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GENERIC DRUG NAME / COMPOUND NUMBER: [S,S]-Reboxetine Succinate / PNU-165442G

PROTOCOL NO.: A6061021

PROTOCOL TITLE: [S,S]-Reboxetine Add-On Trial: A Randomized, Double-Blind, Placebo-Controlled, Multicenter Trial of [S,S]-Reboxetine in Patients With Postherpetic Neuralgia (PHN) Concomitantly Treated With Pregabalin

Study Centers: A total of 46 centers took part in the study and randomized subjects; 9 in Ukraine, 7 in Germany, 5 each in Canada and Sweden, 4 in Norway, 3 in Italy, 2 each in the Czech Republic, Poland, Russian Federation, Spain, and the United Kingdom, 1 each in Latvia, the Netherlands, Austria, and Switzerland.

Study Initiation Date and Final Completion Date: 22 August 2006 to 11 October 2007. The study was terminated prematurely for futility following a planned interim analysis.

Phase of Development: Phase 2

Study Objectives:

- To compare the efficacy of adjunctive treatment of pregabalin with [S,S]-Reboxetine (RBX) against pregabalin monotherapy in subjects with postherpetic neuralgia (PHN)
- To investigate the safety and tolerability of [S,S]-RBX in adjunctive treatment with pregabalin in subjects with PHN

METHODS

Study Design: This was a randomized, double-blind study comparing pregabalin and pregabalin administered with [S,S]-RBX as an adjunctive therapy in subjects diagnosed with PHN. The study was comprised of 4 periods: 1) a 1-week screening period, 2) a 4-week pregabalin treatment (dose optimization) period, 3) a 10-week double-blind randomized treatment period, and 4) a 1-week follow-up period including dose taper for pregabalin.

All subjects who met the entry criteria entered the 1-week screening period during which a daily pain diary was maintained. If, at Visit 2, the severity of pain met the required entry criteria of the study, subjects entered the 4-week pregabalin treatment (dose optimization) period. At Visit 6, all subjects who met the double-blind randomization criteria were randomized to receive either pregabalin with placebo or pregabalin with [S,S]-RBX for a period of 10 weeks. The overall schedule of activities is presented in Table 1**.**

Table 1. Schedule of Activities

Clinic Visit[a]	Screen	Pregabalin Treatment (Dose Optimization)				Double-Blind Treatment						Follow-Up
	V1	V2[b]	V3	V4	V5	V6[c]	V7	V8	V9	V10	V11/Early Term[d]	V12
End of Trial Week						0	1	2	3	6	10	11
Day	-35	-28 (±2)	-21 (±2)	-14 (±2)	-7 (±2)	0 (±2)	7 (±2)	14 (±2)	21 (±2)	42 (±2)	70 (±2)	77 (±2)
Informed consent[e]	X											
Demography	X											
Medical/psychiatric history	X											
Physical examination	X	X				X					X	
Vital signs	X	X	X	X	X	X	X	X	X	X	X	X
12-lead ECG	X					X					X	
Pain Visual Analogue Scale	X	X				X					X	
Hospital Anxiety and Depression Scale	X	X				X					X	
Eysenck Personality Questionnaire	X											
Inclusion/exclusion criteria	X	X										
Daily diaries (pain & sleep)	Daily recordings from V1 to V12											
Medical Outcomes Study-Sleep Scale		X				X					X	
Patient Global Impression of Change						X					X	
Neuropathic Pain Symptom Inventory		X				X					X	
Pain Treatment Satisfaction Scale		X				X					X	
Pregnancy test (urine)[f]	X											
Hematology/biochemistry	X	X				X			X		X	
PK samples[g]									X		X	
Pharmacogenomic sample[h]		X										
Patient telephone contact									X	X		
Concomitant medication	X	X	X	X	X	X	X	X	X	X	X	X
Dispense trial medication		X	X	X	X	X	X	X	X	X	X	
Collect trial medication			X	X	X	X	X	X	X	X	X	X
Adverse events	X	X	X	X	X	X	X	X	X	X	X	X

ECG = electrocardiogram; IEC = Independent Ethics Committee; IRB = Institutional Review Board; PK = pharmacokinetics; Screen = screening; V = visit; VAS = visual analog scale.

Table 1. Schedule of Activities

a. Clinic Visit: a visit window of ±2 days was allowed.
b. V2: criteria for entry to pregabalin treatment (dose optimization); ie, subjects must have had completed at least 4 daily pain diaries over the last 7 days with an average daily pain score ≥4 over the last 7 days, and a score ≥40 mm on the Pain VAS.
c. V6: double-blind treatment criteria (subjects must have had an average daily pain score ≥4 over the last 7 days, a score ≥40 mm on the Pain VAS, maintained a stable pregabalin dosing regimen for at least 7 days prior to Visit 6 and subjects who had received a stable pregabalin dose of 75 mg/day must have had a reduction in average daily pain score of ≥30% from screening).
d. V11: all the assessments at Visit 11 were completed in case of early trial termination.
e. Informed consent: subjects provided written informed consent prior to any trial related procedures being conducted including any necessary wash-out period required for prohibited medications.
f. Pregnancy test: for women of child bearing potential. Pregnancy tests were repeated during the study per requests from IEC/IRBs or if required by local regulations.
g. PK samples: 2 PK samples at V9 and V11 (or early termination) were required. The 2 samples were taken at least 1-2 hours apart.
h. Pharmacogenomic sample: subject to ethical review, approval, and subject consent.

