Sponsor

Novartis

Generic Drug Name

BHQ880

Trial Indication(s)

Smoldering multiple myeloma (SMM) and a high-risk of progression to multiple myeloma

Protocol Number

CBHQ880A2204

Protocol Title

A single-arm, open-label, Phase II clinical trial evaluating disease response following treatment with intravenous BHQ880, a fully human, anti-Dickkopf1 (DKK1) neutralizing antibody in previously untreated patients with high-risk, smoldering multiple myeloma

Clinical Trial Phase

Phase II

Phase of Drug Development

Phase II

Study Start/End Dates

25-May-2011 (first patient first visit) to 27-Nov-2013 (last patient last visit)

Reason for Termination

Not applicable

Study Design/Methodology

This was an open-label, multicenter, single-arm, Phase II study of BHQ880 planned in 40 patients with high-risk SMM. The study was designed to assess the anti-myeloma effect in SMM patients. This study was planned to evaluate whether DKK1 neutralization leads to at least 20% disease response rate (more than 8 out of 40 evaluable patients).

Center

Ten centers in USA, two in Germany and one in France.

Publication

None

Objectives:

Primary objective:

To assess the objective response rate (ORR) (minor response [MR], or better) after six months of treatment with BHQ880 once every 28 days in previously untreated patients with high-risk SMM.

Secondary objectives:

- To characterize the safety and tolerability of BHQ880
- To assess the overall response rate after 12 months of BHQ880 treatment in previously untreated patients with high-risk SMM.
- To characterize single-dose and monthly-repeated dose PK profile of BHQ880 treatment.
- To investigate the potential immunogenicity of BHQ880.
- To evaluate serum DKK1 and DKK4 levels at baseline and following BHQ880 administration.
- Evaluate the effect of BHQ880 on bone metabolism.

Test Products, Dose, and Mode of Administration

BHQ880 was administered at 10 mg/kg in 250 mL 5% Dextrose Injection USP or equivalent as an intravenous infusion over 2 hours on Day 1 of a 28-day treatment cycle.

Statistical Methods

The frequency of each response category as well as ORR (MR or better) and DPR at 6 months were presented. The binomial distribution was used to assess the ORR and DPR following BHQ880 treatment. The ORR and DPR estimates at 6 months were presented with an exact 95% confidence interval.

The overall response rate after 12 cycles of BHQ880 treatment was evaluated by ORR at 12 months of BHQ880 treatment. The ORR at 12 months of BHQ880 was the proportion of responders, with a MR or better observed within 12 cycles following BHQ880 treatment. Overall disease response was determined at 6 and 12 months of BHQ880 treatment.

The percentage change in BMD (corrected value) from baseline to 6 and 12 months of BHQ880 treatment and changes in biomarkers of anabolic bone activity (OC, P1NP) and bone resorption (urine NTx) from baseline in response to BHQ880 treatment were evaluated.

Descriptive statistics of PK parameters including mean, standard deviation, coefficient of variability (CV) (%), minimum, and maximum were presented for the primary (primary PK parameters are AUC0-tlast, Cmax, AR, Tmax, and Tlast) and secondary PK parameters.

Study Population: Key Inclusion/Exclusion Criteria

Adult patients who had been diagnosed with high-risk SMM and had not received any previous anti-myeloma treatment were eligible to participate in the study.

Participant Flow Table

Patient disposition (Full Analysis Set)

	BHQ880 10 mg/kg N=41 n (%)
Subjects treated	
Treatment completed as per protocol	26 (63.4)
Treatment discontinued	15 (36.6)
Primary reason for end of treatment	
Adverse Event(s)	2 (4.9)
Subject withdrew consent	1 (2.4)
Administrative problems	1 (2.4)
Disease progression	11 (26.8)
Treatment duration completed as per protocol	26 (63.4)
Primary reason for study evaluation completion	
Subject withdrew consent	1 (2.4)
Disease progression	3 (7.3)
Follow-up phase completed as per protocol	37 (90.2)

End of study visit occurred 90 days after the last dose of study treatment. Women of childbearing potential were followed for 8 months after last dose.

