Sponsor

Novartis

Generic Drug Name

Panobinostat

Trial Indication(s)

Multiple myeloma

Protocol Number

CLBH589B2206

Protocol Title

A phase Ib, multi-center, open-label, dose-escalation study of oral panobinostat (PAN) when administered in combination with oral lenalidomide and dexamethasone in adult patients with multiple myeloma

Clinical Trial Phase

Phase Ib

Phase of Drug Development

Phase III

Study Start/End Dates

22 Apr 2008 to 08 Nov 2017

Reason for Termination

Novartis decided to terminate study enrollment on 08 Sep 2010 as there were complex changes in the dosing schedule required from safety perspective after a protocol defined routine review of safety data.

Study Design/Methodology

Multicenter, multinational, open-label, dose-finding and safety study of panobinostat when used in combination with lenalidomide and dexamethasone in patients with multiple myeloma. The study consisted of a single treatment arm where escalating doses of panobinostat were administered with fixed doses of oral lenalidomide and dexamethasone. The provisional starting dose of panobinostat was selected as 5mg given orally 3 times weekly. Starting dose of lenalidomide was 25mg/day administered orally, once daily on Days 1 to 21. Dexamethasone starting dose was 40mg/day on Days 1 to 4, 9 to 12, and 17 to 20 for the first 4 cycles, and then 40mg/day orally on Days 1 to 4 for all subsequent cycles. All treatments were configured on 28-day treatment cycle.

Centers

10 centers in 4 countries: Australia (2), France (3), Spain (2) and United States (3)

Objectives:

Primary objective:

To determine the maximum tolerated dose (MTD) of panobinostat (PAN) when used in combination with a fixed dose of lenalidomide and dexamethasone

Secondary objectives:

To characterize the safety and tolerability of the study treatment

To characterize the pharmacokinetic (PK) profile of PAN when administered in combination with lenalidomide (LEN) and dexamethasone, and to evaluate the degree of influence of dexamethasone (DEX) cytochrome P450 (CYP) moderate induction on PAN trough levels

To characterize the pharmacodynamics profile of the study treatment through the analysis of various biomarkers in the context of this combination

To assess the preliminary efficacy of the study treatment

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

Hard gelatin capsules of panobinostat at dose strengths of 5mg or 20mg, administered orally. Lenalidomide was supplied as 5mg and 25mg capsules, administered at a dose of 25mg orally. Dexamethasone was supplied locally by each study site.

Statistical Methods

This study was stopped without determining the MTD, and the dose expansion phase of the study was not initiated. Therefore, the estimation of the MTD (primary endpoint) was not performed based on incidence of DLTs.

For the final CSR the following statistical methods were used:

- Demographic and baseline disease data was listed by subject and/or summarized descriptively by assigned dose group of PAN for FAS. Categorical data was presented as frequencies and percentages. For continuous data, summary statistics (mean, median, standard deviation, minimum and maximum) was presented.

- All AEs recorded during the study were summarized. The incidence of treatment-emergent AEs (new or worsening from baseline) was summarized by system organ class (SOC), severity (based on National Cancer Institute CTCAE v.3), and seriousness of AEs and their relationship to the study treatment. SAEs resulting in death and non-fatal SAEs were listed by patient and tabulated by type of AE.

For the primary CSR (cut-off 31-May-2012), additionally, the following statistical methods were used:

- Evidence of anti-tumor activity of PAN in combination with lenalidomide and dexamethasone was evaluated using BOR, based on the International Uniform Response Criteria for MM by the IMWG and the Guidelines for the Uniform Reporting of Clinical Trials: Report of the 2008 International Myeloma Workshop Consensus Panel I. The proportion of patients with confirmed best overall response of sCR, CR, VGPR, and PR were summarized on the FAS. The Minimal Response (MR) was reported separately as the specific rate of MR was given distinctly from the overall response rate (ORR). Stable Disease (SD) and Progressive Disease (PD) were also summarized for the FAS.
- A separate listing displayed notable laboratory abnormalities (i.e., newly occurring CTC Grade 3 or 4 laboratory toxicities). Laboratory data was summarized by presenting shift tables. Data from ECGs, vital signs and ECOG performance status were listed, notable values were flagged, and any other information collected was listed as appropriate.
- A plot on absolute value and changes from baseline of the three biomarker parameters was displayed for each patient with an involved (kappa or lambda) FLC (more than 100 mg/L at baseline) over time by cohort (logarithmic scale used for the absolute values).
- Pharmacokinetic parameters of panobinostat (area under curve - AUC0-t, AUC0-∞ Cmax, Ctlast, Tlast, t1/2, Cl/F, and Vz/F on Cycle 1 Day 1) were derived from the individual concentration versus time profile using non-compartmental method as implemented in WinNonlin® Pro software (Version 5.2). Summary statistics included n, arithmetic mean, median, standard deviation, geometric mean, coefficient of variation CV (%) and geometric CV (%), minimum and maximum.

Study Population: Key Inclusion/Exclusion Criteria

Inclusion Criteria:

1. Patients must have a diagnosis of active multiple myeloma according to the International Myeloma Working Group criteria (IMWG, 2003), and be deemed by the investigator as requiring treatment.
2. Patients must have received at least one prior line of therapy and their disease has relapsed (Durie et. al., 2006). One prior line of therapy may consist of induction followed by autologous stem cell transplantation.
3. Patients must be suitable (according to their local product information) for treatment with lenalidomide & dexamethasone. Note: patients previously treated with lenalidomide & dexamethasone are eligible to participate in the trial.

4. Adults ≥ 18 years old
5. ECOG Performance Status ≤ 2
6. Life expectancy > 12 weeks
7. Patients must have the following laboratory values:
   - ANC ≥ 1.5 x 109/L
   - Hemoglobin ≥ 9 g/dl
   - Platelets ≥ 100x 109/L
   - Calculated CrCl ≥ 50 mL/min (MDRD Formula)
   - AST and ALT ≤ 2.5 x ULN
   - Serum bilirubin ≤ 1.5 x ULN
   - Albumin > 3.0 g/dl
   - Serum potassium ≥ LLN
   - Total serum calcium [corrected for serum albumin] or ionized calcium ≥LLN
   - Serum magnesium ≥ LLN
   - Serum phosphorus ≥ LLN
   - TSH ≤ LLN and free T4 within normal limits. Patients are permitted to receive thyroid hormone supplements to treat underlying hypothyroidism.
8. Baseline MUGA or ECHO must demonstrate LVEF ≥ the lower limit of the institutional normal
9. Patients participating in the dose-expansion phase of the trial must be willing and able to undergo bone marrow aspirates as per protocol, with/without bone marrow biopsy according to their center's practice
10. Able to sign informed consent and to comply with the protocol