Number of Subjects (Planned and Analyzed): A total of 354 subjects (177 per treatment group) was planned for enrollment in the study in order to detect a treatment difference with 80% power and to allow for a discontinuation rate of 20%. Of the 339 subjects screened for the study, 238 were enrolled and received pregabalin.

Diagnosis and Main Criteria for Inclusion: Male or female subjects of at least 18 years of age must have had pain present for ≥3 months after the healing of shingles skin rash and at Screening must have had a score ≥40 mm on the pain visual analogue scale (VAS). Subjects with significant renal and hepatic impairment or with other severe pain considered to impair the self-assessment of the shingles pain were excluded from the study. In addition, subjects with clinically abnormal electrocardiogram (ECG) were excluded.

Study Treatment: Pregabalin was supplied as grey capsules containing 25 mg, 75 mg, 150 mg, 225 mg, or 300 mg of pregabalin. [S,S]-RBX study treatment was supplied as round white tablets containing 1 mg, 2 mg, or 4 mg of [S,S]-RBX in an extended-release formulation. Matching placebo tablets were also supplied. Pregabalin capsules were administered twice a day or three times a day. [S,S]-RBX or placebo tablets were administered once a day in the morning.

All subjects initially received either 75 or 150 mg total daily dose of pregabalin for 1 week, depending upon their creatinine clearance at screening. After 1 week (Visit 3), all subjects escalated to 150 or 300 mg total daily dose of pregabalin for 1 week depending on their creatinine clearance. After this additional week of pregabalin treatment, subjects who had ongoing pain (subjects whose pain had not been reduced by a minimum of 50% in average daily pain score from Screening) and good tolerance of pregabalin escalated to 300 or 600 mg total daily for 2 weeks depending on their creatinine clearance. Subjects were to complete a 4-week pregabalin treatment period. Subjects unable to maintain a stable dosing regimen or require more than a single one-step dose reduction were withdrawn from the study.

At Visit 6, subjects fulfilling the double-blind randomization criteria continued receiving pregabalin at the same optimized dosing regimen and additionally were randomized to receive either [S,S]-RBX or placebo. Subjects who were randomized to receive [S,S]-RBX followed the escalation regimen shown in Table 2. For subjects who escalated to a 4 mg and 6 mg total daily dose and experienced adverse events (AEs) at that dose, a single 1 step dose reduction to 2 mg and 4 mg total daily dose, respectively, was allowed, guided by individual subject tolerability. Pregabalin was down-titrated over 1 week during the follow up period at the end of the double-blind treatment period.

Table 2. [S,S]-RBX Escalation Regimen

	[S,S]-RBX Escalation Regimen			
Period (days)	1-3	4-7[a]	8-14[a]	15-onward
Dose (mg)	1	2	4	6

RBX = Reboxetine.

a. Dose escalation from Day 7 and Day 14 onward was dependent upon subjects having ongoing pain and good toleration to [S,S]-RBX.

Efficacy Endpoints:

Primary Endpoint:

- Change from Baseline to Week 10 in weekly average pain score. Pain intensity was based on the daily pain diary numerical rating scale of 0-10

Secondary Endpoints:

- Responder rate (30 and 50% reduction in weekly average pain score from Baseline to Week 10)
- Weekly average pain score from the daily pain diary
- Weekly average sleep interference scores from the daily sleep diary
- Pain Visual Analogue Scale (VAS)
- Medical Outcomes Study (MOS)-Sleep Scale
- Patient Global Impression of Change (PGIC)
- Neuropathic Pain Symptom Inventory (NPSI)
- Hospital Anxiety and Depression Scale (HADS)
- Pain Treatment Satisfaction Scale

Safety Evaluations: Safety evaluations included clinical monitoring, vital signs (pulse rate, blood pressure), 12-lead ECGs, AEs, and laboratory tests.

Statistical Methods: Full Analysis Set (FAS) included all randomized subjects who received at least 1 dose of study medication, regardless of whether subject had efficacy data**.** The per protocol population included subjects who completed at least 6 weeks of randomized treatment (ie, subject had an Early Termination Visit later than or equal to 6 weeks, and had completed the daily diary cards up to Day 43). The 'Safety Population' consisted of all subjects who received at least 1 dose of either investigational treatments.

The primary endpoint, change from Baseline in weekly average pain score, was analyzed using an analysis of covariance. Significance tests for the treatment comparisons (adjunctive [S,S]-RBX and pregabalin versus pregabalin monotherapy) were performed at the 1-sided 5% significance level.

As the study was terminated early, only the primary efficacy endpoint and the secondary efficacy endpoints of responder rates, Pain VAS and PGIC were statistically analyzed. Responder rates (30% and 50% reduction from Baseline in weekly average pain score), PGIC were analyzed using logistic regression modeling, with treatment and country as categorical variables and baseline mean daily pain score as covariate.

Remaining secondary efficacy endpoints that were not statistically analyzed included weekly mean pain score, weekly average sleep interference score, MOS-Sleep scale, NPSI, HADS, and PTSS; these endpoints were only summarized and listed.
Safety data were evaluated using descriptive statistics.

