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Sponsor Novartis
Generic Drug Name LBH589
Therapeutic Area of Trial Multiple myeloma
Approved Indication “Investigational”
Protocol Number CLBH589B2203
Title A Phase II study of oral LBH589 in adult patients with multiple myeloma who have received at least two prior lines of therapy and whose disease is refractory to the most recent line of therapy.
Phase of Development Phase II
Study Start/End Dates 16 Apr 2007 to 25 Dec 2009
Study Design/Methodology This was a phase II, single-arm, three-stage, open-label, multicenter, international study of oral panobinostat in patients with multiple myeloma who had received at least two prior lines of therapy (which per initial protocol was to have included bortezomib or lenalidomide) and whose disease was refractory to and progressing under the most recent line of therapy. The patients in the study were a stringently defined refractory population with a high level of unmet medical need. Panobinostat was administered orally, 20mg once-a-day thrice weekly every week. Treatment was to continue until disease progression. Dose modifications (reductions and interruptions) due to toxicity and intolerability were allowed. Patients were to be enrolled in 3 stages to monitor safety and clinical efficacy before exposure of additional patients to study drug. The protocol was amended once (Amendment 1) principally to a) reduce the number of patients required to be enrolled to stage 1 and stage 2 to limit patients’ exposure to panobinostat if results indicated a low level of efficacy. And b) to further narrow prior therapy, revised as bortezomib and at least one of the following: lenalidomide or thalidomide. If 3 or more responders were observed among the 25 patients first enrolled (stage 1) then 32 patients would be enrolled in stage 2. If 12 or more responders were observed among 57 patients in stages 1 and 2 combined, then 87 patients would be enrolled in stage 3. This trial was terminated prior to initiating the enrollment of stages 2 or 3 due to insufficient efficacy. The efficacy threshold for moving from stage 1 to stage 2 of the study (three patients with PR or CR among the first 25 eligible patients in the study out of 38 enrolled), was not met in the targeted patient population, using single agent 20 mg panobinostat oral dosing TIW schedule .

Centers

Multicenter: 27 centers in 6 countries:

- Australia:1
- Canada: 4 sites,
- Germany: 2 sites,
- Spain: 2 sites,
- Italy: 7 sites,
- USA: 11 sites.

Test Product, Dose, and Mode of Administration

Panobinostat 20mg was administered orally once daily, three times a week on days: 1, 3 & 5, then 8, 10 & 12, then 15, 17 & 19 of each cycle), as part of a 3-week (21 days) treatment cycle.

All patients received the same treatment regimen. Panobinostat was supplied by Novartis as 5-mg or 20-mg hard gelatin capsules.

Study Population: Inclusion/Exclusion Criteria and Demographics

Inclusion criteria

1. Adults ≥ 18 years old
2. Subjects must have signed the consent form before undergoing any study specific screening procedures and before participation in this study. The subject must be fully informed by the investigator of the nature and potential risks of participation in this study.
3. Patients must have had a diagnosis of symptomatic multiple myeloma (from IMWG see (Kyle et al,2003) meeting all three of the following criteria:
   - Monoclonal immunoglobulin (spike on electrophoresis, or band on immunofixation) on serum or on 24 hour urine.
   - Bone marrow (clonal) plasma cells or plasmacytoma
   - Related organ or tissue impairment (anemia, hypercalcemia, lytic bone lesions, renal insufficiency, hyperviscosity or recurrent infections) (The Kyle et al 2003 definition of symptomatic Myeloma has been adapted based on the new exclusion criteria defined in protocol amendment 1)
4. Subjects must have received at least two prior lines of therapy and be refractory to the most recent line of therapy according to the following definitions:

   Refractory to most recent line of therapy

   Defined by disease progression during treatment or within 60 – 100 days after the completion of the most recent line of therapy. This includes the development of disease progression during maintenance or consolidation therapy with high dose glucocorticoids, or any other specific MM therapy Sixty days is counted from the point in time when the first response assessment is performed after completion of the last line of therapy. At a maximum, disease progression should be documented within 100 days after the last day of the last dose of any anti-MM therapy, including if last regimen of the most recent line of therapy was ASCT**.** Stable disease patients also part of the IMWG definition are not eligible for this trial.

