Sponsor

Novartis

Generic Drug Name

BHQ880

Therapeutic Area of Trial

Relapsed or refractory myeloma

Approved Indication

Investigational

Protocol Number

CBHQ880A2102

Title

A Phase Ib multicenter dose-determination study, with an adaptive, randomized, placebo-controlled, double-blind phase II, using various repeated IV doses of BHQ880 in combination with zoledronic acid in relapsed or refractory myeloma patients with prior skeletal-related event.

Phase of Development

Phase Ib/II

Study Start/End Dates

14-Jan-2009 (first patient first visit) to 09-Dec-2011 (Last patient last visit)

Study Design/Methodology

This study was a dose determining study to evaluate repeated IV doses of BHQ880 in combination with zoledronic acid in relapsed or refractory myeloma patients with at least one prior skeletal-related event (SRE). The study was originally planned to have two phases. Phase I was a dose escalation phase to assess the MTD and to characterize DLT, and PK of escalating doses of BHQ880 (up to a maximum dose of 40 mg/kg) in combination with and zoledronic acid. Phase II, the dose expansion phase, was not conducted, as the data obtained from the phase I portion indicated that the actual observed SRE rate was too low to meet the primary endpoint of the phase II portion of the study. Amendment 4 introduced a Continuation Segment which permitted continued access to BHQ880 with a reduction in study procedures and laboratory assessments.

Centres

Five centers in United States.

Publication

None

Outcome measures

Primary outcome measures:

- Maximum-tolerated dose (MTD) and dose limiting toxicity (DLT) of escalating doses of BHQ880 in combination with standard anti-myeloma therapy and zoledronic acid.

Secondary outcome measures:

- Skeletal survey (new SREs which are categorized into vertebral or non-vertebral pathologic fractures, spinal cord compression, radiation to bone and surgery to bone) summarized by dose and cycle.
- Pharmacokinetic profile of intravenously administered BHQ880.
- Changes in DKK1 levels and binding kinetics of DKK1/BHQ880 complex in serum.
- Safety profile of BHQ880.

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

BHQ880 powder for solution was supplied in 6 ml. glass vials with rubber stoppers and aluminum flip-off caps containing 100 mg of lyophilized BHQ880. It was administered at dose strength of 3-40 mg/kg via intravenous (IV) infusion on Day 1 of a 28-day cycle. Commercially available zoledronic acid was supplied as 5ml vial containing 4mg of zoledronic acid. It was administered via IV infusion on Day 1 of a 28-day cycle.

Statistical Methods

A Bayesian Logistic Regression Model (BLRM) was used to estimate the DLT rates and the risk of overdosing at different dose levels, and thus guide dose escalation [using the principle of Escalation With Overdose Control (EWOC)] and estimate the MTD. This analysis was based upon the dose-determining set, which consisted of all patients from the safety set for the escalation phase who received a single dose of BHQ880 and were observed for at least 28 days following the first dose or discontinued earlier due to unacceptable toxicity. All other safety tabulations were based on the safety set, which included who received at least one dose of study drug and had at least one valid post-baseline safety assessment. Efficacy analysis was based upon the full analysis set (FAS), which included all patients who received at least one (full or partial) dose of BHQ880 in phase I.

Study Population:

Inclusion Criteria

Patients were to have met the following inclusion criteria to be enrolled in the study:

- Relapsed or refractory multiple myeloma patients that required treatment with a non bortezomib- containing regimen (prior treatment with bortezomib was acceptable)
- The diagnosis of symptomatic multiple myeloma as defined by the following criteria (International Myeloma Working Group):
    - M-protein in serum or urine
    - Clonal bone marrow plasma cells or plasmacytoma

