

**Clinical trial results:**

Multicenter, Double-Blind, Randomized, Placebo-Controlled, Three-Arm, Parallel Group Study to Evaluate the Efficacy and Safety of Oxcarbazepine Extended-Release (OXC XR) (1200 and 2400mg/day) as Adjunctive Therapy in Subjects with Refractory Partial Seizures due to Epilepsy on up to Three Concomitant Anti-epileptic Medications

Summary

EudraCT number	2008-003333-25
Trial protocol	BG
Global end of trial date	29 November 2010

Results information

Result version number	v1 (current)
This version publication date	24 June 2022
First version publication date	24 June 2022

Trial information**Trial identification**

Sponsor protocol code	804P301
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Additional study identifiers

ISRCTN number	-
ClinicalTrials.gov id (NCT number)	NCT00772603
WHO universal trial number (UTN)	-

Notes:

Sponsors

Sponsor organisation name	Supernus Pharmaceuticals, Inc.
Sponsor organisation address	9715 Key West Avenue, Rockville, MD, United States, 20850
Public contact	Jonathan Rubin, MD, Supernus Pharmaceuticals, Inc., jrubin@supernus.com
Scientific contact	Joseph T. Hull, PhD, Supernus Pharmaceuticals, Inc., jhull@supernus.com

Notes:

Paediatric regulatory details

Is trial part of an agreed paediatric investigation plan (PIP)	No
Does article 45 of REGULATION (EC) No 1901/2006 apply to this trial?	No
Does article 46 of REGULATION (EC) No 1901/2006 apply to this trial?	No

Notes:

Results analysis stage

Analysis stage	Final
Date of interim/final analysis	11 August 2011
Is this the analysis of the primary completion data?	Yes
Primary completion date	29 November 2010
Global end of trial reached?	Yes
Global end of trial date	29 November 2010
Was the trial ended prematurely?	No

Notes:

General information about the trial

Main objective of the trial:

The primary objective of this study is to evaluate the efficacy of adjunctive OXC XR (Supernus Pharmaceuticals, Inc.) in the treatment of seizures of partial origin in adults with refractory epilepsy on at least one and up to three other anti-epileptic drugs (AEDs).

Protection of trial subjects:

All potential study participants provided informed consent and were screened to determine his/her eligibility to participate in the study. The screening included a review of medical history and concomitant medication, evaluation of subject's seizure type and frequency, and performing the following clinical assessments: physical exam, neurological exam, vital signs (including blood pressure, pulse rate, respiratory rate, oral body temperature), measure weight and height (body mass index), clinical laboratory testing (hematology/chemistry), electrocardiogram and urine pregnancy test for women of childbearing potential. Eligible subjects who met the inclusion/exclusion criteria, randomized and received study medication were monitored throughout the study, including the above mentioned clinical assessments performed at study visits and assessing concomitant medications and adverse events during treatment and at the end of study.

Background therapy: -

Evidence for comparator: -

Actual start date of recruitment	30 October 2008
Long term follow-up planned	Yes
Long term follow-up rationale	Safety, Efficacy, Ethical reason, Regulatory reason, Scientific research
Long term follow-up duration	12 Months
Independent data monitoring committee (IDMC) involvement?	No

Notes:

Population of trial subjects

Subjects enrolled per country

Country: Number of subjects enrolled	Canada: 2
Country: Number of subjects enrolled	Russian Federation: 90
Country: Number of subjects enrolled	United States: 69
Country: Number of subjects enrolled	Poland: 54
Country: Number of subjects enrolled	Mexico: 45
Country: Number of subjects enrolled	Romania: 24
Country: Number of subjects enrolled	Bulgaria: 53
Country: Number of subjects enrolled	Croatia: 29
Worldwide total number of subjects	366
EEA total number of subjects	160

Notes:

Subjects enrolled per age group	
In utero	0
Preterm newborn - gestational age < 37 wk	0
Newborns (0-27 days)	0
Infants and toddlers (28 days-23 months)	0
Children (2-11 years)	0
Adolescents (12-17 years)	0
Adults (18-64 years)	365
From 65 to 84 years	1
85 years and over	0

Subject disposition

Recruitment

Recruitment details:

This study started to enroll subjects in October of 2008. Randomization of subjects began the earliest in the U.S. (29Dec2008) and later in Mexico (05Oct2009), Eastern Europe (13Nov2009), and Russia (11Feb2010).

Pre-assignment

Screening details:

Adult males and females between 18 and 65 years of age with refractory partial-onset epilepsy of at least 3 countable partial seizures per 28 days on average and being treated with 1 to 3 antiepileptic drugs were eligible. There were 440 subjects screened, 366 subjects randomized, 248 subjects completed the study, and 118 subjects discontinued.

Period 1

Period 1 title	Overall Study (overall period)
Is this the baseline period?	Yes
Allocation method	Randomised - controlled
Blinding used	Double blind
Roles blinded	Subject, Investigator, Monitor, Data analyst, Carer, Assessor

Blinding implementation details:

Randomization for this study was managed centrally by an interactive voice response system (IVRS). Subjects were assigned to OXC XR 2400mg, OXC XR 1200mg, or placebo in a 1:1:1 ratio. During double-blind trial, the subject and all personnel involved with the conduct and interpretation of the study, including Investigators, study site personnel, and Sponsor and CRO clinical staff, will be blinded to treatment assignment. Regardless of treatment assignment, subjects took 4 tablets orally daily.

