



Clinical trial results:

A single-arm, open-label, phase 2 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

Summary

EudraCT number	2010-022029-13
Trial protocol	DE
Global end of trial date	27 November 2013

Results information

Result version number	v1 (current)
This version publication date	13 July 2016
First version publication date	23 July 2015

Trial information

Trial identification

Sponsor protocol code	CBHQ880A2204
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Additional study identifiers

ISRCTN number	-
ClinicalTrials.gov id (NCT number)	NCT01302886
WHO universal trial number (UTN)	-

Notes:

Sponsors

Sponsor organisation name	Novartis Pharma AG
Sponsor organisation address	CH-4002, Basel, Switzerland,
Public contact	Clinical Disclosure Office, Novartis Pharma AG, +41 613241111,
Scientific contact	Clinical Disclosure Office, Novartis Pharma AG, +41 613241111,

Notes:

Paediatric regulatory details

Is trial part of an agreed paediatric investigation plan (PIP)	No
Does article 45 of REGULATION (EC) No 1901/2006 apply to this trial?	No
Does article 46 of REGULATION (EC) No 1901/2006 apply to this trial?	No

Notes:

Results analysis stage

Analysis stage	Final
Date of interim/final analysis	27 November 2013
Is this the analysis of the primary completion data?	No
Global end of trial reached?	Yes
Global end of trial date	27 November 2013
Was the trial ended prematurely?	No

Notes:

General information about the trial

Main objective of the trial:

To assess the overall response rate after BHQ880 treatment in previously untreated patients with high-risk smoldering multiple myeloma (SMM).

Protection of trial subjects:

The study was in compliance with the ethical principles derived from the Declaration of Helsinki and the International Conference on Harmonization (ICH) Good Clinical Practice (GCP) Guidelines. All the local regulatory requirements pertinent to safety of trial subjects were also followed during the conduct of the trial.

Since there are no specific rescue medications for BHQ880, acute allergic reactions or infusion-related reactions could be treated as clinically indicated using accepted guidelines. This included, in the event of anaphylactic reactions, any and all therapies necessary to restore normal cardiopulmonary status. Prophylactic pre-medication could be added if a patient experienced an infusion reaction and sites could then use their own institutional standard of care.

Background therapy: -

Evidence for comparator: -

Actual start date of recruitment	25 May 2011
Long term follow-up planned	No
Independent data monitoring committee (IDMC) involvement?	No

Notes:

Population of trial subjects

Subjects enrolled per country

Country: Number of subjects enrolled	France: 4
Country: Number of subjects enrolled	Germany: 7
Country: Number of subjects enrolled	United States: 30
Worldwide total number of subjects	41
EEA total number of subjects	11

Notes:

Subjects enrolled per age group

In utero	0
Preterm newborn - gestational age < 37 wk	0
Newborns (0-27 days)	0
Infants and toddlers (28 days-23 months)	0

Children (2-11 years)	0
Adolescents (12-17 years)	0
Adults (18-64 years)	24
From 65 to 84 years	17
85 years and over	0

Subject disposition

Recruitment

Recruitment details: -

Pre-assignment

Screening details:

Patients were screened for eligibility over a period of 28 days.

Period 1

Period 1 title	Overall Study (overall period)
Is this the baseline period?	Yes
Allocation method	Not applicable
Blinding used	Not blinded

Arms

Arm title	BHQ880 10mg/kg
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Arm description:

Subjects received BHQ880 for a maximum of twelve 28-day cycles.

Arm type	Experimental
Investigational medicinal product name	BHQ880
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Powder for infusion
Routes of administration	Intravenous use

Dosage and administration details:

BHQ880 was administered at 10 mg/kg in 250 mL of a 5% Dextrose Injection United States Pharmacopeia (USP) or equivalent over 2 hours on Day 1 of a 28-day treatment cycle. The actual body weight in kilograms (kg) recorded at screening was used to calculate the dose for all patients.

