Sponsor

Novartis Pharma GmbH

Generic Drug Name

Panobinostat (LBH589)

Therapeutic Area of Trial

Myelodysplastic Syndrome (MDS)

Approved Indication

Investigational

Protocol Number

CLBH589BDE04

Title

A one year, open label, multicenter trial of LBH589 alone or in combination with ESA in red blood cell transfusion-dependent LOW and INT-1 MDS patients being either refractory to ESA or with a low probability of response – the **GE**rman **PA**nobinostat low **R**isk M**D**S trial – GEPARD study

Study Phase

Phase II

Study Start/End Dates

30 Nov 2009 to 18 Jul 2012

Study Design/Methodology

This phase II study employed a multicenter, open-label trial design. The study was divided into 2 parts. The first part is the core phase of the study designed as an open-label

single arm phase. The treatment period started on day 1 (Visit 2) and was to continue until Visit 10, i.e. for at least 4 months. All patients were to be given oral LBH589 40 mg monotherapy for 4 months.

The second phase was an open-label randomized study phase with 2 parallel treatments arms for patients with SD at Visit 10. Patients with progressive disease were to be discontinued from the study; patients with HI-E at Visit 10 were to be continued on treatment with LBH589 single agent on the current dosage. Patients who were eligible for this phase were randomly assigned to one of 2 parallel treatment arms Group A or Group B at Visit 10A. Patients assigned to Group A received oral LBH589 40 mg as a single agent for a further 4 months. Patients assigned to Group B received oral LBH589 40 mg + ESA 30000 IU/week injected s.c. for 4 months.

Per Amendment 1, starting dose was to be reduced from 40 mg to 30 mg, starting 08 December 2010.

Centers

14 centers in Germany

Outcome Measures

Primary objective

The primary objective of this study was to evaluate the hematological improvement of the erythropoietic system (HI-E) using modified IWG criteria (see table below) in patients treated for 4 months with LBH589 single agent.

Secondary objectives

- To compare the hematological improvement of the erythropoietic system (HI-E) using modified IWG criteria in patients treated for 8 to 12 months with either LBH589 single agent or with LBH589 and ESA combination treatment.
- To evaluate the objective response rate (CR + PR and HI-P and HI-N) at 4, 8 and 12 months of treatment according to modified IWG criteria (see table below).
- To determine the IPSS status as well as the single scoring values of the IPSS for patients at baseline and EOS.
- To determine time to response, event-free survival, progression-free survival (PFS), disease-free survival (DFS), time to cause-specific death, and overall survival (OS) in this patient population.
- To evaluate the safety and tolerability profile of LBH589 and LBH589 + ESA in LOW and INT-1 risk MDS patients treated for up to 12 months.

Modified IWG response criteria for hematologic improvement

Hematologic improvement*	Response criteria (responses must last at least 8 wk)†
Erythroid response (pretreatment, <11 g/dL)	Hgb increase by ≥ 1.5 g/dL Relevant reduction of units of RBC transfusions by an absolute number of at least 4 RBC transfusions/8 wk compared with the pretreatment transfusion number in the previous 8 wk. Only RBC transfusions given for a Hgb of ≤ 9.0 g/dL pretreatment were counted in the RBC transfusion response evaluation†
Platelet response (pretreatment, < 100 x 10^9/L)	Absolute increase of ≥ 30 x 10^9/L for patients starting with > 20 x 10^9/L platelets Increase from < 20 x 10^9/L to > 20 x 10^9/L and by at least 100%†
Neutrophil response (pretreatment, < 1.0 x 10^9/L)	At least 100% increase and an absolute increase > 0.5 x 10^9/L†
Progression or relapse after HI‡	At least 1 of the following: At least 50% decrement from maximum response levels in granulocytes or platelets Reduction in Hgb by ≥1.5 g/dL Transfusion dependence

To convert hemoglobin levels from grams per deciliter to grams per liter, multiply grams per deciliter by 10. To convert hemoglobin levels from grams per deciliter to mmol/L divide it by 1.6

Hgb: hemoglobin; RBC: red blood cell; HI: hematologic improvement.

*Pretreatment counts were based on averages ≤2 measurements (not influenced by transfusions) >1 week apart (modification).

†Modification to IWG response criteria.

‡In the absence of another explanation, such as acute infection, repeated courses of chemotherapy (modification), gastrointestinal bleeding, hemolysis, and so forth. It was recommended that the 2 kinds of erythroid and platelet responses were to be reported overall as well as by the individual response pattern.

