## Sponsor

Novartis

## Generic Drug Name

Panobinostat

## Therapeutic Area of Trial

Advanced hematological malignancies

## Approved Indication

Investigational

## Study Number

CLBH589B2102

## Title

A phase IA/II, two-arm, multi-center, open-label, dose-escalation study of LBH589 administered orally via different dosing schedules in adult patients with advanced hematological malignancies.

## Phase of Development

IA/II

## Study Start/End Dates

06 Mar 2006 to 02 Dec 2009

## Study Design/Methodology

This was a two-arm, open-label, multi-center, Phase IA/II, dose-escalation study of panobinostat administered via two different dosing schedules.

In Arm 1, panobinostat was administered orally, once-a-day, on Monday-Wednesday-Friday (MWF), every week, as part of a 28-day treatment cycle.

In Arm 2, panobinostat was administered orally, once-a-day, on MWF, every other week, as part of a 28-day treatment cycle.

**Dose escalation and expansion**:

After the first cohort was enrolled at the 20 mg dose level, each arm was then divided into two sub-arms, X and Y, based on disease indication. The X sub-arms (1X and 2X) enrolled patients with AML, MDS, MMM, ALL, CMML, CML-BP/AP/CP, aCML, CLL and PLL. The Y sub-arms (1Y and 2Y) enrolled patients with MM, HL and NHL. Therefore, following evaluation of the first dose level (20 mg) the dose escalation phase was conducted in 4 separate sub-arms: 1X, 2X, 1Y and 2Y.

During the dose escalation phase a minimum of 12 evaluable patients were to be treated at the

dose declared to be the MTD for each of the sub-arms (1X, 2X, 1Y and 2Y). Subsequently, enrollment to various dose expansion arms was to occur. Not all of the potential dose expansion arms were opened, as the experience during the dose escalation phase of the study suggested that some diseases (like AML and Hodgkin's lymphoma) were of greater interest, and that the dose intensity of therapy with panobinostat could not be significantly increased with every other week dosing. Hence the following dose expansion arms were opened to enrollment:

- Phase II, Expansion Arm 1A (Stage 1) enrolled patients with AML treated at 60 mg MWF every week (Stage 2 did not open to enrollment).
- Phase IA, Expansion Arm 1D enrolled patients with ALL, MDS, MMM, CMML, aCML, CLL or PLL treated at 60 mg MWF every week as well as patients with HL or NHL treated at 40 mg MWF every week.

## Centers

Seven centers in three countries- Australia (2), Germany (2), United States (3)

## Publication

Dickinson M, Ritchie D, DeAngelo DJ, et al. (2009). Preliminary evidence of disease response to the pan-deacetylase inhibitor panobinostat (LBH589) in refractory Hodgkin Lymphoma. Br J Haematol; 147(1):97-101.

## Objectives

Primary objective(s)

- To determine the maximum tolerated dose (MTD) and dose limiting toxicity (DLT) of single agent panobinostat when administered orally, once-a-day on Monday, Wednesday, Friday (MWF), every week, in adult patients with advanced hematological malignancies which had progressed despite standard therapy or for which no standard therapy existed (Arm 1).
- To determine the MTD and DLT of single agent panobinostat when administered orally, once-a-day on MWF, every other week, in adult patients with advanced hematological malignancies which had progressed despite standard therapy or for which no standard therapy existed (Arm 2).
- To characterize the pharmacokinetic profile of panobinostat, and its potential metabolite(s), after single and repeated doses.

Secondary objective(s)

- To characterize the safety and tolerability of panobinostat, including acute and chronic toxicities
- To assess changes in acetylation of histones H3 and H4, and other non-histone proteins, such as tubulin in leukemic blasts, peripheral blood mononuclear cells, bone marrow cells, and tumor tissues (if available), pre- and post-treatment
- To assess cancer-related chromosomal aberrations, gene mutations, gene expression changes, and protein expression changes in peripheral blood mononuclear cells and/or malignant cells, pre- and post-treatment
- To assess fetal hemoglobin (HbF) levels in red blood cells, pre- and post-treatment
- To evaluate preliminary evidence of anti-leukemic or anti-tumor activity of panobinostat

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

Oral panobinostat was supplied as 5-mg or 20-mg hard gelatin capsules. Dosing was on a flat scale of mg/day, without adjustment for weight or body surface area .Tested dose levels included 20, 30, 40, 60 and 80 mg/day on the MWF every week schedule and 30, 45, 60 and 80 mg/day on the every other week schedule.