   At study screening, PD will be assessed by comparing screening values or symptoms in reference to the baseline (values or symptoms) of their last line of therapy. Should a patient have experienced an initial response on their last line of therapy, PD should be assessed in reference to the lowest values of the initial confirmed response (MR/PR/CR).

Disease progression is defined by having one or more of the following:

- >25% increase in the level of serum monoclonal paraprotein, which must also be an absolute increase of at least 5 g/L and confirmed on a repeat investigation.
- >25% increase in 24-hour urinary light chain excretion, which must also be an absolute increase of at least 200 mg/24 h and confirmed on a repeat investigation.
- >25% increase in plasma cells in a bone marrow aspirate or on bone marrow biopsy, which must also be an absolute increase of at least 10%
- Definite increase in the size of existing lytic bone lesions or soft tissue plasmacytomas.
- Development of new bone lesions or soft tissue plasmacytomas (not including compression fracture).
- Development of hypercalcemia (corrected serum calcium > 11.5 mg/dL or 2.8 mmol/L not attributable to any other cause).

5. Subjects must have previously been treated with bortezomib and at least one of the following: lenalidomide or thalidomide
6. ECOG PS ≤ 2
7. Patients must have the following hematological laboratory values:
   - ANC ≥ 1.5 x 109/L (or ≥1.0 x 109/L if the neutropenia is clinically related to progressive myeloma with bone marrow infiltration of > 50% involvement
   - Hemoglobin ≥ 8.0 g/dl
   - Platelets ≥ 75.0 x 109/L (or ≥ 50.0 x 109/L x if the thrombocytopenia is clinically related to progressive myeloma with bone marrow infiltration > 50% involvement
8. Patients must have the following renal function as shown by :
   - Calculated CrCL > 30ml/min (Cockcroft and Gault formula)
9. Patients must have adequate liver function as shown by:
   - AST and ALT ≤ 2.5 x ULN
   - Serum bilirubin ≤ 1.5 x ULN
   - Albumin ≥ 2.5 g/dl
10. Patients must have the following non-hematological laboratory values:
    - Serum potassium ≥ LLN,
    - Total serum calcium [corrected for serum albumin] or ionized calcium ≥LLN,
    - Serum magnesium ≥ LLN
    - Serum phosphorus ≥ LLN
    - Normal thyroid function (TSH and free T4) (hypothyroidism correctable with supplements is allowed)
11. Baseline MUGA or ECHO must demonstrate LVEF ≥ the lower limit of the institutional normal
12. Patients must be willing and able to undergo bone marrow aspirates as per protocol, with/without bone marrow biopsy according to their center's practice. The bone marrow aspirate /biopsy must be adequate to allow for comparison for the later efficacy response assessments.
13. Patients must have an M component at baseline above a minimum threshold of: 1g/dl (10g/L) for serum M component, or 200mg/24h urine M component.

Exclusion criteria

1. Prior therapy with an HDAC inhibitor for the treatment of MM
2. Patients with non-secretory MM
3. Patients who have received allogenic stem cell transplantation < 12 months prior to study