Number of subjects in period 1	BHQ880 10mg/kg
Started	41
Completed	26
Not completed	15
Subject withdrew consent	1
Disease progression	11
Adverse event, non-fatal	2
Administrative problems	1

Baseline characteristics

Reporting groups

Reporting group title	BHQ880 10mg/kg
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Reporting group description:

Subjects received BHQ880 for a maximum of twelve 28-day cycles.

Reporting group values	BHQ880 10mg/kg	Total	
Number of subjects	41	41	
Age categorical Units: Subjects			
< 65 years	24	24	
>/= 65 years	17	17	
Age continuous Units: years arithmetic mean standard deviation	60.3 ± 10.77	-	
Gender categorical Units: Subjects			
Female	10	10	
Male	31	31	

End points

End points reporting groups

Reporting group title	BHQ880 10mg/kg
Reporting group description:	
Subjects received BHQ880 for a maximum of twelve 28-day cycles.	

Primary: Number of Subjects With Overall Response (OR) of Minor Response (MR) or Better After 6 Months of Treatment with BHQ880

End point title	Number of Subjects With Overall Response (OR) of Minor Response (MR) or Better After 6 Months of Treatment with BHQ880 ^[1]
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End point description:

The Overall Response (OR) was defined as MR or better, with better being partial, very good partial, or complete response. Multiple myeloma (MM) response was evaluated by using modified international multiple myeloma working group (IMWG) criteria. This assessment included M-protein quantification and serum free light chain (FLC) assay following administration of BHQ880. Additionally, urine specimens for M-protein quantification and urine immunofixation, serum samples for serum immunofixation, bone marrow biopsy and aspirate, skeletal surveys, and magnetic resonance imaging (MRI) of the spine were also collected.

This endpoint analyzed the Full Analysis Set (FAS), defined as all patients who received at least one dose (full or partial) of BHQ880.

End point type	Primary
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End point timeframe:

Six 28-day treatment cycles

Notes:

[1] - No statistical analyses have been specified for this primary end point. It is expected there is at least one statistical analysis for each primary end point.

Justification: No statistical analysis was planned for this primary outcome measure.

End point values	BHQ880 10mg/kg			
Subject group type	Reporting group			
Number of subjects analysed	41			
Units: subjects	0			

Statistical analyses

No statistical analyses for this end point

Secondary: Number of Subjects With Overall Response (OR) of Minor Response (MR) or Better After 12 Months of Treatment with BHQ880

End point title	Number of Subjects With Overall Response (OR) of Minor Response (MR) or Better After 12 Months of Treatment with BHQ880
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End point description:

The Overall Response (OR) was defined as MR or better, with better being partial, very good partial, or complete response. Multiple myeloma (MM) response was evaluated by using modified international multiple myeloma working group (IMWG) criteria. This assessment included M-protein quantification and serum free light chain (FLC) assay following administration of BHQ880. Additionally, urine specimens for M-protein quantification and urine immunofixation, serum samples for serum immunofixation, bone marrow biopsy and aspirate, skeletal surveys, and magnetic resonance imaging (MRI) of the spine were

also collected.

This endpoint analyzed the FAS, defined as all patients who received at least one dose (full or partial) of BHQ880.

End point type	Secondary
End point timeframe:	
Twelve 28-day treatment cycles	

End point values	BHQ880 10mg/kg			
Subject group type	Reporting group			
Number of subjects analysed	41			
Units: subjects	0			

Statistical analyses

No statistical analyses for this end point

Secondary: Percent of Subjects with Disease Progression After 12 Months of Treatment with BHQ880

End point title	Percent of Subjects with Disease Progression After 12 Months of Treatment with BHQ880
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End point description:

Progression was defined as progression to active multiple myeloma (PAMM), progressive disease (PD) but not evaluable for PAMM (NEPAMM) and discontinue for clinical PD (UNKPAMM). Assessments of PD included M-protein quantification and serum free light chain (FLC) assay following administration of BHQ880. Additionally, urine specimens for M-protein quantification and urine immunofixation, serum samples for serum immunofixation, bone marrow biopsy and aspirate, skeletal surveys, and magnetic resonance imaging (MRI) of the spine were also collected.