Following completion of cycle 1, patients were allowed to continue treatment with panobinostat until they experienced unacceptable toxicity that precluded any further treatment, disease progression, withdrawal of consent or until treatment was discontinued at the discretion of the investigator.

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

Not applicable

## Criteria for Evaluation

### Efficacy

- Based on the disease indication, the data which was collected could include, but was not limited to, the following: response status; hematology; bone marrow aspirate/biopsy; extramedullary exam; cytogenetics; PET scan; MM specific assessments (e.g., serum and urine M-protein, skeletal survey, evaluation of plasmacytomas, other special labs for disease assessment); and antineoplastic therapies since discontinuation of study drug (i.e., not limited to ≥ 28 days after the last dose of study drug).
- For specific indications, the efficacy was assessed based on the defined disease specific criteria for evaluating response for AML, ALL, MDS (RAEB-1,-2), CMML, CML-BP, CML-AP, CML-CP, aCML, CLL, PLL (T- and B-cell), MMM, MM, HL and NHL.

### Safety and tolerability

Safety assessments consisted of monitoring and recording all adverse events, serious adverse events, and the regular monitoring of laboratory evaluations, physical examinations, vital signs, eight, performance status evaluations, thyroid function tests, and repeat cardiac assessments (including ECG, cardiac enzymes, and MUGA/echocardiogram) and pregnancies.

### Bioanalytics

**Biomarkers**: Blood samples were analyzed for histone acetylation by Western blot analysis. Blood and bone marrow aspirate samples were analyzed by FACS (fluorescent activated cell sorting) assay for changes in protein expression/modification or protein phosphorylation. Quantification of fetal hemoglobin was done to assess the potential induction of HbF by panobinostat.

**Pharmacokinetics**: Serial blood samples were collected from all patients during the dose escalation phase to characterize panobinostat pharmacokinetics. The plasma samples from all patients were assayed for panobinostat concentrations using a validated liquid chromatography-tandem mass spectrometry assay (LC-MS/MS).

## Statistical Methods

**MTD and DLT:** For arms 1X/2X and 1Y/2Y, the toxicity monitoring of this dose escalation trial was based on a 3 parameter version of a Bayesian model to assess the probabilities of dose-limiting toxicity (DLT). Separate but identical models were used for each X and Y group. After each cohort of patients had completed enrollment and a first cycle of treatment, information on these probabilities was updated using current DLT data. Selection of the next dose was based on these probabilities as well as on other clinical information. Information on probabilities of toxicity after each patient cohort was based on the posterior probabilities of DLT. The mean posterior probability of toxicity was summarized.

**Efficacy:** Efficacy analyses were based on investigators' assessments of response from the CRF response status page. The best overall responses were summarized for the patients with HL, MDS

and AML. Patient listings providing response data were produced for all indications. For the patients with AML, the response information was summarized for the dose escalation and dose expansion phases jointly. Additionally, it was also summarized separately for the dose expansion phase. For the patients with HL, the summary table of response was provided for the dose escalation and dose expansion phases together.

**Safety:** All safety analyses were conducted in the dose escalation and dose expansion phases of the study by the four treatment groups and assigned dose cohort: arm 1 with group X or group Y, arm 2 with group X or group Y. The safety data was presented by arms and groups irrespective of the individual indications. Newly occurring or worsening notably abnormal laboratory values of hematology-coagulation and biochemistry were presented additionally. The assessment of safety was based mainly on the frequency of adverse events and on the number of laboratory values that fell outside of pre-determined ranges. Other safety data (e.g., electrocardiogram, vital signs, and special tests) were summarized. All safety data was listed. Data from other tests (e.g. electrocardiogram or vital signs) were listed, notable values were flagged, ECG extreme values were presented by assigned dose schedule and dose level.