RESULTS

Subject Disposition and Demography: Of the 339 subjects screened for the study, 238 were enrolled and received pregabalin during the dose-optimization period. A total of 134 subjects completed this period and were subsequently randomized to either [S,S]-RBX + pregabalin or placebo + pregabalin. For each group 53 subjects completed and 14 subjects discontinued the double-blind treatment period (Table 3).

Table 3. Subject Disposition

Number (%) of Subjects	Pregabalin	[S,S]-RBX + Pregabalin	Placebo + Pregabalin
Treated[a]	238	67	67
Discontinued[b]	104 (43.7)	14 (20.9)	14 (20.9)
Related to study drug	28 (11.8)	11 (16.4)	8 (11.9)
Adverse event	14 (5.9)	9 (13.4)	3 (4.5)
Lack of efficacy	0 (0.0)	1 (1.5)	1 (1.5)
Other	14 (5.9)	1 (1.5)	4 (6.0)
Not related to study drug	76 (31.9)	3 (4.5)	6 (9.0)
Adverse event	4 (1.7)	1 (1.5)	1 (1.5)
Other	69 (29.0)	0 (0.0)	2 (3.0)
Subject defaulted	3 (1.3)	2 (3.0)	3 (4.5)
Completed	134 (56.3)	53 (79.1)	53 (79.1)

RBX = Reboxetine.
a. Received at least one dose of study treatment.
b. Discontinuations occurring outside the lag period (30 days) were attributed to the last study treatment received.

The demographic characteristics were comparable for the 2 randomized treatment groups, as summarized in Table 4. In both the [S,S]-RBX + pregabalin and the placebo + pregabalin groups, more female than male subjects were included. All subjects participating in the study were White. Mean age was 67.2 years for the [S,S]-RBX + pregabalin and 65.3 years for the placebo + pregabalin groups. The treatment groups were comparable with regard to weight and height.

Table 4. Demographic Characteristics

Variable	Pregabalin (Not Randomized) N=104	[S,S]-RBX + Pregabalin N=67	Placebo + Pregabalin N=67
Gender [n (%)]			
Male	39 (37.5)	28 (41.8)	28 (41.8)
Female	65 (62.5)	39 (58.2)	39 (58.2)
Age (years)			
Mean (SD)	64.2 (14.5)	67.2 (11.7)	65.3 (14.4)
Range	23-86	28-84	18-88
Race [n (%)]			
White	104 (100.0)	67 (100.0)	67 (100.0)
Weight (kg)			
Mean (SD)	76.7 (16.5)	74.1 (14.2)	77.7 (16.6)
Range	48.2-139.0	45.0-113.0	46.0-138.0
Height (cm)			
Mean (SD)	166.4 (9.6)	166.6 (9.1)	168.7 (9.9)
Range	144.0-192.0	148.0-188.0	145.0-190.0

N = total number of subjects; n = subjects with pre specified criteria; RBX = Reboxetine; SD = standard deviation.

Efficacy Results: Following a planned interim analysis, the Pfizer Data Monitoring Committee recommended that the study should be stopped prematurely for futility, according to predetermined criteria. Therefore the statistical analysis plan was amended prior to unblinding the study and some secondary efficacy data were only summarized or listed. A statistical analysis was only performed for the primary efficacy endpoint and the secondary efficacy endpoints responder rates, pain VAS and PGIC.

Primary Endpoint: Table 5 shows the weekly mean pain scores during the pregabalin optimization phase and the double-blind treatment phase for the [S,S]-RBX + pregabalin and placebo + pregabalin treatment groups. The mean pain scores decreased during the pregabalin optimization phase (screening to Week 0) in both groups. During the double-blind treatment phase (Week 0 to 10) mean pain scores continued to decrease to a similar degree in both treatment groups (-2.12 and -2.07, respectively), indicating that, in accordance to the randomization criteria, subjects were still in pain at Baseline (Week 0). However, no add-on treatment effect of [S,S]-RBX compared with placebo was observed.

