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

PROTOCOL NO.: A6061031

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 Chronic Painful Diabetic Peripheral Neuropathy (DPN)

Study Centers: A total of 93 centers took part in the study and enrolled subjects; 24 in the United States (US), 5 each in the United Kingdom (UK), Sweden, Ukraine, the Russian Federation, and Argentina, 4 each in Finland, and Estonia, 6 each in India, Canada, and Poland, 7 in Germany, 9 in South Africa, and 2 in Croatia.

Study Initiation and Final Completion Dates: 13 July 2006 and 10 December 2008

The study was terminated prematurely.

Phase of Development: Phase 2b

Study Objectives:

Primary Objective: To assess the long-term safety and tolerability of esreboxetine in subjects with Diabetic Peripheral Neuropathy (DPN).

Secondary Objectives:

- To assess the effect of long-term treatment with esreboxetine on neuropathic pain and health-related quality of life in subjects with DPN;
- To assess the effect of long-term treatment with esreboxetine on the use of pain-related medications for the management of DPN.

METHODS

Study Design: This was a Phase 2b, long-term, randomized, open-label, safety and tolerability trial comparing esreboxetine with routine-care in subjects with DPN. Following Screening (Visit 1) was a 1 week baseline period. At the end of this baseline period (Visit 2), subjects meeting the randomization criteria were randomized to either esreboxetine or routine-care in a 1:1 ratio. The maximum trial duration was 2 years, during which there was

an optional prescreening visit followed by 14 clinic visits. Thereafter a final Clinic Visit (Visit 15) for follow up, was undertaken, 1 week after Visit 14 (Table 1).

Table 1. Schedule of Activities

Protocol Activity	Pre-Screening Visit[a]	Screening Visit	Open Label Treatment Period (Day 8 – Day 729 Inclusive)													Follow Up
			Randomization Visit												End of Treatment/ Early Termination	
Clinic Visit		**V1**	**V2[b]**	**V3[b]**	**V4[b]**	**V5[b]**	**V6[c]**	**V7[c]**	**V8[c]**	**V9[c]**	**V10[c]**	**V11[c]**	**V12[c]**	**V13[c]**	**V14[c]**	**V15[d]**
Day		**1**	**8**	**15**	**22**	**36**	**64**	**92**	**183**	**274**	**365**	**456**	**547**	**638**	**729**	**736**
Week	**-6 to -12**		**1**	**2**	**3**	**5**	**9**	**13**								
Month									**6**	**9**	**12**	**15**	**18**	**21**	**24**	**24.25**
Informed consent[e]	X	X														
Inclusion/exclusion criteria		X														
Urine pregnancy test		X	X													
Medical history and demography		X														
Registration/randomization			X													
Diabetes treatment checklist review		X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
Vital signs		X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
Full physical examination		X									X				X	X
ECG		X						X	X		X		X		X	
Hematology		X		X	X	X	X	X	X	X	X	X	X	X	X	X
Blood chemistry		X		X	X	X	X	X	X	X	X	X	X	X	X	X
HbA1c	X[a]	X						X	X	X	X	X	X	X	X	
Adverse events		X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
Pain VAS		X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
PGIC				X	X	X	X	X	X	X	X	X	X	X	X	X
NPSI		X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
m-BPI-SF		X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
SF-12			X			X		X	X	X	X	X	X	X	X	X
EQ-5D			X						X						X	
ATSS			X				X		X	X	X	X	X	X	X	
De-identified pharmacogenomic sampling			X													
Pain-related medication utilization		X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
Dispense medication			X	X	X	X	X	X	X	X	X	X	X	X		
Collect medication				X	X	X	X	X	X	X	X	X	X	X	X	

Table 1. Schedule of Activities

Protocol Activity	Pre-Screening Visit[a]	Screening Visit	Open Label Treatment Period (Day 8 – Day 729 Inclusive)												Follow Up
			Randomization Visit											End of Treatment/ Early Termination	
Clinic Visit		**V1**	**V2[b]**	**V3[b]**	**V4[b]**	**V5[b]**	**V6[c]**	**V7[c]**	**V8[c]**	**V9[c]**	**V10[c]**	**V11[c]**	**V12[c]**	**V13[c]**	**V14[c]**	**V15[d]**
Day		**1**	**8**	**15**	**22**	**36**	**64**	**92**	**183**	**274**	**365**	**456**	**547**	**638**	**729**	**736**
Week	**-6 to -12**		**1**	**2**	**3**	**5**	**9**	**13**								
Month									**6**	**9**	**12**	**15**	**18**	**21**	**24**	**24.25**

Unscheduled Visits (eg for dose adjustment) might occur at any time from V3-V14.

ATSS = analgesic treatment satisfaction scale; ECG = electrocardiogram; EQ-5D = euroqol-5 dimensions; HbA1c = hemoglobin A1c; m-BPI-SF = modified brief pain inventory – short form; NPSI = neuropathic pain symptoms inventory; PGIC = patient global impression of change; SF-12 = short form 12; V = visit; VAS = visual analogue scale.

a. In the absence of an existing routine-care HbA1c result taken between 6-12 weeks prior to V1, the subject will need to wait until their next routine sample falls within the required 6-12 week window prior to screening. Alternatively, a study specific prescreening HbA1c sample can be taken 6-12 weeks prior to V1.
b. Time window for visit = ±2 days.
c. Time window for visit = ±7 days.
d. V15 must be 1 week ±2 days after V14.
e. Subjects must provide written informed consent prior to any trial related procedures being conducted, including any necessary washout period for prohibited medications and/or the collection of a study specific HbA1c sample b-etween 6 to 12 weeks prior to V1 (where an existing routine-care HbA1c result falling within this time period is not available).

Number of Subjects (Planned and Analyzed): Eight-hundred subjects were planned for enrollment in the study. A total of 786 subjects were randomized to treatment, and of those, 780 (396 esreboxetine and 384 routine-care) were treated. All treated subjects were included in the full analysis set (FAS), adverse event (AE), and safety analysis sets. Three-hundred and eighty-six esreboxetine subjects and 382 routine-care subjects were included in the laboratory data analysis set.

The subjects entered the study were 40 in Argentina, 50 in Canada, 28 in Croatia, 60 in Estonia, 42 in Finland, 23 in Germany, 76 in India, 65 in Poland, 79 in the Russian Federation, 113 in South Africa, 16 in Sweden, 61 in Ukraine, 10 in the UK, and 122 in the US.

Diagnosis and Main Criteria for Inclusion: Subjects with a score of ≥40 mm on the pain Visual Analogue Scale (VAS) at Screening and diagnosed of type 1 or 2 diabetes mellitus with painful, distal, symmetrical, sensorimotor polyneuropathy were included in the study.

Subjects with significant hepatic impairment and other severe pain were excluded from the study because of a concern that this would impair the self-assessment of the DPN pain.

Study Treatment: Esreboxetine extended-release tablet was administered once a day (QD), preferably in the morning. Subjects self-administered their study treatment orally. The study treatment had to be swallowed whole with water ‘and not chewed prior to swallowing. The first dose of study medication was taken at Visit 2 (Randomization Visit). At the end of this baseline period (Visit 2), subjects meeting the randomization criteria were randomized to either esreboxetine or routine-care in a 1:1 ratio. A centralized interactive voice-response system was used for randomization and allocation of treatment. Subjects randomized to esreboxetine followed the dosing regimen in Table 2.

Table 2. Esreboxetine Dosing Regimen

Period (Day)	1-7	8-14	15-729[a]
Dose (mg)	0 (Baseline period)	1	1-8

a. Dose adjustment after Day 14 depended on if subjects had ongoing pain and acceptable toleration of esreboxetine.

Subjects randomized to esreboxetine were treated with 1 mg QD for the first week after Visit 2. At the end of that week, they returned for another visit (Visit 3), where the dose could have been left at 1 mg or, if required for symptomatic reasons, could have been increased to 2 mg. Thereafter, if required, stepwise dose increases were possible using 1 mg increments up to a maximum total daily dose of 8 mg.

Safety and Efficacy Endpoints:

Primary Safety Endpoints:

- Vital signs;
- Physical examination;

- 12-lead electrocardiogram (ECG);
- Hematology/biochemistry;
- Adverse events (AEs).

Secondary Efficacy Endpoints:

- Quality of life assessment;
- Pain Visual Analogue Scale (VAS);
- Patient Global Impression of Change (PGIC);
- Neuropathic Pain Symptom Inventory (NPSI);
- Modified Brief Pain Inventory-Short Form ((m-BPI-SF);
- SF-12 (short form 12) Health Survey;
- Euroqol - 5 dimensions (EQ-5D);
- Analgesic Treatment Satisfaction Scale (ATSS);
- Pain-Related Medication Utilization (PRMU).

Safety Evaluations:

- AE assessments and vital sign measurements (ie, sitting blood pressure (BP) and pulse rate) at all visits;
- Physical examination (including a full neurological examination) conducted at Visits 1, 10, 14, and 15;
- 12-lead ECG recorded after the subject had been resting for 10 minutes at Visits 1, 7, 8, 10, 12, and 14;
- Columbia-Suicide Severity Rating Scale, introduced part way through the study as a protocol amendment; however, given the early termination of the study, no data were collected or stored in the database.
- Clinical laboratory assessments:
    - Hematology samples taken at Visits 1, 3, and all following visits. At Visit 1 (Screening) only, Hepatitis A, B and C were tested;
    - Biochemistry samples taken at Visits 1, 3, and all following visits;

- Hemoglobin A1c (HbA_{1c}) measured at Visits 1, 7, and all following visits, except Visit 15. A study specific prescreening HbA_{1c} sample was taken at least 6 (and not more than 12) weeks prior to Visit 1;

- Urine pregnancy test for women of child bearing potential at Visits 1 and 2.

Statistical Methods: All efficacy endpoints were analyzed using the FAS, including all randomized subjects who received at least 1 dose of study medication, or, if randomized to routine-care, subjects who received routine medication for DPN during the study.

The safety analysis population included randomized subjects who received study medication, or if randomized to routine-care, subjects who received routine medication for DPN during the study.

Efficacy Analyses:

No formal statistical comparison was made between esreboxetine and routine-care. Change from Baseline was calculated and summarized by treatment group and visit for the following items: VAS score, NPSI total score, the 5 dimensions of the NPSI, each question of the m-BPI-SF, and each question of the SF-12 Health Survey. For each, Baseline was defined as data collected at the randomization visit (Visit 2). The change from Baseline in VAS score was also summarized by individual, multiple daily visit assessments according to a subject's final dose of esreboxetine.

The following endpoints were summarized by treatment group and visit: PGIC, each question of the ATSS, and the EQ-5D dimensions.

Use of pain-related medications for the management of DPN was summarized by treatment group for the prior medication 30-day period to characterize prior therapy and for each 3-month treatment period.

In addition, all efficacy endpoints (other than pain-related medication utilization) were summarized as above for subjects with HbA1c at screening of <8% and 8-11%, and for subjects whose HbA1c had changed over the course of the study by <1% and by 1% or greater.

Safety:

Investigator-assigned verbatim AE terms were converted to preferred terms using the Medical Dictionary for Regulatory Activities (version 11.1) for summary analyses. All causality and treatment-related AEs were summarized by body system, incidence and severity, and treatment group. In addition, summaries of serious adverse events (SAEs) and AEs that led to withdrawal were provided.

Clinical laboratory data were summarized to identify clinically important changes and potential median changes from Baseline.

A full listing of physical examination results were presented by treatment group and visit for all subjects in the safety analysis set. Any clinically significant changes from Screening were tabulated by treatment group and visit. Screening was defined as the first visit when data was collected.

All vital signs data (systolic and diastolic BP and heart rate) were listed and summarized by treatment group for all subjects in the safety analysis set. Each parameter was summarized by treatment group and visit, and changes from Baseline by visit were also presented. Baseline was defined as the second visit when data from randomized subjects was collected.

ECG parameters (QT interval, heart rate, QT interval using the Fridericia correction (QTcF), PR interval and QRS interval) at Baseline and changes from Baseline were summarized (number of subjects [n], arithmetic mean, standard deviation (SD), minimum and maximum) by treatment. Clinically significant changes from Baseline were listed. The number (%) of subjects with maximum postdose QTcF values and maximum increases from Baseline were tabulated by treatment and by visit.

RESULTS

Subject Disposition and Demography: A total of 786 subjects were randomized to treatment; of those, 780 (396 esreboxetine and 384 routine-care) were treated with study drug. Six non randomized subjects were discontinued prior to randomization as they were no longer willing to participate in the study. A summary of the disposition of subjects and datasets analyzed is provided in Table 3.

Table 3. Subject Disposition and Datasets Analyzed

Number (%) of Subjects	Esreboxetine	Routine-Care
Assigned study treatment: 786		
Treated[a]	396	384
Completed	0	6 (1.6)
Discontinued	396 (100.0)	378 (98.4)
Subject died	1 (0.3)	1 (0.3)
Related to study drug	314 (79.3)	323 (84.1)
Adverse event	45 (11.4)	8 (2.1)
Insufficient clinical response	7 (1.8)	2 (0.5)
Study terminated by sponsor	262 (66.2)	313 (81.5)
Not related to study drug	81 (20.5)	54 (14.1)
Adverse event	9 (2.3)	10 (2.6)
Does not meet entrance criteria	1 (0.3)	1 (0.3)
Lost to follow-up	9 (2.3)	7 (1.8)
Other	9 (2.3)	3 (0.8)
Protocol violation	9 (2.3)	10 (2.6)
Subject no longer willing to participate in study	43 (10.9)	23 (6.0)
Withdrawn due to pregnancy	1 (0.3)	0
Analyzed for efficacy		
Full analysis set	396 (100.0)	384 (100.0)
Analyzed for safety		
Adverse events	396 (100.0)	384 (100.0)
Laboratory data	386 (97.5)	382 (99.5)
Safety	396 (100.0)	384 (100.0)

a. Six subjects were not randomized and were discontinued prior to randomization as they were no longer willing to participate in the study.

More subjects were female (439 [56.3%], 227 esreboxetine and 212 routine-care) and were White (586 [75.1%], 293 esreboxetine and 293 routine-care). All subjects had a primary diagnosis of diabetic neuropathy; esreboxetine subjects had a mean duration of 4.7 years (range: 0-21.0 years), and routine-care subjects had a mean duration of 4.6 years (range: 0-35.6 years) since first diagnosis. Subject demographics are summarized in Table 4.