- Presence of related organ or tissue impairment (ROTI)
- At least one prior SRE defined as one of the following:
  - Pathologic fracture
  - Spinal cord compression
  - Requirement for either radiation or surgery to bone due to:
    - Pain
    - Prevention of imminent fracture
    - Stabilization of a fracture
- Stable renal function defined as two serum creatinine determinations of < 1.4 mg/dl OR calculated (Cockroft-Gault formula) creatinine clearance (CrCl) > 60 mL/min (Phase I)
- Stable renal function defined as two serum creatinine determinations of < 2.5 mg/dl **OR** calculated (Cockroft-Gault formula) creatinine clearance (CrCl) > 30 mL/min (Phase II)
  - Cockcroft-Gault formula (Cockcroft 1976)
  - CrCl = [140-age (years)] x weight (kg) (x 0.85 for female patients)/[72 x serum creatinine (mg/dL)]
- Current or planned treatment with zoledronic acid
- No symptoms of hyperviscosity, amyloidosis or recurrent infection
- Corrected serum calcium < 12 mg/dl or ionized calcium < 6.5 mg/dL within 14 days prior to registration
- Life expectancy of at least 12 months.
- Ambulatory patients aged 18 years or older
- ECOG performance status ≤ 2Absolute neutrophil count ≥ 1500/mm3
- Platelet count ≥ 75,000/mm3Hemoglobin (Hgb) ≥ 9 g/dl (prior RBC transfusion, recombinant epoetin alfa, or darbepoetin alfa allowed)
- Electrolyte levels ≥ LLN (i.e., potassium, magnesium, phosphorus) correction with supplements was allowed
- AST and ALT ≤ 2.5 x ULN
- Serum bilirubin ≤ 1.5 x ULN
- Patients must have signed the informed consent form and been willing and able to comply with the study protocol

Additional eligibility criteria for the Continuation Segment

- Stable disease or better
- No documented or suspected DLT

Exclusion Criteria

- Known concomitant disease(s) known to influence calcium metabolism including hyperparathyroidism, hyperthyroidism and/or Paget's disease of bone.
- Current active dental problems including
  - Ongoing infection of the teeth or jawbone (maxilla or mandibula)
  - Current exposed bone in the mouth
  - Dental or fixture trauma

- Current or previous osteonecrosis of the jaw
- Slow healing after dental procedures
- Recent (within 6 weeks) or planned dental or jaw surgery during the study (extraction, implants)

- Prior radiation therapy to treat diseases of the mouth
- Patients who were allergic to/intolerant of bisphosphonate therapy
- Acute or chronic liver disease
- Patients with any peripheral neuropathy ≥ CTCAE grade 2
- Other concurrent severe and/or uncontrolled concomitant medical conditions (e.g. uncontrolled diabetes, active or uncontrolled infection, uncontrolled diarrhea) that could have caused unacceptable safety risks or compromise compliance with the protocol
- Angina pectoris ≤ 3 months prior to starting study drug
- Acute myocardial infarction ≤ 6 months prior to starting study drug
- LVEF < 45%
- Other clinically significant heart disease (e.g. symptomatic congestive heart failure, uncontrolled arrhythmia, uncontrolled hypertension, history of labile hypertension, or history of poor compliance with an antihypertensive regimen)
- A past medical history of clinically significant ECG abnormalities or a family history of a prolonged QT-interval syndrome
- Patients who had not recovered from significant grade 3-4 side effects of previous antimyeloma therapy
- Patients who had undergone major surgery ≤ 2 weeks prior to starting study drug or who had not recovered from the side-effects of surgery
- Patients who had received any investigational drug ≤ 5 half lives prior to starting study drug or who had not recovered from side effects of such therapy. Or patients who had received previous investigational monoclonal antibody or radioimmunotherapy drug ≤ 60 days prior to starting study drug or who had not recovered from side effects of such therapy
- Known diagnosis of human immunodeficiency virus (HIV) infection (HIV testing was not mandatory)
- Women of child-bearing potential (WCBP) who were pregnant or breast feeding. WCBP, defined as sexually mature women who had not undergone a hysterectomy or who had not been naturally postmenopausal for at least 24 consecutive months (i.e., who have had menses any time in the preceding 24 consecutive months), must have had a negative serum pregnancy test ≤ 48 hours prior to starting study treatment. In addition, all sexually active WCBP and male patients must have agreed to use adequate contraceptive methods (oral, injectable, or implantable hormonal contraceptive; tubal ligation; intra-uterine device; barrier contraceptive with spermicide; or vasectomized partner) throughout the study and for 6 months after the last dose of the study drug.
- Patients with a history of another primary malignancy that was currently clinically significant or currently required active intervention.
- Patients unwilling or unable to comply with the protocol

Participant Flow

Patient disposition by treatment dose (FAS)

	3 mg/kg N=5 n(%)	10 mg/kg N=10 n(%)	20 mg/kg N=7 n(%)	40 mg/kg N=6 n(%)	All Patients N=28 n(%)
Patient treated					
Treatment discontinued	5(100.0%)	10(100.0%)	7(100.0%)	6(100.0%)	28(100.0%)
Treatment ongoing*	0	0	0	0	0
Primary reason for end of treatment					
Adverse Event(s)	0	1 (10.0%)	1 (14.3%)	0	2 (7.1%)
Patient withdrew consent	1 (20.0%)	4 (40.0%)	1 (14.3%)	2 (33.3%)	8 (28.6%)
Administrative problem(s)	0	1 (10.0%)	1 (14.3%)	1 (16.7%)	3 (10.7%)
Disease Progression	1 (20.0%)	3 (30.0%)	2 (28.6%)	0	6 (21.4%)
Treatment duration completed as per protocol	3 (60.0%)	0	2 (28.6%)	2 (33.3%)	7 (25.0%)
Protocol deviation	0	1 (10.0%)	0	1 (16.7%)	2 (7.1%)

* Patients ongoing at the time of the cut-off 08May2012.