This endpoint analyzed the FAS, defined as all patients who received at least one dose (full or partial) of BHQ880.

End point type	Secondary
End point timeframe:	
Twelve 28-day treatment cycles	

End point values	BHQ880 10mg/kg			
Subject group type	Reporting group			
Number of subjects analysed	41			
Units: percent of subjects				
number (not applicable)	26.8			

Statistical analyses

No statistical analyses for this end point

Secondary: Area Under The Concentration-Time Curve (AUC) From Time Zero Up To The Last Measurable Concentration Sampling Time (0-tlast) of BHQ880

End point title	Area Under The Concentration-Time Curve (AUC) From Time Zero Up To The Last Measurable Concentration Sampling Time (0-tlast) of BHQ880
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End point description:

Pharmacokinetic (PK) parameters were determined for BHQ880 by using non-compartmental methods from the serum concentrations. Blood samples for PK evaluation were drawn pre-infusion and at 2 (± 5 minutes), 24 (± 1 hour), 168, 336, 504, and 672 hours post-infusion during Cycles 1 and 4 and pre-infusion on Day 1 of Cycle 3. Blood samples for BHQ880 serum concentration-time profiles were collected from 15 patients for full PK profiling. Sample volume was 5 mL. Parameters are summarized for a single dose (Cycle 1) and after repeated dosing (Cycle 4). This endpoint analyzed the Pharmacokinetic Analysis Set (PAS), defined as all patients in the Full Analysis Set (FAS) who had at least one blood sample providing evaluable PK data from either Cycle 1 or 4. The FAS was defined as all patients who received at least one dose (full or partial) of BHQ880.

End point type	Secondary
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End point timeframe:

Through four 28-day treatment cycles

End point values	BHQ880 10mg/kg			
Subject group type	Reporting group			
Number of subjects analysed	5			
Units: h. μ g/mL				
geometric mean (geometric coefficient of variation)				
Cycle 1	41350.9 ($\pm$ 30.96)			
Cycle 4	55114.5 ($\pm$ 47.68)			

Statistical analyses

No statistical analyses for this end point

Secondary: Time to Maximal Concentration (Tmax) of BHQ880

End point title	Time to Maximal Concentration (Tmax) of BHQ880
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End point description:

Pharmacokinetic (PK) parameters were determined for BHQ880 by using non-compartmental methods from the serum concentrations. Blood samples for PK evaluation were drawn pre-infusion and at 2 (± 5 minutes), 24 (± 1 hour), 168, 336, 504, and 672 hours post-infusion during Cycles 1 and 4 and pre-infusion on Day 1 of Cycle 3. Blood samples for BHQ880 serum concentration-time profiles were collected from 15 patients for full PK profiling. Sample volume was 5 mL. Parameters are summarized for a single dose (Cycle 1) and after repeated dosing (Cycle 4). This endpoint analyzed the PAS, defined as all patients in the FAS who had at least one blood sample providing evaluable PK data from either Cycle 1 or 4. The FAS was defined as all patients who received at least one dose (full or partial) of BHQ880.

End point type	Secondary
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End point timeframe:

Through four 28-day treatment cycles

End point values	BHQ880 10mg/kg			
Subject group type	Reporting group			
Number of subjects analysed	5			
Units: hours				
median (full range (min-max))				
Cycle 1	2 (2 to 2)			
Cycle 4	2 (2 to 2)			

Statistical analyses

No statistical analyses for this end point

Secondary: Time to Last Measurable Concentration (Tlast) of BHQ880

End point title	Time to Last Measurable Concentration (Tlast) of BHQ880
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End point description:

Pharmacokinetic (PK) parameters were determined for BHQ880 by using non-compartmental methods from the serum concentrations. Blood samples for PK evaluation were drawn pre-infusion and at 2 (± 5 minutes), 24 (± 1 hour), 168, 336, 504, and 672 hours post-infusion during Cycles 1 and 4 and pre-infusion on Day 1 of Cycle 3. Blood samples for BHQ880 serum concentration-time profiles were collected from 15 patients for full PK profiling. Sample volume was 5 mL. Parameters are summarized for a single dose (Cycle 1) and after repeated dosing (Cycle 4).