Table 4. Demographic Characteristics

Number (%) of Subjects	Esreboxetine			Routine-Care		
	Male 169	Female 227	Total 396	Male 172	Female 212	Total 384
Age (years)						
<18	0	0	0	0	0	0
18-44	18 (10.7)	18 (7.9)	36 (9.1)	20 (11.6)	24 (11.3)	44 (11.5)
45-64	109 (64.5)	126 (55.5)	235 (59.3)	114 (66.3)	117 (55.2)	231 (60.2)
≥65	42 (24.9)	83 (36.6)	125 (31.6)	38 (22.1)	71 (33.5)	109 (28.4)
Mean	57.6	59.7	58.8	56.8	58.1	57.5
SD	10.6	10.4	10.5	10	11.2	10.7
Range	19-88	20-84	19-88	25-80	22-82	22-82
Race						
White	126 (74.6)	167 (73.6)	293 (74.0)	128 (74.4)	165 (77.8)	293 (76.3)
Black	5 (3.0)	17 (7.5)	22 (5.6)	5 (2.9)	13 (6.1)	18 (4.7)
Asian	31 (18.3)	38 (16.7)	69 (17.4)	38 (22.1)	31 (14.6)	69 (18.0)
Other	7 (4.1)	5 (2.2)	12 (3.0)	1 (0.6)	3 (1.4)	4 (1.0)
Weight (kg)						
Mean	94.3	82.1	87.3	93.5	82.4	87.4
SD	22.9	18	21	21.2	18.6	20.6
Range	49.0-164.0	38.5-134.8	38.5-164.0	55.0-184.8	42.0-158.1	42.0-184.8
N	169 (100.0)	227 (100.0)	396 (100.0)	172 (100.0)	212 (100.0)	384 (100.0)
Height (cm)						
Mean	175.2	161.1	167.1	174.8	160.3	166.8
SD	8.2	7.2	10.3	7.8	7.3	10.4
Range	147.0-193.0	132.0-182.0	132.0-193.0	154.0-191.0	135.0-183.0	135.0-191.0
N	168 (99.4)	226 (99.6)	394 (99.5)	172 (100.0)	212 (100.0)	384 (100.0)

N = number of subjects; SD = standard deviation.

Efficacy Results:

Pain Visual Analogue Scale: The mean SD change in pain VAS score was -32.3 (29.45) and -29.9 (24.78) for esreboxetine and routine-care subjects, respectively. Summary statistics for the change from Baseline in the pain VAS for the FAS are provided in Table 5.

Table 5. Summary Statistics for the Change From Baseline in the Pain Visual Analogue Scale (FAS)

		VAS Score (mm)					
Visit	**Statistics**	**Esreboxetine**			**Routine-Care**		
		Baseline Score	**Visit Score**	**Change From Baseline**	**Baseline Score**	**Visit Score**	**Change From Baseline**
Screening	N	396	396	-	382	384	-
	Mean	68.1	66.8	-	68.5	68.1	-
Day 8	N	396	396	-	382	382	-
	Mean	68.1	68.1	-	68.5	68.5	-
Day 15	N	374	374	374	377	377	377
	Mean	68.2	59.4	-8.8	68.5	60.3	-8.2
Day 22	N	369	369	369	371	371	371
	Mean	68.2	54.2	-13.9	68.3	56.1	-12.2
Day 36	N	351	351	351	365	365	365
	Mean	68.5	47.1	-21.5	68.3	51.9	-16.4
Day 64	N	332	332	332	363	363	363
	Mean	68.9	41	-28	68.2	48.2	-20
Day 92	N	322	322	322	360	360	360
	Mean	69.1	37.6	-31.5	68.4	45.6	-22.8
Day 183	N	297	297	297	342	342	342
	Mean	69	34.8	-34.2	68.2	43.1	-25
Day 274	N	242	242	242	289	289	289
	Mean	70.1	33.7	-36.4	68.2	42.9	-25.4
Day 365	N	141	141	141	183	183	183
	Mean	70.3	32.7	-37.7	68.9	43.7	-25.2
Day 456	N	88	88	88	114	114	114
	Mean	70.3	27.3	-43	69.1	42.5	-26.6
Day 547	N	34	34	34	47	47	47
	Mean	66.4	30	-36.4	68.7	45.2	-23.6
Day 638	N	6	6	6	15	15	15
	Mean	60.7	30	-30.7	70.1	39	-31.1
EoT/ET	N	350	350	350	352	352	352
	Mean	67.9	35.5	-32.3	68.3	38.5	-29.9
Follow˙up	N	294	294	294	314	314	314
	Mean	67.8	34.4	-33.3	68	37	-31

Baseline was Day 8.
EoT/ET visits were combined.
Where a subject has both of these visits only the later visit is included in the summary.
The score range for Pain VAS is 0 to 100, higher scores indicate more pain.
EoT = End of Treatment; ET = Early Termination; FAS = full analysis set; N = number of subjects at each Visit; VAS = visual analogue scale.

The Neuropathic Pain Symptom Inventory: All evaluable esreboxetine and routine-care subjects demonstrated a decrease in all dimensions of the NPSI (ie, burning [superficial] spontaneous pain, pressing [deep] spontaneous pain, paroxysmal pain, evoked pain, paresthesia/dysethesia) at the end-of-treatment visit. A Summary statistics for this change from Baseline in the total NPSI score for the FAS are provided in Table 6.

Table 6. Summary Statistics for the Change From Baseline in the NPSI (FAS)

Visit	Statistics	Esreboxetine			Routine-Care		
		Baseline Score	Visit Score	Change From Baseline	Baseline Score	Visit Score	Change From Baseline
Dimension 1: Burning (Superficial) Spontaneous Pain							
Screening	N	-	-	-	1	1	0
	Mean	-	-	-	10	9	-
Day 8	N	237	237	0	266	266	0
	Mean	5.9	5.9	-	6.1	6.1	-
Day 15	N	206	206	206	241	241	241
	Mean	6	4.7	-1.2	6.2	5.1	-1
Day 22	N	207	207	207	234	234	234
	Mean	5.9	4.3	-1.6	6.2	4.9	-1.4
Day 36	N	193	193	193	230	230	230
	Mean	5.8	3.7	-2.1	6.2	4.3	-1.9
Day 64	N	185	185	185	232	232	232
	Mean	5.9	3.2	-2.7	6.2	4.2	-2
Day 92	N	174	174	174	225	225	225
	Mean	5.9	2.9	-3	6.1	3.8	-2.3
Day 183	N	165	165	165	208	208	208
	Mean	5.8	2.7	-3.1	6.1	3.9	-2.2
Day 274	N	132	132	132	175	175	175
	Mean	6	2.9	-3	6.1	3.7	-2.4
Day 365	N	84	84	84	117	117	117
	Mean	6	2.6	-3.4	6.3	4.2	-2.1
Day 456	N	50	50	50	71	71	71
	Mean	5.9	2.1	-3.8	6.5	3.9	-2.6
Day 547	N	18	18	18	30	30	30
	Mean	5.9	3.2	-2.7	6.2	4	-2.3
Day 638	N	4	4	4	12	12	12
	Mean	8	4.3	-3.8	5.8	3	-2.8
EoT/ET	N	178	178	178	196	196	196
	Mean	5.8	2.8	-3.1	6.1	3.5	-2.6
Follow-up	N	139	139	139	169	169	169
	Mean	5.9	2.5	-3.4	6.1	3.4	-2.7
Dimension 2: Pressing (Deep) Spontaneous Pain							
Screening	N	-	-	-	1	1	0
	Mean	-	-	-	0	7.5	-
Day 8	N	234	234	0	265	265	0
	Mean	4.8	4.8	-	5.1	5.1	-
Day 15	N	206	206	206	241	241	241
	Mean	4.9	4.1	-0.8	5.2	4.4	-0.8
Day 22	N	207	207	207	234	234	234
	Mean	4.9	3.8	-1.1	5.3	4.2	-1.1
Day 36	N	193	193	193	230	230	230
	Mean	4.9	3.3	-1.6	5.3	3.8	-1.5
Day 64	N	185	185	185	232	232	232
	Mean	4.9	3	-1.9	5.2	3.7	-1.6
Day 92	N	174	174	174	225	225	225
	Mean	4.9	2.6	-2.3	5.2	3.4	-1.8
Day 183	N	165	165	165	208	208	208
	Mean	4.9	2.5	-2.4	5.2	3.4	-1.8
Day 274	N	132	132	132	175	175	175
	Mean	5	2.3	-2.7	5.3	3.2	-2.1
Day 365	N	84	84	84	117	117	117
	Mean	4.9	2.5	-2.3	5.4	3.4	-1.9
Day 456	N	50	50	50	71	71	71
	Mean	5.1	2.1	-3	5.3	3.3	-2
Day 547	N	18	18	18	30	30	30
	Mean	4.9	2.7	-2.2	5.6	4	-1.7

Table 6. Summary Statistics for the Change From Baseline in the NPSI (FAS)

Visit	Statistics	Esreboxetine			Routine-Care		
		Baseline Score	Visit Score	Change From Baseline	Baseline Score	Visit Score	Change From Baseline
Day 638	N	4	4	4	12	12	12
	Mean	6.8	4.5	-2.3	5.5	3.1	-2.4
EoT/ET	N	178	178	178	196	196	196
	Mean	4.7	2.4	-2.3	5.2	3	-2.2
Follow-up	N	139	139	139	169	169	169
	Mean	4.8	2.4	-2.5	5.2	2.9	-2.3
Dimension 3: Paroxysmal Pain							
Screening	N	-	-	-	0	1	0
	Mean	-	-	-	-	8	-
Day 8	N	232	232	0	261	261	0
	Mean	4.9	4.9	-	5.1	5.1	-
Day 15	N	206	206	206	241	241	241
	Mean	4.9	3.9	-1	5.1	4.3	-0.8
Day 22	N	207	207	207	234	234	234
	Mean	5	3.8	-1.2	5.1	4.1	-1
Day 36	N	193	193	193	230	230	230
	Mean	5	3.3	-1.7	5.1	3.7	-1.4
Day 64	N	185	185	185	232	232	232
	Mean	5.1	3	-2.1	5	3.5	-1.6
Day 92	N	174	174	174	225	225	225
	Mean	5	2.5	-2.6	5.1	3.5	-1.5
Day 183	N	165	165	165	208	208	208
	Mean	5	2.4	-2.7	5	3.4	-1.6
Day 274	N	132	132	132	175	175	175
	Mean	5.1	2.5	-2.7	5	3.2	-1.8
Day 365	N	84	84	84	117	117	117
	Mean	5.2	2.3	-2.9	5.3	3.3	-2
Day 456	N	50	50	50	71	71	71
	Mean	5.1	2	-3.1	5.4	3.5	-2
Day 547	N	18	18	18	30	30	30
	Mean	5.4	2.9	-2.6	5.8	3.2	-2.6
Day 638	N	4	4	4	12	12	12
	Mean	7.4	4.5	-2.9	6	3	-3
EoT/ET	N	178	178	178	196	196	196
	Mean	4.8	2.4	-2.5	5	3	-2
Follow-up	N	139	139	139	169	169	169
	Mean	5.1	2.4	-2.6	4.9	2.9	-2
Dimension 4: Evoked Pain							
Screening	N	-	-	-	1	1	0
	Mean	-	-	-	4.3	5.7	-
Day 8	N	233	233	0	263	263	0
	Mean	4.3	4.3	-	4.7	4.7	-
Day 15	N	206	206	206	241	241	241
	Mean	4.5	3.7	-0.8	4.7	4.1	-0.6
Day 22	N	207	207	207	234	234	234
	Mean	4.4	3.5	-0.9	4.8	4.1	-0.7
Day 36	N	193	193	193	230	230	230
	Mean	4.4	3	-1.4	4.7	3.6	-1.2
Day 64	N	185	185	185	232	232	232
	Mean	4.5	2.6	-1.8	4.7	3.5	-1.2
Day 92	N	174	174	174	225	225	225
	Mean	4.5	2.5	-2.1	4.7	3.3	-1.4
Day 183	N	165	165	165	208	208	208
	Mean	4.5	2.2	-2.4	4.6	3.1	-1.5
Day 274	N	132	132	132	175	175	175
	Mean	4.5	2.3	-2.2	4.6	2.9	-1.7

Table 6. Summary Statistics for the Change From Baseline in the NPSI (FAS)

Visit	Statistics	Esreboxetine			Routine-Care		
		Baseline Score	Visit Score	Change From Baseline	Baseline Score	Visit Score	Change From Baseline
Day 365	N	84	84	84	117	117	117
	Mean	4.5	2.3	-2.1	5	3.3	-1.7
Day 456	N	50	50	50	71	71	71
	Mean	4.8	2.3	-2.5	5.1	3.4	-1.7
Day 547	N	18	18	18	30	30	30
	Mean	4.7	2.5	-2.2	5.4	3.5	-1.9
Day 638	N	4	4	4	12	12	12
	Mean	6.3	4.3	-2.1	5.4	3.1	-2.3
EoT/ET	N	178	178	178	196	196	196
	Mean	4.4	2.3	-2	4.6	2.7	-1.9
Follow-up	N	139	139	139	169	169	169
	Mean	4.4	2.3	-2.1	4.7	2.8	-1.9
Dimension 5: Paresthia/Dysethesia							
Screening	N	-	-	-	1	1	0
	Mean	-	-	-	5	6	-
Day 8	N	235	235	0	265	265	0
	Mean	6	6	-	6	6	-
Day 15	N	206	206	206	241	241	241
	Mean	6	4.9	-1.1	6.1	5.1	-1
Day 22	N	207	207	207	234	234	234
	Mean	6.1	4.5	-1.6	6.1	4.9	-1.2
Day 36	N	193	193	193	230	230	230
	Mean	6.1	3.9	-2.2	6.1	4.4	-1.7
Day 64	N	185	185	185	232	232	232
	Mean	6.1	3.5	-2.7	6.1	4.4	-1.7
Day 92	N	174	174	174	225	225	225
	Mean	6.1	3.2	-2.9	6.1	4.1	-2
Day 183	N	165	165	165	208	208	208
	Mean	6.2	3.1	-3.1	6.1	4	-2.1
Day 274	N	132	132	132	175	175	175
	Mean	6.2	3.1	-3.1	6.1	3.8	-2.2
Day 365	N	84	84	84	117	117	117
	Mean	6.4	3.1	-3.3	6.2	4.3	-1.9
Day 456	N	50	50	50	71	71	71
	Mean	6.5	2.7	-3.9	6.4	4.1	-2.3
Day 547	N	18	18	18	30	30	30
	Mean	6.9	3.2	-3.7	6.5	4.3	-2.2
Day 638	N	4	4	4	12	12	12
	Mean	8	5.3	-2.8	6.5	3.5	-3
EoT/ET	N	178	178	178	196	196	196
	Mean	6	3.1	-2.9	6.1	3.7	-2.4
Follow-up	N	139	139	139	169	169	169
	Mean	6.3	3.1	-3.1	6.1	3.4	-2.7
Total Score							
Screening	N	-	-	-	0	1	0
	Mean	-	-	-	-	69	-
Day 8	N	227	227	0	257	257	0
	Mean	50.2	50.2	-	52.7	52.7	-
Day 15	N	206	206	206	241	241	241
	Mean	50.9	41.6	-9.4	53	45.1	-7.8
Day 22	N	207	207	207	234	234	234
	Mean	51	38.8	-12.1	53.4	43.5	-9.9
Day 36	N	193	193	193	230	230	230
	Mean	50.9	33.7	-17.2	53.4	38.9	-14.5
Day 64	N	185	185	185	232	232	232
	Mean	51.5	30.1	-21.4	53	37.7	-15.3