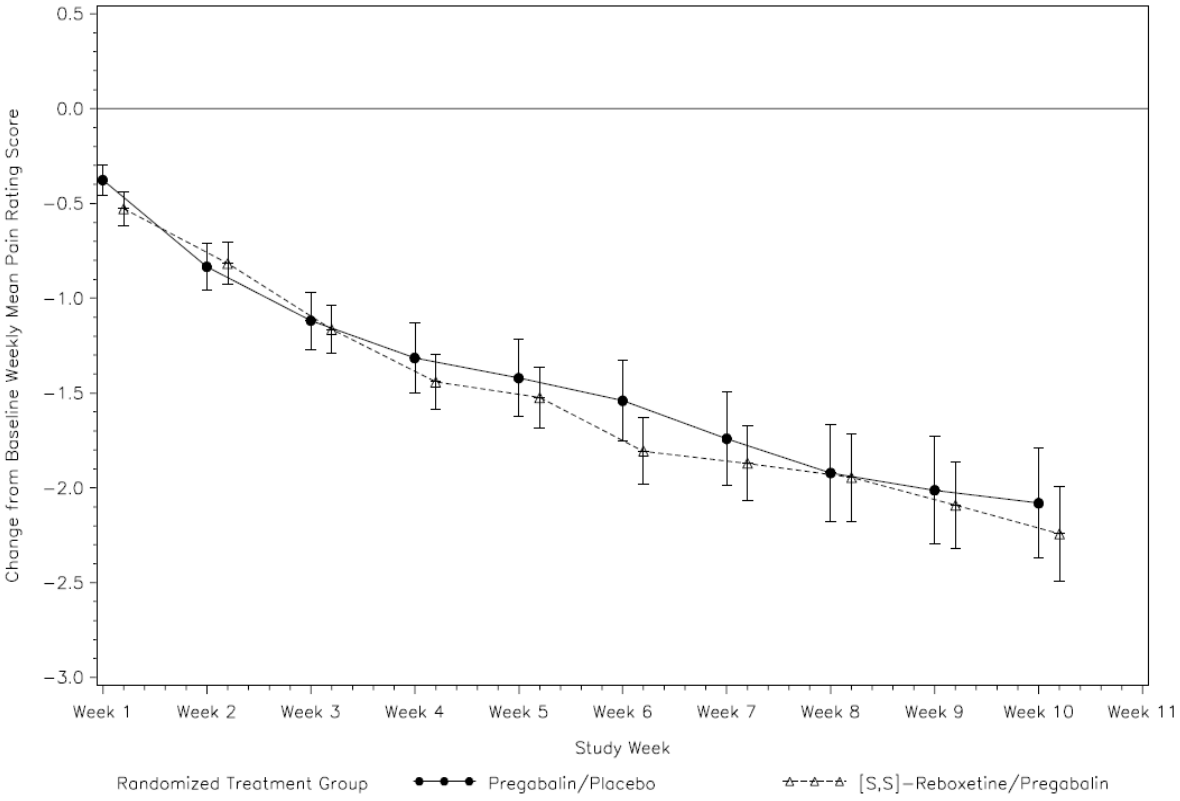
Table 5. Weekly Mean Pain Scores During the Pregabalin Optimization and Double-blind Treatment Phases (Full Analysis Set)

Visit	[S,S]-RBX + Pregabalin N=67				Placebo + Pregabalin N=67			
	n	Mean	Median	SD	n	Mean	Median	SD
Screening	67	7.18	7.40	1.372	67	7.03	7.14	1.242
Week -3	67	6.67	6.83	1.428	67	6.57	6.71	1.378
Week -2	67	6.16	6.17	1.207	67	6.36	6.57	1.351
Week -1	67	5.82	6.00	1.144	67	5.97	6.00	1.238
Week 0	67	5.68	5.57	1.003	67	5.87	5.67	1.190
Week 1	67	5.18	5.00	1.174	67	5.49	5.29	1.194
Week 2	64	4.90	5.00	1.220	64	5.07	5.00	1.431
Week 3	60	4.62	4.69	1.346	63	4.80	4.86	1.572
Week 4	59	4.32	4.00	1.465	59	4.59	4.71	1.722
Week 5	59	4.24	4.43	1.519	59	4.48	4.57	1.759
Week 6	58	3.97	4.00	1.675	59	4.36	4.17	1.878
Week 7	56	3.92	3.79	1.797	55	4.20	4.00	1.925
Week 8	56	3.85	3.67	2.006	55	4.02	4.00	1.999
Week 9	54	3.72	3.14	1.870	54	3.90	4.00	2.090
Week 10	54	3.56	3.36	2.055	53	3.80	3.86	2.113

n = number of subjects contributing to the mean; N = total number of subjects; RBX = Reboxetine; SD = standard deviation.

The changes reported in weekly mean pain score are illustrated graphically for the double-blind treatment phase in Figure 1.

Figure 1. Change From Baseline in Weekly Mean Pain Score (Full Analysis Set)



Secondary Endpoints:

Pain Visual Analogue Scale: Improvements in the VAS were observed in both treatment groups; however, no statistically significant difference between adjunctive [S,S]-RBX + pregabalin and placebo + pregabalin was found (Table 6).

Table 6. Summary Statistics for the Change From Baseline in the Pain Visual Analogue Scale (FAS)

Treatment	Baseline			End of Treatment		
N=67	n	Mean (SD)	Median	n	Mean (SD)	Median
[S,S]-RBX/pregabalin	64	58.75 (11.211)	55.50	64	35.23 (23.809)	40.50
Pregabalin/placebo	62	57.95 (14.097)	56.50	62	36.23 (23.690)	33.00

FAS = full analysis set; n = number of subjects per treatment group as analyzed at Baseline and End of Treatment; N = total number of subjects per treatment group; RBX = Reboxetine; SD = standard deviation.

Responder Rate: The proportion of subjects with a 50% reduction in weekly average pain score from Baseline to an endpoint was similar for the [S,S]-RBX + pregabalin and placebo + pregabalin treatment group, as was the proportion of subjects with a 30% reduction in weekly average pain score. No statistically significant differences between treatments were shown Table 7.

