Sponsor

Novartis

Generic Drug Name

Panobinostat

Therapeutic Area of Trial

Chronic phase chronic myeloid leukemia with resistant disease following treatment with at least two BCR-ABL tyrosine kinase inhibitors.

Approved Indication

Investigational

Study Number

CLBH589B2202

Title

A phase II, multicenter study of oral LBH589 in patients with chronic phase chronic myeloid leukemia with resistant disease following treatment with at least two BCR-ABL tyrosine kinase inhibitors.

Phase of Development

Phase II

Study Start/End Dates

19 Feb 2007 to 30 Sep 2008

Study Design/Methodology

This was a phase II, single-arm, three-stage, open-label, multicenter, international study consisting of two periods: screening period (1-15 days duration for the assessment of patient eligibility), and treatment period. There was no inclusion of a placebo control arm as it would have been unethical and the inclusion of an active control arm would have been inutile given the resistance of these patients to previous treatment with BCR-ABL tyrosine kinase inhibitors (TKIs).
The study was planned to recruit a total of 120 patients in three stages; however, enrollment was ended after 29 of the planned 25 patients were enrolled in Stage 1. This study was terminated prior to initiating enrollment of Stage 2 because of a lack of evidence of activity in Stage 1 in the targeted patient population with the study dosing schedule. All 29 treated patients discontinued study treatment, and were included in the Full Analysis Set, and in the Safety population. Twenty-two patients (75.9%) had at least one post-dose PK measurement and were included in the PK population.

Centers

19 centers: Belgium (3), Germany (2), Spain (1), France (2), Italy (2), Netherlands (1), Poland (1), Russia (2), USA (5)

Publication

None

Objectives

Primary objective(s)

- To assess the major (complete/partial) cytogenetic response (MCyR) rate when treated with oral panobinostat in patients with chronic phase chronic myelogenous leukemia (CML-CP) whose disease was resistant following treatment with at least two BCR-ABL tyrosine kinase inhibitors (TKIs).?

Secondary objective(s)

- Determine the duration of major cytogenetic response (MCyR)
- Determine complete hematologic response (CHR) rate
- Determine the complete cytogenetic response (CCyR) and overall (complete/partial/minor/minimal) cytogenetic response (OCyR) rates
- Determine the major (MMR) and complete (CMR) molecular response rates
- Characterize BCR-ABL mutations of patients at study entry and, in responding patients and at the time of disease progression
- Determine progression free survival time
- Characterize the population pharmacokinetics
- Monitor the QTc interval in patients receiving oral panobinostat
- Evaluate the safety and tolerability profile of oral panobinostat

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

Oral capsules of panobinostat 20 mg o.d. three times a week as part of a 4 week (28 day) treatment cycle. Treatment was administered at the same time each morning, and with an 8 oz / 240 ml of water after a fasting period of at least two hours (water was allowed). Patients could continue treatment until they experienced unacceptable toxicity or disease progression.

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

Not applicable

Criteria for Evaluation

Primary variables

Major cytogenic response obtained from bone marrow assessments.

Other Efficacy variables

Peripheral blood samples and the assessment of extramedullary disease were analyzed to determine complete hematological response and molecular response.

Bioanalytics

BCR-ABL mRNA expression (molecular response) was performed by quantitative polymerase chain reaction (qPCR), and mutational analysis was performed by direct sequencing technology.

Safety and tolerability

Monitoring and recording all adverse events (AEs), serious AEs (SAEs), with their severity and relationship to study drug; regular monitoring of hematology, blood chemistry, coagulation tests, and thyroid function tests; regular measurement of vital signs; physical examination including weight and performance status; repeated cardiac assessments (QTc/ECG monitoring, cardiac imaging); and pregnancies.

Statistical Methods

Efficacy analyses, demographics and baseline characteristics, and study drug exposure data were summarized for the Full Analysis Set (FAS), which included all enrolled patients who received at least one dose of study medication. Because of a lack of evidence of MCyR (primary objective), secondary efficacy endpoints were not analyzed.

