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GENERIC DRUG NAME and/or COMPOUND NUMBER: Esreboxetine / PNU-165442G

PROTOCOL NO.: A6061046

PROTOCOL TITLE: A Multi-Center, Long-Term, Open-Label Study of [SS]-reboxetine (PNU 165442G) Administered Once Daily in Patients With Fibromyalgia

Study Centers: A total of 75 centers took part in the study and randomized subjects; 2 in Belgium, 4 in Canada, 3 in Czech Republic, 3 in France, 7 in Germany, 2 in Korea, 3 in Netherlands, 4 in South Africa, 4 in Sweden, 5 in United Kingdom and 38 in United States.

Study Initiation and Final Completion Dates: 20 October 2007 to 18 May 2009

The study was terminated early.

Phase of Development: Phase 3

Study Objectives:

Primary Objective**:** To assess the long-term safety and tolerability of esreboxetine once daily (QD) in subjects with fibromyalgia

Secondary Objective**:** To assess the long-term efficacy of esreboxetine (QD) in the management of fibromyalgia

METHODS

Study Design: This was a 68 week, open-label, multicenter study to evaluate the safety, tolerability, and efficacy of esreboxetine in subjects with fibromyalgia. Approximately 500 subjects were planned to participate in the study, which comprised 4 phases: (i) 1-week Baseline Period; (ii) 4-week, open-label Dose-escalation Period to target dose of 4 mg/day; (iii) 64-week, open-label Flexible Treatment Period during which subjects received doses in the range of 4 to 10 mg/day; and (iv) 2-week Follow-up Period. At the end of the Baseline Phase, all eligible subjects received esreboxetine in an open-label manner (Table 1).

Table 1. Dosing Regimen

Dosing Regimen	Study Days						
	1-14	15-28	29-42	43-56	57-70	71-140	141-476
Dosage (mg/day)	2	4	6 or 4	8, 6, or 4	10, 8, 6, or 4	10, 8, 6, or 4	10, 8, 6, or 4
Regimen	QD	QD	QD	QD	QD	QD	QD

QD = once daily.

Dose-Escalation Period: Eligible subjects began with a dose of 2 mg/day for 2 weeks (Days 1 to 14). Subjects with good tolerability at 2 mg/day received an increased dose of 4 mg/day for the subsequent 2-week period (Days 15 to 28). Subjects failing to complete the Dose-escalation Period were withdrawn from the study. There was no provision for dose reduction.

Flexible-Dosing Period: After completing the Dose-escalation Period, subjects started a 64-week, Flexible-dose Treatment Period where they were expected to receive esreboxetine doses of either 4, 6, 8, or 10 mg/day. During this period, doses were adjusted based on efficacy and tolerability. A 1-step dose increase or decrease was allowed at the scheduled visits. Under exceptional circumstances where safety was a concern, a dose may have been adjusted at an unscheduled visit at any time in the Flexible Treatment Period. All subjects were asked to return for a Follow-up Visit 2 weeks after completing their respective Termination Visit (or after they had completed dosing) for the assessment of discontinuation emergent signs and symptoms.

The schedule of activities is presented in Table 2.

Table 2. Schedule of Activities

Study Phase:	**Screening**	**Dose-Escalation**			**Flexible-Dosing Treatment**								**Follow-Up**
Duration (Weeks):	**1**	**4**			**64**								**2**
Clinic Visit Number[a]:	**V1**	**V2**	**V3**	**V4**	**V5**	**V6**	**V7**	**V8**	**V9**	**V10**	**V11**	**V12/T**	**V13/FU**
End of Study Week:	**Screening**	**-1**	**2**	**4**	**6**	**8**	**10**	**20**	**32**	**44**	**56**	**68**	**70**
Day[b]:	**-7**	**0**	**14**	**28**	**42**	**56**	**70**	**140**	**224**	**308**	**392**	**476**	**490**
Observation/Procedure													
Informed consent[c]	X												
Inclusion/exclusion	X----------X												
Medical history	X												
Tender point count	X												
Physical examination	X											X	X
Manual tender point survey	X											X	
Abbreviated neurological examination	X												
12-lead ECG	X					X	X		X			X	
Vital signs (BP: supine/standing), and pulse	X	X	X	X	X	X	X	X	X	X	X	X	X
Fasting lipid panel		X											
Clinical labs: pregnancy test[d]	X			X			X	X	X	X	X	X	X
Clinical labs: hematology, chemistry	X		X		X		X	X	X	X	X	X	X
Clinical labs: urinalysis	X		X		X		X	X	X	X	X	X	X
Clinical Labs: ESR at local lab	X												
Clinical labs: pharmacogenomics		X											
AEs		X	X	X	X	X	X	X	X	X	X	X	X
Concomitant medications	X	X	X	X	X	X	X	X	X	X	X	X	X
Study medication review/dosing/dispensing[e]		X	X	X	X	X	X	X	X	X	X	X	
Patient global impression of change			X	X	X	X	X	X	X	X	X	X	
Pain visual analog scale	X	X	X	X	X	X	X	X	X	X	X	X	
Short form-36 health survey		X			X			X	X			X	
Fibromyalgia impact questionnaire		X			X			X	X			X	
Sheehan disability scale		X			X			X	X			X	
Multidimensional assessment of fatigue		X			X			X	X			X	
Beck's Scale for suicide ideation	X	X	X	X	X	X	X	X	X	X	X	X	X
Mini international neuropsychiatric interview	X												
Health care resource utilization	X												

AEs = adverse events; BP = blood pressure; ECG = electrocardiogram; ESR = erythrocyte sedimentation rate; FU = follow-up; V = visit.

a. Telephone contact was to be made between successive visits.

b. The following visit windows were to apply: V1(±0 day), V2-V7(±3 days), V8-V12(±7 days), V13/FU(±3 days).

c. Informed consent was to be obtained prior to any study-related procedures including washout of prohibited medication.

d. First dose of study medication was to occur the day following visit.