Demographic and other baseline characteristics

Demographics by dose (FAS)

	3 mg/kg N=5	10 mg/kg N=10	20 mg/kg N=7	40 mg/kg N=6	All Patients N=28
Age (years)					
Mean	59.4	59.5	57.7	59.7	59.1
SD	10.45	14.18	11.57	15.78	12.64
Median	54.0	63.5	60.0	63.0	61.0
Range	49-73	38-79	39-69	41-78	38-79
Age Group - n(%)					
18 - 64 years	3 (60.0)	5 (50.0)	4 (57.1)	3 (50.0)	15 (53.6)
≥ 65	2 (40.0)	5 (50.0)	3 (42.9)	3 (50.0)	13 (46.4)
Gender - n(%)					
Male	4 (80.0)	6 (60.0)	4 (57.1)	4 (66.7)	18 (64.3)
Female	1 (20.0)	4 (40.0)	3 (42.9)	2 (33.3)	10 (35.7)
Race - n(%)					
Caucasian	4 (80.0)	9 (90.0)	7 (100.0)	4 (66.7)	24 (85.7)
Black	1 (20.0)	1 (10.0)	0	0	2 (7.1)
Other	0	0	0	2 (33.3)	2 (7.1)
Weight (kg)					
Mean	91.88	66.90	77.29	77.57	76.24
SD	47.489	15.806	20.205	21.504	25.923
Median	65.90	61.60	79.10	75.90	68.45
Range	64.5-174.6	46.7-94.2	51.1-114.4	56.4-116.4	46.7-174.6
Height (cm)					

Mean	166.48	165.55	170.57	168.17	167.53
SD	20.471	12.650	12.448	14.811	13.951
Median	160.00	169.00	170.00	169.00	168.00
Range	150.4-201.0	142.0-179.0	152.0-193.0	145.0-188.0	142.0-201.0
ECOG performance status					
0	3 (60.0)	4 (40.0)	2 (28.6)	3 (50.0)	12 (42.9)
1	2 (40.0)	5 (50.0)	4 (57.1)	2 (33.3)	13 (46.4)
2	0	1 (10.0)	1 (14.3)	1 (16.7)	3 (10.7)

Disease history by dose (FAS)

	3 mg/kg N=5	10 mg/kg N=10	20 mg/kg N=7	40 mg/kg N=6	All patients N=28
ISS stage at the initial diagnosis, n (%)					
Stage I	2 (40.0)	2 (20.0)	2 (28.6)	4 (66.7)	10 (35.7)
Stage II	1 (20.0)	3 (30.0)	1 (14.3)	2 (33.3)	7 (25.0)
Stage III	1 (20.0)	4 (40.0)	2 (28.6)	0	7 (25.0)
Missing	1 (20.0)	1 (10.0)	2 (28.6)	0	4 (14.3)
Time since initial diagnosis of multiple myeloma (months)					
n	5	10	7	6	28
Mean (SD)	22.94 (7.936)	33.98 (23.056)	46.25 (18.039)	58.79 (52.301)	40.39 (30.350)
Median	20.40	27.01	48.20	49.69	30.03
Min-Max	17.2-36.6	4.9-84.2	22.7-76.7	3.9-122.3	3.9-122.3
Current ISS stage, n (%)					
Stage I	2 (40.0)	3 (30.0)	2 (28.6)	5 (83.3)	12 (42.9)
Stage II	0	4 (40.0)	1 (14.3)	1 (16.7)	6 (21.4)
Stage III	1 (20.0)	2 (20.0)	2 (28.6)	0	5 (17.9)
Missing	2 (40.0)	1 (10.0)	2 (28.6)	0	5 (17.9)
Patient relapsed or refractory from last treatment, n (%)					
Relapsed	2 (40.0)	2 (20.0)	4 (57.1)	2 (33.3)	10 (35.7)
Refractory	3 (60.0)	8 (80.0)	3 (42.9)	4 (66.7)	18 (64.3)
Time since most recent relapse (months)					
n	2	2	4	2	10
Mean (SD)	1.84 (1.347)	3.12 (3.067)	2.85 (1.214)	4.62 (0.860)	3.06 (1.646)
Median	1.84	3.12	2.38	4.62	2.69
Min-Max	0.9-2.8	1.0-5.3	2.0-4.6	4.0-5.2	0.9-5.3
Immunoglobulin class, n (%)					
IgG	3 (60.0)	7 (70.0)	3 (42.9)	4 (66.7)	17 (60.7)
IgA	2 (40.0)	2 (20.0)	2 (28.6)	0	6 (21.4)
IgM	0	0	1 (14.3)	1 (16.7)	2 (7.1)
Indeterminate*	0	1 (10.0)	1 (14.3)	1 (16.7)	3 (10.7)
Light chain type, n (%)					
Kappa	4 (80.0)	8 (80.0)	5 (71.4)	3 (50.0)	20 (71.4)
Lambda	0	2 (20.0)	1 (14.3)	2 (33.3)	5 (17.9)
Indeterminate	1 (20.0)	0	0	0	1 (3.6)
Missing	0	0	1 (14.3)	1 (16.7)	2 (7.1)

