Sponsor Novartis
Generic Drug Name Panobinostat
Therapeutic Area of Trial Advanced solid tumors
Approved Indication Investigational
Study Number CLBH589B2111
Title A phase Ib open-label, multicenter, cross-over study to investigate the effect of food on the rate and extent of oral Panobinostat absorption in patients with advanced solid tumors.
Phase of Development Phase Ib
Study Start/End Dates 31 Oct 2007 to 15 Feb 2011
Study Design/Methodology This was an open-label, multi-center, crossover food effect study in adult patients with advanced solid tumors. This study consisted of two treatment periods: the core phase (cycle 1) and the extension phase (cycle 2 and subsequent cycles). The core phase used a randomized, three period, six-sequence crossover design to evaluate the effect of food (fasting, high fat and normal food) on the PK of orally administered panobinostat at 20 mg twice weekly. The extension phase provided patients with panobinostat therapy at 45 mg twice weekly if 20 mg twice weekly was tolerated in Cycle 1.
Centres 9 centres in 3 countries: Sweden (2), USA (6), Switzerland (1).
Publication None

Objectives

Primary objective(s)

To determine the rate and extent of panobinostat absorption (C_{max}, AUC_{0-24}, $AUC_{0-tlast}$ and AUC_{0-inf}) under fasting conditions, 30 minutes after starting a high-fat meal, and 60 minutes after starting a normal meal (core phase).

Secondary objective(s)

- To assess the safety and tolerability of oral panobinostat (core and extension phase)
- To assess the efficacy of oral panobinostat (extension phase)

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

Core Phase: Panobinostat 20 mg administered orally twice weekly on a 21-day treatment cycle
Extension Phase: Panobinostat 45 mg administered orally twice weekly on a 21-day treatment cycle

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

None.

Criteria for Evaluation

Primary variables

The primary variables were evaluated with statistical methods to determine C_{max}, T_{max}, AUC_{0-24}, $AUC_{0-\infty}$ when feasible, and $AUC_{0-tlast}$ (only when applicable) of panobinostat.

Secondary variables

Efficacy:

Evidence for clinical efficacy was evaluated as a function of overall objective tumor response based on physician assessment per RECIST Guidelines. Criteria required for determining partial response (PR) or complete response (CR) had to be present for at least 4 weeks.

Safety and tolerability

Safety assessments consisted of monitoring and recording of serious and non-serious adverse events, including laboratory evaluations, physical examination, vital signs, weight, performance status evaluation, thyroid function tests, cardiac imaging, and repeated ECG readings

Statistical Methods

The primary focus was to provide a precise confidence interval (CI) for the geometric mean ratio comparing fed condition to fasting condition of panobinostat PK parameters. A minimum of 30 patients were required.

A formal statistical analysis was performed for C_{max}, AUC_{0-24}, and $AUC_{0-\infty}$ of panobinostat. A linear mixed effects model was fit to the log-transformed PK parameters. Included in the model were sequence (one to six), period (one to three), and treatment (high fat, normal meal, and fasting) as fixed effects and subject nested within sequence as a random effect. The point estimate of the treatment difference and the corresponding 90% confidence intervals were calculated and anti-logged to obtain the point estimate and CI on the linear scale.

Study Population: Inclusion/Exclusion Criteria and Demographics

Inclusion Criteria:

- Patients with histologically or cytologically confirmed advanced solid tumors whose disease has progressed despite standard therapy or for whom no standard therapy existed
- Patients should have had at least one measurable and/or non-measurable lesion as defined by Response evaluation criteria in solid tumors (RECIST) criteria
- Age ≥18 years
- Eastern Cooperative Oncology Group (ECOG) performance status ≤ 2
- Patients must have had the following laboratory values:
- Absolute neutrophil count (ANC) ≥ 1.5 x 10^9 /L (SI units 1.5 x 10^9 /L)