Table 2. Schedule of Activities

e. Serum pregnancy test was to be conducted at V1 only. Urine pregnancy test was to be conducted at other visits.

Number of Subjects (Planned and Analyzed):

Approximately 500 subjects were planned for enrollment into this study. Overall, 893 subjects were screened, 572 subjects were assigned to esreboxetine. Sample size was allowed to change based on actual study discontinuation rates and on regulatory advice.

Diagnosis and Main Criteria for Inclusion: The study included subjects with a diagnosis for fibromyalgia meeting the American College of Rheumatology (ACR) criteria (ie, widespread pain present for at least 3 months, and pain in at least 11 of 18 specific tender point sites) and excluded subjects with other severe pain (e.g. diabetic peripheral neuropathy and post herpetic neurology) that may confound assessment or self-evaluation of the pain associated with fibromyalgia.

Study Treatment: Eligible subjects who successfully completed the Screening Period received open-label esreboxetine tablets at Visit 2. At this visit, subjects began the 4-week, open-label, Dose-escalation Period to a target dose of 4 mg/day. Subjects received doses in the range of 4 to 10 mg/day during a 64-week open-label, Flexible Treatment Period. During the Dose-escalation Period, esreboxetine 2 or 4 mg were administered QD. During the Flexible Treatment Period, esreboxetine 4, 6, 8, or 10 mg were administered QD. All tablets were extended release and were taken orally in the morning.

Efficacy and Safety Endpoints:

Primary Endpoints:

The following parameters were to be assessed in order to determine the safety and tolerability of esreboxetine in patients with fibromyalgia:

- Vital signs (supine/standing blood pressure [BP] and pulse)
- Physical examination
- 12-lead Electrocardiogram (ECG)
- Hematology/Biochemistry
- Adverse events (AEs)

Secondary Endpoints:

Sleep, fatigue, mood disturbance, assessments of pain, health status, and functioning were to be assessed using the following instruments:

- Short-Form 36 Health Survey
- Sheehan Disability Scale
- Multidimensional Assessment of Fatigue

- Fibromyalgia Impact Questionnaire (FIQ)
- Patient Global Impression of Change
- Pain Visual Analog Scale (VAS)

Safety Evaluations:

Safety and tolerability were assessed at designated times. Subject safety and tolerability were assessed through physical examinations, neurological examination, AE, safety laboratory tests, vital signs measurements, and 12-lead ECGs, Beck's Suicidal Ideation Scale and the Mini International Neuropsychiatric Interview. Specific assessments for fibromyalgia included the Tender Point Count, which was performed by the clinician at Visit 1/Screening. This assessment verified a report of pain at a minimum of 11 of 18 specific locations (tender points) when palpated with 4 kg of digital pressure. The Manual Tender Point Survey was also performed by the clinician at Visit 1 and Visit 68/Termination. The subject rated the severity of pain upon palpation at each of the specific 18 tender points defined by the ACR, in addition to 3 control sites, using an 11-point Likert-type scale, which allowed the subject to rate the intensity of pain on a scale from 0 (no pain) to 10 (worst pain subject ever had).

Statistical Methods:

Efficacy data were listed and summarized; no inferential testing was performed. Not all planned endpoints were analyzed. Only the pain VAS and FIQ total scores were summarized by visit, all other endpoints were listed. Changes from Baseline for pain VAS and FIQ were also summarized by visit, where Baseline was defined as data collected at Visit 2.

Investigator terms for AEs were coded using the Medical Dictionary for Regulatory Activities (MedDRA), Version 12.0. All-causality and treatment-related AEs were summarized by body system, incidence, and severity. In addition, summaries of serious adverse events (SAEs) and AEs that led to withdrawal were provided. Clinical laboratory data tabulations include a summary of clinically important changes in laboratory values and a summary of median changes from Baseline. Baseline and median changes from Baseline were presented for ECG parameters and vital signs measurements. Vital signs changes between supine and standing were summarized descriptively.

RESULTS

Subject Disposition and Demography:

A total of 572 subjects were assigned to esreboxetine, and 18 completed treatment. All 572 subjects who received treatment were analyzed for AEs and 559 subjects (97.7%) were analyzed for laboratory data. Table 3 and Table 4 summarize subject disposition. A total of 410 subjects (71.7%) discontinued for reasons related to the study treatment, and 144 subjects (25.2%) discontinued for reasons unrelated to the study treatment.