4. Patients who have had prior allogenic stem cell transplantation and show evidence of active graft-versus-host disease that requires immunosuppressive therapy
5. Patients with amyloidosis
6. Patients with peripheral neuropathy > grade 2
7. Impaired cardiac function or clinically significant cardiac diseases, including any one of the following:
   - Patients with congenital long QT syndrome
   - History or presence of sustained ventricular tachyarrhythmia . (Patients with a history of atrial arrhythmia are eligible but should be discussed with the Sponsor prior to enrollment)
   - Any history of ventricular fibrillation or torsade de pointes
   - Bradycardia defined as HR< 50 bpm. Patients with pacemakers are eligible if HR ≥ 50 bpm.
   - Screening ECG with a QTc > 450 msec
   - Right bundle branch block + left anterior hemi-block (bi-fascicular block)
   - Patients with myocardial infarction or unstable angina ≤ 6 months prior to starting study drug
8. Other clinically significant heart disease (e.g., CHF NY Heart Association class III or IV, uncontrolled hypertension, or history of poor compliance with an antihypertensive regimen)
9. Impairment of GI function or GI disease that may significantly alter the absorption of LBH589
10. Patients with unresolved diarrhea > CTCAE grade 1.
11. Other concurrent severe and/or uncontrolled medical conditions that could cause unacceptable safety risks or compromise compliance with the protocol
12. Patients using medications that have a relative risk of prolonging the QT interval or inducing torsades de pointes if the medications cannot be discontinued or switched to a different medication prior to starting study drug
13. Concomitant use of CYP3A4 inhibitors
14. Patients with an active bleeding diathesis or on any treatment with therapeutic doses of sodium warfarin (Coumadin®) or any other anti-vitamin K drug. Low doses of Coumadin® (e.g., ≤ 2 mg/day), or low doses of any other anti-vitamin K drug, for line patency is allowable
15. Patients who have received chemotherapy, radiation therapy or any investigational drugs, bortezomib or other immunomodulatory therapy (e.g., thalidomide, lenalidomide) or immunotherapy ≤ 3 weeks prior to starting study drug or who have not recovered from side effects of such therapy
16. Patients who have received high-dose corticosteroids as the only component of their most recent line of therapy
17. Patients who have received steroids (e.g., dexamethasone) ≤ 2 weeks prior to starting study treatment or who have not recovered from side effects of such therapy. Concomitant therapy medications that include corticosteroids are allowed if subjects receive < 20 mg of prednisone or equivalent as indicated for other medical conditions (and not as maintenance or an anticancer therapy for MM), or up to 100 mg of hydrocortisone as premedication for administration of certain medications or blood products, while enrolled in this study.
18. Patients whose clinical condition would need valproic acid therapy during study or ≤ 5 days prior to starting drug
19. Patients who have undergone major surgery ≤ 4 weeks prior to starting study drug or who have not recovered from side effects of such therapy
20. Women who are pregnant or breast feeding or women of childbearing potential (WOCBP)not willing to use a double method of contraception during the study and for 3 months after treatment. One of these methods of contraception must be a barrier method. WOCBP are defined as women who have not undergone a hysterectomy or who have not been naturally postmenopausal for at least 12 consecutive months (i.e., who has had menses any time in the preceding 12 consecutive months).

Women of childbearing potential must have a negative serum pregnancy test within 7 days of the first administration of oral LBH589

21. Male patients whose sexual partners are WOCBP not using a double method of contraception during the study and for 3 months after treatment. One of these methods of contraception must be a condom
22. Patients with a current second malignancy or a prior malignancy within the last 5 years except adequately treated basal cell or squamous cell skin cancer or in situ cervical cancer
23. Patients with any significant history of non compliance to medical regimens or unwilling or unable to comply with the protocol or unable to grant reliable informed consent.

Participant flow

Patient disposition as of final database lock	**Panobinostat N = 38 n (%)**
Enrolled[1] (Treated patients)	38 (100.0)
Discontinued treatment[2]	38 (100.0)
Primary reason for end of treatment	
Disease progression	28 (73.7)
Adverse event(s)	5 (13.2)
Abnormal laboratory value(s)	2 (5.3)
Subject withdrew consent	2 (5.3)
Death[3]	1 (2.6)
Discontinued study	14 (36.8)
Primary reason for end of study	
Death[3]	7 (18.4)
Disease progression	7 (18.4)

[1] Treated patients
[2] Patients with a completed End-of-Treatment electronic case report form (eCRF) page.
[3] Includes only those patients for whom death was reported as the primary reason for discontinuation of study.

Primary reasons for discontinuation of treatment or from study are sorted in descending order of frequency.

