## Sponsor

Novartis

## Generic Drug Name

Panobinostat (LBH589)

## Trial Indication

Acute myeloid leukemia (AML)

## Protocol Number

Protocol no. CLBH589G2101

## Protocol Title

A Phase Ib, dose-finding study of oral panobinostat (LBH589) in combination with idarubicin and cytarabine (ara-C) induction and high-dose ara-C-based consolidation therapy in adult patients less than or equal to 65-years-old with acute myeloid leukemia (AML).

## Clinical Trial Phase

Phase Ib

## Phase of Drug Development

I

## Study Start/End Dates

27-Oct-2010 to 06-May-2014

## Reason for Termination (If applicable)

Not applicable

## Study Design/Methodology

This was a multi-center, open-label, dose-escalation Phase Ib study designed to determine the maximum tolerated dose (MTD) and/or recommended Phase II dose (RPIID) of oral panobinostat administered in combination with induction chemotherapy idarubicin and ara-C (3+7) in the Induction Phase, in adult patients with newly diagnosed high-risk AML. Patients who achieved a complete response/remission (CR) or complete remission with incomplete blood count recovery (CRi) during Induction Phase and had no unacceptable toxicity moved to the Consolidation Phase with a combination of high-dose ara-C (HiDAC) and the same dose or one dose level lower of panobinostat received in the Induction Phase. Each treatment cycle consists of a 28-day cycle in both Induction and Consolidation Phase.

In the Induction Phase, the study evaluated escalating doses of oral panobinostat administered orally three times a week for two weeks starting on Day 8 (i.e. D8, D10, D12, D15, D17, D19) of each cycle in combination with a fixed induction dose of standard idarubicin and ara-C chemotherapy (one or two cycles of induction therapy). Starting dose of panobinostat was 20 mg/day.

Induction treatments were given for a maximum of two cycles. Idarubicin and/or ara-C were provided during the first seven days of a cycle, panobinostat was administered on study weeks two and three (days 8 to 21), and no study treatment was given during week four (days 22 to 28). If delay of a treatment cycle lasted longer than 28 days, a bone marrow assessment was required prior to starting the next study cycle. Patients were to be removed from the study treatment if their treatment cycle was delayed ≥ 56 days. No intra-patient dose escalation was allowed throughout the study.

A Bayesian logistic regression model (BLRM) employing the escalation with overdose control (EWOC) principle was used to guide the dose-escalation process and for dose level selection of panobinostat and to estimate the MTD. The MTD for the Induction Phase was defined to be the highest dose of panobinostat which when given together with chemotherapy in the first induction treatment cycle had a less than or equal to 25% probability to produce dose limiting toxicity (DLT) in more than 33.3% of the patients. The potential RPIID was defined as a dose ≤ the MTD/last dose level, evaluated after 22 patients had been treated at that dose. A DLT was defined as an adverse event (AE) or abnormal laboratory value occurring after starting panobinostat during Cycle 1 of induction and assessed as clinically relevant and was considered to be related to the study drug, unrelated to disease, disease progression, inter-current illness, or concomitant medications. The final decision to dose escalate was based on discussion with the team and investigators using the DLT information, the Bayesian logistic model's recommendation as a guideline in the decision making process and clinical synthesis of all the relevant toxicity.

If a patient did not reach a CR or CRi in the Induction Phase (either Cycle 1 or Cycle 2), the patient was considered to be treatment failure and had to be removed from the study. Additionally, if the patient was a candidate for hematopoietic stem cell transplantation, the patient was removed from the study.

During the Consolidation Phase, the patients received HiDAC in combination with panobinostat dose that was equal or one dose level lower than their final Induction Phase dose levels for four treatment cycles.

## Centers

10 centers in 3 countries: Germany (3), Spain (2), and United States (5).

## Publication

None

## Objectives:

The primary objective was to determine the MTD and/or RPIID for Induction Phase of panobinostat when administered in combination with a fixed dose of standard idarubicin and ara-C chemotherapy to adult patients with high-risk AML.

Secondary objectives were to assess the safety profile of panobinostat in combination with a fixed dose of idarubicin and ara-C induction and consolidation therapy, to assess the pharmacokinetic (PK) of oral panobinostat following idarubicin and ara-C induction therapy, and to report the extent of anti-leukemic activity in terms of response rate according to international working group (IWG) response criteria in the Induction Phase.

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

Panobinostat was the investigational drug and was provided as immediate-release hard gelatin capsules in strengths of 5 and 20 mg for oral administration. Panobinostat was given on a flat scale of mg/day, with a starting dose of 20 mg/day.

The chemotherapeutic agent's idarubicin + ara-C were administered in combination with panobinostat and are referred to as the 'combination drugs'. The 'study treatment' therefore consisted of:

- Induction Phase: panobinostat (escalating doses starting with 20 mg/day orally) plus 100 mg/$m^2$/day ara-C as continuous intravenous (iv) infusion plus 12 mg/$m^2$/day idarubicin iv.
- Consolidation Phase: panobinostat (doses from induction treatments) plus 3 g/$m^2$/q12h ara-C (HiDAC) iv.

## Statistical Methods

An adaptive BLRM guided by EWOC was used during the dose escalation in the Induction Phase for determination of the MTD of panobinostat in combination with a fixed dose of ara-C and a fixed dose of idarubicin.

The RPIID was determined based on considerations of the estimated MTD by the adaptive BLRM, if available, along with an overall assessment of safety taking into consideration tolerability data from a possible second induction cycle at all different dose levels tested.

All efficacy analyses were based on full analysis set. The rate of CR, CRi and partial response (PR) was estimated according to IWG criteria in the Induction Phase. The best on-study response (CR, CRi, PR, treatment failure), as categorized by the response criteria, was described by patient based on the Investigator's assessment for the Induction Phase. Patients were followed for treatment failure, relapse and/or death.

All safety analyses were based on safety set. The assessment of safety was based mainly on the frequency of AEs and on the number of laboratory values that fell outside of pre-determined ranges. Other safety data (e.g., Electrocardiograms (ECGs), vital signs, and

special tests) were considered as appropriate. All safety data were listed. Patients were summarized by initial dose level of panobinostat and by study phase.

The PK analysis was performed using the PK set. Summary statistics of panobinostat concentration were presented at each scheduled time point by panobinostat dose.

## Study Population: Key Inclusion/Exclusion Criteria

**Key inclusion criteria:** The patients meeting following criteria were included:

- Age ≥ 18 years and ≤ 65 years and Eastern Cooperative Oncology Group (ECOG) performance status (PS) of ≤ 2.
- Diagnosed with AML according to WHO criteria with ≥ 20% bone marrow blasts by bone marrow aspiration or biopsy and the patient had not been treated for AML.
- Primary or secondary AML patients with high-risk category features according to the following criteria:
    - Treatment-related AML secondary to prior cytotoxic chemotherapy or radiotherapy for an unrelated disease.
    - AML arising after previously diagnosed myelodysplasia (>2 months prior to AML diagnosis) or other antecedent hematologic disorders (including aplastic anemia, polycythemia vera, essential thrombocytopenia, myelofibrosis, paroxysmal nocturnal hemoglobinuria or other hematopoietic disorders). These patients could be treatment-naïve or could have been treated with conventional care regimens for precedent myelodysplasia (MDS)/antecedent hematologic disorders (AHD). Patients who received allogeneic bone marrow transplantation for these conditions were eligible, provided it was >6 months after the transplant and the patients were free of serious complications such as infections or graft-versus-host disease.
    - Cytogenetic groups: Dohner's Intermediate - II and Adverse groups or National Comprehensive Cancer Network intermediate and poor risk groups.
- With laboratory values: Aspartate aminotransferase/serum glutamic oxaloacetic transaminase (AST/SGOT) and alanine aminotransferase/serum glutamic pyruvic transaminase (ALT/SGPT) ≤ 2.5 x upper limit of normal (ULN), serum creatinine levels ≤ 1.5 x ULN, or calculated creatinine clearance ≥ 60 mL/min, serum total bilirubin ≤ 1.5 ULN (or ≤ 3.0 x ULN if patient has Gilbert syndrome), serum potassium, magnesium, phosphorus, within normal limits for institution, and total calcium (corrected for serum albumin) or ionized calcium ≥ lower limit of normal (LLN), and not higher than Common Terminology Criteria for Adverse Events (CTCAE) grade 1 in case of elevated value.

**Key exclusion criteria:** The patients meeting following criteria were excluded:

- Who had "favorable" and "better-risk" cytogenetic prognosis t(15;17), t(8;21), and inv(16) or t(16;16).
- Who had chronic myelogenous leukemia in blast crisis phase and with clinical symptoms suggesting central nervous system (CNS) leukemia and/or central spinal fluid findings for CNS leukemia.

- Who had another primary malignancy <3 years from first dose of study treatment (except for basal or squamous cell carcinoma, in situ cancer of the cervix, or MDS). Patients who had undergone major surgery ≤ 3 weeks prior to starting study treatment or who had not recovered from side effects of such therapy to CTCAE grade <2. Patients who had evidence of mucosal or internal bleeding.
- Who had received prior treatment with deacetylase inhibitors (DACi) and who had received concurrent anti-cancer therapy (standard or other investigational agent other than those defined by the protocol)
- Who had received prior chemotherapy for leukemia, with the following exceptions: (a) emergency leukapheresis; (b) treatment for hyperleukocytosis with hydroxyurea; (c) growth factor/cytokine support; and (d) treatment for MDS/AHD.
- With impaired, cardiac function or who were taking medications with relative risk of prolonging the QT interval or inducing Torsade de pointes, gastrointestinal (GI) function.
- Who had any other concurrent severe and/or uncontrolled medical conditions that could cause unacceptable safety risks or compromise compliance with the protocol.
- Who had a known history of human immunodeficiency virus seropositivity or history of active/treated hepatitis B or C.
- Who had impairment of GI function or GI disease that may significantly alter the absorption of panobinostat (e.g., ulcerative disease, uncontrolled nausea, vomiting, unresolved diarrhea ≥ CTCAE grade 2, malabsorption syndrome, obstruction, or stomach and/or small bowel resection).
- Pregnant or lactating women at screening and/or baseline. Women of child-bearing potential, not willing to use highly effective methods of contraception during dosing and for five terminal half-lives (eight days) and an additional 12 weeks (totaling to 13 weeks) after stopping study treatment.

## Participant Flow Table

**Patient disposition, by dose group of panobinostat during Induction Phase (FAS set)**

| Disposition Reason | PAN 1 5 mg N=11 n (%) | PAN 20 mg N=15 n (%) | PAN 25 mg N=8 n (%) | PAN 20 mg (Expansion phase) N=12 n (%) | All patients N=46 n (%) |
|---|---|---|---|---|---|
| **Enrolled**[1] | 11 (100.0) | 15 (100.0) | 8 (100.0) | 12 (100.0) | 46 (100.0) |
| **Entered consolidation phase** | 8 (72.7) | 5 (33.3) | 2 (25.0) | 4 (33.3) | 19 (41.3) |
| **Discontinued treatment**[2] | 3 (27.3) | 10 (66.7) | 6 (75.0) | 8 (66.7) | 27 (58.7) |
| **Primary reason for end of treatment** | | | | | |
| Abnormal laboratory value(s) | 1 (9.1) | 0 (0.0) | 0 (0.0) | 0 (0.0) | 1 (2.2) |
| Abnormal test procedure result(s) | 0 (0.0) | 1 (6.7) | 0 (0.0) | 0 (0.0) | 1 (2.2) |

| Disposition Reason | PAN 1 5 mg N=11 n (%) | PAN 20 mg N=15 n (%) | PAN 25 mg N=8 n (%) | PAN 20 mg (Expansion phase) N=12 n (%) | All patients N=46 n (%) |
|---|---|---|---|---|---|
| Adverse Event(s) | 1 (9.1) | 3 (20.0) | 3 (37.5) | 1 (8.3) | 8 (17.4) |
| Death[3] | 0 (0.0) | 1 (6.7) | 0 (0.0) | 1 (8.3) | 2 (4.3) |
| Disease progression[4] | 1 (9.1) | 5 (33.3) | 3 (37.5) | 2 (16.7) | 11 (23.9) |
| Lost to follow-up | 0 (0.0) | 0 (0.0) | 0 (0.0) | 1 (8.3) | 1 (2.2) |
| Protocol deviation | 0 (0.0) | 0 (0.0) | 0 (0.0) | 2 (16.7) | 2 (4.3) |
| Subject withdrew consent | 0 (0.0) | 0 (0.0) | 0 (0.0) | 1 (8.3) | 1 (2.2) |
| **Entered post-treatment evaluation[5]** | 2 (18.2) | 7 (46.7) | 5 (62.5) | 1 (8.3) | 15 (32.6) |
| **Primary reason for end of study** | | | | | |
| Death[3] | 0 (0.0) | 1 (6.7) | 0 (0.0) | 3 (25.0) | 4 (8.7) |
| Disease progression[4] | 0 (0.0) | 3 (20.0) | 1 (12.5) | 1 (8.3) | 5 (10.9) |
| Follow up phase completed as per protocol | 1 (9.1) | 1 (6.7) | 0 (0.0) | 0 (0.0) | 2 (4.3) |
| Lost to follow-up | 0 (0.0) | 0 (0.0) | 0 (0.0) | 1 (8.3) | 1 (2.2) |
| New cancer therapy | 2 (18.2) | 5 (33.3) | 5 (62.5) | 2 (16.7) | 14 (30.4) |
| Protocol deviation | 0 (0.0) | 0 (0.0) | 0 (0.0) | 1 (8.3) | 1 (2.2) |

[1]Treated patients in induction phase
[2] Patient completed End of Treatment (EOT) CRF page
[3] Includes only patients for whom death was reported as the primary reason for discontinuation of treatment or study
[4] Disease progression included patients with relapse or treatment failure as per AML IWG criteria.
[5] Includes only patients who agreed to be followed for post-treatment evaluations (based on EOT page)

## Patient disposition, by dose group of panobinostat during Consolidation Phase (FAS)

| Disposition Reason | PAN 15 mg N=8 n (%) | PAN 20 mg N=5 n (%) | PAN 25 mg N=2 n (%) | PAN 20 mg (expansion phase) N=4 n (%) | All patients N=19 n (%) |
|---|---|---|---|---|---|
| **Enrolled[1]** | 8 (100.0) | 5 (100.0) | 2 (100.0) | 4 (100.0) | 19 (100.0) |
| **Discontinued treatment[2]** | 8 (100.0) | 5 (100.0) | 2 (100.0) | 4 (100.0) | 19 (100.0) |
| **Primary reason for end of treatment** | | | | | |
| Administrative problems | 1 (12.5) | 0 (0.0) | 0 (0.0) | 0 (0.0) | 1 (5.3) |
| Adverse Event(s) | 2 (25.0) | 1 (20.0) | 0 (0.0) | 0 (0.0) | 3 (15.8) |
| Death[3] | 0 (0.0) | 0 (0.0) | 0 (0.0) | 1 (25.0) | 1 (5.3) |
| Protocol deviation | 1 (12.5) | 0 (0.0) | 0 (0.0) | 0 (0.0) | 1 (5.3) |
| Subject withdrew consent | 4 (50.0) | 1 (20.0) | 0 (0.0) | 0 (0.0) | 5 (26.3) |

| Disposition Reason | PAN 15 mg N=8 n (%) | PAN 20 mg N=5 n (%) | PAN 25 mg N=2 n (%) | PAN 20 mg (expansion phase) N=4 n (%) | All patients N=19 n (%) |
|---|---|---|---|---|---|
| Treatment duration completed as per protocol | 0 (0.0) | 3 (60.0) | 2 (100.0) | 3 (75.0) | 8 (42.1) |
| **Entered post-treatment evaluation[4]** | 6 (75.0) | 5 (100.0) | 2 (100.0) | 2 (50.0) | 15 (78.9) |
| **Primary reason for end of study** | | | | | |
| Death[3] | 1 (12.5) | 0 (0.0) | 0 (0.0) | 1 (25.0) | 2 (10.5) |
| Disease progression[5] | 0 (0.0) | 0 (0.0) | 1 (50.0) | 0 (0.0) | 1 (5.3) |
| Follow up phase completed as per protocol | 1 (12.5) | 4 (80.0) | 0 (0.0) | 1 (25.0) | 6 (31.6) |
| New cancer therapy | 5 (62.5) | 1 (20.0) | 1 (50.0) | 1 (25.0) | 8 (42.1) |
| Protocol deviation | 1 (12.5) | 0 (0.0) | 0 (0.0) | 0 (0.0) | 1 (5.3) |
| Subject withdrew consent | 0 (0.0) | 0 (0.0) | 0 (0.0) | 1 (25.0) | 1 (5.3) |

[1] Treated patients in consolidation phase
[2] Patient completed End of Treatment CRF page
[3] Includes only patients for whom death was reported as the primary reason for discontinuation of treatment or study
[4] Includes only patients who agreed to be followed for post-treatment evaluations (based on EOT page)
[5] Disease progression included patients with relapse or treatment failure as per AML IWG criteria.

