Sponsor

Novartis

Generic Drug Name

BPS804

Trial Indication(s)

Adults with hypophosphatasia (HPP)

Protocol Number

CBPS804A2202

Protocol Title

An open-label, intra-patient dose-escalation study to evaluate the safety and tolerability, pharmacokinetics, pharmacodynamics and preliminary efficacy of multiple infusions of BPS804 in adults with hypophosphatasia.

Clinical Trial Phase

Phase II

Study Start/End Dates

26-Jul-2011 to 25-Sep-2012

Reason for Termination

Not applicable.

Study Design/Methodology

This was an open label, intra-patient dose-escalating study for 7 weeks followed by a 3.6 months follow-up period post-dose in adult patients with hypophosphatasia. This was an exploratory study to demonstrate the safety and pharmacodynamics effect of BPS804 in adult patients with hypophosphatasia. The three dose levels of BPS804 administered were 5, 10 and 20 mg/kg.

Centers

1 center in 1 country: Germany (1)

Objectives:

Primary objective(s)

- To evaluate safety and tolerability of BPS804 when administered as multiple, dose escalating iv infusions in adults with hypophosphatasia (HPP).
- To determine the changes from baseline in the pharmacodynamic (PD) effect and preliminary efficacy of BPS804 when administered as multiple, dose escalating iv infusions on the serum bone formation marker bone-specific alkaline phosphatase (BSAP) and serum tissue nonspecific alkaline phosphatase (TNSALP).

Secondary objective(s)

- To determine the pharmacokinetic (PK) profile of BPS804 when administered as multiple, dose escalating iv infusions.
- To determine the PD effect of BPS804 on biomarkers as measured by plasma inorganic pyrophosphate (PPi), plasma pyridoxal-5'-phosphate (PLP), plasma phosphoethanolamine (PEA), serum parathyroid hormone (PTH).
- To describe the total/free sclerostin in serum following multiple, dose escalating iv infusions of BPS804.
- To assess the potential immunogenicity of BPS804 when administered as multiple, dose escalating iv infusions.

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

BPS804 as a powder for solution for infusion (lyophilizate in vial); 150 mg per vial.

Statistical Methods

Efficacy/Pharmacodynamics:
The biomarkers bone-specific alkaline phosphatase (BSAP) enzymatic activity and total alkaline phosphatase (ALP) enzymatic activity were analyzed as primary PD endpoints. All patients in the PD population were included in the data analysis. BSAP and ALP values and ratios versus baseline were summarized by time point. Individual time profiles and geometric mean time profiles were also presented. Graphical presentation of these ratios over time by individual plots and geometric mean plots were provided. Baseline was taken as the geometric mean of screening and Day 1 pre-dose for BSAP enzymatic activity and as geometric mean of screening and baseline for ALP enzymatic activity. Statistical analysis was done on log-transformed data and then back transformed to the original scale.

Data from CBPS804A2101 had shown that highest increase for BSAP enzymatic activity was observed in the 29 days following infusion. Therefore, comparison versus study baseline was performed by looking at the average ratio from baseline of Day 2 to Day 29 following the third infusion: this includes assessments performed on Day 30, 36, 43, and 57 and additionally Day 50 for ALP enzymatic activity.

This average ratio from baseline, RAUC, was calculated for each patient as standardized AUC on the log-scale, by applying the trapezoid rule onto the logged ratios, then dividing by the actual length of the time-interval. For reporting, RAUC was back transformed to the original scale, to obtain a weighted geometric average of the ratio from baseline.

The RAUCs were assumed to be independently normally distributed with mean, μ and variance, σ^2. Using non-informative priors for model parameters, a marginal posterior distribution for μ could be obtained; this marginal posterior distribution was a t-distribution with location y and scale $s/\sqrt{n}$, denoted by $t_{n-1}(y, s/\sqrt{n})$; here y is the sample mean and s is the sample standard deviation. This posterior distribution was back transformed (with exp) to the ratio from baseline scale.

The posterior probability was displayed graphically. It was considered a sign for efficacy if the posterior probability for the average ratio from baseline being larger than 1 was at least 90%. The analysis consisted in calculating posterior probability that {RAUC > log(1) | data} and comparing it to the 90% minimum threshold. Additionally, the posterior probability was also calculated for the average ratio from baseline being larger than 0.7, 1.3, 1.54 and 2. This calculation was done separately for BSAP and ALP, and either evidence was considered as being sufficient.

Descriptive statistics including geometric mean was used to summarize the secondary and exploratory PD parameters by time point. Individual time profiles and geometric mean time profiles was presented. Summary statistics including geometric mean was also presented for the ratio versus baseline (taken as the geometric mean of screening and Day 1

pre-dose). Graphical presentation of these ratios over time by individual plots and geometric mean plots was provided. No further statistical analysis of secondary of exploratory endpoints was done.