This endpoint analyzed the PAS, defined as all patients in the FAS who had at least one blood sample providing evaluable PK data from either Cycle 1 or 4. The FAS was defined as all patients who received at least one dose (full or partial) of BHQ880.

End point type	Secondary
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End point timeframe:

Through four 28-day treatment cycles

End point values	BHQ880 10mg/kg			
Subject group type	Reporting group			
Number of subjects analysed	5			
Units: hours				
geometric mean (geometric coefficient of variation)				
Cycle 1	599 (± 15.86)			
Cycle 4	565.5 (± 15.86)			

Statistical analyses

No statistical analyses for this end point

Secondary: Maximum Concentration (Cmax) of BHQ880

End point title	Maximum Concentration (Cmax) of BHQ880
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End point description:

Pharmacokinetic (PK) parameters were determined for BHQ880 by using non-compartmental methods from the serum concentrations. Blood samples for PK evaluation were drawn pre-infusion and at 2 (± 5 minutes), 24 (± 1 hour), 168, 336, 504, and 672 hours post-infusion during Cycles 1 and 4 and pre-infusion on Day 1 of Cycle 3. Blood samples for BHQ880 serum concentration-time profiles were collected from 15 patients for full PK profiling. Sample volume was 5 mL. Parameters are summarized for a single dose (Cycle 1) and after repeated dosing (Cycle 4).

This endpoint analyzed the PAS, defined as all patients in the FAS who had at least one blood sample providing evaluable PK data from either Cycle 1 or 4. The FAS was defined as all patients who received at least one dose (full or partial) of BHQ880.

End point type	Secondary
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End point timeframe:

Through four 28-day treatment cycles

End point values	BHQ880 10mg/kg			
Subject group type	Reporting group			
Number of subjects analysed	5			
Units: $\mu\text{g/mL}$				
geometric mean (geometric coefficient of variation)				
Cycle 1	184.5 ($\pm$ 28.23)			
Cycle 4	216.8 ($\pm$ 32.74)			

Statistical analyses

No statistical analyses for this end point

Secondary: Elimination Half-Life (T_{1/2}) of BHQ880

End point title	Elimination Half-Life (T _{1/2}) of BHQ880
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End point description:

Pharmacokinetic (PK) parameters were determined for BHQ880 by using non-compartmental methods from the serum concentrations. Blood samples for PK evaluation were drawn pre-infusion and at 2 (± 5 minutes), 24 (± 1 hour), 168, 336, 504, and 672 hours post-infusion during Cycles 1 and 4 and pre-infusion on Day 1 of Cycle 3. Blood samples for BHQ880 serum concentration-time profiles were collected from 15 patients for full PK profiling. Sample volume was 5 mL. Parameters are summarized for a single dose (Cycle 1) and after repeated dosing (Cycle 4).

This endpoint analyzed the PAS, defined as all patients in the FAS who had at least one blood sample providing evaluable PK data from either Cycle 1 or 4. The FAS was defined as all patients who received at least one dose (full or partial) of BHQ880.

End point type	Secondary
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End point timeframe:

Through four 28-day treatment cycles

End point values	BHQ880 10mg/kg			
Subject group type	Reporting group			
Number of subjects analysed	5			
Units: days				
geometric mean (geometric coefficient of variation)				
Cycle 1	14.1 (± 46.07)			
Cycle 4	14.7 (± 58.96)			