Table 7. Summary of Logistic Regression Results for Analysis of 30% Reduction in Weekly-average Pain Score From Baseline to Endpoint (FAS)

Treatment Group[a]	n[a]	Total[a]	Proportion[a]	
[S,S]-RBX/pregabalin (N=67)	31	67	0.4627	
Pregabalin/placebo (N=67)	31	67	0.4627	
All treatments (N=134)	62	134	0.4627	
Contrast or Comparison[b]	**Odd Ratio Estimate[b]**	**90% CI[b]**		
[S,S]-RBX/pregabalin/pregabalin/placebo	1.058	(0.554, 2.022)	-	-
Contrast or Comparison[c]	**Df[c]**	**Wald Chi-Square[c]**	**Wald Test 2-Sided p-Value[c]**	**Wald Test 1-Sided p-Value[c]**
[S,S]-reboxetine/pregabalin/pregabalin/placebo	1	0.021	0.8854	0.4427

CI = confidence interval; FAS = full analysis set; n = number of subjects who had a reduction of 30% or more; N = total number of subjects; RBX = Reboxetine.

a. N was count of subjects in the indicated population. Total was the number of subjects used in the analysis.

b. Odds ratio for [S,S]-Reboxetine/pregabalin divided by placebo/pregabalin obtained by PROC LOGISTIC. Ninety percent CI obtained from PROC LOGISTIC using the Wald Test.

c. One-sided p-value based on the Wald test using the 5% significance level.

Weekly Average Sleep Interference Scores From the Daily Sleep Diary: The mean interference scores from the daily sleep diary for subjects in both treatment groups ([S,S]-RBX + pregabalin and placebo + pregabalin) decreased during the pregabalin optimization phase (ie, the change in reported sleep score at Baseline and at End of Treatment) versus the weekly sleep interference scores' change from Baseline (primary endpoint (Figure 1). These mean interference scores continued to decrease at a similar rate during the double-blind treatment phase; these trends are shown by summary statistics (Table 8).

Table 8. Summary Statistics of the Change From Baseline in Endpoint Weekly-Average Sleep Interference Score(FAS)

Weekly Mean Sleep Interference Score (at Baseline and End of Treatment)	Baseline				End of Treatment		
	N	Mean (SD)	Median	Min; Max	N	Mean (SD)	Min; Max
[S,S]-RBX/pregabalin	67	3.91 (2.392)	4.29	0; 8	67	2.31 (2.343)	0; 7.9
Pregabalin/placebo	67	3.78 (2.436)	3.86	0; 8.4	67	2.19 (2.205)	0; 7.3
All treatments	134	3.84 (2.406)	4	0; 8.4	134	2.25 (2.267)	0; 7.9

Change From Baseline				
Weekly Mean Sleep Interference Score	**N**	**Mean (SD)**	**Median**	**Min; Max**
[S,S]-RBX/pregabalin	67	-1.6 (2.08)	-1	-6.3; 2.6
Pregabalin/placebo	67	-1.59 (1.992)	-1.29	-6.9; 2.6
All treatments	134	-1.6 (2.029)	-1.14	-6.9; 2.6

Scores range from 0-10 with higher scores indicating greater sleep interference.
FAS = full analysis set; Max = maximum; Min = minimum; n = number of subjects per treatment group or in both treatment groups; N = total number of subjects contributing to the mean; RBX = Reboxetine; SD = standard deviation.

Medical Outcome Study Sleep Scale: Summary statistics for the analysis of the MOS-sleep scale is summarized in Table 9.

Table 9. Summary Statistics for the MOS-Sleep Scale (FAS)

Variable	Change From Baseline					
	n	Mean	SD	Median	Min	Max
Awaken short of breath						
[S,S]-RBX/pregabalin (N=67)	63	-1.9	23.477	0	-80.0	80.0
Pregabalin/placebo (N=67)	62	-4.19	19.21	0	-60.0	60.0
All treatments (N=134)	125	-3.04	21.411	0	-80.0	80.0
Optimal sleep						
[S,S]-RBX/pregabalin (N=67)	57	0.04	0.499	0	-1.0	1.0
Pregabalin/placebo (N=67)	59	0.02	0.508	0	-1.0	1.0
All treatments (N=134)	116	0.03	0.501	0	-1.0	1.0
Quantity of sleep						
[S,S]-RBX/pregabalin (N=67)	57	0.09	1.584	0	-5.0	4.0
Pregabalin/placebo (N=67)	59	0.07	1.53	0	-6.0	3.0
All treatments (N=134)	116	0.08	1.55	0	-6.0	4.0
Sleep adequacy						
[S,S]-RBX/pregabalin (N=67)	63	12.22	31.132	10	-60.0	90.0
Pregabalin/placebo (N=67)	62	6.45	28.977	0	-50.0	90.0
All treatments (N=134)	125	9.36	30.1	0	-60.0	90.0
Sleep disturbance						
[S,S]-RBX/pregabalin (N=67)	64	-4.92	24.496	0	-77.5	63.0
Pregabalin/placebo (N=67)	62	-6.52	21.67	-5	-68.8	41.0
All treatments (N=134)	126	-5.71	23.07	0	-77.5	63.0
Snoring						
[S,S]-RBX/pregabalin (N=67)	62	-4.84	23.099	0	-60.0	80.0
Pregabalin/placebo (N=67)	59	-2.03	22.802	0	-80.0	80.0
All treatments (N=134)	121	-3.47	22.902	0	-80.0	80.0
Somnolence						
[S,S]-RBX/pregabalin (N=67)	63	-2.59	19.615	0	-60.0	36.7
Pregabalin/placebo (N=67)	62	-0.27	23.487	0	-53.3	46.7
All treatments (N=134)	125	-1.44	21.567	0	-60.0	46.7
Sleep index I						
[S,S]-RBX/pregabalin (N=67)	63	-6.85	19.977	-3.33	-60.0	33.3
Pregabalin/placebo (N=67)	62	-4.91	17.815	-1.33	-50.0	30.7
All treatments (N=134)	125	-5.89	18.884	-3.33	-60.0	33.3
Sleep index II						
[S,S]-RBX/pregabalin (N=67)	64	-6.2	18.597	-2.22	-58.9	37.2
Pregabalin/placebo (N=67)	62	-5.55	17.72	-2.33	-55.0	21.
All treatments (N=134)	126	-5.88	18.101	-2.22	-58.9	37.2