The PK population, consisting of all patients who had at least one panobinostat PK profile was used for all PK analyses. Pharmacokinetic parameters were expressed either as mean, SD, and CV with any geometric means indicated, or as median and range of values. For biomarkers, a frequency table of BCR-ABL mutation and summary statistics of baseline and lowest post-baseline BCR-ABL transcript are provided.

Safety analyses were summarized for the Safety population, which included all patients who received at least one dose of study medication and who had at least one valid post-baseline assessment.

Study Population: Inclusion/Exclusion Criteria and Demographics

Inclusion criteria:

- Male or female patients, aged = 18 years old, diagnosed with Ph+ CML-CP defined as the presence of < 15% blasts in peripheral blood and in bone marrow, < 30% blasts plus promyelocytes in peripheral blood and in bone marrow, < 20% basophils in the peripheral blood, = 100 x 109/L (= 100,000 /mm3) platelets, and no evidence of extramedullary leukemic involvement with the exception of liver or spleen involvement
- Prior treatment with at least two BCR-ABL TKIs, with demonstrated resistance to the most recent BCR-ABL TKI, including imatinib and another BCR-ABL TKI. Resistance was defined as:
  - Primary hematologic resistance defined as the failure to achieve CHR within 6 months of starting therapy, or the failure to achieve CHR with disease progression (confirmed doubling of the white blood cell (WBC) to a value of > 20,000 mm3 despite receiving the maximum tolerated dose (MTD) of therapy)
  - Acquired hematologic resistance or the loss of CHR defined as confirmed white-cell count of > 20,000 mm3, or a platelet count of = 600,000 mm3, or extramedullary disease, or = 5% myelocytes and metamyelocytes, or appearance of blasts or promyelocytes in the peripheral blood
  - Acquired cytogenetic resistance or loss of CyR, defined as an increase in the absolute percentage points of Ph+ positive cells in metaphase from the best response (i.e., lowest percent Ph+ cells) by = 30 %. If the most recent cytogenetic result was > 70% and = 80% Ph+ metaphases, the patient was considered eligible if stable for = 3 months at that level before progression to 100% Ph+ metaphases
- Patients with a history of intolerance to one BCR-ABL TKI should have a demonstrated resistance to their most recent BCR-ABL TKI.
- Patients with intolerance to two or more BCR-ABL TKIs required a history of resistance to or intolerance of interferon-alpha
- Laboratory criteria:
  - Hematology: absolute neutrophil count (ANC) = 1.5 x 109/L, hemoglobin = 8.0 g/dL
  - Serum chemistry: albumin = 3 g/dL; aspartate aminotransferase (AST/GOT) and alanine aminotransferase (ALT/GPT) = 2.5 x upper limit of normal (ULN) or = 5.0 x ULN if the transaminase elevation is due to leukemic involvement; bilirubin = 1.5 x ULN; creatinine = 1.5 x ULN or 24-hour creatinine clearance = 50 mL/min; potassium, phosphorus, magnesium and total calcium (corrected for serum albumin) or serum ionized calcium = lower limit of normal (LLN), TSH and free T4 (thyroxine) within normal limits.
- Eastern Cooperative Oncology Group (ECOG) performance status = 2.
- Baseline MUGA or ECHO with left ventricular ejection fraction (LVEF) = LLN

Exclusion Criteria

- Prior history of CML-AP or CML-BC
- Impaired cardiac function, uncontrolled hypertension, unresolved diarrhea > National Cancer Institute Common Terminology Criteria (CTC) grade 1, impairment of gastrointestinal (GI) function or GI disease that may significantly alter the absorption of oral panobinostat, active bleeding, diathesis, or any other concurrent severe and/or uncontrolled medical conditions
- History of:
  - sustained ventricular tachycardia, ventricular fibrillation or torsades de pointes

- another primary malignancy within 5 years other than curatively treated cancer *in situ* of the cervix, or basal or squamous cell carcinoma of the skin
- non-compliance to medical regimens or the inability to grant informed consent