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

LBH589 was administered orally, once-a-day on MWF, every week, as part of a 4-week (28-day) treatment cycle. All patients were given oral LBH589 40 mg monotherapy for 4 months (16 weeks) in the first part of the study. Per Amendment 1, starting dose was to be reduced from 40 mg to 30 mg. The second phase was an open-label randomized study phase with 2 parallel treatment arms. Patients who were eligible for this phase were randomly assigned to one of 2 parallel treatment arms Group A or Group B. Patients

assigned to Group A received oral LBH589 40 mg / 30 mg as a single agent for a further 4 – 8 months, depending on response and disease status. Accordingly, patients assigned to Group B received oral LBH589 40 mg / 30 mg+ ESA 30000 IU/week injected s.c. for further 4 -8 months (therefore total treatment was up to 12 months).

Study drug and strength	Formulation
LBH589 5 mg	hard capsules
LBH589 20 mg	hard capsules
LBH589 5 mg	hard capsules
LBH589 20 mg	hard capsules
ESA (epoetin alfa (Hexal)	ready-to-use
10000 IU LISY N1	injections
ESA (epoetin alfa (Hexal)	ready-to-use
10000 IU LISY N1	injections

Statistical Methods

The primary efficacy and safety analyses were to be conducted on all patient data at the time all patients who were still receiving study drug had completed at least 4 months of treatment. The additional data for any patients continuing to receive study drug past this time, as allowed by the protocol, were to be further summarized in a report once these patients completed the study (extension phase of the clinical study report). As the study was prematurely terminated following Amendment 2, none of the patients receiving study drug reached the designated cut-off time.

The data from all centers that participate in this protocol were used, so that an adequate number of patients would be available for analysis.

Data were to be summarized with respect to demographic and baseline characteristics, efficacy observations and measurements, safety observations and measurements. Categorical variables were to be summarized by absolute and relative frequencies. Continuous variables were to be summarized by descriptive statistics of mean, standard deviation, minimum, median and maximum. Time-to-event data including rates of affected patients were to be assessed by Kaplan-Meier statistics.

The assessment of safety was to be based mainly on the frequency of adverse events and on the number of laboratory values that fell outside of pre-determined ranges. Other safety data (e.g. electrocardiogram, vital signs, special tests) were to be considered as appropriate. Adverse events were to be summarized by presenting the number and percentage of patients having any adverse event, having an adverse event in each body system and having each individual adverse event. Any other information collected (e.g. severity or relatedness to study medication) were to be listed as appropriate.

With approval of Protocol Amendment 2, no additional patients were enrolled in the study. A total of 34 patients were enrolled and treated. Thus, the sample size required to reject either the null or the alternative hypothesis could not be reached and the decision algorithm, based on 55 patients, could not be applied. The trial was analyzed, and results were interpreted as purely exploratory, using descriptive statistical methods as described

above together with appropriate confidence intervals (CIs). For convenience, two-sided 95% CIs were to be reported.

Where appropriate, the results from the 2 parts of the study are presented separately, making a distinction between data from the single arm part (designated as "core phase" in tables) and the second part of the study after randomization (designated as "randomized phase" in tables).

The **full analysis set (FAS)** consisted of all patients who received at least one dose of study medication. For the randomized phase between Month 4 and Month 12, following the intent-to-treat principle, patients were to be analyzed according to the treatment they were assigned to at randomization.

The **safety set** consisted of all patients who received at least one dose of study drug and had at least one post-baseline safety assessment. The statement that a patient had no AE on the CRF constituted a safety assessment. Patients who received at least one dose of study drug but who had no post-treatment safety data of any kind were to be excluded from the safety population.

The **per-protocol (PP) set (PPS)** was to consist of patients who received at least one dose of the study drug and had no major protocol violation. Relevant protocol deviations that led to exclusion from the PP set included, but were not limited to: use of excluded/forbidden/un-allowed medication; poor compliance; loss to follow-up; missing data in the primary variable.

Due to the low patient numbers and high early discontinuation rate, it was decided by the Sponsor to only analyze the FAS population.

