Sponsor

Novartis

Generic Drug Name

BPS804

Trial Indication(s)

Osteogenesis imperfecta

Protocol Number

CBPS804A2201

Protocol Title

A randomized, open-label intra-patient dose escalation study with an untreated reference group to evaluate safety and tolerability, pharmacokinetics, and pharmacodynamics of multiple infusions of BPS804 in adults with moderate osteogenesis imperfecta.

Clinical Trial Phase

Phase II

Study Start/End Dates

22-Jun-2011 to 05-Dec-2012

Reason for Termination

Not applicable.

Study Design/Methodology

This study was designed to provide information in this rare disease at various BPS804 dose levels with a small number of patients. A reference group of five patients was enrolled in order to monitor the natural disease progression of moderate OI with respect to bone biomarkers and BMD.

Centers

8 centers in 4 countries: Belgium (2), Canada (1), Germany (3), United States (2)

Objectives:

Primary objective(s)

- To evaluate safety and tolerability of BPS804 when administered as multiple, dose escalating iv infusions in adults with moderate OI
- To determine the pharmacodynamic (PD) effect of BPS804 when administered as multiple, dose escalating iv infusions on:
    - Serum bone formation markers:
        - Procollagen I N-terminal propeptide (PINP)
        - Procollagen I C-terminal propeptide (PICP)
        - Osteocalcin (OC)
        - Bone-specific alkaline phosphatase (BSAP)
    - Serum bone resorption markers:
        - C-telopeptides of type I collagen cross-links (CTX-1)
        - N-telopeptides of type I collagen cross-links (NTX-1)
- To evaluate the effect of BPS804 on lumbar spine BMD measured by dual-energy X-ray absorptiometry (DXA)

Secondary objective(s)

- To determine the pharmacokinetic (PK) profile of BPS804 when administered as multiple, dose escalating iv infusions
- 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 i.v. infusions

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

Powder for solution for infusion (lyophilizate in vial) BPS804 150 mg per vial.

Statistical Methods

It was considered a sign for efficacy, if:

- PINP and PICP and BSAP on Day 43 (Day 15 from 20 mg/kg administration)

OR

- BMD by DXA of lumber spine on Day 141 (Day 113 after 20 mg/kg administration) showed significant (2-sided, alpha=0.05) increase versus baseline in the BPS804 group.

Study Population: Key Inclusion/Exclusion Criteria

Inclusion Criteria:

- Osteogenesis imperfecta
- Two or more previous fractures
- Bone mineral density Z-score of ≤ -1.0 and > -4.0

Exclusion Criteria:

- Open epiphyses
- Fracture within last 2 weeks
- Treatment with bisphosphonates/teriparatide (last 6 months)
- Surgery within last year

Participant Flow Table

Patient disposition (safety population)

	BPS804 N=9 n (%)	Reference N=5 n (%)	Total N=14 n (%)
Patients			
Randomized	9 (100)	5 (100)	14 (100)
Completed	9 (100)	4 (80.0)	13 (92.9)
Discontinued	0 (0.0)	1 (20.0)	1 (7.1)
Main cause of discontinuation			
Lost to follow-up	0 (0.0)	1 (20.0)	1 (7.1)

Baseline Characteristics

Demographic summary by treatment group (Safety population)

	BPS804 N=9	Reference N=5	Total N=14
Age (years)			
Mean (SD)	30.7 (13.47)	27.4 (15.47)	29.5 (13.71)
Median	25.0	21.0	21.5
Range	19, 57	19, 55	19, 57
Sex – n (%)			
Male	7 (77.8)	3 (60.0)	10 (71.4)
Female	2 (22.2)	2 (40.0)	4 (28.6)
Predominant Race – n (%)			
Caucasian	9 (100)	5 (100)	14 (100)
Ethnicity – n (%)			
Mixed ethnicity	1 (11.1)	1 (20.0)	2 (14.3)
Other	8 (88.9)	4 (80.0)	12 (85.7)
Weight (kg)			
Mean (SD)	61.84 (14.378)	58.20 (13.034)	60.54 (13.519)
Median	63.90	54.00	59.45
Range	43.5, 80.1	44.0, 75.0	43.5, 80.1
Height (cm)			
Mean (SD)	161.6 (12.19)	162.8 (13.85)	162.0 (12.28)
Median	162.0	161.0	162.0
Range	142, 178	142, 176	142, 178

Weight and height are taken from Screening vital signs evaluations.