Table 6. Summary Statistics for the Change From Baseline in the NPSI (FAS)

Visit	Statistics	Esreboxetine			Routine-Care		
		Baseline Score	Visit Score	Change From Baseline	Baseline Score	Visit Score	Change From Baseline
Day 92	N	174	174	174	225	225	225
	Mean	51.5	26.8	-24.7	53	36	-17
Day 183	N	165	165	165	208	208	208
	Mean	51.6	25.1	-26.6	52.5	34.8	-17.7
Day 274	N	132	132	132	175	175	175
	Mean	52.2	25.5	-26.7	52.7	33	-19.7
Day 365	N	84	84	84	117	117	117
	Mean	52.5	25.5	-27	55.1	36.1	-18.9
Day 456	N	50	50	50	71	71	71
	Mean	53.8	22.4	-31.4	55.9	36	-19.9
Day 547	N	18	18	18	30	30	30
	Mean	54.4	28.3	-26.1	58.2	37.3	-20.9
Day 638	N	4	4	4	12	12	12
	Mean	71.3	45.5	-25.8	58	31.5	-26.5
EoT/ET	N	178	178	178	196	196	196
	Mean	50	25.6	-24.4	52.5	31	-21.4
Follow-up	N	139	139	139	169	169	169
	Mean	51.6	25.2	-26.4	52.7	30.3	-22.3

Baseline was Day 8.
The 5 dimensions are scored from 0 to 10 and the total is scored from 0 to 100, with a higher score giving a worse indication.
EoT = End of Treatment; ET = Early Termination; FAS = full analysis set; N = number of subjects at each Visit; NPSI = neuropathic pain symptom inventory.

Patient Global Impression of Change: At the end-of-treatment visit, a slightly higher number of esreboxetine subjects (188, 54.0%) had a PGIC score of very much/much improved than any other category (160, 46.0%), while a comparable number of subjects in the routine-care group had a PGIC score of very much/much improved (176, 50.3%) or any other category (174, 49.7%). Summary statistics for the PGIC for the FAS are provided in Table 7.

Table 7. Summary Statistics for Patient Global Impression of Change (FAS)

	Visit							
	Day 15	**Day 22**	**Day 36**	**Day 64**	**Day 92**	**Day 183**	**End of Treatment**	**Follow-Up[a]**
[S,S]- Reboxetine (N=792)								
Numbers assessed	369	367	347	330	319	293	348	293
Very much improved	9 (2.4)	14 (3.8)	29 (8.4)	40 (12.1)	54 (16.9)	58 (19.8)	64 (18.4)	47 (16.0)
Much improved	50 (13.6)	78 (21.3)	92 (26.5)	117 (35.5)	120 (37.6)	109 (37.2)	124 (35.6)	99 (33.8)
Minimally improved	140 (37.9)	177 (48.2)	162 (46.7)	123 (37.3)	108 (33.9)	83 (28.3)	86 (24.7)	80 (27.3)
No change	134 (36.3)	76 (20.7)	50 (14.4)	36 (10.9)	22 (6.9)	25 (8.5)	40 (11.5)	44 (15.0)
Minimally worse	29 (7.9)	15 (4.1)	9 (2.6)	9 (2.7)	13 (4.1)	13 (4.4)	17 (4.9)	12 (4.1)
Much worse	5 (1.4)	7 (1.9)	5 (1.4)	5 (1.5)	2 (0.6)	5 (1.7)	12 (3.4)	10 (3.4)
Very much worse	2 (0.5)	0	0	0	0	0	5 (1.4)	1 (0.3)
Very much/much improved	59 (16.0)	92 (25.1)	121 (34.9)	157 (47.6)	174 (54.5)	167 (57.0)	188 (54.0)	146 (49.8)
Any other category	310 (84.0)	275 (74.9)	226 (65.1)	173 (52.4)	145 (45.5)	126 (43.0)	160 (46.0)	147 (50.2)
Routine-Care (N=768)								
Numbers assessed	373	368	362	360	358	341	350	311
Very much improved	7 (1.9)	15 (4.1)	20 (5.5)	28 (7.8)	25 (7.0)	41 (12.0)	51 (14.6)	40 (12.9)
Much improved	41 (11.0)	66 (17.9)	100 (27.6)	101 (28.1)	133 (37.2)	119 (34.9)	125 (35.7)	116 (37.3)
Minimally improved	150 (40.2)	160 (43.5)	145 (40.1)	134 (37.2)	124 (34.6)	108 (31.7)	96 (27.4)	90 (28.9)
No change	154 (41.3)	105 (28.5)	80 (22.1)	70 (19.4)	57 (15.9)	47 (13.8)	52 (14.9)	48 (15.4)
Minimally worse	17 (4.6)	17 (4.6)	14 (3.9)	19 (5.3)	9 (2.5)	12 (3.5)	19 (5.4)	12 (3.9)
Much worse	4 (1.1)	5 (1.4)	2 (0.6)	5 (1.4)	9 (2.5)	13 (3.8)	6 (1.7)	5 (1.6)
Very much worse	0	0	1 (0.3)	3 (0.8)	1 (0.3)	1 (0.3)	1 (0.3)	0
Very much/much improved	48 (12.9)	81 (22.0)	120 (33.1)	129 (35.8)	158 (44.1)	160 (46.9)	176 (50.3)	156 (50.2)
Any other category	325 (87.1)	287 (78.0)	242 (66.9)	231 (64.2)	200 (55.9)	181 (53.1)	174 (49.7)	155 (49.8)

FAS = full analysis set; N = number of subjects in treatment group.
a. N=792 at follow up visit of routine-care treatment group.

The Modified Brief Pain Inventory-Short Form: At the end-of-treatment visit, the scores for all evaluable esreboxetine and routine-care subjects decreased with all m-BPI-SF questions. Summary statistics for the m-BPI-SF for the FAS are provided in Table 8.

Table 8. Summary Statistics for the Change From Baseline in the Modified Brief Pain Inventory – Short Form Diabetic Peripheral Neuropathy (FAS)

Visit	Statistics	Esreboxetine			Routine-Care		
		Baseline Score	Visit Score	Change From Baseline	Baseline Score	Visit Score	Change From Baseline
Q2: How Much Pain Are You Having Right Now?							
Screening	N	265	265	0	262	264	0
	Mean	6	5.4	-	6	5.7	-
Day 8	N	265	265	0	262	262	0
	Mean	6	6	-	6	6	-
Day 15	N	235	235	235	243	243	243
	Mean	6.1	5.1	-0.9	6	5.3	-0.7
Day 22	N	222	222	222	236	236	236
	Mean	6.1	4.8	-1.3	6.1	4.9	-1.2
Day 36	N	214	214	214	225	225	225
	Mean	6	4.3	-1.7	6.1	4.6	-1.5
Day 64	N	185	185	185	217	217	217
	Mean	6.1	3.8	-2.3	6.1	4.4	-1.6
Day 92	N	179	179	179	211	211	211
	Mean	6.2	3.8	-2.5	6.2	4.1	-2
Day 183	N	168	168	168	190	190	190
	Mean	6.3	3.3	-3	6.1	4.1	-2
Day 274	N	124	124	124	155	155	155
	Mean	6.5	3.3	-3.2	6.1	4.1	-2.1
Day 365	N	80	80	80	108	108	108
	Mean	6.3	3.1	-3.1	6.2	4.1	-2
Day 456	N	50	50	50	64	64	64
	Mean	6.5	2.8	-3.6	6.2	4.1	-2.1
Day 547	N	15	15	15	30	30	30
	Mean	5.7	2.7	-2.9	6.2	4.3	-1.9
Day 638	N	4	4	4	11	11	11
	Mean	6.5	4.3	-2.3	6.7	3.8	-2.9
EoT/ET	N	183	183	183	201	201	201
	Mean	6	3.6	-2.5	6	3.7	-2.3
Follow-up	N	160	160	160	175	175	175
	Mean	6	3.5	-2.5	6	3.7	-2.3
Q3: The Worst Pain You Have Had in the Past 24 Hours?							
Screening	N	266	267	0	264	265	0
	Mean	7.3	7.2	-	7.5	7.5	-
Day 8	N	266	266	0	264	264	0
	Mean	7.3	7.3	-	7.5	7.5	-
Day 15	N	235	235	235	243	243	243
	Mean	7.4	6.4	-1	7.5	6.7	-0.8
Day 22	N	222	222	222	236	236	236
	Mean	7.4	6	-1.4	7.6	6.2	-1.3
Day 36	N	214	214	214	225	225	225
	Mean	7.3	5.5	-1.8	7.5	5.9	-1.7
Day 64	N	185	185	185	217	217	217
	Mean	7.4	5	-2.4	7.6	5.7	-1.8
Day 92	N	179	179	179	211	211	211
	Mean	7.5	4.8	-2.6	7.6	5.4	-2.3
Day 183	N	168	168	168	190	190	190
	Mean	7.4	4.2	-3.2	7.6	5.3	-2.2
Day 274	N	124	124	124	155	155	155

Table 8. Summary Statistics for the Change From Baseline in the Modified Brief Pain Inventory – Short Form Diabetic Peripheral Neuropathy (FAS)

Visit	Statistics	Esreboxetine			Routine-Care		
		Baseline Score	Visit Score	Change From Baseline	Baseline Score	Visit Score	Change From Baseline
	Mean	7.6	4.3	-3.3	7.6	5.4	-2.2
Day 365	N	80	80	80	108	108	108
	Mean	7.5	4	-3.5	7.7	5.5	-2.2
Day 456	N	50	50	50	64	64	64
	Mean	7.6	3.9	-3.8	7.8	5.5	-2.3
Day 547	N	15	15	15	30	30	30
	Mean	7.3	4.5	-2.9	7.7	5.6	-2
Day 638	N	4	4	4	11	11	11
	Mean	8.8	5.8	-3	7.9	5.4	-2.5
EoT/ET	N	183	183	183	201	201	201
	Mean	7.3	4.6	-2.7	7.5	5.1	-2.4
Follow-up	N	160	160	160	175	175	175
	Mean	7.2	4.4	-2.8	7.5	4.8	-2.7
Q4: Average Level of Pain You Have Had in Past 24 Hours?							
Screening	N	265	268	0	263	265	0
	Mean	6.1	5.9	-	6.2	6.1	-
Day 8	N	265	265	0	263	263	0
	Mean	6.1	6.1	-	6.2	6.2	-
Day 15	N	235	235	235	243	243	243
	Mean	6.2	5.4	-0.8	6.2	5.5	-0.7
Day 22	N	222	222	222	236	236	236
	Mean	6.2	5.1	-1.1	6.2	5.2	-1
Day 36	N	214	214	214	225	225	225
	Mean	6.1	4.6	-1.5	6.2	4.9	-1.3
Day 64	N	185	185	185	217	217	217
	Mean	6.2	4.2	-1.9	6.2	4.7	-1.5
Day 92	N	179	179	179	211	211	211
	Mean	6.2	4	-2.2	6.3	4.4	-1.8
Day 183	N	168	168	168	190	190	190
	Mean	6.3	3.5	-2.8	6.3	4.3	-1.9
Day 274	N	124	124	124	155	155	155
	Mean	6.5	3.9	-2.7	6.3	4.3	-2
Day 365	N	80	80	80	108	108	108
	Mean	6.5	3.3	-3.2	6.3	4.5	-1.8
Day 456	N	50	50	50	64	64	64
	Mean	6.5	3.2	-3.3	6.4	4.4	-2
Day 547	N	15	15	15	30	30	30
	Mean	5.9	3.7	-2.2	6.3	4.5	-1.8
Day 638	N	4	4	4	11	11	11
	Mean	8	4.8	-3.3	7	4.3	-2.7
EoT/ET	N	183	183	183	201	201	201
	Mean	6.2	3.9	-2.3	6.1	4	-2.2
Follow-up	N	160	160	160	175	175	175
	Mean	6.2	3.8	-2.4	6.1	4	-2.1
Q5A: General Activity							
Screening	N	266	267	0	264	265	0
	Mean	5.4	5.3	-	5.7	5.7	-
Day 8	N	266	266	0	264	264	0
	Mean	5.4	5.4	-	5.7	5.7	-

Table 8. Summary Statistics for the Change From Baseline in the Modified Brief Pain Inventory – Short Form Diabetic Peripheral Neuropathy (FAS)