## Baseline Characteristics

### Demographics by dose group of panobinostat (FAS Induction)

| Demographics Variable | PAN 15 mg N=11 | PAN 20 mg N=15 | PAN 25 mg N=8 | PAN 20 mg (Expansion Phase) N=12 | All patients N=46 |
|---|---|---|---|---|---|
| **Sex -n (%)** | | | | | |
| Female | 2 (18.2) | 8 (53.3) | 3 (37.5) | 8 (66.7) | 21 (45.7) |
| Male | 9 (81.8) | 7 (46.7) | 5 (62.5) | 4 (33.3) | 25 (54.3) |
| **Age (Years)** | | | | | |
| n | 11 | 15 | 8 | 12 | 46 |
| Mean | 44.8 | 52.7 | 46.1 | 56.3 | 50.6 |
| SD | 16.85 | 11.18 | 14.33 | 8.72 | 13.20 |
| Median | 46.0 | 56.0 | 52.5 | 59.5 | 55.5 |
| Minimum | 19.0 | 21.0 | 21.0 | 38.0 | 19.0 |
| Maximum | 65.0 | 64.0 | 59.0 | 64.0 | 65.0 |
| **Race -n (%)** | | | | | |
| Asian | 0 (0.0) | 0 (0.0) | 0 (0.0) | 1 (8.3) | 1 (2.2) |
| Black | 2 (18.2) | 2 (13.3) | 3 (37.5) | 0 (0.0) | 7 (15.2) |

| Demographics Variable | PAN 15 mg N=11 | PAN 20 mg N=15 | PAN 25 mg N=8 | PAN 20 mg (Expansion Phase) N=12 | All patients N=46 |
|---|---|---|---|---|---|
| Caucasian | 9 (81.8) | 13 (86.7) | 5 (62.5) | 10 (83.3) | 37 (80.4) |
| Other | 0 (0.0) | 0 (0.0) | 0 (0.0) | 1 (8.3) | 1 (2.2) |
| Ethnicity -n (%) | | | | | |
| Hispanic/Latino | 1 (9.1) | 3 (20.0) | 0 (0.0) | 1 (8.3) | 5 (10.9) |
| Other | 10 (90.9) | 12 (80.0) | 8 (100.0) | 11 (91.7) | 41 (89.1) |
| **Weight (kg)** | | | | | |
| n | 11 | 15 | 8 | 12 | 46 |
| Mean | 77.1 | 92.3 | 91.0 | 77.9 | 84.7 |
| SD | 9.72 | 24.03 | 20.21 | 16.52 | 19.58 |
| Median | 78.6 | 97.1 | 90.0 | 78.8 | 83.5 |
| Minimum | 61.4 | 50.7 | 61.1 | 51.0 | 50.7 |
| Maximum | 93.1 | 125.2 | 131.3 | 100.5 | 131.3 |
| **Height (cm)** | | | | | |
| n | 11 | 15 | 8 | 12 | 46 |
| Mean | 172.5 | 169.5 | 170.5 | 166.2 | 169.5 |
| SD | 9.47 | 8.63 | 5.71 | 11.73 | 9.33 |
| Median | 175.0 | 168.0 | 171.0 | 166.0 | 168.5 |
| Minimum | 153.0 | 152.0 | 160.0 | 147.0 | 147.0 |
| Maximum | 185.0 | 183.0 | 178.0 | 193.0 | 193.0 |
| **BMI ($kg/m^2$)** | | | | | |
| n | 11 | 15 | 8 | 12 | 46 |
| Mean | 26.1 | 32.0 | 31.4 | 28.1 | 29.4 |
| SD | 3.75 | 7.79 | 7.11 | 4.51 | 6.40 |
| Median | 24.7 | 31.6 | 30.8 | 28.3 | 28.8 |
| Minimum | 21.1 | 20.3 | 19.3 | 21.1 | 19.3 |
| Maximum | 32.6 | 45.1 | 43.9 | 33.9 | 45.1 |
| **ECOG status -n (%)** | | | | | |
| 0 | 6 (54.5) | 6 (40.0) | 1 (12.5) | 4 (33.3) | 17 (37.0) |
| 1 | 4 (36.4) | 7 (46.7) | 6 (75.0) | 6 (50.0) | 23 (50.0) |
| 2 | 1 (9.1) | 2 (13.3) | 1 (12.5) | 2 (16.7) | 6 (13.0) |
| **Respiratory rate (/min)** | | | | | |
| n | 10 | 14 | 7 | 11 | 42 |
| Mean | 16.4 | 17.9 | 18.0 | 18.2 | 17.6 |
| SD | 1.35 | 2.43 | 1.15 | 1.60 | 1.90 |
| Median | 16.0 | 18.0 | 18.0 | 18.0 | 18.0 |
| Minimum | 14.0 | 14.0 | 16.0 | 15.0 | 14.0 |
| Maximum | 18.0 | 24.0 | 20.0 | 20.0 | 24.0 |

| Demographics Variable | PAN 15 mg N=11 | PAN 20 mg N=15 | PAN 25 mg N=8 | PAN 20 mg (Expansion Phase) N=12 | All patients N=46 |
|---|---|---|---|---|---|
| **Body surface area ($m^2$)** | | | | | |
| n | 11 | 15 | 8 | 12 | 46 |
| Mean | 1.9 | 2.1 | 2.1 | 1.9 | 2.0 |
| SD | 0.14 | 0.31 | 0.23 | 0.25 | 0.26 |
| Median | 2.0 | 2.2 | 2.1 | 1.9 | 2.0 |
| Minimum | 1.7 | 1.5 | 1.7 | 1.5 | 1.5 |
| Maximum | 2.1 | 2.5 | 2.5 | 2.3 | 2.5 |

ECOG=Eastern Cooperative Oncology Group; SD=standard deviation
Body Surface Area: BSA[m2]=234.94*(height[cm]**0.422)*(weight[kg]**0.515)/10000
Body Mass Index: BMI [kg/m2]=weight[kg]/(height[m]**2

**Analysis populations, by dose group of panobinostat (all patients)**

| Analysis Set | PAN 15 mg N=11 n (%) | PAN 20 mg N=15 n (%) | PAN 25 mg N=8 n (%) | PAN 20 mg (Expansion Phase) N=12 n (%) | All patients N=46 n (%) |
|---|---|---|---|---|---|
| Full analysis set (induction) | 11 (100.0) | 15 (100.0) | 8 (100.0) | 12 (100.0) | 46 (100.0) |
| Full analysis set (consolidation) | 8 (72.7) | 5 (33.3) | 2 (25.0) | 4 (33.3) | 19 (41.3) |
| Safety analysis set (induction) | 11 (100.0) | 15 (100.0) | 8 (100.0) | 12 (100.0) | 46 (100.0) |
| Safety analysis set (consolidation) | 8 (72.7) | 5 (33.3) | 2 (25.0) | 4 (33.3) | 19 (41.3) |
| Dose determining set | 10 (90.9) | 12 (80.0) | 7 (87.5) | - | 29 (63.0) |
| Pharmacokinetic analysis set | 10 (90.9) | 12 (80) | 8 (100.0) | 10 (83.3) | 40 (87) |

## Summary of Efficacy

## Primary Outcome Result

### Maximum Tolerated Dose (MTD)/Recommended phase II dose (RPIID) determination

**Dose-limiting toxicities during Cycle 1 (28 days) by dose group of panobinostat as per current status of database: posterior estimates of probability of DLT (DDS)**

| Panobinostat dose (mg) | Patients with DLT (observed) | | Posterior probability of DLT | Probability of | | |
|---|---|---|---|---|---|---|
| | Total | n | Mean (SD) | Underdosing [%] | target toxicity [%] | unacceptable or excessive toxicity [%] |
| 15 | 10 | 0 | 18.2 (5.80) | 38.7 | 60.6 | 0.7 |
| 20 | 12 | 4 | 19.5 (6.10) | 30.7 | 68.0 | 1.3 |

| Panobinostat dose (mg) | Patients with DLT (observed) | | Posterior probability of DLT | Probability of | | |
|---|---|---|---|---|---|---|
| | Total | n | Mean (SD) | Underdosing [%] | target toxicity [%] | unacceptable or excessive toxicity [%] |
| 25 | 7 | 3 | 21.0 (6.60) | 23.6 | 73.5 | 2.9 |

Total: number of evaluable patients (included in dose determining set).
n: Number of patients with at least one DLT.
%: percentage is based on total
[1] Under dosing : DLT rate <16%
[2] Targeted toxicity: 16% ≤ DLT rate <33%
[3] Excessive or unacceptable toxicity: DLT rate ≥ 33 %
The maximum next dose level is determined if the probability of unacceptable or excessive toxicity is not exceeding 25%

## Secondary Outcome Result(s)

**Best overall response as per Investigator by dose group of panobinostat (FAS Induction)**

| Best response | PAN 15 mg N=11 n (%) | PAN 20 mg N=15 n (%) | PAN 25 mg N=8 n (%) | PAN 20 mg (Expansion Phase) N=12 n (%) | All patients N=46 n (%) |
|---|---|---|---|---|---|
| Complete remission (CR) | 6 (54.5) | 7 (46.7) | 2 (25.0) | 5 (41.7) | 20 (43.5) |
| Complete remission with incomplete blood count recovery (CRi) | 3 (27.3) | 2 (13.3) | 2 (25.0) | 1 (8.3) | 8 (17.4) |
| Partial remission (PR) | 0 (0.0) | 0 (0.0) | 1 (12.5) | 1 (8.3) | 2 (4.3) |
| Treatment failure | 1 (9.1) | 6 (40.0) | 3 (37.5) | 3 (25.0) | 13 (28.3) |
| Unknown | 1 (9.1) | 0 (0.0) | 0 (0.0) | 2 (16.7) | 3 (6.5) |
| Response rate (CR or CRi) | 9 (81.8) | 9 (60.0) | 4 (50.0) | 6 (50.0) | 28 (60.9) |
| 95% Confidence interval[1] | [48.2, 97.7] | [32.3, 83.7] | [15.7, 84.3] | [21.1, 78.9] | [45.4, 74.9] |

[1]Exact 95% confidence interval (Clopper Pearson) for percentage

## Summary of Safety

The safety profile of panobinostat in combination with ara-C and idarubicin was generally consistent with that observed in earlier panobinostat clinical studies, and was expected based on known safety profile of ara-C and idarubicin combination. As expected the GI and hematological disorders were commonly reported. The most frequently reported AEs were diarrhea, febrile neutropenia, nausea, thrombocytopenia, anemia, vomiting, and decreased appetite. Five on-treatment deaths were reported, due to sepsis (two patients), acute myeloid leukemia, ischemic stroke and cerebral hemorrhage (one patient each). Sepsis in one of the patient was suspected to be related to the study drug by the Investigator. Eight patients (17.4%) discontinued the study treatment due to AEs. Clinically non-significant QTcF changes of 30 to 60 ms from baseline were the most frequent QTcF interval changes observed

across all dose levels. One patient in the 20 mg group recorded a maximum QTcF value between 480 ms and 500 ms in the Induction Phase. No cases of QTcF over 500 ms or Torsade de pointes were reported.

