	AUClast (hr*ng/mL)	AUCtau (hr*ng/mL)	Cmax (ng/mL)	Tmax (hr)
Cycle 1 Day 8					
Alpelisib 270 mg + AUY922 28 mg/m^2, N=10	n	9	5	9	9
	Mean (SD)	16400 (5850)	16600 (6120)	1460 (621)	
	CV% mean	35.8	36.9	42.4	
	Geo-mean	15400	15700	1340	
	CV% Geo-mean	38.4	37.4	48.1	
	Median	15500	15600	1310	4
	Min; Max	8790; 26200	9870; 26100	616; 2370	2.1; 23.1
Alpelisib 270 mg + AUY922 35 mg/m^2, N=3	n	3	1	3	3
	Mean (SD)	21900 (2750)	20600 (-)	1890 (163)	
	CV% mean	12.6		8.6	
	Geo-mean	21700	20600	1890	
	CV% Geo-mean	12.2		8.4	
	Median	20300	20600	1820	6
	Min; Max	20200; 25000	20600; 20600	1780; 2080	1.87; 7.03
Alpelisib 270 mg + AUY922 40 mg/m^2, N=5	n	3	3	3	3
	Mean (SD)	13700 (2700)	13800 (2710)	1280 (454)	
	CV% mean	19.7	19.7	35.6	

Treatment group	Statistics	AUClast (hr*ng/mL)	AUCtau (hr*ng/mL)	Cmax (ng/mL)	Tmax (hr)
	Geo-mean	13500	13600	1220	
	CV% Geo-mean	20.9	21.1	37.1	
	Median	14400	14700	1210	3.05
	Min; Max	10700; 16000	10700; 15900	859; 1760	3.05; 3.3
Cycle 2 Day 1					
Alpelisib 270 mg + AUY922 28 mg/m^2, N=10	n	7	3	7	7
	Mean (SD)	15000 (6510)	16400 (9290)	1070 (412)	
	CV% mean	43.3	56.5	38.5	
	Geo-mean	14000	14900	1020	
	CV% Geo-mean	41.1	57.4	33.7	
	Median	12400	12600	967	6.42
	Min; Max	9170; 27100	9680; 27000	674; 1950	2; 22.5
Alpelisib 270 mg + AUY922 35 mg/m^2, N=3	n	2	1	2	2
	Mean (SD)	21900 (10700)	14500 (-)	1720 (537)	
	CV% mean	48.9		31.2	
	Geo-mean	20500	14500	1680	
	CV% Geo-mean	54.4		32.6	
	Median	21900	14500	1720	4.48
	Min; Max	14300; 29400	14500; 14500	1340; 2100	2.97; 6
Alpelisib 270 mg + AUY922 40 mg/m^2, N=5	n	1	1	1	1
	Mean (SD)	13100 (-)	13400 (-)	1060 (-)	
	CV% mean				
	Geo-mean	13100	13400	1060	
	CV% Geo-mean				
	Median	13100	13400	1060	3.08
	Min; Max	13100; 13100	13400; 13400	1060; 1060	3.08; 3.08

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 Plasma AUY922 by Treatment Group at Cycle 1 Day 8 and Cycle 2 Day 1 (PK Analysis Set)

