Sponsor

Novartis

Generic Drug Name

Panobinostat

Therapeutic Area of Trial

Refractory or relapsed acute myeloid leukemia (AML)

Approved Indication

Not applicable.

Protocol Number

CLBH589B2116

Title

A phase Ib, open-label, multi-center dose-finding study of oral panobinostat (LBH589) in combination with Ara-C and mitoxantrone as salvage therapy for refractory or relapsed acute myeloid leukemia (AML)

Study Phase

Phase Ib

Study Start/End Dates

31-Aug-2009 (first patient first visit)

22-Feb-2012 (last patient last visit)

Study Design/Methodology

This was a phase-Ib, multicenter, dose finding study with a core phase (dose escalation and expansion at MTD) to determine the maximum tolerated dose (MTD) of panobinostat administered in combination with the chemotherapy of Ara-C and mitoxantrone in adult patients with first relapse or primary refractory AML. Once the MTD was determined, which was based on at least 9 evaluable patients treated at this dose level, a minimum of 11 additional evaluable patients were to be enrolled into a dose expansion part to further evaluate safety, tolerability and activity of the study treatment.
This trial also included an optional single agent panobinostat part once the patient had achieved a CR, CRi or PR from the combination therapy. This option was only available to patients that were not candidates for other therapeutic approaches.

Centers

The study was performed in 6 centers in 2 countries: Germany (4) and France (2).

Publication

None.

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

Escalating doses of oral panobinostat (starting dose 20 mg; hard gelatin capsules of 5 and 20 mg) in combination with a fixed dose of chemotherapeutic agents (Ara-C and mitoxantrone).

Statistical Methods

An adaptive Bayesian logistic regression model for combination therapy, including the EWOC principle, was used to guide the dose escalation to determine the MTD of panobinostat in combination with a fixed dose of Ara-C and a fixed dose of mitoxantrone. The MTD was assessed during the first treatment cycle. Based on the posterior distribution of all model parameters, the corresponding posterior distributions for probabilities of a DLT were obtained. Once updated, the distribution summarized the probability that the true probability of a DLT for each dose combination was in one of the following categories:

- ≥ 0% to <20% (under-dosing)
- ≥ 20% to <35% (targeted toxicity)
- ≥ 35% to <60% (excessive toxicity)
- ≥ 60% to ≤ 100% (unacceptable toxicity)

Following the principle of escalation with overdose control, the recommended dose combination after each cohort of patients was the one with the highest posterior probability of DLT in the target interval ≥20% to <35% among the doses fulfilling the overdose criteria, i.e., <25% chance of either excessive or unacceptable toxicity. The maximum inter-cohort dose escalation permitted was 100%. For statistical outputs, the categories for excessive and unacceptable toxicity could be pooled. As an exception, the model was re-evaluated if ≥ 25% and ≥ 2 of the evaluable patients in the cohort experienced DLT before completion of enrollment to the cohort. During the dose-escalation phase, the MTD was principally determined by DLT occurring during the first cycle of therapy. Toxicities occurring after the first cycle of treatment, as well as those that could not be clearly dose-limiting, could also be considered. Dose escalation decisions were driven primarily by the DLT rate at the end of Cycle 1. This was assessed at the following time-points during the study:

- After every DLT occurring within the first cycle of treatment.
- After the first 3 evaluable patients in a regimen reach the end of Cycle 1 or documented discontinuation for a DLT during Cycle 1.

The final recommended MTD of panobinostat in combination with a fixed dose of Ara-C and a fixed dose of mitoxantrone was based on considerations of the respective MTD estimated by the Bayesian logistic regression model and on an overall safety assessment, taking into consideration tolerability data from subsequent cycles. Cohorts could be expanded at any dose level below the MTD for further elaboration of safety as required.