Statistical analyses

No statistical analyses for this end point

Secondary: Total Body Clearance (CL) of BHQ880

End point title	Total Body Clearance (CL) of BHQ880
End point description:	
Pharmacokinetic (PK) parameters were determined for BHQ880 by using non-compartmental methods from the serum concentrations. Blood samples for PK evaluation were drawn pre-infusion and at 2 (±5 minutes), 24 (±1hour), 168 , 336 , 504, and 672 hours post-infusion during Cycles 1 and 4 and pre-infusion on Day 1 of Cycle 3. Blood samples for BHQ880 serum concentration-time profiles were collected from 15 patients for full PK profiling. Sample volume was 5 mL. Parameters are summarized for a single dose (Cycle 1) and after repeated dosing (Cycle 4). This endpoint analyzed the PAS, defined as all patients in the FAS who had at least one blood sample providing evaluable PK data from either Cycle 1 or 4. The FAS was defined as all patients who received at least one dose (full or partial) of BHQ880.	
End point type	Secondary
End point timeframe:	
Through four 28-day treatment cycles	

End point values	BHQ880 10mg/kg			
Subject group type	Reporting group			
Number of subjects analysed	5			
Units: L/h				
geometric mean (geometric coefficient of variation)				
Cycle 1	0.014 (± 72.5242)			
Cycle 4	0.01 (± 107.8479)			

Statistical analyses

No statistical analyses for this end point

Secondary: Apparent Volume of Distribution of BHQ880 During The Terminal Phase (V)

End point title	Apparent Volume of Distribution of BHQ880 During The Terminal Phase (V)
End point description:	
Pharmacokinetic (PK) parameters were determined for BHQ880 by using non-compartmental methods from the serum concentrations. Blood samples for PK evaluation were drawn pre-infusion and at 2 ($\pm$5 minutes), 24 ($\pm$1hour), 168 , 336 , 504, and 672 hours post-infusion during Cycles 1 and 4 and pre-infusion on Day 1 of Cycle 3. Blood samples for BHQ880 serum concentration-time profiles were collected from 15 patients for full PK profiling. Sample volume was 5 mL. Parameters are summarized for a single dose (Cycle 1) and after repeated dosing (Cycle 4). This endpoint analyzed the PAS, defined as all patients in the FAS who had at least one blood sample providing evaluable PK data from either Cycle 1 or 4. The FAS was defined as all patients who received at least one dose (full or partial) of BHQ880.	
End point type	Secondary
End point timeframe:	
Through four 28-day treatment cycles	

End point values	BHQ880 10mg/kg			
Subject group type	Reporting group			
Number of subjects analysed	5			
Units: Liters				
geometric mean (geometric coefficient of variation)				
Cycle 1	7.02 ($\pm$ 42.601)			
Cycle 4	4.92 ($\pm$ 43.931)			

Statistical analyses

No statistical analyses for this end point

Secondary: Accumulation Ratio (AR) of BHQ880 After 4 Cycles of Therapy

End point title	Accumulation Ratio (AR) of BHQ880 After 4 Cycles of Therapy
End point description:	
Pharmacokinetic (PK) parameters were determined for BHQ880 by using non-compartmental methods from the serum concentrations. Blood samples for PK evaluation were drawn pre-infusion and at 2 ($\pm$5 minutes), 24 ($\pm$1hour), 168 , 336 , 504, and 672 hours post-infusion during Cycles 1 and 4 and pre-infusion on Day 1 of Cycle 3. Blood samples for BHQ880 serum concentration-time profiles were collected from 15 patients for full PK profiling. Sample volume was 5 mL. This endpoint analyzed the PAS, defined as all patients in the FAS who had at least one blood sample providing evaluable PK data from either Cycle 1 or 4. The FAS was defined as all patients who received at least one dose (full or partial) of BHQ880.	
End point type	Secondary
End point timeframe:	
Through four 28-day treatment cycles	

End point values	BHQ880 10mg/kg			
Subject group type	Reporting group			
Number of subjects analysed	5			
Units: Cycle 4 Cmax/Cycle 1 Cmax				
geometric mean (geometric coefficient of variation)	1.175 ($\pm$ 13.262)			

Statistical analyses

No statistical analyses for this end point

Secondary: Number of Subjects With Positive Immunogenicity For BHQ880 After Treatment with BHQ880