Treatment group	Statistics	AUClast (hr*ng/mL)	AUC0-168 (hr*ng/mL)	Cmax (ng/mL)	Tmax (hr)
Cycle 1 Day 8					
Alpelisib 270 mg + AUY922 28 mg/m^2, N=10	n	10	9	10	10
	Mean (SD)	1430 (1040)	1310 (683)	495 (90.9)	
	CV% mean	72.8	52.2	18.3	
	Geo-mean	1190	1190	488	
	CV% Geo-mean	65.4	45.7	17.8	
	Median	1080	1090	465	0.525
	Min; Max	619; 3750	658; 2940	383; 668	0.5; 0.967
Alpelisib 270 mg + AUY922 35 mg/m^2, N=3	n	3	3	3	3
	Mean (SD)	2240 (1530)	2240 (1530)	1280 (1230)	
	CV% mean	68.5	68.6	96.3	
	Geo-mean	1940	1940	948	
	CV% Geo-mean	70.3	70.4	116.1	
	Median	1480	1480	671	0.5
	Min; Max	1230; 4000	1230; 4010	470; 2700	0.417; 0.5
Alpelisib 270 mg + AUY922 40 mg/m^2, N=5	n	3	2	3	3
	Mean (SD)	3220 (1920)	2330 (1660)	635 (181)	
	CV% mean	59.7	71.2	28.5	
	Geo-mean	2730	2010	616	
	CV% Geo-mean	88.5	92.1	32.2	
	Median	3530	2330	704	0.867
	Min; Max	1160; 4960	1150; 3500	430; 771	0.417; 0.983
Cycle 2 Day 1					
Alpelisib 270 mg + AUY922 28 mg/m^2, N=10	n	8	7	8	8
	Mean (SD)	1350 (1210)	1080 (708)	434 (125)	
	CV% mean	89.3	65.4	28.7	
	Geo-mean	990	942	417	
	CV% Geo-mean	100.2	57.3	31.1	

Treatment group	Statistics	AUClast (hr*ng/mL)	AUC0-168 (hr*ng/mL)	Cmax (ng/mL)	Tmax (hr)
	Median	882	894	471	0.592
	Min; Max	326; 3780	496; 2600	275; 600	0.25; 1
Alpelisib 270 mg + AUY922 35 mg/m^2, N=3	n	2	2	2	2
	Mean (SD)	1550 (73)	1550 (75.2)	672 (102)	
	CV% mean	4.7	4.8	15.2	
	Geo-mean	1550	1550	668	
	CV% Geo-mean	4.7	4.8	15.3	
	Median	1550	1550	672	0.958
	Min; Max	1500; 1600	1500; 1610	600; 744	0.867; 1.05
Alpelisib 270 mg + AUY922 40 mg/m^2, N=5	n	3	3	3	3
	Mean (SD)	4670 (5620)	3860 (4150)	651 (96.5)	
	CV% mean	120.4	107.5	14.8	
	Geo-mean	2670	2530	647	
	CV% Geo-mean	215.8	162.9	14.8	
	Median	2060	2070	640	0.6
	Min; Max	831; 11100	906; 8600	561; 753	0.5; 1.03

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 Plasma BJP762 by Treatment Group at Cycle 1 Day 8 and Cycle 2 Day 1 (PK Analysis Set)

Treatment group	Statistics	Cmax (ng/mL)	Tmax (hr)	T1/2 (hr)
Cycle 1 Day 8				
Alpelisib 270 mg + AUY922 28 mg/m^2, N=10	n	10	10	8
	Mean (SD)	955 (537)		32.5 (14.2)
	CV% mean	56.3		43.6
	Geo-mean	799		28.9
	CV% Geo-mean	76.4		60.5
	Median	982	0.983	31.2
	Min; Max	210; 1880	0.517; 1.08	10.6; 49.9
Alpelisib 270 mg + AUY922 35 mg/m^2, N=3	n	3	3	2
	Mean (SD)	1590 (1020)		45.1 (19.6)

Treatment group	Statistics	Cmax (ng/mL)	Tmax (hr)	T1/2 (hr)
	CV% mean	63.9		43.4
	Geo-mean	1400		42.9
	CV% Geo-mean	64.3		47.3
	Median	1070	1.08	45.1
	Min; Max	939; 2760	0.917; 1.08	31.2; 58.9
Alpelisib 270 mg + AUY922 40 mg/m^2, N=5	n	3	3	2
	Mean (SD)	1310 (370)		31 (3.17)
	CV% mean	28.2		10.2
	Geo-mean	1270		30.9
	CV% Geo-mean	32.1		10.3
	Median	1490	0.983	31
	Min; Max	887; 1560	0.867; 1.13	28.8; 33.2
Cycle 2 Day 1				
Alpelisib 270 mg + AUY922 28 mg/m^2, N=10	n	8	8	8
	Mean (SD)	920 (605)		31.6 (6.52)
	CV% mean	65.8		20.6
	Geo-mean	768		31.1
	CV% Geo-mean	71.8		20.3
	Median	810	0.992	29.9
	Min; Max	282; 2140	0.5; 1.1	25.3; 41.1
Alpelisib 270 mg + AUY922 35 mg/m^2, N=3	n	2	2	1
	Mean (SD)	2000 (325)		36.5 (-)
	CV% mean	16.3		
	Geo-mean	1990		36.5
	CV% Geo-mean	16.4		
	Median	2000	0.958	36.5
	Min; Max	1770; 2230	0.867; 1.05	36.5; 36.5
Alpelisib 270 mg + AUY922 40 mg/m^2, N=5	n	3	3	2
	Mean (SD)	1510 (1130)		28 (1.04)
	CV% mean	74.7		3.7
	Geo-mean	1270		28
	CV% Geo-mean	79.3		3.7
	Median	972	1.03	28