Study Population: Inclusion/Exclusion Criteria and Demographics

Patients with cytopathologically confirmed diagnosis of AML according to World Health Organization (WHO) criteria were included with the following key inclusion criteria:

- Relapsed after receiving up to 1 prior induction regimen (first relapse) or patients who are refractory (no CR) to not more than one prior combination chemotherapy induction regimen.
- Age more than 18 years
- Eastern Cooperative Oncology Group (ECOG) performance status ≤ 2

and key exclusion criteria:

- Concurrent therapy with any other investigational agent
- Patients who received cumulative doses (or its equivalent to other anthracyclines) of more than 360 mg/m2 of doxorubicin
- Central nervous system (CNS) involvement
- LVEF below 45%

Participant Flow

Patient disposition by initial dose group of panobinostat – core phase (Full analysis set)

Disposition reason	Panobinostat					Total N = 59 n (%)
	20 mg N = 5 n (%)	30 mg N = 8 n (%)	40 mg N = 10 n (%)	50 mg N = 30 n (%)	60 mg N = 6 n (%)	
Enrolled[1]	5 (100.0)	8 (100.0)	10 (100.0)	30 (100.0)	6 (100.0)	59 (100.0)
Completed (core)study	5 (100.0)	8 (100.0)	10 (100.0)	30 (100.0)	6 (100.0)	59 (100.0)
Treatment (core) ongoing[2]	0	0	0	0	0	0
Discontinued treatment (core)	5 (100.0)	8 (100.0)	10 (100.0)	30 (100.0)	6 (100.0)	59 (100.0)
Primary reason for end of treatment (core)						
Adverse Event(s)	1 (20.0)	1 (12.5)	2 (20.0)	2 (6.7)	2 (33.3)	8 (13.6)
Abnormal laboratory value(s)	0	0	0	0	0	0
Abnormal test procedure result(s)	0	1 (12.5)	0	1 (3.3)	0	2 (3.4)
Subject withdrew consent	0	2 (25.0)	1 (10.0)	0	0	3 (5.1)
Lost to follow-up	0	0	0	1 (3.3)	0	1 (1.7)
Administrative problems	1 (20.0)	1 (12.5)	0	0	0	2 (3.4)
Death[3]	0	1 (12.5)	2 (20.0)	6 (20.0)	1 (16.7)	10 (16.9)
Disease progression	3 (60.0)	0	1 (10.0)	3 (10.0)	0	7 (11.9)
Treatment duration completed as per protocol	0	2 (25.0)	4 (40.0)	17(56.7)	3 (50.0)	26 (44.1)
Protocol deviation	0	0	0	0	0	0
Reason missing	0	0	0	0	0	0
Primary reason for end of (core) study						
Subject withdrew consent	0	2 (25.0)	1 (10.0)	0	0	3 (5.1)
Lost to follow-up	0	0	0	1 (3.3)	0	1 (1.7)
Administrative problems	1 (20.0)	1 (12.5)	0	0	0	2 (3.4)
Death[4]	0	1 (12.5)	2 (20.0)	7 (23.3)	1 (16.7)	11 (18.6)
Disease progression	2 (40.0)	0	1 (10.0)	3 (10.0)	0	6 (10.2)
Protocol deviation	0	0	1 (10.0)	0	0	1 (1.7)
Follow up phase completed as per protocol	1 (20.0)	3 (37.5)	3 (30.0)	19 (63.3)	5(83.3)	31 (52.5)
Reason missing	0	0	0	0	0	0
Entered extension phase of the study	1 (20.0)	1 (12.5)	2 (20.0)	0	0	4 (6.8)

[1] Treated with at least one non-zero dose of any component of study treatment
[2] Patients still on treatment at the time of database lock (26-Oct-2012).
[3] Includes only those patients for whom death was reported as the primary reason for discontinuation of study treatment
[4] Includes only those patients for whom death was reported as the primary reason for study evaluation completion.

Baseline Characteristics

Demographic characteristics by initial dose group of panobinostat – core phase (Full analysis set)