Safety:
Safety analysis was based on the safety set. All information obtained on adverse events was listed. Time since last dose and last dose level applied was indicated in the listing. The number and percentage of patients with adverse events was tabulated by body system and preferred term. A patient with multiple adverse events within a body system or preferred term was only counted once towards the total of this body system or preferred term.

Adverse events were also tabulated by study period. The periods for adverse event tabulation were from dose administration up to next dose administration if a further dose was given, and from dose administration to End of study for the last dose administration of a patient. An adverse event starting in one period and continuing into the next period was counted only in the onset period. A patient with multiple adverse events by body system or preferred term within a period was only counted once towards the total of this body system or preferred term and period.

Due to the expected accumulation of drug exposure and the different length of periods, this tabulation did not support an unbiased dose-response relationship for adverse events. However, it was expected that qualitative changes in safety pattern across dose ranges could be detected if present. Key interpretation was however based on the adverse events tabulation across the pooled trial period. No further inferential analysis of safety data was foreseen.

Pharmacokinetics:

All patients with evaluable PK data were included in the pharmacokinetic data analysis.

Biofluid concentrations were expressed in µg/mL. All concentrations below the limit of quantification (LLOQ) or missing data were labeled as such in the concentration data listings. Concentrations below the LLOQ were treated as zero in summary statistics for concentration data only. They were not considered for calculation of PK parameters (with the exception of the pre-dose samples).

Descriptive statistics of pharmacokinetic parameters included mean, standard deviation, and coefficient of variance, minimum and maximum. When a geometric mean was presented it was stated as such. Since Tmax was generally

evaluated by a nonparametric method, median values and ranges were given for this parameter. No formal assessment of dose proportionality or accumulation was planned. Pharmacokinetic parameters might be only used for PK/PD exploration.

Study Population: Key Inclusion/Exclusion Criteria

Inclusion Criteria:

- Male and female patients 18 to 60 years of age in good health (other than pre-established clinical diagnosis of HPP) as determined by past medical history, physical examination, vital signs, electrocardiogram, and laboratory tests at screening.
- Previously established clinical diagnosis of HPP with confirmed ALPL mutation by genetic test and as manifested by:
- Serum alkaline phosphatase levels below the age-adjusted normal range and
- Radiologic evidence of osteopenia or osteomalacia or
- History of plasma PLP at least twice the upper limit of normal range or
- History of rickets, or history of premature loss of decidious teeth, or bone deformity consistent with osteomalacia or past rickets, or past non-traumatic fracture, pseudofracture, or non-healing fracture.
- 25-(OH) vitamin D3 serum level of ≥20 ng/mL.
- Normocalcemia with serum calcium ≥8.5 mg/dL and ≤10.2 mg/dL and normal phosphate levels (2.4 - 4.1 mg/dL) (or according to local laboratory ranges).

Exclusion Criteria:

- A history of clinically significant ECG abnormalities.
- History of malignancy of any organ system (other than localized basal cell carcinoma of the skin and for skeletal malignancies see below), within the past 5 years, regardless of whether there is evidence of local recurrence or metastases.
- History of skeletal malignancies or bone metastases at any time.
- History of external beam radiation to the skeleton.
- Open epiphyses as judged by the Investigator based on previous clinical assessments.
- Patients with suspected neural foraminal stenosis (e.g., at cervical, spinal, or lumbar site) as judged by the Investigator which could be caused by disc herniation and are described as sciatic pain, tingling, burning sensation with numbness and/or weakness.

- History of or concomitant diseases such as hypo-/hyperparathyroidism, hypo-/hyperthyroidism, Pagets disease, previous neck surgery involving partial or complete thyroidectomy and abnormal thyroid function or thyroid disease or other endocrine disorders or conditions.
- Treatment with any anti-resorptive medication (e.g., oral and/or injectable), bisphosphonates and/or teriparatide (e.g., ForteoTM) within the last 6 months.
- Exposure to blood products or monoclonal antibodies within previous 12 months.
- Any deformation of the spine (e.g., severe scoliosis, ankylosing spondylitis) or the hip which would preclude proper acquisition of lumbar spine or hip BMD by DXA.