- Treatments:
  - Therapeutic doses of sodium warfarin or any other anti-vitamin K drug (low doses for line patency were allowed)
  - Candidate for hematopoietic stem cell transplantation (HSCT)
  - Prior HDACi treatment of CML, concomitant use of drugs with a risk of causing QTc prolongation or torsades de pointes, CYP3A4/5 inhibitors, anti-cancer therapy or radiation therapy, valproic acid (within 5 days prior to study drug treatment or during the study), chemotherapy or major surgery (within 3 weeks), immunotherapy (within 1 week), BCR-ABL TKI = 1 week of first treatment with panobinostat (hydroxyurea, anagrelide or leukaphereses were permitted before the study, and then at the investigators discretion in accordance with Study protocol)
  - Female patients who were pregnant or breast feeding or patients of reproductive potential not willing to use a double method of contraception (including a barrier method) during the study and 3 months after the end of treatment. Women of childbearing potential (WOCBP) required a negative serum pregnancy test within 7 days of the first administration of panobinostat. Male patients whose sexual partners were WOCBP not willing to use a double method of contraception including condom during the study and 3 months after the end of treatment.
  - Positive for human immunodeficiency virus (HIV); baseline testing was not required

Number of Subjects

Patient disposition – n (%) of patients (Full Analysis Set)

		Panobinostat N = 29 n (%)
Enrolled [1] (Treated patients)		29 (100.0)
Discontinued treatment [2]		29 (100.0)
Primary reason for end of treatment	Disease progression	19 (65.5)
	Adverse event(s)	5 (17.2)
	Subject withdrew consent	2 (6.9)
	Administrative problems	1 (3.4)
	New cancer therapy	1 (3.4)
	Protocol deviation	1 (3.4
Discontinued study		17 (58.6)
Primary reason for study discontinuation	Disease progression	11 (37.9)
	Death [3]	3 (10.3)
	New anti-neoplastic therapy	3 (10.3

[1] Treated patients [2] Patient completed End of Treatment CRF page

[3] Includes only patients for whom death was reported as the primary reason for discontinuation of study.

Percentage (%) is calculated using the study drug treatment phase enrolled population as the denominator. Primary reasons for discontinuation of treatment or from study are sorted in descending order of frequency.

Demographic and Background Characteristics

Baseline demographic summary (Full Analysis Set)

Demographic variable		Panobinostat N = 29
Sex – n (%)	Female	9 (31.0)
	Male	20 (69.0)
Age (years)	n	29
	Mean (SD)	53.8 (12.22)
	Median	56.0
	Min - max	31.0, 75.0
Age category (years) – n (%)	< 65	25 (86.2)
	= 65	4 (13.8)
Race – n (%)	Caucasian	26 (89.7)
	Black	2 (6.9)
	Asian	1 (3.4)
Weight (kg)	n	29
	Mean (SD)	78.6 (20.51)
	Median	78.5
	Min - max	45.0 - 137.2
Height (cm)	n	28
	Mean (SD)	171.0 (8.70)
	Median	171.5
	Min - max	154.0 - 183.0

SD = standard deviation, Min – max = range of minimum to maximum value

Summary of panobinostat PK parameters following the Day 1 dose (PK population)

Statistics	T_{max} (hr)	C_{max} (ng/mL)	AUC_{0-24} (ng*hr/ml)	C_{last} (ng/mL)	T_{last} (hr)
n	16	16	12	19	19
mean (SD)		9.1 (4.01)	96.0 (41.37)	1.8 (2.02)	24.7 (16.19)
CV% mean		44.1	43.1	112.6	65.6
median	1.5	8.1	81.5	0.9	23.8
min - max	0.2 - 3.6	2.8 - 19.8	41.0 - 174.0	0.5 - 7.8	3.2 - 48.0

SD = standard deviation

CV = Coefficient of variation

min – max = range of minimum to maximum

Safety Results

Adverse events, regardless of study drug relationship, by primary system organ class and preferred term (Preferred term occurring in at least 10% of the population) (Safety population)

