Sponsor

Novartis

Generic Drug Name

BHQ880

Therapeutic Area of Trial

Multiple myeloma and renal insufficiency

Approved Indication

Investigational

Protocol Number

CBHQ880A2203

Title

A double-blind, placebo-controlled, randomized Phase 2 study of BHQ880, an anti-Dickkopf1 (DKK1) monoclonal antibody (mAb), in patients with untreated multiple myeloma and renal insufficiency

Study Phase

Phase 2

Study Start/End Dates

19-Jan-2012 (first patient first visit) to 02-May-2013 (Early termination date)

The reason for early termination of the study was limited enrollment secondary to changes in standard of care therapy for enrolled patient population patients with untreated multiple myeloma and renal insufficiency. The study was terminated early after completion of the open-label cohort.

Study Design/Methodology

The study was initially planned to be conducted as a single arm, open-label, run-in cohort study of 6 to 8 patients to evaluate the safety and PK profile of BHQ880 in combination with bortezomib and dexamethasone, followed by a multicenter, double-blind, placebo-controlled, randomized Phase 2 study of BHQ880 in combination with bortezomib and dexamethasone in patients with untreated multiple myeloma (MM) and renal insufficiency. However, due to limited accrual secondary to an evolving SOC and the likelihood that the randomized portion of the study would not enroll, it was no longer feasible to conduct the randomized phase of the study as originally designed.

Centers

5 centers in 2 countries: United Kingdom (3), Spain (2).

Publication

There are no publications based on this study.

Outcome Measures

Efficacy was not powered for analysis because of the low requirement. Due to early closure of the study, analyses of efficacy were not performed.

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

Intravenous infusion of BHQ880 at dose of 10 mg/kg on Day 1 of each 21 day cycle, in combination with intravenous injection of bortezomib (1.3 mg/m^2 on Days 1, 4, 8, and 11) and oral dexamethasone (20 mg on Days 1,2,4,5,8,9,11,12) for up to 9 cycles.

Statistical Methods

Due to the early closure of the study after the open-label phase, only the following objectives were analyzed: 1) characterization of the safety and tolerability of BHQ880 in combination with bortezomib and dexamethasone, 2) characterization of the PK profiles of BHQ880 and bortezomib.

The primary objective of assessing the efficacy of BHQ880 compared with placebo in combination with bortezomib/dexamethasone in terms of the time from randomization to the first skeletal related event (SRE) in patients with untreated MM and renal insufficiency was not analyzed due to the early closure of the study after the open-label run-in phase.

The secondary objective was to evaluate the safety and tolerability of BHQ880. The endpoints were the occurrence of AEs and SAEs, assessments of laboratory values, and immunogenicity for patients in the open-label run-in phase. For all safety analyses, the safety set was used. All listings and tables were presented using descriptive statistics (quantitative data) and contingency tables (qualitative data). Safety data was also listed by patient.

The overall observation period was divided into three mutually exclusive segments:

1. Pre-treatment period: from day of patient's signed informed consent to the day before first dose of study medication.
2. On-treatment period: from day of first dose of study medication to 21 days after last dose of study medication
3. Post-treatment period: starting at Day 22 after last dose of study medication.

The PK secondary objective was to evaluate the PK profiles of BHQ880 and bortezomib when administered in combination. The endpoints were BHQ880 and bortezomib PK parameters including the Cmax, Tmax, AUC0-tlast, Tlast, t1/2, and accumulation ratio of BHQ880. The pharmacokinetic analysis set (PAS) was used for this secondary objective.

Descriptive statistics of PK parameters included mean, standard deviation and coefficient of variability (CV) (%), minimum, and maximum. Summary statistics were presented for BHQ880 serum concentrations at each scheduled time point. Along with simple summary statistics, CV (%) for arithmetic mean, geometric mean, and CV (%) for geometric mean are presented.

Due to the early closure of the study after the open-label phase, the originally planned analysis of bone mineral density and overall response rate as the secondary endpoints in the randomization phase could not be conducted as planned.

Study Population: Inclusion/Exclusion Criteria and Demographics

Inclusion criteria

Patients who met all of the following criteria were eligible for inclusion in this study:

1. Able to provide written informed consent before any screening procedures.
2. Patients ≥ 55 years of age and not eligible for stem cell transplantation. Younger patients could be considered for enrollment on a case-by-case basis after discussion with the Sponsor, provided that they met all eligibility criteria.
3. Confirmed diagnosis of MM.
4. Life expectancy of more than 6 months in the absence of intervention.
5. Not received previous or current antimyeloma therapies with the exception of 1 dose of bortezomib, radiation therapy or surgery for treatment of SRE associated with initial diagnosis of MM and steroids for symptomatic control of disease.
6. Eastern Co-operative Oncology Group (ECOG) Performance status of 0 to 1.
7. Serum creatinine clearance < 30 mL/min (0.5 mL/sec) (calculated using Cockcroft Gault formula).
8. Had the following laboratory values within 7 days before the first dose of study drug:
    a. Hemoglobin ≥ 8 g/dL (80 g/L) (erythropoietin and red blood cell transfusion therapy were allowed); platelet count ≥ 50000/mm^3 (50×10^9/L) absolute neutrophil count (ANC) ≥ 1,000/mm^3 (1×10^9/L).
    b. Total bilirubin ≤ 1 × upper limit of normal (ULN); aspartate aminotransaminase (AST) and alanine aminotransferase (ALT) ≤ 2.5×ULN; alkaline phosphatase ≤ 2.5× ULN.
9. Recovered from the effects of any prior surgery or radiotherapy.

