## Sponsor

Novartis

## Generic Drug Name

Panobinostat

## Trial Indication(s)

Patients with advanced solid tumors and varying degrees of renal function

## Protocol Number

CLBH589X2105

## Protocol Title

A phase I, open-label, multi-center study to evaluate the pharmacokinetics and safety of oral panobinostat in patients with advanced solid tumors and varying degrees of renal function.

## Clinical Trial Phase

Phase I.

## Phase of Drug Development

Phase III.

## Study Start/End Dates

03-Mar-2010 (first patient first visit).

30-Jun-2014 (last patient last visit).

## Reason for Termination (If applicable)

Not applicable.

## Study Design/Methodology

This is a phase I, open-label, multicenter study to evaluate the pharmacokinetics (PK) and safety of 30 mg oral panobinostat in patients with advanced solid tumors and various degrees of renal function (group 1: normal; group 2: mild; group 3: moderate; group 4: severe). It consists of a core phase of 7 days and an extension phase. In the core phase, patients received a single oral dose of 30 mg panobinostat. In the extension phase, patients received 30 mg oral panobinostat three times weekly in 28-day cycles, until disease progression, unacceptable toxicity or withdrawal of consent. Dose reduction was allowed for the management of adverse events. The starting dose for patients with severe renal dysfunction in the extension phase was

30 mg orally on a three times a week every other week based on safety assessments available from all groups, including at least 3 patients from group 3. Serial blood samples for assessing the PK of panobinostat were obtained at pre-specified time points. Approximately 40 patients needed to be enrolled in order to have an adequate number of patients in the study (10 evaluable patients per group for the first 3 groups, up to 6 patients in the 4th group).

## Centers

5 centers in 4 participating countries (US 1; The Netherlands 2, Switzerland 1, United Kingdom 1).

## Publication

None

## Objectives:

Primary objective: to assess the effect of varying degrees of renal function (as defined by CrCl) on the pharmacokinetics of panobinostat.

Secondary objectives

- To assess the effect of various degrees of renal function on the safety of panobinostat.
- To evaluate whether there is a relationship between pharmacokinetics (PK) and safety parameters in patients with various degrees of renal function.

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

Oral panobinostat was supplied as 5 mg, 15 mg or 20 mg hard gelatin capsules and was given on a flat scale of mg on a given day. The capsules were packaged in HDPE bottles with plastic child resistant closures.

## Statistical Methods

A formal statistical analysis was performed for primary PK parameters of panobinostat: T1/2, AUC0 48h, AUC0-inf, and Cmax. A linear model was fitted to the log-transformed PK parameters with the renal function groups (normal, mild, moderate, and severe) as a fixed effect. For this analysis, the mild, moderate and severe groups were considered as the tests, while the normal group was the reference. The point estimate of the treatment difference and the corresponding 90% confidence intervals (CI) were calculated and anti-logged to obtain the point estimate and CI on the linear scale for the ratio of geometric means of the test as compared with the reference. Comparisons were performed between each dysfunction group and the normal group. Primary urine PK parameters were not analyzed by a statistical model.

Baseline BSA and age were included in the primary analysis model. Results from the full model with all relevant covariates were reported.

For Tmax, point estimates and 90% CIs of the difference between test and reference were provided using non-parametric methods (Hodges-Lehmann estimate and Moses CI).

Summary statistics of plasma PK parameters were presented for panobinostat and its metabolites (BJB432, M36.9, M40.8 and M43.5 [AFN835]) and for urine PK parameters of panobinostat.