Max = maximum, Min = minimum, SD= standard deviation
*: non-secretory

Outcome measures

Analysis of MTD - Summary of posterior distribution of DLT rates at end of study (Dose determining set)

Dose (mg/kg)	Posterior probabilities that Pr(DLT) is in interval:					Quantile		
	0-0.16	0.16-0.33	0.33-1	Mean	SD	2.5%	50%	97.5%
3	1	0	0	0.023	0.018	0.003	0.018	0.071
10	0.998	0.0002	0	0.034	0.025	0.005	0.028	0.099
20	0.991	0.0009	0	0.044	0.033	0.007	0.036	0.129
40	0.961	0.0038	0.001	0.058	0.046	0.008	0.046	0.181

Efficacy results

New skeletal-related events (SREs) by dose and cycle (FAS)

	3 mg/kg N=5 n (%)	10 mg/kg N=10 n (%)	20 mg/kg N=7 n (%)	40 mg/kg N=6 n (%)	All patients N=28 n (%)
Baseline					
Symptomatic SRE					
Yes	3 (60.0)	6 (60.0)	5 (71.4)	3 (50.0)	17 (60.7)
No	0	1 (10.0)	0	0	1 (3.6)
Missing	1 (20.0)	0	0	0	1 (3.6)
Skeletal related events					
Pathologic fractures - vertebral	3 (60.0)	3 (30.0)	1 (14.3)	0	7 (25.0)
Pathologic fractures - non vertebral	0	2 (20.0)	2 (28.6)	0	4 (14.3)
Spinal cord compression	0	3 (30.0)	0	2 (33.3)	5 (17.9)
Radiation to bone	1 (20.0)	0	3 (42.9)	0	4 (14.3)
Surgery to bone	0	0	0	1 (16.7)	1 (3.6)
Cycle 2					
Symptomatic SRE					
Yes	0	1 (10.0)	0	0	1 (3.6)
No	0	0	0	0	0
Skeletal related events					
Spinal cord compression	0	1 (10.0)	0	0	1 (3.6)
Cycle 4					
Symptomatic SRE					
Yes	0	0	0	1 (16.7)	1 (3.6)
No	0	0	0	0	0
Skeletal related events					
Pathologic fractures - non vertebral	0	0	0	1 (16.7)	1 (3.6)
Cycle 6					
Symptomatic SRE					
Yes	1 (20.0)	0	0	0	1 (3.6)

No	0	0	0	0	0
Skeletal related events					
Pathologic fractures - vertebral	1 (20.0)	0	0	0	1 (3.6)
Cycle 12					
Symptomatic SRE					
Yes	0	1 (10.0)	0	0	1 (3.6)
No	0	0	0	0	0
Skeletal related events					
Pathologic fractures - non vertebral	0	1 (10.0)	0	0	1 (3.6)
Cycle 22					
Symptomatic SRE					
Yes	0	0	0	1 (16.7)	1 (3.6)
No	0	0	0	0	0
Skeletal related events					
Pathologic fractures - vertebral	0	0	0	1 (16.7)	1 (3.6)

Summary of PK parameters for serum BHQ880 by dose and cycle (cycle 1 and 2) (FAS)