Exclusion criteria

Patients were eligible for this study if they did not meet any of the following criteria:

1. Past or current history of neoplasm other than the entry diagnosis, with the exception of treated non-melanoma skin cancer, carcinoma in situ of the cervix, superficial bladder cancer or other cancers cured by local therapy alone, and a disease-free survival ≥ 3 years.
2. Prior intravenous bisphosphonate therapy at any time or oral bisphosphonate therapy within 4 months of study entry.
3. Hypercalcemia requiring calcium regulating therapy other than steroids.
4. Concomitant Paget's disease of bone or uncorrected hyperparathyroidism.

5. Common Toxicity Criteria for Adverse Events (CTCAE) grade ≥ 2 neuropathy.
6. Impaired cardiac function including any one of the following:
   a. Long QT syndrome or a known family history of long QT syndrome.
   b. Corrected QT interval (QTc) >470 milliseconds on Baseline electrocardiogram (ECG) (using corrected QT interval using Fridericia [QTcF]).
   c. Clinically significant uncontrolled heart disease (e.g., unstable angina, congestive heart failure, uncontrolled hypertension, ventricular or atrial arrhythmias)
7. Known human immunodeficiency virus (HIV), known active hepatitis B, or known or suspected hepatitis C infection
8. Any serious or active medical or psychiatric illness that could, in the Investigator's opinion potentially interfere with the treatment plan outlined in the protocol
9. Treatment with an investigational product within 28 days before the first dose of study treatment
10. Known hypersensitivity to boron containing agents
11. Pregnant or nursing (lactating) women, where pregnancy was defined as the state of a female after conception and until the termination of gestation, confirmed by a positive serum human chorionic gonadotropin (hCG) laboratory test (>5 mIU/mL or 5 IU/L);
12. Women of child-bearing potential, defined as all women physiologically capable of becoming pregnant, including women whose career, lifestyle, or sexual orientation precluded intercourse with a male partner and women whose partners were sterilized by vasectomy or other means, unless they were using two birth control methods. The two methods can be a double barrier method or a barrier method plus a hormonal method.
    a. Adequate barrier methods of contraception included: diaphragm, condom (by the partner), intrauterine device (copper or hormonal), sponge, or spermicide.
    b. Hormonal contraceptives included any marketed contraceptive agent that included an estrogen and/or a progestational agent.
    c. Reliable contraception should have been maintained throughout the study and for 8 months following administration of the last BHQ880 dose.
    d. Women were considered postmenopausal and not of child bearing potential if they have had 12 months of natural (spontaneous) amenorrhea with an appropriate clinical profile (e.g., age appropriate, history of vasomotor symptoms) or 6 months of spontaneous amenorrhea with serum follicle-stimulating hormone (FSH) levels >40 mIU/mL (40 IU/L).

Participant Flow

Patient disposition (all patients treated)

	BHQ880 10 mg/kg N=9 n (%)
Patients treated	
Treatment completed as per protocol	2 (22.2)
Treatment discontinued	7 (77.8)

	BHQ880 10 mg/kg N=9 n (%)
Primary reason for end of treatment	
Adverse events	3 (33.3)
Patient withdrew consent	2 (22.2)
Treatment duration completed as per protocol	2 (22.2)
Protocol deviation	2 (22.2)
Primary reason for study evaluation completion	
Patient withdrew consent	2 (22.2)
Death	2 (22.2)
Follow up phase completed as per protocol	5 (55.6)

Baseline Characteristics

Demographic summary at baseline (Safety set)

Demographic Variable	BHQ880 10 mg/kg N=9
Age (Years)	
Mean (SD)	67.2 (8.6)
Median	68.0
25th, 75th Percentile	64.0, 72.0
Minimum	53.0
Maximum	77.0
Age category (Years)	
< 65	3 (33.3%)
≥ 65	6 (66.7%)
Sex	
Female	3 (33.3%)
Male	6 (66.7%)
Race	
Caucasian	8 (88.9%)
Black	1 (11.1%)
Ethnicity	
Hispanic/Latino	2 (22.2%)
Other	7 (77.8%)
Weight (kg)	
Mean (SD)	74.6 (8.89)
Median	76.5
25^{th}, 75^{th} Percentile	67.7, 82.8
Minimum	61.0
Maximum	85.4
Height (cm)	
Mean (SD)	168.2 (10.71)

Demographic Variable	**BHQ880 10 mg/kg N=9**
Median	173.0
25th, 75th Percentile	161.0, 175.0
Minimum	150.0
Maximum	183.0
WHO/ECOG performance status	
0	1 (11.1%)
1	7 (77.8%)
2	1 (11.1%)