Study Population: Inclusion/Exclusion Criteria and Demographics

Inclusion criteria (per Amendment 1):

1. Signed and dated written informed consent by the patient prior to performance of any study-specific procedures or assessments. Procedures conducted as part of the subject's routine clinical management (e.g., blood count, number of RBC transfusions) and obtained prior to signing of informed consent may be utilized for screening purposes provided these procedures are conducted as specified in the protocol.
2. Patients of either gender and age ≥18 years
3. De novo (not therapy-related) MDS LOW or INT-1 according to IPSS
4. Red blood cell transfusion dependency of at least 4 Units within the last 8 weeks before visit 2 (baseline). Only RBC transfusions given for a Hgb ≤9.0 g/dL and >9.0g/dL, if clinically indicated (e.g. coronary heart disease, long distance travel), respectively, will count
5. Either refractory to ESA or displaying a low chance (score ≤1 according to Hellström-Lindberg, see also Figure 2-1 of study protocol in Appendix 16.1.1) of response

6. No disease-specific treatment (e.g. Revlimid, Vidaza) within 4 weeks prior to visit 2 (baseline). Treatment for transfusional iron overload with EMA-approved drugs is allowed.
7. Age-adjusted normal cardiac, kidney, liver function (creatinine <1.5 mg/dL unless MDS-related, total bilirubin < 2.0 x upper normal limits)
8. Patients must have the following laboratory values or corrected to within normal limits with supplements prior to visit 2 (baseline):
    - Potassium ≥ Lower Limit of Normal (LLN)
    - Magnesium ≥ LLN
    - Phosphorus ≥ LLN
    - Total calcium (corrected for serum albumin) ≥ LLN
    - Aspartate aminotransferase (AST) and alanine aminotransferase (ALT) ≤2.5 x Upper Limit of Normal (ULN) or ≤5.0 x ULN if hepatic involvement is present
    - Serum bilirubin ≤ 1.5 x ULN
    - Serum creatinine ≤ 1.5 x ULN or 24-hour creatinine clearance ≥ 50 mL/min
    - Clinically euthyroid (TSH and free T4) (hypothyroidism correctable with supplements is allowed)
9. Females of childbearing potential must use double-barrier contraception, oral contraceptive plus barrier contraceptive, or must have undergone clinically documented total hysterectomy and/or bilateral oophorectomy, bilateral tubal ligation or be postmenopausal defined by amenorrhea for at least 12 months. Only contraception with a pearl-Index below 1% should be considered.
10. Male patients are willing to use a barrier method of contraception (a condom) during the study and for 2 months after the study evaluation completion treatment.

Exclusion criteria

1. Known hypersensitivity to study drugs or their compounds
2. Concomitant use of ESA
3. Concomitant use of any other investigational drug
4. Other malignancy that is not in remission for least 1 year
5. HIV or other uncontrolled infection
6. Any peripheral neuropathy ≥ CTCAE grade 2
7. Unresolved diarrhea ≥ CTCAE grade 2
8. Platelet Count ≤75 x 10^9/L

9. Impaired cardiac function or clinically significant cardiac diseases, including any one of the following:

- LVEF ≤ Lower Limit of institutional Normal (LLN) as assessed by echocardiography
- Complete left bundle branch block
- Obligate use of a cardiac pacemaker
- Congenital long QT syndrome
- History or presence of ventricular tachyarrhythmia
- Presence of unstable atrial fibrillation (ventricular response >100 bpm). Patients with stable atrial fibrillation are allowed in the study provided they do not meet other exclusion criteria
- Clinically significant resting bradycardia (<50 bpm)
- QTc > 470 msecs on screening ECG
- Right bundle branch block + left anterior hemiblock (bifasicular block)
- Angina pectoris ≤3 months prior to starting study drug
- Acute myocardial infarction ≤3 months prior to starting study drug
- Other clinically significant heart disease (e.g., CHF, uncontrolled hypertension, history of labile hypertension, or history of poor compliance with an antihypertensive regimen)
- History (within previous 6 months prior to starting study drug) of deep venous thrombosis (DVT) or cerebrovascular accident (CVA)

10. Impairment of GI function or GI disease that may significantly alter the absorption of LBH589 (e.g. acute or chronic ulcerative diseases, uncontrolled nausea, vomiting, diarrhea, malabsorption syndrome, or small bowel resection)
11. Other concurrent severe and/or uncontrolled medical conditions (e.g., uncontrolled diabetes, active or uncontrolled infection, uncontrolled chronic obstructive or chronic restrictive pulmonary disease) that could cause unacceptable safety risks or compromise compliance with the protocol
12. History of non-compliance to medical regimens and patients who are considered potentially unreliable and/or not cooperative
13. History of drug or alcohol abuse within the 12 months prior to starting study drug
14. Pregnancy or breast feeding

