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COMPOUND NUMBER: PH-797804

THERAPEUTIC AREA AND FDA APPROVED INDICATIONS: This drug is not marketed in the United States.

NATIONAL CLINICAL TRIAL NO.: NCT00614705

PROTOCOL NO.: A6631013

PROTOCOL TITLE: A Four Week, Multi-Center, Randomized, Double-Blind, Placebo-Controlled, Parallel-Group, Phase 2a Study of PH-797804 in the Treatment of Post-Herpetic Neuralgia

Study Centers: This study was conducted at a total of 25 centers: 1 in Chile, 4 in the Russian Federation, 5 in Spain (2 centers enrolled but did not enter subjects), 3 in Sweden, 8 in Ukraine (1 center enrolled but did not enter subjects) and 4 in the United Kingdom (1 center enrolled but did not enter subjects).

Study Initiation and Completion Dates: 02 April 2008 to 05 December 2008

Phase of Development: Phase 2a

Study Objectives:

- To evaluate the efficacy of PH-797804 in subjects with post-herpetic neuralgia (PHN).
- To evaluate the safety and tolerability of PH-797804 in subjects with PHN.
- To collect blood samples for pharmacokinetic (PK) analysis of PH-797804 in subjects with PHN.

METHODS

Study Design: This was a multi-center, randomized, double-blind, placebo-controlled, parallel-group, Phase 2a study of PH-797804 in the treatment of PHN. The study comprised of a 1-week screening period, a 4-week randomized treatment period and a 2-week follow-up period.

Subjects who met the entry criteria at Visit 1 (V1) entered the 1-week screening period, during which daily pain scores were recorded utilizing a telephone interactive voice response (IVR) daily diary system. If the severity of pain met the relevant randomization criteria of

the study, subjects entered the double-blind treatment phase where they were randomized in a 1:1 ratio to either PH-797804 6 mg or placebo, once daily.

Treatment began with the morning dose on the day after randomization. Subjects attended the clinic for visits at Weeks 1, 2 and 4 during the 4-week treatment phase (Visits 3, 4, 6). Telephone contact was made by the center with subjects between Visits 4 and 6, to assess compliance with IVR diary recordings and treatment regime. A final clinic visit (Visit 7) for follow-up was undertaken 2 weeks after Visit 6. The duration of the study was approximately 7 weeks.

Number of Subjects (Planned and Analyzed): It was planned to screen approximately 145 subjects to provide approximately 80 randomized subjects at Visit 2 (V2); 80 subjects were treated and analyzed.

Diagnosis and Main Criteria for Inclusion: Subjects were males or females of non-childbearing potential, aged at least 18 years. Subjects must have had pain present for more than 3 months after healing of the Herpes zoster skin rash. Subjects who had undergone neurolytic or neurosurgical therapy including skin excisions for PHN or who had other severe pain, which may have impaired the self-assessment of the pain due to PHN, were excluded. Subjects with active or latent tuberculosis, as determined by a QuantiFERON-Gold test™, were excluded.

Study Treatment: PH-797804 (3 mg) and matching placebo capsules were supplied by the sponsor. Subjects were required to take 2 capsules as instructed once per day.

Efficacy Evaluations: Efficacy evaluations included the daily pain rating scale, Neuropathic Pain Symptom Inventory (NPSI) and Patient Global Impression of Change (PGIC).

Pharmacokinetic Evaluations: One plasma PK sample was collected for population PK analysis at each of the clinic visits during the treatment period.

Safety Evaluations: Safety evaluations included clinical monitoring, vital signs (heart rate, blood pressure), 12-lead electrocardiograms (ECGs), adverse events (AEs), safety laboratory tests and physical examinations (including skin assessments).