Cycle PK Parameter (Unit)	3 mg/kg (N=5)	10 mg/kg (N=10)	20 mg/kg (N=7)	40 mg/kg (N=6)	All patients (N=28)
Cycle 1					
$AUC_{0\text{-}168h}$ (h.mg/mL)	3.49 (46.4)	19.34 (31.13)	41.35 (26.40)	92.75 (35.71)	24.30 (93.69)
$AUC_{0\text{-}672h}$ (h.mg/mL)	6.63 (61.43)	37.58 (35.05)	84.08 (36.31)	190.15 (45.48)	52.64 (96.77)
T_{max} (h)	2.0000 [0.083 - 164.000]	1.0830 [0.033 - 2.667]	1.9500 [0.083 - 2.000]	1.1665 [0.083 - 2.167]	1.9750 [0.033 - 164.000]
C_{max} (ug/mL)	46.242 (48.429)	244.511 (58.653)	391.795 (21.085)	938.976 (32.536)	272.618 (86.676)
C_{last} (ug/mL)	1.969 (101.942)	10.481 (144.367)	54.364 (56.959)	74.538 (68.877)	17.867 (122.439)
T_{last} (h)	465.749 (40.636)	633.353 (39.260)	567.195 (44.294)	690.105 (18.663)	594.040 (36.756)
$T_{1/2}$ (day)	5.36 (94.07)	7.99 (57.24)	13.11 (57.25)	13.16 (46.06)	9.37 (62.05)
CL (L/day)	0.74301 (61.97090)	0.41323 (42.46445)	0.31897 (74.03911)	0.29342 (54.21047)	0.39968 (69.21026)
V (L)	5.912 (68.195)	4.361 (82.135)	5.077 (20.073)	4.892 (33.378)	4.902 (59.977)
Cycle 2					
$AUC_{0\text{-}168h}$ (h.mg/mL)	5.38 (40.80)	23.11 (15.79)	58.95 (37.30)	123.53 (21.68)	33.51 (88.43)
$AUC_{0\text{-}672h}$ (h.mg/mL)	10.87 (62.81)	47.15 (12.97)	136.77 (40.89)	272.81 (34.97)	73.42 (93.75)
T_{max} (h)	0.0830[0.083 - 2.000]	0.1670[0.050 - 21.250]	0.1665[0.083 - 23.950]	2.0000[0.167 - 2.500]	0.2085[0.050 - 23.950]
C_{max} (ug/mL)	50.072 (44.246)	217.133 (16.264)	490.835 (31.977)	1133.896 (13.257)	302.437 (86.794)
C_{last} (ug/mL)	6.311 (90.579)	28.091 (61.094)	91.593 (60.034)	108.410 (75.349)	40.175 (109.823)

T_{last} (h)	504.928 (35.568)	613.537 (24.524)	632.789 (10.374)	809.839 (19.925)	636.086 (25.297)
$T_{1/2}$ (day)	9.75 (111.07)	12.09 (52.55)	13.74 (40.19)	16.12 (55.72)	12.85 (61.97)
CL (L/day)	0.42517 (72.43862)	0.24322 (25.88280)	0.22683 (88.03408)	0.18084 (82.07787)	0.24694 (78.26902)
V (L)	5.655 (66.475)	3.951 (32.114)	4.536 (34.504)	3.755 (24.756)	4.329 (46.947)

Values are median (range) for T_{max}, and Geo mean (CV% mean) for all other parameters
CV% = CV% geo-mean = sqrt (exp (variance for log transformed data)-1*100)