Table 3. Subject Disposition and Subjects Analyzed

Number of Subjects	Esreboxetine n (%)
Screened:	893
Assigned to treatment	572
Treated	572
Completed	18 (3.1)
Discontinued	554 (96.9)
Analyzed for efficacy	
FAS	572 (100)
Analyzed for safety	
AEs	572 (100)
Laboratory data	559 (97.7)
Safety analysis set	572 (100)

Discontinuations occurring outside the lag period were attributed to the last study treatment received.
AEs = adverse events; FAS = full analysis set; n = number of subjects.

Table 4. Discontinuations from Study

Number of Subjects	Esreboxetine N=572 n (%)
Discontinuations	
Related to study drug	410 (71.7)
AE	186 (32.5)
Insufficient clinical response	28 (4.9)
Study terminated by Sponsor	196 (34.3)
Not related to study drug	144 (25.2)
AE	18 (3.1)
Does not meet entrance criteria	5 (0.9)
Lost to Follow-up	24 (4.2)
Other	26 (4.5)
Protocol violation	15 (2.6)
Subject no longer willing to participate in study	56 (9.8)
Total	554 (96.9)

AE = adverse event; N = number of subjects; n = number of subjects meeting specified criteria.

All 572 subjects were diagnosed with fibromyalgia. The mean duration of fibromyalgia since first subject diagnosis was 6.5 years. The mean duration of treatment was 140.0 days, ranging between 1 and 489 days. A total of 77 subjects were exposed for over 1 year, and 265 subjects (188+77) were exposed to the study treatment for over 6 months (Table 5).

Table 5. Duration of Treatment

Duration Category (Days)	Esreboxetine N=572
≤1	8
2–14	64
15–28	53
29–90	119
91–180	63
181–364	188
≥365	77
Median duration (range)	140.0 (1–489)

Duration was defined as the total number of dosing days from the first to the last day of each study treatment, inclusive.
N = number of subjects.

Subject demography is summarized in Table 6.

Table 6. Demographic Characteristics

	Esreboxetine		
	Male	Female	Total
Number of subjects	52	520	572
Hormonal Status			
Premenarchal[a]		1 (0.2)	1 (0.2)
Premenopausal		231 (44.4)	231 (44.4)
Postmenopausal		288 (55.4)	288 (55.4)
Age (years)			
<18	0	0	0
18-44	20 (38.5)	164 (31.5)	184 (32.2)
45-65	29 (55.8)	296 (56.9)	325 (56.8)
>65	3 (5.8)	60 (11.5)	63 (11.0)
Mean	47.4	50.2	49.9
SD	10.3	11.7	11.6
Range	20-74	18-81	18-81
Race			
White	50 (96.2)	476 (91.5)	526 (92.0)
Black	1 (1.9)	13 (2.5)	14 (2.4)
Asian	0	19 (3.7)	19 (3.3)
Other	1 (1.9)	12 (2.3)	13 (2.3)
Weight (kg)			
Mean	89.1	79.0	79.9
SD	17.5	19.9	19.9
Range	57.7–132.0	42.9–160.6	42.9–160.6
N	52 (100.0)	520 (100.0)	572 (100.0)
Height (cm)			
Mean	177.1	163.6	164.8
SD	9.4	6.8	8.1
Range	162.0–222.0	138.5–186.0	138.5–222.0
N	51 (98.1)	520 (100.0)	571 (99.8)

SD = standard deviation.
a. One subject had their hormonal status erroneously recorded as premenarchal.

Efficacy Results:

Table 7 summarizes the change from Baseline for pain VAS. The efficacy of esreboxetine required several weeks to consolidate, evidenced by a trend toward an overall decrease from Baseline for pain VAS scores over time. At Week 2 mean decrease from Baseline for pain VAS was -10.2, which changed to -27.4 by Week 10. The mean decrease from Baseline for pain VAS was similar at Weeks 20 and 44 (-30.5 and -31.2, respectively), with a maximum drop in pain severity at Week 68 (-47.3). Although only 18 subjects contributed to the Week 68 data, efficacy of esreboxetine in those subjects who remained on study was good (efficacy in early terminators was less robust).

Table 7. Summary Statistics and Change From Baseline for Pain Visual Analogue Scale (FAS)

Visit	Descriptive Statistics	Baseline Score	Visit Score	Change From Baseline
Week 2	Mean (SE)	70.4 (0.8)	60.2 (1.0)	-10.2 (0.9)
(N=495)	SD	17.6	21.59	20.35
	90% CI	[68.85, 71.88]	[58.26, 62.08]	[-11.99, -8.40]
	Min-Max	5–100	1–100	-97–66
Week 10	Mean (SE)	70.4 (0.9)	43.1 (1.4)	-27.4 (1.4)
(N=340)	SD	16.79	25.60	26.44
	90% CI	[68.64, 72.22]	[40.34, 45.80]	[-30.18, -24.54]
	Min-Max	7–100	0–98	-95–58
Week 20	Mean (SE)	70.7 (1.0)	40.2 (1.5)	-30.5 (1.7)
(N=286)	SD	16.88	25.69	27.87
	90% CI	[68.74, 72.67]	[37.21, 43.19]	[-33.74, -27.26]
	Min-Max	7–100	0–98	-91–59
Week 44	Mean (SE)	71.2 (1.4)	40.0 (2.2)	-31.2 (2.3)
(N=143)	SD	16.85	26.64	27.99
	90% CI	[68.42, 73.99]	[35.60, 44.41]	[-35.83, -26.58]
	Min-Max	7-100	0-93	-89-53
Week 68	Mean (SE)	76.2 (3.7)	28.8 (6.4)	-47.3 (7.3)
(N=18)	SD	15.84	27.25	30.82
	90% CI	[68.29, 84.04]	[15.28, 42.38]	[-62.66, -32.01]
	Min-Max	43–100	0–82	-90-27
ET	Mean (SE)	69.3 (0.8)	53.1 (1.2)	-16.2 (1.2)
(N=492)	SD	17.41	27.61	26.32
	90% CI	[67.73, 70.82]	[50.67, 55.56]	[-18.49, -13.83]
	Min-Max	5-100	0–100	-91–55

