Sponsor

Novartis

Generic Drug Name

Panobinostat (PAN)

Trial Indication(s)

Myelodysplastic Syndromes (MDS), Chronic Myelomonocytic Leukemia (CMML) or Acute Myeloid Leukemia (AML)

Protocol Number

CLBH589H1101

Protocol Title

A phase Ib, open-label, multi-center, dose-escalation study of oral Panobinostat (LBH589) administered with 5-Azacitidine (Vidaza®) in adult Japanese patients with Myelodysplastic Syndromes (MDS), Chronic Myelomonocytic Leukemia (CMML) or Acute Myeloid Leukemia (AML)

Clinical Trial Phase

Ib

Phase of Drug Development

III

Study Start/End Dates

30-Aug-2012 to 11-May-2014

Study Design/Methodology

This was a single arm, open label, dose-escalation study of PAN in combination with a fixed dose of 5-Azacitidine (5-Aza) in a 28-day cycle in Japanese adult patients with the International Prognostic Scoring System intermediate-2 (IPSS INT-2) or high risk MDS, CMML, or AML not eligible for hematopoietic stem cell transplant (HSCT).

This study was composed of two periods: pharmacokinetics (PK) run-in period and combination treatment period. First, during PK run-in period, a single dose of PAN 20 mg or 30 mg was administered alone. Following the PK run-in period, combination treatment with 5-Aza started (combination treatment period: Cycle 1, Cycle 2, and subsequent cycles).

Centers

7 centers in one country: Japan

Publication

None

Objectives:

Primary objective:

- To confirm the safety and tolerability of oral PAN of two dose levels in combination with a fixed dose of 5-Aza in adult Japanese patients with MDS, CMML or AML.

Key secondary objectives:

- To characterize the PK of PAN administered alone
- To characterize PK of PAN in combination with 5-Aza in the targeted patient populations

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

In PK run-in period, oral PAN of 20 mg or 30 mg was dosed on Day 1. Neither PAN nor 5-Aza was administered on Day 2 and 3.

In combination treatment period (a 28-day cycle), oral PAN of 20 mg or 30 mg was given on Day 3 and 5 in the first week. In the second week, PAN was given three times a week on Day 8, 10 and 12. In the third week, PAN was given once (Day 15). Up to a total of six doses of PAN was given per one cycle. The dose of 5-Aza was fixed at 75 mg/m^2 and was given in a 7-day schedule of administration.

Statistical Methods

The primary objective of this study was to confirm the safety and tolerability of oral PAN of two dose levels in combination with a fixed dose of 5-Aza in adult Japanese patients with MDS, CMML or AML. An adaptive BLRM and dose-escalation criteria including the EWOC principle was used to guide the dose escalation to determine the MTD of PAN in combination with a fixed dose of 5-Aza. The dose limiting toxicity (DLT) was assessed during the PK run-in and first treatment cycle. Each cohort consisted of a minimum of 3 patients fully evaluable for therapy-related toxicities over the first cycle of treatment. Posterior probabilities of the DLT from the model were summarized. Selection of the next dose was based on these probabilities as well as on other safety and laboratory data.

All AEs recorded during the study were summarized. The incidences of treatment-emergent AEs (new or worsening from baseline) were summarized by system organ class (SOC), severity based on the National Cancer Institute's Common Terminology Criteria for Adverse Events (NCI CTCAE version 4.03), type of AE and AE related to the study treatment. SAEs resulting in death and non-fatal SAEs were listed by patient and tabulated by type of AE and initial dose group of PAN.

Plasma PAN levels were collected during PK run-in, Cycle 1 on Days 4, 5, and 8, and were summarized by study day and time point. The individual and mean plasma concentrations were displayed graphically.