Baseline Characteristics

Demographic and other baseline characteristics (Full Analysis Set)

Demographic variable	BHQ880 10 mg/kg N=41
Age (Years)	
n	41
Mean (SD)	60.3 (10.77)
Median (Range)	63.0 (42, 84)
25^{th}, 75^{th} percentile	52.0, 69.0
Age category (Years), n (%)	
≤ 65	24 (58.5)
≥ 65	17 (41.5)
Sex, n (%)	
Male	31 (75.6)
Female	10 (24.4)
Race, n (%)	
Caucasian	41 (100.0)
Ethnicity, n (%)	

Demographic variable	BHQ880 10 mg/kg N=41
Hispanic/Latino	2 (4.9)
Mixed ethnicity	2 (4.9)
Other	37 (90.2)
Weight (kg)	
n	41
Mean (SD)	83.10 (17.402)
Median (Range)	81.20 (55.9, 122.0)
25^{th}, 75^{th} percentile	69.00, 94.10
Height (cm)	
n	40
Mean (SD)	173.3 (9.74)
Median (Range)	175.4 (154,189)
25^{th}, 75^{th} percentile	165.7, 180.0
Missing	1
ECOG performance status, n (%)	
0	36 (87.8)
1	5 (12.2)

Summary of Efficacy

Primary Outcome Result(s)

Summary of best disease response at 6 months and 12 months of treatment (Full Analysis Set)

	BHQ880 10 mg/kg N=41	
	Month 6	Month 12
Best response, n (%)		
Complete response (CR)	0	0
Very good partial response (VGPR)	0	0
Partial response (PR)	0	0
Minor response (MR)	0	0
Stable disease (SD)	30 (73.2)	23 (56.1)
Progressive disease (PD)	0	3 (7.3)
Progression to active multiple myeloma (PAMM[1])	7 (17.1)	11 (26.8)
Discontinued for other reasons (UNK)	1 (2.4)	4 (9.8)
Not evaluable (NE)	3 (7.3)	0
Disease progression rate (PAMM)		
n (%)	7 (17.1)	11 (26.8)
95% CI2	(7.2, 32.1)	(14.2, 42.9)
Overall response rate (CR+VGPR+PR+MR)		
n (%)	0	0
95% CI[2]	(0.0, 8.6)	(0.0, 8.6)

	BHQ880 10 mg/kg N=41	
	Month 6	Month 12

[1] PAMM included responses, “Progression to active multiple myeloma (PAMM)”, “PD but not evaluable for PAMM (NEPAMM)” and “Discontinue for clinical PD (UNKPAMM)”.
[2] 95% CI was estimated using an exact binomial distribution.

Secondary Outcome Results

ORR at 12 months following BHQ880 treatment

There were no patients with a response of CR, VGPR, PR, or MR (ORR: 0; 95% CI: 0.0, 8.6). The DPR (95% CI) at 12 months was 26.8% (14.2, 42.9) (see table above of primary outcome results).

Pharmacokinetic results

Summary of PK parameters by Cycle (Pharmacokinetic Analysis Set)

PK Parameter (Unit)	Cycle 1	Cycle 4
AUC (0-tlast) (h.µg/mL)	n=5	n=5
	41350.9 (30.96)	55114.5 (47.68)
Tmax (h)	n=5	n=5
	2.0 (2 to 2)	2.0 (2 to 2)
Cmax (µg/mL)- PK group 1	n=5	n=5
	184.5 (28.23)	216.8 (32.74)
Cmax (µg/mL)- PK group 2	n=33	n=29
	179.8 (20.30)	217.9 (31.96)
Cmax (µg/mL)- Combined	n=38	n=34
	180.4 (21.03)	217.7 (31.55)
Tlast (h)	n=5	n=5
	599.0 (15.86)	565.5 (15.86)
t1/2 (day)	n=5	n=5
	14.1 (46.07)	14.7 (58.96)
CL (L/h)	n=5	n=5
	0.014 (72.5242)	0.010 (107.8479)
V (L)	n=5	n=5
	7.02 (42.601)	4.92 (43.931)
AR		n=5
		1.175 (13.262)

Values are median (range) for Tmax, and geometric mean (CV%) for all other parameters.
All PK parameters were calculated using intensive PK group (Group 1), except where indicated.

