PFIZER INC.

These results are supplied for informational purposes only.
Prescribing decisions should be made based on the approved package insert.
For publications based on this study, see associated bibliography.

PROPRIETARY DRUG NAME®/GENERIC DRUG NAME: [S,S]-Reboxetine succinate/Esreboxetine

THERAPEUTIC AREA AND FDA APPROVED INDICATIONS: Not Applicable

NATIONAL CLINICAL TRIAL NO.: NCT 00354094

PROTOCOL NO.: A6061030

PROTOCOL TITLE: A Phase 2b Long-Term, Randomized, Open-Label, Safety and Tolerability Trial Comparing [S,S]-Reboxetine (PNU-165442g) with Routine Care in Patients with Postherpetic Neuralgia (PHN)

Study Centers: Total of 32 centers: 4 in Argentina, 2 in Canada, 2 in Chile, 6 in India, 4 in Lithuania, 1 in Mexico, 1 in Spain, 1 in Sweden, 6 in the United Kingdom, and 5 in the United States.

Study Initiation and Completion Dates: 03 November 2006 to 21 September 2007. This study was terminated prematurely by the sponsor because of a lack of sufficient clinical response to [S,S]-Reboxetine ([S,S]-RBX) observed in other studies within the PHN development program.

Phase of Development: Phase 2b

Study Objectives: The primary objective was to assess the long-term safety and tolerability of [S,S]-RBX in subjects with PHN. The secondary objectives were to assess the effect of long-term treatment with [S,S]-RBX on neuropathic pain and health-related quality of life in subjects with PHN, and to assess the effect of long-term treatment with [S,S]-RBX on the use of pain-related medications for the management of PHN. Health-related quality of life was not assessed in Croatia, Argentina, Chile, India and Lithuania because validated translations of subject completed questionnaires were not available in these countries. This change to the protocol is documented in Country Amendment 1 (26 May 2006).

METHODS

Study Design: This was a randomized, open-label, safety and tolerability study comparing [S,S]-RBX with routine care treatment in subjects with PHN. Following the screening visit (Visit 1 [V1]) was a 1-week baseline period. At the end of this baseline period (V2), subjects meeting the randomization criteria were randomized to either [S,S]-RBX or routine care treatment in a 1:1 ratio. Approximately 600 subjects were to be randomized at V2. The

maximum trial duration was to be 2 years, during which 14 clinic visits were planned. Thereafter, a final clinic visit (V15) for follow up was to be undertaken, 1 week after V14.

Subjects randomized to [S,S]-RBX received 1 mg once daily for the first week after V2. At the end of this week, they returned for their third visit (V3) where the dose could remain at 1 mg or be increased to 2 mg, guided by individual efficacy and tolerability considerations. Stepwise dose increase could occur at any time after Day 12. Thereafter, if required for symptomatic reasons, stepwise dose increase in 1 mg increments was permitted as long as the subject had been on the previous dose for at least 5 days. The maximum total daily dose of [S,S]-RBX was 8 mg, with the intention of balancing efficacy with tolerability. Provision was made in the protocol for a reduction in dose by 1 mg decrements for tolerability reasons, provided that the subjects had taken the previous dose at least once, to a minimum total daily dose of 1 mg. Dose adjustment was permitted either at a scheduled clinic visit, or at an unscheduled visit. Following dose adjustment, the subject was contacted by telephone, within 1 week, to assess tolerability of the new dose level

Subjects randomized to routine care treatment received treatment optimized for them on an individual basis. The investigator was free to provide whatever pharmacological (other than reboxetine/Edronax or opioids) or other treatment considered optimal for management of the subject's pain, taking into consideration any side effects associated with this individualized therapy. This treatment arm was intended to reflect current routine best medical practice in the management of neuropathic pain. It thus provided a comparative context for the interpretation of the safety and tolerability data obtained for [S,S]-RBX.

There was a Global Amendment (28 June 2007) made to the Final Protocol, which did not affect the study design and conduct presented in this Synopsis Report.

This study was terminated prematurely by the sponsor because of a lack of clinical response to [S,S]-RBX observed in other studies within the PHN program.

Number of Subjects (Planned and Analyzed): Six hundred (600) subjects were planned to be randomized. Seventy-eight (78) subjects were assigned to study treatment. Thirty-nine (39) subjects received [S,S]-RBX and 38 subjects received routine care treatment. No subject completed the study: all subjects were discontinued from the study.

Diagnosis and Main Criteria for Inclusion: This study included male or female subjects with PHN who were at least 18 years old, had pain present for at least 3 months after healing of the herpes zoster skin rash and with scores ≥40 on the Pain Visual Analogue Scale (VAS).