The score range for the pain visual analogue scale was 0 to 100, with higher scores indicating more pain.
CI = confidence interval; ET = early termination; FAS = full analysis set; N = number of subjects;
SD = standard deviation; SE = standard error.

Table 8 summarizes the change from Baseline for FIQ total score. As with pain VAS, mean changes from Baseline for FIQ total score showed an overall decrease from Baseline over time. At Week 6 mean decrease from Baseline for FIQ total score was -13.09, which increased to 18.47 and 18.27 by Weeks 20 and 32, respectively, with a maximum drop in

mean FIQ total score at Week 68 (-30.72). Although only 18 subjects contributed to the Week 68 data, efficacy of esreboxetine in those subjects who remained on study was good.

Table 8. Summary Statistics and Change From Baseline for Fibromyalgia Impact Questionnaire (FAS)

Visit	Descriptive Statistics	Baseline Score	Visit Score	Change From Baseline
Week 6	Mean (SE)	57.57 (0.73)	44.48 (0.92)	-13.09 (0.86)
(N=401)	SD	14.64	18.46	17.15
	90% CI	[56.13,59.00]	[42.67,46.29]	[-14.77,-11.40]
	Min-Max	5.1–91.0	1.0–95.6	-63.6–46.7
Week 20	Mean (SE)	57.23 (0.85)	38.76 (1.22)	-18.47 (1.14)
(N=288)	SD	14.38	20.68	19.31
	90% CI	[55.56,58.90]	[36.36,41.16]	[-20.71,-16.23]
	Min-Max	14.3–91.0	0.9–85.8	-82.0–48.1
Week 32	Mean (SE)	56.67 (0.94)	38.41 (1.33)	-18.27 (1.33)
(N=286)	SD	14.64	20.69	20.75
	90% CI	[54.82,58.53]	[35.79,41.03]	[-20.89,-15.64]
	Min-Max	14.3–90.1	1.0–85.2	-69.6–51.2
Week 68	Mean (SE)	55.78 (2.44)	25.06 (4.47)	-30.72 (5.01)
(N=18)	SD	10.37	18.96	21.24
	90% CI	[50.62,60.94]	[15.63,34.49]	[-41.29,-20.16]
	Min-Max	40.0–73.7	1.0–64.1	-60.4–8.5
ET	Mean (SE)	56.66 (0.67)	48.97 (0.96)	-7.69 (0.86)
(N=491)	SD	14.94	21.23	19.11
	90% CI	[55.34,57.99]	[47.08,50.85]	[-9.39,-6.00]
	Min-Max	5.1–91.0	0.0–95.3	-69.8–44.6

The score range for the Fibromyalgia Impact Questionnaire total score was 0 to 100, with higher scores indicating more impairment.
CI = confidence interval; ET = early termination; FAS = full analysis set; N = number of subjects; SD = standard deviation; SE = standard error.

There was an overall decrease in FIQ scores, mean decreases from Baseline of -18.27 at Week 32 and -30.72 at Week 68. Similar decreases in FIQ scores from Baseline were noted by dose, with a decrease of -19.50 after administration of 10 mg esreboxetine at Week 32 and -32.86 at Week 68.

Safety Results:

There were no deaths in the study. Twenty-five (25) subjects experienced SAEs. No subjects were discontinued due to abnormal laboratory results. Of the 2733 AEs, 1421 were mild, 1111 were moderate, and 201 were severe.

Adverse Events: Table 9 summarizes treatment-emergent AEs (all causalities and treatment-related).

Table 9. Treatment-Emergent Adverse Events – All Causality and Treatment-Related

Parameter	Number (%) of Subjects
Subjects evaluable for AEs	572
All causality	
Number of AEs	2733
Subjects with AEs	517 (90.4)
Subjects with serious AEs	25 (4.4)
Subjects with severe AEs	106 (18.5)
Subjects discontinued due to AEs	202 (35.3)
Subjects with dose reduced or temporary discontinuation due to AEs	90 (15.7)
Treatment-related	
Number of AEs	1938
Subjects with AEs	465 (81.3)
Subjects with serious AEs	7 (1.2)
Subjects with severe AEs	81 (14.2)
Subjects discontinued due to AEs	182 (31.8)
Subjects with dose reduced or temporary discontinuation due to AEs	76 (13.3)

Except for the number of AEs, subjects were counted only once per treatment in each row.
Serious Adverse Events were according to the Investigator's assessment.
AEs and SAEs are not separated out.
AEs = adverse events; MedDRA = Medical Dictionary for Regulatory Activities; SAE = serious adverse event.