Visit	Statistics	Esreboxetine			Routine-Care		
		Baseline Score	Visit Score	Change From Baseline	Baseline Score	Visit Score	Change From Baseline
Day 15	N	235	235	235	243	243	243
	Mean	5.5	4.4	-1.1	5.8	5	-0.8
Day 22	N	222	222	222	236	236	236
	Mean	5.5	4.1	-1.4	5.8	4.6	-1.2
Day 36	N	214	214	214	225	225	225
	Mean	5.5	3.8	-1.7	5.8	4.4	-1.4
Day 64	N	185	185	185	217	217	217
	Mean	5.6	3.6	-2	5.8	4.3	-1.5
Day 92	N	179	179	179	211	211	211
	Mean	5.6	3.4	-2.2	6	4.1	-1.8
Day 183	N	168	168	168	190	190	190
	Mean	5.6	3.1	-2.5	5.8	4	-1.8
Day 274	N	124	124	124	155	155	155
	Mean	6	3.2	-2.7	5.9	4	-1.9
Day 365	N	80	80	80	108	108	108
	Mean	5.6	3	-2.7	6.1	4	-2.1
Day 456	N	50	50	50	64	64	64
	Mean	5.7	2.9	-2.7	6.2	4.6	-1.6
Day 547	N	15	15	15	30	30	30
	Mean	4.7	3.2	-1.5	6.2	4.2	-2
Day 638	N	4	4	4	11	11	11
	Mean	7	4.3	-2.8	6.5	3.9	-2.6
EoT/ET	N	183	183	183	201	201	201
	Mean	5.5	3.1	-2.3	5.8	3.7	-2.1
Follow-up	N	160	160	160	175	175	175
	Mean	5.5	3.3	-2.2	5.8	3.7	-2.1
Q5B: Mood							
Screening	N	265	268	0	262	265	0
	Mean	5.3	5.1	-	5.6	5.6	-
Day 8	N	265	265	0	262	262	0
	Mean	5.3	5.3	-	5.6	5.6	-
Day 15	N	235	235	235	243	243	243
	Mean	5.3	4.2	-1.2	5.7	4.5	-1.1
Day 22	N	222	222	222	236	236	236
	Mean	5.3	4	-1.3	5.7	4.3	-1.4
Day 36	N	214	214	214	225	225	225
	Mean	5.3	3.6	-1.7	5.7	4	-1.6
Day 64	N	185	185	185	217	217	217
	Mean	5.3	3.5	-1.7	5.6	4.1	-1.5
Day 92	N	179	179	179	211	211	211
	Mean	5.3	3.2	-2.1	5.7	3.9	-1.8
Day 183	N	168	168	168	190	190	190
	Mean	5.3	3	-2.3	5.7	3.7	-2
Day 274	N	124	124	124	155	155	155
	Mean	5.6	3.2	-2.4	5.8	3.8	-2
Day 365	N	80	80	80	108	108	108
	Mean	5.3	3	-2.3	6	3.8	-2.1
Day 456	N	50	50	50	64	64	64
	Mean	5.4	2.9	-2.4	6	4.2	-1.8

Table 8. Summary Statistics for the Change From Baseline in the Modified Brief Pain Inventory – Short Form Diabetic Peripheral Neuropathy (FAS)

Visit	Statistics	Esreboxetine			Routine-Care		
		Baseline Score	Visit Score	Change From Baseline	Baseline Score	Visit Score	Change From Baseline
Day 547	N	15	15	15	30	30	30
	Mean	4.8	3.8	-1	5.4	3.7	-1.7
Day 638	N	4	4	4	11	11	11
	Mean	6.5	4.5	-2	4.4	3.5	-0.9
EoT/ET	N	183	183	183	201	201	201
	Mean	5.3	3.2	-2.1	5.7	3.4	-2.2
Follow-up	N	160	160	160	175	175	175
	Mean	5.2	3	-2.2	5.6	3.3	-2.3
Q5C: Walking Ability							
Screening	N	266	268	0	264	265	0
	Mean	5.6	5.5	-	6.2	6.1	-
Day 8	N	266	266	0	264	264	0
	Mean	5.6	5.6	-	6.2	6.2	-
Day 15	N	235	235	235	243	243	243
	Mean	5.7	4.7	-1	6.2	5.2	-1
Day 22	N	222	222	222	236	236	236
	Mean	5.7	4.5	-1.2	6.3	4.8	-1.4
Day 36	N	214	214	214	225	225	225
	Mean	5.6	3.9	-1.7	6.2	4.6	-1.6
Day 64	N	185	185	185	217	217	217
	Mean	5.8	3.8	-2	6.3	4.7	-1.6
Day 92	N	179	179	179	211	211	211
	Mean	5.8	3.6	-2.3	6.4	4.3	-2.1
Day 183	N	168	168	168	190	190	190
	Mean	5.8	3.1	-2.7	6.3	4.4	-1.9
Day 274	N	124	124	124	155	155	155
	Mean	6.2	3.6	-2.6	6.4	4.3	-2
Day 365	N	80	80	80	108	108	108
	Mean	5.8	3.5	-2.3	6.5	4.6	-1.9
Day 456	N	50	50	50	64	64	64
	Mean	6	3.4	-2.6	6.6	4.8	-1.8
Day 547	N	15	15	15	30	30	30
	Mean	5.2	3.7	-1.5	6.5	4.5	-2
Day 638	N	4	4	4	11	11	11
	Mean	8	4.3	-3.8	6.8	3.6	-3.2
EoT/ET	N	183	183	183	201	201	201
	Mean	5.7	3.7	-2.1	6.3	4	-2.2
Follow-up	N	160	160	160	175	175	175
	Mean	5.8	3.5	-2.3	6.4	4	-2.3
Q5D: Relations With Other People							
Screening	N	264	268	0	264	264	0
	Mean	4	3.9	-	4.5	4.4	-
Day 8	N	264	264	0	264	264	0
	Mean	4	4	-	4.5	4.5	-
Day 15	N	235	235	235	243	243	243
	Mean	4.1	3.6	-0.5	4.6	3.8	-0.8
Day 22	N	222	222	222	236	236	236
	Mean	4	3.3	-0.7	4.6	3.6	-1
Day 36	N	214	214	214	225	225	225

Table 8. Summary Statistics for the Change From Baseline in the Modified Brief Pain Inventory – Short Form Diabetic Peripheral Neuropathy (FAS)

Visit	Statistics	Esreboxetine			Routine-Care		
		Baseline Score	Visit Score	Change From Baseline	Baseline Score	Visit Score	Change From Baseline
	Mean	4	3.1	-1	4.6	3.5	-1.1
Day 64	N	185	185	185	217	217	217
	Mean	4	2.9	-1.1	4.6	3.5	-1.1
Day 92	N	179	179	179	211	211	211
	Mean	4.1	2.6	-1.5	4.7	3.3	-1.4
Day 183	N	168	168	168	190	190	190
	Mean	4.2	2.3	-1.8	4.7	3.3	-1.4
Day 274	N	124	124	124	155	155	155
	Mean	4.5	2.5	-2	4.9	3.3	-1.7
Day 365	N	80	80	80	108	108	108
	Mean	4.3	2.6	-1.7	5.1	3.3	-1.7
Day 456	N	50	50	50	64	64	64
	Mean	4.6	2.4	-2.2	5.3	3.6	-1.7
Day 547	N	15	15	15	30	30	30
	Mean	3.5	3.5	-0.1	5.1	3.5	-1.5
Day 638	N	4	4	4	11	11	11
	Mean	5.8	4.5	-1.3	4.5	2.7	-1.7
EoT/ET	N	183	183	183	201	201	201
	Mean	4	2.6	-1.5	4.5	2.8	-1.7
Follow-up	N	160	160	160	175	175	175
	Mean	4.1	2.6	-1.5	4.5	2.9	-1.6
Q5E: Sleep							
Screening	N	266	268	0	262	265	0
	Mean	6	6.2	-	6.3	6.4	-
Day 8	N	266	266	0	262	262	0
	Mean	6	6	-	6.3	6.3	-
Day 15	N	235	235	235	243	243	243
	Mean	6.2	5.4	-0.9	6.4	5.3	-1.1
Day 22	N	222	222	222	236	236	236
	Mean	6.1	5	-1.2	6.4	4.7	-1.7
Day 36	N	214	214	214	225	225	225
	Mean	6.2	4.4	-1.7	6.4	4.5	-1.9
Day 64	N	185	185	185	217	217	217
	Mean	6.2	4	-2.2	6.4	4.5	-1.8
Day 92	N	179	179	179	211	211	211
	Mean	6.3	4.1	-2.2	6.5	4.5	-2.1
Day 183	N	168	168	168	190	190	190
	Mean	6.2	3.4	-2.8	6.4	4.2	-2.2
Day 274	N	124	124	124	155	155	155
	Mean	6.6	3.7	-2.9	6.6	4.3	-2.3
Day 365	N	80	80	80	108	108	108
	Mean	6.3	3.5	-2.8	6.8	4.4	-2.3
Day 456	N	50	50	50	64	64	64
	Mean	6.4	2.9	-3.5	6.8	4.8	-2
Day 547	N	15	15	15	30	30	30
	Mean	5.7	3.5	-2.1	6.6	4.3	-2.3
Day 638	N	4	4	4	11	11	11
	Mean	7.3	4.5	-2.8	6.5	3.8	-2.7
EoT/ET	N	183	183	183	201	201	201

Table 8. Summary Statistics for the Change From Baseline in the Modified Brief Pain Inventory – Short Form Diabetic Peripheral Neuropathy (FAS)

Visit	Statistics	Esreboxetine			Routine-Care		
		Baseline Score	Visit Score	Change From Baseline	Baseline Score	Visit Score	Change From Baseline
	Mean	6	3.7	-2.3	6.4	4	-2.3
Follow-up	N	160	160	160	175	175	175
	Mean	6	3.5	-2.5	6.5	3.9	-2.6
Q5F: Normal Work, Including Housework							
Screening	N	266	268	0	263	264	0
	Mean	5.2	5.1	-	5.7	5.7	-
Day 8	N	266	266	0	263	263	0
	Mean	5.2	5.2	-	5.7	5.7	-
Day 15	N	235	235	235	243	243	243
	Mean	5.3	4.3	-1	5.8	4.9	-0.9
Day 22	N	222	222	222	236	236	236
	Mean	5.3	4.1	-1.2	5.8	4.6	-1.2
Day 36	N	214	214	214	225	225	225
	Mean	5.3	3.6	-1.6	5.7	4.3	-1.5
Day 64	N	185	185	185	217	217	217
	Mean	5.4	3.5	-1.9	5.8	4.4	-1.4
Day 92	N	179	179	179	211	211	211
	Mean	5.5	3.3	-2.2	5.9	4	-1.9
Day 183	N	168	168	168	190	190	190
	Mean	5.5	3.1	-2.4	5.8	4	-1.7
Day 274	N	124	124	124	155	155	155
	Mean	6	3.2	-2.7	5.9	4	-1.9
Day 365	N	80	80	80	108	108	108
	Mean	5.6	3.1	-2.6	6.1	4.1	-2
Day 456	N	50	50	50	64	64	64
	Mean	5.8	3.1	-2.7	6.2	4.4	-1.8
Day 547	N	15	15	15	30	30	30
	Mean	4.9	3.9	-1	6.3	4.5	-1.8
Day 638	N	4	4	4	11	11	11
	Mean	7.5	3.8	-3.8	7	3.8	-3.2
EoT/ET	N	183	183	183	201	201	201
	Mean	5.2	3.3	-2	5.8	3.7	-2.1
Follow-up	N	160	160	160	175	175	175
	Mean	5.2	3.2	-2	5.9	3.6	-2.2
Q5G: Enjoyment of Life							
Screening	N	266	268	0	264	265	0
	Mean	5.4	5.3	-	5.7	5.9	-
Day 8	N	266	266	0	264	264	0
	Mean	5.4	5.4	-	5.7	5.7	-
Day 15	N	235	235	235	243	243	243
	Mean	5.5	4.3	-1.2	5.8	4.9	-0.9
Day 22	N	222	222	222	236	236	236
	Mean	5.4	4	-1.4	5.9	4.5	-1.4
Day 36	N	214	214	214	225	225	225
	Mean	5.5	3.6	-1.9	5.8	4.2	-1.6
Day 64	N	185	185	185	217	217	217
	Mean	5.6	3.5	-2.1	5.9	4.2	-1.6
Day 92	N	179	179	179	211	211	211
	Mean	5.5	3.3	-2.2	5.9	4.1	-1.9

Table 8. Summary Statistics for the Change From Baseline in the Modified Brief Pain Inventory – Short Form Diabetic Peripheral Neuropathy (FAS)

Visit	Statistics	Esreboxetine			Routine-Care		
		Baseline Score	Visit Score	Change From Baseline	Baseline Score	Visit Score	Change From Baseline
Day 183	N	168	168	168	190	190	190
	Mean	5.6	3.1	-2.5	5.9	3.9	-2
Day 274	N	124	124	124	155	155	155
	Mean	6	3.1	-2.8	6.1	4	-2.1
Day 365	N	80	80	80	108	108	108
	Mean	5.6	3.3	-2.3	6.2	4.2	-2
Day 456	N	50	50	50	64	64	64
	Mean	5.7	3	-2.7	6.2	4.5	-1.7
Day 547	N	15	15	15	30	30	30
	Mean	5.4	4.1	-1.3	6	4.2	-1.8
Day 638	N	4	4	4	11	11	11
	Mean	7.8	4	-3.8	5.4	3.5	-1.9
EoT/ET	N	183	183	183	201	201	201
	Mean	5.4	3.3	-2.1	5.8	3.6	-2.2
Follow-up	N	160	160	160	175	175	175
	Mean	5.3	3.2	-2.1	5.9	3.4	-2.4

Baseline was Day 8.
All questions are scored from 0 to 10, with a higher score giving a worse indication.
EoT = End of Treatment; ET = Early Termination; FAS = full analysis set; N = number of subjects at each Visit.

Short Form-12 Health Survey: Questions 1, 5, 6a and 6b were scored from 1 to 5, with a higher score giving a worse indication. Questions 3, 4, 6c, and 7 were scored from 1 to 5 and Question 2 was scored from 1 to 3, with a higher score giving a better indication. At the end-of-treatment visit, all esreboxetine and routine-care subjects had improved scores for all questions. Summary statistics for the SF-12 Health Survey for the FAS are provided in Table 9.