Exclusion criteria

1. Prior exposure to a HDAC inhibitor compound used in the treatment of MM.
2. Primary refractory MM
3. Patients who have received allogeneic stem cell transplantation < 12 months prior to entering the study.
4. Patients who have had prior allogeneic stem cell transplantation and show evidence of active graft-versus-host disease that requires immunosuppressive therapy.
5. Peripheral neuropathy > CTCAE grade 2
6. Impaired cardiac function or clinically significant cardiac diseases, including any one of the following:
   - Patients with congenital long QT syndrome

- History or presence of sustained ventricular tachyarrhythmia. (Patients with a history of atrial arrhythmia are eligible but should be discussed with the Sponsor prior to enrollment)
- Any history of ventricular fibrillation or torsade de pointes
- Bradycardia defined as HR< 50 bpm. Patients with pacemakers are eligible if HR ≥ 50 bpm.
- Screening ECG with a QTc > 450 msec
- Right bundle branch block + left anterior hemiblock (bifascicular block)
- Patients with myocardial infarction or unstable angina ≤ 6 months prior to starting study drug
- Other clinically significant heart disease (e.g., CHF NY Heart Association class III or IV , uncontrolled hypertension, history of labile hypertension, or history of poor compliance with an antihypertensive regimen)

7. Impairment of GI function or GI disease that may significantly alter the absorption of LBH589
8. Patients with diarrhea > CTCAE grade 1
9. Other concurrent severe and/or uncontrolled medical conditions (e.g., uncontrolled diabetes or active or uncontrolled infection) including abnormal laboratory values, that could cause unacceptable safety risks or compromise compliance with the protocol
10. Patients using medications that have a relative risk of prolonging the QT interval or inducing torsade de pointes if treatment cannot be discontinued or switched to a different medication prior to starting study drug
11. Concomitant use of CYP3A4 inhibitors
12. Patients with a history of Deep Vein Thrombosis or thromboembolism within < 6 months prior to starting study treatment
13. Patients for whom prophylactic anticoagulation therapy (eg. 325mg aspirin PO daily or warfarin (Coumadin®) 1-2 mg/day, or any other coumarin-derivative anticoagulants) is not an option.
14. Patients who have received targeted agents within 2 weeks or within 5 half-lives of the agent and active metabolites (which ever is longer) and who have not recovered from side effects of those therapies.
15. Patients who have 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 have not yet recovered from side effects of such therapies.
16. Patients who have undergone major surgery ≤ 4 weeks prior to starting study drug or who have not recovered from side effects of such therapy
17. Women who are pregnant or breast feeding, or women of childbearing potential (WOCBP) who are unable to use two reliable forms of contraception simultaneously, unless continuous abstinence from heterosexual contact is the chosen method. WOCBP are defined as sexually mature women who have not undergone a hysterectomy or who have not been naturally postmenopausal for at least 24 consecutive months (i.e., who has had menses any time in the preceding 24 consecutive months). WOCBP should have 2negative

pregnancy tests (sensitivity of at least 50 mIU/L) prior to beginning therapy. The first test should be performed within 10-14 days of commencing study treatment, and the second test within 24hr prior to receiving the first dose of study treatment.

18. Male patients whose sexual partners are WOCBP and who are unable to use a latex condom during sexual contact (even if they have undergone a vasectomy).
19. Patients with a prior malignancy within the last 5 years (except for basal or squamous cell carcinoma, or *in situ* cancer of the cervix)
20. Patients with any significant history of non-compliance to medical regimens or unwilling or unable to comply with the instructions given to him/her by the study staff.

Participant Flow Table

Subject disposition by dose level of panobinostat (FAS) – cut-off date 14Feb2018

	PAN 5 mg N = 8 n (%)	PAN 10 mg N = 8 n (%)	PAN 20 mg N = 21 n (%)	PAN 25 mg N = 9 n (%)	All Subjects N = 46 n (%)
Subjects					
Enrolled [1]	8 (100.0)	8 (100.0)	21 (100.0)	9 (100.0)	46 (100.0)
Discontinued treatment [2]	8 (100.0)	8 (100.0)	21 (100.0)	9 (100.0)	46 (100.0)
Primary reason for end of treatment					
- Abnormal laboratory value(s)	0 (0)	1 (12.5)	0 (0)	0 (0)	1 (2.2)
- Adverse Event(s)	3 (37.5)	3 (37.5)	8 (38.1)	4 (44.4)	18 (39.1)
- Death [3]	0	0	4 (19)	0	4 (8.7)
- Disease progression	3 (37.5)	3 (37.5)	5 (23.8)	4 (44.4)	15 (32.6)
- Protocol deviation	0	0	1 (4.8)	0	1 (2.2)
- Subject withdrew consent	2 (25.0)	1 (12.5)	3 (14.3)	1 (11.1)	7 (15.2)

[1] Treated with at least one dose of study treatment.

[2] Subject completed End of Treatment CRF page.

[3] Includes only those subjects for whom death was reported as the primary reason for discontinuation of treatment.

Baseline Characteristics

Demographic summary by dose level of panobinostat (FAS) – cut-off date 14Feb2018

Demographic variable	PAN 5 mg N = 8	PAN 10 mg N = 8	PAN 20 mg N = 21	PAN 25 mg N = 9	All Subjects N = 46
Sex – n (%)					
Female	1 (12.5)	2 (25.0)	9 (42.9)	5 (55.6)	17 (37.0)
Male	7 (87.5)	6 (75.0)	12 (57.1)	4 (44.4)	29 (63.0)
Age (years)					
n	8	8	21	9	46
Mean (SD)	64.9 (8.54)	60.6 (5.66)	59.1 (10.56)	56.1 (10.84)	59.8 (9.72)
Median (Min-Max)	65.0 (50.0 - 80.0)	59.5 (54.0 - 71.0)	60.0 (41.0 - 81.0)	57.0 (42.0 - 73.0)	60.5 (41.0 - 81.0)
Age category – n (%)					
< 65 years	3 (37.5)	6 (75.0)	16 (76.2)	7 (77.8)	32 (69.6)
≥ 65 years	5 (62.5)	2 (25.0)	5 (23.8)	2 (22.2)	14 (30.4)
Race – n (%)					
Caucasian	8 (100.0)	8 (100.0)	20 (95.2)	9 (100.0)	45 (97.8)
Black	0	0	1 (4.8)	0	1 (2.2)
Ethnicity – n (%)					
Hispanic/Latino	0	2 (25.0)	10 (47.6)	3 (33.3)	15 (32.6)
Other	8 (100.0)	5 (62.5)	11 (52.4)	6 (66.7)	30 (65.2)
Mixed ethnicity	0	1 (12.5)	0	0	1 (2.2)
ECOG performance status – n (%)					
0	2 (25.0)	2 (25.0)	11 (52.4)	8 (88.9)	23 (50.0)
1	5 (62.5)	6 (75.0)	8 (38.1)	1 (11.1)	20 (43.5)
2	0	0	2 (9.5)	0	2 (4.3)
Missing	1 (12.5)	0	0	0	1 (2.2)
Weight (kg)					