Demographic variable	Panobinostat					Total N=59
	20 mg N=5	30 mg N=8	40 mg N=10	50 mg N=30	60 mg N=6	
Sex - n (%)						
Female	1 (20.0)	2 (25.0)	5 (50.0)	14 (46.7)	4 (66.7)	26 (44.1)
Male	4 (80.0)	6 (75.0)	5 (50.0)	16 (53.3)	2 (33.3)	33 (55.9)
Age (years)						
n	5	8	10	30	6	59
Mean	52.4	53.5	50.9	56.2	66.0	55.6
SD	20.91	13.21	14.98	12.49	5.37	13.54
Median	53.0	52.0	54.0	60.5	66.0	60.0
Minimum	19	35	22	26	60	19
Maximum	72	70	68	76	73	76
Age category - n (%)						
< 65	3 (60.0)	5 (62.5)	8 (80.0)	20 (66.7)	3 (50.0)	39 (66.1)
≥ 65	2 (40.0)	3 (37.5)	2 (20.0)	10 (33.3)	3 (50.0)	20 (33.9)
Race - n (%)						
Caucasian	5 (100.0)	8 (100.0)	9 (90.0)	28 (93.3)	6 (100.0)	56 (94.9)
Black	0	0	1 (10.0)	0	0	1(1.7)
Asian	0	0	0	1(3.3)	0	1(1.7)
Native American	0	0	0	0	0	0
Pacific Islander	0	0	0	0	0	0
Other	0	0	0	1(3.3)	0	1(1.7)
Body weight (kg)						
n	5	8	10	30	6	59
Mean	79.22	79.58	70.32	74.50	63.47	73.76
SD	18.312	18.979	14.597	17.925	6.408	16.863
Median	86.00	78.00	68.95	71.10	62.50	71.20
Minimum	52.0	59.6	51.0	47.5	55.0	47.5
Maximum	97.3	121.0	94.5	123.0	73.8	123.0
Body mass index (kg/m²)						
N	5	8	10	30	6	59
Mean	25.90	25.93	23.96	25.31	22.93	24.97
SD	3.847	5.180	4.818	5.271	2.606	4.817
Median	26.54	24.95	22.88	25.42	22.59	24.49
Minimum	21.1	21.9	18.1	17.4	20.2	17.4
Maximum	31.1	38.2	33.1	38.8	27.1	38.8
Body surface area (m²)						
N	5	8	10	30	6	59

Mean	1.96	1.97	1.83	1.88	1.72	1.88
SD	0.284	0.253	0.209	0.254	0.090	0.240
Median	2.08	1.96	1.84	1.82	1.73	1.84
Minimum	1.5	1.7	1.5	1.5	1.6	1.5
Maximum	2.2	2.5	2.1	2.5	1.9	2.5
Body height (cm)						
N	5	8	10	30	6	59
Mean	173.80	174.63	171.30	171.30	166.50	171.47
SD	9.985	6.632	8.001	9.414	3.886	8.494
Median	177.00	177.00	170.50	170.00	165.00	172.00
Minimum	157.0	165.0	160.0	154.0	163.0	154.0
Maximum	182.0	182.0	187.0	188.0	174.0	188.0
ECOG PS						
PS = 0	4 (80.0)	3 (37.5)	7 (70.0)	11 (36.7)	3 (50.0)	28 (47.5)
PS = 1	1 (20.0)	5 (62.5)	2 (20.0)	18 (60.0)	2 (33.3)	28 (47.5)
PS = 2	0	0	1 (10.0)	1(3.3)	1 (16.7)	3(5.1)
PS > 2	0	0	0	0	0	0

ECOG PS: Eastern Cooperative Oncology Group performance status

Outcome measures

Safety Results

Dose-limiting toxicities by initial dose group of panobinostat (MTD-determining set)

	Panobinostat					
	20 mg N = 5 n (%)	30 mg N = 6 n (%)	40 mg N = 9 n (%)	50 mg N = 23 n (%)	60 mg N = 5 n (%)	Total N = 48 n (%)
Cycle 1						
Total no. of patients with DLT	0	0	1 (11.1)	3 (13.0)	3 (60.0)	7 (14.6)
Total no. of DLTs	0	0	2	7	7	16

DLT: dose limiting toxicity; MTD: maximum tolerated dose
Subject 26/8 in the 50 mg dose group was reported as DLT in error. This patient was enrolled in the dose expansion part of the study and therefore not part of the MTD defining set.
Percentages are referring to the number of patient in the MTD-determining set exposed.