Disease characteristics by treatment group at study entry (Safety population)

	BPS804 N=9	Reference N=5	Total N=14
Lumbar spine z-score			
Mean (SD)	-2.59 (1.191)	-2.18 (0.514)	-2.44 (0.997)
Median	-2.30	-2.07	-2.19
Range	-4.9, -1.1	-2.9, -1.5	-4.9, -1.1
Yrs. on bisphosphonates			
N	2	1	3
Mean (SD)	8.53 (4.882)	15.46 (-)	10.84 (5.283)
Median	8.53	15.46	11.99
Range	5.1, 12.0	15.5, 15.5	5.1, 15.5
Subjects with D43 Biomarker data – n (%)			
	9(100)	5(100)	14(100)
Subjects with D141 BMD data – n (%)			
	9(100)	4(80.0)	13(92.9)

Lumbar spine z-score is taken at screening.

Years on bisphosphonates is calculated from the medical history page, by taking the difference between the earliest start date of bisphosphonates medication and date of screening.

Summary of Efficacy

Primary Outcome Result(s)

One-sample t-test analysis results for primary PD variables

	Parameter	PINP		PICP		BSAP		OC		BMD	
		BPS804	Reference	BPS804	Reference	BPS804	Reference	BPS804	Reference	BPS804	Reference
Baseline	N	9	5	9	5	9	5	9	5	9	4
	Geometric Mean	44.89	26.99	50.02	28.41	36.48	42.80	31.31	29.24	0.77	0.82
Day 43	N	9	5	9	5	9	5	9	5		
	Geometric Mean	82.81	28.50	76.39	29.83	58.00	37.28	45.14	23.66		
Day 141	N									9	4
	Geometric Mean									0.80	0.82
	Ratio of Geometric Means [90% CI]	1.84 [1.65, 2.06]	1.06 [0.83, 1.34]	1.53 [1.27, 1.84]	1.05 [0.87, 1.26]	1.59 [1.36, 1.86]	0.87 [0.53, 1.42]	1.44 [1.17, 1.78]	0.81 [0.48, 1.36]	1.04 [1.01, 1.07]	1.01 [1.00, 1.01]
	P-value (2-sided)	<.001	0.651	0.003	0.600	<.001	0.582	0.012	0.436	0.038	0.138

Two-sample t-test analysis of the primary PD variables

	BPS804		Reference			
Parameter	N	Geometric Mean	N	Geometric Mean	Ration of geometric means [90% CI]	P-value (1-sided)
PINP	9	1.84	5	1.06	1.75 [1.43, 2.14]	<0.001
PICP	9	1.53	5	1.05	1.45 [1.11, 1.90]	0.014
BSAP	9	1.59	5	0.87	1.83 [1.27, 2.62]	0.006
OC	9	1.44	5	0.81	1.78 [1.17, 2.71]	0.015

Secondary Outcome Result(s)

Summary statistics of sclerostin serum levels Pharmacodynamic (PD) analysis set Treatment: BPS804

Day	Statistic	Concentration (ng/mL)
1	n	9
	Mean (SD)	6.43 (19.3)
	CV% mean	300.0
	Geo-mean	
	CV% geo-mean	
	Median	0.00
	[Min; Max]	[0.00;57.9]
8	n	9
	Mean (SD)	50.6 (16.3)
	CV% mean	32.3
	Geo-mean	48.7
	CV% geo-mean	28.8
	Median	45.2
	[Min; Max]	[37.8;87.6]

15	n	9
	Mean (SD)	56.4 (18.0)
	CV% mean	31.9
	Geo-mean	54.0
	CV% geo-mean	31.6
	Median	46.8
	[Min; Max]	[39.5;86.0]
29	n	9
	Mean (SD)	63.9 (19.5)
	CV% mean	30.6
	Geo-mean	61.6
	CV% geo-mean	28.6
	Median	58.4
	[Min; Max]	[40.8;105]
36	n	9
	Mean (SD)	72.2 (35.0)
	CV% mean	48.4
	Geo-mean	66.1
	CV% geo-mean	44.9
	Median	61.0
	[Min; Max]	[37.3;140]
43	n	9
	Mean (SD)	69.2 (26.8)
	CV% mean	38.7
	Geo-mean	65.7
	CV% geo-mean	33.3
	Median	66.6
	[Min; Max]	[40.3;136]

57	n	9
	Mean (SD)	79.2 (24.1)
	CV% mean	30.4
	Geo-mean	76.5
	CV% geo-mean	27.3
	Median	77.6
	[Min; Max]	[54.8;136]
85	n	9
	Mean (SD)	47.4 (16.0)
	CV% mean	33.9
	Geo-mean	45.0
	CV% geo-mean	35.4
	Median	46.7
	[Min; Max]	[24.5;78.5]
113	n	6
	Mean (SD)	19.1 (16.2)
	CV% mean	84.5
	Geo-mean	
	CV% geo-mean	
	Median	18.9
	[Min; Max]	[0.00;46.3]
141	n	9
	Mean (SD)	4.97 (6.27)
	CV% mean	126.2
	Geo-mean	
	CV% geo-mean	
	Median	3.46
	[Min; Max]	[0.00;18.4]