- Hemoglobin ≥ 9 g/dL (SI units 90 g/L)
- Platelets (plt) ≥ 100 x 10^9/L (SI units 100 x 10^9/L)
- Serum potassium, magnesium, and phosphorus ≥ the lower limit of normal (LLN)
- Serum total calcium (corrected for serum albumin) ≥ LLN
- Aspartate aminotransferase (AST) and alanine aminotransferase (ALT) ≤ 2.5 x upper limit of normal (ULN)
- Serum bilirubin ≤ 1.5 x ULN
- Serum albumin ≥ 3.0 g/dL (SI units 30 g/L)
- Serum creatinine ≤ 1.5 x ULN or estimated creatinine clearance using Cockroft-Gault ≥ 50 mL/min
- Thyroid stimulating hormone (TSH) ≤ ULN and free thyroxine (T4) within normal limit (WNL) (Patients were permitted to receive thyroid hormone supplements to treat underlying hypothyroidism)
- Note: Potassium, calcium, magnesium, and/or phosphorus supplements were permitted to be given to correct values that were < LLN, but these were to be documented as corrected prior to patients being enrolled on the study.
- Written informed consent obtained prior to any study-specific screening procedures
- Patients were to be willing and able to comply with protocol-specific assessments, including but not limited to multiple blood draws and dietary requirements
- Ability to swallow capsules or tablets
- Life expectancy of greater than 12 weeks

Exclusion Criteria:

- Patients with active central nervous system (CNS) disease or brain metastases, except those who have been previously treated and stable for at least 3 months
- Patients with a second primary malignancy that was currently clinically significant or requiring active intervention
- Prior chemotherapy ≤ 3 weeks prior to randomization. Patients must have had recovered from all therapy-related toxicities
- Prior biologic immunotherapy including monoclonal antibodies or experimental therapy ≤ 4 weeks prior to randomization. Patients must have had recovered from all therapy-related toxicities
- Patients who had undergone major surgery ≤ 2 weeks prior to starting study drug or who had not recovered from side effects of such therapy
- Patients with unresolved diarrhea ≥ National Cancer Institute (NCI) common toxicity criteria (CTC) grade 1
- Impaired cardiac function, including any one of the following:
    - Cardiac - left ventricular ejection fraction (LVEF) < the lower limit of institutional normal, as determined by echocardiogram (ECHO) or multiple uptake gated acquisition scan (MUGA)
    - Complete left bundle branch block, obligate use of a cardiac pacemaker, congenital

long QT syndrome, history or presence of sustained ventricular tachyarrhythmias, any history of ventricular fibrillation or torsades de pointes, clinically significant resting bradycardia (< 50 beats per minute), QTcF > 450 ms on screening electrocardiogram (ECG), or right bundle branch block + left anterior hemiblock (bifascicular block)

  - Presence of unstable atrial fibrillation (ventricular response rate > 100 bpm). Patients with stable atrial fibrillation were allowed in the study provided they did not meet the other cardiac exclusion criteria
  - Myocardial infarction or unstable angina ≤ 6 months prior to starting study drug
  - Congestive heart failure (New York Heart Association functional classification III-IV)
  - Other clinically significant heart disease (e.g. congestive heart failure, cardiomyopathy, cardiac artery disease, uncontrolled hypertension, history of labile hypertension, or history of poor compliance with an antihypertensive regimen).
- Acute or chronic liver or renal disease with impaired hepatic or renal functions
- Patients who used medications that had a relative risk of prolonging the QT interval or inducing torsades de pointes, if such treatment could not be discontinued or switched to a different medication prior to starting study drug
- Patients who used medications that inhibit CYP3A4/5 enzymes if such treatment could not be discontinued or switched to a different medication prior to starting study drug
- Patients who received valproic acid for any medical condition during the study or within 5 days prior to first panobinostat treatment
- Impairment of gastrointestinal (GI) function or GI disease that might have significantly altered the absorption of panobinostat (e.g. ulcerative disease, uncontrolled nausea, vomiting, diarrhea, malabsorption syndrome, obstruction, or stomach and/or small bowel resection)
- Concomitant use of any anti-cancer therapy
- Other concurrent severe and/or uncontrolled medical conditions (e.g. uncontrolled diabetes, active or uncontrolled infection, chronic obstructive or chronic restrictive pulmonary disease) that could have caused unacceptable safety risks or compromised compliance with the protocol
- Female patients who were pregnant or breastfeeding or patients of reproductive potential not willing to use a double method of contraception during the study and for 3 months after the end of treatment (EOT). (Women of childbearing potential [WOCBP] were to have a negative serum pregnancy test within 7 days of the first administration of panobinostat)
- Male patients whose sexual partners were WOCBP not using a double method of contraception that included a condom during the study and for 3 months after EOT

Number of Subjects

Patient disposition (Randomized set)