Table 9. Summary Statistics for the Change From Baseline in the Short Form-12 Health Survey (FAS)

Visit	Statistics	Esreboxetine			Routine-Care		
		Baseline Score	Visit Score	Change From Baseline	Baseline Score	Visit Score	Change From Baseline
Q1: In General, How Would You Rate Your Health?							
Day 8	N	267	267	-	265	265	-
	Mean	3.7	3.7	-	3.8	3.8	-
Day 36	N	238	241	238	250	247	246
	Mean	3.7	3.5	-0.2	3.8	3.6	-0.2
Day 92	N	215	218	215	246	243	242
	Mean	3.7	3.3	-0.4	3.8	3.5	-0.3
Day 183	N	201	203	200	231	230	230
	Mean	3.8	3.3	-0.4	3.8	3.5	-0.4
Day 274	N	156	159	156	186	186	186
	Mean	3.8	3.3	-0.5	3.8	3.4	-0.4
Day 365	N	98	98	96	128	127	127
	Mean	3.7	3.3	-0.4	3.9	3.5	-0.3
Day 456	N	58	59	57	76	74	74
	Mean	3.7	3.2	-0.5	3.8	3.5	-0.3
Day 547	N	23	23	22	36	36	36
	Mean	3.6	3.2	-0.4	3.6	3.3	-0.3
Day 638	N	4	4	4	12	12	12
	Mean	3.8	3	-0.8	3.3	3	-0.3
EoT/ET	N	89	79	78	202	189	188
	Mean	3.6	3.2	-0.3	3.8	3.4	-0.3
Follow-up	N	30	28	28	147	145	144
	Mean	3.5	3.2	-0.3	3.7	3.3	-0.4
Q2a: Does Your Health Limit Moderate Activities?							
Day 8	N	266	266	-	265	265	-
	Mean	1.8	1.8	-	1.7	1.7	-
Day 36	N	237	240	236	250	246	245
	Mean	1.8	2	0.2	1.7	1.9	0.1
Day 92	N	214	217	213	246	244	243
	Mean	1.8	2.1	0.3	1.8	1.9	0.1
Day 183	N	200	202	198	231	229	229
	Mean	1.8	2.1	0.3	1.8	2	0.2
Day 274	N	155	159	155	186	185	185
	Mean	1.8	2	0.2	1.8	2	0.2
Day 365	N	97	98	95	128	126	126
	Mean	1.8	2.2	0.3	1.8	1.9	0.1
Day 456	N	57	59	56	76	74	74
	Mean	1.8	2.2	0.3	1.8	1.9	0.2
Day 547	N	23	23	22	36	36	36
	Mean	2	2	0	1.9	1.9	0
Day 638	N	4	4	4	12	12	12
	Mean	1.8	1.8	0	2.1	2.1	0
EoT/ET	N	88	79	77	202	189	188
	Mean	1.9	2.1	0.2	1.7	1.9	0.2
Follow-up	N	29	28	27	147	145	144
	Mean	2	2	0	1.8	2	0.3
Q2b: Does Your Health Limit Climbing Stairs?							
Day 8	N	267	267	-	265	265	-
	Mean	1.6	1.6	-	1.5	1.5	-

Table 9. Summary Statistics for the Change From Baseline in the Short Form-12 Health Survey (FAS)

Visit	Statistics	Esreboxetine			Routine-Care		
		Baseline Score	Visit Score	Change From Baseline	Baseline Score	Visit Score	Change From Baseline
Day 36	N	238	238	235	250	245	244
	Mean	1.6	1.8	0.2	1.5	1.7	0.1
Day 92	N	215	218	215	246	244	243
	Mean	1.6	1.9	0.3	1.5	1.7	0.2
Day 183	N	201	202	199	231	229	229
	Mean	1.6	1.8	0.2	1.5	1.8	0.2
Day 274	N	156	159	156	186	186	186
	Mean	1.6	1.8	0.2	1.5	1.8	0.2
Day 365	N	98	98	96	128	127	127
	Mean	1.5	1.9	0.3	1.5	1.7	0.2
Day 456	N	58	59	57	76	74	74
	Mean	1.5	1.9	0.4	1.4	1.7	0.2
Day 547	N	23	23	22	36	36	36
	Mean	1.7	1.8	0	1.5	1.7	0.2
Day 638	N	4	4	4	12	12	12
	Mean	1.3	1.5	0.3	1.4	1.9	0.5
EoT/ET	N	89	79	78	202	189	188
	Mean	1.7	1.8	0.2	1.6	1.7	0.2
Follow-up	N	30	27	27	147	145	144
	Mean	1.7	1.8	0.1	1.6	1.8	0.2
Q3a: Accomplished Less Due to Physical Health?							
Day 8	N	268	268	-	266	266	-
	Mean	2.8	2.8	-	2.6	2.6	-
Day 36	N	239	239	237	251	247	247
	Mean	2.7	3	0.3	2.5	2.8	0.2
Day 92	N	216	218	216	247	245	245
	Mean	2.7	3.2	0.4	2.6	3	0.4
Day 183	N	202	204	202	232	231	231
	Mean	2.7	3.2	0.5	2.6	3	0.5
Day 274	N	157	159	157	186	186	186
	Mean	2.8	3.1	0.3	2.5	3	0.5
Day 365	N	99	99	98	128	127	127
	Mean	2.8	3.3	0.4	2.5	3	0.4
Day 456	N	59	59	58	76	74	74
	Mean	2.8	3.4	0.6	2.5	2.9	0.4
Day 547	N	23	23	22	36	36	36
	Mean	3.1	3.4	0.3	2.5	3	0.5
Day 638	N	4	4	4	12	12	12
	Mean	2.5	3.8	1.3	2.6	3	0.4
EoT/ET	N	89	79	78	203	190	190
	Mean	2.9	3.4	0.5	2.5	3	0.4
Follow-up	N	30	27	27	148	145	145
	Mean	3	3.2	0.1	2.6	3.1	0.5
Q3b: Limited Type of Activity due to Physical Health?							
Day 8	N	266	266	-	264	264	-
	Mean	2.9	2.9	-	2.7	2.7	-
Day 36	N	237	239	235	249	245	243
	Mean	2.9	3.1	0.2	2.7	2.9	0.2
Day 92	N	215	217	214	245	243	241

Table 9. Summary Statistics for the Change From Baseline in the Short Form-12 Health Survey (FAS)

Visit	Statistics	Esreboxetine			Routine-Care		
		Baseline Score	Visit Score	Change From Baseline	Baseline Score	Visit Score	Change From Baseline
	Mean	2.9	3.3	0.4	2.7	3	0.3
Day 183	N	201	203	200	230	230	228
	Mean	2.9	3.4	0.5	2.7	3.1	0.4
Day 274	N	156	157	154	185	186	185
	Mean	2.9	3.2	0.3	2.6	3.1	0.5
Day 365	N	98	99	97	128	127	127
	Mean	3	3.4	0.3	2.6	3	0.3
Day 456	N	58	58	57	76	72	72
	Mean	2.9	3.4	0.5	2.6	3	0.4
Day 547	N	23	23	22	36	36	36
	Mean	3.1	3.4	0.3	2.6	3.1	0.5
Day 638	N	4	4	4	12	12	12
	Mean	2	3.8	1.8	2.6	3.3	0.7
EoT/ET	N	88	79	77	202	188	187
	Mean	3	3.4	0.4	2.7	3.1	0.4
Follow-up	N	30	26	26	147	144	143
	Mean	3.2	3.3	0.1	2.7	3.1	0.4
Q4a: Accomplished Less due to Emotional Problems?							
Day 8	N	268	268	-	266	266	-
	Mean	3.2	3.2	-	3.1	3.1	-
Day 36	N	239	239	237	251	247	247
	Mean	3.2	3.4	0.2	3.1	3.3	0.2
Day 92	N	216	218	216	247	245	245
	Mean	3.1	3.5	0.3	3.1	3.3	0.2
Day 183	N	202	204	202	232	231	231
	Mean	3.1	3.5	0.4	3.1	3.4	0.3
Day 274	N	157	159	157	186	186	186
	Mean	3.1	3.5	0.4	3	3.4	0.3
Day 365	N	99	99	98	128	127	127
	Mean	3.1	3.5	0.4	3.1	3.3	0.2
Day 456	N	59	59	58	76	74	74
	Mean	3.1	3.6	0.5	2.9	3.3	0.4
Day 547	N	23	23	22	36	36	36
	Mean	3.3	3.4	-0.1	3	3.4	0.5
Day 638	N	4	4	4	12	12	12
	Mean	3.3	3.5	0.3	3.3	3.6	0.3
EoT/ET	N	89	78	77	203	190	190
	Mean	3.4	3.7	0.3	3.1	3.4	0.3
Follow-up	N	30	27	27	148	145	145
	Mean	3.3	3.4	0	3.1	3.4	0.3
Q4b: Worked Less Carefully due to Emotional Problems?							
Day 8	N	266	266	-	266	266	-
	Mean	3.3	3.3	-	3.2	3.2	-
Day 36	N	237	239	235	251	245	245
	Mean	3.3	3.5	0.2	3.2	3.4	0.2
Day 92	N	214	218	214	247	242	242
	Mean	3.3	3.7	0.4	3.2	3.4	0.2
Day 183	N	200	203	199	232	230	230
	Mean	3.2	3.6	0.3	3.2	3.5	0.3

Table 9. Summary Statistics for the Change From Baseline in the Short Form-12 Health Survey (FAS)

Visit	Statistics	Esreboxetine			Routine-Care		
		Baseline Score	Visit Score	Change From Baseline	Baseline Score	Visit Score	Change From Baseline
Day 274	N	156	159	156	186	186	186
	Mean	3.2	3.6	0.4	3.2	3.5	0.3
Day 365	N	98	97	95	128	127	127
	Mean	3.2	3.6	0.4	3.2	3.3	0.2
Day 456	N	58	58	57	76	74	74
	Mean	3.2	3.6	0.5	3.1	3.4	0.3
Day 547	N	23	22	21	36	36	36
	Mean	3.5	3.7	0.1	3.2	3.4	0.2
Day 638	N	4	4	4	12	12	12
	Mean	3.5	3.8	0.3	3.6	3.9	0.3
EoT/ET	N	88	79	77	203	190	190
	Mean	3.4	3.7	0.4	3.2	3.5	0.3
Follow-up	N	30	27	27	148	145	145
	Mean	3.4	3.4	0	3.1	3.5	0.4
Q5: Did Pain Interfere With Your Normal Work?							
Day 8	N	268	268	-	265	265	-
	Mean	3.2	3.2	-	3.4	3.4	-
Day 36	N	239	237	235	250	246	246
	Mean	3.2	2.7	-0.5	3.4	3	-0.5
Day 92	N	216	217	215	246	245	244
	Mean	3.3	2.5	-0.8	3.4	2.9	-0.5
Day 183	N	202	203	201	231	228	228
	Mean	3.3	2.4	-0.8	3.4	2.7	-0.7
Day 274	N	157	159	157	185	185	185
	Mean	3.3	2.5	-0.7	3.4	2.8	-0.7
Day 365	N	99	99	98	127	126	125
	Mean	3.3	2.4	-0.9	3.4	2.9	-0.6
Day 456	N	59	58	57	76	74	74
	Mean	3.3	2.5	-0.8	3.4	2.9	-0.5
Day 547	N	23	23	22	36	36	36
	Mean	3.3	2.4	-0.8	3.4	2.8	-0.5
Day 638	N	4	4	4	12	12	12
	Mean	3.8	3	-0.8	3.4	2.8	-0.6
EoT/ET	N	89	78	77	203	190	190
	Mean	3	2.4	-0.6	3.4	2.8	-0.6
Follow-up	N	30	27	27	148	145	145
	Mean	3	2.6	-0.3	3.4	2.8	-0.6
Q6a: How Much Have You Felt Calm and Peaceful?							
Day 8	N	269	269	-	266	266	-
	Mean	3	3	-	3	3	-
Day 36	N	240	238	237	251	246	246
	Mean	3	2.8	-0.2	3	2.8	-0.2
Day 92	N	217	218	217	247	244	244
	Mean	3	2.7	-0.3	3	2.8	-0.3
Day 183	N	203	203	202	232	230	230
	Mean	3	2.6	-0.4	3	2.8	-0.3
Day 274	N	158	158	157	186	186	186
	Mean	3	2.7	-0.3	3	2.7	-0.3
Day 365	N	100	99	99	128	127	127

Table 9. Summary Statistics for the Change From Baseline in the Short Form-12 Health Survey (FAS)

Visit	Statistics	Esreboxetine			Routine-Care		
		Baseline Score	Visit Score	Change From Baseline	Baseline Score	Visit Score	Change From Baseline
	Mean	2.9	2.5	-0.4	3	2.7	-0.3
Day 456	N	60	59	59	76	73	73
	Mean	2.9	2.4	-0.5	3.1	2.8	-0.3
Day 547	N	24	23	23	36	36	36
	Mean	2.9	2.5	-0.3	3	2.6	-0.4
Day 638	N	4	4	4	12	12	12
	Mean	3.8	3.5	-0.3	2.9	2.9	0
EoT/ET	N	89	76	75	203	189	189
	Mean	2.9	2.6	-0.3	3	2.7	-0.3
Follow-up	N	30	27	27	148	146	146
	Mean	2.7	2.6	0	3	2.6	-0.4
Q6b: How Much Have you had a lot of Energy?							
Day 8	N	269	269	-	266	266	-
	Mean	3.5	3.5	-	3.5	3.5	-
Day 36	N	240	236	235	251	245	245
	Mean	3.5	3.2	-0.3	3.5	3.4	-0.1
Day 92	N	217	218	217	247	244	244
	Mean	3.5	3.2	-0.4	3.5	3.3	-0.1
Day 183	N	203	202	201	232	226	226
	Mean	3.5	3.1	-0.4	3.5	3.3	-0.2
Day 274	N	158	158	157	186	186	186
	Mean	3.5	3.1	-0.4	3.5	3.3	-0.2
Day 365	N	100	99	99	128	126	126
	Mean	3.4	3	-0.4	3.5	3.3	-0.2
Day 456	N	60	59	59	76	73	73
	Mean	3.4	3.1	-0.3	3.5	3.4	-0.2
Day 547	N	24	23	23	36	36	36
	Mean	3.4	3.1	-0.3	3.3	3	-0.3
Day 638	N	4	4	4	12	12	12
	Mean	3.8	3.8	0	3.3	2.8	-0.6
EoT/ET	N	89	76	75	203	189	189
	Mean	3.3	3	-0.3	3.4	3.2	-0.1
Follow-up	N	30	27	27	148	146	146
	Mean	2.7	2.7	0	3.4	3.1	-0.3
Q6c: How Much Have you Felt Downhearted/Depressed?							
Day 8	N	269	269	-	266	266	-
	Mean	3.4	3.4	-	3.5	3.5	-
Day 36	N	240	237	236	251	243	243
	Mean	3.3	3.6	0.3	3.5	3.6	0.1
Day 92	N	217	216	215	247	245	245
	Mean	3.3	3.6	0.3	3.5	3.6	0.1
Day 183	N	203	201	200	232	230	230
	Mean	3.3	3.7	0.4	3.5	3.5	0
Day 274	N	158	159	158	186	185	185
	Mean	3.2	3.6	0.4	3.4	3.6	0.2
Day 365	N	100	98	98	128	125	125
	Mean	3.3	3.7	0.4	3.5	3.4	0
Day 456	N	60	58	58	76	73	73
	Mean	3.3	3.5	0.2	3.4	3.5	0.1