End point title	Number of Subjects With Positive Immunogenicity For BHQ880 After Treatment with BHQ880
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End point description:

Blood sampling for BHQ880 immunogenicity was collected from all patients within 3 hours before the BHQ880 infusion began on Day 1 of Cycles 1, 3, 6, 9, and 12. The samples were analyzed by using a validated Biomolecular Interaction Analysis binding method. Sample volume at each collection was 2 mL. Positive immunogenicity was defined as a value greater than the lower limit of quantification. This endpoint analyzed the FAS, defined as all patients who received at least one dose (full or partial) of BHQ880.

End point type	Secondary
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End point timeframe:

Twelve 28-day treatment cycles

End point values	BHQ880 10mg/kg			
Subject group type	Reporting group			
Number of subjects analysed	41			
Units: Subjects				
Cycle 1	2			
Cycle 3	1			
Cycle 6	1			
Cycle 9	1			
Cycle 12	1			

Statistical analyses

No statistical analyses for this end point

Secondary: Change From Baseline in The Concentration of Dickkopf 1 (DKK1) After Treatment With BHQ880

End point title	Change From Baseline in The Concentration of Dickkopf 1 (DKK1) After Treatment With BHQ880
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End point description:

Determination of total DKK1 levels in serum was done by using a validated DKK1 assay. Baseline values were defined as the last non-missing value before the first BHQ dose. A positive value indicates that the concentration has increased.

This endpoint analyzed the FAS, defined as all patients who received at least one dose (full or partial) of BHQ880.

End point type	Secondary
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End point timeframe:

Through four 28-day treatment cycles 672 hours post dose

End point values	BHQ880 10mg/kg			
Subject group type	Reporting group			
Number of subjects analysed	3			
Units: ng/ml				
arithmetic mean (standard deviation)				
Cycle 1	45.31 (± 16.077)			
Cycle 4	39.03 (± 5.114)			

Statistical analyses

No statistical analyses for this end point

Secondary: Percent Change From Baseline in Bone Mineral Density After 6 Months of Treatment with BHQ880

End point title	Percent Change From Baseline in Bone Mineral Density After 6 Months of Treatment with BHQ880
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End point description:

Dual energy x-ray absorptiometry scans were performed to evaluate bone metabolism and explore the anabolic effect of BHQ880 on bone by measuring bone density. A negative value indicates that bone density has decreased.

This endpoint analyzed the FAS, defined as all patients who received at least one dose (full or partial) of BHQ880.

End point type	Secondary
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End point timeframe:

Six 28-day treatment cycles

End point values	BHQ880 10mg/kg			
Subject group type	Reporting group			
Number of subjects analysed	41 ^[2]			
Units: g/cm ²				
arithmetic mean (standard deviation)				
L1-L4 Lumbar spine	-0.514 (± 4.017)			

Total hip with proximal femur	-0.415 ($\pm$ 4.0326)			
Forearm	-1.065 ($\pm$ 3.5605)			

Notes:

[2] - n for lumbar spine = 39; n for hip = 37; n for forearm = 31

Statistical analyses

No statistical analyses for this end point

Secondary: Percent Change From Baseline in Bone Mineral Density After 12 Months of Treatment with BHQ880

End point title	Percent Change From Baseline in Bone Mineral Density After 12 Months of Treatment with BHQ880
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End point description:

Dual energy x-ray absorptiometry scans were performed to evaluate bone metabolism and explore the anabolic effect of BHQ880 on bone by measuring bone density. A negative value indicates that bone density has decreased.

This endpoint analyzed the FAS, defined as all patients who received at least one dose (full or partial) of BHQ880.