## Study Population: Key Inclusion/Exclusion Criteria

Patients were eligible for inclusion if they met the following criteria:

1. Patient was ≥ 18 years of age,
2. Patient had an Eastern Cooperative Oncology Group (ECOG) performance status (PS) of ≤ 2,
3. Patient had documented diagnosis of advanced solid tumor for which no standard systemic therapy existed,
4. Patient had the following laboratory values within 2 weeks of starting study drug (laboratory tests were allowed to be repeated in order to obtain acceptable values before failure at Screening was concluded):
    a. Creatinine clearance according to a 24-hour urine CrCL (specific criteria for allocation of patients by renal function):
        - ≥ 80 mL/min for the normal renal function patients;
        - ≥ 50 - <80 mL/min for the mildly renal impaired patents;
        - ≥ 30 - <50 mL/min for the moderately impaired patients;
        - <30 mL/min for severely renal impaired patients, if applicable.
    b. Urinalysis: protein (proteinuria) ≤ +2 by dipstick method, or <100 mg/dL by quantitative method and blood (hematuria) ≤ +1 by dipstick method for normal renal function group patients,
    c. Hemoglobin ≥ 9 g/dL,
    d. Absolute neutrophil count (ANC) ≥ 1.5 x $10^9$/L,
    e. Platelet count ≥ 100 x $10^9$/L,
    f. Aspartate aminotransferase/serum glutamic oxaloacetic transaminase (AST/SGOT) and alanine transaminase/serum glutamic pyruvate transaminase (ALT/SGPT) ≤ 2.5 x upper limit of normal (ULN) (or ≤ 5 x ULN if transaminase elevation is due to disease involvement),
    g. Serum total bilirubin ≤ 1.5 x ULN,
    h. Patient with normal renal function should have serum potassium, magnesium, total calcium (corrected for serum albumin) or ionized calcium within normal limits.

**Note**: Potassium, magnesium and sodium supplements may be given to correct values that are < lower limit of normal (LLN).

5. Patient was able to swallow capsules,
6. Sexually active patients (men and women of child bearing potential WOCBP) were required to use double barrier method of contraception during the course of the study and for 3 months after completing study treatment. WOCBP were defined as sexually mature

women who had not undergone a hysterectomy or who had not been naturally postmenopausal for at least 12 consecutive months,

7. Patient had signed a written informed consent prior to any screening procedures.

## Participant Flow Table

### Patient disposition, by renal function groups – Full analysis set

| Disposition | Normal (N=11) n (%) | Mild (N=10) n (%) | Moderate (N=10) n (%) | Severe (N=6) n (%) | All patients (N=37) n (%) |
|---|---|---|---|---|---|
| **Primary reason for end of treatment** | | | | | |
| Disease progression | 4 (36.4) | 8 (80.0) | 7 (70.0) | 2 (33.3) | 21 (56.8) |
| Adverse Event(s) | 4 (36.4) | 2 (20.0) | 1 (10.0) | 1 (16.7) | 8 (21.6) |
| Subject withdrew consent | 2 (18.2) | 0 | 2 (20.0) | 1 (16.7) | 5 (13.5) |
| Administrative problems | 0 | 0 | 0 | 2 (33.3) | 2 (5.4) |
| Death | 1 (9.1) | 0 | 0 | 0 | 1 (2.7) |
| **Primary reason for study evaluation completion** | | | | | |
| Disease progression | 4 (36.4) | 7 (70.0) | 6 (60.0) | 2 (33.3) | 19 (51.4) |
| Death | 3 (27.3) | 1 (10.0) | 1 (10.0) | 1 (16.7) | 6 (16.2) |
| F/u phase compl as per prot. | 3 (27.3) | 2 (20.0) | 0 | 1 (16.7) | 6 (16.2) |
| Subject withdrew consent | 1 (9.1) | 0 | 2 (20.0) | 1 (16.7) | 4 (10.8) |
| Administrative problems | 0 | 0 | 0 | 1 (16.7) | 1 (2.7) |
| Lost to follow-up | 0 | 0 | 1 (10.0) | 0 | 1 (2.7) |