Table 9. Summary Statistics for the Change From Baseline in the Short Form-12 Health Survey (FAS)

Visit	Statistics	Esreboxetine			Routine-Care		
		Baseline Score	Visit Score	Change From Baseline	Baseline Score	Visit Score	Change From Baseline
Day 547	N	24	22	22	36	36	36
	Mean	3.4	3.7	0.3	3.6	3.7	0.1
Day 638	N	4	4	4	12	12	12
	Mean	3.5	3.3	-0.3	3.7	4.1	0.4
EoT/ET	N	89	78	77	203	189	189
	Mean	3.4	3.7	0.3	3.5	3.6	0.1
Follow-up	N	30	27	27	148	146	146
	Mean	3.5	3.8	0.2	3.5	3.7	0.2
Q7: Has Your Health Interfered With Your Social Life?							
Day 8	N	269	269	-	265	265	-
	Mean	3.3	3.3	-	3.3	3.3	-
Day 36	N	240	238	237	250	247	246
	Mean	3.3	3.6	0.3	3.2	3.4	0.2
Day 92	N	217	217	216	246	245	244
	Mean	3.3	3.8	0.4	3.3	3.5	0.3
Day 183	N	203	202	201	231	230	229
	Mean	3.3	3.6	0.3	3.3	3.6	0.3
Day 274	N	158	159	158	186	186	186
	Mean	3.3	3.6	0.3	3.2	3.6	0.4
Day 365	N	100	98	98	128	126	126
	Mean	3.3	3.7	0.4	3.2	3.4	0.2
Day 456	N	60	59	59	76	73	73
	Mean	3.3	3.9	0.5	3.2	3.5	0.3
Day 547	N	24	23	23	36	36	36
	Mean	3.6	3.8	0.2	3.4	3.4	0
Day 638	N	4	4	4	12	12	12
	Mean	3	3.5	0.5	3.5	3.7	0.2
EoT/ET	N	89	78	77	202	189	188
	Mean	3.5	3.8	0.2	3.3	3.6	0.3
Follow-up	N	30	27	27	147	146	145
	Mean	3.5	3.9	0.4	3.2	3.5	0.3

Due to limitations of space, it is not possible to reproduce the text of the questionnaire in full and all questions have been abbreviated. Questions 3 to 7 are preceded by a variation of the following, 'During the past week how much/how much of the time/have you'.
Questions 1, 5, 6a and 6b are scored from 1 to 5, with a higher score giving a worse indication. Questions 3, 4, 6c and 7 are scored from 1 to 5 and question 2 is scored from 1 to 3, with a higher score giving a better indication.
EoT = End of Treatment; ET = Early Termination; FAS = full analysis set; N = number of subjects at each Visit.

Euroqol-5 Dimensions (EQ-5D): At the end-of-treatment visit, out of the total number of evaluable subjects (N=229 esreboxetine and 237 routine-care), the majority of both esreboxetine and routine-care subjects had no or some problem for all EQ-5D assessments. Summary statistics for the EQ-5D for the FAS are provided in Table 10.

Table 10. Summary Statistics for the EQ-5D (FAS)

	Esreboxetine			Routine-Care		
	N=396	N=396	N=396	N=384	N=384	N=384
	Day 8	Day 183	End of Treatment	Day 8	Day 183	End of Treatment
Mobility						
Number assessed	269	203	229	264	230	237
No problem	54 (20.1)	76 (37.4)	92 (40.2)	42 (15.9)	72 (31.3)	74 (31.2)
Some problem	213 (79.2)	127 (62.6)	136 (59.4)	222 (84.1)	158 (68.7)	163 (68.8)
Extreme problem	1 (0.4)	0	1 (0.4)	0	0	0
Missing condition	1 (0.4)	0	0	0	0	0
Usual activity						
Number assessed	269	203	229	264	230	237
No problem	86 (32.0)	89 (43.8)	115 (50.2)	60 (22.7)	68 (29.6)	87 (36.7)
Some problem	175 (65.1)	111 (54.7)	107 (46.7)	195 (73.9)	160 (69.6)	145 (61.2)
Extreme problem	7 (2.6)	3 (1.5)	4 (1.7)	9 (3.4)	0	5 (2.1)
Missing condition	1 (0.4)	0	3 (1.3)	0	2 (0.9)	0
Self-care						
Number assessed	269	203	229	264	230	237
No problem	199 (74.0)	162 (79.8)	179 (78.2)	178 (67.4)	171 (74.3)	181 (76.4)
Some problem	65 (24.2)	41 (20.2)	46 (20.1)	81 (30.7)	56 (24.3)	51 (21.5)
Extreme problem	2 (0.7)	0	0	1 (0.4)	1 (0.4)	1 (0.4)
Missing condition	3 (1.1)	0	4 (1.7)	4 (1.5)	2 (0.9)	4 (1.7)
Pain/discomfort						
Number assessed	269	203	229	264	230	237
No problem	5 (1.9)	41 (20.2)	52 (22.7)	2 (0.8)	18 (7.8)	34 (14.3)
Some problem	190 (70.6)	149 (73.4)	153 (66.8)	184 (69.7)	190 (82.6)	183 (77.2)
Extreme problem	73 (27.1)	13 (6.4)	23 (10.0)	78 (29.5)	22 (9.6)	19 (8.0)
Missing condition	1 (0.4)	0	1 (0.4)	0	0	1 (0.4)
Anxiety/depression						
Number assessed	269	203	229	264	230	237
No problem	97 (36.1)	108 (53.2)	119 (52.0)	111 (42.0)	100 (43.5)	117 (49.4)
Some problem	149 (55.4)	91 (44.8)	100 (43.7)	127 (48.1)	119 (51.7)	113 (47.7)
Extreme problem	20 (7.4)	3 (1.5)	9 (3.9)	26 (9.8)	9 (3.9)	7 (3.0)
Missing condition	3 (1.1)	1 (0.5)	1 (0.4)	0	2 (0.9)	0

EQ-5D = Euroqol-5 dimensions; FAS = full analysis set; N = number of subjects at each treatment group.

Analgesic Treatment Satisfaction Scale: At the end-of-treatment visit, the majority of both esreboxetine and routine-care subjects who responded to the ATSS gave responses that the study drug was very effective or somewhat effective in relieving pain; 51 esreboxetine (24.2%) and 52 routine-care subjects (25.0%) responded that it was very effective, and 49 esreboxetine (23.2%) and 69 routine-care subjects (33.2%) responded that it was somewhat effective. Summary statistics for the ATSS for the FAS are provided in Table 11.

Table 11. Summary Statistics for the Analgesic Treatment Satisfaction Scale (FAS)

Visit	Question	Response	Esreboxetine (N=396)			Routine-Care (N=384)		
			Prescribed	Non-Prescribed	Others	Prescribed	Non-Prescribed	Others
Day 8	Effective in relieving pain	NA	147 (61.3)	135 (58.4)	135	141 (58.8)	127 (57.5)	137
		Extremely effective	7 (2.9)	1 (0.4)	1	5 (2.1)	1 (0.5)	0
		Very effective	17 (7.1)	6 (2.6)	3	11 (4.6)	5 (2.3)	0
		Somewhat effective	34 (14.2)	40 (17.3)	3	44 (18.3)	37 (16.7)	6
		A little effective	29 (12.1)	37 (16.0)	2	25 (10.4)	31 (14.0)	4
		Not at all effective	6 (2.5)	11 (4.8)	1	12 (5.0)	19 (8.6)	0
		Missing	205	214	299	183	202	275
	Satisfied or dissatisfied	NA	161 (66.8)	140 (61.4)	137	148 (62.4)	141 (64.7)	133
		Extremely satisfied	6 (2.5)	2 (0.9)	1	2 (0.8)	1 (0.5)	0
		Very satisfied	12 (5.0)	3 (1.3)	2	13 (5.5)	4 (1.8)	0
		Somewhat satisfied	32 (13.3)	42 (18.4)	3	38 (16.0)	35 (16.1)	3
		A little dissatisfied	17 (7.1)	25 (11.0)	1	21 (8.9)	24 (11.0)	6
		Extremely dissatisfied	12 (5.0)	15 (6.6)	1	14 (5.9)	12 (5.5)	0
		Missing	204	217	299	186	205	280
	Recommend	NA	168 (69.7)	141 (63.8)	132	148 (62.7)	136 (63.3)	128
		Would recommend	33 (13.7)	21 (9.5)	3	36 (15.3)	18 (8.4)	5
		Would not recommend	10 (4.1)	24 (10.9)	1	18 (7.6)	25 (11.6)	0
		Uncertain	29 (12.0)	34 (15.4)	12	32 (13.6)	35 (16.3)	5
		Missing	204	224	296	187	208	284
Day 64	Effective in relieving pain	NA	70 (35.5)	109 (63.4)	104	40 (17.7)	115 (64.2)	98
		Extremely effective	10 (5.1)	3 (1.7)	5	9 (4.0)	1 (0.6)	1
		Very effective	38 (19.3)	6 (3.5)	7	57 (25.2)	7 (3.9)	0
		Somewhat effective	54 (27.4)	28 (16.3)	3	73 (32.3)	23 (12.8)	3
		A little effective	21 (10.7)	20 (11.6)	4	33 (14.6)	23 (12.8)	9
		Not at all effective	4 (2.0)	5 (2.9)	2	14 (6.2)	9 (5.0)	1
		Missing	230	255	301	189	236	302
	Satisfied or dissatisfied	NA	69 (35.0)	116 (68.2)	98	37 (16.7)	114 (65.9)	100
		Extremely satisfied	9 (4.6)	1 (0.6)	5	11 (5.0)	3 (1.7)	1
		Very satisfied	47 (23.9)	10 (5.9)	9	69 (31.1)	9 (5.2)	3
		Somewhat satisfied	53 (26.9)	30 (17.6)	3	73 (32.9)	28 (16.2)	2
		A little dissatisfied	14 (7.1)	11 (6.5)	4	22 (9.9)	12 (6.9)	5
		Extremely dissatisfied	5 (2.5)	1 (0.6)	0	10 (4.5)	6 (3.5)	1
		Missing	230	257	307	193	242	302
	Recommend	NA	66 (34.2)	114 (67.5)	95	35 (16.1)	109 (64.1)	91
		Would recommend	86 (44.6)	23 (13.6)	14	129 (59.4)	28 (16.5)	7
		Would not recommend	13 (6.7)	10 (5.9)	4	17 (7.8)	17 (10.0)	4

Table 11. Summary Statistics for the Analgesic Treatment Satisfaction Scale (FAS)

Visit	Question	Response	Esreboxetine (N=396)			Routine-Care (N=384)		
			Prescribed	Non-Prescribed	Others	Prescribed	Non-Prescribed	Others
		Uncertain	28 (14.5)	21 (12.4)	6	35 (16.1)	15 (8.8)	5
		Missing	234	258	307	198	245	307
Day 183	Effective in relieving pain	NA	44 (24.6)	106 (67.1)	94	35 (17.3)	94 (60.3)	95
		Extremely effective	11 (6.1)	2 (1.3)	5	9 (4.5)	2 (1.3)	0
		Very effective	49 (27.4)	9 (5.7)	7	63 (31.2)	9 (5.8)	16
		Somewhat effective	55 (30.7)	26 (16.5)	6	67 (33.2)	24 (15.4)	5
		A little effective	18 (10.1)	13 (8.2)	5	19 (9.4)	19 (12.2)	1
		Not at all effective	2 (1.1)	2 (1.3)	2	9 (4.5)	8 (5.1)	0
		Missing	236	257	296	209	255	294
	Satisfied or dissatisfied	NA	47 (26.4)	102 (67.5)	92	34 (17.0)	100 (64.1)	93
		Extremely satisfied	14 (7.9)	2 (1.3)	5	17 (8.5)	2 (1.3)	2
		Very satisfied	48 (27.0)	8 (5.3)	9	53 (26.5)	9 (5.8)	13
		Somewhat satisfied	53 (29.8)	28 (18.5)	10	72 (36.0)	29 (18.6)	3
		A little dissatisfied	16 (9.0)	11 (7.3)	1	18 (9.0)	11 (7.1)	3
		Extremely dissatisfied	0	0	1	6 (3.0)	5 (3.2)	0
		Missing	237	264	297	211	255	297
	Recommend	NA	49 (27.7)	107 (72.8)	91	33 (16.3)	95 (62.1)	90
		Would recommend	89 (50.3)	22 (15.0)	16	127 (62.6)	23 (15.0)	21
		Would not recommend	3 (1.7)	4 (2.7)	4	9 (4.4)	13 (8.5)	1
		Uncertain	36 (20.3)	14 (9.5)	8	34 (16.7)	22 (14.4)	4
		Missing	238	268	296	208	258	295
Day 274	Effective in relieving pain	NA	45 (30.6)	86 (72.3)	85	11 (6.5)	91 (64.5)	78
		Extremely effective	10 (6.8)	2 (1.7)	2	11 (6.5)	0	2
		Very effective	40 (27.2)	8 (6.7)	8	67 (39.9)	6 (4.3)	9
		Somewhat effective	40 (27.2)	13 (10.9)	3	52 (31.0)	26 (18.4)	5
		A little effective	12 (8.2)	9 (7.6)	3	22 (13.1)	14 (9.9)	5
		Not at all effective	0	1 (0.8)	0	5 (3.0)	4 (2.8)	1
		Missing	271	299	317	245	272	313
	Satisfied or dissatisfied	NA	44 (29.9)	83 (71.6)	77	13 (7.7)	92 (66.7)	78
		Extremely satisfied	14 (9.5)	2 (1.7)	2	13 (7.7)	0	2
		Very satisfied	42 (28.6)	6 (5.2)	6	65 (38.7)	6 (4.3)	8
		Somewhat satisfied	33 (22.4)	15 (12.9)	5	54 (32.1)	28 (20.3)	5
		A little dissatisfied	13 (8.8)	8 (6.9)	2	20 (11.9)	11 (8.0)	3
		Extremely dissatisfied	1 (0.7)	2 (1.7)	0	3 (1.8)	1 (0.7)	2
		Missing	271	302	326	245	275	315
	Recommend	NA	47 (32.6)	83 (72.2)	74	12 (7.2)	85 (62.0)	73