Table 10 summarizes treatment-emergent AEs occurring in at least 2% of subjects. The most frequently reported AEs were dry mouth, constipation, insomnia, headache, nausea, hyperhidrosis, and dizziness. The majority of treatment-emergent AEs were judged to be related to the study treatment.

Table 10. Treatment-Emergent Adverse Events Occurring in ≥2% of Subjects: All-Causality and Treatment-Related

MedDRA Preferred Term	All-Causality N (%)	Treatment-Related N (%)
Cardiac disorders	90 (15.7)	81 (14.2)
Palpitations	32 (5.6)	29 (5.1)
Tachycardia	46 (8.0)	43 (7.5)
Ear and labyrinth disorders	41 (7.2)	35 (6.1)
Vertigo	24 (4.2)	23 (4.0)
Gastrointestinal disorders	331 (57.9)	305 (53.3)
Abdominal pain	14 (2.4)	6 (1.0)
Constipation	139 (24.3)	133 (23.3)
Diarrhoea	17 (3.0)	8 (1.4)
Dry mouth	195 (34.1)	193 (33.7)
Dyspepsia	17 (3.0)	14 (2.4)
Nausea	85 (14.9)	73 (12.8)
Vomiting	15 (2.6)	8 (1.4)
General disorders and administration site conditions	147 (25.7)	124 (21.7)
Asthenia	14 (2.4)	11 (1.9)
Chills	23 (4.0)	23 (4.0)
Fatigue	53 (9.3)	41 (7.2)
Feeling cold	15 (2.6)	15 (2.6)
Irritability	19 (3.3)	17 (3.0)
Oedema peripheral	12 (2.1)	7 (1.2)
Infections and infestations	174 (30.4)	26 (4.5)
Bronchitis	13 (2.3)	1 (0.2)
Influenza	14 (2.4)	1 (0.2)
Nasopharyngitis	40 (7.0)	3 (0.5)
Sinusitis	27 (4.7)	2 (0.3)
Upper respiratory tract infection	33 (5.8)	2 (0.3)
Urinary tract infection	33 (5.8)	11 (1.9)
Investigations	71 (12.4)	54 (9.4)
Heart rate increased	17 (3.0)	15 (2.6)
Metabolism and nutrition disorders	50 (8.7)	45 (7.9)
Anorexia	20 (3.5)	20 (3.5)
Decreased appetite	19 (3.3)	18 (3.1)
Musculoskeletal and connective tissue disorders	142 (24.8)	57 (10.0)
Arthralgia	28 (4.9)	10 (1.7)
Back pain	16 (2.8)	1 (0.2)
Fibromyalgia	13 (2.3)	5 (0.9)
Muscle spasms	38 (6.6)	24 (4.2)
Pain in extremity	15 (2.6)	6 (1.0)
Nervous system disorders	237 (41.4)	203 (35.5)
Dizziness	72 (12.6)	66 (11.5)
Dysgeusia	15 (2.6)	15 (2.6)
Headache	99 (17.3)	84 (14.7)
Hypoaesthesia	15 (2.6)	15 (2.6)
Migraine	18 (3.1)	10 (1.7)
Paraesthesia	23 (4.0)	21 (3.7)
Somnolence	20 (3.5)	17 (3.0)
Tremor	14 (2.4)	13 (2.3)
Psychiatric disorders	251 (43.9)	231 (40.4)
Anxiety	30 (5.2)	20 (3.5)
Depression	27 (4.7)	17 (3.0)

Table 10. Treatment-Emergent Adverse Events Occurring in ≥2% of Subjects: All-Causality and Treatment-Related

MedDRA Preferred Term	All-Causality N (%)	Treatment-Related N (%)
Insomnia	135 (23.6)	125 (21.9)
Nervousness	12 (2.1)	11 (1.9)
Sleep disorder	42 (7.3)	41 (7.2)
Skin and subcutaneous tissue disorders	163 (28.5)	130 (22.7)
Hyperhidrosis	85 (14.9)	80 (14.0)
Rash	16 (2.8)	8 (1.4)
Vascular disorders	102 (17.8)	94 (16.4)
Flushing	15 (2.6)	14 (2.4)
Hot flush	47 (8.2)	40 (7.0)
Hypertension	17 (3.0)	15 (2.6)
Peripheral coldness	31 (5.4)	29 (5.1)

Subjects were counted once per treatment in each row.
This table includes data up to 30 days after last dose of study drug.
MedDRA (version 12.0) coding dictionary applied.
N = number of subjects; MedDRA = Medical Dictionary for Regulatory Activities.

Serious Adverse events:

A total of 30 SAE events terms were recorded in 25 subjects. Table 11 summarizes all-causality SAEs. Of these, 8 events recorded in 7 subjects were considered to treatment-related. Table 12 summarizes treatment-emergent SAEs judged related to the study treatment.