Demographic variable	PAN 5 mg N = 8	PAN 10 mg N = 8	PAN 20 mg N = 21	PAN 25 mg N = 9	All Subjects N = 46
n	8	8	21	9	46
Mean (SD)	81.4 (20.03)	84.9 (17.86)	74.4 (12.11)	69.9 (12.28)	76.6 (15.22)
Median (Min-Max)	78.8 (53.8 - 123.8)	83.5 (59.0 - 108.8)	75.0 (53.0 - 95.0)	67.0 (51.0 - 94.0)	74.5 (51.0 - 123.8)
Height (cm)					
n	7	8	20	8	43
Mean (SD)	173.4 (9.64)	176.3 (6.80)	169.6 (8.74)	165.8 (7.96)	170.7 (8.86)
Median (Min-Max)	178.0 (156.0 - 183.0)	179.5 (165.0 - 185.0)	165.5 (154.0 - 185.0)	166.5 (155.0 - 176.0)	170.0 (154.0 - 185.0)
Body surface area (m^2)[1]					
n	7	8	20	8	43
Mean (SD)	2.0 (0.27)	2.1 (0.23)	1.9 (0.19)	1.8 (0.22)	1.9 (0.23)
Median (Min-Max)	2.0 (1.6 - 2.5)	2.1 (1.7 - 2.4)	1.9 (1.6 - 2.2)	1.9 (1.5 - 2.2)	1.9 (1.5 - 2.5)

-SD Standard deviation.

-ECOG Eastern Cooperative Oncology Group.

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

Summary of Efficacy

Primary Outcome Result(s)

Maximum tolerated dose (MTD) of Panobinostat when used in combination with a fixed dose of lenalidomide and dexamethasone
After a total of 46 patients had been enrolled into the dose escalation phase, it was concluded that the dosing regimen and schedule needed to be changed for the combination used in this study, based on a review of the accrued safety data and evolution of medical practice on usage of dexamethasone. It was decided that recommended dosing regimen and schedule for this combination would be better implemented in a new study, rather than in a complex protocol amendment. Hence, this study was stopped without determining the MTD, and the dose expansion phase of the study was not initiated

Secondary Outcome Result(s)

Best confirmed overall response as per investigator's assessment by dose level of Panobinostat (Full analysis set) – cut-off date 31May2012

	PAN 5 mg N=8 n (%)	PAN 10 mg N=8 n (%)	PAN 20 mg N=21 n (%)	PAN 25 mg N=9 n (%)	All Patients N=46 n (%)
Stringent Complete response (sCR)	0	0	0	1 (11.1)	1 (2.2)
Complete Response (CR)	0	0	3 (14.3)	0	3 (6.5)
Very Good Partial Response (VGPR)	4 (50.0)	0	0	1 (11.1)	5 (10.9)
Partial Response (PR)	2 (25.0)	1 (12.5)	5 (23.8)	2 (22.2)	10 (21.7)
Minimal Response (MR)	0	1 (12.5)	0	0	1 (2.2)
Stable Disease (SD)	1 (12.5)	6 (75.0)	6 (28.6)	3 (33.3)	16 (34.8)
Clinical Relapse	0	0	0	0	0
Progressive Disease (PD)	1 (12.5)	0	1 (4.8)	0	2 (4.3)
Unknown	0	0	6 (28.6)	2 (22.2)	8 (17.4)
Response rate (sCR, CR, VGPR, PR)	6 (75.0)	1 (12.5)	8 (38.1)	4 (44.4)	19 (41.3)
95% Confidence interval [1]	(34.9, 96.8)	(0.3, 52.7)	(18.1, 61.6)	(13.7, 78.8)	(27.0, 56.8)

[1] The confidence interval is calculated in term of the Clopper-Pearson Method

Best confirmed overall response as per investigator's assessment for patients with measurable disease at baseline by dose level of panobinostat (Full analysis set) – cut-off date 31May2012

	PAN 5 mg			PAN 10 mg			PAN 20 mg			PAN 25 mg			All Patients		
	Total	n	(%)	Total	n	(%)	Total	n	(%)	Total	n	(%)	Total	n	(%)
Stringent Complete response (sCR)	7	0	0	8	0	0	19	0	0	8	1	12.5	42	1	2.4
Complete Response (CR)	7	0	0	8	0	0	19	2	10.5	8	0	0	42	2	4.8
Very Good Partial Response (VGPR)	7	4	57.1	8	0	0	19	0	0	8	1	12.5	42	5	11.9
Partial Response (PR)	7	1	14.3	8	1	12.5	19	5	26.3	8	2	25.0	42	9	21.4
Minimal Response (MR)	7	0	0	8	1	12.5	19	0	0	8	0	0	42	1	2.4
Stable Disease (SD)	7	1	14.3	8	6	75.0	19	5	26.3	8	2	25.0	42	14	33.3
Clinical Relapse	7	0	0.0	8	0	0	19	0	0.0	8	0	0	42	0	0
Progressive Disease (PD)	7	1	14.3	8	0	0	19	1	5.3	8	0	0	42	2	4.8
Unknown	7	0	0	8	0	0	19	6	31.6	8	2	25.0	42	8	19.0
Response rate (sCR, CR, VGPR, PR)	7	5	71.4	8	1	12.5	19	7	36.8	8	4	50.0	42	17	40.5

Total : number of patients with measurable disease at baseline

Percentages are based on Total

Best confirmed overall response as per investigator's assessment for relapsed-and-refractory patients by dose level of panobinostat (Full analysis set) – cut-off date 31May2012

	PAN 5 mg			PAN 10 mg			PAN 20 mg			PAN 25 mg			All Patients		
	Total	n	(%)	Total	n	(%)	Total	n	(%)	Total	n	(%)	Total	n	(%)
Stringent Complete response (sCR)	5	0	0	6	0	0	13	0	0	6	1	16.7	30	1	3.3
Complete Response (CR)	5	0	0	6	0	0	13	1	7.7	6	0	0	30	1	3.3
Very Good Partial Response (VGPR)	5	3	60.0	6	0	0	13	0	0	6	1	16.7	30	4	13.3
Partial Response (PR)	5	1	20.0	6	0	0	13	3	23.1	6	0	0	30	4	13.3
Minimal Response (MR)	5	0	0	6	0	0	13	0	0	6	0	0	30	0	0
Stable Disease (SD)	5	0	0	6	6	100.0	13	4	30.8	6	2	33.3	30	12	40.0
Clinical Relapse	5	0	0	6	0	0	13	0	0	6	0	0	30	0	0
Progressive Disease (PD)	5	1	20.0	6	0	0	13	0	0	6	0	0	30	1	3.3
Unknown	5	0	0	6	0	0	13	5	38.5	6	2	33.3	30	7	23.3
Response rate (sCR, CR, VGPR, PR)	5	4	80.0	6	0	0	13	4	30.8	6	2	33.3	30	10	33.3