Table 11. Summary Statistics for the Analgesic Treatment Satisfaction Scale (FAS)

Visit	Question	Response	Esreboxetine (N=396)			Routine-Care (N=384)		
			Prescribed	Non-Prescribed	Others	Prescribed	Non-Prescribed	Others
		Would recommend	69 (47.9)	17 (14.8)	9	113 (67.7)	22 (16.1)	15
		Would not recommend	7 (4.9)	4 (3.5)	2	11 (6.6)	10 (7.3)	3
		Uncertain	21 (14.6)	11 (9.6)	7	31 (18.6)	20 (14.6)	8
		Missing	274	303	326	246	276	314
Day 456	Effective in relieving pain	NA	15 (27.3)	29 (64.4)	22	4 (6.5)	29 (51.8)	30
		Extremely effective	7 (12.7)	0	3	9 (14.5)	0	0
		Very effective	18 (32.7)	9 (20.0)	1	18 (29.0)	7 (12.5)	5
		Somewhat effective	13 (23.6)	3 (6.7)	2	20 (32.3)	13 (23.2)	1
		A little effective	2 (3.6)	3 (6.7)	1	9 (14.5)	4 (7.1)	2
		Not at all effective	0	1 (2.2)	0	2 (3.2)	3 (5.4)	1
		Missing	346	356	372	330	336	353
	Satisfied or dissatisfied	NA	16 (29.1)	30 (68.2)	23	5 (8.1)	34 (61.8)	30
		Extremely satisfied	6 (10.9)	2 (4.5)	4	10 (16.1)	0	0
		Very satisfied	18 (32.7)	5 (11.4)	0	22 (35.5)	5 (9.1)	5
		Somewhat satisfied	15 (27.3)	6 (13.6)	1	15 (24.2)	12 (21.8)	0
		A little dissatisfied	0	0	1	7 (11.3)	1 (1.8)	0
		Extremely dissatisfied	0	1 (2.3)	0	3 (4.8)	3 (5.5)	0
		Missing	346	357	372	330	337	357
	Recommend	NA	16 (29.1)	32 (71.1)	19	5 (8.1)	32 (61.5)	30
		Would recommend	33 (60.0)	8 (17.8)	6	40 (64.5)	10 (19.2)	6
		Would not recommend	1 (1.8)	4 (8.9)	0	8 (12.9)	3 (5.8)	0
		Uncertain	5 (9.1)	1 (2.2)	0	9 (14.5)	7 (13.5)	1
		Missing	346	356	376	330	340	355
Day 638	Effective in relieving pain	NA	1 (33.3)	1 (25.0)	1	1 (8.3)	5 (45.5)	6
		Extremely effective	0	0	0	2 (16.7)	0	0
		Very effective	0	1 (25.0)	0	5 (41.7)	2 (18.2)	0
		Somewhat effective	1 (33.3)	0	1	1 (8.3)	2 (18.2)	0
		A little effective	1 (33.3)	2 (50.0)	0	3 (25.0)	1 (9.1)	1
		Not at all effective	0	0	0	0	1 (9.1)	0
		Missing	393	392	394	374	375	379
	Satisfied or dissatisfied	NA	1 (33.3)	1 (25.0)	1	2 (16.7)	6 (54.5)	6
		Extremely satisfied	0	0	0	1 (8.3)	0	0
		Very satisfied	0	0	0	5 (41.7)	1 (9.1)	0
		Somewhat satisfied	1 (33.3)	1 (25.0)	1	3 (25.0)	3 (27.3)	1
		A little dissatisfied	1 (33.3)	2 (50.0)	0	0	0	0
		Extremely dissatisfied	0	0	0	1 (8.3)	1 (9.1)	0

Table 11. Summary Statistics for the Analgesic Treatment Satisfaction Scale (FAS)

Visit	Question	Response	Esreboxetine (N=396)			Routine-Care (N=384)		
			Prescribed	Non-Prescribed	Others	Prescribed	Non-Prescribed	Others
		Missing	393	392	394	374	375	379
	Recommend	NA	1 (33.3)	1 (25.0)	1	1 (8.3)	5 (50.0)	6
		Would recommend	1 (33.3)	2 (50.0)	1	9 (75.0)	2 (20.0)	0
		Would not recommend	0	0	0	1 (8.3)	1 (10.0)	0
		Uncertain	1 (33.3)	1 (25.0)	0	1 (8.3)	2 (20.0)	1
		Missing	393	392	394	374	376	379
EoT/ET	Effective in relieving pain	NA	67 (31.8)	116 (67.4)	99	39 (18.8)	119 (64.3)	116
		Extremely effective	18 (8.5)	3 (1.7)	5	20 (9.6)	1 (0.5)	3
		Very effective	51 (24.2)	8 (4.7)	5	52 (25.0)	12 (6.5)	11
		Somewhat effective	49 (23.2)	25 (14.5)	7	69 (33.2)	32 (17.3)	8
		A little effective	20 (9.5)	18 (10.5)	6	21 (10.1)	18 (9.7)	3
		Not at all effective	6 (2.8)	2 (1.2)	2	7 (3.4)	3 (1.6)	2
		Missing	207	246	294	206	229	271
	Satisfied or dissatisfied	NA	63 (30.1)	121 (69.9)	98	34 (16.3)	123 (67.2)	110
		Extremely satisfied	22 (10.5)	4 (2.3)	4	27 (13.0)	1 (0.5)	4
		Very satisfied	51 (24.4)	7 (4.0)	7	51 (24.5)	14 (7.7)	10
		Somewhat satisfied	49 (23.4)	26 (15.0)	11	74 (35.6)	34 (18.6)	5
		A little dissatisfied	15 (7.2)	13 (7.5)	1	17 (8.2)	9 (4.9)	4
		Extremely dissatisfied	9 (4.3)	2 (1.2)	1	5 (2.4)	2 (1.1)	1
		Missing	209	245	296	206	231	280
	Recommend	NA	69 (33.0)	117 (69.6)	100	37 (17.9)	121 (66.5)	109
		Would recommend	94 (45.0)	28 (16.7)	17	116 (56.0)	30 (16.5)	22
		Would not recommend	16 (7.7)	10 (6.0)	4	19 (9.2)	11 (6.0)	0
		Uncertain	30 (14.4)	13 (7.7)	7	35 (16.9)	20 (11.0)	5
		Missing	209	250	290	207	232	278

EoT = End of Treatment; ET = Early Termination; FAS = full analysis set; NA = not applicable; N = number of subjects at each treatment group.

The Pain-Related Medication Utilization (PRMU) Questionnaire: The majority of subjects (defined as >100 subjects in both treatment groups) used other drugs (97 esreboxetine and 101 routine-care), gabapentin (neurontin) (52 esreboxetine and 65 routine-care), and tricyclic antidepressants (eg, amitriptyline, nortriptyline) (59 esreboxetine and 57 routine-care). Summary statistics for the PRMU for the FAS are provided in Table 12.

Table 12. Summary Statistics for Pain-Related Medication Utilization (FAS)

Name of Medication	Esreboxetine (N=396)	Routine-Care (N=384)
Pregabalin (lyrica)	39 (9.8)	40 (10.4)
Gabapentin (neurontin)	52 (13.1)	65 (16.9)
Other antiepileptics (eg, carbamazepine, lamotrigine)	38 (9.6)	39 (10.2)
Short-acting opioids (eg, percocet, vicodin)	11 (2.8)	16 (4.2)
Long-acting opioids (eg, oxycontin)	4 (1.0)	2 (0.5)
Tramadol (ultram)	22 (5.6)	22 (5.7)
Tricyclic antidepressants (eg, amitriptyline, nortriptyline)	59 (14.9)	57 (14.8)
Ssris/snris	17 (4.3)	18 (4.7)
Lidoderm (lidocaine) patch	4 (1.0)	0
Other topical agents	17 (4.3)	15 (3.9)
Other specify	97 (24.5)	101 (26.3)

FAS = full analysis set; N = number of subjects at each treatment group.

The decision was made to terminate the study on 08 August 2008 on the basis of results from another Phase 2 Proof of Concept study, which demonstrated futility (ie, the observed mean difference between treatments was -0.5 or more, fulfilling the pre-specified criteria for futility), as recommended by the Data Monitoring Committee. Given the decision taken concerning Phase 2 Proof of Concept study, the DPN development program was terminated (including Study A6061031), and only summary study results are presented in this synopsis report.

Safety Results: A total of 293 esreboxetine subjects (74.0%) and 258 routine-care subjects (67.2%) experienced at least 1 AE during the study; 211 esreboxetine subjects (53.3%) and 88 routine-care (22.9%) had at least 1 treatment-related AE per the Investigator.

A summary of all-causality treatment-emergent non SAEs by system organ class (SOC) and preferred term are provided in Table 13.

Table 13. Treatment-Emergent Nonserious Adverse Events by System Organ Class and Preferred Term ≥2% Threshold (All Causalities)

Number (%) of Subjects With Adverse Events by: System Organ Class MedDRA (Version 11.1) Preferred Term	Esreboxetine n (%)	Routine-Care n (%)
Number (%) of Subjects:		
Evaluable for adverse events	396	384
With adverse events	237 (59.8)	193 (50.3)
Cardiac disorders	15 (3.8)	5 (1.3)
Tachycardia	15 (3.8)	5 (1.3)
Gastrointestinal disorders	122 (30.8)	51 (13.3)
Constipation	66 (16.7)	13 (3.4)
Diarrhoea	17 (4.3)	19 (4.9)
Dry mouth	43 (10.9)	14 (3.6)
Nausea	25 (6.3)	12 (3.1)
General disorders and administration site conditions	48 (12.1)	37 (9.6)
Asthenia	12 (3.0)	8 (2.1)
Chest pain	8 (2.0)	6 (1.6)
Fatigue	13 (3.3)	9 (2.3)
Oedema peripheral	6 (1.5)	15 (3.9)
Peripheral coldness	11 (2.8)	0
Infections and infestations	61 (15.4)	70 (18.2)
Bronchitis	9 (2.3)	14 (3.6)
Influenza	9 (2.3)	7 (1.8)
Nasopharyngitis	14 (3.5)	10 (2.6)
Sinusitis	7 (1.8)	11 (2.9)
Upper respiratory tract infection	20 (5.1)	28 (7.3)
Urinary tract infection	9 (2.3)	12 (3.1)
Injury, poisoning and procedural complications	7 (1.8)	8 (2.1)
Fall	7 (1.8)	8 (2.1)
Investigations	10 (2.5)	0
Heart rate increased	10 (2.5)	0
Metabolism and nutrition disorders	22 (5.6)	14 (3.6)
Hyperglycaemia	8 (2.0)	7 (1.8)
Hypoglycaemia	14 (3.5)	7 (1.8)
Musculoskeletal and connective tissue disorders	42 (10.6)	35 (9.1)
Arthralgia	9 (2.3)	14 (3.6)
Muscle spasms	16 (4.0)	5 (1.3)
Musculoskeletal pain	8 (2.0)	5 (1.3)
Osteoarthritis	3 (0.8)	8 (2.1)
Pain in extremity	12 (3.0)	11 (2.9)
Nervous system disorders	62 (15.7)	62 (16.1)
Dizziness	34 (8.6)	25 (6.5)
Headache	28 (7.1)	20 (5.2)
Somnolence	8 (2.0)	24 (6.3)
Psychiatric disorders	38 (9.6)	2 (0.5)
Insomnia	38 (9.6)	2 (0.5)
Renal and urinary disorders	9 (2.3)	4 (1.0)
Dysuria	9 (2.3)	4 (1.0)
Respiratory, thoracic and mediastinal disorders	3 (0.8)	11 (2.9)
Cough	3 (0.8)	11 (2.9)
Skin and subcutaneous tissue disorders	51 (12.9)	7 (1.8)
Hyperhidrosis	41 (10.4)	4 (1.0)
Pruritus	13 (3.3)	3 (0.8)

Table 13. Treatment-Emergent Nonserious Adverse Events by System Organ Class and Preferred Term ≥2% Threshold (All Causalities)

Number (%) of Subjects With Adverse Events by: System Organ Class MedDRA (Version 11.1) Preferred Term	Esreboxetine n (%)	Routine-Care n (%)
Vascular disorders	13 (3.3)	20 (5.2)
Hypertension	13 (3.3)	20 (5.2)

Subjects are only counted once per treatment for each row.
Includes data up to 30 days after last dose of study drug.
MedDRA = Medical Dictionary for Regulatory Activities; n = number of subjects with adverse events.

A summary of treatment-related adverse events by system organ class and preferred term is provided in Table 14.

Table 14. Treatment-Related Adverse Events ≥2% Threshold

System Organ Class MedDRA (Version 11.1) Preferred Term	Esreboxetine (n=396) N (%)	Routine-Care (n=384) N (%)
Gastrointestinal disorders	109 (27.5)	36 (9.4)
Constipation	57 (14.4)	7 (1.8)
Diarrhoea	10 (2.5)	8 (2.1)
Dry mouth	41 (10.4)	12 (3.1)
Nausea	20 (5.1)	7 (1.8)
General disorders and administration site conditions	34 (8.6)	12 (3.1)
Asthenia	8 (2.0)	0
Fatigue	9 (2.3)	6 (1.6)
Peripheral coldness	8 (2.0)	0
Investigations	25 (6.3)	5 (1.3)
Heart rate increased	10 (2.5)	0
Musculoskeletal and connective tissue disorders	13 (3.3)	4 (1.0)
Muscle spasms	10 (2.5)	0
Nervous system disorders	60 (15.2)	47 (12.2)
Dizziness	29 (7.3)	19 (4.9)
Headache	16 (4.0)	5 (1.3)
Somnolence	7 (1.8)	22 (5.7)
Psychiatric disorders	41 (10.4)	4 (1.0)
Insomnia	27 (6.8)	0
Skin and subcutaneous tissue disorders	47 (11.9)	7 (1.8)
Hyperhidrosis	35 (8.8)	4 (1.0)
Total preferred term events	482	146

AEs and SAEs are not separated out.
Includes data up to 30 days after last dose of study drug.
AEs = adverse events; MedDRA = Medical Dictionary for Regulatory Activities; N = number of subjects with AE in a treatment group; n = number of subjects evaluable for AEs; SAEs = serious adverse events.

