Sponsor

Novartis Pharma AG

Generic Drug Name

Panobinostat

Therapeutic Area of Trial

Chronic Myeloid Leukemia

Approved Indication

Investigational

Study Number

LBH589B2211

Title

A phase II, multicentre study of oral LBH589 in patients with accelerated phase or blast phase (blast crisis) 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

23 Feb 2007 to 26 Aug 2008

Study Design/Methodology

A phase II, single arm, three-stage, open-label, multi-center, international study consisting of two periods: screening period (1-15 days duration for the assessment of patient eligibility), and treatment period. No comparator drug or placebo was utilized since it would have been unethical to include a placebo control arm in the study. Also an active control arm would have been inutile given the resistance of the patients to previous treatment with BCR-ABL TKIs. Panobinostat 20 mg was administered orally once a day, three times a week as part of a 4 week (28 day) treatment cycle.

Centres

20 centers in 7 countries: Canada (2), Germany (1), France (4), Italy (5), Poland (2), Russia (1), USA (5)

Publication

None

Objectives

Primary objective

- The primary objective was to assess the hematologic response (which includes complete hematologic response (CHR), no evidence of leukemia (NEL) and return to chronic phase (RTC)) rate in patients with accelerated phase (AP) or blast crisis (BC) CML whose disease was resistant following treatment with at least two BCR-ABL Tyrosine kinase inhibitors when treated with oral panobinostat.

Secondary objectives

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

Test Product, Dose, and Mode of Administration

Panobinostat 20 mg was administered orally 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).

Reference Product, Dose, and Mode of Administration

Not applicable

Criteria for Evaluation

Primary variables

- Complete hematologic response (CHR) and no evidence of leukemia (NEL) and of the return to chronic phase.
- Hematologic responses were to be confirmed after 4 weeks.

Secondary variables

- Safety assessments consisting of monitoring and recording all AEs and serious adverse events (SAEs) with respect to their relationship to study drug.
- Regular monitoring of hematology, blood chemistry, coagulation tests, thyroid function tests and regular monitoring of vital signs.

Safety and tolerability

- Discussed under secondary variable.

Pharmacology

- For pharmacokinetic analysis blood samples were collected from patients on day 1, 3, 8 and 9 of the treatment cycle.

Other

- BCR-ABL mRNA expression (molecular response) by qPCR(quantitative polymerase chain reaction).
- Mutational analysis by directing sequencing.

Statistical Methods

Efficacy analyses, demographics and baseline characteristics were summarized for the Full Analysis Set (FAS), which included all enrolled patients who received at least one dose of study medication. 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. Quantitative data were summarized by appropriate descriptive statistics such as mean, standard deviation (SD), median, minimum, and maximum. The Pharmacokinetic (PK) population included all patients with at least one PK collection of panobinostat, and was use 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.

Study Population:

Inclusion Criteria

- Male and female patients = 18 years of age, providing written informed consent prior to participation with a diagnosis of Ph+ CML either:

Accelerated phase defined as the presence of at least one of the following:

  - = 15% but < 30% blasts in peripheral blood or in bone marrow
  - = 30% blasts plus promyelocytes in peripheral blood or bone marrow (providing that < 30% blasts present in bone marrow)
  - = 20% basophils in the peripheral blood
  - Thrombocytopenia <100 X 10^9/L unrelated to sole therapy

Blast phase (blast crisis) defined as the presence of at least one of the following:

  - = 30% blasts in the blood, or in bone marrow, or both
  - Extramedullary infiltrates of leukemic cells other than liver or spleen involvement

- Prior treatment with at least two BCR-ABL TKIs, including imatinib and another BCRABL TKIs. Resistance to a BCR-ABL TKI for this study was defined as:
  - Progression from chronic phase to either accelerated phase or blast crisis
  - Progression from accelerated phase to blast crisis
  - No hematologic response (defined as not achieving CHR, NEL or RTC) within 3 months of starting therapy
  - Increasing blast counts in peripheral blood of increasing marrow leukemic infiltrate (MLI, the percent marrow blasts multiplied by marrow cellularity)
- History of intolerance to one BCR-ABL TKI (defined as discontinuation of treatment due to either grade 3 or 4 adverse events related to treatment) if demonstrating a resistance to the most recent BCR-ABL TKI. Intolerance was defined as discontinuation of treatment due to either grade 3 or 4 treatment-related AE or a grade 2 treatment-related AE persisting for = one month or recurring more than three times despite dose reduction
- Laboratory criteria:
  - Serum albumin = 3g/dL
  - AST/SGOT and ALT/SGPT = 2.5 x upper limit of normal (ULN) or = 5.0 x ULN if the transaminase elevation is due to leukemic involvement
  - Serum bilirubin = 1.5 x ULN
  - Serum creatinine = 1.5 x ULN or 24-hour creatinine clearance = 50 ml/min
  - Serum potassium, phosphorus, magnesium, and serum total calcium (corrected for serum albumin) or serum ionized calcium = LLN. Supplementation was allowed to correct potassium, calcium, and magnesium values prior to enrollment.
  - TSH and free T4 within normal limits (WNL) (patients may have been on thyroid hormone replacement)
- Baseline MUGA (multiple uptake gated acquisition scan) or ECHO with LVEF = the institutional LLN.
- Eastern Cooperative Oncology Group (ECOG) Performance Status of = 2.