Participant Flow

Patient disposition (FAS)

Core Phase

	Total

Patients	n (%)
Screened	34 (100.0)
Treated	34 (100.0)
Withdrawn before Visit 10	14 (41.2)
Completed Visit 10 (Month 4)	20 (58.8)
Withdrawn before Randomization (Total)	21 (61.8)

Randomized Phase

	Total	LBH589	LBH589 + ESA	Not randomized
	n (%)	n (%)	n (%)	n (%)
Completed Visit 10A	13 (100.0)	6 (100.0)	6 (100.0)	1 (100.0)
Withdrawn before Visit 19	12 (92.3)	5 (83.3)	6 (100.0)	1 (100.0)
Early completion of Visit 19/EOS	11 (84.6)	5 (83.3)	5 (83.3)	1 (100.0)
Early completion, Visit 19 not done	1 (7.7)	0 (0.0)	1 (7.7)	0 (0.0)
Regular completion of Visit 19/EOS	1 (7.7)	1 (16.7)	0 (0.0)	0 (0.0)
Total early withdrawals	12 (92.3)	5 (83.3)	6 (100.0)	1 (100.0)

Number of patients completed and discontinued prematurely, by reason for discontinuation (FAS)

Core Phase

	Total N=34
Patients	**n (%)**
Included (Visit 2)	34 (100.0)
Treated	34 (100.0)
Treatment discontinued	14 (41.2)
Primary reason for withdrawal	
Adverse event(s)	8 (23.5)
Abnormal laboratory value	1 (2.9)
Abnormal test procedure result	0 (0.0)
Unsatisfactory therapeutic effect	2 (5.9)
Subject's condition no longer requires study treatment	0 (0.0)
Protocol violation	2 (5.9)
Subject withdrew consent	1 (2.9)
Loss to follow-up	0 (0.0)
Administrative problems	0 (0.0)
Death	0 (0.0)

Randomized Phase

	Total N=13	LBH589 N=6	LBH589 + ESA N=6	Not randomized N=1
Patients	**n (%)**	**n (%)**	**n (%)**	**n (%)**
Treatment discontinued	12 (92.3)	5 (83.3)	6 (100.0)	1 (100.0)
Primary reason for withdrawal				
Adverse event(s)	3 (23.1)	0 (0.0)	2 (33.3)	1 (100.0)
Abnormal laboratory value	1 (7.7)	0 (0.0)	1 (16.7)	0 (0.0)
Abnormal test procedure result	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
Unsatisfactory therapeutic effect	6 (46.2)	5 (83.3)	1 (16.7)	0 (0.0)
Subject's condition no longer requires study treatment	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
Protocol violation	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
Subject withdrew consent	2 (15.4)	0 (0.0)	2 (33.3)	0 (0.0)
Loss to follow-up	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
Administrative problems	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
Death	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)

Baseline Characteristics

Demographic summary by treatment group (FAS)

Characte-ristic	Statistics	Core Phase	Randomized Phase			
			Total	LBH589	LBH589 + ESA	Not randomized
		N=34 (%)	N=13 (%)	N=6 (%)	N=6 (%)	N=1 (%)
Sex						
Male	n (%)	24 (70.6)	8 (61.5)	4 (66.7)	3 (50.0)	1 (100.0)
Female	n (%)	10 (29.4)	5 (38.5)	2 (33.3)	3 (50.0)	0 (0.0)
Age (years)	n	34	13	6	6	1
	<60	9 (26.5)	5 (38.5)	2 (33.3)	3 (50.0)	0 (0.0)
	60-69	14 (41.2)	6 (46.2)	2 (33.3)	3 (50.0)	1 (100.0)
	≥70	11 (32.4)	2 (15.4)	2 (33.3)	0 (0.0)	0 (0.0)
	Mean	65.4	63.2	64.5	60.3	65.0
	StD	7.70	9.10	11.81	6.56	NA
	Minimum	51	51	51	53	65
	Median	66.0	65.2	65.5	59.5	65.0
	Maximum	81	80	80	69	65
Race	n (%)	34 (100.0)	13 (100.0)	6 (100.0)	6 (100.0)	1 (100.0)
Caucasian	n (%)	34 (100.0)	13 (100.0)	6 (100.0)	6 (100.0)	1 (100.0)
Height (cm)	n	34	13	6	6	1
	Mean	173.1	171.9	176.0	168.0	171.0
	StD	8.07	8.21	7.87	7.82	NA
	Minimum	156.0	159.0	166.0	159.0	171.0
	Median	173.5	171.0	178.5	167.0	171.0
	Maximum	189.0	186.0	186.0	180.0	171.0
Weight (kg)	n	33	13	6	6	1
	Mean	80.8	82.0	81.5	80.3	96.0
	StD	13.24	12.98	15.22	11.39	NA
	Minimum	53.0	57.0	57.0	68.0	96.0
	Median	80.0	80.0	84.0	80.0	96.0
	Maximum	110.0	98.0	97.0	98.0	96.0
BMI* (kg/m^2)	n	33	13	6	6	1
	Mean	26.8	27.7	26.2	28.4	32.8
	StD	3.25	3.56	3.86	2.63	NA
	Minimum	18.8	20.4	20.4	25.3	32.8
	Median	26.7	27.2	26.6	28.4	32.8
	Maximum	32.8	32.8	30.3	31.6	32.8