Scores range from 0-100 with higher scores indicating more impairment in that subscale (with the exception of sleep adequacy, optimal sleep, and quantity of sleep). For those exceptions higher scores indicate less impairment.
Max = maximum; Min = minimum; MOS = Medical Outcome Study; n = total number of subjects contributing to the mean; N = count of subjects in the indicated population; RBX = Reboxetine; SD = standard deviation.

Patient Global Impression of Change: At the end of the study, about 50% of subjects in the [S,S]-RBX + pregabalin and the placebo + pregabalin treatment group rated their overall status as 'much improved' or 'very much improved' (Table 10).

Table 10. Proportional Odds Logistic Regression Analysis for Patient Global Impression of Change (FAS)

Subject Status[a] n (%)	**[S,S]-Reboxetine/Pregabalin[a] (N=67)**	**Pregabalin/Placebo[a] (N=67)**		
Numbers assessed	63	60		
Very much improved	13 (20.6)	8 (13.3)		
Much improved	21 (33.3)	22 (36.7)		
Minimally improved	17 (27.0)	20 (33.3)		
No change	11 (17.5)	8 (13.3)		
Minimally worse	1 (1.6)	1 (1.7)		
Very much worse	0	1 (1.7)		
Improved	51 (81.0)	50 (83.3)		
No change	11 (17.5)	8 (13.3)		
Worsened	1 (1.6)	2 (3.3)		
Odd Ratio Estimate				
Contrast or Comparison	**Odds Ratio Estimate[b, c]**	**90% CI[d]**		
[S,S]-RBX/pregabalin / pregabalin/placebo	0.605	(0.221, 1.655)		
Test for treatment comparisons				
Treatment Comparison	**Df**	**Wald Chi-Square**	**2-sided p-Value**	**1-sided p-Value[e]**
[S,S]-RBX/pregabalin vs. pregabalin/placebo	1	0.676	0.411	0.7945

PGIC analysis was carried out on 3 categories (Improved, No Change, Worsened) at Week 10/EOS.
CI = confidence interval; FAS = full analysis set; n = number of subjects who had a change in PGIC; N = total number of subjects; PGIC = patient global impression of change; RBX = Reboxetine.

a. Number of observations in treatment group used in the model.
b. For [S,S] - RBX/pregabalin divided by placebo/pregabalin.
c. Obtained from PROC LOGISTIC.
d. Obtained from PROC LOGISTIC using WALD test.
e. p-Value based on the 1-sided Wald test using the 5% significance level.

Neuropathic Pain Symptom Inventory: Summary statistics for the analysis of the NPSI is summarized in Table 11.

Table 11. Summary Statistics for the Change From Baseline in the Neuropathic Pain Symptom Inventory (FAS)

Variable	Change From Baseline					
	n[a]	Mean	SD	Median	Min	Max
Burning (superficial)						
[S,S]-RBX/pregabalin (N=67)	64	1.61	3.274	1	9	8
Pregabalin/placebo (N=67)	61	0.82	2.546	1	5	8
All Treatments (N=134)	125	1.22	2.956	1	9	8
Pressure (deep)						
[S,S]-RBX/pregabalin (N=67)	64	0.88	1.812	0.5	6	5
Pregabalin/placebo (N=67)	58	0.59	2.453	0.5	6	7.5
All Treatments (N=134)	122	0.74	2.137	0.5	6	7.5
Paroxysmal						
[S,S]-RBX/pregabalin (N=67)	63	1.13	2.665	0.5	8.5	5.5
Pregabalin/placebo (N=67)	57	1.02	2.234	1	6.5	6
All Treatments (N=134)	120	1.08	2.46	0.5	8.5	6
Evoked						
[S,S]-RBX/pregabalin (N=67)	64	1.09	2.319	1	6.3	4.3
Pregabalin/placebo (N=67)	62	0.87	2.318	0.67	5.7	3.3
All Treatments (N=134)	126	0.98	2.312	1	6.3	4.3
Paresthesia/dysesthesia						
[S,S]-RBX/pregabalin (N=67)	63	0.73	1.992	0.5	5	3
Pregabalin/placebo (N=67)	60	1.02	2.413	0.5	6.5	5
All Treatments (N=134)	123	0.87	2.203	0.5	6.5	5
Total Score						
[S,S]-RBX/pregabalin (N=67)	62	0.55	15.858	8.5	47	14
Pregabalin/placebo (N=67)	55	9.16	18.139	7	55	36
All Treatments (N=134)	117	9.9	16.908	7	55	36

Scores range from 0-10 with higher scores indicating greater severity of pain or abnormal sensations in the past 24 hours. Max = maximum; Min = minimum; n = total number of subjects contributing to the mean; N = count of subjects in the indicated population; RBX = Reboxetine; SD = standard deviation.
a. This was the total number of subjects contributing to the mean.

