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PROPRIETARY DRUG NAME®/GENERIC DRUG NAME: Lyrica® / Pregabalin

PROTOCOL NO.: A9001464

PROTOCOL TITLE: A Phase 4 Multicenter, Open-Label, Pilot Study of Pregabalin and Prediction of Treatment Response in Patients With Postherpetic Neuralgia

Study Centers: Five centers in 4 countries took part in this study and enrolled subjects; 2 in Austria, 1 in Germany, 1 in South Africa, and 1 in the United State of America (USA).

Study Initiation Date and Final Completion Dates: 19 October 2012 (date of first subject enrollment) to 12 June 2013 (date of last subject completed). Due to insufficient subject enrollment, the study was terminated early, on 29 April 2013.

Phase of Development: Phase 4

Study Objectives:

Primary Objective: The primary objective was to obtain pilot prospective data to explore whether sensory symptom cluster analysis is useful for predicting treatment response in post herpetic neuralgia (PHN).

- Phenotype PHN subjects entering study with sensory symptom clustering using the PainPREDICT, PainDETECT and neuropathic pain symptom inventory (NPSI) questionnaires, "baseline pain interference with sleep", Patient Health Questionnaire–8 (PHQ-8), Generalized Anxiety Disorder 7-item (GAD-7), as well as Pain Catastrophizing Scale (PCS) questionnaire.

- Find "responders" and "non-responders" to treatment (pregabalin).

- Compare distribution of phenotypes within "responder" and "non-responder" groups.

Secondary Objective: The secondary objective was to evaluate the safety and tolerability of pregabalin in this population and to evaluate the efficacy of pregabalin to relieve pain and to improve global assessment, anxiety and depression, functional status, and sleep.

METHODS

Study Design: This was a Phase 4, open-label, pilot study of pregabalin and prediction of treatment response in PHN subjects. The reason for this unplanned termination was due to feasibility issues related to the low enrollment of PHN subjects. The decision to terminate the study was not related to any safety issues.

Subjects were initially screened and had a baseline period of 1 week to assess their overall pain. Subjects were asked to complete a daily pain and pain interference with sleep assessment on the telephone using an Interactive Voice Recognition System (IVRS). This was completed from Visit 1 screening to Visit 7 or early termination visit.

The investigator administered pregabalin in a flexible dose-escalation regimen titrated in accordance with individual response and tolerability as determined by the investigator. Pregabalin was added to the subject's existing therapy for neuropathic pain. The duration of the treatment period was 6 weeks (4 weeks dose optimization +2 weeks fixed dose), with a 1-week taper/placebo washout administered at the end of study (EOS) with weekly safety assessments.

At Visit 2, subjects should have had completed at least 4 daily pain diaries over the past 7 days (baseline), have had an average daily pain score of ≥4 (daily pain diary), and have had pain fluctuation of no more than a 4 point difference from the highest to the lowest score during the baseline period. The study design is presented in Table 1.

Table 1. Schedule of Activities

Study	**Screen/Baseline**	**Dose Optimization**				**Fixed Dose**		**F/U**
Visit number	V1[a]	V2[b]	V3	V4	V5	V6[c]	V7/ET[d]	V8
End of week	W-1	0	1	2	3	4	6	7
End of day		1	8	15	22	29	43	50
Study day	D-21 to D-1	D1	D8	D15	D22	D29	D43	D50
Visit type	Clinic	Clinic	Clinic	Clinic	Clinic	Clinic	Clinic	Clinic
Visit window	1 - 21 days	NA	±3 days	±3 days	±3 days	±3 days	±3 days	±3 days
Informed consent[e]	X							
Demography	X							
Inclusion/exclusion criteria	X	X						
Medical history	X							
Physical examination/abbreviated Neurological examination	X						X	
Vital signs	X	X	X	X	X	X	X	X
12 lead electrocardiogram	X							
Clinical labs	X						X	
C-SSRS[f]	X	X	X	X	X	X	X	X
PHQ-8 and GAD-7	X	X					X	
Adverse events	X	X	X	X	X	X	X	X
Prior/concomitant medication	X	X	X	X	X	X	X	X
Dispense study medication/dosing diary		X	X	X	X	X	X	
Assess for potential dosing adjustments			X	X	X	X		
Electronic-diary user training[g]	X							
Subject use of IVRS daily pain and pain interference with sleep assessment	X	X	X	X	X	X	X	
Review adherence to and understanding of IVRS		X	X	X	X	X	X	X
Weekly numeric rating scale for Pain(weekly NRS-Pain)[h]	X	X						
Patient global impression of change							X	
Brief pain inventory-short form		X					X	
Short-form 12 health survey		X					X	
Pain Catastrophizing scale		X						
PainDETECT/PainPREDICT	X	X	X	X	X	X	X	X
Neuropathic pain symptom inventory	X	X	X	X	X	X	X	X
Actigraphy device with a score option[i]	X					X		