Study Population:

Key Inclusion Criteria:

The study population consisted of Japanese patients with the age of ≥ 20 years old who were candidates for treatment with 5-Aza and present with one of the following:

- Intermediate-2 or high-risk MDS according to the IPSS. OR
- AML with multilineage dysplasia and maximum of 30% blasts ((former Refractory anemia with excess blasts in transformation (RAEB-t) according to French-American-British (FAB)) OR
- CMML

Key exclusion Criteria

Patients with relapsed/refractory AML and patients who had received prior treatment with deacetylase inhibitors (DACi) and/or 5-Aza or decitabine were not eligible for this study.

Participant Flow Table

Disposition Reason	PAN 20 mg + 5-Aza N=5 n (%)	PAN 30 mg + 5-Aza N=6 n (%)	All patients N=11 n (%)
Patients treated			
Treatment ongoing	0	0	0
End of treatment	5 (100.0)	6 (100.0)	11 (100.0)
Primary reason for end of treatment			
Adverse event	3 (60.0)	2 (33.3)	5 (45.5)
Withdrawal of consent	0	3 (50.0)	3 (27.3)
Disease progression	2 (40.0)	1 (16.7)	3 (27.3)

Baseline Characteristics

Demographics by treatment cohort (FAS)

Demographics	PAN 20 mg + 5-Aza N=5	PAN 30 mg + 5-Aza N=6	All patients N=11
Age (Years)			
N	5	6	11
Mean	66.6	66.0	66.3
Standard Deviation	8.08	7.59	7.42
Median	71.0	70.0	71.0
Minimum	54	54	54
Maximum	73	72	73
Age category (Years) - n (%)			
<65	2 (40.0)	2 (33.3)	4 (36.4)
>= 65	3 (60.0)	4 (66.7)	7 (63.6)

Demographics	PAN 20 mg + 5-Aza N=5	PAN 30 mg + 5-Aza N=6	All patients N=11
Sex- n (%)			
Female	1 (20.0)	2 (33.3)	3 (27.3)
Male	4 (80.0)	4 (66.7)	8 (72.7)
Race- n (%)			
Asian	5 (100.0)	6 (100.0)	11 (100.0)
Ethnicity- n (%)			
Japanese	5 (100.0)	6 (100.0)	11 (100.0)
Weight (Kg)			
N	5	6	11
Mean	53.46	58.00	55.94
Standard Deviation	13.888	11.186	12.056
Median	49.40	55.70	50.00
Minimum	42.3	48.3	42.3
Maximum	77.7	78.4	78.4
Height (cm)			
N	5	6	11
Mean	162.40	164.43	163.51
Standard Deviation	8.012	9.797	8.649
Median	167.90	163.65	167.10
Minimum	151.3	150.0	150.0
Maximum	168.3	175.1	175.1
Body surface area (m^2)			
N	5	6	11
Mean	1.554	1.631	1.596
Standard Deviation	0.2169	0.1611	0.1828
Median	1.497	1.615	1.523
Minimum	1.34	1.43	1.34
Maximum	1.92	1.89	1.92
ECOG PS- n (%)			
0	4 (80.0)	5 (83.3)	9 (81.8)
1	1 (20.0)	1 (16.7)	2 (18.2)

Disease history by cohort-MDS (FAS)

Variable	PAN 20 mg + 5-Aza N=5 n (%)	PAN 30 mg + 5-Aza N=2 n (%)	All patients N=7 n (%)
Time from initial diagnosis to start of treatment (months)			
N	5	2	7
Mean	1.59	1.08	1.45
Standard Deviation	1.345	0.418	1.138
Median	1.15	1.08	1.15
Minimum	0.0	0.8	0.0