Hospital Anxiety and Depression Scale: Summary statistics for the analysis of the HADS is summarized in Table 12.

Table 12. Summary Statistics of the Change From Baseline in the HADS (FAS)

Variable	Change From Baseline					
	n[a]	Mean	SD	Median	Min	Max
Anxiety total score						
[S,S]-RBX/pregabalin (N=67)	64	0.36	2.118	0	8	6
Pregabalin/placebo (N=67)	61	0.26	3.055	0	7	13
All treatments (N=134)	125	0.06	2.625	0	8	13
Depression total score						
[S,S]-RBX/pregabalin (N=67)	64	0.34	1.954	0	5	5
Pregabalin/placebo (N=67)	61	0.66	3.016	0	6	14
All treatments (N=134)	125	0.14	2.567	0	6	14

Scores range from 0-21 with high scores indicating severe mood disturbance. FAS = full analysis set; HADS = Hospital Anxiety and Depression Scale; Max = maximum; Min = minimum; n = total number of subjects contributing to the mean; N = count of subjects in the indicated population; RBX = Reboxetine; SD = standard deviation.

a. This was the total number of subjects contributing to the mean.

Safety Results

The treatment emergent AEs (TEAEs) reported most frequently were dizziness followed by dry mouth and somnolence on pregabalin, dry mouth followed by dizziness on [S,S]-RBX + pregabalin, and dizziness followed by fatigue and edema peripheral on placebo + pregabalin (Table 13).

Table 13. Treatment-Emergent Non Serious Adverse Events for Events Having a Frequency Rate ≥5%

System Organ Class and MedDRA Preferred Term	Pregabalin n (%)	[S,S]-RBX/Pregabalin n (%)	Pregabalin/Placebo n (%)
Number (%) of subjects: evaluable for AEs	238	67	67
Number (%) of subjects: with AEs	132 (55.5)	36 (53.7)	28 (41.8)
Ear and labyrinth disorders	14 (5.9)	6 (9.0)	3 (4.5)
Vertigo	14 (5.9)	6 (9.0)	3 (4.5)
Eye disorders	13 (5.5)	1 (1.5)	3 (4.5)
Vision blurred	13 (5.5)	1 (1.5)	3 (4.5)
Gastrointestinal disorders	44 (18.5)	24 (35.8)	8 (11.9)
Constipation	14 (5.9)	8 (11.9)	1 (1.5)
Dry mouth	25 (10.5)	16 (23.9)	5 (7.5)
Nausea	10 (4.2)	4 (6.0)	3 (4.5)
General disorders and administration site conditions	39 (16.4)	10 (14.9)	14 (20.9)
Asthenia	6 (2.5)	4 (6.0)	3 (4.5)
Fatigue	23 (9.7)	6 (9.0)	6 (9.0)
Oedema peripheral	10 (4.2)	0	6 (9.0)
Infections and infestations	5 (2.1)	4 (6.0)	1 (1.5)
Nasopharyngitis	5 (2.1)	4 (6.0)	1 (1.5)
Nervous system disorders	91 (38.2)	16 (23.9)	15 (22.4)
Dizziness	71 (29.8)	14 (20.9)	11 (16.4)
Headache	14 (5.9)	1 (1.5)	1 (1.5)
Somnolence	25 (10.5)	2 (3.0)	4 (6.0)
Psychiatric disorders	5 (2.1)	4 (6.0)	1 (1.5)
Insomnia	5 (2.1)	4 (6.0)	1 (1.5)

Subjects were only counted once per treatment for each row.
Included data up to 30 days after last dose of study drug.
MedDRA (version 10.1) coding dictionary applied.
AEs = Adverse events; MedDRA = Medical Dictionary for Regulatory Activities; n = number of subjects with AEs; RBX = Reboxetine.

The overall number of TEAEs reported during the study and the number of subjects who experienced treatment-related TEAEs are summarized in Table 14.

Table 14. Incidence of Treatment-Emergent Adverse Events (Treatment-Related)