Table 1. Schedule of Activities

Study	Screen/Baseline	Dose Optimization	Fixed Dose	F/U

C-SSRS=Columbia suicidality severity rating scale, D=day, ET=end of treatment, F/U=follow-up, GAD-7=Generalized Anxiety Disorder 7-item, IVRS=interactive voice recognition system, NA=not applicable, NRS=numerical rating scale, PHQ-8=patient health questionnaire 8, V=visit, W=week,

a. V1 (screening/baseline) could occurred between 21 days – 1 day prior to V2 (enrollment) based on the amount of time required for screening procedures, such as washout of prohibited concomitant medication, urine collection for creatinine clearance testing or the risk assessment by a qualified mental health professional. A 7-day minimum between Visit 1 and Visit 2 is required to establish baseline diary pain level. The maximum 21 day screening period did not include prior completion of the informed consent.

b. V2 was the open label visit for subjects eligible for enrolment.

c. V6 was the end of the dose optimization phase. The dose was fixed at this visit.

d. V7/ET was required for subjects who discontinued any portion of the open-label phase. At this visit, 1 week taper medication was dispensed.

e. Informed consent was to be completed prior to performing any other study procedures, including any medication changes made to participate in the study. Any such medication changes were to be considered for medical appropriateness to protect subject well-being. Informed consent could be obtained on a separate date in advance of Visit 1 procedures; for example, informed consent could be obtained 30 days prior to Visit 1 to allow for washout of medications.

f. Subsequent risk assessment could be required based on scores.

g. Electronic daily diary was completed via telephone using an IVRS. Included the daily pain NRS and the Subjective Sleep Questionnaire and was completed by the subject daily throughout the study in the evening at bedtime. Train subject in use of Electronic Daily Diary, log subject on IVRS daily diary system and hand out user manuals.

h. One week recall period.

i. The ActiSCORE device (watch-like) was dispensed at Visit 1 and worn through to Visit 2, then dispensed at Visit 6 and worn through to Visit 7/ET.

Number of Subjects (Planned and Analyzed): A maximum of up to 200 subjects was planned to be screened in order to have 100 evaluable subjects completing this study. Overall, 24 subjects were screened, 9 subjects were enrolled at 5 centers in 4 countries (3 subjects in Austria, 2 subjects in Germany, 3 subjects in South Africa and 1 subject in USA), and only 8 subjects completed the study. The study was terminated prematurely due to feasibility issues related to the low enrollment of PHN subjects, and no efficacy analyses were performed.

Diagnosis and Main Criteria for Inclusion: Eligible subjects had pain present for >3 months after the healing of the herpes zoster skin rash, at screening (Visit 1) and baseline (Visit 2), subjects had a score of ≥4 on the Numeric Rating Scale (NRS) for Pain (1 week recall period), at baseline (Visit 2), at least 4 pain diaries were to completed satisfactorily within the last 7 days and the average pain score was to be ≥4.

Excluded were subjects with other severe pain that could confound assessment or self evaluation of the pain due to PHN, neurolytic or neurosurgical therapy for PHN, skin conditions in the affected dermatome that could alter sensation.