Exclusion Criteria

- Impaired cardiac function, uncontrolled hypertension, unresolved diarrhea > 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 CIS of the cervix, or basal or squamous cell carcinoma of the skin, or
  - 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 HDAC (histone deacetylase) inhibitor 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 (within 3 weeks), immunotherapy (within 1 week), BCR-ABL kinase inhibitor = 1 week of first treatment with panobinostat
- Females who were pregnant, breast feeding or of reproductive potential: For inclusion, women of childbearing potential (WOCBP) required a negative serum pregnancy test in the 7 days prior to the first administration of oral panobinostat and use of an effective method of birth control. Male patients whose sexual partners were WOCBP not using an effective birth control were excluded.
- International normalized ratio (INR) or partial thromboplastin time (PTT) > 1.5 x I
- Known positivity for human immunodeficiency virus (HIV) or hepatitis C; baseline testing for HIV and hepatitis C was not required.

Demographic and Background Characteristics

Variable	
N (ITT)	27
Females : males	13: 14
Mean age, years (SD)	56.6 ± 12.38
Mean weight, kg (SD)	72.0 ± 14.76
Mean height, cm (SD)	170.2 (10.31)
Race	
White n(%)	22 (81.5)
Black n (%)	4 (14.8)
Other n (%)	1 (3.7)

Number of Subjects

Patient disposition is provided as discontinuation of study treatment, and as discontinuation from the study

	N (%)
Planned	25

Enrolled * (treated patients)	27 (100)
Intent-to-treat population (ITT) n (%)	27 (100)
Discontinued**	27 (100)
Primary reason for end of treatment	
Abnormal laboratory value (s)	2 (7.4)
Adverse event(s)	5 (18.5)
Disease progression	19 (70.4)
New cancer therapy	1 (3.7)
Discontinued study	18 (66.7%)
Primary reason for end of study	
Death***	5 (18.5)
Disease progression	12 (44.4)
New cancer therapy	1 (3.7)

* Treated patients

**Patients completed end of treatment CRF page

*** Includes only patients for whom death was reported as the primary reason for discontinuation

The median treatment duration was 17 days and ranged from 1-59 days. The short duration of treatment is attributed to a high early treatment discontinuation rate. The leading cause of treatment discontinuation was disease progression (19 patients; 70.4%). This occurred despite some allowance of overlapping cytotoxic therapy by oral hydroxyurea.

Primary Objective Result

None of the 27 enrolled patients met the criteria for confirmed hematologic response, following-treatment with oral panobinostat with the trial dosing schedule, as defined in the protocol (CHR, NEL, or RTC) at the end of study. The biologic activity observed in some, however, did not meet the 4 weeks duration required by protocol. Therefore, this trial was terminated prior to initiating the enrollement of Stages 2 or 3 due to lack of evidence of activity at Stage 1 with the trial dosing schedule. Also because of a lack of evidence of hematologic response (primary objective), secondary efficacy endpoints were not analyzed. According to the study protocol, this trial was terminated prior to initiating the enrollment of Stages 2 or 3 because of a lack of evidence of activity at Stage 1 in the targeted patient population with the trial dosing schedule.