Summary of total DKK1 levels (ng/mL) in serum by dose and cycle

Cycle: cycle 1

Scheduled Sampling Timepoint (h)	Statistics	3 mg/kg (N = 5)	10 mg/kg (N = 10)	20 mg/kg (N = 7)	40 mg/kg (N = 6)	All patients (N = 28)
0 (predose)	N	4	8	7	3	22
	Mean (SD)	3.87 (1.465)	6.93 (3.512)	4.85 (2.726)	2.73 (0.781)	5.14 (2.996)
	Median	3.32	6.35	4.48	3.13	4.16
	[Min; Max]	[2.8; 6.0]	[3.3; 13.8]	[2.3; 10.5]	[1.8; 3.2]	[1.8; 13.8]
	[25th; 75th]	[3.0; 4.7]	[4.0; 8.9]	[2.78; 5.44]	[1.8; 3.2]	[3.2; 6.3]
0.083	N	4	6	6	5	21
	Mean (SD)	5.00 (2.748)	10.60 (6.823)	10.03 (10.492)	3.48 (1.469)	7.68 (7.126)
	Median	4.75	9.58	5.83	3.32	5.54
	[Min; Max]	[1.9; 8.6]	[3.0; 22.8]	[2.5; 30.5]	[1.9; 5.54]	[1.9; 30.5]
	[25th; 75th]	[3.1; 6.9]	[6.1; 12.4]	[3.9; 11.6]	[2.4; 4.3]	[3.3; 9.3]
2	N	4	9	7	5	25
	Mean (SD)	6.93 (3.575)	10.39 (6.896)	16.29 (21.177)	6.023 (2.7211)	10.61 (12.118)
	Median	7.16	9.69	6.53	6.005	6.98
	[Min; Max]	[2.6; 10.8]	[2.1; 26.2]	[3.0; 60.5]	[2.19; 9.56]	[2.1; 60.5]
	[25th; 75th]	[4.1; 9.8]	[6.5; 12.9]	[4.6; 27.1]	[5.09; 7.27]	[5.1; 10.0]
24	N	4	9	7	6	26
	Mean (SD)	23.48 (26.749)	42.86 (43.609)	74.51 (78.803)	19.15 (18.620)	42.93 (52.245)
	Median	13.62	26.07	20.81	15.14	19.97
	[Min; Max]	[3.9; 62.8]	[6.8; 125.5]	[6.6; 199.3]	[2.7; 52.7]	[2.7; 199.3]
	[25th; 75th]	[7.0; 40.0]	[13.2; 52.3]	[12.0; 152.5]	[4.0; 25.3]	[10.1; 52.7]
168	N	5	6	6	6	23
	Mean (SD)	41.51 (21.632)	56.24 (35.433)	115.13 (127.850)	50.62 (41.652)	66.93 (73.239)
	Median	31.59	50.75	62.63	42.63	47.83
	[Min; Max]	[17.9; 64.8]	[17.4; 103.4]	[8.1; 302.9]	[9.8; 120.2]	[8.1; 302.9]

	[25th; 75th]	[29.0; 64.2]	[22.5; 92.7]	[14.3; 240.2]	[13.78; 74.71]	[17.9; 92.7]
336	N	4	7	5	5	21
	Mean (SD)	37.03 (6.760)	113.45 (90.827)	135.71 (113.139)	65.22 (46.027)	92.71 (82.989)
	Median	35.07	75.31	114.37	40.41	50.64
	[Min; Max]	[31.3; 46.6]	[18.9; 269.7]	[9.9; 320.5]	[18.2; 126.2]	[9.9; 320.5]
	[25th; 75th]	[32.45; 41.62]	[47.8; 187.5]	[111.7; 122.1]	[40.0; 101.3]	[36.6; 122.1]
504	N	4	5	5	6	20
	Mean (SD)	26.90 (13.154)	126.86 (114.762)	127.76 (120.556)	52.98 (31.329)	84.93 (89.971)
	Median	22.51	98.57	123.14	49.47	55.69
	[Min; Max]	[16.8; 45.8]	[23.1; 320.4]	[11.7; 319.5]	[21.8; 100.5]	[11.7; 320.4]
	[25th; 75th]	[18.1; 35.7]	[66.3; 125.9]	[40.5; 143.9]	[24.9; 71.7]	[24.0; 111.8]

CV% = coefficient of variation (%) = sd/mean*100
CV% geo-mean = sqrt (exp (variance for log transformed data)-1)*100

Safety Results

Adverse events, regardless of study drug relationship, by primary system organ class (safety set)

Primary system organ class	3 mg/kg N=5 n (%)	10 mg/kg N=10 n (%)	20 mg/kg N=7 n (%)	40 mg/kg N=6 n (%)	All patients N=28 n (%)
Any primary system organ class	5(100.0)	9 (90.0)	7(100.0)	6(100.0)	27 (96.4)
General Disorders and Administration Site Conditions	5(100.0)	6 (60.0)	4 (57.1)	5 (83.3)	20 (71.4)
Musculoskeletal and Connective Tissue Disorders	3 (60.0)	6 (60.0)	6 (85.7)	5 (83.3)	20 (71.4)
Gastrointestinal Disorders	3 (60.0)	7 (70.0)	4 (57.1)	5 (83.3)	19 (67.9)
Infections and Infestations	3 (60.0)	7 (70.0)	4 (57.1)	4 (66.7)	18 (64.3)
Metabolism and Nutrition Disorders	3 (60.0)	7 (70.0)	4 (57.1)	3 (50.0)	17 (60.7)
Respiratory, Thoracic and Mediastinal Disorders	2 (40.0)	4 (40.0)	4 (57.1)	3 (50.0)	13 (46.4)
Blood and Lymphatic System Disorders	2 (40.0)	7 (70.0)	2 (28.6)	1 (16.7)	12 (42.9)
Nervous System Disorders	2 (40.0)	3 (30.0)	4 (57.1)	3 (50.0)	12 (42.9)
Psychiatric Disorders	4 (80.0)	3 (30.0)	1 (14.3)	3 (50.0)	11 (39.3)
Injury, Poisoning and Procedural Complications	2 (40.0)	3 (30.0)	2 (28.6)	3 (50.0)	10 (35.7)
Vascular Disorders	1 (20.0)	5 (50.0)	1 (14.3)	2 (33.3)	9 (32.1)
Skin And Subcutaneous Tissue Disorders	2 (40.0)	1 (10.0)	2 (28.6)	3 (50.0)	8 (28.6)
Renal and Urinary Disorders	2 (40.0)	3 (30.0)	1 (14.3)	1 (16.7)	7 (25.0)
Investigations	2 (40.0)	1 (10.0)	0	3 (50.0)	6 (21.4)
Cardiac Disorders	0	3 (30.0)	1 (14.3)	1 (16.7)	5 (17.9)
Eye Disorders	1 (20.0)	1 (10.0)	2 (28.6)	1 (16.7)	5 (17.9)
Ear and Labyrinth Disorders	0	1 (10.0)	0	2 (33.3)	3 (10.7)