## Baseline Characteristics

### Demographics and other baseline characteristics, by renal function groups – Full analysis set

| Demographic variable | Normal (N=11) | Mild (N=10) | Moderate (N=10) | Severe (N=6) | All patients (N=37) |
|---|---|---|---|---|---|
| **Age (years)** | | | | | |
| n | 11 | 10 | 10 | 6 | 37 |
| Mean | 58.09 | 62.70 | 67.00 | 63.17 | 62.57 |
| SD | 11.149 | 6.111 | 11.690 | 7.521 | 9.876 |
| Median | 60.00 | 62.50 | 70.00 | 66.50 | 64.00 |

| Demographic variable | Normal (N=11) | Mild (N=10) | Moderate (N=10) | Severe (N=6) | All patients (N=37) |
|---|---|---|---|---|---|
| Min | 40.0 | 52.0 | 41.0 | 51.0 | 40.0 |
| Max | 71.0 | 73.0 | 81.0 | 70.0 | 81.0 |
| **Sex** | | | | | |
| Male | 8 (72.7) | 8 (80.0) | 6 (60.0) | 5 (83.3) | 27 (73.0) |
| Female | 3 (27.3) | 2 (20.0) | 4 (40.0) | 1 (16.7) | 10 (27.0) |
| **Race** | | | | | |
| Caucasian | 10 (90.9) | 10 (100.0) | 10 (100.0) | 6 (100.0) | 36 (97.3) |
| Missing | 1 (9.1) | 0 (0.0) | 0 (0.0) | 0 (0.0) | 1 (2.7) |
| **Ethnicity** | | | | | |
| Hispanic/Latino | 2 (18.2) | 0 (0.0) | 0 (0.0) | 0 (0.0) | 2 (5.4) |
| Other | 8 (72.7) | 9 (90.0) | 10 (100.0) | 6 (100.0) | 33 (89.2) |
| Mixed Ethnicity | 0 (0.0) | 1 (10.0) | 0 (0.0) | 0 (0.0) | 1 (2.7) |
| Missing | 1 (9.1) | 0 (0.0) | 0 (0.0) | 0 (0.0) | 1 (2.7) |
| **Weight (kg)** | | | | | |
| n | 11 | 10 | 10 | 6 | 37 |
| Mean | 71.67 | 83.92 | 88.61 | 87.00 | 82.05 |
| SD | 17.260 | 12.594 | 23.960 | 25.159 | 20.093 |
| Median | 71.80 | 89.20 | 88.25 | 88.85 | 83.60 |
| Min | 46.6 | 53.0 | 56.5 | 52.6 | 46.6 |
| Max | 105.0 | 94.9 | 136.8 | 123.9 | 136.8 |
| **Height (cm)** | | | | | |
| n | 11 | 10 | 9 | 6 | 36 |
| Mean | 174.82 | 174.70 | 174.22 | 177.67 | 175.11 |
| SD | 7.387 | 5.774 | 8.467 | 9.288 | 7.367 |
| Median | 173.00 | 175.00 | 178.00 | 181.00 | 178.00 |
| Min | 165.0 | 165.0 | 164.0 | 159.0 | 159.0 |
| Max | 187.0 | 183.0 | 188.0 | 183.0 | 188.0 |
| **Body mass index ($kg/m^2$)** | | | | | |
| n | 11 | 10 | 9 | 6 | 36 |
| Mean | 23.24 | 27.47 | 29.06 | 27.88 | 26.64 |
| SD | 4.281 | 3.984 | 6.261 | 9.087 | 5.974 |
| Median | 24.33 | 27.97 | 29.10 | 26.67 | 26.20 |
| Min | 16.1 | 19.5 | 21.0 | 16.4 | 16.1 |
| Max | 31.7 | 33.6 | 42.2 | 39.8 | 42.2 |
| **Body surface area ($m^2$)** | | | | | |
| n | 11 | 10 | 9 | 6 | 36 |
| Mean | 1.86 | 2.01 | 2.07 | 2.05 | 1.99 |