Baseline Characteristics

Demographic Variable	Panobinostat N=38
Sex	
Female	14 (36.8%)
Male	24 (63.2%)
Age (Years)	
n	38
Mean (SD)	60 (6.58)
Median	61
Minimum, maximum	43, 72
Age category (Years)	
< 65	26(68.4%)
≥ 65	12(31.6%)
Race	
Black	5 (13.2%)
Caucasian	31 (81.6%)
Other	1 (2.6%)
Pacific islander	1 (2.6%)
Weight (kg)	
n	37
Mean	79.8
SD	16.32
Median	80.3
Minimum	51.0
Maximum	120.9
Height (cm)	
n	36
Mean	170.6
SD	10.12
Median	172.5
Minimum	150.0
Maximum	188.0

Disease characteristics

Disease characteristics	Panobinostat N=38
Time since first diagnosis of MM to the start of treatment	
≥ 6 months - < 1 year	1(2.6%)
≥ 1 year - < 2 years	3 (7.9%)
≥ 2 years - < 5 years	14 (36.8%)
≥ 5 years	20(52.6%)

Time since refractory to the last line of therapy to the start of treatment[a]	
< 2 months	29(76.3%)
≥ 2 months - < 3 months	1(2.6%)
≥ 3 months - < 6 months	3(7.9%)
Prior lines of therapy with	
Bortezomib, lenalidomide and thalidomide	24(63.2%)
Bortezomib, lenalidomide only	1(2.6%)
Bortezomib, thalidomide only	6(15.8%)
Lenalidomide, thalidomide only	3(7.9%)
Bortezomib only	2(5.3%)
Lenalidomide only	1(2.6%)
Thalidomide only[a]	1(2.6%)
Number of prior lines of therapies - Medications	
1	1(2.6%)
2-4	14(36.8%)
5-7	18(47.4%)
8-10	4(10.5%)
> 10	1 (2.6%)
Performance status (ECOG)	
0	9(23.7%)
1	26(68.4%)
2	3(7.9%)

[a] N=33 (excluding non refractory patients),

[b] There were no patients who received thalidomide alone. A patient received lenalidomide, but lenalidomide was incorrectly coded and is not included in the table for this patient.

Safety Results

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

	Panobinostat N=38	
Primary system organ class Preferred term	**All grades n (%)**	**Grade 3/4 n (%)**
Any primary system organ class	**38(100.0)**	**30(78.9)**
Blood and lymphatic system disorders	29(76.3)	23(60.5)
Thrombocytopenia	15(39.5)	10(26.3)
Anemia	13(34.2)	7(18.4)
Neutropenia	13(34.2)	12(31.6)
Eye disorders	4(10.5)	0(0.00)
Gastrointestinal disorders	31(81.6)	4(10.5)
Nausea	21(55.3)	1(2.6)
Diarrhea	16(42.1)	1(2.6)
Vomiting	14(36.8)	1(2.6)
Constipation	5(13.2)	0(0.00)
Abdominal pain upper	4(10.5)	0(0.00)
General disorders and administration site conditions	25(65.8)	4(10.5)
Fatigue	18(47.4)	2(5.3)
Pyrexia	10(26.3)	0(0.00)
Edema peripheral	8(21.1)	1(2.6)
Infections and infestations	16(42.1)	7(18.4)
Pneumonia	5(13.2)	2(5.3)
Upper respiratory tract infection	4(10.5)	1(2.6)
Investigations	16(42.1)	4(10.5)
Blood creatinine increased	9(23.7)	1(2.6)
Weight decreased	4(10.5)	1(2.6)
Metabolism and nutrition disorders	18(47.4)	5(13.2)
Anorexia	6(15.8)	0(0.00)
Hypercalcemia	6(15.8)	3(7.9)
Hypokalemia	6(15.8)	3(7.9)
Hypomagnesemia	4(10.5)	0(0.00)
Musculoskeletal and connective tissue disorders	17(44.7)	6(15.8)
Back pain	13(34.2)	3(7.9)
Nervous system disorders	20(52.6)	5(13.2)
Headache	8(21.1)	0(0.00)
Somnolence	5(13.2)	1(2.6)
Dysgeusia	4(10.5)	0(0.00)
Psychiatric disorders	9(23.7)	3(7.9)
Renal and urinary disorders	6(15.8)	2(5.3)