Disposition	A-B-C N=5 n (%)	A-C-B N=6 n (%)	B-C-A N=7 n (%)	B-A-C N=5 n (%)	C-A-B N=6 n (%)	C-B-A N=7 n (%)	All Patients N=36 n (%)
End of treatment							
Primary reason for end of treatment							
Abnormal laboratory value(s)	0	0	0	0	0	1 (14.3)	1 (2.8)
Disease progression	4 (80.0)	3 (50.0)	6 (85.7)	4 (80.0)	5 (83.3)	5 (71.4)	27 (75.0)
Adverse Event(s)	0	2 (33.3)	0	1 (20.0)	1 (16.7)	0	4 (11.1)
Administrative problems	1 (20.0)	0	1 (14.3)	0	0	0	2 (5.6)
Subject withdrew consent	0	1 (16.7)	0	0	0	1 (14.3)	2 (5.6)
Study evaluation completion							
Primary reason for study evaluation completion							
Disease progression	4 (80.0)	4 (66.7)	6 (85.7)	4 (80.0)	5 (83.3)	4 (57.1)	27 (75.0)
Subject withdrew consent	0	2 (33.3)	0	1 (20.0)	0	1 (14.3)	4 (11.1)
Administrative problems	1 (20.0)	0	1 (14.3)	0	0	0	2 (5.6)
Death	0	0	0	0	1 (16.7)	1 (14.3)	2 (5.6)
New cancer therapy	0	0	0	0	0	1 (14.3)	1 (2.8)

A= Fasting, B= 30 min after starting a high fat meal, C= 60 min after starting a normal meal.
End of study treatment is defined as the time in which panobinostat administration is permanently discontinued due to any reason (e.g. disease progression, AEs, withdrew consent)
Study evaluation completion: Patients who discontinued from study treatment for reasons other than death, progression of disease or commencement of new antineoplastic therapies will be followed until such events occur.

Demographic and Background Characteristics

Demographics and other baseline characteristics (Randomized set)

Demographic Variable	A-B-C N=5 n (%)	A-C-B N=6 n (%)	B-C-A N=7 n (%)	B-A-C N=5 n (%)	C-A-B N=6 n (%)	C-B-A N=7 n (%)	All Patients N=36 n (%)
Age (Years)							
N	5	6	7	5	6	7	36
Mean	64.20	63.67	57.29	57.00	60.17	64.86	61.22
SD	15.611	16.621	10.161	15.540	12.545	10.238	12.800
Median	71.00	62.00	63.00	62.00	64.50	67.00	63.00
Min	45.0	45.0	40.0	30.0	41.0	50.0	30.0
Max	79.0	83.0	68.0	69.0	74.0	76.0	83.0

Sex							
Male	2 (40.0)	3 (50.0)	4 (57.1)	3 (60.0)	3 (50.0)	6 (85.7)	21 (58.3)
Female	3 (60.0)	3 (50.0)	3 (42.9)	2 (40.0)	3 (50.0)	1 (14.3)	15 (41.7)
Race							
Caucasian	3 (60.0)	6 (100.0)	6 (85.7)	5 (100.0)	6 (100.0)	7 (100.0)	33 (91.7)
Black	2 (40.0)	0	0	0	0	0	2 (5.6)
Asian	0	0	1 (14.3)	0	0	0	1 (2.8)
Ethnicity							
Mixed Ethnic-ity	0	0	1 (14.3)	0	1 (16.7)	0	2 (5.6)
Other	5 (100.0)	6 (100.0)	6 (85.7)	5 (100.0)	5 (83.3)	7 (100.0)	34 (94.4)
Weight (kg)							
N	5	6	7	5	6	7	36
Mean	77.68	67.03	79.23	75.16	87.57	71.37	76.28
SD	19.462	12.101	20.272	21.031	10.846	10.060	16.213
Median	73.50	66.40	77.20	70.10	86.90	72.30	74.95
Min	61.4	55.0	52.6	56.4	71.0	52.7	52.6
Max	110.2	87.2	111.7	110.0	100.0	83.0	111.7
Height (cm)							
N	5	6	7	5	6	7	36
Mean	170.80	162.33	167.71	165.40	170.17	174.86	168.72
SD	12.755	12.723	11.996	8.706	9.326	5.610	10.495
Median	167.00	164.50	165.00	163.00	171.50	177.00	168.50
Min	159.0	142.0	154.0	156.0	153.0	167.0	142.0
Max	188.0	180.0	182.0	178.0	180.0	183.0	188.0
BMI (kg/m^2)							
N	5	6	7	5	6	7	36
Mean	26.27	25.73	27.83	27.72	30.48	23.32	26.81
SD	2.872	5.194	4.692	8.550	5.002	3.014	5.232
Median	25.20	27.02	28.36	24.26	30.83	24.39	26.11
Min	24.3	17.0	21.9	19.6	22.9	18.9	17.0
Max	31.2	31.3	33.7	41.4	36.2	27.1	41.4
BSA (m^2)							
N	5	6	7	5	6	7	36
Mean	1.91	1.73	1.91	1.84	2.03	1.86	1.88
SD	0.302	0.174	0.305	0.244	0.140	0.150	0.229
Median	1.85	1.74	1.88	1.82	2.04	1.90	1.86
Min	1.6	1.5	1.5	1.6	1.9	1.6	1.5
Max	2.4	2.0	2.4	2.2	2.2	2.0	2.4
Baseline ECOG performance status							