Immune System Disorders	0	1 (10.0)	0	1 (16.7)	2 (7.1)
Endocrine Disorders	1 (20.0)	0	0	0	1 (3.6)
Reproductive System and Breast Disorders	0	1 (10.0)	0	0	1 (3.6)

Primary system organ classes are presented in descending frequency.

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 adverse events is counted only once in the “Any primary system organ class” row.

Commonly reported adverse events, regardless of study drug relationship, occurring in ≥10% patients by preferred term and dose (Safety set)

	3 mg/kg N=5		10 mg/kg N=10		20 mg/kg N=7		40 mg/kg N=6		All Patients N=28	
Preferred Term	All grades n (%)	Grade 3/4 n (%)	All grades n (%)	Grade 3/4 n (%)	All grades n (%)	Grade 3/4 n (%)	All grades n (%)	Grade 3/4 n (%)	All grades n (%)	Grade 3/4 n (%)
Total	5 (10)	3 (60)	9 (90)	8 (80)	7 (100)	4 (57.1)	6 (100)	5 (83.3)	27 (96.4)	20 (71.4)
Fatigue	4 (80)	1 (20)	5 (50)	0	1 (14.3)	0	3 (50)	1 (16.7)	13 (46.4)	2 (7.1)
Constipation	2 (40)	0	4 (40)	0	3 (42.9)	0	2 (33.3)	0	11 (39.3)	0
Hypokalaemia	2 (40)	1 (20)	5 (50)	1 (10)	2 (28.6)	0	2 (33.3)	1 (16.7)	11 (39.3)	3 (10.7)
Arthralgia	3 (60)	0	3 (30)	0	2 (28.6)	0	1 (16.7)	0	9 (32.1)	0
Anaemia	1 (20)	1 (20)	6 (60)	2 (20)	1 (14.3)	1 (14.3)	0	0	8 (28.6)	4 (14.3)
Hypomagnesaemia	2 (40)	0	2 (20)	0	2 (28.6)	0	2 (33.3)	0	8 (28.6)	0
Insomnia	4 (80)	0	1 (10)	0	1 (14.3)	0	2 (33.3)	0	8 (28.6)	0
Nausea	1 (20)	0	2 (20)	0	2 (28.6)	0	3 (50)	0	8 (28.6)	0
Pyrexia	1 (20)	0	3 (30)	0	2 (28.6)	0	2 (33.3)	0	8 (28.6)	0
Thrombocytopenia	0	0	4 (40)	4 (40)	2 (28.6)	2 (28.6)	1 (16.7)	1 (16.7)	7 (25)	7 (25)
Back Pain	2 (40)	0	1 (10)	0	3 (42.9)	0	0	0	6 (21.4)	0
Diarrhoea	0	0	3 (30)	0	2 (28.6)	0	1 (16.7)	0	6 (21.4)	0
Dyspnoea	1 (20)	0	1 (10)	0	1 (14.3)	0	3 (50)	2 (33.3)	6 (21.4)	2 (7.1)
Headache	0	0	1 (10)	0	2 (28.6)	0	3 (50)	0	6 (21.4)	0