Participant Flow Table

	Total (BPS804) N=8 n (%)
Patients	
Completed	7 (87.5)
Discontinued	1 (12.5)
Main cause of discontinuation	
Adverse event(s)	1 (12.5)

N= Total number of patients; n= no. of patients

Baseline Characteristics

		Total (BPS804) N=8
Age (years)	Mean (SD)	47.8 (16.9)
	Median	52.5
	Range	21 - 69
Gender – n (%)	Male	2 (25)
	Female	6 (75)

		Total (BPS804) N=8
Predominant Race – n (%)	Caucasian	8 (100)
Ethnicity – n (%)	Other	8 (100)
Height (cm)	Mean (SD)	161.2 (7.9)
	Median	161.5
	Range	150 - 176
Weight (kg)	Mean (SD)	66.1 (8.9)
	Median	67.5
	Range	51 - 76
BMI (kg/m^2)	Mean (SD)	25.5 (3.2)
	Median	27.3
	Range	21 - 29

Summary of Efficacy

Primary Outcome Result(s)

Bayesian analysis results on alkaline phosphatase average ratio (pharmacodynamic analysis set)

	Posterior				
				Credibility Interval	
Treatment effect	Mean	SD	Median	10%	90%
Average ratio	1.37	0.09	1.37	1.27	1.48
Probability (Average ratio > 0.7 | data)	100%				
Probability (Average ratio > 1 | data)	100%				
Probability (Average ratio > 1.3 | data)	81%				
Probability (Average ratio > 1.54 | data)	3%				
Probability (Average ratio > 2 | data)	0%				

Secondary Outcome Result(s)

Summary statistics of PK parameters

PK Parameters	Statistic	BPS804 5 mg/kg n=7	BPS804 10 mg/kg n=7	BPS804 20 mg/kg n=7
AUClast (day*µg/mL)	Mean ± SD	699.3 ± 132.0	NC	8080.6 ± 2211.2
AUCinf (day*µg/mL)	Mean ± SD	NC	NC	8127.5 ± 2192.6
Cmax (µg/mL)	Mean ± SD	158 ± 36	314 ± 71	679 ± 140
Tmax (hour)	Median (min-max)	2.53 (1.92 – 23.5)	2.00 (1.93 – 2.21)	2.00 (1.95 – 8.05)
T1/2 (day)	Mean ± SD	NC	NC	11.80 ± 2.12

n = No. of patients in corresponding treatment arm; NC = Not calculated

Summary of Safety

Safety Results

Serious Adverse Events by System Organ Class

	BPS804
No. (%) of subjects studied	8
Primary system organ class	
Cardiac disorders	
angina pectoris	1
Respiratory, thoracic and mediastinal disorders	
dyspnea	1

Adverse events overall and frequently affected system organ classes - n (%) of patients (safety analysis set)

	Total N=8 n (%)
Patients with at least one adverse event	6 (75.0)
Primary system organ class	
Musculoskeletal and connective tissue disorders	6 (75.0)
Gastrointestinal disorders	4 (50.0)
Nervous system disorders	4 (50.0)
General disorders and administration site conditions	3 (37.5)
Infections and infestations	3 (37.5)
Eye disorders	2 (25.0)
Cardiac disorders	1 (12.5)
Renal and urinary disorders	1 (12.5)
Respiratory, thoracic and mediastinal disorders	1 (12.5)
Skin and subcutaneous tissue disorders	1 (12.5)
Vascular disorders	1 (12.5)

Adverse events by SOC are presented in descending order of frequency in total column.
N= Total number of patients; n= Number of patients experienced adverse events.

Adverse events overall and most frequent events - n (%) of patients (safety Analysis set)

	Total N=8 n (%)
Patients with adverse event(s)	6 (75.0)

	Total N=8 n (%)
Pain in extremity	3 (37.5)
Arthralgia	2 (25.0)
Bone pain	2 (25.0)
Headache	2 (25.0)
Myalgia	2 (25.0)
Nasopharyngitis	2 (25.0)
Toothache	2 (25.0)
Angina pectoris	1 (12.5)
Arthritis	1 (12.5)
Cervical root pain	1 (12.5)
Cheilitis	1 (12.5)
Dyspnoea	1 (12.5)
Erythema	1 (12.5)
Eye irritation	1 (12.5)
Eye swelling	1 (12.5)
Fatigue	1 (12.5)
Feeling hot	1 (12.5)
Frequent bowel movements	1 (12.5)
Hypertension	1 (12.5)
Micturition urgency	1 (12.5)
Migraine	1 (12.5)
Nausea	1 (12.5)
Non-cardiac chest pain	1 (12.5)
Odynophagia	1 (12.5)
Oedema mouth	1 (12.5)
Oedema peripheral	1 (12.5)
Paraesthesia	1 (12.5)
Rash pustular	1 (12.5)

Adverse events by preferred terms are presented in descending order of frequency in total column.

N= Total number of patients; n= Number of patients experienced adverse events

Date of Clinical Trial Report

05-Mar-2013