* BMI: Body Mass Index; StD: standard deviation

Safety Results

Number of patients (n) with AEs and number of AEs by SOC (FAS)

Primary SOC	Core Phase N=34		Randomized Phase LBH589 N=6		LBH589 + ESA N=6		Not randomized N=1	
	n (%) patients	No. of AEs	n (%) patients	No. of AEs	n (%) patients	No of AEs	n (%) patients	No of AEs
All AEs	34 (100.0)	410	6 (100.0)	44	6 (100.0)	30	1 (100.0)	6
Gastrointestinal disorders	33 (97.1)	112	4 (66.7)	7	3 (50.0)	8	1 (100.0)	1
General disorders and administration site conditions	23 (67.6)	53	5 (83.3)	7	1 (16.7)	1	0 (0.0)	0
Blood and lymphatic system disorders	22 (64.7)	88	1 (16.7)	6	2 (33.3)	7	0 (0.0)	0
Metabolism and nutrition disorders	16 (47.1)	20	0 (0.0)	0	1 (16.7)	1	0 (0.0)	0
Investigations	13 (38.2)	26	4 (66.7)	6	1 (16.7)	1	0 (0.0)	0
Infections and infestations	13 (38.2)	16	2 (33.3)	4	2 (33.3)	5	1 (100.0)	1
Musculoskeletal and connective tissue disorders	12 (35.3)	19	2 (33.3)	6	3 (50.0)	4	1 (100.0)	2
Skin and subcutaneous tissue disorders	11 (32.4)	13	0 (0.0)	0	0 (0.0)	0	1 (100.0)	1
Nervous system disorders	8 (23.5)	13	0 (0.0)	0	0 (0.0)	0	0 (0.0)	0
Cardiac disorders	6 (17.6)	6	0 (0.0)	0	0 (0.0)	0	0 (0.0)	0
Ear and labyrinth disorders	6 (17.6)	7	0 (0.0)	0	0 (0.0)	0	0 (0.0)	0
Endocrine disorders	6 (17.6)	6	0 (0.0)	0	0 (0.0)	0	0 (0.0)	0
Respiratory, thoracic and mediastinal disorders	6 (17.6)	8	3 (50.0)	4	0 (0.0)	0	0 (0.0)	0
Vascular disorders	4 (11.8)	5	2 (33.3)	3	1 (16.7)	1	0 (0.0)	0
Renal and urinary disorders	3 (8.8)	4	0 (0.0)	0	0 (0.0)	0	0 (0.0)	0
Injury, poisoning and procedural complications	2 (5.9)	3	0 (0.0)	0	2 (33.3)	2	0 (0.0)	0
Psychiatric disorders	2 (5.9)	2	1 (16.7)	1	0 (0.0)	0	0 (0.0)	0
Eye disorders	2 (5.9)	2	0 (0.0)	0	0 (0.0)	0	1 (100.0)	1
Immune system disorders	2 (5.9)	3	0 (0.0)	0	0 (0.0)	0	0 (0.0)	0
Neoplasms benign, malignant and unspecified (incl cysts and polyps)	2 (5.9)	2	0 (0.0)	0	0 (0.0)	0	0 (0.0)	0
Hepatobiliary disorders	1 (2.9)	1	0 (0.0)	0	0 (0.0)	0	0 (0.0)	0
Surgical and medical procedures	1 (2.9)	1	0 (0.0)	0	0 (0.0)	0	0 (0.0)	0

AEs grouped by SOC are presented in descending order of patient numbers (n) in the core group.