	Panobinostat N = 29 n (%)	
Primary system organ class Preferred term	**All grades**	**Grade 3/4**
Any primary system organ class	28 (96.6)	14 (48.3)
Blood and lymphatic system disorders	13 (44.8)	9 (31.0)
Thrombocytopenia	7 (24.1)	3 (10.3)
Anemia	6 (20.7)	4 (13.8)
Neutropenia	3 (10.3)	3 (10.3)
Cardiac disorders	3 (10.3)	1 (3.4)
Gastrointestinal disorders	17 (58.6)	1 (3.4)
Nausea	10 (34.5)	1 (3.4)
Diarrhea	7 (24.1)	0 (0.0)
Vomiting	5 (17.2)	0 (0.0)
Constipation	4 (13.8)	0 (0.0)
Dyspepsia	3 (10.3)	0 (0.0)
General disorders and administration site conditions	20 (69.0)	1 (3.4)
Fatigue	8 (27.6)	1 (3.4)
Pyrexia	6 (20.7)	0 (0.0)
Edema peripheral	5 (17.2)	0 (0.0)
Asthenia	3 (10.3)	0 (0.0)
Infections and infestations	9 (31.0)	2 (6.9)
Investigations	10 (34.5)	4 (13.8)
White blood cell count increased	4 (13.8)	2 (6.9)
Metabolism and nutrition disorders	12 (41.4)	2 (6.9)

Anorexia	5 (17.2)	0 (0.0)
Hypertriglyceridemia	3 (10.3)	0 (0.0)
Hyperuricemia	3 (10.3)	0 (0.0)
Musculoskeletal and connective tissue disorders	8 (27.6)	1 (3.4)
Myalgia	4 (13.8)	0 (0.0)
Nervous system disorders	6 (20.7)	0 (0.0)
Headache	3 (10.3)	0 (0.0)
Respiratory, thoracic and mediastinal disorders	6 (20.7)	1 (3.4)
Cough	4 (13.8)	0 (0.0)
Skin and subcutaneous tissue disorders	8 (27.6)	0 (0.0)
Dry skin	3 (10.3)	0 (0.0)
Rash	3 (10.3)	0 (0.0)
Vascular disorders	4 (13.8)	1 (3.4)

Primary system organ classes (PSOCs) are sorted in alphabetical order and preferred terms are sorted in descending frequency, as reported in the all grades column.

A subject with multiple occurrences of an adverse event (AE) is counted once in the AE category.

A subject with multiple AEs within a PSOC is counted once for the PSOC.

Most frequent adverse events (Safety population)

The most frequently reported AEs were nausea (10 patients; 34.5%), fatigue (8 patients; 27.6%), thrombocytopenia, and diarrhea (each preferred term reported in a total of 7 patients; 24.1%)

Deaths, other serious or clinically significant adverse events or discontinuations due to AEs (Safety population)

	Panobinostat N = 29 n (%)
Patients with AE(s) [1]	28 (96.6)
Serious or other significant events	
All deaths [2]	3 (10.3)
Deaths on treatment [3]	0 (0.0)
All SAEs	4 (13.8)
Study drug-related SAE	1 (3.4)
AEs leading to discontinuation [4]	6 (20.7)

AE(s) = adverse events SAEs = Serious adverse events

[1] AEs that occurred on treatment and up to 28 days after the last dose of study drug.

[2] Includes deaths as reported in end of treatment and study evaluation completion, CRF pages.

[3] Includes deaths up to 28 days after the last dose of study drug.

[4] As reported in AE CRF page

PID 0602/00003 had SAEs of pneumonia, febrile neutropenia, sepsis, multi-organ failure, and acute cardiac failure which occurred during the follow-up period, and are not included in this table.

Other Relevant Findings

In accordance with study design, this study was terminated because of a lack of evidence of activity in Stage 1 in the targeted patient population with the trial dosing schedule. The decision was made in accordance with the study design specified in the protocol.

Date of Clinical Trial Report

16 Mar 2009

Date Inclusion on Novartis Clinical Trial Results Database

5 Oct 2009

Date of Latest Update