Probabilities of DLT for study treatment as derived from the Bayesian logistic regression model by dose level of panobinostat as per investigator dose escalation meeting

Panobinostat dose group	Proportion of patients with DLT (observed)	Mean (SD) of posterior p(DLT)	Probability of under dosing (%)	Probability of target toxicity (%)	Probability of unacceptable or excessive toxicity (%)
20	0/5	11.4 (6.80)	88	12	0
30	0/5	13.6 (6.60)	82.3	17.5	1
40	1/7	17.3 (6.50)	66.9	32.5	6
50	2/11	23.3 (7.00)	33.5	60.6	5.9
60	3/6	31.9 (9.60)	9.5	56.1	34.4

DLT: dose limiting toxicity; MTD: maximum tolerated dose
MTD determining set as determined by dose escalating meetings
Under dosing: DLT rate < 20%
Targeted toxicity: 20 % ≤ DLT rate < 35%
Unacceptable or excessive toxicity: DLT rate ≥ 35 %
The maximum next dose level is determined if the probability of unacceptable or excessive toxicity is not exceeding 25%.

Summary of adverse event categories by initial dose group of panobinostat – core phase (Safety set)

	Panobinostat					Total
	20 mg N =5 n (%)	30 mg N =8 n (%)	40 mg N =10 n (%)	50 mg N =30 n (%)	60 mg N =6 n (%)	N =59 n (%)
Adverse events (AEs)[1]	5 (100.0)	8 (100.0)	10 (100.0)	30 (100.0)	6 (100.0)	59 (100.0)
Suspected to be drug-related	4 (80.0)	6 (75.0)	10 (100.0)	29 (96.7)	6 (100.0)	55 (93.2)
Grade 3-4 AEs	5 (100.0)	8 (100.0)	10 (100.0)	30 (100.0)	6 (100.0)	59 (100.0)
Suspected to be drug-related	3 (60.0)	6 (75.0)	9 (90.0)	29 (96.7)	5 (83.3)	52 (88.1)
On-treatment death[2]	0	1 (12.5)	2 (20.0)	7 (23.3)	1 (16.7)	11 (18.6)
Suspected to be drug-related	0	0	0	0	0	0
Serious adverse events (SAEs)	3 (60.0)	3 (37.5)	9 (90.0)	17 (56.7)	4 (66.7)	36 (61.0)
Suspected to be drug-related	0	1 (12.5)	3 (30.0)	7 (23.3)	2 (33.3)	13 (22.0)
AEs leading to discontinuation	1 (20.0)	2 (25.0)	3 (30.0)	10 (33.3)	3 (50.0)	19 (32.2)
Suspected to be drug-related	0	1 (12.5)	2 (20.0)	5 (16.7)	3 (50.0)	11 (18.6)
Attributable to SAEs	1 (20.0)	1 (12.5)	2 (20.0)	8 (26.7)	1 (16.7)	13 (22.0)
Attributable to SAEs suspected to be drug-related	0	1 (12.5)	1 (10.0)	3 (10.0)	1 (16.7)	6 (10.2)
Other significant AEs	5 (100.0)	8 (100.0)	10 (100.0)	30 (100.0)	6 (100.0)	59 (100.0)
AEs leading to dose adjustment/ temporary interruption of study drug	0	2 (25.0)	0	6 (20.0)	0	8 (13.6)
AEs requiring additional therapy[3]	5 (100.0)	8 (100.0)	10 (100.0)	30 (100.0)	6 (100.0)	59 (100.0)

[1] Adverse events occurring more than 28 days after the discontinuation of study treatment of the core phase are not summarized

[2] Deaths occurring more than 28 days after the discontinuation of study treatment of the core phase are not summarized

[3] Additional therapy included all non-drug therapy and concomitant medications

Adverse Events by System Organ Class

Frequent adverse events (> 10%) regardless of study drug relationship by primary system organ class, preferred term and initial dose group of panobinostat – core phase (Safety set)