No restrictions	2 (40.0)	2 (33.3)	1 (14.3)	2 (40.0)	3 (50.0)	2 (28.6)	12 (33.3)
Only light work	3 (60.0)	3 (50.0)	6 (85.7)	2 (40.0)	3 (50.0)	4 (57.1)	21 (58.3)
Only self care	0	1 (16.7)	0	1 (20.0)	0	1 (14.3)	3 (8.3)

A = Fasting, B = 30 min after starting a high fat meal, C = 60 min after starting a normal meal.

Demographics and other baseline characteristics (Randomized patients who entered the Extension phase)

Demographic Variable	All patients (N = 29)
Age (year)	
N	29
Mean	59.48
SD	12.963
Median	63.00
Min	30.0
Max	83.0
Sex	
Male	16 (55.2)
Female	13 (44.8)
Race	
Caucasian	26 (89.7)
Black	2 (6.9)
Asian	1 (3.4)
Ethnicity	
Mixed ethnicity	2 (6.9)
Other	27 (93.1)
Weight (kg)	
N	29
Mean	77.39
SD	15.439
Median	77.20
Min	52.6
Max	110.2
Height (cm)	
N	29
Mean	168.17
SD	9.625
Median	167.00
Min	153.0
Max	188.0
BMI (kg/m^2)	
N	29
Mean	27.39
SD	5.166
Median	26.56
Min	17.0
Max	41.4

BSA (m2)	
N	29
Mean	1.89
SD	0.216
Median	1.86
Min	1.5
Max	2.4
Baseline ECOG performance status	
No restrictions	12 (41.4)
Only light work	15 (51.7)
Only self care	2 (6.9)

Note: A = fasting, B = 30 min after starting a high fat meal, C = 60 min after starting a normal meal.
BMI (kg/m^2) = weight (kg) / height $(cm)^2$.
BSA (m^2) = sqrt [weight (kg) * height $(cm)]^2$.

Primary Objective Result(s)

Summary of panobinostat PK parameters by treatment (PK set)

PK parameter (unit)	Fasting (N = 33)	High Fat (N = 34)	Normal meal (N = 31)
Cmax (ng/mL)	22.7 (86.02)	11.94 (63.36)	13.7 (64.87)
AUC(0-24) (h.ng/mL)	126.3 (61.20)	93.7 (58.35)	96.2 (57.93)
AUC(0-inf) (h.ng/mL)	176.4 (58.52)	143.89 (58.86)	152.7 (58.87)
T_{max} (h)	1.50 (0.50- 6.00)	4.00 (1.00- 8.07)	2.50 (0.50- 6.00)
$T_{1/2}$ (h)	14.5 (32.21)	13.7 (35.75)	15.7 (48.72)

Values are median (range) for Tmax and arithmetic mean (CV%) for all other parameters

Summary of statistical analysis of panobinostat primary PK parameters (PK set)

				Treatment comparison			
						90% CI	
PK parame-ter	Treatment	n*	Adjusted Geo-mean	Comp.	Geo-mean Ratio	Lower	Upper
Cmax (ng/mL)	Fasting	33	17.5				
	High Fat	34	9.8	H : F	0.56	0.446	0.704
	Normal Meal	31	11.2	N : F	0.64	0.504	0.811
AUC(0-24) (h.ng/mL)	Fasting	31	106.4				
	High Fat	34	83.7	H : F	0.79	0.695	0.890
	Normal Meal	28	82.9	N : F	0.78	0.682	0.890
AUC(0-inf) (h.ng/mL)	Fasting	24	140.7				
	High Fat	25	118.6	H : F	0.84	0.738	0.962
	Normal Meal	19	121.6	N : F	0.86	0.746	1.002
AUC(0-tlast) (h.ng/mL)	Fasting	33	115.3				
	High Fat	34	99.0	H : F	0.86	0.725	1.015
	Normal Meal	31	83.7	N : F	0.73	0.609	0.864
Tmax (h)**	Fasting	33	1.50				
	High Fat	34	4.00	H : F	2.48	-2.000	7.020