Hypophosphataemia	2 (40)	1 (20)	2 (20)	0	2 (28.6)	1 (14.3)	0	0	6 (21.4)	2 (7.1)
Neuropathy Peripheral	1 (20)	0	1 (10)	0	3 (42.9)	0	1 (16.7)	0	6 (21.4)	0
Oedema Peripheral	0	0	1 (10)	1 (10)	2 (28.6)	0	3 (50)	0	6 (21.4)	1 (3.6)
Pain In Extremity	0	0	0	0	4 (57.1)	1 (14.3)	2 (33.3)	0	6 (21.4)	1 (3.6)
Pneumonia	1 (20)	1 (20)	3 (30)	2 (20)	0	0	2 (33.3)	2 (33.3)	6 (21.4)	5 (17.9)
Upper Respiratory Tract Infection	1 (20)	0	2 (20)	0	3 (42.9)	0	0	0	6 (21.4)	0
Abdominal Pain	1 (20)	0	2 (20)	1 (10)	0	0	2 (33.3)	1 (16.7)	5 (17.9)	2 (7.1)
Cough	0	0	1 (10)	0	2 (28.6)	0	2 (33.3)	0	5 (17.9)	0
Hypotension	0	0	3 (30)	2 (20)	0	0	2 (33.3)	1 (16.7)	5 (17.9)	3 (10.7)
Neutropenia	1 (20)	1 (20)	2 (20)	1 (10)	1 (14.3)	1 (14.3)	1 (16.7)	1 (16.7)	5 (17.9)	4 (14.3)
Sinusitis	1 (20)	0	2 (20)	1 (10)	0	0	2 (33.3)	0	5 (17.9)	1 (3.6)
Bone Pain	1 (20)	0	0	0	1 (14.3)	0	2 (33.3)	1 (16.7)	4 (14.3)	1 (3.6)
Dizziness	2 (40)	0	2 (20)	0	0	0	0	0	4 (14.3)	0
Muscle Spasms	1 (20)	0	0	0	3 (42.9)	0	0	0	4 (14.3)	0
Sepsis	0	0	4 (40)	2 (20)	0	0	0	0	4 (14.3)	2 (7.1)
Syncope	0	0	2 (20)	1 (10)	1 (14.3)	1 (14.3)	1 (16.7)	0	4 (14.3)	2 (7.1)
Asthenia	0	0	2 (20)	0	0	0	1 (16.7)	0	3 (10.7)	0
Hyperglycaemia	1 (20)	0	1 (10)	0	1 (14.3)	0	0	0	3 (10.7)	0
Hypertension	0	0	1 (10)	0	1 (14.3)	0	1 (16.7)	0	3 (10.7)	0
Leukopenia	0	0	3 (30)	3 (30)	0	0	0	0	3 (10.7)	3 (10.7)
Muscular Weakness	0	0	0	0	0	0	3 (50)	2 (33.3)	3 (10.7)	2 (7.1)
Pain	0	0	0	0	0	0	3 (50.0)	1 (16.7)	3 (10.7)	1 (3.6)

Stomatitis	1 (20)	0	2 (20)	0	0	0	0	0	3 (10.7)	0
Vomiting	0	0	1 (10)	0	2 (28.6)	0	0	0	3 (10.7)	0

Preferred terms are sorted 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 adverse events is counted only once in the "Total" row.

Serious Adverse Events and Deaths

Summary of deaths and adverse events - Safety set

	3 mg/kg N=5 n (%)	10 mg/kg N=10 n (%)	20 mg/kg N=7 n (%)	40 mg/kg N=6 n (%)	All Patients N=28 n (%)
Any AE	5(100.0)	9 (90.0)	7(100.0)	6(100.0)	27 (96.4)
Any grade 3/4 AE	3 (60.0)	8 (80.0)	4 (57.1)	5 (83.3)	20 (71.4)
Any AE suspected to be related to study drug	3 (60.0)	4 (40.0)	2 (28.6)	1 (16.7)	10 (35.7)
Any AE that resulted in study drug dose interruption	3 (60.0)	2 (20.0)	1 (14.3)	3 (50.0)	9 (32.1)
Any AE that resulted in study drug discontinuation	0	1 (10.0)	1 (14.3)	0	2 (7.1)
Any SAE	1 (20.0)	8 (80.0)	3 (42.9)	4 (66.7)	16 (57.1)
Death	0	0	1 (14.3)	0	1 (3.6)

A patient with multiple occurrences of an AE under one treatment group is counted only once for the AE in that treatment group.

A patient with multiple AEs is only counted once in the "Any AE" row.

Other Relevant Findings

None

Date of Clinical Trial Report

05-Sep-2012

Date Inclusion on Novartis Clinical Trial Results Database

07-Nov-2012

Date of Latest Update