Potential immunogenicity of BHQ880

Immunogenicity by cycle (Full Analysis Set)

	BHQ880
	10 mg/kg

	N=41
C1D1	
NO	37 (90.2)
BLQ	1 (2.4)
ALQ	2 (4.9)
Missing	1 (2.4)
C3D1	
NO	35 (85.4)
ALQ	1 (2.4)
Missing	5 (12.2)
C6D1	
NO	30 (73.2)
ALQ	1 (2.4)
Missing	10 (24.4)
C9D1	
NO	21 (51.2)
ALQ	1 (2.4)
Missing	19 (46.3)
C12D1	
NO	15 (36.6)
ALQ	1 (2.4)
Missing	25 (61.0)

NO: No immunogenicity, BLQ: positive immunogenicity < LLOQ, ALQ: positive immunogenicity > LLOQ.

Evaluation of baseline free serum DKK1 after BHQ880 treatment

Summary of total DKK1 level in serum (Full Analysis Set)

		DKK1		
Schedule sampling timepoint (h)	**Statistics**	**PK Group 1**	**PK Group 2**	**Overall**
Baseline	n	5	33	38
	Mean (SD)	2.57 (1.554)	3.94 (1.908)	3.76 (1.905)
	Median	2.82	3.86	3.69
	[Min; Max]	[0.00; 4.15]	[0.00; 11.50]	[0.00; 11.50]
	[25^{th}; 75^{th}]	[2.59; 3.27]	[3.07; 4.67]	[3.06; 4.53]
Cycle 1				
Baseline	n	3		3
	Mean (SD)	1.95 (1.725)		1.95 (1.725)
	Median	2.59		2.59
	[Min; Max]	[0.00; 3.27]		[0.00; 3.27]
	[25^{th}; 75^{th}]	[0.00; 3.27]		[0.00; 3.27]
Hour 672	n	3		3
	Mean (SD)	47.27 (16.384)		47.27 (16.384)
	Median	39.4		39.4
	[Min; Max]	[36.30; 66.10]		[36.30; 66.10]
	[25^{th}; 75^{th}]	[36.30; 66.10]		[36.30; 66.10]

Change from baseline	n	3		3
	Mean (SD)	45.31 (16.077)		45.31 (16.077)
	Median	39.4		39.4
	[Min; Max]	[33.03; 63.51]		[33.03; 63.51]
	[25th; 75th]	[33.03; 63.51]		[33.03; 63.51]
% Change from baseline	n	2		2
	Mean (SD)	1731.11 (1019.670)		1731.11 (1019.670)
	Median	1731.11		1731.11
	[Min; Max]	[1010.09; 2452.12]		[1010.09; 2452.12]
	[25th; 75th]	[1010.09; 2452.12]		[1010.09; 2452.12]
Cycle 4				
Baseline	n	3		3
	Mean (SD)	2.47 (2.187)		2.47 (2.187)
	Median	3.27		3.27
	[Min; Max]	[0.00; 4.15]		[0.00; 4.15]
	[25th; 75th]	[0.00; 4.15]		[0.00; 4.15]
Hour 672	n	3		3
	Mean (SD)	41.50 (4.468)		41.50 (4.468)
	Median	42.9		42.9
	[Min; Max]	[36.50; 45.10]		[36.50; 45.10]
	[25th; 75th]	[36.50; 45.10]		[36.50; 45.10]
Change from base	n	3		3
	Mean (SD)	39.03 (5.114)		39.03 (5.114)
	Median	40.95		40.95
	[Min; Max]	[33.23; 42.90]		[33.23; 42.90]
	[25th; 75th]	[33.23; 42.90]		[33.23; 42.90]
% Change from baseline	n	2		2
	Mean (SD)	1001.48 (20.832)		1001.48 (20.832)
	Median	1001.48		1001.48
	[Min; Max]	[986.75; 1016.21]		[986.75; 1016.21]
	[25th; 75th]	[986.75; 1016.21]		[986.75; 1016.21]
Maximum % Change	n	4	29	33
	Mean (SD)	2435.69 (1351.369)	1666.69 (939.481)	1759.91 (1004.222)
	Median	2059.02	1661.01	1661.01
	[Min; Max]	[1361.77; 4262.93]	[358.17; 4670.11]	[358.17; 4670.11]
	[25th; 75th]	[1414.02; 3457.35]	[962.26; 2218.41]	[1115.95; 2259.81]

Baseline value was defined as the last non-missing value before first BHQ dose.

PK Group 1: More intense (more time points) PK profile;

PK Group 2: Less intense profile (measurements at only pre-infusion and 2 hours post-infusion).