	Normal Meal	31	2.50	N : F	1.45	-2.500	2.017

Fasting (F), High (H) and Normal (N): panobinostat taken under fasting, 30 min after starting a high fat meal or 60 min after starting a normal meal.
n* = number of patients with non-missing values.
Geo-mean = geometric mean. Geo-mean, Geo-mean ratio and 90% CI are determined from a mixed effect model for log-PK parameters with fixed effects (sequence, period, and treatment) and a random effect (patient nested with sequence).

** For Tmax, median is presented under “Geo-mean”, median difference under “Geo-mean ratio”, minimum and maximum difference under “Lower” and “Upper”.

Secondary Objective Result(s)

Best overall response (Efficacy set)

Best overall response	**Panobinostat (N = 36)** **n (%)**
Complete response	0
Partial response	1 (2.8)
Stable disease	6 (16.7)
Progressive disease	21 (58.3)
Unknown	8 (22.2)
CR/PR	1 (2.8)
95% CI	(0.07, 14.53)

Note: evaluation is based on investigator’s evaluation.
The 95% CI was computed using the Binomial method.

Safety Results

Adverse Events by System Organ Class

Adverse events, regardless of study drug relationship, by primary system organ class –core phase (Safety set)

Primary System Organ Class	All Patients (N=36) n (%)	
	Any Grade	Grade 3-4
Any primary system organ class	**34 (94.4)**	**8 (22.2)**
Gastrointestinal disorders	22 (61.1)	3 (8.3)
General disorders and administration site conditions	21 (58.3)	3 (8.3)
Musculoskeletal and connective tissue disorders	12 (33.3)	1 (2.8)
Metabolism and nutrition disorders	11 (30.6)	1 (2.8)
Blood and lymphatic system disorders	8 (22.2)	1 (2.8)
Nervous system disorders	8 (22.2)	0
Respiratory, thoracic and mediastinal disorders	8 (22.2)	1 (2.8)
Infections and infestations	7 (19.4)	1 (2.8)
Investigations	7 (19.4)	1 (2.8)
Psychiatric disorders	5 (13.9)	1 (2.8)
Cardiac disorders	4 (11.1)	1 (2.8)
Vascular disorders	3 (8.3)	0
Injury, poisoning, and procedural complications	2 (5.6)	1 (2.8)
Skin and subcutaneous tissue disorders	2 (5.6)	0
Ear and labyrinth disorders	1 (2.8)	0
Endocrine disorders	1 (2.8)	0
Eye disorders	1 (2.8)	0
Hepatobiliary disorders	1 (2.8)	0
Immune system disorders	1 (2.8)	0
Neoplasms benign, malignant, and unspecified (incl. cysts and polyps)	1 (2.8)	0
Renal and urinary disorders	1 (2.8)	0
Reproductive system and breast disorders	1 (2.8)	1 (2.8)

Adverse events, regardless of study drug relationship, by primary system organ class - extension phase (Safety set patients who entered the extension phase)

Primary System Organ Class	All Patients (N= 29) n (%)	
	Any Grade	Grade 3-4
Any primary system organ class	**26 (89.7)**	**19 (65.5)**
General disorders and administration site conditions	21 (72.4)	7 (24.1)
Gastrointestinal disorders	20 (69.0)	5 (17.2)
Investigations	17 (58.6)	8 (27.6)
Blood and lymphatic system disorders	16 (55.2)	11 (37.9)
Respiratory, thoracic and mediastinal disorders	13 (44.8)	0
Metabolism and nutrition disorders	14 (48.3)	1 (3.4)
Nervous system disorders	11 (37.9)	1 (3.4)
Musculoskeletal and connective tissue disorders	10 (34.5)	1 (3.4)
Infections and infestations	8 (27.6)	2 (6.9)
Psychiatric disorders	6 (20.7)	0
Renal and urinary disorders	5 (17.2)	0
Skin and subcutaneous tissue disorders	5 (17.2)	0
Cardiac disorders	2 (6.9)	0
Ear and labyrinth disorders	2 (6.9)	0
Injury, poisoning, and procedural complications	2 (6.9)	0
Eye disorders	1 (3.4)	0
Neoplasms benign, malignant, and unspecified (incl. cysts and polyps)	1 (3.4)	1 (3.4)
Reproductive system and breast disorders	2 (6.9)	0
Vascular disorders	2 (6.9)	0