## Safety Results

**Adverse events, regardless of study drug relationship by primary system organ class and dose group of panobinostat during Induction Phase (SAS)**

| | PAN 15 mg N=11 | | PAN 20 mg N=15 | | PAN 25 mg N=8 | | PAN 20 mg (Expansion Phase) N=12 | | All patients N=46 | |
|---|---|---|---|---|---|---|---|---|---|---|
| **System organ class** | **Any grades n (%)** | **Grade 3/4 n (%)** | **Any grades n (%)** | **Grade 3/4 n (%)** | **Any grades n (%)** | **Grade 3/4 n (%)** | **Any grades n (%)** | **Grade 3/4 n (%)** | **Any grades n (%)** | **Grade 3/4 n (%)** |
| **Any primary system organ class** | | | | | | | | | | |
| **Total** | 11 (100.0) | 11 (100.0) | 15 (100.0) | 15 (100.0) | 8 (100.0) | 8 (100.0) | 12 (100.0) | 11 (91.7) | 46 (100.0) | 45 (97.8) |
| Gastrointestinal disorders | 11 (100.0) | 1 (9.1) | 15 (100.0) | 3 (20.0) | 8 (100.0) | 2 (25.0) | 12 (100.0) | 1 (8.3) | 46 (100.0) | 7 (15.2) |
| Blood and lymphatic system disorders | 11 (100.0) | 11 (100.0) | 14 (93.3) | 14 (93.3) | 8 (100.0) | 8 (100.0) | 9 (75.0) | 8 (66.7) | 42 (91.3) | 41 (89.1) |
| General disorders and administration site conditions | 9 (81.8) | 0 (0.0) | 14 (93.3) | 2 (13.3) | 8 (100.0) | 2 (25.0) | 11 (91.7) | 2 (16.7) | 42 (91.3) | 6 (13.0) |
| Skin and subcutaneous tissue disorders | 9 (81.8) | 0 (0.0) | 14 (93.3) | 0 (0.0) | 7 (87.5) | 0 (0.0) | 10 (83.3) | 1 (8.3) | 40 (87.0) | 1 (2.2) |
| Metabolism and nutrition disorders | 8 (72.7) | 1 (9.1) | 14 (93.3) | 7 (46.7) | 6 (75.0) | 1 (12.5) | 10 (83.3) | 3 (25.0) | 38 (82.6) | 12 (26.1) |
| Infections and infestations | 9 (81.8) | 3 (27.3) | 11 (73.3) | 7 (46.7) | 6 (75.0) | 3 (37.5) | 8 (66.7) | 4 (33.3) | 34 (73.9) | 17 (37.0) |
| Respiratory, thoracic and mediastinal disorders | 7 (63.6) | 1 (9.1) | 12 (80.0) | 3 (20.0) | 7 (87.5) | 2 (25.0) | 7 (58.3) | 3 (25.0) | 33 (71.7) | 9 (19.6) |
| Investigations | 6 (54.5) | 2 (18.2) | 13 (86.7) | 8 (53.3) | 4 (50.0) | 3 (37.5) | 7 (58.3) | 2 (16.7) | 30 (65.2) | 15 (32.6) |
| Musculoskeletal and connective tissue disorders | 7 (63.6) | 0 (0.0) | 10 (66.7) | 0 (0.0) | 5 (62.5) | 0 (0.0) | 7 (58.3) | 0 (0.0) | 29 (63.0) | 0 (0.0) |
| Nervous system disorders | 6 (54.5) | 2 (18.2) | 12 (80.0) | 0 (0.0) | 4 (50.0) | 0 (0.0) | 6 (50.0) | 1 (8.3) | 28 (60.9) | 3 (6.5) |
| Psychiatric disorders | 7 (63.6) | 0 (0.0) | 8 (53.3) | 1 (6.7) | 2 (25.0) | 0 (0.0) | 8 (66.7) | 2 (16.7) | 25 (54.3) | 3 (6.5) |
| Vascular disorders | 5 (45.5) | 1 (9.1) | 3 (20.0) | 1 (6.7) | 6 (75.0) | 0 (0.0) | 6 (50.0) | 1 (8.3) | 20 (43.5) | 3 (6.5) |

| System organ class | PAN 15 mg N=11 | | PAN 20 mg N=15 | | PAN 25 mg N=8 | | PAN 20 mg (Expansion Phase) N=12 | | All patients N=46 | |
|---|---|---|---|---|---|---|---|---|---|---|
| | Any grades n (%) | Grade 3/4 n (%) | Any grades n (%) | Grade 3/4 n (%) | Any grades n (%) | Grade 3/4 n (%) | Any grades n (%) | Grade 3/4 n (%) | Any grades n (%) | Grade 3/4 n (%) |
| Cardiac disorders | 1 (9.1) | 0 (0.0) | 9 (60.0) | 3 (20.0) | 2 (25.0) | 0 (0.0) | 6 (50.0) | 1 (8.3) | 18 (39.1) | 4 (8.7) |
| Injury, poisoning and procedural complications | 5 (45.5) | 0 (0.0) | 6 (40.0) | 0 (0.0) | 1 (12.5) | 0 (0.0) | 3 (25.0) | 1 (8.3) | 15 (32.6) | 1 (2.2) |
| Eye disorders | 2 (18.2) | 0 (0.0) | 4 (26.7) | 1 (6.7) | 3 (37.5) | 0 (0.0) | 4 (33.3) | 0 (0.0) | 13 (28.3) | 1 (2.2) |
| Renal and urinary disorders | 3 (27.3) | 0 (0.0) | 5 (33.3) | 2 (13.3) | 1 (12.5) | 0 (0.0) | 2 (16.7) | 0 (0.0) | 11 (23.9) | 2 (4.3) |
| Hepatobiliary disorders | 1 (9.1) | 1 (9.1) | 4 (26.7) | 2 (13.3) | 0 (0.0) | 0 (0.0) | 1 (8.3) | 1 (8.3) | 6 (13.0) | 4 (8.7) |
| Reproductive system and breast disorders | 1 (9.1) | 0 (0.0) | 2 (13.3) | 1 (6.7) | 2 (25.0) | 0 (0.0) | 0 (0.0) | 0 (0.0) | 5 (10.9) | 1 (2.2) |
| Ear and labyrinth disorders | 1 (9.1) | 0 (0.0) | 1 (6.7) | 0 (0.0) | 2 (25.0) | 0 (0.0) | 0 (0.0) | 0 (0.0) | 4 (8.7) | 0 (0.0) |
| Immune system disorders | 0 (0.0) | 0 (0.0) | 0 (0.0) | 0 (0.0) | 1 (12.5) | 0 (0.0) | 0 (0.0) | 0 (0.0) | 1 (2.2) | 0 (0.0) |
| Neoplasms benign, malignant and unspecified (incl cysts and polyps) | 0 (0.0) | 0 (0.0) | 1 (6.7) | 0 (0.0) | 0 (0.0) | 0 (0.0) | 0 (0.0) | 0 (0.0) | 1 (2.2) | 0 (0.0) |

Primary system organ classes are presented in descending frequency, as reported in the “Any grades” column for “All patients”.
A patient with multiple occurrences of an AE is counted only once in the AE category.
Adverse events occurring more than 28 days after the discontinuation of study treatment are not summarized.

**Adverse events, regardless of study drug relationship by primary system organ class and dose group of panobinostat during Consolidation Phase (SAS)**

| | PAN 15 mg N=8 | | PAN 20 mg N=5 | | PAN 25 mg N=2 | | PAN 20 mg (Expansion Phase) N=4 | | All patients N=19 | |
|---|---|---|---|---|---|---|---|---|---|---|
| System organ class | Any grades n (%) | Grade 3/4 n (%) | Any grades n (%) | Grade 3/4 n (%) | Any grades n (%) | Grade 3/4 n (%) | Any grades n (%) | Grade 3/4 n (%) | Any grades n (%) | Grade 3/4 n (%) |
| **Any primary system organ class** | | | | | | | | | | |
| **Total** | 8 (100.0) | 8 (100.0) | 5 (100.0) | 5 (100.0) | 2 (100.0) | 2 (100.0) | 4 (100.0) | 4 (100.0) | 19 (100.0) | 19 (100.0) |
| Gastrointestinal disorders | 8 (100.0) | 1 (12.5) | 5 (100.0) | 1 (20.0) | 2 (100.0) | 0 (0.0) | 3 (75.0) | 1 (25.0) | 18 (94.7) | 3 (15.8) |
| Blood and lymphatic system disorders | 7 (87.5) | 7 (87.5) | 5 (100.0) | 5 (100.0) | 2 (100.0) | 2 (100.0) | 3 (75.0) | 3 (75.0) | 17 (89.5) | 17 (89.5) |
| Respiratory, thoracic and mediastinal disorders | 6 (75.0) | 1 (12.5) | 5 (100.0) | 2 (40.0) | 2 (100.0) | 0 (0.0) | 4 (100.0) | 1 (25.0) | 17 (89.5) | 4 (21.1) |
| Skin and subcutaneous tissue disorders | 7 (87.5) | 0 (0.0) | 5 (100.0) | 0 (0.0) | 2 (100.0) | 0 (0.0) | 3 (75.0) | 1 (25.0) | 17 (89.5) | 1 (5.3) |
| General disorders and administration site conditions | 6 (75.0) | 1 (12.5) | 5 (100.0) | 2 (40.0) | 2 (100.0) | 0 (0.0) | 3 (75.0) | 0 (0.0) | 16 (84.2) | 3 (15.8) |
| Metabolism and nutrition disorders | 5 (62.5) | 2 (25.0) | 4 (80.0) | 3 (60.0) | 1 (50.0) | 0 (0.0) | 3 (75.0) | 0 (0.0) | 13 (68.4) | 5 (26.3) |
| Nervous system disorders | 5 (62.5) | 0 (0.0) | 3 (60.0) | 1 (20.0) | 1 (50.0) | 0 (0.0) | 3 (75.0) | 1 (25.0) | 12 (63.2) | 2 (10.5) |
| Infections and infestations | 5 (62.5) | 5 (62.5) | 2 (40.0) | 2 (40.0) | 2 (100.0) | 2 (100.0) | 2 (50.0) | 2 (50.0) | 11 (57.9) | 11 (57.9) |
| Musculoskeletal and connective tissue disorders | 3 (37.5) | 0 (0.0) | 5 (100.0) | 0 (0.0) | 1 (50.0) | 1 (50.0) | 2 (50.0) | 0 (0.0) | 11 (57.9) | 1 (5.3) |

| | | | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|
| Injury, poisoning and procedural complications | 3 (37.5) | 0 (0.0) | 3 (60.0) | 0 (0.0) | 0 (0.0) | 0 (0.0) | 2 (50.0) | 0(0.0) | 8 (42.1) | 0 (0.0) |
| Investigations | 2 (25.0) | 0 (0.0) | 1 (20.0) | 0 (0.0) | 2 (100.0) | 2 (100.0) | 3 (75.0) | 0 (0.0) | 8 (42.1) | 2 (10.5) |
| Psychiatric disorders | 3 (37.5) | 0 (0.0) | 2 (40.0) | 0 (0.0) | 0 (0.0) | 0 (0.0) | 2 (50.0) | 0 (0.0) | 7 (36.8) | 0 (0.0) |
| Cardiac disorders | 3 (37.5) | 0 (0.0) | 3 (60.0) | 0 (0.0) | 0 (0.0) | 0 (0.0) | 0 (0.0) | 0 (0.0) | 6 (31.6) | 0 (0.0) |
| Eye disorders | 1 (12.5) | 0 (0.0) | 0 (0.0) | 0 (0.0) | 1 (50.0) | 0 (0.0) | 2 (50.0) | 0 (0.0) | 4 (21.1) | 0 (0.0) |
| Renal and urinary disorders | 0 (0.0) | 0 (0.0) | 1 (20.0) | 0 (0.0) | 1 (50.0) | 0 (0.0) | 1 (25.0) | 0 (0.0) | 3 (15.8) | 0 (0.0) |
| Reproductive system and breast disorders | 0 (0.0) | 0 (0.0) | 1 (20.0) | 0 (0.0) | 1 (50.0) | 1 (50.0) | 1 (25.0) | 0 (0.0) | 3 (15.8) | 1 (5.3) |
| Hepatobiliary disorders | 0 (0.0) | 0 (0.0) | 0 (0.0) | 0 (0.0) | 0 (0.0) | 0 (0.0) | 1 (25.0) | 1 (25.0) | 1 (5.3) | 1 (5.3) |
| Immune system disorders | 0 (0.0) | 0 (0.0) | 0 (0.0) | 0 (0.0) | 0 (0.0) | 0 (0.0) | 1 (25.0) | 0 (0.0) | 1 (5.3) | 0 (0.0) |
| Vascular disorders | 0 (0.0) | 0 (0.0) | 0 (0.0) | 0 (0.0) | 1 (50.0) | 0 (0.0) | 0 (0.0) | 0 (0.0) | 1 (5.3) | 0 (0.0) |

Primary system organ classes are presented in descending frequency, as reported in the “Any grades” column for “All patients”.
A patient with multiple occurrences of an AE is counted only once in the AE category.
Adverse events occurring more than 28 days after the discontinuation of study treatment are not summarized.

**Adverse events, regardless of study drug relationship by preferred term and dose group of panobinostat during Induction Phase (with an incidence of 15% or greater in any dose group, SAS)**

| | **PAN 15 mg N=11** | | **PAN 20 mg N=15** | | **PAN 25 mg N=8** | | **PAN 20 mg (Expansion Phase) N=12** | | **All patients N=46** | |
|---|---|---|---|---|---|---|---|---|---|---|
| **Preferred term** | **Any grades n (%)** | **Grade 3/4 n (%)** | **Any grades n (%)** | **Grade 3/4 n (%)** | **Any grades n (%)** | **Grade 3/4 n (%)** | **Any grades n (%)** | **Grade 3/4 n (%)** | **Any grades n (%)** | **Grade 3/4 n (%)** |
| Diarrhoea | 10 (90.9) | 0 (0.0) | 12 (80.0) | 1 (6.7) | 7 (87.5) | 2 (25.0) | 10 (83.3) | 1 (8.3) | 39 (84.8) | 4 (8.7) |
| Febrile neutropenia | 9 (81.8) | 8 (72.7) | 11 (73.3) | 10 (66.7) | 5 (62.5) | 5 (62.5) | 6 (50.0) | 6 (50.0) | 31 (67.4) | 29 (63.0) |
| Nausea | 5 (45.5) | 0 (0.0) | 10 (66.7) | 0 (0.0) | 4 (50.0) | 0 (0.0) | 8 (66.7) | 0 (0.0) | 27 (58.7) | 0 (0.0) |