Study Treatment: [S,S]-RBX study treatment was presented as round white tablets containing 1, 2 or 4 mg of [S,S]-RBX in an extended release formulation. An oral dose of [S,S]-RBX at 1, 2, 3, 4, 5, 6, 7 or 8 mg was to be swallowed whole with water once daily for the duration of the study. Subjects receiving routine care treatment received treatment optimized for them on an individual basis.

Efficacy Evaluations: The pain VAS used a 100 mm line to represent pain of increasing intensity from no pain (0) to worst possible pain (100). The Patient Global Impression of

Change (PGIC) is a subject-rated instrument that measured change in the subject's overall status on a 7-point scale ranging from 1 (very much improved) to 7 (very much worse). The Neuropathic Pain Symptom Inventory (NPSI) is a self-administered questionnaire designed to evaluate the different symptoms of neuropathic pain. The NPSI includes 10 descriptors quantified on a (0-10) numerical scale and 2 temporal items. The Modified Brief Pain Inventory-Short Form (m-BPI-SF) is a self-administered questionnaire developed to assess the severity of pain and the impact of pain on daily functions during a 24-hour period prior to evaluation. The Short-Form 12 Health Survey (SF-12) is a generic measure of health status. The Euroqol-5 Dimensions (EQ-5D) descriptive system consists of 5 dimensions: mobility, self-care, usual activity, pain/discomfort, and anxiety/depression. Each dimension has 3 levels designated simply as no problem, some problem or extreme problem. The Analgesic Treatment Satisfaction Scale measures subjects' level of satisfaction with their prescription and non-prescription pain medications, and other treatments. For the Pain-related Medication Utilization, subjects were required to respond to questions about their utilization of medications for neuropathic pain. NPSI, m-BPI-SF, SF-12, EQ-5D and the Analgesic Treatment Satisfaction Scale were not assessed in Croatia, Argentina, Chile, India and Lithuania because validated translations of subject completed questionnaires were not available in these countries. This change to the protocol is documented in Country Amendment 1 (26 May 2006).

Some of the assessments were not performed as per protocol at 1 site in India because of a lack of training. This lack of compliance has been recorded in a Trial Master File.

Pharmacogenomic Evaluations: Biological samples were collected from subjects who wished to participate in additional research for de-identified genetic analysis. This additional research was described in the Clinical Pharmacogenomics Supplement.

Safety Evaluations: Safety evaluations included vital signs (systolic and diastolic blood pressure [BP] and heart rate [HR]), physical examination, 12-lead electrocardiogram (ECG), adverse events (AEs), and hematology and biochemistry safety laboratory tests.

Statistical Methods: No formal statistical methods were used and no formal statistical comparison between [S,S]-RBX and routine care was performed. All efficacy and safety data were listed and summarized by treatment group. The mean change from baseline in VAS over time was presented graphically by treatment.

RESULTS

Subject Disposition and Demography: Six hundred (600) subjects were planned to be randomized. Seventy-eight (78) subjects were assigned to study treatment. Thirty-nine (39) subjects received [S,S]-RBX and 38 subjects received routine care treatment. For 1 subject, who was randomized to [S,S]-RBX but not treated, the pain VAS, NPSI, vital signs and ECG data were collected and have been summarized in some tables. No subject completed the study: all subjects were discontinued from the study. Twenty-eight (28) subjects who received [S,S]-RBX and 33 subjects who received routine care treatment were recorded as being discontinued due to other reasons related to study treatment because the study was prematurely terminated by the sponsor. One subject who received [S,S]-RBX and 1 subject who received routine care treatment were discontinued due to an AE related to the study

treatment. Ten (10) subjects who received [S,S]-RBX and 4 subjects who received routine care treatment were discontinued due to reasons not related to the study treatment. All subjects who received [S,S]-RBX and all subjects who received routine care treatment were included in the full analysis set and safety analysis set, which both included all subjects who had received at least 1 dose of study treatment.

Table S1. Subject Evaluation Groups

	Number of Subjects		
	All	[S,S]-RBX	Routine Care
Planned	600		
Screened	78		
Assigned to study treatment	78		
Treated		39	38
Completed		0	0
Discontinued		39	38
Analyzed for efficacy			
Full analysis set[a]		39	38
Analyzed for safety			
Adverse events		39	38
Laboratory data		39	35
Safety analysis set[a]		39	38

[a] All subjects who received at least 1 dose of study treatment.