| Demographic variable | Normal (N=11) | Mild (N=10) | Moderate (N=10) | Severe (N=6) | All patients (N=37) |
|---|---|---|---|---|---|
| SD | 0.256 | 0.177 | 0.336 | 0.305 | 0.272 |
| Median | 1.81 | 2.10 | 2.11 | 2.09 | 2.04 |
| Min | 1.5 | 1.6 | 1.6 | 1.6 | 1.5 |
| Max | 2.3 | 2.1 | 2.6 | 2.5 | 2.6 |
| **Baseline ECOG performance status** | | | | | |
| 0 | 1 (9.1) | 4 (40.0) | 2 (20.0) | 1 (16.7) | 8 (21.6) |
| 1 | 9 (81.8) | 6 (60.0) | 8 (80.0) | 3 (50.0) | 26 (70.3) |
| 2 | 1 (9.1) | 0 (0.0) | 0 (0.0) | 2 (33.3) | 3 (8.1) |

## Primary Outcome Result(s)

**Summary of panobinostat plasma PK parameters, by renal function groups (PK set)**

| PK Parameter (unit) | Normal (N=11) | Mild (N=10) | Moderate (N=10) | Severe (N=6) |
|---|---|---|---|---|
| Tmax (h) | 1.02 (0.5-4.0) | 1.0 (0.5-4.3) | 1.0 (0.5-2.0) | 0.75 (0.5-4.0) |
| Cmax (ng/mL) | 31.0 (116.7) | 18.2 (68.6) | 29.6 (92.5) | 14.0 (82.2) |
| AUC0-48 (ng*h/mL) | 188.7 (87.5) | 117.7 (66.8) | 177.3 (77.3) | 111.2 (49.1) |
| AUC0-inf (ng*h/mL) | 224.5 (98.6) | 144.3 (62.1) | 223.1 (76.7) | 131.7 (49.5) |
| AUClast (ng*h/mL) | 206.9 (99.3) | 133.4 (65.4) | 204.5 (76.6) | 124.7 (49.2) |
| CL/F (L/h) | 133.7 (98.6) | 207.9 (62.1) | 134.5 (76.7) | 227.8 (49.5) |
| Vz/F (L) | 5646 (41.7) | 9922 (82.9) | 6404 (76.9) | 9039 (31.7) |
| T1/2 (h) | 29.3 (56.9) | 33.1(26.0) | 33.0 (21.5) | 27.5 (23.8) |
| Clast (ng/mL) | 0.37 (61.2) | 0.20 (46.7) | 0.37 (75.4) | 0.18 (36.0) |
| Tlast (h) | 96.0 (24.1- 96.4) | 96.0 (95.6- 96.2) | 96.0 (96.0- 96.7) | 96.0 (72.0- 96.3) |

**Summary of panobinostat urine PK parameters, by renal function groups (PK set)**

| PK Parameter (unit) | Normal (N=11) | Mild (N=10) | Moderate (N=10) | Severe (N=6) |
|---|---|---|---|---|
| %Xu | 1.83 (0.29 - 2.95) | 0.73 (0.20 - 2.71) | 0.75 (0.21 - 1.93) | 0.20 (0.07 - 0.32) |
| CLr (mL/h) | 1.39 (13.0) | 1.24 (7.29) | 1.32 (5.10) | 1.28 (8.55) |