Respiratory, thoracic and mediastinal disorders	18(47.4)	1(2.6)
Dyspnoea	9(23.7)	1(2.6)
Skin and subcutaneous tissue disorders	6(15.8)	0(0.00)

Preferred term in at least 10% of the population. System organ classes 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 AE under one treatment is counted only once in the AE category for that treatment.
A subject with multiple adverse events within a primary system organ class is counted only once in the total row.

Deaths, other serious adverse events, discontinuations due to AE

	Panobinostat N=38 n (%)
Patients with AE(s)[1]	38(100.0%)
Serious or other significant events	
All deaths[2]	7(18.4%)
On treatment deaths[3]	3(7.9%)
All SAE	17(44.7%)
Study-drug-related SAEs	3(7.9%)
AEs Leading to discontinuation[4]	8(21.1%)

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, study evaluation completion, and survival eCRF pages.
[3] Deaths up to 28 days after the last dose of study drug
[4] As reported in AE eCRF page

Pharmacokinetics

Summary statistics of panobinostat PK parameters on Days 1 and 8

Day	Statistics	T_{max} (hr)	C_{max} (ng/mL)	AUC_{0-24} (ng*hr/ml)	Clast (ng/mL)	Tlast (hr)
1	n	27	27	27	27	27
	Mean (SD)		7.6 (5.52)	72.0 (36.10)	0.3 (0.18)	
	CV% mean		72.6	50.1	61.4	
	Geo-mean		6.1	64.7	0.3	
	CV% geo-mean		74.4	49.4	61.3	
	Median	1.7	5.5	68	0.2	47.8
	[Min; Max]	[0.2, 5.2]	[1.4, 21.5]	[23.0, 178.0]	[0.1, 0.9]	[24, 50.2]
8	n	22	22	21	22	22
	Mean (SD)		9.7 (6.51)	81.6 (37.56)	1.1 (1.13)	
	CV% mean		67.2	46	98.6	
	Geo-mean		8	74.2	0.9	
	CV% geo-mean		74.8	47.5	70.2	
	Median	1.2	7.6	74	1	24.3
	[Min; Max]	[0.2; 23.7]	[1.3; 31.3]	[23.0; 172.0]	[0.3; 5.9]	[3.3; 28.0]

Summary statistics of BJB432 PK parameters on Days 1 and 8

Day	Statistics	T_{max} (hr)	C_{max} (ng/mL)	AUC_{0-24} (ng.hr/ml)	Clast (ng/mL)	Tlast (hr)
1	n	27	27	27	27	27
	Mean (SD)		0.9 (0.53)	15.2 (8.39)	0.5 (0.38)	
	CV% mean		57.9	55.2	69.4	
	Geo-mean		0.8	13	0.5	
	CV% geo-mean		62.5	64.4	68.2	
	Median	24	0.8	12	0.4	47.9
	[Min; Max]	[1.7; 47.5]	[0.3; 2.2]	[3.0; 37.0]	[0.1; 1.7]	[24.5; 50.2]
8	n	21	21	13	21	21
	Mean (SD)		1.8 (0.96)	32.5 (17.67)	1.6 (0.93)	
	CV% mean		52.4	54.4	57.8	
	Geo-mean		1.6	28.4	1.4	
	CV% geo-mean		54.7	57.9	59.7	
	Median	22.2	1.7	30	1.5	24.3
	[Min; Max]	[0.8; 26.2]	[0.6; 4.8]	[13.0; 68.0]	[0.5; 4.4]	[3.3; 28.0]

Date of Clinical Trial Report 01 June 2012
Date Inclusion on Novartis Clinical Trial Results Database 5 March 2010
Date of Latest Update 10 July 2012