Total : number of relapsed-and-refractory patients

Percentages: are based on Total

Summary statistics of pharmacokinetic parameters for panobinostat (PAN) on Day 1 by actual initial dose of panobinostat (PK set) – cut-off date 31May2012

Treatment	Statistics	AUCinf (ng·h/mL)	AUClast (ng·h/mL)	Cmax (ng/mL)	Tmax (h)	T1/2 (h)	CL/F (L/h)	Vz/F (L)
PAN 5 mg	n	8	8	8	8	8	8	8
	Mean (SD)	22.79 (25.1)	10.14(8.6)	1.87 (0.8)		15.35 (27.3)	438 (288)	3634 (1846)
	CV% mean	110	84.89	41.87		177.62	65.87	50.79
	Geo-mean	15.18	7.51	1.74		6.93	329	3294
	CV% geo-mean	113.26	99.51	40.52		165.39	113.26	48.60
	Median	12.50	7.16	1.60	1.26	4.15	410	3115
	[Min]	6.02	2.37	1.00	0.75	2.61	60	1880
	[Max]	79.44	27.03	3.45	4.00	82.18	830	7460
PAN 10 mg	n	8	8	8	8	8	8	8
	Mean (SD)	37.52 (34.1)	31.38 (31.2)	7.89 (5.8)		4.40 (2.5)	499 (423)	2710 (2473)
	CV% mean	91.01	99.58	74.03		55.58	84.77	91.25
	Geo-mean	27.11	20.40	5.84		3.90	369	2078
	CV% geo-mean	104.91	136.35	109.59		54.47	104.91	82.01
	Median	26.83	21.10	7.39	1.25	3.48	377	1593
	[Min]	7.02	4.15	1.70	0.50	2.11	90	1030
	[Max]	109.07	94.95	18.20	3.00	8.74	1430	8150
PAN 20 mg	n	21	21	21	21	21	21	21
	Mean (SD)	90.85 (44.4)	75.93 (41.9)	13.91 (9.2)		11.51 (4.7)	295 (206)	4397 (3205)
	CV% mean	48.88	55.26	66.11		40.76	69.84	72.89
	Geo-mean	79.85	61.53	11.37		10.42	250	3763
	CV% geo-mean	59.81	91.63	77.93		52.67	59.81	56.84
	Median	80.97	68.13	10.20	1.00	11.51	247	3756
	[Min]	20.32	5.56	1.57	0.42	3.29	100	1400

Treatment	Statistics	AUCinf (ng·h/mL)	AUClast (ng·h/mL)	Cmax (ng/mL)	Tmax (h)	T1/2 (h)	CL/F (L/h)	Vz/F (L)
	[Max]	194.42	167.66	42.50	2.50	18.76	980	16810
PAN 25 mg	n	9	9	9	9	9	9	9
	Mean (SD)	117.55 (43.7)	102.53 (38.7)	20.03 (10.9)		13.57 (5.4)	241 (89.7)	4437 (1926)
	CV% mean	37.16	37.71	54.32		39.73	37.17	43.42
	Geo-mean	110.35	96.02	17.26		12.62	227	4124
	CV% geo-mean	39.40	40.38	66.74		42.51	39.40	41.23
	Median	115.90	103.36	16.10	1.00	11.74	216	4224
	[Min]	64.23	53.02	5.60	0.50	7.14	140	2370
	[Max]	178.56	167.55	38.40	3.00	20.88	390	8770

Values are median (range) for Tmax and Tlast, and geometric mean (CV %) for all other parameters.

CV% = coefficient of variation (%) = SD/mean*100.

CV% geometric mean = sqrt (exp (variance for log transformed data)-1)*100.

Summary of Safety

Safety Results

Duration of exposure to study treatment by dose level of panobinostat (Safety set) – cut-off date 14Feb2018

Duration of exposure	PAN 5 mg N = 8	PAN 10 mg N = 8	PAN 20 mg N = 21	PAN 25 mg N = 9	All Subjects N = 46
Exposure categories (months)					
< 1	0	2 (25.0)	8 (38.1)	2 (22.2)	12 (26.1)
≥ 1 and < 3	1 (12.5)	2 (25.0)	4 (19.0)	0	7 (15.2)
≥ 3 and < 6	4 (50.0)	2 (25.0)	5 (23.8)	4 (44.4)	15 (32.6)
≥ 6 and < 9	0	1 (12.5)	2 (9.5)	2 (22.2)	5 (10.9)

Duration of exposure	PAN 5 mg N = 8	PAN 10 mg N = 8	PAN 20 mg N = 21	PAN 25 mg N = 9	All Subjects N = 46
≥ 9 and < 12	1 (12.5)	0	0	1 (11.1)	2 (4.3)
≥ 12	2 (25.0)	1 (12.5)	2 (9.5)	0	5 (10.9)
Exposure (days)					
n	**8**	**8**	**21**	**9**	**46**
Mean (SD)	281 (286.65)	400 (881.70)	257 (698.79)	156 (105.67)	266 (598.66)
Median (Min-Max)	153 (36 - 920)	103 (14 - 2576)	57 (8 - 3220)	140 (5 - 334)	108 (5 - 3220)

-SD: - standard deviation.

Note: Duration of exposure (days) = [(date of last administration of study treatment – (date of first administration of study treatment) + 1].

Adverse events, regardless of study drug relationship, by primary system organ class and dose level of panobinostat (Safety set) – cut-off date 14Feb2018

Primary System Organ Class	PAN 5 mg N = 8	PAN 10 mg N = 8	PAN 20 mg N = 21	PAN 25 mg N = 9	All Subjects N = 46
Any system organ class (Total)	8 (100.0)	8 (100.0)	21 (100.0)	9 (100.0)	46 (100.0)
Gastrointestinal disorders	8 (100.0)	6 (75.0)	19 (90.5)	9 (100.0)	42 (91.3)
General disorders and administration site conditions	8 (100.0)	6 (75.0)	19 (90.5)	9 (100.0)	42 (91.3)
Blood and lymphatic system disorders	4 (50.0)	6 (75.0)	16 (76.2)	8 (88.9)	34 (73.9)
Metabolism and nutrition disorders	3 (37.5)	7 (87.5)	14 (66.7)	9 (100.0)	33 (71.7)
Infections and infestations	7 (87.5)	3 (37.5)	14 (66.7)	7 (77.8)	31 (67.4)
Respiratory, thoracic and mediastinal disorders	5 (62.5)	5 (62.5)	13 (61.9)	7 (77.8)	30 (65.2)
Nervous system disorders	7 (87.5)	7 (87.5)	10 (47.6)	6 (66.7)	30 (65.2)
Musculoskeletal and connective tissue disorders	8 (100.0)	3 (37.5)	11 (52.4)	5 (55.6)	27 (58.7)
Investigations	3 (37.5)	4 (50.0)	13 (61.9)	2 (22.2)	22 (47.8)
Psychiatric disorders	2 (25.0)	5 (62.5)	11 (52.4)	2 (22.2)	20 (43.5)