**Summary of statistical analysis of panobinostat PK parameters, by renal function groups (PK set)**

| | | | | | Treatment Comparison | | |
|---|---|---|---|---|---|---|---|
| | | | | | | 90% CI | |
| PK Parameter (unit) | Group | n* | Adjusted Geo-mean | Comparison | Geo-mean Ratio | Lower | Upper |

| | | | | | Treatment Comparison | | |
|---|---|---|---|---|---|---|---|
| | | | | | | 90% CI | |
| PK Parameter (unit) | Group | n* | Adjusted Geo-mean | Comparison | Geo-mean Ratio | Lower | Upper |
| Cmax (ng/mL) | Normal | 11 | 29.593 | | | | |
| | Mild | 10 | 18.336 | Mild: Normal | 0.620 | 0.331 | 1.160 |
| | Moderate | 9 | 32.795 | Mod: Normal | 1.108 | 0.561 | 2.188 |
| | Severe | 6 | 14.183 | Severe: Normal | 0.479 | 0.231 | 0.995 |
| Tmax (h) | Normal | 11 | 1.017 | | | | |
| | Mild | 10 | 1.000 | Mild - Normal | -0.008 | -0.967 | 0.500 |
| | Moderate | 10 | 1.000 | Mod - Normal | -0.017 | -0.967 | 0.500 |
| | Severe | 6 | 0.750 | Severe - Normal | -0.008 | -1.183 | 0.500 |
| AUC0-inf (ng*h/mL) | Normal | 11 | 217.852 | | | | |
| | Mild | 10 | 145.139 | Mild: Normal | 0.666 | 0.386 | 1.150 |
| | Moderate | 9 | 227.945 | Mod: Normal | 1.046 | 0.579 | 1.891 |
| | Severe | 6 | 133.613 | Severe: Normal | 0.613 | 0.325 | 1.158 |
| AUClast (ng*h/mL) | Normal | 11 | 199.933 | | | | |
| | Mild | 10 | 134.234 | Mild: Normal | 0.671 | 0.387 | 1.165 |
| | Moderate | 9 | 210.027 | Mod: Normal | 1.051 | 0.578 | 1.910 |
| | Severe | 6 | 126.484 | Severe: Normal | 0.633 | 0.333 | 1.202 |
| AUC0-48 (ng*h/mL) | Normal | 11 | 181.444 | | | | |
| | Mild | 10 | 118.523 | Mild: Normal | 0.653 | 0.384 | 1.112 |
| | Moderate | 9 | 182.975 | Mod: Normal | 1.008 | 0.566 | 1.796 |
| | Severe | 6 | 113.041 | Severe: Normal | 0.623 | 0.335 | 1.158 |
| AUC0-96 (ng*h/mL) | Normal | 11 | 202.523 | | | | |
| | Mild | 10 | 134.277 | Mild: Normal | 0.663 | 0.386 | 1.138 |
| | Moderate | 9 | 210.030 | Mod: Normal | 1.037 | 0.577 | 1.862 |
| | Severe | 6 | 127.057 | Severe: Normal | 0.627 | 0.335 | 1.176 |