Statistical Methods: The primary endpoint was the change from baseline (defined as the mean of the last 7 pre-treatment pain scores) to end of treatment in weekly average pain score (based on the last 7 available on-treatment readings). The primary analysis was carried out with the Full Analysis Set (FAS) using an analysis of covariance (ANCOVA) with treatment as a fixed effect and baseline as a covariate. In order to investigate treatment effects over time, a mixed model repeated measures (MMRM) analysis was performed, with baseline value, treatment, week and treatment by week as fixed effects terms in the model. Subject was fitted as a random effect. The mean daily pain rating score change from baseline to end of treatment was classified into 2 defined categories (responder/non-responder).
Two definitions of a responder were used: subjects with ≥30% or ≥50% decrease in mean pain. Pain responders at the end of treatment were analyzed by logistic regression fitting treatment as a categorical variable. The analysis also fitted the baseline pain score as a covariate.

The end of treatment NPSI was analyzed using ANCOVA with baseline value, treatment, week and treatment by week as fixed effects terms in the model. Subject was fitted as a random effect. A separate analysis was conducted for the total score and the 5 clinically relevant dimensions of neuropathic pain syndromes. The PGIC at the end of treatment was analyzed using proportional odds logistic regression fitting treatment as a categorical variable (but with no covariate).

There was no formal statistical analysis of the PK and safety data.

RESULTS

Subject Disposition and Demography: A total of 165 subjects were screened; 80 subjects were assigned to treatment, with similar proportions of subjects receiving PH-797804 and placebo (Table S1). In total 72 subjects completed the study and 8 subjects discontinued, including 2 subjects who discontinued due to AEs (1 treatment-related).

Table S1. Subject Evaluation Groups

Number of Subjects	PH-797804	Placebo
Screened 165		
Assigned to Study Treatment	41	39
Treated	41	39
Completed	35	37
Discontinued	6	2
Adverse Event (Related to Study Drug)	0	1
Adverse Event (Not Related to Study Drug)	1	0
Lost to Follow-Up	1	0
Other	3	0
Subject no Longer Willing to Participate	1	1
Analyzed for Efficacy		
Full Analysis Set	38	39
Per Protocol Population	33	35
Analyzed for Safety		
Adverse Events	41	39
Laboratory Data	38	38

Demography: All subjects were white. The proportion of male and female subjects was similar for the study and for each treatment group. Mean age, weight, height and body mass index were similar for the 2 groups. All subjects had a primary diagnosis of PHN, with duration since first diagnosis ranging from 0.2 to 8.5 years.

Efficacy Results: There was no evidence of a difference between PH-797804 and placebo in the change from baseline in weekly average pain score to end of treatment. For both treatments, the average pain score decreased by more than 2 points by the end of treatment, from approximately 6.5 points at baseline to approximately 4.5 points (Table S2). There was

no significant difference between PH-797804 and placebo in change from baseline at the end of treatment (treatment difference 0.16; 80% confidence interval [CI]: -0.38, 0.71) or for the weekly average pain scores (Weeks 1, 2, 3 and 4), with both treatments showing a similar reduction in weekly average pain scores over time.

The proportion of subjects showing 30% and 50% reductions in weekly average pain score from baseline to endpoint was similar for both treatments.

Table S2. Summary of Changes from Baseline in Average Pain Scores (FAS)

	PH-797804 (N=38)	Placebo (N=39)
Baseline		
Mean (SD)	6.66 (1.12)	6.59 (1.27)
n	38	39
Week 1		
Change from Baseline – Adjusted Mean (SE)	-0.69 (0.160)	-0.71 (0.158)
Difference vs Placebo (SE) [80% CI]	0.02 (0.225) [-0.27, 0.31]	-
n	38	39
Week 2		
Change from Baseline – Adjusted Mean (SE)	-1.43 (0.196)	-1.32 (0.191)
Difference vs Placebo (SE) [80% CI]	-0.11 (0.274) [-0.46, 0.24]	-
n	35	38
Week 3		
Change from Baseline – Adjusted Mean (SE)	-2.20 (0.274)	-1.86 (0.265)
Difference vs Placebo (SE) [80% CI]	-0.34 (0.381) [-0.83, 0.15]	-
n	35	38
Week 4		
Change from Baseline – Adjusted Mean (SE)	-2.35 (0.321)	-2.39 (0.310)
Difference vs Placebo (SE) [80% CI]	0.04 (0.446) [-0.54, 0.61]	-
n	35	37
End of Treatment[a]		
Change from Baseline – Adjusted Mean (SE)	-2.16 (0.300)	-2.32 (0.296)
Difference vs Placebo (SE) [80% CI]	0.16 (0.421) [-0.38, 0.71]	-
n	38	39

CI = confidence interval; SD = standard deviation; SE = standard error;
N = number of subjects; n = number of subjects who had data used in the analysis
[a] End of Treatment was defined as the mean of the last 7 on-treatment pain scores. If fewer than 7 scores were recorded post-baseline then the available scores were used to determine mean pain score at end of treatment.