Generally, baseline and demographic characteristics of subjects who received [S,S]-RBX and subjects who received routine care were similar. A total of 15 male and 24 female subjects who received [S,S]-RBX and a total of 16 male and 22 female subjects who received routine care treatment participated in the study. The mean age for subjects who received [S,S]-RBX was 70.7 years (range: 40-88 years) and the mean age for subjects who received routine care treatment was 66.2 years (range: 32-85 years). The majority of subjects in both groups were aged >65 years. Of all subjects who received [S,S]-RBX, 29 were white and 10 were Asian and of all subjects who received routine care treatment, 29 were white, 1 was black and 8 were Asian. The mean duration since first diagnosis of PHN for subjects who received [S,S]-RBX was 2.5 years (range: 0.0 to 22.3 years) and for subjects who received routine care treatment was 2.2 years (range: 0.1 to 15.5 years). The most frequently occurring concurrent medical condition was hypertension (16 of 39 subjects who received [S,S]-RBX and 17 of 38 subjects who received routine care treatment).

Efficacy Results: No notable differences in pain VAS, NPSI and PGIC were observed between subjects who received [S,S]-RBX and subjects who received routine care treatment. The results for mBPI-SF, SF-12, EQ-5D, analgesic treatment satisfaction scale, and pain-related medication utilization were reported, but not summarized.

Pharmacogenomic Results: Pharmacogenomic analyses were described in the Clinical Pharmacogenomics Supplement.

Safety Results: No deaths were reported for any subject in this study. Over the course of this study, 73 treatment-emergent AEs (TEAEs) were observed in 22 of the 39 subjects who received [S,S]-RBX; 52 of these TEAEs, which were observed in 20 subjects, were considered treatment-related. Forty-one (41) TEAEs were observed in 18 of the 38 subjects

who received routine care treatment; 17 of these TEAEs, which were observed in 12 subjects, were considered treatment-related. All treatment-related TEAEs observed in subjects who received [S,S]-RBX and subjects who received routine care treatment were of mild or moderate severity. Two subjects (1 in each treatment group) had a severe AE; neither of these was treatment-related and both were reported as SAEs.

Two subjects who received [S,S]-RBX had SAEs. One subject had 2 SAEs of urinary tract infection and diabetes mellitus, and 1 subject had 1 SAE of prostatomegaly. The urinary tract infection, which occurred after study treatment stopped, was of mild severity, and the prostatomegaly was of moderate severity; both AEs were assessed as not being related to treatment, and resolved. Diabetes mellitus was severe and was ongoing. One subject who received routine care treatment had an SAE of syncope, which was severe, and resolved.

A discrepancy was observed in the causality recorded for the SAE of syncope. The ARISg database stated that the SAE of syncope was considered related to treatment, whereas the cause of this SAE was reported as concomitant treatment (possibly tegretol) in the Oracle Clinical database. Under these circumstances, the SAE of syncope was considered to be treatment-related.

Three subjects who received [S,S]-RBX were discontinued from the study because of TEAEs. Two subjects were discontinued due to SAEs of diabetes mellitus and urinary tract infection, and prostatomegaly, respectively, and one subject had 2 TEAEs of constipation and dizziness, which led to discontinuation. These TEAEs/SAEs were of mild or moderate severity, with the exception of diabetes mellitus, which was severe. The TEAEs of dizziness and constipation were assessed as being related to treatment. One subject who received routine care treatment was discontinued from the study due to a TEAE of dizziness, which was of moderate severity and assessed as being related to the study treatment. No subjects who received [S,S]-RBX were temporarily discontinued or had dose reduction as a result of an AE. In contrast, 2 subjects who received routine care treatment had a dose reduction because of TEAEs (somnolence and dizziness) that were assessed as being treatment-related.

A discrepancy was observed in the number of subjects discontinued due to AEs between the AE summary table, which reported 8 subjects in total: 5 subjects who received [S,S]-RBX and 3 subjects who received routine care treatment, and the discontinuation summary tables, which reported 4 subjects in total: 3 subjects who received [S,S]-RBX and 1 subject who received routine care treatment. A discrepancy between 2 tables was also observed in the discontinuations from the study due to AEs for subjects who received [S,S]-RBX: 6 AEs were reported in 1 table and 5 AEs were reported in the other table. These discrepancies occurred because the tables summarized data from different pages in the CRF (the AE log page and the final status page) and the information between these pages was inconsistent.

The most frequently reported all causality TEAEs for subjects who received [S,S]-RBX were constipation, dry mouth, and headache. A notably higher number of subjects who received [S,S]-RBX reported all causality TEAEs of constipation, dry mouth, and headache compared with subjects who received routine care treatment. The same number of subjects reported treatment-related and all causality TEAEs of constipation and dry mouth. However, only 3 subjects who received [S,S]-RBX reported a treatment-related TEAE of headache. A

higher number of subjects who received routine care treatment reported an all causality and treatment-related TEAE of dizziness compared with subjects who received [S,S]-RBX. The same numbers of subjects reported treatment-related and all causality TEAEs of dizziness.