Variable	PAN 20 mg + 5-Aza N=5 n (%)	PAN 30 mg + 5-Aza N=2 n (%)	All patients N=7 n (%)
Maximum	3.2	1.4	3.2
Time category from initial diagnosis to start of treatment, n (%)			
< 1 month	2 (40.0)	1 (50.0)	3 (42.9)
>= 1 month - < 3 months	2 (40.0)	1 (50.0)	3 (42.9)
>= 3 months - < 6 months	1 (20.0)	0	1 (14.3)
WHO classification			
RCMD (Refractory cytopenia with multilineage dysplasia)	0	2 (100.0)	2 (28.6)
RAEB-1	3 (60.0)	0	3 (42.9)
RAEB-2	2 (40.0)	0	2 (28.6)
FAB classification			
Refractory anemia (RA)	0	2 (100.0)	2 (28.6)
RAEB	5 (100.0)	0	5 (71.4)
Cytogenetics at initial diagnosis			
Done	5 (100.0)	2 (100.0)	7 (100.0)
Intermediate			
+8	1 (20.0)	0	1 (14.3)
Single miscellaneous	1 (20.0)	0	1 (14.3)
Double abnormalities	1 (20.0)	0	1 (14.3)
Poor			
Complex (i.e. >=3 abnormalities)	0	2 (100.0)	2 (28.6)
Chromosome 7 abnormalities	2 (40.0)	0	2 (28.6)
Missing/Unknown	3 (60.0)	0	3 (42.9)
IPSS risk category at study enrollment			
Intermediate -2 (combined score 1.5 - 2.0)	4 (80.0)	2 (100.0)	6 (85.7)
High (combined score >= 2.5)	1 (20.0)	0	1 (14.3)
Disease status at study enrollment:			
Previously untreated	5 (100.0)	2 (100.0)	7 (100.0)
Therapy-related MDS			
No	4 (80.0)	0	4 (57.1)
Yes	0	2 (100.0)	2 (28.6)
Missing/Unknown	1 (20.0)	0	1 (14.3)

Disease history by cohort-CMML (FAS)

Variable	PAN 20 mg + 5-Aza N=0 n (%)	PAN 30 mg + 5-Aza N=4 n (%)	All patients N=4 n (%)
Time from initial diagnosis to start of treatment (months)			
N	-	4	4
Mean	-	5.7	5.7
Standard Deviation	-	4.41	4.41
Median	-	6.2	6.2
Minimum	-	0	0
Maximum	-	10	10
Time category from initial diagnosis to start of treatment, n (%)			
< 1 month	-	1 (25.0)	1 (25.0)
>= 1 month - < 3 months	-	0	0
>= 3 months - < 6 months	-	1 (25.0)	1 (25.0)
>= 6 months - < 12 months	-	2 (50.0)	2 (50.0)
WHO classification at internal diagnosis - CMML			
CMML - Myelodysplastic disease	-	1 (25.0)	1 (25.0)
CMML - Myeloproliferative disease	-	3 (75.0)	3 (75.0)
Cytogenetics at initial diagnosis:			
Other chromosomal abnormalities	-	1 (25.0)	1 (25.0)
Missing/Unknown	-	3 (75.0) [1]	3 (75.0)
Other chromosomal abnormalities			
Missing/Unknown	-	4 (100.0) [2]	4 (100.0)
Disease status at study enrollment			
Previously untreated	-	4 (100.0)	4 (100.0)

1 Three patients were judged as no chromosomal abnormality by investigators.
2 One patient was judged as chromosomal abnormality and three patients were judged as no chromosomal abnormality by investigators.

Summary of Efficacy

Primary Outcome Result(s)

Refer to Safety Result section for primary outcome result.

Secondary Outcome Result(s)

Best overall response rates by cohort- MDS (FAS)

	PAN 20 mg + 5-Aza N=5 n (%)	PAN 30 mg + 5-Aza N=2 n (%)	All patients N=7 n (%)
Best overall response			
Complete Remission (CR)	0	1 (50.0)	1 (14.3)
Partial Remission (PR)	0	0	0
Bone Marrow (BM-CR)	0	0	0
Stable disease (SD)	3 (60.0)	1 (50.0)	4 (57.1)
Progressive Disease (PD)	1 (20.0)	0	1 (14.3)
Not Assessed	1 (20.0)	0	1 (14.3)
Clinical response (CR, Bone marrow CR, PR)	0	1 (50.0)	1 (14.3)