Primary System Organ Class	PAN 5 mg N = 8	PAN 10 mg N = 8	PAN 20 mg N = 21	PAN 25 mg N = 9	All Subjects N = 46
Skin and subcutaneous tissue disorders	6 (75.0)	3 (37.5)	4 (19.0)	5 (55.6)	18 (39.1)
Vascular disorders	2 (25.0)	3 (37.5)	5 (23.8)	4 (44.4)	14 (30.4)
Cardiac disorders	3 (37.5)	2 (25.0)	7 (33.3)	0	12 (26.1)
Renal and urinary disorders	2 (25.0)	2 (25.0)	5 (23.8)	2 (22.2)	11 (23.9)
Injury, poisoning and procedural complications	3 (37.5)	2 (25.0)	3 (14.3)	1 (11.1)	9 (19.6)
Eye disorders	3 (37.5)	1 (12.5)	3 (14.3)	2 (22.2)	9 (19.6)
Endocrine disorders	0	2 (25.0)	1 (4.8)	2 (22.2)	5 (10.9)
Hepatobiliary disorders	0	1 (12.5)	3 (14.3)	1 (11.1)	5 (10.9)
Neoplasms benign, malignant and unspecified (incl cysts and polyps)	0	1 (12.5)	3 (14.3)	1 (11.1)	5 (10.9)
Immune system disorders	0	0	1 (4.8)	1 (11.1)	2 (4.3)
Ear and labyrinth disorders	0	0	0	1 (11.1)	1 (2.2)
Reproductive system and breast disorders	0	0	0	1 (11.1)	1 (2.2)

- Primary system organ classes are sorted in descending frequency, as reported in the “All subjects” column.

Adverse events reported in at least 10.0% of all subjects regardless of study drug relationship, by preferred term and dose level of panobinostat (Safety set) – cut-off date 14Feb2018

Preferred term	PAN 5 mg N = 8 n (%)	PAN 10 mg N = 8 n (%)	PAN 20 mg N = 21 n (%)	PAN 25 mg N = 9 n (%)	All Subjects N = 46 n (%)
Any Preferred term (Total)	**8 (100.0)**	**8 (100.0)**	**21 (100.0)**	**9 (100.0)**	**46 (100.0)**
Neutropenia	2 (25.0)	4 (50.0)	13 (61.9)	8 (88.9)	27 (58.7)
Thrombocytopenia	1 (12.5)	3 (37.5)	13 (61.9)	8 (88.9)	25 (54.3)
Anaemia	2 (25.0)	3 (37.5)	13 (61.9)	6 (66.7)	24 (52.2)
Diarrhoea	2 (25.0)	3 (37.5)	13 (61.9)	6 (66.7)	24 (52.2)

Preferred term	PAN 5 mg N = 8 n (%)	PAN 10 mg N = 8 n (%)	PAN 20 mg N = 21 n (%)	PAN 25 mg N = 9 n (%)	All Subjects N = 46 n (%)
Hypokalaemia	2 (25.0)	5 (62.5)	11 (52.4)	4 (44.4)	22 (47.8)
Nausea	2 (25.0)	4 (50.0)	11 (52.4)	5 (55.6)	22 (47.8)
Pyrexia	5 (62.5)	2 (25.0)	9 (42.9)	5 (55.6)	21 (45.7)
Asthenia	1 (12.5)	3 (37.5)	8 (38.1)	6 (66.7)	18 (39.1)
Constipation	4 (50.0)	1 (12.5)	10 (47.6)	3 (33.3)	18 (39.1)
Fatigue	6 (75.0)	3 (37.5)	7 (33.3)	2 (22.2)	18 (39.1)
Decreased appetite	2 (25.0)	2 (25.0)	5 (23.8)	6 (66.7)	15 (32.6)
Hypocalcaemia	0	2 (25.0)	7 (33.3)	4 (44.4)	13 (28.3)
Muscle spasms	6 (75.0)	2 (25.0)	3 (14.3)	1 (11.1)	12 (26.1)
Weight decreased	2 (25.0)	3 (37.5)	6 (28.6)	1 (11.1)	12 (26.1)
Oedema peripheral	0	2 (25.0)	4 (19.0)	5 (55.6)	11 (23.9)
Upper respiratory tract infection	4 (50.0)	2 (25.0)	4 (19.0)	1 (11.1)	11 (23.9)
Hyperglycaemia	0	3 (37.5)	7 (33.3)	0	10 (21.7)
Hypophosphataemia	1 (12.5)	1 (12.5)	4 (19.0)	4 (44.4)	10 (21.7)
Insomnia	1 (12.5)	1 (12.5)	7 (33.3)	1 (11.1)	10 (21.7)
Back pain	3 (37.5)	1 (12.5)	3 (14.3)	2 (22.2)	9 (19.6)
Dysgeusia	1 (12.5)	2 (25.0)	3 (14.3)	3 (33.3)	9 (19.6)
Febrile neutropenia	0	4 (50.0)	4 (19.0)	1 (11.1)	9 (19.6)
Headache	2 (25.0)	2 (25.0)	3 (14.3)	2 (22.2)	9 (19.6)
Rash	3 (37.5)	2 (25.0)	2 (9.5)	2 (22.2)	9 (19.6)
Cough	1 (12.5)	1 (12.5)	3 (14.3)	3 (33.3)	8 (17.4)
Leukopenia	0	1 (12.5)	3 (14.3)	4 (44.4)	8 (17.4)
Vomiting	0	1 (12.5)	6 (28.6)	1 (11.1)	8 (17.4)
Dizziness	1 (12.5)	1 (12.5)	5 (23.8)	0	7 (15.2)
Hypomagnesaemia	0	2 (25.0)	3 (14.3)	2 (22.2)	7 (15.2)
Muscular weakness	3 (37.5)	2 (25.0)	2 (9.5)	0	7 (15.2)

Preferred term	PAN 5 mg N = 8 n (%)	PAN 10 mg N = 8 n (%)	PAN 20 mg N = 21 n (%)	PAN 25 mg N = 9 n (%)	All Subjects N = 46 n (%)
Neuropathy peripheral	3 (37.5)	1 (12.5)	2 (9.5)	1 (11.1)	7 (15.2)
Pain in extremity	3 (37.5)	1 (12.5)	2 (9.5)	1 (11.1)	7 (15.2)
Hyponatraemia	2 (25.0)	0	3 (14.3)	1 (11.1)	6 (13.0)
Orthostatic hypotension	0	0	3 (14.3)	3 (33.3)	6 (13.0)
Pneumonia	1 (12.5)	1 (12.5)	2 (9.5)	2 (22.2)	6 (13.0)
Respiratory tract infection	0	1 (12.5)	4 (19.0)	1 (11.1)	6 (13.0)
Abdominal pain	1 (12.5)	2 (25.0)	2 (9.5)	0	5 (10.9)
Dyspnoea	3 (37.5)	0	2 (9.5)	0	5 (10.9)
Dyspnoea exertional	0	1 (12.5)	2 (9.5)	2 (22.2)	5 (10.9)
Epistaxis	0	1 (12.5)	3 (14.3)	1 (11.1)	5 (10.9)

- Preferred terms are sorted in descending frequency as reported in the "All subjects" column
- A subject with multiple occurrences of an AE under one treatment is counted only once in the AE category for that treatment.
- A subject with multiple AEs within a preferred term is counted only once for that treatment.