End point type	Secondary
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End point timeframe:

Twelve 28-day treatment cycles

End point values	BHQ880 10mg/kg			
Subject group type	Reporting group			
Number of subjects analysed	41 ^[3]			
Units: g/cm ²				
arithmetic mean (standard deviation)				
L1-L4 Lumbar spine	0.043 ($\pm$ 3.7152)			
Total hip with proximal femur	0.499 ($\pm$ 3.5958)			
Forearm	-1.044 ($\pm$ 3.57)			

Notes:

[3] - n for lumbar spine = 30; n for hip = 30; n for forearm = 23

Statistical analyses

No statistical analyses for this end point

Secondary: Percent Change From Baseline in The Concentration of Osteocalcin After Treatment With BHQ880

End point title	Percent Change From Baseline in The Concentration of Osteocalcin After Treatment With BHQ880
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End point description:

The concentration of osteocalcin in serum was determined to evaluate bone metabolism and explore the anabolic effect of BHQ880 on bone. A positive value indicates that the concentration has increased.

This endpoint analyzed the FAS, defined as all patients who received at least one dose (full or partial) of BHQ880.

End point type	Secondary
End point timeframe:	
Twelve 28-day treatment cycles	

End point values	BHQ880 10mg/kg			
Subject group type	Reporting group			
Number of subjects analysed	33			
Units: µg/L				
arithmetic mean (standard deviation)	20.59 (± 28.119)			

Statistical analyses

No statistical analyses for this end point

Secondary: Percent Change From Baseline in The Concentration of Procollagen Type 1 N-terminal Polypeptide (P1NP) After Treatment With BHQ880

End point title	Percent Change From Baseline in The Concentration of Procollagen Type 1 N-terminal Polypeptide (P1NP) After Treatment With BHQ880
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End point description:

The concentration of P1NP in serum was determined to evaluate bone metabolism and explore the anabolic effect of BHQ880 on bone. A positive value indicates that the concentration has increased. This endpoint analyzed the FAS, defined as all patients who received at least one dose (full or partial) of BHQ880.

End point type	Secondary
End point timeframe:	
Twelve 28-day treatment cycles	

End point values	BHQ880 10mg/kg			
Subject group type	Reporting group			
Number of subjects analysed	33			
Units: ng/mL				
arithmetic mean (standard deviation)	8.16 (± 35.162)			

Statistical analyses

No statistical analyses for this end point

Secondary: Percent Change From Baseline in The Concentration of N-terminal Telopeptide of Type 1 Collagen (NTx) After Treatment With BHQ880

End point title	Percent Change From Baseline in The Concentration of N-terminal Telopeptide of Type 1 Collagen (NTx) After Treatment With BHQ880
End point description:	
The concentration of NTx in urine, corrected for creatinine, was determined to evaluate bone metabolism and explore the anabolic effect of BHQ880 on bone. A positive value indicates that the concentration has increased.	
This endpoint analyzed the FAS, defined as all patients who received at least one dose (full or partial) of BHQ880.	
End point type	Secondary
End point timeframe:	
Twelve 28-day treatment cycles	

End point values	BHQ880 10mg/kg			
Subject group type	Reporting group			
Number of subjects analysed	28			
Units: nmol bone collagen equivalent (BCE)				
arithmetic mean (standard deviation)	9.17 (± 53.918)			

Statistical analyses

No statistical analyses for this end point

Adverse events

Adverse events information

Timeframe for reporting adverse events:

Serious Adverse Events are monitored from date of First Patient First Visit (FPFV) until Last Patient Last Visit (LPLV). All other adverse events are monitored from First Patient First Treatment until Last Patient Last Visit.

Assessment type	Systematic
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Dictionary used

Dictionary name	MedDRA
Dictionary version	15.1

Reporting groups

Reporting group title	BHQ880 10mg/kg
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Reporting group description:

BHQ880 10mg/kg

Serious adverse events	BHQ880 10mg/kg		
Total subjects affected by serious adverse events			
subjects affected / exposed	3 / 41 (7.32%)		
number of deaths (all causes)	0		
number of deaths resulting from adverse events	0		
Neoplasms benign, malignant and unspecified (incl cysts and polyps)			
Renal cell carcinoma			
subjects affected / exposed	1 / 41 (2.44%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Breast cancer in situ			
subjects affected / exposed	1 / 41 (2.44%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Infections and infestations			
Pneumonia			
subjects affected / exposed	1 / 41 (2.44%)		
occurrences causally related to treatment / all	2 / 2		
deaths causally related to treatment / all	0 / 0		