## Secondary Outcome Result(s)

## Summary of Safety

## Safety Results

### Adverse events, regardless of study drug relationship, by primary system organ class and renal function groups

| Primary system organ class | Normal (N=11) n (%) | Mild (N=10) n (%) | Moderate (N=10) n (%) | Severe (N=6) n (%) | All patients (N=37) n (%) |
|---|---|---|---|---|---|
| - Total | 11 (100.0) | 10 (100.0) | 10 (100.0) | 6 (100.0) | 37 (100.0) |
| Gastrointestinal disorders | 11 (100.0) | 9 (90.0) | 9 (90.0) | 5 (83.3) | 34 (91.9) |
| General disorders and administration site conditions | 11 (100.0) | 9 (90.0) | 9 (90.0) | 5 (83.3) | 34 (91.9) |
| Metabolism and nutrition disorders | 7 (63.6) | 7 (70.0) | 8 (80.0) | 5 (83.3) | 27 (73.0) |
| Investigations | 6 (54.5) | 5 (50.0) | 8 (80.0) | 4 (66.7) | 23 (62.2) |
| Blood and lymphatic system disorders | 5 (45.5) | 8 (80.0) | 4 (40.0) | 4 (66.7) | 21 (56.8) |
| Respiratory, thoracic and mediastinal disorders | 9 (81.8) | 4 (40.0) | 6 (60.0) | 0 (0.0) | 19 (51.4) |
| Infections and infestations | 4 (36.4) | 5 (50.0) | 5 (50.0) | 2 (33.3) | 16 (43.2) |
| Nervous system disorders | 4 (36.4) | 3 (30.0) | 6 (60.0) | 1 (16.7) | 14 (37.8) |
| Musculoskeletal and connective tissue disorders | 2 (18.2) | 4 (40.0) | 4 (40.0) | 0 (0.0) | 10 (27.0) |
| Renal and urinary disorders | 0 (0.0) | 3 (30.0) | 5 (50.0) | 1 (16.7) | 9 (24.3) |
| Vascular disorders | 2 (18.2) | 3 (30.0) | 3 (30.0) | 1 (16.7) | 9 (24.3) |
| Skin and subcutaneous tissue disorders | 2 (18.2) | 3 (30.0) | 0 (0.0) | 2 (33.3) | 7 (18.9) |
| Cardiac disorders | 1 (9.1) | 2 (20.0) | 3 (30.0) | 0 (0.0) | 6 (16.2) |
| Psychiatric disorders | 2 (18.2) | 2 (20.0) | 1 (10.0) | 1 (16.7) | 6 (16.2) |
| Hepatobiliary disorders | 2 (18.2) | 1 (10.0) | 0 (0.0) | 1 (16.7) | 4 (10.8) |
| Neoplasms benign, malignant and unspecified (incl cysts and polyps) | 2 (18.2) | 1 (10.0) | 0 (0.0) | 0 (0.0) | 3 (8.1) |

| Primary system organ class | Normal (N=11) n (%) | Mild (N=10) n (%) | Moderate (N=10) n (%) | Severe (N=6) n (%) | All patients (N=37) n (%) |
|---|---|---|---|---|---|
| Endocrine disorders | 1 (9.1) | 0 (0.0) | 1 (10.0) | 0 (0.0) | 2 (5.4) |
| Injury, poisoning and procedural complications | 0 (0.0) | 1 (10.0) | 0 (0.0) | 0 (0.0) | 1 (2.7) |

Primary system organ classes are presented by descending order of frequencies, as reported in the column of 'all patients'.
A patient with multiple occurrences of an AE under one group is counted only once in the AE category for that group.
A patient with multiple adverse events within a primary system organ class is counted only once in the total row.

## Adverse events, regardless of study drug relationship, (reported in 3 patients or more) by preferred term and renal function groups – Safety set