System Organ Class and MedDRA Preferred Term	Pregabalin (N=238) n (%)	[S,S]-RBX/Pregabalin (N=67) n (%)	Pregabalin/Placebo (N=67) n (%)
Ear and labyrinth disorders	15 (6.3)	5 (7.5)	3 (4.5)
Vertigo	14 (5.9)	5 (7.5)	3 (4.5)
Eye disorders	21 (8.8)	4 (6.0)	6 (9.0)
Vision blurred	12 (5.0)	1 (1.5)	3 (4.5)
Gastrointestinal disorders	50 (21.0)	25 (37.3)	9 (13.4)
Constipation	13 (5.5)	8 (11.9)	1 (1.5)
Dry mouth	24 (10.1)	16 (23.9)	5 (7.5)
General disorders and administration site conditions	43 (18.1)	12 (17.9)	13 (19.4)
Asthenia	6 (2.5)	4 (6.0)	3 (4.5)
Fatigue	23 (9.7)	6 (9.0)	6 (9.0)
Oedema peripheral	9 (3.8)	0	5 (7.5)
Nervous system disorders	100 (42.0)	19 (28.4)	16 (23.9)
Dizziness	69 (29.0)	14 (20.9)	11 (16.4)
Headache	12 (5.0)	1 (1.5)	0
Somnolence	25 (10.5)	2 (3.0)	4 (6.0)
Psychiatric disorders	14 (5.9)	8 (11.9)	5 (7.5)
Insomnia	5 (2.1)	4 (6.0)	1 (1.5)
Skin and subcutaneous tissue disorders	8 (3.4)	4 (6.0)	4 (6.0)

Included data up to 30 days after last dose of study drug.
MedDRA (version 10.1) coding dictionary applied.
AEs and SAEs are not separated out in this table.
AE = adverse event; MedDRA = Medical Dictionary for Regulatory Activities; n = number of subjects with AEs; N = total number of subjects; RBX = Reboxetine; SAEs = serious adverse events.

Discontinuation: Thirty-four pregabalin-treated subjects, 2 subjects on [S,S]-RBX + pregabalin and 6 subjects on placebo + pregabalin had a dose reduction or were temporarily discontinued due to TEAEs; all of these AEs were related to study medication. Consistent with AEs leading to permanent discontinuations, AEs leading to temporary discontinuations were most frequently related to nervous system disorders.

Eighteen pregabalin-treated subjects, 10 subjects on [S,S]-RBX + pregabalin and 4 subjects on placebo + pregabalin discontinued due to TEAEs; of these, 14 subjects on pregabalin, 9 subjects on [S,S]-RBX + pregabalin and 3 subjects on placebo + pregabalin were discontinued due to treatment-related AEs.

Serious Adverse Events and Deaths: A total of 7 SAEs were reported in 6 subjects; 4 pregabalin-treated subjects and 2 placebo + pregabalin treated subjects reported SAEs. For 1 subject the SAE started on Day 0, prior to study drug intake, and was thus considered a nonserious baseline TEAE.

Table 15. Serious Adverse Events

Serial Number	Drug	MedDRA Preferred Term	Sponsor/ Investigator Causality	AE Start Day	Drug Stop Day	Action taken	Outcome
1	Pregabalin 300 mg	Sinobronchitis[a]	No/Other	11	NA	No action taken	Recovered
2	Pregabalin 75 mg	Gastroenteritis viral	No/Other illness	0[b]	3	Permanently discontinued[c]	Recovered
3	Pregabalin/placebo 600 mg/0 mg	Syncope	No/Other illness	56	NA	No action taken	Recovered
4	Pregabalin 150 mg	Thrombophlebitis	No/Other illness	7	7	Permanently discontinued	Recovered
5	Pregabalin 600 mg	Cerebrovascular accident	No/Other illness	15	15	Permanently discontinued	Recovering
	Pregabalin 600 mg	Hypertension	No/Other illness	15	15	Permanently discontinued	Recovering
6	Pregabalin/placebo 150 mg/0 mg	Hypertensive crisis	No/Other illness	16	16	Permanently discontinued	Recovered

AE = adverse event; MedDRA = Medical Dictionary for Regulatory Activities; NA = not applicable; SAE = serious adverse event.

a. The SAE was listed as ‘pneumonia’.
b. Baseline SAE.
c. The action taken is given as ‘temporarily discontinued’.

The overall incidence of laboratory abnormalities did not differ notably between groups. No noteworthy differences were observed for the [S,S]-RBX + pregabalin and the placebo + pregabalin groups with regard to changes in BP. For 1 subject on pregabalin and 1 subject on [S,S]-RBX + pregabalin the AE BP decreased was documented. Two subjects on pregabalin, 2 subjects on [S,S]-RBX + pregabalin and 1 subject on placebo + pregabalin had the AE hypertension. For 1 subject on [S,S]-RBX + pregabalin the SAE hypertensive crisis and for 1 subject on pregabalin the AE hypotension were documented. The vast majority of ECG results were normal or abnormal but not clinically significant. Clinically significant abnormal ECG findings were not recorded for any pregabalin- or [S,S]-RBX + pregabalin-treated subject. The vast majority of physical examination findings were considered by the Investigator as being normal at Screening, and no changes were seen from baseline during the study.

CONCLUSIONS:

- This study was terminated prematurely by the Pfizer Data Monitoring Committee for futility following a planned interim analysis, according to predetermined criteria.

- This decision was supported by the final analysis of the study's primary efficacy endpoint (change from Baseline to endpoint in weekly average pain score, which was derived from the subjects' daily interactive voice response diary records of pain), that showed no clinically and statistically significant difference between the two adjunctive treatments [S,S]-RBX + pregabalin and placebo + pregabalin.

- Results for the secondary efficacy endpoints generally confirmed those obtained for the primary endpoint.

- The study demonstrated that the adjunctive therapy [S,S]-RBX + pregabalin was generally well-tolerated in this subject population and no new emergent AE were observed with this therapy.