System organ class Preferred term	Panobinostat											
	20 mg N =5		30 mg N =8		40 mg N =10		50 mg N =30		60 mg N =6		Total N =59	
	Any grade n (%)	Grade 3/4 n (%)	Any grade n (%)	Grade 3/4 n (%)	Any grade n (%)	Grade 3/4 n (%)	Any grade n (%)	Grade 3/4 n (%)	Any grade n (%)	Grade 3/4 n (%)	Any grade n (%)	Grade 3/4 n (%)
Any primary system organ class	**5 (100.0)**	**5 (100.0)**	**8 (100.0)**	**8 (100.0)**	**10 (100.0)**	**10 (100.0)**	**30 (100.0)**	**30 (100.0)**	**6 (100.0)**	**6 (100.0)**	**59 (100.0)**	**59 (100.0)**
Gastrointestinal disorders	**5 (100.0)**	**0**	**7 (87.5)**	**0**	**10 (100.0)**	**5 (50.0)**	**30 (100.0)**	**12 (40.0)**	**6 (100.0)**	**4 (66.7)**	**58 (98.3)**	**21 (35.6)**
Diarrhoea	4 (80.0)	0	3 (37.5)	0	10 (100.0)	2 (20.0)	27 (90.0)	8 (26.7)	6 (100.0)	4 (66.7)	50 (84.7)	14 (23.7)
Nausea	5 (100.0)	0	5 (62.5)	0	9 (90.0)	1 (10.0)	26 (86.7)	3 (10.0)	5 (83.3)	0	50 (84.7)	4 (6.8)
Vomiting	4 (80.0)	0	5 (62.5)	0	9 (90.0)	2 (20.0)	23 (76.7)	2 (6.7)	4 (66.7)	0	45 (76.3)	4 (6.8)
Abdominal pain	2 (40.0)	0	2 (25.0)	0	8 (80.0)	1 (10.0)	14 (46.7)	3 (10.0)	5 (83.3)	0	31 (52.5)	4 (6.8)
Stomatitis	1 (20.0)	0	2 (25.0)	0	2 (20.0)	0	11 (36.7)	1 (3.3)	3 (50.0)	0	19 (32.2)	1 (1.7)
Constipation	1 (20.0)	0	2 (25.0)	0	2 (20.0)	0	8 (26.7)	0	1 (16.7)	0	14 (23.7)	0
Abdominal pain upper	0	0	0	0	0	0	9 (30.0)	0	0	0	9 (15.3)	0
Dyspepsia	1 (20.0)	0	1 (12.5)	0	0	0	3 (10.0)	0	2 (33.3)	0	7 (11.9)	0
Flatulence	0	0	0	0	4 (40.0)	0	3 (10.0)	0	0	0	7 (11.9)	0
Dry mouth	1 (20.0)	0	1 (12.5)	0	1 (10.0)	0	3 (10.0)	0	0	0	6 (10.2)	0
Dysphagia	1 (20.0)	0	3 (37.5)	0	0	0	2 (6.7)	0	0	0	6 (10.2)	0
General disorders and administration site conditions	**5 (100.0)**	**0**	**8 (100.0)**	**1 (12.5)**	**9 (90.0)**	**1 (10.0)**	**30 (100.0)**	**9 (30.0)**	**6 (100.0)**	**0**	**58 (98.3)**	**11 (18.6)**
Fatigue	4 (80.0)	0	5 (62.5)	0	3 (30.0)	1 (10.0)	16 (53.3)	1 (3.3)	2 (33.3)	0	30 (50.8)	2 (3.4)
Oedema peripheral	3 (60.0)	0	3 (37.5)	0	3 (30.0)	0	12 (40.0)	1 (3.3)	6 (100.0)	0	27 (45.8)	1 (1.7)