| Preferred term | Normal (N=11) n (%) | Mild (N=10) n (%) | Moderate (N=10) n (%) | Severe (N=6) n (%) | All patients (N=37) n (%) |
|---|---|---|---|---|---|
| - Total | 11 (100.0) | 10 (100.0) | 10 (100.0) | 6 (100.0) | 37 (100.0) |
| Fatigue | 10 (90.9) | 6 (60.0) | 8 (80.0) | 4 (66.7) | 28 (75.7) |
| Nausea | 7 (63.6) | 4 (40.0) | 8 (80.0) | 2 (33.3) | 21 (56.8) |
| Diarrhoea | 7 (63.6) | 5 (50.0) | 2 (20.0) | 4 (66.7) | 18 (48.6) |
| Dyspnoea | 7 (63.6) | 3 (30.0) | 5 (50.0) | 0 | 15 (40.5) |
| Anaemia | 4 (36.4) | 5 (50.0) | 2 (20.0) | 3 (50.0) | 14 (37.8) |
| Decreased appetite | 5 (45.5) | 4 (40.0) | 3 (30.0) | 2 (33.3) | 14 (37.8) |
| Thrombocytopenia | 2 (18.2) | 5 (50.0) | 3 (30.0) | 2 (33.3) | 12 (32.4) |
| Vomiting | 4 (36.4) | 1 (10.0) | 5 (50.0) | 1 (16.7) | 11 (29.7) |
| Constipation | 1 (9.1) | 4 (40.0) | 3 (30.0) | 1 (16.7) | 9 (24.3) |
| Dehydration | 1 (9.1) | 3 (30.0) | 3 (30.0) | 2 (33.3) | 9 (24.3) |
| Platelet count decreased | 4 (36.4) | 1 (10.0) | 3 (30.0) | 1 (16.7) | 9 (24.3) |
| Oedema peripheral | 2 (18.2) | 1 (10.0) | 3 (30.0) | 2 (33.3) | 8 (21.6) |
| Urinary tract infection | 1 (9.1) | 2 (20.0) | 3 (30.0) | 2 (33.3) | 8 (21.6) |
| Headache | 1 (9.1) | 2 (20.0) | 4 (40.0) | 0 | 7 (18.9) |
| Hyperkalaemia | 0 | 1 (10.0) | 4 (40.0) | 2 (33.3) | 7 (18.9) |
| Abdominal pain | 1 (9.1) | 3 (30.0) | 2 (20.0) | 0 | 6 (16.2) |
| Dizziness | 4 (36.4) | 1 (10.0) | 1 (10.0) | 0 | 6 (16.2) |
| Dysgeusia | 0 | 2 (20.0) | 3 (30.0) | 1 (16.7) | 6 (16.2) |
| Pyrexia | 2 (18.2) | 3 (30.0) | 1 (10.0) | 0 | 6 (16.2) |
| Weight decreased | 1 (9.1) | 2 (20.0) | 2 (20.0) | 1 (16.7) | 6 (16.2) |
| Blood creatinine increased | 0 | 3 (30.0) | 1 (10.0) | 1 (16.7) | 5 (13.5) |
| Hyponatraemia | 2 (18.2) | 2 (20.0) | 1 (10.0) | 0 | 5 (13.5) |

| Preferred term | Normal (N=11) n (%) | Mild (N=10) n (%) | Moderate (N=10) n (%) | Severe (N=6) n (%) | All patients (N=37) n (%) |
|---|---|---|---|---|---|
| Insomnia | 1 (9.1) | 2 (20.0) | 1 (10.0) | 1 (16.7) | 5 (13.5) |
| Ascites | 2 (18.2) | 1 (10.0) | 0 | 1 (16.7) | 4 (10.8) |
| Haematuria | 0 | 1 (10.0) | 3 (30.0) | 0 | 4 (10.8) |
| Hypertension | 0 | 2 (20.0) | 2 (20.0) | 0 | 4 (10.8) |
| Hypoalbuminaemia | 0 | 2 (20.0) | 1 (10.0) | 1 (16.7) | 4 (10.8) |
| Leukocytosis | 2 (18.2) | 1 (10.0) | 0 | 1 (16.7) | 4 (10.8) |
| Muscle spasms | 1 (9.1) | 2 (20.0) | 1 (10.0) | 0 | 4 (10.8) |
| Pulmonary embolism | 2 (18.2) | 0 | 2 (20.0) | 0 | 4 (10.8) |
| Stomatitis | 1 (9.1) | 1 (10.0) | 1 (10.0) | 1 (16.7) | 4 (10.8) |
| Back pain | 1 (9.1) | 1 (10.0) | 1 (10.0) | 0 | 3 (8.1) |
| Blood alkaline phosphatase increased | 1 (9.1) | 1 (10.0) | 1 (10.0) | 0 | 3 (8.1) |
| Cough | 2 (18.2) | 1 (10.0) | 0 | 0 | 3 (8.1) |
| Hypokalaemia | 0 | 1 (10.0) | 1 (10.0) | 1 (16.7) | 3 (8.1) |
| Hypoxia | 1 (9.1) | 1 (10.0) | 1 (10.0) | 0 | 3 (8.1) |
| Oral candidiasis | 1 (9.1) | 1 (10.0) | 1 (10.0) | 0 | 3 (8.1) |
| Upper respiratory tract infection | 1 (9.1) | 1 (10.0) | 1 (10.0) | 0 | 3 (8.1) |

Preferred terms are sorted in descending frequency, as reported in 'all patients' column.
A patient with multiple occurrences of an AE under one group is counted only once in the AE category for that group.
A patient with multiple adverse events is counted only once in the total row.