WHO/ECOG performance status: 0 – Fully active, able to carry on all pre-disease performance without restriction; 1 – Restricted in physically strenuous activity but ambulatory and able to carry out work of a light or sedentary nature, e.g., light house work, office work; 2 – Ambulatory and capable of all self care but unable to carry out any work activities. Up and about more than 50% of waking hours; 3 – Capable of only limited self care, confined to bed or chair more than 50% of waking hours

Safety Results

Adverse events reported by at least 15%, irrespective of causality by preferred term (safety set)

N=9 Preferred term	**All Grades n (%)**	**Grade 3/4 n (%)**
Any adverse event		
Total	8 (88.9)	7 (77.8)
Diarrhea	4 (44.4)	1 (11.1)
Back pain	3 (33.3)	2 (22.2)
Rectal hemorrhage	3 (33.3)	0
Anemia	2 (22.2)	2 (22.2)
Arthralgia	2 (22.2)	1 (11.1)
Dizziness	2 22.2)	0
Fatigue	2 (22.2)	1 (11.1)
Myopathy	2 (22.2)	1 (11.1)
Urinary tract infection	2 (22.2)	0
Vomiting	2 (22.2)	0

Preferred terms are sorted in descending frequency of all grades.
A patient with multiple occurrences of an AE is counted only once in that AE category.
Only AEs occurring during treatment or within 21 days of the last study medication are reported.

Serious Adverse Events and Deaths

Serious adverse events, regardless of study drug relationship, by primary system organ class, and preferred term (safety set)

Primary system organ class Preferred term	**BHQ880 10 mg/kg N=9 n (%)**
Any primary system organ class	

Primary system organ class Preferred term	BHQ880 10 mg/kg N=9 n (%)
Total	7 (77.8)
Infections and infestations	
Total	3 (33.3)
Gastroenteritis	1 (11.1)
Lower respiratory tract infection	1 (11.1)
Urinary tract infection	1 (11.1)
Viral infection	1 (11.1)
Respiratory, thoracic and mediastinal disorders	
Total	3 (33.3)
Chronic obstructive pulmonary disease	1 (11.1)
Epistaxis	1 (11.1)
Pleural effusion	1 (11.1)
General disorders and administration site conditions	
Total	2 (22.2)
Fatigue	1 (11.1)
General physical health deterioration	1 (11.1)
Renal and urinary disorders	
Total	2 (22.2)
Renal failure acute	1 (11.1)
Renal impairment	1 (11.1)
Cardiac disorders	
Total	1 (11.1)
Atrial flutter	1 (11.1)
Gastrointestinal disorders	
Total	1 (11.1)
Diarrhea	1 (11.1)
Gastrointestinal hemorrhage	1 (11.1)
Investigations	
Total	1 (11.1)
Blood creatine increased	1 (11.1)
Metabolism and nutrition disorders	
Total	1 (11.1)
Fluid overload	1 (11.1)
Musculoskeletal and connective tissue disorders	
Total	1 (11.1)
Arthralgia	1 (11.1)
Nervous system disorders	
Total	1 (11.1)
Aphasia	1 (11.1)
Psychiatric disorders	
Total	1 (11.1)

Primary system organ class Preferred term	BHQ880 10 mg/kg N=9 n (%)
Confusional state	1 (11.1)
Vascular disorders	
Total	1 (11.1)
Hypertension	1 (11.1)

Primary system organ classes are presented alphabetically; preferred terms are sorted within primary system organ class alphabetically.

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 within a primary system organ class is counted only once in the total row.

Only AEs occurring during treatment or within 21 days of the last study medication are reported.

Summary of adverse events and deaths (safety set)

AE category	BHQ880 10 mg/kg N=9 All grades n (%)	BHQ880 10 mg/kg N=9 Grade 3/4 n (%)
All deaths [1]	2 (22.2)	
On-treatment deaths [2]	0	
Adverse events (AEs)	8 (88.9)	7 (77.8)
Suspected to be drug-related	2 (22.2)	0
Serious adverse events	7 (77.8)	6 (66.7)
Suspected to be drug-related	0	0
AEs leading to discontinuation	3 (33.3)	3 (33.3)
Suspected to be drug-related	0	0
AEs leading to dose interruption/change	6 (66.7)	5 (55.6)
Suspected to be drug-related	0	0
AEs requiring additional therapy [3]	8 (88.9)	7 (77.8)
Suspected to be drug-related	0	0

Categories are not mutually exclusive. Patients with multiple events in the same category are counted only once in that category. Patients with events in more than 1 category are counted once in each of those categories.

[1] All deaths include deaths during treatment or within 90 days after last dose of study drug.

[2] On-treatment deaths include deaths during treatment or within 21 days after last dose of study drug.

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

Other Relevant Findings

None

Date of Clinical Trial Report

27-Jan-2014

Date Inclusion on Novartis Clinical Trial Results Database

18-Feb-2014

Date of Latest Update