**Biomarkers:** Summary statistics and percentage changes from baseline were provided for the biomarkers viz. acetylation of histones H3 and H4, Immunohistochemistry (IHC) (pStat3, acetylated H3, and Hsp70), Fetal hemoglobin (HbF) using full analysis set.

**Pharmacokinetics:** The individual and mean plasma concentrations of panobinostat (as expressed in ng/mL) versus time profiles of panobinostat were displayed graphically. Pharmacokinetic parameters of panobinostat were derived from the individual concentration versus time profile using noncompartmental methods. Summary statistics including N, arithmetic mean, SD, CV%, geometric mean, geometric CV%, median, minimum and maximum was presented for $C_{max}$, $AUC_{0-24}$, $AUC_{0-48}$, and $AUC_{0-\infty}$. Trough levels were listed and summarized. For $T_{max}$ and $T_{last}$ median, minimum and maximum was presented.

## Study Population: Inclusion/Exclusion Criteria and Demographics

Inclusion criteria and dosing

- Adult patients with a cytopathologically or histopathologically confirmed diagnosis of an advanced hematological malignancy (AML, ALL, MDS [RAEB-1,-2], MMM, CML – CP/AP/BP, CMML, aCML, CLL, PLL, MM, HL, and NHL [including mantle cell lymphoma and follicular lymphoma; excluding CTCL and Burkitt's lymphoma]) which had progressed despite standard therapy, or for which no standard therapy existed; or, were considered inappropriate candidates for standard therapy

For the two dose expansion arms:

**Group A:** Patients with a cytopathologically confirmed diagnosis of AML who had either relapsed after or were refractory to standard therapy; or, were considered inappropriate candidates for standard therapy; or, were elderly patients with high risk factors presenting with *de novo* AML.

**Group D:** Patients with a cytopathologically or histopathologically confirmed diagnosis of relapsed/refractory ALL, MDS (RAEB-1,-2), MMM, CMML, aCML, CLL, PLL (T- and B-cell), HL, and NHL (excluding CTCL and Burkitt's lymphoma).

Patients with multiple myeloma who did not have measurable serum M-protein or measurable

urine M-protein were to have measurable increased concentrations of free light chains (using FreeLite™).

Patients with Hodgkin's or Non-Hodgkin's lymphoma should have had at least one measurable or evaluable lesion as defined by the Cheson Response Criteria for Non-Hodgkin's Lymphoma.

Exclusion criteria

- Cytopathologically confirmed CSF (cerebrospinal fluid) infiltration. No concurrent brain metastases or leukemic infiltration of the CSF. However, patients with a prior history of brain metastases from another indication or a prior history of leukemic infiltration of the CSF, who demonstrated resolution of the CNS involvement and no evidence of CNS involvement at baseline were eligible.
- Any peripheral neuropathy ≥ CTCAE grade 2 and unresolved diarrhea ≥ CTCAE grade 2
- Impaired cardiac function or clinically significant cardiac diseases, impairment of GI function or GI disease that could significantly alter the absorption of panobinostat and acute or chronic liver disease, acute or chronic renal disease.
- Treatment with specified CYP3A4 inhibitors or medications with risk of prolonging the QT interval
- Treatment with any hematopoietic colony-stimulating growth factors (e.g., G-CSF, GMCSF) ≤ 2 weeks prior to starting study drug. Erythropoietin or darbepoetin therapy, if initiated before enrollment, could be continued.
- Treatment with therapeutic doses of sodium warfarin (Coumadin®). Low doses of Coumadin® (e.g., ≤ 2 mg/day) for line patency were allowable.

**Number of patients:**

A total of up to 308 patients were planned to be enrolled in the study. A total of 176 patients with advanced hematological malignancies were enrolled in the study.

In total, 110 patients enrolled in the dose escalation phase were evaluable for MTD determination. A total of 140 patients had at least one PK profile available for analysis and thus were included in the pharmacokinetics set.