For all NPSI dimensions, there were decreases compared to baseline for both treatments. There was no significant treatment difference for the total score, although for the paroxysmal pain dimension, the change from baseline was greater for PH-797804 compared to placebo (treatment difference -0.37; 80% CI: -0.66, -0.07).

For both treatments, most subjects (>97%) recorded their PGIC as either no change or improved at the end of treatment. The proportion of subjects with improved PGIC was greater for the placebo group (82%) compared to the PH-797804 group (71%); however, there was no overall significant treatment difference for the PGIC.

Pharmacokinetic Results: Population pharmacokinetic analyses were not performed; however, plasma concentrations of PH-797804 were summarized by visit. Mean plasma concentrations of PH-797804 were 53.4, 56.8 and 62.2 ng/mL at Week 1, Week 2 and Week 4/early termination, respectively.

Safety Results: The number of subjects with AEs (all causalities) was similar for the PH-797804 and placebo treatment groups (Table S3). Treatment-related AEs were more common for the PH-797804 treatment group. Most AEs were mild or moderate in severity. Two subjects permanently discontinued due to AEs. One subject had an SAE: a 62-year old male was dosed with PH-797804 on Day 1 and was discontinued from the study following diagnosis of chronic lymphocytic leukemia on Day 5; the diagnosis was based on analysis of the screening blood test taken prior to study drug treatment. There were no deaths and no subjects had their dose reduced or temporarily discontinued due to AEs.

Table S3. Frequency of Treatment-Emergent Adverse Events

	PH-797804		Placebo	
Number of Subjects	**All Causalities**	**Treatment Related**	**All Causalities**	**Treatment Related**
Evaluable for AEs	41	41	39	39
Number of AEs	32	21	17	7
With AEs	17	12	15	7
With SAEs	1	0	0	0
With Severe AEs	2	1	0	0
Discontinued due to AEs	1	0	1	1

AEs = adverse events; SAEs = serious adverse events

The most common system organ class for AEs was ‘Gastrointestinal disorders’. The most frequent AE was rash (preferred terms rash or rash papular), reported for 5 subjects (12%) in the PH-797804 treatment group (treatment-related in 3 subjects), but no subjects in the placebo group (Table S4). Three subjects had elevated liver enzymes that were reported as AEs; all received PH-797804, and the elevations were considered to be mild in severity and treatment-related.

Table S4. Incidence of Most Common Treatment-Emergent Adverse Events by Preferred Term

Number of Subjects with Preferred Term	PH-797804 (N=41)		Placebo (N=39)	
	All Causalities	Treatment Related	All Causalities	Treatment Related
Rash/Rash papular	5	3	0	0
Nausea	3	3	1	1
Transaminases increased	2	2	0	0
Dizziness	2	1	0	0
Nasopharyngitis	1	1	2	0
Diarrhea	0	0	3	2
Insomnia	0	0	2	2

N = number of subjects
Only adverse events reported by >1 subject in 1 or both treatment groups are summarized

The most common laboratory abnormality (from a normal baseline) was elevation in urine WBCs: for subjects who were analyzed for the parameter, abnormalities were reported in 21% (3/14 subjects) of subjects receiving PH-797804 and 18% (3/17 subjects) of subjects receiving placebo. These abnormalities were not considered to be clinically significant.

There were no marked changes in vital signs or ECG parameters.

CONCLUSIONS:

- PH-797804 did not demonstrate any efficacy relative to treatment with placebo. Both treatment groups achieved a greater than 2-point reduction in pain score at end of treatment.
- PH-797804 was safe and well tolerated in this study.
- Mean plasma concentrations of PH-797804 were similar for Week 1, Week 2 and Week 4/early termination.