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

Adverse events, regardless of study drug relationship, by preferred term (occurring in at least 10% of the patients) - core phase (Safety set)

Preferred term	All patients (N = 36) n (%)	
	Any Grade	Grade 3-4
Any preferred term: total	34 (94.4)	8 (22.2)
Fatigue	18 (50.0)	3 (8.3)
Nausea	15 (41.7)	2 (5.6)
Vomiting	10 (27.8)	2 (5.6)
Constipation	7 (19.4)	0
Diarrhea	7 (19.4)	1 (2.8)
Headache	6 (16.7)	0
Abdominal pain	5 (13.9)	0
Pyrexia	5 (13.9)	0
Thrombocytopenia	5 (13.9)	0
Hypokalemia	4 (11.1)	0
Insomnia	4 (11.1)	0

Adverse events, regardless of study drug relationship, by preferred term occurring in at least 10% of the patients) - extension phase (Safety set patients who entered the extension phase)

Preferred term	All patients (N = 29) n (%)	
	Any Grade	Grade 3-4
Total	**26 (89.7)**	**19 (65.5)**
Thrombocytopenia	15 (51.7)	11 (37.9)
Fatigue	14 (48.3)	5 (17.2)
Nausea	12 (41.4)	1 (3.4)
Anorexia	10 (34.5)	0
Diarrhoea	10 (34.5)	1 (3.4)
Vomiting	9 (31.0)	2 (6.9)
Dyspnea	7 (24.1)	0
Abdominal pain	6 (20.7)	1 (3.4)
Platelet count decreased	6 (20.7)	3 (10.3)
Anaemia	5 (17.2)	1 (3.4)
Cough	5 (17.2)	0
Headache	5 (17.2)	0
Muscle spasms	4 (13.8)	0
Oedema peripheral	4 (13.8)	1 (3.4)
Back pain	3 (10.3)	0

Blood creatinine increased	3 (10.3)	0
Blood phosphorus decreased	3 (10.3)	1 (3.4)
Constipation	3 (10.3)	0
Dry mouth	3 (10.3)	0
Dysgeusia	3 (10.3)	0
Pyrexia	3 (10.3)	0
Rash	3 (10.3)	0
Urinary tract infection	3 (10.3)	0

Serious Adverse Events and Deaths

Deaths, other serious or clinically significant adverse events or related discontinuations - core phase (Safety set)

Serious or significant events	Fasting (N = 34) n (%)	High Fat (N = 36) n (%)	Normal meal (N = 34) n (%)	All patients (N = 36) n (%)
All deaths	0	1 (2.8)	0	1 (2.8)
On treatment deaths*	0	1 (2.8)	0	1 (2.8)
All SAEs	4 (11.8)	2 (5.6)	2 (5.9)	7 (19.4)
Study-drug related SAEs	1 (2.9)	0	1 (2.9)	2 (5.6)
AEs leading to discontinuation	0	0	1 (2.9)	1 (2.8)

* Includes deaths up to 28 days after last dose of study drug.
Including events happened in the core phase.
If an AE/death occurred after taking study drug in treatment x and prior to taking the study drug in treatment x + 1 (or up to the end of study), this AE/death was accounted for under the treatment given in treatment x.

Deaths, other serious or clinically significant adverse events or related discontinuations - extension phase (Safety set patients who entered the extension phase)

Serious or significant events	All patients (N = 29) n (%)
All deaths	2* (6.8)
On treatment deaths	1* (3.4)
All SAEs	7 (24.1)
Study-drug related SAEs	2 (6.9)
AEs leading to discontinuation	4 (13.8)
Clinically significant AEs	1 (3.4)

Note: * includes deaths up to 28 days after last dose of study drug.
Including events happened in the extension phase.

Date of Clinical Trial Report 17 Aug 2011
Date Inclusion on Novartis Clinical Trial Results Database 9 Jan 2012
Date of Latest Update