Table 11. Treatment-Emergent Serious Adverse Events: All-Causality

System Organ Class and MedDRA Preferred Term	All-Causality N=572 n (%)
Cardiac disorders	3 (0.5)
Brugada syndrome	1 (0.2)
Myocardial infarction	2 (0.3)
Gastrointestinal disorders	5 (0.9)
Abdominal pain	1 (0.2)
Abdominal pain upper	1 (0.2)
Abdominal strangulated hernia	1 (0.2)
Anal fissure	1 (0.2)
Anal skin tags	1 (0.2)
Haemorrhoids	1 (0.2)
Pancreatitis acute	1 (0.2)
General disorders and administration site conditions	3 (0.5)
Chest pain	3 (0.5)
Immune system disorders	2 (0.3)
Hypersensitivity	2 (0.3)
Infections and infestations	2 (0.3)
Acute sinusitis	1 (0.2)
Post procedural sepsis	1 (0.2)
Injury, poisoning and procedural complications	2 (0.3)
Epicondylitis	1 (0.2)
Road traffic accident	1 (0.2)
Investigations	1 (0.2)
Medical observations	1 (0.2)
Musculoskeletal and connective tissue disorders	1 (0.2)
Intervertebral disc protrusion	1 (0.2)
Neoplasms benign, malignant and unspecified (incl cysts and polyps)	1 (0.2)
Glioblastoma multiforme	1 (0.2)
Nervous system disorders	1 (0.2)
Syncope	1 (0.2)
Psychiatric disorders	1 (0.2)
Depression	1 (0.2)
Renal and urinary disorders	3 (0.5)
Bladder prolapse	1 (0.2)
Nephrolithiasis	1 (0.2)
Urinary incontinence	1 (0.2)
Skin and subcutaneous tissue disorders	1 (0.2)
Hypoaesthesia facial	1 (0.2)
Surgical and medical procedures	2 (0.3)
Cholecystectomy	1 (0.2)
Spinal fusion surgery	1 (0.2)
Vascular disorders	1 (0.2)
Hypertensive crisis	1 (0.2)

Subjects were counted once per treatment in each row.
This table includes data up to 30 days after last dose of study drug.
MedDRA (version 12.0) coding dictionary applied.
N = number of subjects; n = number of subjects meeting specified criteria; MedDRA = Medical Dictionary for Regulatory Activities.

Table 12. Serious Adverse Events Judged Related to the Study Treatment

Age/Sex (Years)	Sex	Esreboxetine Dose	SAE (MedDRA Preferred Term)	SAE Onset Day	Action Taken	Outcome
21	F	4 mg	Syncope	51	PDC	Resolved
51	F	6 mg	Myocardial infarction	59	PDC	Resolved
39	F	6 mg	Brugada syndrome	42	PDC	Ongoing
56	F	8 mg	Urinary incontinence	232	TDC	Resolved
62	F	8 mg	Hypersensitivity	48	PDC	Resolved
75	F	8 mg	Chest pain	304	PT[a]	Resolved
		8 mg	Hypertensive crisis	310	PT[a]	Resolved
51	F	10 mg	Chest pain	201	PDC	Resolved

AE = adverse event; F = female; MedDRA = Medical Dictionary for Regulatory Activities; PDC = permanently discontinued; PT = post therapy; SAE = serious adverse event; TDC = temporarily discontinued.
a. The subject was hospitalized.

Discontinuations: Table 13 summarizes discontinuations due to all-causality AEs. Most AEs leading to discontinuation were judged to be treatment-related. The majority of subjects discontinuing the study due to AEs did so early in the study whilst on lower doses over the course of titration. Most AEs leading to discontinuation were insomnia, constipation, nausea, headache, hyperhidrosis, dizziness, and depression. The discontinuation rates due to these more common AEs was still relatively low and the remainder of discontinuations was made up of 1 or 2 subjects discontinuing due to a broad array of other miscellaneous AE terms.

The frequency of subjects discontinuing early could be related to the study design where there was a long titration period to the effective dose level. The benefit-risk ratio perceived by subjects at the lowest dose level may have caused subjects to lose confidence in the drug to help them with their symptoms. Subjects may have elected to withdraw from the study, citing AEs as the reason for discontinuation instead of lack of efficacy.

Table 13. Adverse Events (All-Causality and Treatment-Related) Leading to Permanent Discontinuation in ≥2 Subjects

Advesre Events by System Organ class and MedDRA Preferred term	Number (%) of Subjects Discontinued N=572	
	All-Causality n (%)	Treatment-Related n (%)
Insomnia	20 (3.5)	20 (3.5)
Constipation	12 (2.1)	10 (1.7)
Nausea	11 (1.9)	11 (1.9)
Headache	13 (2.3)	13 (2.3)
Hyperhidrosis	10 (1.7)	10 (1.7)
Dizziness	10 (1.7)	10 (1.7)
Depression	11 (1.9)	7 (1.2)
Tachycardia	6 (1.0)	6 (1.0)
Sleep disorder	6 (1.0)	6 (1.0)
Palpitations	5 (0.9)	5 (0.9)
Vertigo	5 (0.9)	5 (0.9)
Dry mouth	5 (0.9)	5 (0.9)
Heart rate increased	5 (0.9)	5 (0.9)
Anxiety	5 (0.9)	3 (0.5)
Dyspepsia	3 (0.5)	3 (0.5)
Chest pain	3 (0.5)	1 (0.2)
Irritability	3 (0.5)	3 (0.5)
Fibromyalgia	3 (0.5)	3 (0.5)
Hot flush	3 (0.5)	3 (0.5)
Hypertension	4 (0.7)	4 (0.7)
Ventricular extrasystoles	2 (0.3)	2 (0.3)
Drug intolerance	2 (0.3)	1 (0.2)
Malaise	2 (0.3)	2 (0.3)
Blood pressure increased	2 (0.3)	2 (0.3)
Weight decreased	2 (0.3)	2 (0.3)
Balance disorder	2 (0.3)	2 (0.3)
Migraine	2 (0.3)	1 (0.2)
Paraesthesia	2 (0.3)	2 (0.3)
Syncope	2 (0.3)	2 (0.3)
Derealisation	2 (0.3)	2 (0.3)
Nervousness	2 (0.3)	1 (0.2)
Suicidal ideation	2 (0.3)	1 (0.2)
Urinary retention	2 (0.3)	2 (0.3)
Flushing	2 (0.3)	2 (0.3)
Angina pectoris	1 (0.2)	1 (0.2)
Atrial tachycardia	1 (0.2)	1 (0.2)
Brugada syndrome	1 (0.2)	1 (0.2)
Bundle branch block left	1 (0.2)	1 (0.2)
Myocardial infarction	1 (0.2)	1 (0.2)
Tinnitus	1 (0.2)	1 (0.2)
Eye haemorrhage	1 (0.2)	1 (0.2)
Vision blurred	1 (0.2)	1 (0.2)
Gastrooesophageal reflux disease	1 (0.2)	1 (0.2)
Irritable bowel syndrome	1 (0.2)	1 (0.2)
Pancreatitis	1 (0.2)	0
Vomiting	1 (0.2)	1 (0.2)
Chills	1 (0.2)	1 (0.2)
Fatigue	1 (0.2)	1 (0.2)