Study Treatment: Pregabalin capsules containing 75 mg, 150 mg, 225 mg, or 300 mg were supplied in bottles by the sponsor.

Pregabalin was administered in accordance with United States Package Insert dose administration guidelines (300-600 mg/day dosed BID; 150 mg/day starting dose). Dose optimization occurred during the first 4 weeks; for the next 2 weeks subjects received a fixed dose; followed by a 1 week taper/washout period.

During the first week of treatment, subjects received the starting dose of pregabalin of 150 mg/day. Subjects were then optimized to a dose of 300, 450 or 600 mg/day pregabalin based on efficacy and tolerability at each weekly visit: Visit 3 (Week 1), Visit 4 (Week 2), Visit 5 (Week 3) and Visit 6 (Week 4). The dose may have been decreased at or between the weekly visits, up to and including Visit 6 (Week 4). The dose was only changed by 1 step up or down at a time (eg, 150 mg/day to 300 mg/day, or 450 mg/day to 300 mg/day). After the end of the fourth week (Visit 6), no further dose optimization was permitted. Subjects unable to tolerate a dose of at least 300 mg/day by Visit 6 (Week 4) were discontinued from the study.

During the next 2 weeks, the dose was fixed at 300 mg/day, 450 mg/day or 600 mg/day. Daily doses were achieved by BID dosing. Subjects unable to tolerate the fixed dose of study medication were discontinued from the study

Efficacy:

Primary Efficacy Endpoints:

The change in the daily pain diary (Numerical Rating Scale) mean pain score at the EOS (Week 6) compared with baseline.

Secondary Efficacy Endpoints:

- Proportion of subjects within each phenotype groups as determined by sensory symptom clustering using the PainPREDICT, PainDETECT and NPSI questionnaires, "baseline pain interference with sleep", PHQ-8, GAD-7 as well as PCS questionnaire.
- Proportions of subjects with ≥30% and ≥50% pain reduction based on daily pain diary.
- Proportion of phenotypes within the 30% and 50% responder groups.
- Pain NRS; 1 week recall period.
- NPSI.
- Patient Global Impression of Change (PGIC).
- Short Form 12v2 Health Survey (SF-12v2).
- The change in the daily sleep interference diary (Numerical Rating Scale, NRS) mean pain score at the end of the study (Week 6) compared with baseline.
- PHQ-8; GAD-7 questionnaire.
- Brief Pain Inventory (BPI-sf).

Safety Evaluations:

The following safety variables were assessed:

Safety laboratory variables (performed at a central laboratory): hematology, clinical chemistry and urinalysis (at V1, and V7/ end of treatment (ET)) and T4/thyroid-stimulating hormone, B12/folate, serum pregnancy test, and estimated creatinine clearance (all at V1); physical examination: general appearance, weight, skin, head, eyes, ears, nose, throat, chest, cardiovascular system, gastrointestinal system, neurological system and an edema assessment (at V1, V7/ET, and additional assessments as required). Clinically important changes were to be reported as AEs; vital signs (at all clinic visits) and 12-lead electrocardiogram (ECG) (at V1), both for assessment of any clinically important changes; suicidality assessment (PHQ-8, C-SSRS and the need for mental health risk assessments at screening and during the study). Adverse events (AEs) were accessed throughout the study (Table 1).

Statistical Methods:

Analysis Sets:

- Full Analysis Set (FAS): Intent-to-Treat (ITT) Population: All subjects who were treated (ie, received at least 1 dose of study medication) and had at least 1 post-Visit 2 efficacy evaluation. This was the efficacy analysis set.

- Safety Analysis Set: Safety Population: All subjects who had received at least 1 dose of study medication were included in this analysis.

The efficacy endpoints were to be summarized using ITT population. Continuous variables were to be descriptively summarized at each week and at endpoint (last observation carried forward [LOCF]) by presenting the number (n), mean, median, standard deviation (SD), maximum, and minimum.