Table S2. Incidence of Treatment-emergent Adverse Events (All Causalities) by System Organ Class and MedDRA Preferred Term

	Number of Subjects with TEAEs	
System organ class	[S,S]-RBX (N=39)	Routine Care Treatment (N=38)
MedDRA preferred term	n	n
Gastrointestinal disorders		
Constipation	9	0
Dry mouth	8	2
Infections and infestations		
Bronchitis	0	3
Nasopharyngitis	2	2
Urinary tract infection	2	1
Metabolism and nutrition disorders		
Anorexia	3	0
Nervous system disorders		
Dizziness	3	6
Headache	4	0
Paraesthesia	2	0
Somnolence	1	2
Psychiatric disorders		
Insomnia	3	2
Renal and urinary disorders		
Dysuria	2	0
Reproductive system and breast disorders		
Erectile dysfunction	3	0
Prostatism	2	0
Skin and subcutaneous tissue disorders		
Hyperhidrosis	2	0

MedDRA = Medical Dictionary for Regulatory Activities; N = number of subjects; n = number of subjects with treatment-emergent adverse event; TEAE = treatment-emergent adverse event.
Treatment-emergent adverse events are presented for those reported for 2 or more subjects in either treatment group.

Abnormal laboratory test results post baseline for subjects with normal baseline values were reported in 8 out of 39 subjects who received [S,S]-RBX and 8 out of 35 subjects who received routine care treatment. Abnormal laboratory test results post baseline for subjects with abnormal baseline values were reported for 1 out of 24 subjects who received [S,S]-RBX and 4 out of 19 subjects who received routine care treatment. No notable difference was observed between subjects who received [S,S]-RBX and subjects who received routine care treatment in the incidences of hematology and biochemistry safety test abnormalities.

No notable mean change from baseline in systolic or diastolic BP was observed in subjects who received [S,S]-RBX. No notable difference in mean systolic or diastolic BP was observed between subjects who received [S,S]-RBX and subjects who received routine care treatment. A slightly higher mean change from baseline in HR was observed at the majority

of time points in subjects who received [S,S]-RBX compared with subjects who received routine care treatment. One subject who received routine care treatment reported a moderate AE of orthostatic hypotension, which was considered related to study treatment and was resolved within 1 day.

A slight mean decrease from baseline in RR and PR interval was observed in subjects who received [S,S]-RBX compared with a slight mean increase in RR and PR interval in subjects who received routine care treatment. No notable mean change from baseline in QRS interval was observed in subjects who received [S,S]-RBX and no notable difference in mean QRS interval was observed between subjects who received [S,S]-RBX and subjects who received routine care treatment. Slight mean increases from baseline in QTcF intervals at Day 92 were observed in subjects who received [S,S]-RBX (mean [SD] change from baseline 13 [±27.79] msec, range -6 to 63 msec) compared with no change from baseline in subjects who received routine care treatment (mean [SD] change from baseline 2.6 [±18.55] msec, range -21 to 40 msec). The QTcF interval at the end of treatment was comparable with the baseline level for both subjects receiving [S,S]-RBX and subjects receiving routine care treatment. One subject (Subject 10401001 [female]) who received [S,S]-RBX had a QTcF interval >450 msec at baseline, which decreased to <450 msec during the study. One subject (Subject 10711001 [male]) who received [S,S]-RBX had a QTcF interval above the normal range (>430 msec) during the study (within normal range at baseline) and 1 subject (Subject 10451002 [male]) who received [S,S]-RBX had a QTcF interval >430 msec at baseline (no values were recorded during the study). Two subjects (Subjects 10181005 [male] and 10711006 [female]) who received routine care treatment had a QTcF interval above the normal range (>430 msec [male] or >450 msec [female]) during the study (within normal range at baseline) and 3 subjects (Subjects 10591001 [male], 10711002 [female], and 10861001 [male]) who received routine care had QTcF intervals above the normal range at baseline. These were recorded prior to treatment and either did not change during the study (Subjects 10591001 and 10711002) or no values were recorded during the study (Subject 10861001). No subject receiving either [S,S]-RBX or routine care treatment had a QTcF interval >500 msec. No ECG evaluation was reported as an AE.

One subject who received [S,S]-RBX and 1 subject who received routine care treatment had a significant change from baseline in the physical examination at the final visit. For the subject who received [S,S]-RBX, this change was reported as a mild AE of dry lips, which was considered related to study treatment and was still present at the end of the study.

No other safety tests, vital signs parameters, ECG evaluation, or physical examination findings were reported as an AE.

CONCLUSIONS: This study was terminated early by the sponsor because of lack of clinical response to [S,S]-RBX in previous studies within the PHN development programme.

- In this study, similar efficacy was observed in subjects who received [S,S]-RBX and subjects who received routine care treatment at all doses studied.

- The long-term safety results in this study reflected the known safety profile for [S,S]-RBX and no new AEs were reported.