All AEs with frequencies of 3 or more by PT (FAS)

Preferred Term	Core Phase N=34		Randomized Phase					
			LBH589 N=6		LBH589 + ESA N=6		Not randomized N=1	
	No of AEs	%	No of AEs	%	No of AEs	%	No of AEs	%
All	410	100.0	44	100.0	30	100.0	6	100.0
Diarrhoea	46	11.2	2	4.5	7	23.3	0	0.0
Thrombocytopenia	42	10.2	2	4.5	5	16.7	0	0.0
Fatigue	30	7.3	1	2.3	0	0.0	0	0.0
Neutropenia	26	6.2	2	4.5	2	6.7	0	0.0
Nausea	22	5.3	1	2.3	1	3.3	0	0.0
Vomiting	12	2.9	1	2.3	0	0.0	0	0.0
Asthenia	11	2.7	0	0.0	0	0.0	0	0.0
Anorexia	11	2.7	0	0.0	0	0.0	0	0.0
Leukopenia	10	2.4	1	2.3	0	0.0	0	0.0
Weight decreased	9	2.2	4	9.1	0	0.0	0	0.0
Myalgia	7	1.7	1	2.3	0	0.0	0	0.0
Vertigo	6	1.5	0	0.0	0	0.0	0	0.0
Hypothyroidism	6	1.5	0	0.0	0	0.0	0	0.0
GGT-increased	6	1.5	0	0.0	0	0.0	0	0.0
Muscle spasms	5	1.2	0	0.0	2	6.6	0	0.0
Dyspepsia	5	1.2	1	2.3	0	0.0	0	0.0
Alopecia	5	1.2	0	0.0	0	0.0	0	0.0
Anaemia	4	1.0	1	2.3	0	0.0	0	0.0
Abdominal pain	4	1.0	0	0.0	0	0.0	0	0.0
Nasopharyngitis	4	1.0	1	2.3	1	3.3	0	0.0
Dysgeusia	4	1.0	0	0.0	0	0.0	0	0.0
Headache	4	1.0	0	0.0	0	0.0	0	0.0
Lymphopenia	3	0.7	0	0.0	0	0.0	0	0.0
Abdominal pain upper	3	0.7	1	2.3	0	0.0	0	0.0
Constipation	3	0.7	1	2.3	0	0.0	0	0.0
Pyrexia	3	0.7	0	0.0	0	0.0	0	0.0
Hypersensitivity	3	0.7	0	0.0	0	0.0	0	0.0
Blood alkaline phosphatase increased	3	0.7	0	0.0	0	0.0	0	0.0
Blood TSH increased	3	0.7	0	0.0	0	0.0	0	0.0
Haemochromatosis	3	0.7	0	0.0	1	3.3	0	0.0
Back pain	3	0.7	2	4.5	1	3.3	1	16.7
Dyspnoea	3	0.7	0	0.0	0	0.0	0	0.0

AEs (only those with frequency ≥3 in the core phase) are presented in descending order of AE frequency in the core phase group. GGT=gamma-glutamyltransferase; THS= thyroid-stimulating hormone

Number of patients with significant AEs (FAS)

	Core Phase	Randomized Phase		
		LBH589	LBH589 + ESA	Not randomized
	N=34	N=6	N=6	N=1
Patients with AEs	**n (%)**	**n (%)**	**n (%)**	**n (%)**
With suspected drug relation	31 (91.2)	3 (50.0)	4 (66.7)	1 (100.0)
Leading to permanent discontinuation	12 (35.3)	0 (0.0)	0 (0.0)	1 (100.0)
Requiring dose adjustment	22 (64.7)	0 (0.0)	3 (50.0)	0 (0.0)
Requiring additional therapy	34 (100.0)	4 (66.7)	5 (83.3)	1 (100.0)
Considered as serious AEs	11 (32.4)	1 (16.7)	1 (16.7)	1 (100.0)
Leading to death	1 (2.9)	0 (0.0)	0 (0.0)	0 (0.0)

Other Relevant Findings

There were no further important findings

Date of Clinical Trial Report

03 July 2013

Date Inclusion on Novartis Clinical Trial Results Database

01 August 2013

Date of Latest Update