Pyrexia	2 (40.0)	0	4 (50.0)	1 (12.5)	6 (60.0)	0	12 (40.0)	2 (6.7)	2 (33.3)	0	26 (44.1)	3 (5.1)
Asthenia	2 (40.0)	0	1 (12.5)	0	2 (20.0)	0	8 (26.7)	1 (3.3)	4 (66.7)	0	17 (28.8)	1 (1.7)
Catheter site related reaction	0	0	3 (37.5)	0	3 (30.0)	0	5 (16.7)	0	0	0	11 (18.6)	0
Chills	2 (40.0)	0	2 (25.0)	0	1 (10.0)	0	6 (20.0)	0	0	0	11 (18.6)	0
Injection site reaction	1 (20.0)	0	2 (25.0)	0	2 (20.0)	0	6 (20.0)	0	0	0	11 (18.6)	0
Non-cardiac chest pain	1 (20.0)	0	2 (25.0)	0	1 (10.0)	0	4 (13.3)	0	1 (16.7)	0	9 (15.3)	0
Metabolism and nutrition disorders	**5 (100.0)**	**1 (20.0)**	**8 (100.0)**	**3 (37.5)**	**9 (90.0)**	**2 (20.0)**	**27 (90.0)**	**9 (30.0)**	**6 (100.0)**	**4 (66.7)**	**55 (93.2)**	**19 (32.2)**
Hypokalaemia	3 (60.0)	1 (20.0)	7 (87.5)	1 (12.5)	5 (50.0)	1 (10.0)	17 (56.7)	5 (16.7)	5 (83.3)	2 (33.3)	37 (62.7)	10 (16.9)
Decreased appetite	4 (80.0)	0	5 (62.5)	1 (12.5)	3 (30.0)	1 (10.0)	14 (46.7)	1 (3.3)	4 (66.7)	0	30 (50.8)	3 (5.1)
Hypocalcaemia	2 (40.0)	0	3 (37.5)	1 (12.5)	5 (50.0)	1 (10.0)	11 (36.7)	2 (6.7)	3 (50.0)	1 (16.7)	24 (40.7)	5 (8.5)
Fluid retention	0	0	1 (12.5)	0	2 (20.0)	0	4 (13.3)	0	1 (16.7)	0	8 (13.6)	0
Blood and lymphatic system disorders	**4 (80.0)**	**4 (80.0)**	**6 (75.0)**	**6 (75.0)**	**9 (90.0)**	**9 (90.0)**	**29 (96.7)**	**29 (96.7)**	**6 (100.0)**	**6 (100.0)**	**54 (91.5)**	**54 (91.5)**
Thrombocytopenia	3 (60.0)	3 (60.0)	3 (37.5)	3 (37.5)	9 (90.0)	9 (90.0)	23 (76.7)	23 (76.7)	5 (83.3)	5 (83.3)	43 (72.9)	43 (72.9)
Febrile neutropenia	4 (80.0)	4 (80.0)	4 (50.0)	4 (50.0)	4 (40.0)	4 (40.0)	23 (76.7)	23 (76.7)	3 (50.0)	3 (50.0)	38 (64.4)	38 (64.4)
Anaemia	2 (40.0)	2 (40.0)	4 (50.0)	2 (25.0)	8 (80.0)	4 (40.0)	16 (53.3)	12 (40.0)	4 (66.7)	4 (66.7)	34 (57.6)	24 (40.7)
Neutropenia	1 (20.0)	1 (20.0)	2 (25.0)	2 (25.0)	2 (20.0)	2 (20.0)	10 (33.3)	10 (33.3)	0	0	15 (25.4)	15 (25.4)
Leukopenia	2 (40.0)	2 (40.0)	3 (37.5)	3 (37.5)	0	0	6 (20.0)	6 (20.0)	0	0	11 (18.6)	11 (18.6)
Infections and infestations	**3 (60.0)**	**2 (40.0)**	**6 (75.0)**	**2 (25.0)**	**8 (80.0)**	**6 (60.0)**	**27 (90.0)**	**20 (66.7)**	**5 (83.3)**	**3 (50.0)**	**49 (83.1)**	**33 (55.9)**
Pneumonia	2 (40.0)	1 (20.0)	1 (12.5)	1 (12.5)	0	0	3 (10.0)	3 (10.0)	1 (16.7)	1 (16.7)	7 (11.9)	6 (10.2)
Sepsis	1 (20.0)	0	0	0	1 (10.0)	1 (10.0)	4 (13.3)	4 (13.3)	1 (16.7)	1 (16.7)	7 (11.9)	6 (10.2)
Investigations	**5 (100.0)**	**4 (80.0)**	**7 (87.5)**	**5 (62.5)**	**5 (50.0)**	**2 (20.0)**	**26 (86.7)**	**18 (60.0)**	**3 (50.0)**	**3 (50.0)**	**46 (78.0)**	**32 (54.2)**
Haemoglobin decreased	3 (60.0)	2 (40.0)	4 (50.0)	3 (37.5)	0	0	9 (30.0)	7 (23.3)	1 (16.7)	1 (16.7)	17 (28.8)	13 (22.0)
Weight decreased	2 (40.0)	0	1 (12.5)	0	1 (10.0)	0	8 (26.7)	0	1 (16.7)	0	13 (22.0)	0
Weight increased	1 (20.0)	0	3 (37.5)	0	1 (10.0)	0	7 (23.3)	1 (3.3)	1 (16.7)	0	13 (22.0)	1 (1.7)