**Deaths, other serious or clinically significant adverse events or related discontinuations, by renal function groups**

| Serious or significant events | Normal (N=11) n (%) | Mild (N=10) n (%) | Moderate (N=10) n (%) | Severe (N=6) n (%) | All patients (N=37) n (%) |
|---|---|---|---|---|---|
| All deaths | 3 (27.3) | 1 (10.0) | 1 (10.0) | 1 (16.7) | 6 (16.2) |
| On treatment deaths | 2 (18.2) | 1 (10.0) | 0 (0.0) | 0 (0.0) | 3 (8.1) |
| All SAEs | 7 (63.6) | 6 (60.0) | 4 (40.0) | 3 (50.0) | 20 (54.1) |
| Study-drug-related SAEs | 1 (9.1) | 3 (30.0) | 2 (20.0) | 3 (50.0) | 9 (24.3) |
| AEs leading to discontinuation | 4 (36.4) | 2 (20.0) | 1 (10.0) | 1 (16.7) | 8 (21.6) |
| Clinically significant AEs | 11 (100.0) | 10 (100.0) | 10 (100.0) | 6 (100.0) | 37 (100.0) |

| Serious or significant events | Normal (N=11) n (%) | Mild (N=10) n (%) | Moderate (N=10) n (%) | Severe (N=6) n (%) | All patients (N=37) n (%) |
|---|---|---|---|---|---|

Except for the 'all deaths' row, all other rows only include events happened on or after the first dose and up to 28 days after last dose of study drug.
The source listings have all events shown. Clinically significant AEs are defined as Asthenia, Fatigue, Cardiac failure, Diarrhea, Hemorrhage, Hepatic dysfunction, Hypothyroidism, Pneumonia, Sepsis, Ischaemic colitis, Ischaemic heart disease, Anemia, Cytopenia, Leukopenia, Thrombocytopenia, QT prolongation, Hepatitis B Infection, Acute renal failure, Tachyarrhythmia, Venous Thromboembolism.

## Other Relevant Findings

No apparent relationship was observed between Cmax and worst QTcF prolongation in this study. Similarly, no apparent relationship was observed between grade 4 thrombocytopenia and exposures across patients with various degree of renal impairment.

## Conclusion:

Results from the interim CSR (cut-off date: 20-May-2013) revealed that renal impairment of mild, moderate and severe degree did not increase systemic exposure of panobinostat as compared to those with normal renal function. Furthermore various degrees of renal impairment did not adversely impact the safety profile of panobinostat in advanced cancer patients. Patients with renal impairment (mild to severe) should be treated with the same starting dose of panobinostat as patients with normal renal function.

Three patients were ongoing at the time of interim cut-off date (20-May-2013). Two patients prematurely discontinued the study drug due to administrative problems, and one patient withdrew his consent. Additional information from the 3 ongoing patients supported the PK and safety conclusions drawn from the interim CSR.

Therapeutic management of cancer patients with renal impairment should aim at assuring that effective doses are delivered. As for patients with normal renal function, monitoring of patients with renal dysfunction and treatment modifications should apply based on patient's safety and tolerability. The lack of data on end stage renal failure patients suggests particular caution should be taken when administering panobinostat in this vulnerable patient population.

## Date of Clinical Trial Report

23-Mar-2015

## Date of Initial Inclusion on Novartis Clinical Trial Results website

23-Apr-2015

## Date of Latest Update

Not applicable.

## Reason for Update

Not applicable.