| | PAN 15 mg N=11 | | PAN 20 mg N=15 | | PAN 25 mg N=8 | | PAN 20 mg (Expansion Phase) N=12 | | All patients N=46 | |
|---|---|---|---|---|---|---|---|---|---|---|
| **Preferred term** | **Any grades n (%)** | **Grade 3/4 n (%)** | **Any grades n (%)** | **Grade 3/4 n (%)** | **Any grades n (%)** | **Grade 3/4 n (%)** | **Any grades n (%)** | **Grade 3/4 n (%)** | **Any grades n (%)** | **Grade 3/4 n (%)** |
| Thrombocytopenia | 10 (90.9) | 10 (90.9) | 9 (60.0) | 9 (60.0) | 3 (37.5) | 3 (37.5) | 4 (33.3) | 4 (33.3) | 26 (56.5) | 26 (56.5) |
| Anaemia | 9 (81.8) | 8 (72.7) | 9 (60.0) | 8 (53.3) | 4 (50.0) | 4 (50.0) | 3 (25.0) | 3 (25.0) | 25 (54.3) | 23 (50.0) |
| Vomiting | 4 (36.4) | 0 (0.0) | 7 (46.7) | 0 (0.0) | 3 (37.5) | 0 (0.0) | 10 (83.3) | 0 (0.0) | 24 (52.2) | 0 (0.0) |
| Decreased appetite | 6 (54.5) | 0 (0.0) | 9 (60.0) | 0 (0.0) | 2 (25.0) | 0 (0.0) | 6 (50.0) | 1 (8.3) | 23 (50.0) | 1 (2.2) |
| Oedema peripheral | 3 (27.3) | 0 (0.0) | 8 (53.3) | 0 (0.0) | 5 (62.5) | 0 (0.0) | 5 (41.7) | 0 (0.0) | 21 (45.7) | 0 (0.0) |
| Constipation | 6 (54.5) | 0 (0.0) | 6 (40.0) | 0 (0.0) | 3 (37.5) | 0 (0.0) | 4 (33.3) | 0 (0.0) | 19 (41.3) | 0 (0.0) |
| Pyrexia | 5 (45.5) | 0 (0.0) | 7 (46.7) | 0 (0.0) | 2 (25.0) | 1 (12.5) | 5 (41.7) | 1 (8.3) | 19 (41.3) | 2 (4.3) |
| Rash | 4 (36.4) | 0 (0.0) | 6 (40.0) | 0 (0.0) | 5 (62.5) | 0 (0.0) | 4 (33.3) | 0 (0.0) | 19 (41.3) | 0 (0.0) |
| Fatigue | 3 (27.3) | 0 (0.0) | 10 (66.7) | 2 (13.3) | 1 (12.5) | 0 (0.0) | 3 (25.0) | 0 (0.0) | 17 (37.0) | 2 (4.3) |
| Headache | 4 (36.4) | 0 (0.0) | 6 (40.0) | 0 (0.0) | 3 (37.5) | 0 (0.0) | 4 (33.3) | 0 (0.0) | 17 (37.0) | 0 (0.0) |
| Hypokalaemia | 2 (18.2) | 0 (0.0) | 9 (60.0) | 4 (26.7) | 2 (25.0) | 1 (12.5) | 4 (33.3) | 1 (8.3) | 17 (37.0) | 6 (13.0) |
| Chills | 3 (27.3) | 0 (0.0) | 5 (33.3) | 0 (0.0) | 4 (50.0) | 0 (0.0) | 4 (33.3) | 0 (0.0) | 16 (34.8) | 0 (0.0) |
| Abdominal pain | 0 (0.0) | 0 (0.0) | 8 (53.3) | 0 (0.0) | 2 (25.0) | 1 (12.5) | 4 (33.3) | 0 (0.0) | 14 (30.4) | 1 (2.2) |
| Pruritus | 5 (45.5) | 0 (0.0) | 4 (26.7) | 0 (0.0) | 2 (25.0) | 0 (0.0) | 3 (25.0) | 0 (0.0) | 14 (30.4) | 0 (0.0) |
| Back pain | 3 (27.3) | 0 (0.0) | 4 (26.7) | 0 (0.0) | 3 (37.5) | 0 (0.0) | 3 (25.0) | 0 (0.0) | 13 (28.3) | 0 (0.0) |
| Insomnia | 3 (27.3) | 0 (0.0) | 4 (26.7) | 0 (0.0) | 1 (12.5) | 0 (0.0) | 5 (41.7) | 0 (0.0) | 13 (28.3) | 0 (0.0) |
| Stomatitis | 3 (27.3) | 0 (0.0) | 4 (26.7) | 0 (0.0) | 1 (12.5) | 0 (0.0) | 5 (41.7) | 0 (0.0) | 13 (28.3) | 0 (0.0) |
| Cough | 1 (9.1) | 0 (0.0) | 6 (40.0) | 0 (0.0) | 3 (37.5) | 0 (0.0) | 2 (16.7) | 0 (0.0) | 12 (26.1) | 0 (0.0) |
| Hypotension | 3 (27.3) | 0 (0.0) | 2 (13.3) | 1 (6.7) | 4 (50.0) | 0 (0.0) | 3 (25.0) | 1 (8.3) | 12 (26.1) | 2 (4.3) |
| Anxiety | 2 (18.2) | 0 (0.0) | 4 (26.7) | 0 (0.0) | 1 (12.5) | 0 (0.0) | 3 (25.0) | 0 (0.0) | 10 (21.7) | 0 (0.0) |

| | PAN 15 mg N=11 | | PAN 20 mg N=15 | | PAN 25 mg N=8 | | PAN 20 mg (Expansion Phase) N=12 | | All patients N=46 | |
|---|---|---|---|---|---|---|---|---|---|---|
| **Preferred term** | **Any grades n (%)** | **Grade 3/4 n (%)** | **Any grades n (%)** | **Grade 3/4 n (%)** | **Any grades n (%)** | **Grade 3/4 n (%)** | **Any grades n (%)** | **Grade 3/4 n (%)** | **Any grades n (%)** | **Grade 3/4 n (%)** |
| Dizziness | 2 (18.2) | 0 (0.0) | 5 (33.3) | 0 (0.0) | 1 (12.5) | 0 (0.0) | 2 (16.7) | 0 (0.0) | 10 (21.7) | 0 (0.0) |
| Neutropenia | 3 (27.3) | 3 (27.3) | 3 (20.0) | 3 (20.0) | 2 (25.0) | 2 (25.0) | 2 (16.7) | 2 (16.7) | 10 (21.7) | 10 (21.7) |
| Dyspepsia | 1 (9.1) | 0 (0.0) | 4 (26.7) | 0 (0.0) | 0 (0.0) | 0 (0.0) | 4 (33.3) | 0 (0.0) | 9 (19.6) | 0 (0.0) |
| Epistaxis | 1 (9.1) | 0 (0.0) | 5 (33.3) | 0 (0.0) | 1 (12.5) | 0 (0.0) | 2 (16.7) | 0 (0.0) | 9 (19.6) | 0 (0.0) |
| Petechiae | 4 (36.4) | 0 (0.0) | 3 (20.0) | 0 (0.0) | 1 (12.5) | 0 (0.0) | 1 (8.3) | 0 (0.0) | 9 (19.6) | 0 (0.0) |
| Dyspnoea | 2 (18.2) | 0 (0.0) | 3 (20.0) | 1 (6.7) | 2 (25.0) | 1 (12.5) | 1 (8.3) | 1 (8.3) | 8 (17.4) | 3 (6.5) |
| Hypoxia | 0 (0.0) | 0 (0.0) | 3 (20.0) | 3 (20.0) | 2 (25.0) | 0 (0.0) | 3 (25.0) | 2 (16.7) | 8 (17.4) | 5 (10.9) |
| Pneumonia | 0 (0.0) | 0 (0.0) | 4 (26.7) | 2 (13.3) | 2 (25.0) | 2 (25.0) | 2 (16.7) | 1 (8.3) | 8 (17.4) | 5 (10.9) |
| Abdominal distension | 2 (18.2) | 0 (0.0) | 4 (26.7) | 0 (0.0) | 0 (0.0) | 0 (0.0) | 1 (8.3) | 0 (0.0) | 7 (15.2) | 0 (0.0) |
| Haemoglobin decreased | 1 (9.1) | 1 (9.1) | 6 (40.0) | 5 (33.3) | 0 (0.0) | 0 (0.0) | 0 (0.0) | 0 (0.0) | 7 (15.2) | 6 (13.0) |
| Haemorrhoids | 2 (18.2) | 0 (0.0) | 2 (13.3) | 0 (0.0) | 3 (37.5) | 0 (0.0) | 0 (0.0) | 0 (0.0) | 7 (15.2) | 0 (0.0) |
| Hypertension | 0 (0.0) | 0 (0.0) | 1 (6.7) | 0 (0.0) | 3 (37.5) | 0 (0.0) | 3 (25.0) | 1 (8.3) | 7 (15.2) | 1 (2.2) |
| Hypophosphataemia | 2 (18.2) | 1 (9.1) | 4 (26.7) | 4 (26.7) | 0 (0.0) | 0 (0.0) | 1 (8.3) | 0 (0.0) | 7 (15.2) | 5 (10.9) |
| Pain | 0 (0.0) | 0 (0.0) | 2 (13.3) | 0 (0.0) | 0 (0.0) | 0 (0.0) | 5 (41.7) | 0 (0.0) | 7 (15.2) | 0 (0.0) |
| Alanine aminotransferase increased | 1 (9.1) | 0 (0.0) | 4 (26.7) | 1 (6.7) | 0 (0.0) | 0 (0.0) | 1 (8.3) | 0 (0.0) | 6 (13.0) | 1 (2.2) |
| Atrial fibrillation | 1 (9.1) | 0 (0.0) | 3 (20.0) | 0 (0.0) | 1 (12.5) | 0 (0.0) | 1 (8.3) | 0 (0.0) | 6 (13.0) | 0 (0.0) |
| Erythema | 1 (9.1) | 0 (0.0) | 3 (20.0) | 0 (0.0) | 1 (12.5) | 0 (0.0) | 1 (8.3) | 0 (0.0) | 6 (13.0) | 0 (0.0) |
| Hyperglycaemia | 1 (9.1) | 0 (0.0) | 3 (20.0) | 1 (6.7) | 2 (25.0) | 0 (0.0) | 0 (0.0) | 0 (0.0) | 6 (13.0) | 1 (2.2) |
| Hypocalcaemia | 1 (9.1) | 0 (0.0) | 4 (26.7) | 2 (13.3) | 1 (12.5) | 0 (0.0) | 0 (0.0) | 0 (0.0) | 6 (13.0) | 2 (4.3) |

| | PAN 15 mg N=11 | | PAN 20 mg N=15 | | PAN 25 mg N=8 | | PAN 20 mg (Expansion Phase) N=12 | | All patients N=46 | |
|---|---|---|---|---|---|---|---|---|---|---|
| **Preferred term** | **Any grades n (%)** | **Grade 3/4 n (%)** | **Any grades n (%)** | **Grade 3/4 n (%)** | **Any grades n (%)** | **Grade 3/4 n (%)** | **Any grades n (%)** | **Grade 3/4 n (%)** | **Any grades n (%)** | **Grade 3/4 n (%)** |
| Procedural pain | 3 (27.3) | 0 (0.0) | 2 (13.3) | 0 (0.0) | 0 (0.0) | 0 (0.0) | 1 (8.3) | 0 (0.0) | 6 (13.0) | 0 (0.0) |
| Abdominal pain upper | 1 (9.1) | 0 (0.0) | 3 (20.0) | 0 (0.0) | 1 (12.5) | 0 (0.0) | 0 (0.0) | 0 (0.0) | 5 (10.9) | 0 (0.0) |
| Aspartate aminotransferase increased | 0 (0.0) | 0 (0.0) | 4 (26.7) | 1 (6.7) | 0 (0.0) | 0 (0.0) | 1 (8.3) | 0 (0.0) | 5 (10.9) | 1 (2.2) |
| Depression | 0 (0.0) | 0 (0.0) | 2 (13.3) | 0 (0.0) | 0 (0.0) | 0 (0.0) | 3 (25.0) | 1 (8.3) | 5 (10.9) | 1 (2.2) |
| Haematuria | 1 (9.1) | 0 (0.0) | 3 (20.0) | 0 (0.0) | 0 (0.0) | 0 (0.0) | 1 (8.3) | 0 (0.0) | 5 (10.9) | 0 (0.0) |
| Hyperhidrosis | 0 (0.0) | 0 (0.0) | 4 (26.7) | 0 (0.0) | 0 (0.0) | 0 (0.0) | 1 (8.3) | 0 (0.0) | 5 (10.9) | 0 (0.0) |
| International normalised ratio increased | 1 (9.1) | 0 (0.0) | 2 (13.3) | 1 (6.7) | 0 (0.0) | 0 (0.0) | 2 (16.7) | 0 (0.0) | 5 (10.9) | 1 (2.2) |
| Neutrophil count decreased | 0 (0.0) | 0 (0.0) | 2 (13.3) | 2 (13.3) | 2 (25.0) | 2 (25.0) | 1 (8.3) | 1 (8.3) | 5 (10.9) | 5 (10.9) |
| Sinus tachycardia | 0 (0.0) | 0 (0.0) | 4 (26.7) | 0 (0.0) | 1 (12.5) | 0 (0.0) | 0 (0.0) | 0 (0.0) | 5 (10.9) | 0 (0.0) |
| Urinary tract infection | 1 (9.1) | 0 (0.0) | 1 (6.7) | 0 (0.0) | 1 (12.5) | 0 (0.0) | 2 (16.7) | 0 (0.0) | 5 (10.9) | 0 (0.0) |
| Wheezing | 2 (18.2) | 0 (0.0) | 1 (6.7) | 0 (0.0) | 1 (12.5) | 0 (0.0) | 1 (8.3) | 0 (0.0) | 5 (10.9) | 0 (0.0) |
| Abdominal discomfort | 0 (0.0) | 0 (0.0) | 0 (0.0) | 0 (0.0) | 1 (12.5) | 0 (0.0) | 3 (25.0) | 0 (0.0) | 4 (8.7) | 0 (0.0) |
| Alopecia | 2 (18.2) | 0 (0.0) | 0 (0.0) | 0 (0.0) | 0 (0.0) | 0 (0.0) | 2 (16.7) | 0 (0.0) | 4 (8.7) | 0 (0.0) |
| Arthralgia | 0 (0.0) | 0 (0.0) | 2 (13.3) | 0 (0.0) | 0 (0.0) | 0 (0.0) | 2 (16.7) | 0 (0.0) | 4 (8.7) | 0 (0.0) |
| Catheter site pain | 0 (0.0) | 0 (0.0) | 1 (6.7) | 0 (0.0) | 1 (12.5) | 0 (0.0) | 2 (16.7) | 0 (0.0) | 4 (8.7) | 0 (0.0) |
| Fluid overload | 1 (9.1) | 0 (0.0) | 1 (6.7) | 0 (0.0) | 0 (0.0) | 0 (0.0) | 2 (16.7) | 0 (0.0) | 4 (8.7) | 0 (0.0) |
| Gingival bleeding | 3 (27.3) | 0 (0.0) | 1 (6.7) | 0 (0.0) | 0 (0.0) | 0 (0.0) | 0 (0.0) | 0 (0.0) | 4 (8.7) | 0 (0.0) |
| Haematoma | 2 (18.2) | 1 (9.1) | 0 (0.0) | 0 (0.0) | 0 (0.0) | 0 (0.0) | 2 (16.7) | 0 (0.0) | 4 (8.7) | 1 (2.2) |