Secondary Objective 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)

	N=27, n(%)	
System organ class, preferred term	All grades	Grade 3/4
Any primary system organ class	27 (100)	22 (81.5)
Blood and lymphatic system disorders- total	19 (70.4)	19 (70.4)
Thrombocytopenia	12 (44.4)	12 (44.4)
Anemia	10 (37.0)	9 (33.3)
Leukocytosis	4 (14.8)	3 (11.1)

Neutopenia	3 (11.1)	3 (11.1)
Cardiac disorders- total	4 (14.8)	1 (3.7)
Tachycardia	3 (11.1)	1 (3.7)
Gastrointestinal disorders- total	14 (51.9)	1 (3.7)
Diarrhea	10 (37.0)	0 (0.0)
Nausea	6 (22.2)	0 (0.0)
Abdominal pain	4 (14.8)	1 (3.7)
Vomiting	4 (14.8)	1 (3.7)
Abdominal pain upper	3 (11.1)	0 (0.0)
Stomatitis	3 (11.1)	0 (0.0)
General disorders and administration site conditions- total	19 (70.4)	6 (22.2)
Pyrexia	11 (40.7)	2 (7.4)
Asthenia	4 (14.8)	1 (3.7)
Edema peripheral	4 (14.8)	0 (0.0)
Fatigue	3 (11.1)	0 (0.0)
Pain	3 (11.1)	0 (0.0)
Infections and infestations- total	8 (29.6)	4 (14.8)
Pneumonia	3 (11.1)	1 (3.7)
Injury, poisoning and procedural complications-total	3 (11.1)	2 (7.4)
Investigations-total	9 (33.3)	6 (29.6)
White blood cell count increased	3 (11.1)	2 (7.4)
Metabolism and nutrition disorders-total	16 (59.3)	8 (29.6)
Hyperuricemia	5 (18.5)	1 (3.7)
Hypokalemia	5 (16.5)	3 (11.1)
Hyperkalemia	3 (11.1)	2 (7.4)
Hyponatremia	3 (11.1)	2 (7.4)
Musculoskeletal and connective disorders-total	6 (29.6)	2 (7.4)
Back Pain	3 (11.1)	0 (0.0)
Pain in extremity	3 (11.1)	2 (7.4)
Nervous system disorder-total	8 (29.6)	5 (18.5)
Renal and urinary disorders-total	5 (18.5)	1 (3.7)
Renal failure	3 (11.1)	1 (3.7)
Respiratory, thoracic and mediastinal disorders	9 (33.3)	5 (18.5)
Dyspnea	5 (18.5)	2 (7.4)
Skin and subcutaneous disorders	4 (14.8)	0 (0.0)
Vascular disorders	5 (18.5)	1 (3.7)

Adverse events related to study drug, by primary system organ class

	N (%)
Randomized patients	27
Patients with drug-related AE	17 (62.9)
Drug-related AEs by primary system organ class	
Gastrointestinal disorders	10 (37.0)

Blood and lymphatic system disorders	7 (25.9)
General disorders and administration site conditions	7 (25.9)
Metabolism and nutrition disorders	4 (14.8)
Investigations	1 (3.7)
Infections and infestations	1 (3.7)
Musculoskeletal and connective tissue disorder	1 (3.7)
Nervous system disorders	1 (3.7)
Renal and urinary disorders	1 (3.7)

Deaths, other serious or AEs related to discontinuation

	N =27, n(%)
Patients with AEs[1]	27 (100)
Serious or other significant events	
All deaths[2]	16 (59.3)
Deaths on treatment[3]	6 (22.2)
All SAEs	13 (48.1)
Study-drug related SAE	3 (11.1)
AEs leading to discontinuation	8 (29.6)

[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, study evaluation completion, and survival eCRF pages.
[3] Deaths upto to 28 days after the last dose of study drug

Other Relevant Findings

Pharmacokinetic parameters

Day 1

Statistics	T_{max} (hr)	C_{max} (ng/mL)	AUC_{0-24} (ng*hr/ml)
n	16	16	
Mean (SD)		13.5 (7)	139 (61)
CV %		51.7	44
Median	1.5	12.1	114
Day 8			
n	15	15	12
Mean (SD)		20.9 (15)	148 (69)
CV %		72.1	47
Median	1.5	17.8	138

BCR-ABL transcript

No reduction in mean BCR-ABL control gene transcript over time was observed.

Patients with notable QTcF interval values

ECG QTcF parameter	Panobinostat N = 27 n (%)
Maximum post-baseline QTcF value	
Number of patients with at least one post-baseline assessment:	27 (100.0)
>480 ms - = 500 ms	1 (3.7)
>500 ms	0 (0.0)
Maximum QTcF increase from baseline [1]	
Number of patients with at least one baseline and one post baseline assessment	26 (96.3)
>30 ms - = 60 ms	6 (23.1)
>60 ms	0 (0.0)

[1] As compared to the baseline value. Baseline is defined as the average of all pre-treatment ECGs on Day 1 visit. Percentage is based upon the evaluable patients.

However no clinically significant laboratory or ECG abnormalities were reported in the study.

Date of Clinical Trial Report

7 Jan 2009

Date Inclusion on Novartis Clinical Trial Results Database

5 Oct 2009

Date of Latest Update