Grade 3 or 4 adverse events reported in at least 5.0% of all subjects regardless of study drug relationship by preferred term and dose level of panobinostat (Safety set) – cut-off date 14Feb2018

Preferred term	PAN 5 mg N = 8 n (%)	PAN 10 mg N = 8 n (%)	PAN 20 mg N = 21 n (%)	PAN 25 mg N = 9 n (%)	All Subjects N = 46 n (%)
Any Preferred term					
-Total	**8 (100.0)**	**5 (62.5)**	**21 (100.0)**	**8 (88.9)**	**42 (91.3)**
Neutropenia	2 (25.0)	3 (37.5)	13 (61.9)	8 (88.9)	26 (56.5)
Thrombocytopenia	1 (12.5)	2 (25.0)	12 (57.1)	8 (88.9)	23 (50.0)
Anaemia	1 (12.5)	3 (37.5)	7 (33.3)	5 (55.6)	16 (34.8)

Preferred term	PAN 5 mg N = 8 n (%)	PAN 10 mg N = 8 n (%)	PAN 20 mg N = 21 n (%)	PAN 25 mg N = 9 n (%)	All Subjects N = 46 n (%)
Febrile neutropenia	0	3 (37.5)	4 (19.0)	1 (11.1)	8 (17.4)
Leukopenia	0	1 (12.5)	3 (14.3)	4 (44.4)	8 (17.4)
Hypokalaemia	0	2 (25.0)	3 (14.3)	3 (33.3)	8 (17.4)
Fatigue	2 (25.0)	1 (12.5)	3 (14.3)	1 (11.1)	7 (15.2)
Hypocalcaemia	0	1 (12.5)	4 (19.0)	2 (22.2)	7 (15.2)
Hypophosphataemia	0	1 (12.5)	2 (9.5)	3 (33.3)	6 (13.0)
Asthenia	0	0	4 (19.0)	1 (11.1)	5 (10.9)
Respiratory tract infection	0	1 (12.5)	3 (14.3)	1 (11.1)	5 (10.9)
Hyponatraemia	2 (25.0)	0	2 (9.5)	1 (11.1)	5 (10.9)
Decreased appetite	2 (25.0)	0	1 (4.8)	1 (11.1)	4 (8.7)
Muscular weakness	1 (12.5)	2 (25.0)	1 (4.8)	0	4 (8.7)
Hyperglycaemia	0	0	3 (14.3)	0	3 (6.5)
Lymphopenia	1 (12.5)	0	1 (4.8)	1 (11.1)	3 (6.5)
Diarrhoea	0	1 (12.5)	1 (4.8)	1 (11.1)	3 (6.5)

- Preferred terms are sorted descending frequency as reported in the "All subjects" column
- A subject with multiple occurrences of an AE under one treatment is counted only once in the AE category for that treatment.
- A subject with multiple AEs within a preferred term is counted only once for that treatment.

Adverse events reported in at least 5.0% of all subjects suspected to be study treatment-related by preferred term and dose level of panobinostat (Safety set) – cut-off date 14Feb2018

Preferred term	PAN 5 mg N = 8 n (%)	PAN 10 mg N = 8 n (%)	PAN 20 mg N = 21 n (%)	PAN 25 mg N = 9 n (%)	All Subjects N = 46 n (%)

Preferred term	PAN 5 mg N = 8 n (%)	PAN 10 mg N = 8 n (%)	PAN 20 mg N = 21 n (%)	PAN 25 mg N = 9 n (%)	All Subjects N = 46 n (%)
Any Preferred term					
-Total	**8 (100.0)**	**8 (100.0)**	**20 (95.2)**	**9 (100.0)**	**45 (97.8)**
Neutropenia	1 (12.5)	4 (50.0)	12 (57.1)	7 (77.8)	24 (52.2)
Thrombocytopenia	0	3 (37.5)	13 (61.9)	7 (77.8)	23 (50.0)
Diarrhoea	2 (25.0)	3 (37.5)	10 (47.6)	4 (44.4)	19 (41.3)
Nausea	1 (12.5)	4 (50.0)	9 (42.9)	5 (55.6)	19 (41.3)
Anaemia	2 (25.0)	1 (12.5)	9 (42.9)	6 (66.7)	18 (39.1)
Fatigue	6 (75.0)	3 (37.5)	7 (33.3)	2 (22.2)	18 (39.1)
Decreased appetite	2 (25.0)	2 (25.0)	5 (23.8)	5 (55.6)	14 (30.4)
Asthenia	0	2 (25.0)	6 (28.6)	4 (44.4)	12 (26.1)
Muscle spasms	4 (50.0)	2 (25.0)	3 (14.3)	1 (11.1)	10 (21.7)
Dysgeusia	1 (12.5)	2 (25.0)	3 (14.3)	3(33.3)	9 (19.6)
Hypokalaemia	2 (25.0)	3 (37.5)	3 (14.3)	0	8 (17.4)
Pyrexia	1 (12.5)	0	5 (23.8)	2 (22.2)	8 (17.4)
Weight decreased	1 (12.5)	2 (25.0)	4 (19)	1 (11.1)	8 (17.4)
Headache	1 (12.5)	2 (25.0)	3 (14.3)	1 (11.1)	7 (15.2)
Muscular weakness	3 (37.5)	2 (25.0)	2 (9.5)	0	7 (15.2)
Oedema peripheral	0	2 (25.0)	3 (14.3)	2 (22.2)	7 (15.2)
Hyperglycaemia	0	3 (37.5)	3 (14.3)	0	6 (13.0)
Insomnia	1 (12.5)	1 (12.5)	3 (14.3)	1 (11.1)	6 (13.0)
Constipation	0	1 (12.5)	4 (19.0)	0	5 (10.9)
Febrile neutropenia	0	1 (12.5)	4 (19.0)	0	5 (10.9)
Rash	1 (12.5)	1 (12.5)	1 (4.8)	2 (22.2)	5 (10.9)
Leukopenia	0	1 (12.5)	1 (4.8)	2 (22.2)	4 (8.7)
Orthostatic hypotension	0	0	2 (9.5)	2 (22.2)	4 (8.7)
Vomiting	0	1 (12.5)	2 (9.5)	1 (11.1)	4 (8.7)