Frequency threshold for reporting non-serious adverse events: 5 %

Non-serious adverse events	BHQ880 10mg/kg		
Total subjects affected by non-serious adverse events			
subjects affected / exposed	36 / 41 (87.80%)		
Nervous system disorders			
Headache			
subjects affected / exposed	4 / 41 (9.76%)		
occurrences (all)	5		
Sciatica			
subjects affected / exposed	3 / 41 (7.32%)		
occurrences (all)	4		
Blood and lymphatic system disorders			
Anaemia			
subjects affected / exposed	6 / 41 (14.63%)		
occurrences (all)	7		
General disorders and administration site conditions			
Chills			
subjects affected / exposed	6 / 41 (14.63%)		
occurrences (all)	6		
Fatigue			
subjects affected / exposed	15 / 41 (36.59%)		
occurrences (all)	30		
Pyrexia			
subjects affected / exposed	9 / 41 (21.95%)		
occurrences (all)	16		
Gastrointestinal disorders			
Abdominal pain			
subjects affected / exposed	3 / 41 (7.32%)		
occurrences (all)	3		
Constipation			
subjects affected / exposed	4 / 41 (9.76%)		
occurrences (all)	4		
Diarrhoea			
subjects affected / exposed	4 / 41 (9.76%)		
occurrences (all)	4		
Gastrooesophageal reflux disease			
subjects affected / exposed	3 / 41 (7.32%)		
occurrences (all)	3		

Nausea subjects affected / exposed occurrences (all)	4 / 41 (9.76%) 5		
Respiratory, thoracic and mediastinal disorders Dyspnoea subjects affected / exposed occurrences (all)	4 / 41 (9.76%) 5		
Skin and subcutaneous tissue disorders Rash subjects affected / exposed occurrences (all)	3 / 41 (7.32%) 3		
Psychiatric disorders Anxiety subjects affected / exposed occurrences (all) Insomnia subjects affected / exposed occurrences (all)	3 / 41 (7.32%) 3 3 / 41 (7.32%) 3		
Musculoskeletal and connective tissue disorders Arthralgia subjects affected / exposed occurrences (all) Back pain subjects affected / exposed occurrences (all) Bone pain subjects affected / exposed occurrences (all) Musculoskeletal chest pain subjects affected / exposed occurrences (all) Musculoskeletal pain subjects affected / exposed occurrences (all) Neck pain	10 / 41 (24.39%) 13 10 / 41 (24.39%) 10 3 / 41 (7.32%) 3 4 / 41 (9.76%) 4 3 / 41 (7.32%) 3		

subjects affected / exposed occurrences (all)	3 / 41 (7.32%) 3		
Pain in extremity subjects affected / exposed occurrences (all)	6 / 41 (14.63%) 7		
Infections and infestations			
Nasopharyngitis subjects affected / exposed occurrences (all)	5 / 41 (12.20%) 7		
Upper respiratory tract infection subjects affected / exposed occurrences (all)	5 / 41 (12.20%) 5		

More information

Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? Yes

Date	Amendment
25 January 2012	This amendment introduced the following important changes: The main purpose of the amendment was to modify the prohibition on concomitant hormone replacement therapy for patients who have been receiving that therapy for at least 6 months. Patients who had been receiving long-term hormone replacement therapy and for whom those effects on bone would be considered stable could be enrolled in the study without having to discontinue that therapy. In addition, the analyses of several serum bone biomarkers which supported a secondary endpoint were removed. The requirement for assessment of vital signs during and after drug infusion was also removed, based on the data and safety profile from Phase I studies. For improved site and patient compliance and protocol execution, time windows around laboratory assessments were added and redundant laboratory testing was removed.

Notes:

Interruptions (globally)

Were there any global interruptions to the trial? No

Limitations and caveats

None reported