Table 13. Adverse Events (All-Causality and Treatment-Related) Leading to Permanent Discontinuation in ≥2 Subjects

Advesre Events by System Organ class and MedDRA Preferred term	Number (%) of Subjects Discontinued N=572	
	All-Causality n (%)	Treatment-Related n (%)
Oedema peripheral	1 (0.2)	1 (0.2)
Hypersensitivity	1 (0.2)	1 (0.2)
Sinusitis	1 (0.2)	1 (0.2)
Road traffic accident	1 (0.2)	0
Alanine aminotransferase increased	1 (0.2)	1 (0.2)
Blood creatine phosphokinase increased	1 (0.2)	1 (0.2)
Weight increased	1 (0.2)	1 (0.2)
Anorexia	1 (0.2)	1 (0.2)
Intervertebral disc protrusion	1 (0.2)	0
Muscle fatigue	1 (0.2)	1 (0.2)
Muscle spasms	1 (0.2)	1 (0.2)
Rotator cuff syndrome	1 (0.2)	0
Glioblastoma multiforme	1 (0.2)	0
Diabetic neuropathy	1 (0.2)	0
Formication	1 (0.2)	1 (0.2)
Hypoaesthesia	1 (0.2)	1 (0.2)
Hypotonia	1 (0.2)	1 (0.2)
Lethargy	1 (0.2)	1 (0.2)
Restless legs syndrome	1 (0.2)	1 (0.2)
Tremor	1 (0.2)	1 (0.2)
Affect lability	1 (0.2)	0
Agitation	1 (0.2)	1 (0.2)
Dysphoria	1 (0.2)	1 (0.2)
Libido decreased	1 (0.2)	1 (0.2)
Mood altered	1 (0.2)	1 (0.2)
Tearfulness	1 (0.2)	1 (0.2)
Dysuria	1 (0.2)	1 (0.2)
Pollakiuria	1 (0.2)	1 (0.2)
Urinary incontinence	1 (0.2)	1 (0.2)
Ejaculation disorder	1 (0.2)	1 (0.2)
Erectile dysfunction	1 (0.2)	1 (0.2)
Dyspnoea	1 (0.2)	1 (0.2)
Dermatitis allergic	1 (0.2)	1 (0.2)
Erythema	1 (0.2)	1 (0.2)
Pruritus	1 (0.2)	1 (0.2)
Urticaria	1 (0.2)	1 (0.2)
Orthostatic hypotension	1 (0.2)	1 (0.2)
Peripheral coldness	1 (0.2)	1 (0.2)

If the same subject in a given treatment had more than one occurrence in the same preferred term event category, only the most severe occurrence was taken.
Subjects were counted only once per treatment in each row. For the TESS algorithm any missing severities were imputed as severe unless the subject experienced another occurrence of the same event in a given treatment for which severity was recorded. In this case, the reported severity was summarized. Missing baseline severities were imputed as mild.
This table includes data up to 30 days after last dose of study drug.
MedDRA (version 12.0) coding dictionary applied.
N = number of subjects evaluable for AEs; n = number of subjects discontinued; MedDRA = Medical Dictionary for Regulatory Activities; TESS = treatment-emergent signs and symptoms.

Laboratory Results: Clinically significant laboratory results were captured as AEs. Out of range laboratory tests with results meeting predefined in 2% to 3% of subjects included: total neutrophils, basophils and eosinophils (absolute), potassium, and creatine kinase. The most frequently reported laboratory abnormalities (% of subjects) included urine bacteria (51%), urine leukocytes (28%), C reactive protein (20%), urine crystals (16%), urine glucose (9%), urine nitrites (9%), urine specific gravity (6%), urine pH (4%), and urine protein (4%).