Effect of BHQ880 on bone

Summary of bone mineral density assessed by DXA (Full Analysis Set)

Visit	Statistics	L1-L4 Lumbar spine (g/cm^2)	Total hip with proximal femur (g/cm^2)	Forearm (g/cm^2)
Baseline[1]	n	39	39	32
	Mean	1.0820	0.9497	0.6577
	SD	0.20471	0.14054	0.09307
Baseline[2]	n	39	37	31
	Mean	1.0820	0.9437	0.6564
	SD	0.20471	0.14181	0.09429
Cycle 7 Day 1	n	39	37	31
	Mean	1.0754	0.9396	0.6484
	SD	0.20362	0.14624	0.08821
% Change from baseline	n	39	37	31
	Mean	-0.514	-0.415	-1.065
	SD	4.0170	4.0326	3.5605
Baseline[3]	n	30	30	23
	Mean	1.0958	0.9603	0.6738
	SD	0.21761	0.14585	0.09540
EOT	n	30	30	23
	Mean	1.0969	0.9657	0.6654
	SD	0.22352	0.15522	0.08721
% Change from baseline	n	30	30	23
	Mean	0.043	0.499	-1.044
	SD	3.7152	3.5958	3.5700

[1] It is for all patients.

[2] It is only for patients who have data at both baseline and C7D1.

[3] It is only for patients who have data at both baseline and EOT.

Corrected values of BMD are used for lumbar spine and hip; uncorrected values of BMD are used for forearm.

EOT: End Of Treatment

Effect of BHQ880 on bone metabolism (bone biomarkers)

Summary of bone biomarkers by visit (Full Analysis Set)

Visit	Statistics	Osteocalcin (ug/L)	P1NP (ng/mL)	uNTx/Cr (nmol BCE)
Baseline	n	40	40	39
	Mean (SD)	21.89	50.25	43.13
	SD	9.392	21.601	18.569
	Median	19.43	46.94	37.00
	[Min; Max]	[10.9; 60.4]	[22.6; 129.4]	[19.0; 101.0]
	[25th; 75th]	[16.58; 23.37]	[34.87; 58.03]	[30.00; 50.00]
Cycle 6 Day 1	n	36	36	35
	Mean	23.97	48.01	41.91
	SD	12.240	22.732	18.043
	Median	20.29	41.86	37.00
	[Min; Max]	[10.1; 69.1]	[17.7; 113.1]	[16.0; 88.0]

Visit	Statistics	Osteocalcin (ug/L)	P1NP (ng/mL)	uNTx/Cr (nmol BCE)
	[25th; 75th]	[17.00; 26.25]	[33.30; 57.63]	[28.00; 51.00]
% Change from baseline	n	36	36	35
	Mean	11.87	0.16	3.46
	SD	31.392	28.433	30.930
	Median	8.03	-4.29	-3.85
	[Min; Max]	[-33.3; 126.9]	[-55.2; 96.8]	[-39.5; 82.6]
	[25th; 75th]	[-4.14; 24.22]	[-18.43; 13.37]	[-18.18; 19.15]
Cycle 12 Day 1	n	26	26	25
	Mean	22.26	42.37	35.96
	SD	10.624	20.948	13.303
	Median	21.54	40.74	32.00
	[Min; Max]	[10.2; 66.6]	[23.4; 131.9]	[15.0; 68.0]
	[25th; 75th]	[15.64; 23.80]	[28.86; 47.01]	[26.00; 44.00]
% Change from baseline	n	26	26	25
	Mean	12.95	-1.49	3.05
	SD	22.363	23.376	33.207
	Median	12.42	-2.33	-4.00
	[Min; Max]	[-37.8; 57.4]	[-42.1; 67.9]	[-65.1; 75.8]
	[25th; 75th]	[-1.93; 25.79]	[-9.56; 7.70]	[-17.86; 25.64]
End Of Treatment	n	33	33	28
	Mean	24.73	49.89	44.96
	SD	11.144	31.016	29.994
	Median	22.23	43.32	39.00
	[Min; Max]	[12.8; 72.0]	[19.3; 192.4]	[13.0; 167.0]
	[25th; 75th]	[19.15; 25.97]	[35.08; 53.92]	[25.50; 53.00]
% Change from baseline	n	33	33	28
	Mean	20.59	8.16	9.17
	SD	28.119	35.162	53.918
	Median	19.06	4.65	-5.41
	[Min; Max]	[-32.4; 92.7]	[-38.0; 119.1]	[-48.0; 240.8]
	[25th; 75th]	[1.63; 32.82]	[-17.70; 14.73]	[-17.71; 24.87]
Maximum % Change from baseline	n	40	40	39
	Mean	34.15	30.42	49.98
	SD	31.450	37.276	49.834
	Median	27.27	16.86	39.60
	[Min; Max]	[-8.3; 143.3]	[-18.6; 146.8]	[-21.2; 240.8]
	[25th; 75th]	[18.32; 50.91]	[6.67; 47.78]	[18.42; 67.39]