Summary statistics of sclerostin serum levels Pharmacodynamic (PD) analysis set Treatment: Reference

Day	Statistic	Concentration (ng/mL)
43	n	4
	Mean (SD)	0.00 (0.00)
	CV% mean	
	Geo-mean	
	CV% geo-mean	
	Median	0.00
	[Min; Max]	[0.00;0.00]
141	n	4
	Mean (SD)	0.00 (0.00)
	CV% mean	
	Geo-mean	
	CV% geo-mean	
	Median	0.00
	[Min; Max]	[0.00;0.00]

Summary statistics of PK parameters

PK Parameters	Statistic	BPS804 5 mg/kg n=9	BPS804 10 mg/kg n=9	BPS804 20 mg/kg n=9
AUClast (day*µg/mL)	Mean ± SD	604.2 ± 160.0	NC	8458.3 ± 2512.5
AUCinf (day*µg/mL)	Mean ± SD	NC	NC	8541.7 ± 2533.3
Cmax (µg/mL)	Mean ± SD	175 ± 34	365 ± 86	746 ± 169
Tmax (hour)	Median (min-max)	2.12 (1.95 – 4.18)	2.07 (1.97 – 2.38)	2.20 (2.00 – 11.1)
T1/2 (day)	Mean ± SD	NC	NC	9.58 ± 1.39

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

Summary of Safety

Safety Results

Serious Adverse Events by System Organ Class

	BPS804 N=9	Reference N=5
General disorders and administration site conditions		
goiter	0	1

Incidence of AEs by preferred term (at least 1percent incidence in any group) (Safety set)

	BPS804 N=9 n (%)	Reference N=5 n (%)	Total N=14 n (%)
Subjects with AE(s)	9 (100)	4 (80.0)	13 (92.9)
Preferred term			
Headache	2 (22.2)	2 (40.0)	4 (28.6)
Influenza	2 (22.2)	1 (20.0)	3 (21.4)
Arthralgia	1 (11.1)	1 (20.0)	2 (14.3)
Fatigue	2 (22.2)	0 (0.0)	2 (14.3)
Abdominal pain upper	0 (0.0)	1 (20.0)	1 (7.1)
Ankle fracture	1 (11.1)	0 (0.0)	1 (7.1)
Bursitis	1 (11.1)	0 (0.0)	1 (7.1)
Cough	1 (11.1)	0 (0.0)	1 (7.1)
Diarrhoea	1 (11.1)	0 (0.0)	1 (7.1)
Excoriation	1 (11.1)	0 (0.0)	1 (7.1)
Foot fracture	1 (11.1)	0 (0.0)	1 (7.1)
Fungal skin infection	1 (11.1)	0 (0.0)	1 (7.1)
Goitre	0 (0.0)	1 (20.0)	1 (7.1)
Insomnia	0 (0.0)	1 (20.0)	1 (7.1)
Joint dislocation	1 (11.1)	0 (0.0)	1 (7.1)
Laryngitis	1 (11.1)	0 (0.0)	1 (7.1)
Muscle strain	1 (11.1)	0 (0.0)	1 (7.1)
Musculoskeletal pain	0 (0.0)	1 (20.0)	1 (7.1)
Myalgia	1 (11.1)	0 (0.0)	1 (7.1)
Nausea	1 (11.1)	0 (0.0)	1 (7.1)
Oropharyngeal pain	1 (11.1)	0 (0.0)	1 (7.1)
Pain	0 (0.0)	1 (20.0)	1 (7.1)
Pain in extremity	0 (0.0)	1 (20.0)	1 (7.1)
Pharyngitis	1 (11.1)	0 (0.0)	1 (7.1)
Presyncope	1 (11.1)	0 (0.0)	1 (7.1)
Prostatitis	0 (0.0)	1 (20.0)	1 (7.1)
Scapula fracture	1 (11.1)	0 (0.0)	1 (7.1)
Sinusitis	0 (0.0)	1 (20.0)	1 (7.1)
Temperature intolerance	1 (11.1)	0 (0.0)	1 (7.1)
Viral upper respiratory tract infection	0 (0.0)	1 (20.0)	1 (7.1)
Vomiting	1 (11.1)	0 (0.0)	1 (7.1)
Vulvovaginal candidiasis	0 (0.0)	1 (20.0)	1 (7.1)

AEs by preferred terms are presented in descending order of frequency in total group.

Date of Clinical Trial Report

08-Aug-2013