Best overall response rates by cohort- CMML (FAS)

	PAN 20 mg + 5-Aza N=0 n (%)	PAN 30 mg + 5-Aza N=4 n (%)	All patients N=4 n (%)
Best overall response			
Complete Remission (CR)	-	0	0
Partial Remission (PR)	-	0	0
Bone Marrow (BM-CR)	-	0	0
Stable disease (SD)	-	4 (100.0)	4 (100.0)
Progressive Disease (PD)	-	0	0
Clinical response (CR, Bone marrow CR, PR)	-	0	0

Summary of Safety

Safety Results

AEs (at least 20% in either group), regardless of relationship to study treatment, by primary SOC, PT and cohort (Safety set)

Primary SOC PT	PAN 20 mg + 5-Aza N=5 n (%)	PAN 30 mg + 5-Aza N=6 n (%)	All patients N=11 n (%)
Any primary SOC	**5 (100.0)**	**6 (100.0)**	**11 (100.0)**
Blood and lymphatic system disorders	**3 (60.0)**	**6 (100.0)**	**9 (81.8)**

Primary SOC PT	PAN 20 mg + 5-Aza N=5 n (%)	PAN 30 mg + 5-Aza N=6 n (%)	All patients N=11 n (%)
Thrombocytopenia	2 (40.0)	6 (100.0)	8 (72.7)
Anaemia	1 (20.0)	5 (83.3)	6 (54.5)
Neutropenia	2 (40.0)	4 (66.7)	6 (54.5)
Leukopenia	0	5 (83.3)	5 (45.5)
Febrile neutropenia	1 (20.0)	3 (50.0)	4 (36.4)
Lymphopenia	1 (20.0)	2 (33.3)	3 (27.3)
Cardiac disorders	**1 (20.0)**	**0**	**1 (9.1)**
Supraventricular tachycardia	1 (20.0)	0	1 (9.1)
Congenital, familial and genetic disorders	**1 (20.0)**	**0**	**1 (9.1)**
Colour blindness	1 (20.0)	0	1 (9.1)
Eye disorders	**1 (20.0)**	**0**	**1 (9.1)**
Conjunctivitis	1 (20.0)	0	1 (9.1)
Gastrointestinal disorders	**4 (80.0)**	**6 (100.0)**	**10 (90.9)**
Constipation	2 (40.0)	4 (66.7)	6 (54.5)
Nausea	2 (40.0)	4 (66.7)	6 (54.5)
Diarrhoea	1 (20.0)	4 (66.7)	5 (45.5)
Gingival bleeding	0	3 (50.0)	3 (27.3)
Stomatitis	1 (20.0)	2 (33.3)	3 (27.3)
Vomiting	2 (40.0)	1 (16.7)	3 (27.3)
Mouth haemorrhage	0	2 (33.3)	2 (18.2)
Proctalgia	1 (20.0)	1 (16.7)	2 (18.2)
General disorders and administration site conditions	**3 (60.0)**	**6 (100.0)**	**9 (81.8)**
Pyrexia	2 (40.0)	4 (66.7)	6 (54.5)
Injection site reaction	1 (20.0)	4 (66.7)	5 (45.5)
Malaise	0	3 (50.0)	3 (27.3)
Fatigue	1 (20.0)	1 (16.7)	2 (18.2)
Oedema peripheral	1 (20.0)	1 (16.7)	2 (18.2)
Immune system disorders	**1 (20.0)**	**0**	**1 (9.1)**
Hypersensitivity	1 (20.0)	0	1 (9.1)
Infections and infestations	**3 (60.0)**	**1 (16.7)**	**4 (36.4)**
Gingivitis	1 (20.0)	1 (16.7)	2 (18.2)
Lung infection	1 (20.0)	0	1 (9.1)
Pneumonia	1 (20.0)	0	1 (9.1)
Upper respiratory tract infection	1 (20.0)	0	1 (9.1)
Investigations	**4 (80.0)**	**5 (83.3)**	**9 (81.8)**
Blood creatinine increased	1 (20.0)	5 (83.3)	6 (54.5)
Blood phosphorus increased	0	3 (50.0)	3 (27.3)
Neutrophil count decreased	2 (40.0)	1 (16.7)	3 (27.3)
Alanine aminotransferase increased	0	2 (33.3)	2 (18.2)
Aspartate aminotransferase increased	1 (20.0)	1 (16.7)	2 (18.2)