Platelet count decreased	0	0	4 (50.0)	4 (50.0)	0	0	7 (23.3)	7 (23.3)	1 (16.7)	1 (16.7)	12 (20.3)	12 (20.3)
C-reactive protein increased	3 (60.0)	1 (20.0)	2 (25.0)	1 (12.5)	2 (20.0)	0	2 (6.7)	1 (3.3)	1 (16.7)	1 (16.7)	10 (16.9)	4 (6.8)
Alanine aminotransferase increased	2 (40.0)	1 (20.0)	0	0	0	0	6 (20.0)	3 (10.0)	1 (16.7)	1 (16.7)	9 (15.3)	5 (8.5)
Aspartate aminotransferase increased	2 (40.0)	1 (20.0)	0	0	0	0	6 (20.0)	2 (6.7)	1 (16.7)	1 (16.7)	9 (15.3)	4 (6.8)
Electrocardiogram QT prolonged	0	0	1 (12.5)	0	0	0	6 (20.0)	3 (10.0)	1 (16.7)	0	8 (13.6)	3 (5.1)
White blood cell count decreased	0	0	3 (37.5)	3 (37.5)	1 (10.0)	1 (10.0)	3 (10.0)	3 (10.0)	0	0	7 (11.9)	7 (11.9)
Respiratory, thoracic and mediastinal disorders	**4 (80.0)**	**0**	**5 (62.5)**	**3 (37.5)**	**6 (60.0)**	**2 (20.0)**	**24 (80.0)**	**5 (16.7)**	**4 (66.7)**	**1 (16.7)**	**43 (72.9)**	**11 (18.6)**
Epistaxis	1 (20.0)	0	2 (25.0)	1 (12.5)	3 (30.0)	0	12 (40.0)	0	1 (16.7)	0	19 (32.2)	1 (1.7)
Dyspnoea	2 (40.0)	0	2 (25.0)	1 (12.5)	1 (10.0)	0	10 (33.3)	2 (6.7)	1 (16.7)	0	16 (27.1)	3 (5.1)
Cough	2 (40.0)	0	1 (12.5)	0	1 (10.0)	0	6 (20.0)	0	1 (16.7)	0	11 (18.6)	0
Pleural effusion	0	0	0	0	2 (20.0)	1 (10.0)	3 (10.0)	0	2 (33.3)	1 (16.7)	7 (11.9)	2 (3.4)
Skin and subcutaneous tissue disorders	**4 (80.0)**	**0**	**4 (50.0)**	**0**	**8 (80.0)**	**1 (10.0)**	**23 (76.7)**	**0**	**4 (66.7)**	**0**	**43 (72.9)**	**1 (1.7)**
Rash	2 (40.0)	0	3 (37.5)	0	5 (50.0)	0	10 (33.3)	0	2 (33.3)	0	22 (37.3)	0
Petechiae	2 (40.0)	0	2 (25.0)	0	5 (50.0)	0	7 (23.3)	0	1 (16.7)	0	17 (28.8)	0
Hyperhidrosis	3 (60.0)	0	2 (25.0)	0	1 (10.0)	0	5 (16.7)	0	0	0	11 (18.6)	0
Alopecia	0	0	0	0	3 (30.0)	1 (10.0)	3 (10.0)	0	1 (16.7)	0	7 (11.9)	1 (1.7)
Dry skin	0	0	1 (12.5)	0	1 (10.0)	0	3 (10.0)	0	1 (16.7)	0	6 (10.2)	0
Musculoskeletal and connective tissue disorders	**2 (40.0)**	**0**	**4 (50.0)**	**0**	**7 (70.0)**	**1 (10.0)**	**19 (63.3)**	**3 (10.0)**	**4 (66.7)**	**0**	**36 (61.0)**	**4 (6.8)**
Back pain	0	0	1 (12.5)	0	4 (40.0)	0	6 (20.0)	1 (3.3)	3 (50.0)	0	14 (23.7)	1 (1.7)