Treatment group	Statistics	Cmax (ng/mL)	Tmax (hr)	T1/2 (hr)
	Min; Max	753; 2810	1; 1.12	27.3; 28.8

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

Secondary Outcome Result(s)

Not applicable due to early termination of the study.

Summary of Safety

Safety Results

Adverse Events by System Organ Class (Safety Set)

System organ class	Alpelisib 270 mg + AUY922 28 mg/m2 N=10 n (%)	Alpelisib 270 mg + AUY922 35 mg/m2 N=3 n (%)	Alpelisib 270 mg + AUY922 40 mg/m2 N=5 n (%)	All patients N=18 n (%)
Any primary system organ class	**10 (100)**	**3 (100)**	**5 (100)**	**18 (100)**
Gastrointestinal disorders	10 (100)	2 (66.7)	5 (100)	17 (94.4)
General disorders and administration site conditions	10 (100)	3 (100)	4 (80.0)	17 (94.4)
Metabolism and nutrition disorders	9 (90.0)	3 (100)	4 (80.0)	16 (88.9)
Investigations	8 (80.0)	1 (33.3)	4 (80.0)	13 (72.2)
Skin and subcutaneous tissue disorders	8 (80.0)	0	2 (40.0)	10 (55.6)
Musculoskeletal and connective tissue disorders	6 (60.0)	0	3 (60.0)	9 (50.0)
Nervous system disorders	5 (50.0)	1 (33.3)	2 (40.0)	8 (44.4)
Vascular disorders	5 (50.0)	0	3 (60.0)	8 (44.4)
Psychiatric disorders	3 (30.0)	1 (33.3)	2 (40.0)	6 (33.3)
Eye disorders	3 (30.0)	1 (33.3)	1 (20.0)	5 (27.8)
Blood and lymphatic system disorders	4 (40.0)	0	0	4 (22.2)
Respiratory, thoracic and mediastinal disorders	4 (40.0)	0	0	4 (22.2)
Cardiac disorders	2 (20.0)	0	1 (20.0)	3 (16.7)
Infections and infestations	1 (10.0)	0	2 (40.0)	3 (16.7)
Neoplasm benign, malignant and unspecified (incl cysts and polyps)	2 (20.0)	0	1 (20.0)	3 (16.7)
Ear and labyrinth disorders	1 (10.0)	0	0	1 (5.6)
Injury, poisoning and procedural complications	1 (10.0)	0	0	1 (5.6)
Renal and urinary disorders	1 (10.0)	0	0	1 (5.6)
Reproductive system and breast disorders	0	0	1 (20.0)	1 (5.6)

System organ class	Alpelisib 270 mg + AUY922 28 mg/m2 N=10 n (%)	Alpelisib 270 mg + AUY922 35 mg/m2 N=3 n (%)	Alpelisib 270 mg + AUY922 40 mg/m2 N=5 n (%)	All patients N=18 n (%)
Primary system organ classes are presented by descending frequency A patient with multiple occurrences of an AE is counted only once for that AE A patient with multiple events within a primary system organ class is counted only once in the total row Includes all AEs on study and up to 30 days after last dose				

Most Frequently Reported (at least 10% incidence in any group) Adverse Events Overall by Preferred Term n (%) (Safety set)