P1NP: Procollagen type 1 N-terminal propeptide; uNTx/Cr: Creatinine corrected urine N-terminal telopeptide of type 1 collagen (NTx).

Serum DKK4 levels and DKK1 levels in plasma cells at baseline and following BHQ880 administration

The protocol-specified endpoints related to serum DKK4 levels and DKK1 levels in plasma cells were not analyzed because appropriate assays were not available at the time of analysis.

Summary of Safety

Safety Results

Serious adverse events, regardless of causality, by primary system organ class and preferred term (Safety set)

Primary System Organ Class Preferred Term	BHQ880 10 mg/kg N=41 n (%)
Any primary system organ class	3 (7.3)
Infections and infestations	
Pneumonia	1 (2.4)
Neoplasms benign, malignant and unspecified (incl cysts and polyps)	
Total	2 (4.9)
Breast cancer in situ	1 (2.4)
Renal cell carcinoma	1 (2.4)

Primary system organ classes are presented alphabetically. Preferred terms are sorted within primary system organ class in descending frequency.

A subject with multiple occurrences of an AE under one treatment was counted only once in the AE category for that treatment.

A subject with multiple adverse events is counted only once in the total row.

Deaths, SAEs, AEs, and other significant AEs (Safety set)

	BHQ880 10 mg/kg N=41
Deaths	0
On-treatment deaths	0
Due to study indication	0
Due to other reasons	0
SAEs	3 (7.3)
Study drug related SAEs	1 (2.4)
Discontinued due to SAEs	2 (4.9)
AEs	39 (95.1)
Study drug related AEs	22 (53.7)
Discontinued due to AEs	3 (7.3)
Grade 3 or 4 AEs	6 (14.6)

Other Relevant Findings

Not Applicable

Conclusion:

- BHQ880 was safe and well tolerated over multiple cycles of therapy. As with previous studies with BHQ880 (CBHQ880A2102, CBHQ880A2203), there were no significant or unanticipated AEs associated with therapy. Though two patients did develop primary malignancies during the study, these events were unrelated to the study drug.

- BHQ880 demonstrated no direct anti-myeloma effect in smoldering multiple myeloma patients. However, most patients in the study did not experience progression to active multiple myeloma consistent with the natural history of the disease.
- Mean terminal phase T1/2 was approximately 14 days after both Cycle 1 and Cycle 4. The accumulation ratio after the 4^{th} infusion was 1.18, the mean total systemic clearance for BHQ880 was low and Vss was similar to blood volume.
- Target engagement with both single and multiple doses of BHQ880 was clearly demonstrated by the rise in total DKK1 (free DKK1 along with DKK1 complexed with BHQ880).
- Maximal capture and plateau of total DKK1 was reached by day 28 after the first infusion and throughout dosing cycles, suggesting that the current dose and regimen of 10 mg/kg every 28 days bind all available DKK1.
- There was evidence of anabolic bone activity as measured by bone strength changes assessed by serial QCT at the spine.
- Changes in levels of biomarkers of anabolic bone activity (OC, P1NP), and bone resorption (uNTx) in response to BHQ880 treatment were variable and transitory. No significant overall effect of BHQ880 was noted.
- Single-agent BHQ880 treatment resulted in the first evidence of anabolic bone activity using a novel imaging modality that can detect changes earlier than DXA scans in patients with SMM receiving no other antimyeloma therapy

Date of Clinical Trial Report

21 Aug 2014

Date of Initial Inclusion on Novartis Clinical Trial Results website

7 Oct 2014

Date of Latest Update

Reason for Update