Pain in extremity	1 (20.0)	0	2 (25.0)	0	1 (10.0)	1 (10.0)	7 (23.3)	1 (3.3)	2 (33.3)	0	13 (22.0)	2 (3.4)
Nervous system disorders	**4 (80.0)**	**0**	**4 (50.0)**	**0**	**7 (70.0)**	**3 (30.0)**	**16 (53.3)**	**4 (13.3)**	**4 (66.7)**	**0**	**35 (59.3)**	**7 (11.9)**
Headache	4 (80.0)	0	2 (25.0)	0	6 (60.0)	1 (10.0)	10 (33.3)	1 (3.3)	3 (50.0)	0	25 (42.4)	2 (3.4)
Dizziness	1 (20.0)	0	2 (25.0)	0	0	0	8 (26.7)	0	0	0	11 (18.6)	0
Vascular disorders	**4 (80.0)**	**0**	**6 (75.0)**	**1 (12.5)**	**6 (60.0)**	**0**	**13 (43.3)**	**1 (3.3)**	**5 (83.3)**	**2 (33.3)**	**34 (57.6)**	**4 (6.8)**
Hypertension	3 (60.0)	0	3 (37.5)	1 (12.5)	4 (40.0)	0	7 (23.3)	1 (3.3)	2 (33.3)	0	19 (32.2)	2 (3.4)
Haematoma	0	0	0	0	2 (20.0)	0	3 (10.0)	0	1 (16.7)	0	6 (10.2)	0
Thrombophlebitis	0	0	1 (12.5)	0	0	0	3 (10.0)	0	2 (33.3)	0	6 (10.2)	0
Psychiatric disorders	**2 (40.0)**	**0**	**3 (37.5)**	**0**	**5 (50.0)**	**0**	**16 (53.3)**	**1 (3.3)**	**5 (83.3)**	**0**	**31 (52.5)**	**1 (1.7)**
Anxiety	0	0	0	0	0	0	5 (16.7)	0	2 (33.3)	0	7 (11.9)	0
Insomnia	1 (20.0)	0	1 (12.5)	0	1 (10.0)	0	2 (6.7)	0	1 (16.7)	0	6 (10.2)	0
Restlessness	0	0	0	0	4 (40.0)	0	1 (3.3)	0	1 (16.7)	0	6 (10.2)	0
Cardiac disorders	**4 (80.0)**	**1 (20.0)**	**1 (12.5)**	**0**	**7 (70.0)**	**2 (20.0)**	**15 (50.0)**	**2 (6.7)**	**3 (50.0)**	**1 (16.7)**	**30 (50.8)**	**6 (10.2)**
Tachycardia	3 (60.0)	0	1 (12.5)	0	1 (10.0)	0	6 (20.0)	0	0	0	11 (18.6)	0
Bradycardia	0	0	0	0	2 (20.0)	0	8 (26.7)	0	0	0	10 (16.9)	0
Injury, poisoning and procedural complications	**1 (20.0)**	**1 (20.0)**	**2 (25.0)**	**0**	**1 (10.0)**	**0**	**11 (36.7)**	**0**	**2 (33.3)**	**0**	**17 (28.8)**	**1 (1.7)**
Fall	0	0	1 (12.5)	0	1 (10.0)	0	2 (6.7)	0	2 (33.3)	0	6 (10.2)	0
Hepatobiliary disorders	**1 (20.0)**	**0**	**0**	**0**	**4 (40.0)**	**1 (10.0)**	**2 (6.7)**	**1 (3.3)**	**2 (33.3)**	**1 (16.7)**	**9 (15.3)**	**3 (5.1)**
Hyperbilirubinaemia	1 (20.0)	0	0	0	3 (30.0)	1 (10.0)	1 (3.3)	0	1 (16.7)	1 (16.7)	6 (10.2)	2 (3.4)
Ear and labyrinth disorders	**1 (20.0)**	**0**	**1 (12.5)**	**0**	**2 (20.0)**	**0**	**2 (6.7)**	**0**	**1 (16.7)**	**0**	**7 (11.9)**	**0**
Vertigo	1 (20.0)	0	0	0	2 (20.0)	0	2 (6.7)	0	1 (16.7)	0	6 (10.2)	0

Other Relevant Findings None
Date of Clinical Trial Report Final CSR: 13-Feb-2013
Date Inclusion on Novartis Clinical Trial Results Database 22-Feb-2013
Date of Latest Update