Preferred term	Alpelisib 270 mg + AUY922 28 mg/m2 N=10 n (%)	Alpelisib 270 mg + AUY922 35 mg/m2 N=3 n (%)	Alpelisib 270 mg + AUY922 40 mg/m2 N=5 n (%)	All patients N=18 n (%)
Patients with at least one adverse event	**10 (100)**	**3 (100)**	**5 (100)**	**18 (100)**
Fatigue	8 (80.0)	3 (100)	4 (80.0)	15 (83.3)
Diarrhoea	7 (70.0)	2 (66.7)	3 (60.0)	12 (66.7)
Decreased appetite	4 (40.0)	2 (66.7)	4 (80.0)	10 (55.6)
Hyperglycaemia	5 (50.0)	2 (66.7)	3 (60.0)	10 (55.6)
Nausea	7 (70.0)	0	2 (40.0)	9 (50.0)
Lipase increased	4 (40.0)	1 (33.3)	2 (40.0)	7 (38.9)
Vomiting	4 (40.0)	0	3 (60.0)	7 (38.9)
Weight decreased	4 (40.0)	1 (33.3)	2 (40.0)	7 (38.9)
Abdominal pain	3 (30.0)	1 (33.3)	1 (20.0)	5 (27.8)
Hypertension	2 (20.0)	0	3 (60.0)	5 (27.8)
Abdominal pain upper	3 (30.0)	0	1 (20.0)	4 (22.2)
Amylase increased	3 (30.0)	0	1 (20.0)	4 (22.2)
Anaemia	4 (40.0)	0	0	4 (22.2)
Constipation	2 (20.0)	0	2 (40.0)	4 (22.2)
Dysgeusia	3 (30.0)	0	1 (20.0)	4 (22.2)
Headache	4 (40.0)	0	0	4 (22.2)
Pyrexia	3 (30.0)	0	1 (20.0)	4 (22.2)
Vision blurred	2 (20.0)	1 (33.3)	1 (20.0)	4 (22.2)
Accommodation disorder	2 (20.0)	0	1 (20.0)	3 (16.7)
Blood creatine phosphokinase increased	2 (20.0)	0	1 (20.0)	3 (16.7)
Blood creatinine increased	2 (20.0)	0	1 (20.0)	3 (16.7)
Erythema	2 (20.0)	0	1 (20.0)	3 (16.7)

Preferred term	Alpelisib 270 mg + AUY922 28 mg/m2 N=10 n (%)	Alpelisib 270 mg + AUY922 35 mg/m2 N=3 n (%)	Alpelisib 270 mg + AUY922 40 mg/m2 N=5 n (%)	All patients N=18 n (%)
Gastroesophageal reflux disease	3 (30.0)	0	0	3 (16.7)
Pain in extremity	3 (30.0)	0	0	3 (16.7)
Rash maculo-papular	2 (20.0)	0	1 (20.0)	3 (16.7)
Alanine aminotransferase increased	2 (20.0)	0	0	2 (11.1)
Alopecia	2 (20.0)	0	0	2 (11.1)
Anxiety	0	1 (33.3)	1 (20.0)	2 (11.1)
Aspartate aminotransferase increased	2 (20.0)	0	0	2 (11.1)
Back pain	1 (10.0)	0	1 (20.0)	2 (11.1)
Blood creatine phosphokinase MB increased	2 (20.0)	0	0	2 (11.1)
Cough	2 (20.0)	0	0	2 (11.1)
Deep vein thrombosis	2 (20.0)	0	0	2 (11.1)
Dry mouth	1 (10.0)	0	1 (20.0)	2 (11.1)
Dyspepsia	1 (10.0)	1 (33.3)	0	2 (11.1)
Dyspnoea	2 (20.0)	0	0	2 (11.1)
Gamma glutamyltransferase increased	2 (20.0)	0	0	2 (11.1)
Hyperhidrosis	2 (20.0)	0	0	2 (11.1)
Hypocalcaemia	2 (20.0)	0	0	2 (11.1)
Hypomagnesaemia	2 (20.0)	0	0	2 (11.1)
Insomnia	1 (10.0)	0	1 (20.0)	2 (11.1)
Musculoskeletal pain	2 (20.0)	0	0	2 (11.1)
Oedema peripheral	2 (20.0)	0	0	2 (11.1)
Pain	2 (20.0)	0	0	2 (11.1)
Peripheral sensory neuropathy	1 (10.0)	1 (33.3)	0	2 (11.1)
Pruritus	1 (10.0)	0	1 (20.0)	2 (11.1)
Stomatitis	2 (20.0)	0	0	2 (11.1)
Tachycardia	2 (20.0)	0	0	2 (11.1)