For categorical variables, descriptive summary statistics were to be consisted of the number and percentage of subjects in each category. All percentages were to be rounded to 1 decimal point.

To explore whether sensory symptom cluster analysis is useful for predicting treatment response in subjects with PHN, the phenotype of all ITT subjects were to be identified using 3 different approaches (with or without the baseline PHQ-8, GAD-7 Pain Related Sleep Interference Score Scale, PCS): PainDETECT at baseline; PainPREDICT at baseline; NPSI at baseline.

Then for each of the above phenotypes the distribution of the pregabalin responders were to be compared (using 30% and 50%).

All secondary analysis were to be conducted on the ITT population, unless specified otherwise. Continuous endpoints were to be summarized using descriptive statistics: n, mean, SD, minimum, median and maximum, and the number of missing observations. This was to be performed at baseline, at endpoint (Week 6 or LOCF) and for the change from baseline at endpoint (LOCF). For discrete endpoints: frequency and percentage for each category, and number of missing data (missing data were to be excluded when calculating the percentages relative to the total sample). This was to be performed at baseline, at endpoint (Week 6 or LOCF).

RESULTS

Subject Disposition and Demography: A total of 24 subjects were screened, of which 9 subjects at 5 study centers were enrolled and received at least 1 dose of pregabalin during the study. Eight subjects completed the study; 1 subject was prematurely withdrawn from the study.

Of the 9 subjects enrolled, 2 were male and 7 were female; 3 were of black race and 6 were white; aged between 19-75 years; weight ranged from 49 kg to 134 kg; and height ranged from 154 cm to 196 cm.

Efficacy Results: No efficacy analyses were performed, as the study was terminated prematurely. The reason for this unplanned termination was due to feasibility issues related to the low enrollment of PHN subjects.

Safety Results: Eight of 9 enrolled subjects experienced a total of 16 TEAEs during the study; all the TEAEs were of mild or moderate severity. All TEAEs are summarized in Table 2.

Table 2. Treatment-emergent Adverse Events; All Causality (Treatment-Related)

Adverse Events (Preferred Term)	Number of Subjects With Adverse Events
Dizziness[a, b]	4 (4)
Somnolence	1 (1)
Upper respiratory tract infection	1 (0)
Oedema peripheral	2 (2)
Nausea	1 (1)
Fatigue	2 (2)
Dry mouth[b]	2 (2)
Sedation	1 (1)
Muscle rigidity	1 (1)

a. One subject had dizziness on 2 occasions.
b. Treatment-emergent adverse events (1 subject with dizziness and 1 subject with dry mouth) still present at the time of reporting.

There was no serious adverse event reported in this study and no subject died. One subject discontinued due to TEAE (Table 3).

Table 3. Summary of Discontinuation Due to Adverse Event

Subject Serial No.	Adverse Event	Severity	Treatment Related
1	oedema peripheral	moderate	Yes

No clinically significant abnormal findings in ECG results at screening were noted. No clinically significant values for any safety laboratory variable at V1 (screening) or V7 (Week 6) were noted. No laboratory value related AEs were reported. Only 1 subject presented changes from baseline examinations (pitting edema+1 was noted for this subject at V7 [Week 6]). No clinically significant changes in neurological examinations were noted from baseline.

The majority of the scores for the PHQ-8 assessment ranged from 0-4 (15 results out of 27) and 5-10 (10 results out of 27) representing mild and moderate depression respectively. Only 2 subjects reported a score >10 which represented moderately severe depression, but none reached the score of 15 that was defined as threshold for a potential suicidal risk. There were no positive responses to the C-SSRS assessment done at baseline and throughout the study and no expression of suicidal ideation or behavior. None of the subjects met the criteria for mental health risk assessment for any of the visits.

CONCLUSIONS: The primary objective of the study was to obtain pilot prospective data to explore whether sensory symptom cluster analysis is useful for predicting treatment response in PHN. Due to insufficient subject enrollment the study was terminated early. Pregabalin was generally well tolerated and no new or unexpected safety concerns were identified.