Primary SOC PT	PAN 20 mg + 5-Aza N=5 n (%)	PAN 30 mg + 5-Aza N=6 n (%)	All patients N=11 n (%)
Blood urea increased	0	2 (33.3)	2 (18.2)
C-reactive protein increased	0	2 (33.3)	2 (18.2)
Lymphocyte count decreased	1 (20.0)	1 (16.7)	2 (18.2)
Platelet count decreased	2 (40.0)	0	2 (18.2)
Protein total decreased	0	2 (33.3)	2 (18.2)
Blood alkaline phosphatase increased	1 (20.0)	0	1 (9.1)
Gamma-glutamyltransferase increased	1 (20.0)	0	1 (9.1)
Haemoglobin decreased	1 (20.0)	0	1 (9.1)
Weight decreased	1 (20.0)	0	1 (9.1)
White blood cell count decreased	1 (20.0)	0	1 (9.1)
Metabolism and nutrition disorders	**3 (60.0)**	**6 (100.0)**	**9 (81.8)**
Decreased appetite	3 (60.0)	6 (100.0)	9 (81.8)
Hyperuricaemia	0	3 (50.0)	3 (27.3)
Hypoalbuminaemia	1 (20.0)	2 (33.3)	3 (27.3)
Hyperglycaemia	0	2 (33.3)	2 (18.2)
Hyperkalaemia	0	2 (33.3)	2 (18.2)
Hypokalaemia	1 (20.0)	1 (16.7)	2 (18.2)
Dehydration	1 (20.0)	0	1 (9.1)
Hypophosphataemia	1 (20.0)	0	1 (9.1)
Nervous system disorders	**0**	**2 (33.3)**	**2 (18.2)**
Headache	0	2 (33.3)	2 (18.2)
Psychiatric disorders	**2 (40.0)**	**0**	**2 (18.2)**
Insomnia	2 (40.0)	0	2 (18.2)
Respiratory, thoracic and mediastinal disorders	**0**	**2 (33.3)**	**2 (18.2)**
Epistaxis	0	2 (33.3)	2 (18.2)
Skin and subcutaneous tissue disorders	**3 (60.0)**	**4 (66.7)**	**7 (63.6)**
Pruritus	0	3 (50.0)	3 (27.3)
Purpura	2 (40.0)	1 (16.7)	3 (27.3)
Rash	0	3 (50.0)	3 (27.3)
Urticaria	1 (20.0)	2 (33.3)	3 (27.3)
Petechiae	1 (20.0)	0	1 (9.1)

- Primary SOCs are presented alphabetically; PTs are sorted within primary SOC in descending frequency, as reported in the "All patients" column.
- A patient with multiple occurrences of an AE under one treatment is counted only once in the AE category for that treatment.
- A patient with multiple AEs within a primary SOC is counted only once in the total row.