A patient with multiple occurrences of an AE is counted only once for that AE
A patient with multiple events within a preferred term class is counted only once in the total row
Includes all AEs on study and up to 30 days after last dose

Serious Adverse Events

System organ class Preferred term	Alpelisib 270 mg + AUY922 28 mg/m2 N=10 n (%)	Alpelisib 270 mg + AUY922 35 mg/m2 N=3 n (%)	Alpelisib 270 mg + AUY922 40 mg/m2 N=5 n (%)	All patients N=18 n (%)
Any primary SOC total	5 (50.0)	**0**	3 (60.0)	8 (44.4)
Gastrointestinal disorders total	2 (20.0)	0	0	2 (11.1)
Abdominal pain	1 (10.0)	0	0	1 (5.6)
Gastric haemorrhage	1 (10.0)	0	0	1 (5.6)
Infections and infestations	0	0	2 (40.0)	2 (11.1)
Device and related infection	0	0	1 (20.0)	1 (5.6)
Sinusitis	0	0	1 (20.0)	1 (5.6)
Respiratory, thoracic and mediastinal disorders	2 (20.0)	0	0	2 (11.1)
Dyspnoea	1 (10.0)	0	0	1 (5.6)
Pulmonary embolism	1 (10.0)	0	0	1 (5.6)
Vascular disorders	2 (20.0)	0	0	2 (11.1)
Deep vein thrombosis	1 (10.0)	0	0	1 (5.6)
Embolism	1 (10.0)	0	0	1 (5.6)
Blood and lymphatic system disorders	1 (10.0)	0	0	1 (5.6)
Anaemia	1 (10.0)	0	0	1 (5.6)
Eye disorders	1 (10.0)	0	0	1 (5.6)
Diplopia	1 (10.0)	0	0	1 (5.6)
Investigations	0	0	1 (20.0)	1 (5.6)
Lipase increased	0	0	1 (20.0)	1 (5.6)
Metabolism and nutrition disorders	0	0	1 (20.0)	1 (5.6)
Hyperglycaemia	0	0	1 (20.0)	1 (5.6)
Neoplasms benign, malignant and unspecified (incl cysts and polyps)	1 (10.0)	0	0	1 (5.6)
Metastases to meninges	1 (10.0)	0	0	1 (5.6)
Nervous system disorders	1 (10.0)	0	0	1 (5.6)
Brain oedema	1 (10.0)	0	0	1 (5.6)
Dysarthria	1 (10.0)	0	0	1 (5.6)
Headache	1 (10.0)	0	0	1 (5.6)

Primary SOCs are presented by descending frequency; preferred terms are sorted within primary SOC in descending frequency, as reported in the 'All patients' column.
A patient with multiple occurrences of an AE is counted only once, and at the highest grade observed for that AE.
Includes all AEs on study and up to 30 days after last dose.

Deaths

One patient died 25 days after the last dose of study drug due to gastric cancer and due to the event anemia.

Other Relevant Findings

None

Conclusion:

The study was terminated early due to slower than expected enrollment of the targeted population and the primary endpoint of determining the MTD and/or RDE was not met.

The PK of alpelisib at 270 mg/day was consistent across the different treatment groups independent of the AUY922 dose, confirming that AUY922 does not influence the PK of alpelisib. Compared to historical, clinical single agent data at the same dose level overall exposure of alpelisib was lower both after single and multiple doses, possibly due to physiological changes in advanced or metastatic gastric cancer. Given the limits of high variability and low patient number, the PK of AUY922 can be described as unchanged in the presence of alpelisib.

The safety profile of the combination of alpelisib and AUY922 was similar to what was reported to date in other ongoing studies.

Date of Clinical Trial Report

06-Feb-2015

Date of Initial Inclusion on Novartis Clinical Trial Results website

23-Feb-2015

Date of Latest Update

Not applicable

Reason for Update

Not applicable