| Preferred term | PAN 15 mg N=11 | | PAN 20 mg N=15 | | PAN 25 mg N=8 | | PAN 20 mg (Expansion Phase) N=12 | | All patients N=46 | |
|---|---|---|---|---|---|---|---|---|---|---|
| | Any grades n (%) | Grade 3/4 n (%) | Any grades n (%) | Grade 3/4 n (%) | Any grades n (%) | Grade 3/4 n (%) | Any grades n (%) | Grade 3/4 n (%) | Any grades n (%) | Grade 3/4 n (%) |
| Hyperbilirubinaemia | 0 (0.0) | 0 (0.0) | 3 (20.0) | 2 (13.3) | 0 (0.0) | 0 (0.0) | 1 (8.3) | 1 (8.3) | 4 (8.7) | 3 (6.5) |
| Hyponatraemia | 0 (0.0) | 0 (0.0) | 4 (26.7) | 1 (6.7) | 0 (0.0) | 0 (0.0) | 0 (0.0) | 0 (0.0) | 4 (8.7) | 1 (2.2) |
| Injection site reaction | 1 (9.1) | 0 (0.0) | 3 (20.0) | 0 (0.0) | 0 (0.0) | 0 (0.0) | 0 (0.0) | 0 (0.0) | 4 (8.7) | 0 (0.0) |
| Lymphadenopathy | 1 (9.1) | 0 (0.0) | 1 (6.7) | 0 (0.0) | 0 (0.0) | 0 (0.0) | 2 (16.7) | 0 (0.0) | 4 (8.7) | 0 (0.0) |
| Neck pain | 0 (0.0) | 0 (0.0) | 3 (20.0) | 0 (0.0) | 0 (0.0) | 0 (0.0) | 1 (8.3) | 0 (0.0) | 4 (8.7) | 0 (0.0) |
| Night sweats | 2 (18.2) | 0 (0.0) | 1 (6.7) | 0 (0.0) | 0 (0.0) | 0 (0.0) | 1 (8.3) | 0 (0.0) | 4 (8.7) | 0 (0.0) |
| Oral pain | 0 (0.0) | 0 (0.0) | 1 (6.7) | 0 (0.0) | 1 (12.5) | 0 (0.0) | 2 (16.7) | 0 (0.0) | 4 (8.7) | 0 (0.0) |
| Pain in extremity | 1 (9.1) | 0 (0.0) | 1 (6.7) | 0 (0.0) | 2 (25.0) | 0 (0.0) | 0 (0.0) | 0 (0.0) | 4 (8.7) | 0 (0.0) |
| Platelet count decreased | 1 (9.1) | 1 (9.1) | 1 (6.7) | 1 (6.7) | 2 (25.0) | 2 (25.0) | 0 (0.0) | 0 (0.0) | 4 (8.7) | 4 (8.7) |
| Rash maculo-papular | 1 (9.1) | 0 (0.0) | 0 (0.0) | 0 (0.0) | 1 (12.5) | 0 (0.0) | 2 (16.7) | 1 (8.3) | 4 (8.7) | 1 (2.2) |
| Respiratory failure | 0 (0.0) | 0 (0.0) | 0 (0.0) | 0 (0.0) | 1 (12.5) | 1 (12.5) | 3 (25.0) | 3 (25.0) | 4 (8.7) | 4 (8.7) |
| Tachycardia | 0 (0.0) | 0 (0.0) | 2 (13.3) | 0 (0.0) | 0 (0.0) | 0 (0.0) | 2 (16.7) | 0 (0.0) | 4 (8.7) | 0 (0.0) |
| Transfusion reaction | 1 (9.1) | 0 (0.0) | 3 (20.0) | 0 (0.0) | 0 (0.0) | 0 (0.0) | 0 (0.0) | 0 (0.0) | 4 (8.7) | 0 (0.0) |
| Asthenia | 1 (9.1) | 0 (0.0) | 0 (0.0) | 0 (0.0) | 0 (0.0) | 0 (0.0) | 2 (16.7) | 1 (8.3) | 3 (6.5) | 1 (2.2) |
| Bacterial infection | 0 (0.0) | 0 (0.0) | 3 (20.0) | 3 (20.0) | 0 (0.0) | 0 (0.0) | 0 (0.0) | 0 (0.0) | 3 (6.5) | 3 (6.5) |
| Bradycardia | 0 (0.0) | 0 (0.0) | 1 (6.7) | 0 (0.0) | 0 (0.0) | 0 (0.0) | 2 (16.7) | 0 (0.0) | 3 (6.5) | 0 (0.0) |
| Delirium | 0 (0.0) | 0 (0.0) | 1 (6.7) | 0 (0.0) | 0 (0.0) | 0 (0.0) | 2 (16.7) | 0 (0.0) | 3 (6.5) | 0 (0.0) |
| Hypomagnesaemia | 0 (0.0) | 0 (0.0) | 1 (6.7) | 0 (0.0) | 0 (0.0) | 0 (0.0) | 2 (16.7) | 0 (0.0) | 3 (6.5) | 0 (0.0) |
| Left ventricular dysfunction | 0 (0.0) | 0 (0.0) | 3 (20.0) | 2 (13.3) | 0 (0.0) | 0 (0.0) | 0 (0.0) | 0 (0.0) | 3 (6.5) | 2 (4.3) |
| Leukopenia | 2 (18.2) | 2 (18.2) | 0 (0.0) | 0 (0.0) | 1 (12.5) | 1 (12.5) | 0 (0.0) | 0 (0.0) | 3 (6.5) | 3 (6.5) |

| Preferred term | PAN 15 mg N=11 | | PAN 20 mg N=15 | | PAN 25 mg N=8 | | PAN 20 mg (Expansion Phase) N=12 | | All patients N=46 | |
|---|---|---|---|---|---|---|---|---|---|---|
| | Any grades n (%) | Grade 3/4 n (%) | Any grades n (%) | Grade 3/4 n (%) | Any grades n (%) | Grade 3/4 n (%) | Any grades n (%) | Grade 3/4 n (%) | Any grades n (%) | Grade 3/4 n (%) |
| Oral disorder | 2 (18.2) | 0 (0.0) | 1 (6.7) | 0 (0.0) | 0 (0.0) | 0 (0.0) | 0 (0.0) | 0 (0.0) | 3 (6.5) | 0 (0.0) |
| Rash generalized | 0 (0.0) | 0 (0.0) | 1 (6.7) | 0 (0.0) | 0 (0.0) | 0 (0.0) | 2 (16.7) | 0 (0.0) | 3 (6.5) | 0 (0.0) |
| Toothache | 0 (0.0) | 0 (0.0) | 1 (6.7) | 0 (0.0) | 0 (0.0) | 0 (0.0) | 2 (16.7) | 0 (0.0) | 3 (6.5) | 0 (0.0) |
| Blood phosphorus decreased | 0 (0.0) | 0 (0.0) | 0 (0.0) | 0 (0.0) | 0 (0.0) | 0 (0.0) | 2 (16.7) | 1 (8.3) | 2 (4.3) | 1 (2.2) |
| Blood potassium decreased | 0 (0.0) | 0 (0.0) | 0 (0.0) | 0 (0.0) | 0 (0.0) | 0 (0.0) | 2 (16.7) | 0 (0.0) | 2 (4.3) | 0 (0.0) |
| Catheter site erythema | 2 (18.2) | 0 (0.0) | 0 (0.0) | 0 (0.0) | 0 (0.0) | 0 (0.0) | 0 (0.0) | 0 (0.0) | 2 (4.3) | 0 (0.0) |
| Cheilitis | 2 (18.2) | 0 (0.0) | 0 (0.0) | 0 (0.0) | 0 (0.0) | 0 (0.0) | 0 (0.0) | 0 (0.0) | 2 (4.3) | 0 (0.0) |
| Dermatitis allergic | 0 (0.0) | 0 (0.0) | 0 (0.0) | 0 (0.0) | 2 (25.0) | 0 (0.0) | 0 (0.0) | 0 (0.0) | 2 (4.3) | 0 (0.0) |
| Dysarthria | 0 (0.0) | 0 (0.0) | 0 (0.0) | 0 (0.0) | 0 (0.0) | 0 (0.0) | 2 (16.7) | 0 (0.0) | 2 (4.3) | 0 (0.0) |
| Dysgeusia | 2 (18.2) | 0 (0.0) | 0 (0.0) | 0 (0.0) | 0 (0.0) | 0 (0.0) | 0 (0.0) | 0 (0.0) | 2 (4.3) | 0 (0.0) |
| Enterococcal infection | 0 (0.0) | 0 (0.0) | 0 (0.0) | 0 (0.0) | 0 (0.0) | 0 (0.0) | 2 (16.7) | 2 (16.7) | 2 (4.3) | 2 (4.3) |
| Folliculitis | 2 (18.2) | 0 (0.0) | 0 (0.0) | 0 (0.0) | 0 (0.0) | 0 (0.0) | 0 (0.0) | 0 (0.0) | 2 (4.3) | 0 (0.0) |
| Hyperphosphataemia | 0 (0.0) | 0 (0.0) | 0 (0.0) | 0 (0.0) | 0 (0.0) | 0 (0.0) | 2 (16.7) | 0 (0.0) | 2 (4.3) | 0 (0.0) |
| Muscle spasms | 0 (0.0) | 0 (0.0) | 0 (0.0) | 0 (0.0) | 0 (0.0) | 0 (0.0) | 2 (16.7) | 0 (0.0) | 2 (4.3) | 0 (0.0) |
| Rhinorrhoea | 2 (18.2) | 0 (0.0) | 0 (0.0) | 0 (0.0) | 0 (0.0) | 0 (0.0) | 0 (0.0) | 0 (0.0) | 2 (4.3) | 0 (0.0) |

Preferred terms are presented in descending frequency, as reported in the “Any grades” column for “All patients”.
A patient with multiple occurrences of an AE is counted only once in the AE category.
Adverse events occurring more than 28 days after the discontinuation of study treatment are not summarized.

**Adverse events, regardless of study drug relationship by preferred term and dose group of panobinostat during Consolidation Phase (with an incidence of 15% or greater in any dose group, SAS)**

| | PAN 15 mg N=8 | | PAN 20 mg N=5 | | PAN 25 mg N=2 | | PAN 20 mg (Expansion Phase) N=4 | | All patients N=19 | |
|---|---|---|---|---|---|---|---|---|---|---|
| Preferred term | Any grades n (%) | Grade 3/4 n (%) | Any grades n (%) | Grade 3/4 n (%) | Any grades n (%) | Preferred term | Any grades n (%) | Grade 3/4 n (%) | Any grades n (%) | Grade 3/4 n (%) |
| Febrile neutropenia | 4 (50.0) | 4 (50.0) | 5 (100.0) | 5 (100.0) | 2 (100.0) | 2 (100.0) | 3 (75.0) | 3 (75.0) | 14 (73.7) | 14 (73.7) |
| Thrombocytopenia | 6 (75.0) | 6 (75.0) | 5 (100.0) | 5 (100.0) | 1 (50.0) | 1 (50.0) | 2 (50.0) | 2 (50.0) | 14 (73.7) | 14 (73.7) |
| Anaemia | 6 (75.0) | 6 (75.0) | 4 (80.0) | 3 (60.0) | 1 (50.0) | 1 (50.0) | 1 (25.0) | 1 (25.0) | 12 (63.2) | 11 (57.9) |
| Fatigue | 4 (50.0) | 0 (0.0) | 3 (60.0) | 0 (0.0) | 1 (50.0) | 0 (0.0) | 1 (25.0) | 0 (0.0) | 9 (47.4) | 0 (0.0) |
| Headache | 3 (37.5) | 0 (0.0) | 3 (60.0) | 1 (20.0) | 1 (50.0) | 0 (0.0) | 2 (50.0) | 0 (0.0) | 9 (47.4) | 1 (5.3) |
| Nausea | 3 (37.5) | 0 (0.0) | 4 (80.0) | 0 (0.0) | 0 (0.0) | 0 (0.0) | 2 (50.0) | 0 (0.0) | 9 (47.4) | 0 (0.0) |
| Chills | 1 (12.5) | 0 (0.0) | 2 (40.0) | 0 (0.0) | 2 (100.0) | 0 (0.0) | 2 (50.0) | 0 (0.0) | 7 (36.8) | 0 (0.0) |
| Neutropenia | 3 (37.5) | 3 (37.5) | 2 (40.0) | 2 (40.0) | 1 (50.0) | 0 (0.0) | 1 (25.0) | 1 (25.0) | 7 (36.8) | 6 (31.6) |
| Rash | 2 (25.0) | 0 (0.0) | 2 (40.0) | 0 (0.0) | 1 (50.0) | 0 (0.0) | 2 (50.0) | 0 (0.0) | 7 (36.8) | 0 (0.0) |
| Constipation | 3 (37.5) | 0 (0.0) | 2 (40.0) | 0 (0.0) | 1 (50.0) | 0 (0.0) | 0 (0.0) | 0 (0.0) | 6 (31.6) | 0 (0.0) |
| Decreased appetite | 2 (25.0) | 0 (0.0) | 3 (60.0) | 0 (0.0) | 1 (50.0) | 0 (0.0) | 0 (0.0) | 0 (0.0) | 6 (31.6) | 0 (0.0) |
| Diarrhoea | 1 (12.5) | 0 (0.0) | 3 (60.0) | 0 (0.0) | 1 (50.0) | 0 (0.0) | 1 (25.0) | 0 (0.0) | 6 (31.6) | 0 (0.0) |
| Dyspnoea | 1 (12.5) | 0 (0.0) | 2 (40.0) | 0 (0.0) | 1 (50.0) | 0 (0.0) | 2 (50.0) | 0 (0.0) | 6 (31.6) | 0 (0.0) |
| Hypokalaemia | 4 (50.0) | 2 (25.0) | 2 (40.0) | 1 (20.0) | 0 (0.0) | 0 (0.0) | 0 (0.0) | 0 (0.0) | 6 (31.6) | 3 (15.8) |
| Pyrexia | 2 (25.0) | 0 (0.0) | 3 (60.0) | 0 (0.0) | 0 (0.0) | 0 (0.0) | 1 (25.0) | 0 (0.0) | 6 (31.6) | 0 (0.0) |
| Sepsis | 3 (37.5) | 3 (37.5) | 0 (0.0) | 0 (0.0) | 1 (50.0) | 1 (50.0) | 2 (50.0) | 2 (50.0) | 6 (31.6) | 6 (31.6) |
| Vomiting | 2 (25.0) | 0 (0.0) | 1 (20.0) | 0 (0.0) | 1 (50.0) | 0 (0.0) | 2 (50.0) | 0 (0.0) | 6 (31.6) | 0 (0.0) |