## Patient Disposition (Full Analysis Set)

| Patient disposition n(%) | Arm 1 Group X N=86 | Arm 1 Group Y N=34 | Arm 2 Group X N=33 | Arm 2 Group Y N=23 | All N=176 |
|---|---|---|---|---|---|
| Discontinued study | 86(100.0%) | 34(100.0%) | 33(100.0%) | 23(100.0%) | 176(100.0%) |
| Primary reason for discontinuation of study | | | | | |
| Administrative problems | 5 (5.8%) | 1 (2.9%) | 0 (0.0%) | 2 (8.7%) | 8 (4.5%) |
| Adverse Event(s) | 27 (31.4%) | 7 (20.6%) | 9 (27.3%) | 2 (8.7%) | 45 (25.6%) |
| Death | 3 (3.5%) | 3 (8.8%) | 1 (3.0%) | 1 (4.3%) | 8 (4.5%) |
| Disease pro- | 44 (51.2%) | 20 (58.8%) | 20 (60.6%) | 15 (65.2%) | 99 (56.3%) |

| | | | | | |
|---|---|---|---|---|---|
| gression | | | | | |
| Subject with-drew consent | 7 (8.1%) | 3 (8.8%) | 3 (9.1%) | 3 (13.0%) | 16 (9.1%) |

## Demographic and Background Characteristics (Full analysis set)

| **Demograph-ics and base-line characte-ristics** | **Arm 1 Group X N=86** | **Arm 1 Group Y N=34** | **Arm 2 Group X N=33** | **Arm 2 Group Y N=23** | **All N=176** |
|---|---|---|---|---|---|
| Gender-n (%) | | | | | |
| Female | 31 (36.0%) | 13 (38.2%) | 12 (36.4%) | 5 (21.7%) | 61 (34.7%) |
| Male | 55 (64.0%) | 21 (61.8%) | 21 (63.6%) | 18 (78.3%) | 115 (65.3%) |
| Age (years) | | | | | |
| Mean (SD) | 64.2 (12.11) | 41.1 (17.27) | 68.7 (8.75) | 48.3 (17.41) | 58.5 (16.97) |
| **Race (n%)** | | | | | |
| Asian | 4 (4.7%) | 0 (0.0%) | 0 (0.0%) | 0 (0.0%) | 4 (2.3%) |
| Black | 3 (3.5%) | 1 (2.9%) | 2 (6.1%) | 0 (0.0%) | 6 (3.4%) |
| Caucasian | 78 (90.7%) | 31 (91.2%) | 29 (87.9%) | 23 (100%) | 161 (91.5%) |
| Others | 1 (1.2%) | 2 (5.9%) | 2 (6.1%) | 0 (0.0%) | 5 (2.8%) |

## Primary Objective Result(s)

**MTD and DLT:** In the patients with Group X indications, the MTD was determined to be 60 mg MWF for the every week schedule. The MTD was not formally determined for Group X patients on the every other week schedule. Fatigue was the principal DLT observed in patients with Group X indications on the every week schedule. In the patients with Group Y indications, the recommended phase II dose (RPIID) was determined to be 40 mg MWF for the every week schedule and 60 mg MWF for the every other week schedule. Thrombocytopenia was the principal DLT in the patients with Group Y indications on both of these schedules.

**Pharmacokinetics**: Panobinostat was rapidly absorbed with Tmax observed within 1-2 hours following oral administration. Panobinostat exposures generally increased dose-proportionally up to 60 mg after a single or multiple doses. Minimal drug accumulation was observed with MWF every week dosing, and the mean terminal half-life was approximately 18 hours.

## Secondary Objectives Result (s)

**Efficacy results**

AML

In the FAS, 59 AML patients on the every week schedule were treated at various dose levels of panobinostat from 20 to 80 mg MWF every week. Complete remission was achieved in two patients and partial remission occurred in one patient, all three of whom were treated at a dose of 60 mg. In addition, 24 AML patients were treated on the every other week schedule at doses of 30 to 80 mg: partial remission was observed in one patient treated at the dose of 60 mg.

HL

Out of the 22 HL patients on the every week schedule treated at doses from 30 to 60 mg, one patient treated at 40 mg achieved a complete response. Of the 10 patients treated at doses from 45 to 60 mg on the every other week schedule, one patient treated at the 60 mg dose achieved a complete response. Partial responses were also observed in patients on both schedules. Of the 22 HL patients treated on the every week schedule, PR was seen at the 30 mg (one patient) and 40 mg (three patients) dose levels. Of the 10 HL patients treated on the every other week schedule, PR was observed at the 45 mg (one patient) and 60 mg (two patients) dose levels. The overall response rate (CR + PR) for the 32 patients with HL was 28.1% (9/32).