Vital Signs Results: Most subjects' vital signs results were within normal ranges for this subject population. There were no clear trends observed for supine or standing mean systolic BP and diastolic BP, and mean changes from baseline were minor. In terms of heart rate, there appeared to be a mean increase between Weeks 2 and 44. Mean increases from baseline for supine heart rate ranged between 7.8 bpm at Week 2 and 14.0 bpm at Week 44. For standing heart rate, mean increases from baseline ranged between 10.0 bpm at Week 2 and 14.6 bpm at Week 44, with a mean increase at Follow-up of 8.6 bpm (Table 14).

Table 14. Vital Signs Mean Changes From Baseline

		Change From Baseline					
Vital Signs Parameters (mmHg)	**Baseline Week -1**	**Week 2**	**Week 4**	**Week 6**	**Week 8**	**Week 20**	**Week 44**
Supine SBP	124.7	-0.5	1.0	1.0	0.4	-0.1	-0.0
Standing SBP	125.2	-.34	-3.3	-2.7	-2.7	-3.4	-3.7
Supine DBP	77.0	1.0	2.2	2.6	2.7	2.1	2.6
Standing DBP	80.1	0.1	0.3	1.2	1.2	0.8	1.2
Supine HR	71.4	7.8	10.5	10.4	11.4	12.6	14.0
Standing HR	77.1	10.0	12.7	12.4	13.7	14.2	14.6

Week 68 was not included in this table because only 18 subjects contributed to the means; early termination results are not included due to the wide variation in duration on treatment.
DBP = diastolic blood pressure; HR = heart rate; SBP = systolic blood pressure.

Table 15 summarizes mean postural changes for vital signs (calculated by subtracting the supine value from the standing value). There was no appreciable difference between standing and supine mean systolic BP or diastolic BP; however, the means between Week 2 and Week 44 were slightly less than 0 for systolic BP, and slightly greater than 0 for diastolic BP. In terms of heart rate, mean postural changes ranged between 5.7 bpm at screening and Week -1, respectively, and 8.1 bpm at Week 6. The difference between standing and supine heart rates began to decrease thereafter, with a difference of 6.2 bpm at Week 44. Approximately 20% and 44% of subjects had heart rates exceeding 100 bpm while supine and standing, respectively.

Table 15. Vital Signs Mean Postural Changes

Vital Signs Parameters (mmHg)	Baseline Week -1	Week 2	Week 4	Week 6	Week 8	Week 20	Week 44
Postural SBP change	0.5	-2.6	-3.8	-3.2	-2.5	-2.9	-3.6
Postural DBP change	3.1	2.0	1.3	1.7	1.7	1.7	1.6
Postural HR change	5.7	8.0	8.0	8.1	7.9	7.3	6.2

Week 68 was not included in this table because only 18 subjects contributed to the means; early termination results are not included due to the wide variation in duration on treatment.
DBP = diastolic blood pressure; HR = heart rate; SBP = systolic blood pressure.

Electrocardiogram Results: Table 16 summarizes the incidence of subjects with ECG results meeting criteria of possible clinical concern. Most subjects had maximum time corresponding to the beginning of depolarization to repolarization of the ventricles, corrected for heart rate using Fridericia's formula (QTcF) results <450 msec, and most increases from Baseline were <30 msec. Four (04) females had QTcF results ≥470 msec, and 5 females had increases from Baseline ≥60 msec. Increases from Baseline above 60 msec ranged between 60 and 77 msec. No consistent trends emerged with respect to ECG parameters measured, and no arrhythmogenic potential of concern was identified.

Table 16. Number (%) of Subjects With QTcF Maximum Values and Maximum Increases From Screening Meeting Criteria for Potential Clinical Concern.

Parameter	Criteria	Females N=519 n (%)	Males N=52 n (%)
Maximum values (msec)	<450	500 (96.3)	47 (90.4)
	450-<470	15 (2.9)	5 (9.6)
	≥470	4 (0.8)	0
Parameter	**Criteria**	**Females N=475 n (%)**	**Males N=49 n (%)**
Maximum increase from screening (msec)	Change <30	444 (93.5)	47 (95.9)
	30≤ Change ≤60	26 (5.5)	2 (4.1)
	Change ≥60	5 (1.1)	0

Means of replicates were used in the calculations.
N = number of subjects; n = number of subjects in each category; QTcF = In electrocardiography, the time corresponding to the beginning of depolarization to repolarization of the ventricles, corrected for heart rate using Fridericia's formula.

CONCLUSIONS:

- Esreboxetine flexibly titrated in the dose range of 2 to 10 mg QD appeared to have an acceptable safety profile in this group of male and female subjects with fibromyalgia.
- The most commonly reported AEs were primarily gastrointestinal symptoms (dry mouth, constipation, nausea), insomnia, headache, hyperhidrosis, and dizziness.
- Discontinuations due to AEs were common in this study.

- Overall increases in HR were observed at all active dose levels, and may be of clinical relevance in subjects with pre-existing cardiac decompensation. Overall mean changes in BP were minimal, and unlikely to be clinical importance. No significant overall mean changes in ECG parameters were observed, and there was no indication of pro-arrhythmic potential.

- Overall, pain VAS scores tended to decrease after dosing with QD administration of esreboxetine, flexibly titrated in the dose range 2 to 10 mg. Overall, FIQ scores tended to decrease after dosing with QD administration of esreboxetine at 2, 4, 6, 8 and 10 mg.