| Preferred term | PAN 15 mg N=8 Any grades n (%) | PAN 15 mg N=8 Grade 3/4 n (%) | PAN 20 mg N=5 Any grades n (%) | PAN 20 mg N=5 Grade 3/4 n (%) | PAN 25 mg N=2 Any grades n (%) | Preferred term | PAN 20 mg (Expansion Phase) N=4 Any grades n (%) | PAN 20 mg (Expansion Phase) N=4 Grade 3/4 n (%) | All patients N=19 Any grades n (%) | All patients N=19 Grade 3/4 n (%) |
|---|---|---|---|---|---|---|---|---|---|---|
| Abdominal pain | 0 (0.0) | 0 (0.0) | 3 (60.0) | 0 (0.0) | 1 (50.0) | 0 (0.0) | 1 (25.0) | 1 (25.0) | 5 (26.3) | 1 (5.3) |
| Back pain | 2 (25.0) | 0 (0.0) | 2 (40.0) | 0 (0.0) | 0 (0.0) | 0 (0.0) | 0 (0.0) | 0 (0.0) | 4 (21.1) | 0 (0.0) |
| Dyspepsia | 2 (25.0) | 0 (0.0) | 2 (40.0) | 0 (0.0) | 0 (0.0) | 0 (0.0) | 0 (0.0) | 0 (0.0) | 4 (21.1) | 0 (0.0) |
| Epistaxis | 3 (37.5) | 0 (0.0) | 1 (20.0) | 0 (0.0) | 0 (0.0) | 0 (0.0) | 0 (0.0) | 0 (0.0) | 4 (21.1) | 0 (0.0) |
| Hypophosphataemia | 1 (12.5) | 0 (0.0) | 3 (60.0) | 3 (60.0) | 0 (0.0) | 0 (0.0) | 0 (0.0) | 0 (0.0) | 4 (21.1) | 3 (15.8) |
| Insomnia | 1 (12.5) | 0 (0.0) | 2 (40.0) | 0 (0.0) | 0 (0.0) | 0 (0.0) | 1 (25.0) | 0 (0.0) | 4 (21.1) | 0 (0.0) |
| Pruritus | 1 (12.5) | 0 (0.0) | 2 (40.0) | 0 (0.0) | 1 (50.0) | 0 (0.0) | 0 (0.0) | 0 (0.0) | 4 (21.1) | 0 (0.0) |
| Stomatitis | 2 (25.0) | 1 (12.5) | 2 (40.0) | 0 (0.0) | 0 (0.0) | 0 (0.0) | 0 (0.0) | 0 (0.0) | 4 (21.1) | 1 (5.3) |
| Anxiety | 2 (25.0) | 0 (0.0) | 0 (0.0) | 0 (0.0) | 0 (0.0) | 0 (0.0) | 1 (25.0) | 0 (0.0) | 3 (15.8) | 0 (0.0) |
| Arthralgia | 1 (12.5) | 0 (0.0) | 1 (20.0) | 0 (0.0) | 0 (0.0) | 0 (0.0) | 1 (25.0) | 0 (0.0) | 3 (15.8) | 0 (0.0) |
| Dysuria | 0 (0.0) | 0 (0.0) | 1 (20.0) | 0 (0.0) | 1 (50.0) | 0 (0.0) | 1 (25.0) | 0 (0.0) | 3 (15.8) | 0 (0.0) |
| Musculoskeletal pain | 1 (12.5) | 0 (0.0) | 1 (20.0) | 0 (0.0) | 0 (0.0) | 0 (0.0) | 1 (25.0) | 0 (0.0) | 3 (15.8) | 0 (0.0) |
| Oropharyngeal pain | 0 (0.0) | 0 (0.0) | 3 (60.0) | 0 (0.0) | 0 (0.0) | 0 (0.0) | 0 (0.0) | 0 (0.0) | 3 (15.8) | 0 (0.0) |
| Pain in extremity | 2 (25.0) | 0 (0.0) | 0 (0.0) | 0 (0.0) | 0 (0.0) | 0 (0.0) | 1 (25.0) | 0 (0.0) | 3 (15.8) | 0 (0.0) |
| Petechiae | 1 (12.5) | 0 (0.0) | 2 (40.0) | 0 (0.0) | 0 (0.0) | 0 (0.0) | 0 (0.0) | 0 (0.0) | 3 (15.8) | 0 (0.0) |
| Rash pruritic | 1 (12.5) | 0 (0.0) | 0 (0.0) | 0 (0.0) | 0 (0.0) | 0 (0.0) | 2 (50.0) | 0 (0.0) | 3 (15.8) | 0 (0.0) |
| Transfusion reaction | 1 (12.5) | 0 (0.0) | 2 (40.0) | 0 (0.0) | 0 (0.0) | 0 (0.0) | 0 (0.0) | 0 (0.0) | 3 (15.8) | 0 (0.0) |
| Abdominal distension | 1 (12.5) | 0 (0.0) | 0 (0.0) | 0 (0.0) | 1 (50.0) | 0 (0.0) | 0 (0.0) | 0 (0.0) | 2 (10.5) | 0 (0.0) |
| Abdominal pain upper | 1 (12.5) | 0 (0.0) | 0 (0.0) | 0 (0.0) | 0 (0.0) | 0 (0.0) | 1 (25.0) | 0 (0.0) | 2 (10.5) | 0 (0.0) |

| Preferred term | PAN 15 mg N=8 Any grades n (%) | PAN 15 mg N=8 Grade 3/4 n (%) | PAN 20 mg N=5 Any grades n (%) | PAN 20 mg N=5 Grade 3/4 n (%) | PAN 25 mg N=2 Any grades n (%) | Preferred term | PAN 20 mg (Expansion Phase) N=4 Any grades n (%) | PAN 20 mg (Expansion Phase) N=4 Grade 3/4 n (%) | All patients N=19 Any grades n (%) | All patients N=19 Grade 3/4 n (%) |
|---|---|---|---|---|---|---|---|---|---|---|
| Asthenia | 0 (0.0) | 0 (0.0) | 2 (40.0) | 1 (20.0) | 0 (0.0) | 0 (0.0) | 0 (0.0) | 0 (0.0) | 2 (10.5) | 1 (5.3) |
| Bacteraemia | 0 (0.0) | 0 (0.0) | 1 (20.0) | 1 (20.0) | 0 (0.0) | 0 (0.0) | 1 (25.0) | 1 (25.0) | 2 (10.5) | 2 (10.5) |
| Blood blister | 0 (0.0) | 0 (0.0) | 0 (0.0) | 0 (0.0) | 0 (0.0) | 0 (0.0) | 2 (50.0) | 0 (0.0) | 2 (10.5) | 0 (0.0) |
| Contusion | 1 (12.5) | 0 (0.0) | 0 (0.0) | 0 (0.0) | 0 (0.0) | 0 (0.0) | 1 (25.0) | 0 (0.0) | 2 (10.5) | 0 (0.0) |
| Cough | 1 (12.5) | 0 (0.0) | 0 (0.0) | 0 (0.0) | 1 (50.0) | 0 (0.0) | 0 (0.0) | 0 (0.0) | 2 (10.5) | 0 (0.0) |
| Dizziness | 1 (12.5) | 0 (0.0) | 1 (20.0) | 0 (0.0) | 0 (0.0) | 0 (0.0) | 0 (0.0) | 0 (0.0) | 2 (10.5) | 0 (0.0) |
| Erythema | 1 (12.5) | 0 (0.0) | 1 (20.0) | 0 (0.0) | 0 (0.0) | 0 (0.0) | 0 (0.0) | 0 (0.0) | 2 (10.5) | 0 (0.0) |
| Eye pain | 0 (0.0) | 0 (0.0) | 0 (0.0) | 0 (0.0) | 0 (0.0) | 0 (0.0) | 2 (50.0) | 0 (0.0) | 2 (10.5) | 0 (0.0) |
| Gastrointestinal haemorrhage | 0 (0.0) | 0 (0.0) | 1 (20.0) | 1 (20.0) | 0 (0.0) | 0 (0.0) | 1 (25.0) | 1 (25.0) | 2 (10.5) | 2 (10.5) |
| Haemoglobin decreased | 0 (0.0) | 0 (0.0) | 1 (20.0) | 0 (0.0) | 1 (50.0) | 1 (50.0) | 0 (0.0) | 0 (0.0) | 2 (10.5) | 1 (5.3) |
| Haemoptysis | 1 (12.5) | 0 (0.0) | 0 (0.0) | 0 (0.0) | 0 (0.0) | 0 (0.0) | 1 (25.0) | 1 (25.0) | 2 (10.5) | 1 (5.3) |
| Hypomagnesaemia | 0 (0.0) | 0 (0.0) | 2 (40.0) | 0 (0.0) | 0 (0.0) | 0 (0.0) | 0 (0.0) | 0 (0.0) | 2 (10.5) | 0 (0.0) |
| Hypoxia | 1 (12.5) | 0 (0.0) | 1 (20.0) | 1 (20.0) | 0 (0.0) | 0 (0.0) | 0 (0.0) | 0 (0.0) | 2 (10.5) | 1 (5.3) |
| Malaise | 2 (25.0) | 1 (12.5) | 0 (0.0) | 0 (0.0) | 0 (0.0) | 0 (0.0) | 0 (0.0) | 0 (0.0) | 2 (10.5) | 1 (5.3) |
| Muscle spasms | 1 (12.5) | 0 (0.0) | 0 (0.0) | 0 (0.0) | 0 (0.0) | 0 (0.0) | 1 (25.0) | 0 (0.0) | 2 (10.5) | 0 (0.0) |
| Myalgia | 0 (0.0) | 0 (0.0) | 2 (40.0) | 0 (0.0) | 0 (0.0) | 0 (0.0) | 0 (0.0) | 0 (0.0) | 2 (10.5) | 0 (0.0) |
| Oedema peripheral | 1 (12.5) | 0 (0.0) | 0 (0.0) | 0 (0.0) | 0 (0.0) | 0 (0.0) | 1 (25.0) | 0 (0.0) | 2 (10.5) | 0 (0.0) |
| Oral pain | 2 (25.0) | 0 (0.0) | 0 (0.0) | 0 (0.0) | 0 (0.0) | 0 (0.0) | 0 (0.0) | 0 (0.0) | 2 (10.5) | 0 (0.0) |

| Preferred term | PAN 15 mg N=8 Any grades n (%) | PAN 15 mg N=8 Grade 3/4 n (%) | PAN 20 mg N=5 Any grades n (%) | PAN 20 mg N=5 Grade 3/4 n (%) | PAN 25 mg N=2 Any grades n (%) | Preferred term | PAN 20 mg (Expansion Phase) N=4 Any grades n (%) | PAN 20 mg (Expansion Phase) N=4 Grade 3/4 n (%) | All patients N=19 Any grades n (%) | All patients N=19 Grade 3/4 n (%) |
|---|---|---|---|---|---|---|---|---|---|---|
| Pain | 0 (0.0) | 0 (0.0) | 1 (20.0) | 0 (0.0) | 0 (0.0) | 0 (0.0) | 1 (25.0) | 0 (0.0) | 2 (10.5) | 0 (0.0) |
| Pharyngitis | 1 (12.5) | 0 (0.0) | 0 (0.0) | 0 (0.0) | 0 (0.0) | 0 (0.0) | 1 (25.0) | 0 (0.0) | 2 (10.5) | 0 (0.0) |
| Pulmonary mass | 0 (0.0) | 0 (0.0) | 0 (0.0) | 0 (0.0) | 1 (50.0) | 0 (0.0) | 1 (25.0) | 1 (25.0) | 2 (10.5) | 1 (5.3) |
| Rash maculo-papular | 1 (12.5) | 0 (0.0) | 0 (0.0) | 0 (0.0) | 0 (0.0) | 0 (0.0) | 1 (25.0) | 1 (25.0) | 2 (10.5) | 1 (5.3) |
| Rhinorrhoea | 1 (12.5) | 0 (0.0) | 0 (0.0) | 0 (0.0) | 0 (0.0) | 0 (0.0) | 1 (25.0) | 0 (0.0) | 2 (10.5) | 0 (0.0) |
| Sinus headache | 1 (12.5) | 0 (0.0) | 0 (0.0) | 0 (0.0) | 0 (0.0) | 0 (0.0) | 1 (25.0) | 0 (0.0) | 2 (10.5) | 0 (0.0) |
| Tachycardia | 1 (12.5) | 0 (0.0) | 1 (20.0) | 0 (0.0) | 0 (0.0) | 0 (0.0) | 0 (0.0) | 0 (0.0) | 2 (10.5) | 0 (0.0) |
| Toothache | 1 (12.5) | 0 (0.0) | 1 (20.0) | 0 (0.0) | 0 (0.0) | 0 (0.0) | 0 (0.0) | 0 (0.0) | 2 (10.5) | 0 (0.0) |
| Weight decreased | 1 (12.5) | 0 (0.0) | 0 (0.0) | 0 (0.0) | 0 (0.0) | 0 (0.0) | 1 (25.0) | 0 (0.0) | 2 (10.5) | 0 (0.0) |
| Abdominal discomfort | 0 (0.0) | 0 (0.0) | 0 (0.0) | 0 (0.0) | 0 (0.0) | 0 (0.0) | 1 (25.0) | 0 (0.0) | 1 (5.3) | 0 (0.0) |
| Alanine aminotransferase increased | 0 (0.0) | 0 (0.0) | 0 (0.0) | 0 (0.0) | 0 (0.0) | 0 (0.0) | 1 (25.0) | 0 (0.0) | 1 (5.3) | 0 (0.0) |
| Arteriosclerosis coronary artery | 0 (0.0) | 0 (0.0) | 1 (20.0) | 0 (0.0) | 0 (0.0) | 0 (0.0) | 0 (0.0) | 0 (0.0) | 1 (5.3) | 0 (0.0) |
| Aspartate aminotransferase increased | 0 (0.0) | 0 (0.0) | 0 (0.0) | 0 (0.0) | 0 (0.0) | 0 (0.0) | 1 (25.0) | 0 (0.0) | 1 (5.3) | 0 (0.0) |
| Bacterial infection | 0 (0.0) | 0 (0.0) | 1 (20.0) | 1 (20.0) | 0 (0.0) | 0 (0.0) | 0 (0.0) | 0 (0.0) | 1 (5.3) | 1 (5.3) |
| Blood albumin decreased | 0 (0.0) | 0 (0.0) | 0 (0.0) | 0 (0.0) | 1 (50.0) | 0 (0.0) | 0 (0.0) | 0 (0.0) | 1 (5.3) | 0 (0.0) |
| Blood creatinine | 0 (0.0) | 0 (0.0) | 0 (0.0) | 0 (0.0) | 0 (0.0) | 0 (0.0) | 1 (25.0) | 0 (0.0) | 1 (5.3) | 0 (0.0) |

| Preferred term | PAN 15 mg N=8 Any grades n (%) | PAN 15 mg N=8 Grade 3/4 n (%) | PAN 20 mg N=5 Any grades n (%) | PAN 20 mg N=5 Grade 3/4 n (%) | PAN 25 mg N=2 Any grades n (%) | Preferred term | PAN 20 mg (Expansion Phase) N=4 Any grades n (%) | PAN 20 mg (Expansion Phase) N=4 Grade 3/4 n (%) | All patients N=19 Any grades n (%) | All patients N=19 Grade 3/4 n (%) |
|---|---|---|---|---|---|---|---|---|---|---|
| decreased | | | | | | | | | | |
| Blood creatinine increased | 0 (0.0) | 0 (0.0) | 0 (0.0) | 0 (0.0) | 1 (50.0) | 0 (0.0) | 0 (0.0) | 0 (0.0) | 1 (5.3) | 0 (0.0) |
| Blood magnesium decreased | 0 (0.0) | 0 (0.0) | 0 (0.0) | 0 (0.0) | 0 (0.0) | 0 (0.0) | 1 (25.0) | 0 (0.0) | 1 (5.3) | 0 (0.0) |
| Blood phosphorus decreased | 0 (0.0) | 0 (0.0) | 0 (0.0) | 0 (0.0) | 0 (0.0) | 0 (0.0) | 1 (25.0) | 0 (0.0) | 1 (5.3) | 0 (0.0) |
| Blood potassium decreased | 0 (0.0) | 0 (0.0) | 0 (0.0) | 0 (0.0) | 0 (0.0) | 0 (0.0) | 1 (25.0) | 0 (0.0) | 1 (5.3) | 0 (0.0) |
| Blood pressure decreased | 0 (0.0) | 0 (0.0) | 0 (0.0) | 0 (0.0) | 0 (0.0) | 0 (0.0) | 1 (25.0) | 0 (0.0) | 1 (5.3) | 0 (0.0) |
| Bone marrow failure | 0 (0.0) | 0 (0.0) | 1 (20.0) | 1 (20.0) | 0 (0.0) | 0 (0.0) | 0 (0.0) | 0 (0.0) | 1 (5.3) | 1 (5.3) |
| Breast pain | 0 (0.0) | 0 (0.0) | 0 (0.0) | 0 (0.0) | 0 (0.0) | 0 (0.0) | 1 (25.0) | 0 (0.0) | 1 (5.3) | 0 (0.0) |
| Breath sounds abnormal | 0 (0.0) | 0 (0.0) | 0 (0.0) | 0 (0.0) | 0 (0.0) | 0 (0.0) | 1 (25.0) | 0 (0.0) | 1 (5.3) | 0 (0.0) |
| Catheter site pain | 0 (0.0) | 0 (0.0) | 1 (20.0) | 0 (0.0) | 0 (0.0) | 0 (0.0) | 0 (0.0) | 0 (0.0) | 1 (5.3) | 0 (0.0) |
| Cellulitis | 0 (0.0) | 0 (0.0) | 0 (0.0) | 0 (0.0) | 1 (50.0) | 1 (50.0) | 0 (0.0) | 0 (0.0) | 1 (5.3) | 1 (5.3) |
| Cerebral haemorrhage | 0 (0.0) | 0 (0.0) | 0 (0.0) | 0 (0.0) | 0 (0.0) | 0 (0.0) | 1 (25.0) | 1 (25.0) | 1 (5.3) | 1 (5.3) |
| Chronic obstructive pulmonary disease | 0 (0.0) | 0 (0.0) | 0 (0.0) | 0 (0.0) | 0 (0.0) | 0 (0.0) | 1 (25.0) | 0 (0.0) | 1 (5.3) | 0 (0.0) |
| Chronic tonsillitis | 0 (0.0) | 0 (0.0) | 1 (20.0) | 0 (0.0) | 0 (0.0) | 0 (0.0) | 0 (0.0) | 0 (0.0) | 1 (5.3) | 0 (0.0) |
| Clostridium difficile colitis | 0 (0.0) | 0 (0.0) | 0 (0.0) | 0 (0.0) | 1 (50.0) | 1 (50.0) | 0 (0.0) | 0 (0.0) | 1 (5.3) | 1 (5.3) |
| Clostridium difficile | 0 (0.0) | 0 (0.0) | 0 (0.0) | 0 (0.0) | 0 (0.0) | 0 (0.0) | 1 (25.0) | 0 (0.0) | 1 (5.3) | 0 (0.0) |