MDS

Of the 9 MDS patients on the every week schedule, the investigator's assessment was not reported for one patient and stable disease was observed in four patients treated at 30 mg (1 patient), 40 mg (1 patient) and 60 mg (2 patients). The remaining four patients were assessed as having progressive disease, with one patient each at dose levels of 20 mg, 40 mg, 60 mg and 80 mg. Out of the two MDS patients treated on the every other week schedule, one showed partial remission at 60 mg and the other had stable disease at 45 mg.

Other hematologic malignancies

Signs of anti-tumor activity were also observed in patients with the following diseases: CIMF - 4 patients with Clinical Improvement; MM - 1 patient with PR; CLL - 1 patient with PR; and NHL - 2 patients with PR.

**Biomarkers**: Analysis of histone acetylation in peripheral blood mononuclear cells showed that the acetylation of histones increased after treatment with panobinostat and occurred in the majority of patients. A trend toward fetal hemoglobin induction was observed in both Arm 1 and Arm 2. Immunohistochemical analysis of pStat3, Hsp70, and acetylated histone 3 in bone marrow samples was inconclusive. This was the result of multiple factors, including the limited number of specimens for analysis, data variability and differences in drug doses.

## Safety Results

Overall, 118 patients died in the study, with 42 deaths reported while on treatment or within the follow up period of up to 28 days after the last administration of study drug. Of these deaths on study, 35 occurred in Group X and 7 occurred in Group Y. Disease progression was the reason for death in majority of the patients. In total, two deaths in Group X were suspected to be related to panobinostat, along with the possibility of an alternative etiology (pulmonary hemorrhage con-

sequent to bronchopulmonary aspergillosis and multi-organ failure). None of the deaths in Group Y was suspected to be related to the study medication.

The most commonly reported AEs, both regardless of causality and suspected to be related to panobinostat, were nausea, diarrhea and fatigue. In addition, thrombocytopenia was one of the most common suspected AEs seen in Group Y patients in both Arms 1 and 2. Thrombocytopenia was the most common grade 3 and 4 adverse event, regardless of causality, in both of the arms and groups.

Other safety findings were unremarkable. All thyroid-related abnormalities recorded as AEs were deemed grade 1/2 in nature by the investigators. QTcF prolongation was noted at high dose levels, with an absolute QTcF ≥ 500 ms noted in 5 patients on the weekly schedule (60 and 80 mg doses) and in 1 patient on the every other week schedule (80 mg dose). Increases of > 60 ms in QTcF were observed in 10 patients on the weekly schedule (9 of the 10 patients were treated at 60 or 80 mg) and in 5 patients on the every other week schedule (3 of the 5 patients were treated at 60 or 80 mg).

## Serious Adverse Events and Deaths

**Deaths, serious adverse events, or AE-related discontinuations-Safety population**

| | Arm 1 Group X N=86 n (%) | Arm 1 Group Y N=34 n (%) | Arm 2 Group X N=33 n (%) | Arm 2 Group Y N=23 n (%) | All N=176 n (%) |
|---|---|---|---|---|---|
| All deaths | 64 (74.4%) | 14 (41.2%) | 29 (87.9%) | 11 (47.8%) | 118 (67.0%) |
| On treatment deaths | 23 (26.7%) | 6 (17.6%) | 12 (36.4%) | 1 (4.3%) | 42 (23.9%) |
| All SAEs | 66 (76.7%) | 15 (44.1%) | 28 (84.8%) | 14 (60.9%) | 123 (69.9%) |
| Study-drug-related SAEs | 29 (33.7%) | 3 (8.8%) | 3 (9.1%) | 3 (13.0%) | 38 (21.6%) |
| AEs leading to discontinuation | 26 (30.2%) | 8 (23.5%) | 7 (21.2%) | 3 (13.0%) | 44 (25.0%) |

## Date of Clinical Trial Report

20 Oct 2010

## Date Inclusion on Novartis Clinical Trial Results Database

4 Jan 2011

## Date of Latest Update