Preferred term	PAN 5 mg N = 8 n (%)	PAN 10 mg N = 8 n (%)	PAN 20 mg N = 21 n (%)	PAN 25 mg N = 9 n (%)	All Subjects N = 46 n (%)
Abdominal pain	0	1 (12.5)	2 (9.5)	0	3 (6.5)
Dizziness	0	0	3 (14.3)	0	3 (6.5)
Gastrooesophageal reflux disease	1 (12.5)	0	2 (9.5)	0	3 (6.5)
Neuropathy peripheral	2 (25.0)	0	1 (4.8)	0	3 (6.5)

- Preferred terms are sorted descending frequency as reported in the "All subjects" column
- A subject with multiple occurrences of an AE under one treatment is counted only once in the AE category for that treatment.
- A subject with multiple AEs within a preferred term is counted only once for that treatment.

On-treatment deaths by preferred term and dose level of panobinostat (Safety set) – cut-off date 14Feb2018

Principal cause of death	PAN 5mg N = 8 n (%)	PAN 10mg N = 8 n (%)	PAN 20mg N = 21 n (%)	PAN 25mg N = 9 n (%)	All subjects N = 46 n (%)
Total number of on-treatment deaths	**0**	**0**	**6 (28.6)**	**1 (11.1)**	**7 (15.2)**
Other	0	0	6 (28.6)	1 (11.1)	7 (15.2)
Study indication caused death	0	0	0	0	0
Any preferred term / principal cause of death	0	0	6 (28.6)	1 (11.1)	7 (15.2)
Respiratory failure	0	0	3 (14.3)	0	3 (6.5)
Bronchial disorder	0	0	1 (4.8)	0	1 (2.2)
Intestinal perforation	0	0	0	1 (11.1)	1 (2.2)
Multiple organ dysfunction syndrome	0	0	1 (4.8)	0	1 (2.2)
Myocardial infarction	0	0	1 (4.8)	0	1 (2.2)

- Principal cause of death is presented in descending order of frequency in the “All subjects” column

AE preferred terms are sorted within principal cause also by descending frequency in the “All subjects” column.

- On-treatment deaths are deaths which occurred up to 28 days after the last date of study treatment.

Serious adverse events, regardless of study drug relationship, by primary system organ class (in at least 10.0% of all subjects), preferred term and dose level of panobinostat (safety set) – cut-off date 14Feb2018

Primary system organ class Preferred term	PAN 5 mg N = 8 n (%)	PAN 10 mg N = 8 n (%)	PAN 20 mg N = 21 n (%)	PAN 25 mg N = 9 n (%)	All subjects N = 46 n (%)
-Any primary system organ class	3 (37.5)	5 (62.5)	18 (85.7)	7 (77.8)	33 (71.7)
Blood and lymphatic system disorders	0	3 (37.5)	5 (23.8)	4 (44.4)	12 (26.1)
Febrile neutropenia	0	3 (37.5)	4 (19.0)	1 (11.1)	8 (17.4)
Thrombocytopenia	0	0	1 (4.8)	3 (33.3)	4 (8.7)
Anaemia	0	0	0	2 (22.2)	2 (4.3)
Neutropenia	0	0	0	2 (22.2)	2 (4.3)
Cardiac disorders	1 (12.5)	0	4 (19.0)	0	5 (10.9)
Atrial fibrillation	1 (12.5)	0	1 (4.8)	0	2 (4.3)
Acute myocardial infarction	0	0	1 (4.8)	0	1 (2.2)
Bradycardia	0	0	1 (4.8)	0	1 (2.2)
Rhythm idioventricular	0	0	1 (4.8)	0	1 (2.2)
Ventricular extrasystoles	0	0	1 (4.8)	0	1 (2.2)
Gastrointestinal disorders	0	0	2 (9.5)	3 (33.3)	5 (10.9)
Diarrhoea	0	0	0	3 (33.3)	3 (6.5)
Haematemesis	0	0	1 (4.8)	0	1 (2.2)
Intestinal perforation	0	0	0	1 (11.1)	1 (2.2)

Primary system organ class Preferred term	PAN 5 mg N = 8 n (%)	PAN 10 mg N = 8 n (%)	PAN 20 mg N = 21 n (%)	PAN 25 mg N = 9 n (%)	All subjects N = 46 n (%)
Nausea	0	0	1 (4.8)	0	1 (2.2)
Pneumatosis intestinalis	0	0	0	1 (11.1)	1 (2.2)
Vomiting	0	0	1 (4.8)	0	1 (2.2)
General disorders and administration site conditions	1 (12.5)	1 (12.5)	7 (33.3)	5 (55.6)	14 (30.4)
Pyrexia	1 (12.5)	1 (12.5)	2 (9.5)	4 (44.4)	8 (17.4)
Asthenia	0	0	2 (9.5)	0	2 (4.3)
General physical health deterioration	0	0	1 (4.8)	1 (11.1)	2 (4.3)
Fatigue	0	0	1 (4.8)	0	1 (2.2)
Multiple organ dysfunction syndrome	0	0	1 (4.8)	0	1 (2.2)
Non-cardiac chest pain	0	0	1 (4.8)	0	1 (2.2)
Infections and infestations	2 (25.0)	2 (25.0)	8 (38.1)	5 (55.6)	17 (37.0)
Respiratory tract infection	0	1 (12.5)	3 (14.3)	1 (11.1)	5 (10.9)
Pneumonia	0	1 (12.5)	1 (4.8)	2 (22.2)	4 (8.7)
Bacterial infection	1 (12.5)	0	0	0	1 (2.2)
Cellulitis	1 (12.5)	0	0	0	1 (2.2)
Escherichia sepsis	0	0	1 (4.8)	0	1 (2.2)
Gastrointestinal candidiasis	0	0	0	1 (11.1)	1 (2.2)
H1N1 influenza	0	0	1 (4.8)	0	1 (2.2)
Hepatitis B	0	0	1 (4.8)	0	1 (2.2)
Influenza	0	0	1 (4.8)	0	1 (2.2)
Listeria sepsis	0	0	0	1 (11.1)	1 (2.2)