| Preferred term | PAN 15 mg N=8 Any grades n (%) | PAN 15 mg N=8 Grade 3/4 n (%) | PAN 20 mg N=5 Any grades n (%) | PAN 20 mg N=5 Grade 3/4 n (%) | PAN 25 mg N=2 Any grades n (%) | PAN 25 mg N=2 Preferred term | PAN 20 mg (Expansion Phase) N=4 Any grades n (%) | PAN 20 mg (Expansion Phase) N=4 Grade 3/4 n (%) | All patients N=19 Any grades n (%) | All patients N=19 Grade 3/4 n (%) |
|---|---|---|---|---|---|---|---|---|---|---|
| infection | | | | | | | | | | |
| Colitis | 0 (0.0) | 0 (0.0) | 0 (0.0) | 0 (0.0) | 0 (0.0) | 0 (0.0) | 1 (25.0) | 1 (25.0) | 1 (5.3) | 1 (5.3) |
| Conjunctival haemorrhage | 0 (0.0) | 0 (0.0) | 0 (0.0) | 0 (0.0) | 1 (50.0) | 0 (0.0) | 0 (0.0) | 0 (0.0) | 1 (5.3) | 0 (0.0) |
| Dehydration | 0 (0.0) | 0 (0.0) | 1 (20.0) | 1 (20.0) | 0 (0.0) | 0 (0.0) | 0 (0.0) | 0 (0.0) | 1 (5.3) | 1 (5.3) |
| Delirium | 0 (0.0) | 0 (0.0) | 0 (0.0) | 0 (0.0) | 0 (0.0) | 0 (0.0) | 1 (25.0) | 0 (0.0) | 1 (5.3) | 0 (0.0) |
| Dry skin | 0 (0.0) | 0 (0.0) | 1 (20.0) | 0 (0.0) | 0 (0.0) | 0 (0.0) | 0 (0.0) | 0 (0.0) | 1 (5.3) | 0 (0.0) |
| Dysphagia | 0 (0.0) | 0 (0.0) | 1 (20.0) | 0 (0.0) | 0 (0.0) | 0 (0.0) | 0 (0.0) | 0 (0.0) | 1 (5.3) | 0 (0.0) |
| Dysphonia | 0 (0.0) | 0 (0.0) | 1 (20.0) | 0 (0.0) | 0 (0.0) | 0 (0.0) | 0 (0.0) | 0 (0.0) | 1 (5.3) | 0 (0.0) |
| Dyspnoea exertional | 0 (0.0) | 0 (0.0) | 1 (20.0) | 0 (0.0) | 0 (0.0) | 0 (0.0) | 0 (0.0) | 0 (0.0) | 1 (5.3) | 0 (0.0) |
| Ecchymosis | 1 (12.5) | 0 (0.0) | 0 (0.0) | 0 (0.0) | 0 (0.0) | 0 (0.0) | 0 (0.0) | 0 (0.0) | 1 (5.3) | 0 (0.0) |
| Endophthalmitis | 0 (0.0) | 0 (0.0) | 0 (0.0) | 0 (0.0) | 0 (0.0) | 0 (0.0) | 1 (25.0) | 1 (25.0) | 1 (5.3) | 1 (5.3) |
| Enterococcal bacteraemia | 0 (0.0) | 0 (0.0) | 1 (20.0) | 1 (20.0) | 0 (0.0) | 0 (0.0) | 0 (0.0) | 0 (0.0) | 1 (5.3) | 1 (5.3) |
| Escherichia infection | 0 (0.0) | 0 (0.0) | 0 (0.0) | 0 (0.0) | 1 (50.0) | 1 (50.0) | 0 (0.0) | 0 (0.0) | 1 (5.3) | 1 (5.3) |
| Escherichia urinary tract infection | 0 (0.0) | 0 (0.0) | 1 (20.0) | 0 (0.0) | 0 (0.0) | 0 (0.0) | 0 (0.0) | 0 (0.0) | 1 (5.3) | 0 (0.0) |
| Eye infection | 0 (0.0) | 0 (0.0) | 0 (0.0) | 0 (0.0) | 0 (0.0) | 0 (0.0) | 1 (25.0) | 1 (25.0) | 1 (5.3) | 1 (5.3) |
| Eyelid oedema | 0 (0.0) | 0 (0.0) | 0 (0.0) | 0 (0.0) | 1 (50.0) | 0 (0.0) | 0 (0.0) | 0 (0.0) | 1 (5.3) | 0 (0.0) |
| Female genital tract fistula | 0 (0.0) | 0 (0.0) | 1 (20.0) | 0 (0.0) | 0 (0.0) | 0 (0.0) | 0 (0.0) | 0 (0.0) | 1 (5.3) | 0 (0.0) |
| Fluid overload | 0 (0.0) | 0 (0.0) | 0 (0.0) | 0 (0.0) | 0 (0.0) | 0 (0.0) | 1 (25.0) | 0 (0.0) | 1 (5.3) | 0 (0.0) |

| Preferred term | PAN 15 mg N=8 Any grades n (%) | PAN 15 mg N=8 Grade 3/4 n (%) | PAN 20 mg N=5 Any grades n (%) | PAN 20 mg N=5 Grade 3/4 n (%) | PAN 25 mg N=2 Any grades n (%) | PAN 25 mg N=2 Preferred term | PAN 20 mg (Expansion Phase) N=4 Any grades n (%) | PAN 20 mg (Expansion Phase) N=4 Grade 3/4 n (%) | All patients N=19 Any grades n (%) | All patients N=19 Grade 3/4 n (%) |
|---|---|---|---|---|---|---|---|---|---|---|
| Gastrooesophageal reflux disease | 0 (0.0) | 0 (0.0) | 1 (20.0) | 0 (0.0) | 0 (0.0) | 0 (0.0) | 0 (0.0) | 0 (0.0) | 1 (5.3) | 0 (0.0) |
| Gingival bleeding | 0 (0.0) | 0 (0.0) | 0 (0.0) | 0 (0.0) | 0 (0.0) | 0 (0.0) | 1 (25.0) | 0 (0.0) | 1 (5.3) | 0 (0.0) |
| Haematochezia | 0 (0.0) | 0 (0.0) | 1 (20.0) | 1 (20.0) | 0 (0.0) | 0 (0.0) | 0 (0.0) | 0 (0.0) | 1 (5.3) | 1 (5.3) |
| Haemorrhoids | 0 (0.0) | 0 (0.0) | 1 (20.0) | 0 (0.0) | 0 (0.0) | 0 (0.0) | 0 (0.0) | 0 (0.0) | 1 (5.3) | 0 (0.0) |
| Hiccups | 0 (0.0) | 0 (0.0) | 1 (20.0) | 1 (20.0) | 0 (0.0) | 0 (0.0) | 0 (0.0) | 0 (0.0) | 1 (5.3) | 1 (5.3) |
| Hyperbilirubinaemia | 0 (0.0) | 0 (0.0) | 0 (0.0) | 0 (0.0) | 0 (0.0) | 0 (0.0) | 1 (25.0) | 1 (25.0) | 1 (5.3) | 1 (5.3) |
| Hyperglycaemia | 0 (0.0) | 0 (0.0) | 1 (20.0) | 0 (0.0) | 0 (0.0) | 0 (0.0) | 0 (0.0) | 0 (0.0) | 1 (5.3) | 0 (0.0) |
| Hyperphosphataemia | 0 (0.0) | 0 (0.0) | 0 (0.0) | 0 (0.0) | 0 (0.0) | 0 (0.0) | 1 (25.0) | 0 (0.0) | 1 (5.3) | 0 (0.0) |
| Hypersensitivity | 0 (0.0) | 0 (0.0) | 0 (0.0) | 0 (0.0) | 0 (0.0) | 0 (0.0) | 1 (25.0) | 0 (0.0) | 1 (5.3) | 0 (0.0) |
| Hyperuricaemia | 0 (0.0) | 0 (0.0) | 0 (0.0) | 0 (0.0) | 0 (0.0) | 0 (0.0) | 1 (25.0) | 0 (0.0) | 1 (5.3) | 0 (0.0) |
| Hypocalcaemia | 0 (0.0) | 0 (0.0) | 0 (0.0) | 0 (0.0) | 0 (0.0) | 0 (0.0) | 1 (25.0) | 0 (0.0) | 1 (5.3) | 0 (0.0) |
| Hyponatraemia | 0 (0.0) | 0 (0.0) | 0 (0.0) | 0 (0.0) | 0 (0.0) | 0 (0.0) | 1 (25.0) | 0 (0.0) | 1 (5.3) | 0 (0.0) |
| Hypotension | 0 (0.0) | 0 (0.0) | 0 (0.0) | 0 (0.0) | 1 (50.0) | 0 (0.0) | 0 (0.0) | 0 (0.0) | 1 (5.3) | 0 (0.0) |
| Increased tendency to bruise | 0 (0.0) | 0 (0.0) | 0 (0.0) | 0 (0.0) | 0 (0.0) | 0 (0.0) | 1 (25.0) | 0 (0.0) | 1 (5.3) | 0 (0.0) |
| Jaundice | 0 (0.0) | 0 (0.0) | 0 (0.0) | 0 (0.0) | 0 (0.0) | 0 (0.0) | 1 (25.0) | 0 (0.0) | 1 (5.3) | 0 (0.0) |
| Klebsiella infection | 0 (0.0) | 0 (0.0) | 0 (0.0) | 0 (0.0) | 1 (50.0) | 1 (50.0) | 0 (0.0) | 0 (0.0) | 1 (5.3) | 1 (5.3) |
| Large intestine perforation | 0 (0.0) | 0 (0.0) | 0 (0.0) | 0 (0.0) | 0 (0.0) | 0 (0.0) | 1 (25.0) | 1 (25.0) | 1 (5.3) | 1 (5.3) |

| | PAN 15 mg N=8 | | PAN 20 mg N=5 | | PAN 25 mg N=2 | | PAN 20 mg (Expansion Phase) N=4 | | All patients N=19 | |
|---|---|---|---|---|---|---|---|---|---|---|
| Preferred term | Any grades n (%) | Grade 3/4 n (%) | Any grades n (%) | Grade 3/4 n (%) | Any grades n (%) | Preferred term | Any grades n (%) | Grade 3/4 n (%) | Any grades n (%) | Grade 3/4 n (%) |
| Left ventricular dysfunction | 0 (0.0) | 0 (0.0) | 1 (20.0) | 0 (0.0) | 0 (0.0) | 0 (0.0) | 0 (0.0) | 0 (0.0) | 1 (5.3) | 0 (0.0) |
| Lung infection | 0 (0.0) | 0 (0.0) | 0 (0.0) | 0 (0.0) | 1 (50.0) | 1 (50.0) | 0 (0.0) | 0 (0.0) | 1 (5.3) | 1 (5.3) |
| Melaena | 0 (0.0) | 0 (0.0) | 1 (20.0) | 0 (0.0) | 0 (0.0) | 0 (0.0) | 0 (0.0) | 0 (0.0) | 1 (5.3) | 0 (0.0) |
| Mouth haemorrhage | 0 (0.0) | 0 (0.0) | 1 (20.0) | 0 (0.0) | 0 (0.0) | 0 (0.0) | 0 (0.0) | 0 (0.0) | 1 (5.3) | 0 (0.0) |
| Muscle strain | 0 (0.0) | 0 (0.0) | 0 (0.0) | 0 (0.0) | 0 (0.0) | 0 (0.0) | 1 (25.0) | 0 (0.0) | 1 (5.3) | 0 (0.0) |
| Muscular weakness | 0 (0.0) | 0 (0.0) | 1 (20.0) | 0 (0.0) | 0 (0.0) | 0 (0.0) | 0 (0.0) | 0 (0.0) | 1 (5.3) | 0 (0.0) |
| Musculoskeletal chest pain | 0 (0.0) | 0 (0.0) | 0 (0.0) | 0 (0.0) | 1 (50.0) | 1 (50.0) | 0 (0.0) | 0 (0.0) | 1 (5.3) | 1 (5.3) |
| Nasal congestion | 0 (0.0) | 0 (0.0) | 0 (0.0) | 0 (0.0) | 0 (0.0) | 0 (0.0) | 1 (25.0) | 0 (0.0) | 1 (5.3) | 0 (0.0) |
| Neck pain | 0 (0.0) | 0 (0.0) | 1 (20.0) | 0 (0.0) | 0 (0.0) | 0 (0.0) | 0 (0.0) | 0 (0.0) | 1 (5.3) | 0 (0.0) |
| Neutrophil count decreased | 0 (0.0) | 0 (0.0) | 0 (0.0) | 0 (0.0) | 1 (50.0) | 1 (50.0) | 0 (0.0) | 0 (0.0) | 1 (5.3) | 1 (5.3) |
| Non-cardiac chest pain | 0 (0.0) | 0 (0.0) | 1 (20.0) | 1 (20.0) | 0 (0.0) | 0 (0.0) | 0 (0.0) | 0 (0.0) | 1 (5.3) | 1 (5.3) |
| Oral candidiasis | 0 (0.0) | 0 (0.0) | 1 (20.0) | 0 (0.0) | 0 (0.0) | 0 (0.0) | 0 (0.0) | 0 (0.0) | 1 (5.3) | 0 (0.0) |
| Oral disorder | 0 (0.0) | 0 (0.0) | 1 (20.0) | 0 (0.0) | 0 (0.0) | 0 (0.0) | 0 (0.0) | 0 (0.0) | 1 (5.3) | 0 (0.0) |
| Overdose | 0 (0.0) | 0 (0.0) | 1 (20.0) | 0 (0.0) | 0 (0.0) | 0 (0.0) | 0 (0.0) | 0 (0.0) | 1 (5.3) | 0 (0.0) |
| Penile swelling | 0 (0.0) | 0 (0.0) | 0 (0.0) | 0 (0.0) | 1 (50.0) | 1 (50.0) | 0 (0.0) | 0 (0.0) | 1 (5.3) | 1 (5.3) |
| Platelet count decreased | 0 (0.0) | 0 (0.0) | 0 (0.0) | 0 (0.0) | 1 (50.0) | 1 (50.0) | 0 (0.0) | 0 (0.0) | 1 (5.3) | 1 (5.3) |
| Pneumonia fungal | 0 (0.0) | 0 (0.0) | 0 (0.0) | 0 (0.0) | 0 (0.0) | 0 (0.0) | 1 (25.0) | 1 (25.0) | 1 (5.3) | 1 (5.3) |
| Procedural pain | 0 (0.0) | 0 (0.0) | 1 (20.0) | 0 (0.0) | 0 (0.0) | 0 (0.0) | 0 (0.0) | 0 (0.0) | 1 (5.3) | 0 (0.0) |