Deaths, serious adverse events, and other significant AEs

	PAN 20 mg + 5-Aza N=5 n (%)	PAN 30 mg + 5-Aza N=6 n (%)	All patients N=11 n (%)

	PAN 20 mg + 5-Aza N=5 n (%)	PAN 30 mg + 5-Aza N=6 n (%)	All patients N=11 n (%)
On-treatment death [1]	**0**	**1 (16.7)**	**1 (9.1)**
Serious adverse events	**2 (40.0)**	**1 (16.7)**	**3 (27.3)**
Other significant AEs			
AEs leading to discontinuation	3 (60.0)	2 (33.3)	5 (45.5)
AEs requiring dose adjustment or interruptions	4 (80.0)	5 (83.3)	9 (81.8)

1 Patients who died within 30 days after last dose of study drug or other deaths reported on end of treatment page.

Other Relevant Findings

Summary of pharmacokinetic parameters of PAN by cohort (Pharmacokinetic analysis set)

Treatment	Statistics	AUC0-48h (ng*h/mL)	AUClast (ng*h/mL)	AUCinf (ng*h/mL)	Cmax (ng/mL)	Tmax (h)	T1/2 (h)	CL/F (L/h)	Vz/F (L)
PAN 20 mg	n	5	5	5	5	5	5	5	5
	Mean (SD)	87.7 (46.17)	87.7 (46.09)	94.4 (51.93)	15.39 (10.738)	N/A	12.4 (3.13)	272.27 (142.156)	4471.1 (1731.57)
	CV% mean	52.63	52.56	54.99	69.761	N/A	25.23	52.212	38.73
	Geo-mean	78.1	78.1	83.1	12.99	N/A	12.1	240.69	4201.1
	CV% geo-mean	58.50	58.43	62.02	69.892	N/A	24.45	62.016	41.69
	Median	70.9	70.9	75.2	10.20	2.000	11.8	265.99	4511.1
	[Min; Max]	[43; 142]	[43; 142]	[45; 153]	[6.6; 33.2]	[0.47; 2.00]	[9; 17]	[130.6; 445.4]	[2424; 7006]
PAN 30 mg	n	6	6	6	6	6	6	6	6
	Mean (SD)	177.2 (71.44)	177.2 (71.39)	190.8 (79.84)	30.78 (12.180)	N/A	13.4 (2.14)	176.85 (59.971)	3304.7 (877.93)
	CV% mean	40.32	40.29	41.83	39.567	N/A	15.99	33.910	26.57
	Geo-mean	167.1	167.1	179.2	28.77	N/A	13.2	167.43	3195.7
	CV% geo-mean	37.67	37.65	39.09	42.476	N/A	15.69	39.086	30.11
	Median	166.2	166.3	175.3	29.65	1.500	12.9	171.36	3373.6
	[Min; Max]	[110; 310]	[110; 310]	[117; 339]	[16.5; 49.3]	[0.90; 2.98]	[11; 17]	[88.4; 256.1]	[1899; 4525]

- n = number of patients with evaluable PK data.
- SD: Standard Deviation
- N/A: Not Applicable
- CV% = coefficient of variation (%) = sd/mean*100
- CV% geo-mean = sqrt (exp (variance for log transformed data)-1)*100

Conclusion:

- The dose level of 20 mg or 30 mg of panobinostat in combination with 5-Azacitidine was considered to be safe and tolerable in Japanese patients with targeted patient population who were candidates for treatment with 5-Azacitidine.
- The combination treatment showed no apparent new or unexpected safety signals and acceptable safety profile in Japanese patients with the targeted patient population. The incidence of reported all Grade adverse events was generally higher in panobinostat 30 mg cohort than in panobinostat 20 mg cohort. Most of the reported Grade 3 or 4 adverse events were hematological events that were also more frequently reported in panobinostat 30 mg cohort.
- Panobinostat exposure increased with ascending doses from 20 mg and 30 mg, and the combination use of 5-Azacitidine did not appear to affect panobinostat plasma concentrations.
- The combination treatment of panobinostat with 5-Azacitidine showed some preliminary anti-leukemic activities in one Japanese patient with the targeted patient population.

Date of Clinical Trial Report

15-Jan-2015

Date of Initial Inclusion on Novartis Clinical Trial Results website

10-Feb-2015

Date of Latest Update

Reason for Update