Primary system organ class Preferred term	PAN 5 mg N = 8 n (%)	PAN 10 mg N = 8 n (%)	PAN 20 mg N = 21 n (%)	PAN 25 mg N = 9 n (%)	All subjects N = 46 n (%)
Lower respiratory tract infection	0	0	1 (4.8)	0	1 (2.2)
Lower respiratory tract infection fungal	0	0	0	1 (11.1)	1 (2.2)
Pneumococcal infection	0	0	1 (4.8)	0	1 (2.2)
Sepsis syndrome	0	0	0	1 (11.1)	1 (2.2)
Septic embolus	0	0	1 (4.8)	0	1 (2.2)
Septic shock	0	0	0	1 (11.1)	1 (2.2)
Staphylococcal infection	0	0	1 (4.8)	0	1 (2.2)
Tooth infection	0	0	0	1 (11.1)	1 (2.2)
Respiratory, thoracic and mediastinal disorders	0	0	6 (28.6)	1 (11.1)	7 (15.2)
Respiratory failure	0	0	4 (19.0)	0	4 (8.7)
Aspiration	0	0	1 (4.8)	0	1 (2.2)
Cough	0	0	0	1 (11.1)	1 (2.2)
Dyspnoea	0	0	1 (4.8)	0	1 (2.2)
Dyspnoea exertional	0	0	1 (4.8)	0	1 (2.2)
Pulmonary embolism	0	0	1 (4.8)	0	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 subjects" column
- A subject with multiple occurrences of an AE under one treatment is counted only once in the AE category for that treatment.
- A subject with multiple adverse events within a primary system organ class is counted only once in the total row.

Adverse events, leading to study drug discontinuation, by system organ class, preferred term and dose level of panobinostat (Safety set) – cut-off date 14Feb2018

Primary System Organ Class Preferred term	PAN 5 mg N = 8	PAN 10 mg N = 8	PAN 20 mg N = 21	PAN 25 mg N = 9	All subjects N = 46
Any primary system organ class (Total)	3 (37.5)	4 (50.0)	12 (57.1)	4 (44.4)	23 (50.0)
Blood and lymphatic system disorders	1 (12.5)	1 (12.5)	3 (14.3)	2 (22.2)	7 (15.2)
Neutropenia	1 (12.5)	1 (12.5)	0	1 (11.1)	3 (6.5)
Thrombocytopenia	0	0	1 (4.8)	2 (22.2)	3 (6.5)
Febrile neutropenia	0	0	2 (9.5)	0	2 (4.3)
Anaemia	1 (12.5)	0	0	0	1 (2.2)
Cardiac disorders	0	0	2 (9.5)	0	2 (4.3)
Acute myocardial infarction	0	0	1 (4.8)	0	1 (2.2)
Rhythm idioventricular	0	0	1 (4.8)	0	1 (2.2)
Gastrointestinal disorders	0	0	0	1 (11.1)	1 (2.2)
Intestinal perforation	0	0	0	1 (11.1)	1 (2.2)
Pneumatosis intestinalis	0	0	0	1 (11.1)	1 (2.2)
General disorders and administration site conditions	2 (25.0)	2 (25.0)	5 (23.8)	1 (11.1)	10 (21.7)
Fatigue	2 (25.0)	1 (12.5)	2 (9.5)	0	5 (10.9)
Asthenia	0	0	1 (4.8)	0	1 (2.2)
Chest discomfort	0	1 (12.5)	0	0	1 (2.2)
General physical health deterioration	0	0	0	1 (11.1)	1 (2.2)
Multiple organ dysfunction syndrome	0	0	1 (4.8)	0	1 (2.2)
Non-cardiac chest pain	0	0	1 (4.8)	0	1 (2.2)
Oedema peripheral	0	0	1 (4.8)	0	1 (2.2)
Infections and infestations	0	0	3 (14.3)	0	3 (6.5)
Pneumococcal infection	0	0	1 (4.8)	0	1 (2.2)
Pneumonia	0	0	1 (4.8)	0	1 (2.2)
Respiratory tract infection	0	0	1 (4.8)	0	1 (2.2)

Primary System Organ Class Preferred term	PAN 5 mg N = 8	PAN 10 mg N = 8	PAN 20 mg N = 21	PAN 25 mg N = 9	All subjects N = 46
Investigations	1 (12.5)	1 (12.5)	2 (9.5)	0	4 (8.7)
Electrocardiogram QT prolonged	0	1 (12.5)	1 (4.8)	0	2 (4.3)
Alanine aminotransferase increased	0	0	1 (4.8)	0	1 (2.2)
Aspartate aminotransferase increased	0	0	1 (4.8)	0	1 (2.2)
Weight decreased	1 (12.5)	0	0	0	1 (2.2)
Metabolism and nutrition disorders	1 (12.5)	0	1 (4.8)	0	2 (4.3)
Decreased appetite	1 (12.5)	0	1 (4.8)	0	2 (4.3)
Respiratory, thoracic and mediastinal disorders	0	0	2 (9.5)	0	2 (4.3)
Aspiration	0	0	1 (4.8)	0	1 (2.2)
Respiratory failure	0	0	1 (4.8)	0	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 subjects" column

- A subject with multiple occurrences of an AE under one treatment is counted only once in the AE category for that treatment.

- A subject with multiple adverse events within a primary system organ class is counted only once in the total row.

Other Relevant Findings

Conclusion:

This was a Phase Ib study in which escalating doses of oral panobinostat (PAN) (5, 10, 20, and 25 mg) were administered in combination with a fixed dose of lenalidomide and dexamethasone. The study was planned to determine MTD at a certain dose level and to assess the safety and tolerability.

The enrollment of the subjects was stopped in September-2010 without determining the MTD of PAN. This decision was taken after a protocol defined routine review of safety data from 46 subjects in the dose escalation phase, indicating a need for several changes in dosing regimen and

schedule for several components of this combination. The toxicity of the combination regimen used in the study was considered unacceptably high by the study team and the steering committee on the basis of the following points.

- A very high rate of discontinuations due to AE, which was 37.5-57.1% across all the cohorts.
- An unacceptably high rate of the most severe grade 4 neutropenia and thrombocytopenia in the cohorts with PAN ≥ 20 mg.
- It was also considered that while the overall response rate observed in the whole study population was encouraging, there was no clear evidence of dose relationship with the exception that the few CR and sCR were observed only in the cohorts with a dose of PAN ≥ 20 mg, i.e. associated with high toxicity.

The most common SAEs were pyrexia, febrile neutropenia, and respiratory tract infection.

The AEs observed in this study were as expected in this patient population and for this class of drugs. Generally, a trend towards increasing incidences of AEs, grade 3 or 4 AEs, AEs suspected to be related to study treatment and AEs leading to discontinuations were observed with increasing doses of PAN, in combination with fixed doses of lenalidomide and dexamethasone.

Date of Clinical Trial Report

16 July 2018

Author:

Sandi Marchese, Clinical Disclosure Office, is the content owner and subject matter expert.

Reason for Change:

Primarily related to SOP-7012386: Statutory Registry and Results Posting (P&SP 015)

Removed the last three fields of the template;

- Date of Initial Inclusion on Novartis Clinical Trial Results website
- Date of Latest Update
- Reason for Update

CAUTION to End Users: When using a Native (Original) Copy – Ensure the most current version from ESOPS Webconsumer is used to ensure procedural compliance.