| Preferred term | PAN 15 mg N=8 Any grades n (%) | PAN 15 mg N=8 Grade 3/4 n (%) | PAN 20 mg N=5 Any grades n (%) | PAN 20 mg N=5 Grade 3/4 n (%) | PAN 25 mg N=2 Any grades n (%) | Preferred term | PAN 20 mg (Expansion Phase) N=4 Any grades n (%) | PAN 20 mg (Expansion Phase) N=4 Grade 3/4 n (%) | All patients N=19 Any grades n (%) | All patients N=19 Grade 3/4 n (%) |
|---|---|---|---|---|---|---|---|---|---|---|
| Productive cough | 0 (0.0) | 0 (0.0) | 0 (0.0) | 0 (0.0) | 1 (50.0) | 0 (0.0) | 0 (0.0) | 0 (0.0) | 1 (5.3) | 0 (0.0) |
| Pruritus generalised | 0 (0.0) | 0 (0.0) | 0 (0.0) | 0 (0.0) | 0 (0.0) | 0 (0.0) | 1 (25.0) | 0 (0.0) | 1 (5.3) | 0 (0.0) |
| Pseudomonal bacteraemia | 0 (0.0) | 0 (0.0) | 0 (0.0) | 0 (0.0) | 1 (50.0) | 1 (50.0) | 0 (0.0) | 0 (0.0) | 1 (5.3) | 1 (5.3) |
| Pupils unequal | 0 (0.0) | 0 (0.0) | 0 (0.0) | 0 (0.0) | 0 (0.0) | 0 (0.0) | 1 (25.0) | 0 (0.0) | 1 (5.3) | 0 (0.0) |
| Rash erythematous | 0 (0.0) | 0 (0.0) | 0 (0.0) | 0 (0.0) | 1 (50.0) | 0 (0.0) | 0 (0.0) | 0 (0.0) | 1 (5.3) | 0 (0.0) |
| Renal pain | 0 (0.0) | 0 (0.0) | 0 (0.0) | 0 (0.0) | 1 (50.0) | 0 (0.0) | 0 (0.0) | 0 (0.0) | 1 (5.3) | 0 (0.0) |
| Rhinitis | 0 (0.0) | 0 (0.0) | 1 (20.0) | 0 (0.0) | 0 (0.0) | 0 (0.0) | 0 (0.0) | 0 (0.0) | 1 (5.3) | 0 (0.0) |
| Skin lesion | 0 (0.0) | 0 (0.0) | 1 (20.0) | 0 (0.0) | 0 (0.0) | 0 (0.0) | 0 (0.0) | 0 (0.0) | 1 (5.3) | 0 (0.0) |
| Swollen tongue | 0 (0.0) | 0 (0.0) | 0 (0.0) | 0 (0.0) | 0 (0.0) | 0 (0.0) | 1 (25.0) | 0 (0.0) | 1 (5.3) | 0 (0.0) |
| Tachypnoea | 0 (0.0) | 0 (0.0) | 0 (0.0) | 0 (0.0) | 0 (0.0) | 0 (0.0) | 1 (25.0) | 0 (0.0) | 1 (5.3) | 0 (0.0) |
| Upper-airway cough syndrome | 0 (0.0) | 0 (0.0) | 0 (0.0) | 0 (0.0) | 1 (50.0) | 0 (0.0) | 0 (0.0) | 0 (0.0) | 1 (5.3) | 0 (0.0) |
| Urinary tract infection | 0 (0.0) | 0 (0.0) | 1 (20.0) | 0 (0.0) | 0 (0.0) | 0 (0.0) | 0 (0.0) | 0 (0.0) | 1 (5.3) | 0 (0.0) |
| Urinary tract infection pseudomonal | 0 (0.0) | 0 (0.0) | 0 (0.0) | 0 (0.0) | 1 (50.0) | 1 (50.0) | 0 (0.0) | 0 (0.0) | 1 (5.3) | 1 (5.3) |
| Vaginal haemorrhage | 0 (0.0) | 0 (0.0) | 1 (20.0) | 0 (0.0) | 0 (0.0) | 0 (0.0) | 0 (0.0) | 0 (0.0) | 1 (5.3) | 0 (0.0) |
| Vision blurred | 0 (0.0) | 0 (0.0) | 0 (0.0) | 0 (0.0) | 0 (0.0) | 0 (0.0) | 1 (25.0) | 0 (0.0) | 1 (5.3) | 0 (0.0) |
| Wheezing | 0 (0.0) | 0 (0.0) | 0 (0.0) | 0 (0.0) | 0 (0.0) | 0 (0.0) | 1 (25.0) | 0 (0.0) | 1 (5.3) | 0 (0.0) |
| White blood cell count | 0 (0.0) | 0 (0.0) | 0 (0.0) | 0 (0.0) | 1 (50.0) | 1 (50.0) | 0 (0.0) | 0 (0.0) | 1 (5.3) | 1 (5.3) |

| Preferred term | PAN 15 mg N=8 Any grades n (%) | PAN 15 mg N=8 Grade 3/4 n (%) | PAN 20 mg N=5 Any grades n (%) | PAN 20 mg N=5 Grade 3/4 n (%) | PAN 25 mg N=2 Any grades n (%) | Preferred term | PAN 20 mg (Expansion Phase) N=4 Any grades n (%) | PAN 20 mg (Expansion Phase) N=4 Grade 3/4 n (%) | All patients N=19 Any grades n (%) | All patients N=19 Grade 3/4 n (%) |
|---|---|---|---|---|---|---|---|---|---|---|
| decreased | | | | | | | | | | |

Preferred terms are presented in descending frequency, as reported in the “Any grades” column for “All patients”.
A patient with multiple occurrences of an AE is counted only once in the AE category.
Adverse events occurring more than 28 days after the discontinuation of study treatment are not summarized.

**Deaths, serious adverse events, discontinuation to adverse events and clinically notable adverse events by dose group of panobinostat during Induction Phase (SAS)**

| | PAN 15 mg N=11 n (%) | PAN 20 mg N=15 n (%) | PAN 25 mg N=8 n (%) | PAN 20 mg (Expansion Phase) N=12 n (%) | All patients N=46 n (%) |
|---|---|---|---|---|---|
| Patients with AE(s)[1] | 11 (100.0) | 15 (100.0) | 8 (100.0) | 12 (100.0) | 46 (100.0) |
| On treatment deaths[2] | 0 (0.0) | 0 (0.0) | 0 (0.0) | 3 (25.0) | 3 (6.5) |
| Serious Adverse Events | 4 (36.4) | 9 (60.0) | 2 (25.0) | 4 (33.3) | 19 (41.3) |
| AEs leading to study drug discontinuation | 1 (9.1) | 3 (20.0) | 3 (37.5) | 1 (8.3) | 8 (17.4) |
| Clinically notable adverse events[3] | 11 (100.0) | 15 (100.0) | 8 (100.0) | 12 (100.0) | 46 (100.0) |
| Grade 3/4 clinically notable adverse events[3] | 11 (100.0) | 14 (93.3) | 8 (100.0) | 9 (75.0) | 42 (91.3) |
| AEs of grade 3/4 suspected to be related to study drug | 8 (72.7) | 14 (93.3) | 5 (62.5) | 7 (58.3) | 34 (73.9) |

[1] Adverse events occurring more than 28 days after the discontinuation of study treatment are not summarized.
[2] Deaths occurring more than 28 days after the discontinuation of study treatment are not summarized.
[3] Clinically notable adverse events are the events for which there is a specific clinical interest in connection with panobinostat or events which are similar in nature.

## Other Relevant Findings

### Pharmacokinetic results

**Summary of panobinostat PK parameter by dose group of panobinostat (PK analysis set)**

| PAN dose group | Statistics | AUCinf (ng*h/mL) | AUC0-24 (ng*h/mL) | AUClast (ng*h/mL) | Cmax (ng/mL) | Tmax (hr) | T1/2 (hr) | CL/F (L/hr) | Vz/F (L) |
|---|---|---|---|---|---|---|---|---|---|
| **PAN 15 mg N=10** | n | 10 | 10 | 10 | 10 | 10 | 10 | 10 | 10 |
| | Mean (SD) | 56.8 (27.4) | 47.3 (22.0) | 49.5 (23.0) | 6.45 (2.50) | N/A | 9.39 (1.91) | 333 (186) | 4500 (2560) |
| | CV% mean | 48.2 | 46.4 | 46.4 | 38.7 | N/A | 20.3 | 55.9 | 57.0 |
| | Geo-mean | 50.8 | 42.5 | 44.5 | 6.03 | N/A | 9.22 | 295 | 3920 |
| | CV% geo-mean | 54.7 | 54.6 | 54.4 | 40.2 | N/A | 20.5 | 54.7 | 58.6 |
| | Median | 53.1 | 44.4 | 46.7 | 5.66 | 3.00 | 8.74 | 289 | 3800 |
| | [Min; Max] | [19.3; 111] | [15.8; 86.6] | [16.7; 90.7] | [3.00; 11.3] | [0.500; 3.05] | [6.84; 12.6] | [135; 777] | [2100; 10100] |
| **PAN 20 mg N=12** | n | 11 | 11 | 11 | 11 | 11 | 11 | 11 | 11 |
| | Mean (SD) | 86.3 (43.9) | 72.5 (36.0) | 75.4 (37.4) | 14.9 (11.1) | N/A | 9.88 (1.61) | 326 (235) | 4450 (2790) |
| | CV% mean | 50.9 | 49.7 | 49.6 | 74.6 | N/A | 16.3 | 72.0 | 62.6 |
| | Geo-mean | 74.3 | 62.6 | 65.2 | 10.8 | N/A | 9.76 | 269 | 3790 |
| | CV% geo-mean | 68.2 | 68.0 | 67.4 | 121.1 | N/A | 16.4 | 68.2 | 62.8 |
| | Median | 93.1 | 82.1 | 84.7 | 11.5 | 1.05 | 9.70 | 215 | 2930 |
| | [Min; Max] | [23.9; 170] | [19.4; 136] | [20.6; 143] | [1.44; 35.7] | [0.983; 7.00] | [7.98; 11.8] | [118; 838] | [2000; 10100] |
| **PAN 25 mg N=8** | n | 8 | 8 | 8 | 8 | 8 | 8 | 8 | 8 |

| PAN dose group | Statistics | AUCinf (ng*h/mL) | AUC0-24 (ng*h/mL) | AUClast (ng*h/mL) | Cmax (ng/mL) | Tmax (hr) | T1/2 (hr) | CL/F (L/hr) | Vz/F (L) |
|---|---|---|---|---|---|---|---|---|---|
| | Mean (SD) | 92.6 (45.5) | 81.8 (42.9) | 84.7 (43.7) | 13.5 (9.92) | N/A | 8.05 (1.60) | 316 (115) | 3620 (1220) |
| | CV% mean | 49.1 | 52.4 | 51.7 | 73.6 | N/A | 19.9 | 36.5 | 33.7 |
| | Geo-mean | 85.0 | 74.6 | 77.3 | 11.2 | N/A | 7.91 | 294 | 3360 |
| | CV% geo-mean | 44.3 | 45.5 | 45.1 | 67.8 | N/A | 19.8 | 44.3 | 48.8 |
| | Median | 81.1 | 70.7 | 73.2 | 11.0 | 2.02 | 7.81 | 308 | 3780 |
| | [Min; Max] | [53.0; 192] | [46.1; 179] | [48.1; 183] | [5.33; 36.1] | [1.25; 4.90] | [6.21; 10.7] | [131; 471] | [1170; 5280] |
| **PAN 20 mg (Expansion Phase) N=10** | n | 10 | 10 | 10 | 10 | 10 | 10 | 10 | 10 |
| | Mean (SD) | 108 (28.7) | 96.6 (28.1) | 96.5 (27.2) | 16.2 (6.37) | N/A | 7.33 (3.05) | 204 (77.7) | 2050 (934) |
| | CV% mean | 26.7 | 29.1 | 28.2 | 39.3 | N/A | 41.7 | 38.2 | 45.7 |
| | Geo-mean | 103 | 92.7 | 92.4 | 15.0 | N/A | 6.47 | 193 | 1810 |
| | CV% geo-mean | 32.3 | 32.3 | 34.0 | 47.3 | N/A | 64.8 | 32.3 | 63.2 |
| | Median | 111 | 98.8 | 103 | 16.4 | 1.98 | 7.94 | 180 | 2040 |
| | [Min; Max] | [49.7; 150] | [49.7; 137] | [43.2; 141] | [6.05; 26.4] | [1.00; 5.00] | [2.19; 11.1] | [133; 402] | [472; 3530] |

n: number of subjects with non-missing values.
CV=coefficient of variation (%)=sd/mean*100
CV% geo-mean=sqrt (exp [variance for log transformed data]-1)*100.

## Conclusion

The MTD of panobinostat with fixed dose of idarubicin and ara-C in adult patients with high risk-AML was not reached per BLRM criteria when escalating panobinostat from 15 mg/day to 25 mg/day. The RPIID for future studies in setting of high risk-AML was considered to be 20 mg of panobinostat when administered in combination with a fixed dose of idarubicin and ara-C. The safety profile of panobinostat in combination with ara-C and idarubicin was generally consistent with that observed in earlier clinical studies, and was expected based on known safety profile of ara-C and idarubicin combination. Panobinostat in combination with idarubicin and ara-C demonstrated clinical activity in adult patients with high-risk AML. Twenty-eight patients achieved CR or CRi corresponding to a response rate of 60.9% (95% CI: 45.4, 74.9).

## Date of Clinical Trial Report

27-Apr-2015

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

5-May-2015

## Date of Latest Update

## Reason for Update