The summary of treatment emergent SAEs by SOC and preferred term in the treatment groups esreboxetine and routine-care are presented in Table 15.

Table 15. Treatment-Emergent Serious Adverse Events by System Organ Class and Preferred Term (All Causalities)

Number (%) of Subjects With Adverse Events by: System Organ Class and MedDRA (Version 11.1) Preferred Term	Esreboxetine n (%)	Routine-Care n (%)
Number (%) of subjects:		
Evaluable for adverse events	396	384
With adverse events	45 (11.4)	40 (10.4)
Blood and lymphatic system disorders	1 (0.3)	2 (0.5)
Anaemia	1 (0.3)	1 (0.3)
Leukocytosis	0	1 (0.3)
Cardiac disorders	12 (3.0)	6 (1.6)
Acute coronary syndrome	1 (0.3)	0
Acute myocardial infarction	0	1 (0.3)
Angina unstable	1 (0.3)	0
Atrial fibrillation	3 (0.8)	2 (0.5)
Atrial flutter	0	1 (0.3)
Cardiac failure	0	2 (0.5)
Coronary artery disease	1 (0.3)	0
Coronary artery occlusion	0	1 (0.3)
Myocardial infarction	3 (0.8)	0
Myocardial ischaemia	2 (0.5)	1 (0.3)
Sinus tachycardia	1 (0.3)	0
Tachycardia	1 (0.3)	0
Ventricular tachycardia	1 (0.3)	0
Congenital, familial and genetic disorders	1 (0.3)	0
Hamartoma	1 (0.3)	0
Eye disorders	3 (0.8)	1 (0.3)
Cataract	2 (0.5)	1 (0.3)
Optic ischaemic neuropathy	1 (0.3)	0
Retinopathy	1 (0.3)	0
Gastrointestinal disorders	1 (0.3)	4 (1.0)
Abdominal pain	0	2 (0.5)
Ascites	0	1 (0.3)
Diarrhoea	0	1 (0.3)
Gastrointestinal haemorrhage	1 (0.3)	0
Varices oesophageal	0	1 (0.3)
General disorders and administration site conditions	6 (1.5)	2 (0.5)
Asthenia	1 (0.3)	0
Chest pain	3 (0.8)	1 (0.3)
Oedema	0	1 (0.3)
Oedema peripheral	1 (0.3)	1 (0.3)
Pyrexia	2 (0.5)	0
Hepatobiliary disorders	1 (0.3)	1 (0.3)
Cholelithiasis	1 (0.3)	0
Hepatic cirrhosis	0	1 (0.3)
Infections and infestations	8 (2.0)	14 (3.6)
Appendicitis	1 (0.3)	1 (0.3)
Bronchitis	1 (0.3)	1 (0.3)
Bronchopneumonia	0	1 (0.3)
Cellulitis	1 (0.3)	1 (0.3)
Gangrene	1 (0.3)	1 (0.3)
Gastroenteritis	1 (0.3)	2 (0.5)
Lobar pneumonia	0	1 (0.3)

Table 15. Treatment-Emergent Serious Adverse Events by System Organ Class and Preferred Term (All Causalities)

Number (%) of Subjects With Adverse Events by: System Organ Class and MedDRA (Version 11.1) Preferred Term	Esreboxetine n (%)	Routine-Care n (%)
Localised infection	1 (0.3)	0
Lower respiratory tract infection	1 (0.3)	0
Osteomyelitis	0	1 (0.3)
Pharyngitis	0	1 (0.3)
Pneumonia	0	3 (0.8)
Postoperative wound infection	1 (0.3)	0
Pulmonary tuberculosis	0	1 (0.3)
Sinusitis	0	2 (0.5)
Urinary tract infection	0	1 (0.3)
Injury, poisoning and procedural complications	1 (0.3)	6 (1.6)
Ankle fracture	0	1 (0.3)
Brain contusion	0	1 (0.3)
Dislocation of vertebra	0	1 (0.3)
Drug toxicity	0	1 (0.3)
Foot fracture	0	1 (0.3)
Lower limb fracture	0	1 (0.3)
Procedural pain	0	1 (0.3)
Tendon rupture	1 (0.3)	0
Investigations	5 (1.3)	0
Blood creatine phosphokinase increased	1 (0.3)	0
Blood glucose fluctuation	1 (0.3)	0
Blood pressure increased	1 (0.3)	0
Electrocardiogram QT prolonged	1 (0.3)	0
Electrocardiogram T wave inversion	1 (0.3)	0
Metabolism and nutrition disorders	12 (3.0)	3 (0.8)
Dehydration	3 (0.8)	1 (0.3)
Diabetes mellitus	0	1 (0.3)
Diabetic ketoacidosis	0	1 (0.3)
Hyperglycaemia	4 (1.0)	0
Hyperkalaemia	2 (0.5)	0
Hypoglycaemia	3 (0.8)	0
Hyponatraemia	2 (0.5)	0
Musculoskeletal and connective tissue disorders	4 (1.0)	0
Arthralgia	2 (0.5)	0
Musculoskeletal chest pain	1 (0.3)	0
Pain in extremity	1 (0.3)	0
Neoplasms benign, malignant and unspecified (including cysts and polyps)	1 (0.3)	1 (0.3)
Basal cell carcinoma	0	1 (0.3)
Malignant melanoma	0	1 (0.3)
Sarcoma	1 (0.3)	0
Nervous system disorders	6 (1.5)	4 (1.0)
Carpal tunnel syndrome	1 (0.3)	1 (0.3)
Loss of consciousness	1 (0.3)	1 (0.3)
Lumbar radiculopathy	1 (0.3)	0
Migraine	1 (0.3)	0
Syncope	1 (0.3)	1 (0.3)
Syncope vasovagal	0	1 (0.3)
Transient ischaemic attack	1 (0.3)	0

Table 15. Treatment-Emergent Serious Adverse Events by System Organ Class and Preferred Term (All Causalities)

Number (%) of Subjects With Adverse Events by: System Organ Class and MedDRA (Version 11.1) Preferred Term	Esreboxetine n (%)	Routine-Care n (%)
Psychiatric disorders	1 (0.3)	2 (0.5)
Confusional state	0	1 (0.3)
Depression	1 (0.3)	0
Mental disorder	0	1 (0.3)
Suicide attempt	0	1 (0.3)
Renal and urinary disorders	4 (1.0)	2 (0.5)
Nephrolithiasis	1 (0.3)	0
Nephropathy	0	1 (0.3)
Renal colic	1 (0.3)	0
Renal failure acute	0	1 (0.3)
Renal pain	1 (0.3)	0
Urinary retention	1 (0.3)	0
Reproductive system and breast disorders	1 (0.3)	0
Prostatomegaly	1 (0.3)	0
Respiratory, thoracic and mediastinal disorders	2 (0.5)	1 (0.3)
Asthma	1 (0.3)	0
Dyspnoea	1 (0.3)	0
Oropharyngeal pain	0	1 (0.3)
Skin and subcutaneous tissue disorders	3 (0.8)	4 (1.0)
Drug eruption	0	1 (0.3)
Neuropathic ulcer	2 (0.5)	0
Rash	1 (0.3)	1 (0.3)
Skin ulcer	1 (0.3)	2 (0.5)
Surgical and medical procedures	3 (0.8)	1 (0.3)
Alcohol detoxification	1 (0.3)	0
Arthrodesis	1 (0.3)	0
Parathyroid gland operation	0	1 (0.3)
Peripheral nerve decompression	1 (0.3)	0
Vascular disorders	5 (1.3)	2 (0.5)
Aortic stenosis	1 (0.3)	0
Haematoma	0	1 (0.3)
Haemorrhage	1 (0.3)	0
Hypertension	2 (0.5)	1 (0.3)
Hypertensive crisis	1 (0.3)	0
Hypotension	1 (0.3)	0

Subjects are only counted once per treatment for each row.
Includes data up to 30 days after last dose of study drug.
MedDRA = Medical Dictionary for Regulatory Activities; n = number of subjects with adverse events.

The treatment related SAEs are presented in Table 16.

Table 16. Serious Adverse Events (Treatment-Related)

Sex/Age	Event[a]	Action Taken	Outcome
Esreboxetine			
Female/57	Hypotension[b]	Permanently withdrawn	Recovered/Resolved
	Sinus tachycardia[b]	Permanently withdrawn	Recovered/Resolved
	Electrocardiogram T wave inversion[b]	Permanently withdrawn	Recovered/Resolved
Female/51	Loss of consciousness	Permanently withdrawn	Recovered/Resolved
Male/60	Renal colic	Permanently withdrawn	Recovered/Resolved
Female/77	Hyperkalemia	Dose not changed	Fatal
	Hyponatremia	Dose not changed	Fatal
	Blood creatinine phosphokinase increased	Dose not changed	Fatal
Male/65	Atrial fibrillation	Permanently withdrawn	Recovered/Resolved
Male/53	Urinary retention	Dose not changed	Unknown
Routine-Care			
Female/37	Suicide attempt	Permanently withdrawn	Unknown

a. Unless otherwise specified, serious adverse event was attributed to esreboxetine.
b. Suspect drug: tolterodine tartrate.

The subjects discontinued from the study are presented in Table 17.

Table 17. Discontinuations From Study

Number (%) of Subjects	Esreboxetine	Routine-Care
	396	384
Discontinuations		
Subject died	1 (0.3)	1 (0.3)
Related to study drug	314 (79.3)	323 (84.1)
Adverse event	45 (11.4)	8 (2.1)
Insufficient clinical response	7 (1.8)	2 (0.5)
Study terminated by sponsor	262 (66.2)	313 (81.5)
Not related to study drug	81 (20.5)	54 (14.1)
Adverse event	9 (2.3)	10 (2.6)
Does not meet entrance criteria	1 (0.3)	1 (0.3)
Lost to follow-up	9 (2.3)	7 (1.8)
Other	9 (2.3)	3 (0.8)
Protocol violation	9 (2.3)	10 (2.6)
Subject no longer willing to participate in study	43 (10.9)	23 (6.0)
Withdrawn due to pregnancy	1 (0.3)	0
Total	396 (100.0)	378 (98.4)

Incidence of Clinical Laboratory Test Abnormalities: For subjects with laboratory test values within the normal limits at Baseline (386 esreboxetine and 382 routine-care), 152 esreboxetine (39%) and 150 routine-care subjects (39%) had at least 1 laboratory test abnormality that met the specified criteria (ie, according to the Sponsor's data standards) while on study treatment or during the lag period.

Ninety-two esreboxetine subjects (25%) and 94 routine-care subjects (26%) had at least 1 abnormal laboratory test result reaching both primary and secondary criteria for abnormality during study treatment or during the lag period.

Laboratory tests that were deemed clinically significant by the Investigator were reported as AEs. The most frequent laboratory tests reported as AEs (experienced by ≥5 subjects in

either treatment group) included increased blood creatinine (6 esreboxetine subjects [1.5%] and 3 routine-care subjects [0.8%]), increased blood urea (5 esreboxetine subjects [1.3%]), and increased HbA_{1c} (3 esreboxetine subjects [0.8%] and 5 routine-care subjects [1.3%]).

Vital Signs: Overall, mean and median changes from Baseline to endpoint in systolic and diastolic BP were small and generally unremarkable. There was a small increase in pulse rate compared with baseline in the [SS]-RBX treatment group that was not observed in the routine-care group. This has been observed in previous [SS]-RBX studies, but the findings from placebo controlled studies should be considered to provide more substantive evidence in this regard.

Vital sign measurements that were deemed clinically significant by the Investigator were reported as AEs and included the following: tachycardia (15 esreboxetine subjects [3.8%] and 5 routine-care subjects [1.3%]), increased heart rate (10 esreboxetine subjects [2.5%]), sinus tachycardia (7 esreboxetine subjects [1.8%] and 1 routine-care subject [0.3%]), increased BP (5 esreboxetine subjects [1.3%]), increased systolic BP (1 routine-care subject [0.3%]), decreased blood pressure (1 esreboxetine subject [0.3%]).

12-Lead Electrocardiogram: Overall, changes in changes in ECG findings from Baseline were small and generally unremarkable. ECG findings that were deemed clinically significant by the Investigator were reported as AEs and included the following: palpitations (5 esreboxetine subjects [1.3%]), ECG signs of myocardial ischemia (1 routine-care subject [0.3%]), cardiac murmur (1 routine-care subject [0.3%]), ECG QT prolonged (1 esreboxetine subject [0.3%] and 2 routine-care subjects [0.5%]), ECG ST-T segment abnormal (1 esreboxetine subject [0.3%]), decreased ECG T wave amplitude (1 esreboxetine subject [0.3%]), and ECG T wave inversion (1 esreboxetine subject [0.3%]).

CONCLUSIONS:

- This study was terminated early by the Sponsor on 08 August 2008. Overall, 643 subjects (300 esreboxetine and 343 routine-care) were treated for at least 6 months, and 367 subjects (155 esreboxetine and 212 routine-care) were treated for at least 1 year.

- Overall, there were no differences in neuropathic pain or other efficacy outcomes including health-related quality of life between esreboxetine and routine-care subjects.

- Esreboxetine was well tolerated, and there were no new or unexpected safety findings or treatment-emergent AEs experienced during this study. The majority of AEs experienced by esreboxetine subjects, ie, constipation and dry mouth, were similar to those previously reported in other esreboxetine studies. Additionally, the increase in pulse rate in the esreboxetine-treated subjects was similar to the increase seen in previous esreboxetine studies.