Arms

Are arms mutually exclusive?	Yes
Arm title	Placebo

Arm description:

Subjects take four identical tablets orally once daily. All four tablets are non-active and are identical to active tablets.

Arm type	Placebo
Investigational medicinal product name	Placebo
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Tablet
Routes of administration	Oral use

Dosage and administration details:

Subjects will take placebo QD along with adjunctive therapy with stable doses of at least one and up to three other AEDs.

Arm title	2400mg/day SPN-804
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Arm description:

Subjects take four identical tablets orally once daily. All four tablets are active drug each containing 600mg OXC XR and are identical to non-active tablets.

Arm type	Experimental
Investigational medicinal product name	Oxcarbazepine extended-release (OXC XR)
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Tablet
Routes of administration	Oral use

Dosage and administration details:

Subjects will take 2400mg total daily dose of OXC XR once a day (QD) along with adjunctive therapy

with stable doses of at least one and up to three other AEDs (cannot include OXC).

Arm title	1200mg/day SPN-804
Arm description: Subjects take four identical tablets orally once daily. Two tablets are active drug each containing 600mg OXC XR and the other two tablets are non-active.	
Arm type	Experimental
Investigational medicinal product name	Oxcarbazepine extended-release (OXC XR)
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Tablet
Routes of administration	Oral use

Dosage and administration details:

Subjects will take 1200mg total daily dose of OXC XR once a day (QD) along with adjunctive therapy with stable doses of at least one and up to three other AEDs (cannot include OXC).

Number of subjects in period 1	Placebo	2400mg/day SPN-804	1200mg/day SPN-804
Started	121	123	122
Completed	95	71	82
Not completed	26	52	40
Consent withdrawn by subject	6	11	10
Physician decision	1	-	-
Others	-	2	-
Adverse event, non-fatal	10	37	18
Other	2	-	-
Subject Non-compliance	4	1	6
Protocol Violation	1	-	1
Lost to follow-up	2	1	5

Baseline characteristics

Reporting groups

Reporting group title	Placebo
Reporting group description:	
Subjects take four identical tablets orally once daily. All four tablets are non-active and are identical to active tablets.	
Reporting group title	2400mg/day SPN-804
Reporting group description:	
Subjects take four identical tablets orally once daily. All four tablets are active drug each containing 600mg OXC XR and are identical to non-active tablets.	
Reporting group title	1200mg/day SPN-804
Reporting group description:	
Subjects take four identical tablets orally once daily. Two tablets are active drug each containing 600mg OXC XR and the other two tablets are non-active.	

Reporting group values	Placebo	2400mg/day SPN-804	1200mg/day SPN-804
Number of subjects	121	123	122
Age categorical			
Number of Adult Subjects by Age Category by Treatment Group			
Units: Subjects			
In utero	0	0	0
Preterm newborn infants (gestational age < 37 wks)	0	0	0
Newborns (0-27 days)	0	0	0
Infants and toddlers (28 days-23 months)	0	0	0
Children (2-11 years)	0	0	0
Adolescents (12-17 years)	0	0	0
Adults (18-64 years)	120	123	122
From 65-84 years	1	0	0
85 years and over	0	0	0
Age continuous			
Mean and Standard Deviation of Adult Subjects by Treatment Group			
Units: years			
arithmetic mean	39.1	38.5	39.1
standard deviation	± 12.49	± 11.58	± 11.51
Gender categorical			
Number of Male and Female Subjects by Treatment Group			
Units: Subjects			
Female	67	64	71
Male	54	59	51
Race			
Number of Subjects By Race by Treatment Group			
Units: Subjects			
White	112	108	108
Black	1	1	5
Asian	0	1	1
American Indian or Alaska Native	0	1	0
Other	8	12	8

Reporting group values	Total		
Number of subjects	366		
Age categorical			
Number of Adult Subjects by Age Category by Treatment Group			
Units: Subjects			
In utero	0		
Preterm newborn infants (gestational age < 37 wks)	0		
Newborns (0-27 days)	0		
Infants and toddlers (28 days-23 months)	0		
Children (2-11 years)	0		
Adolescents (12-17 years)	0		
Adults (18-64 years)	365		
From 65-84 years	1		
85 years and over	0		
Age continuous			
Mean and Standard Deviation of Adult Subjects by Treatment Group			
Units: years			
arithmetic mean			
standard deviation	-		
Gender categorical			
Number of Male and Female Subjects by Treatment Group			
Units: Subjects			
Female	202		
Male	164		
Race			
Number of Subjects By Race by Treatment Group			
Units: Subjects			
White	328		
Black	7		
Asian	2		
American Indian or Alaska Native	1		
Other	28		

End points

End points reporting groups

Reporting group title	Placebo
Reporting group description: Subjects take four identical tablets orally once daily. All four tablets are non-active and are identical to active tablets.	
Reporting group title	2400mg/day SPN-804
Reporting group description: Subjects take four identical tablets orally once daily. All four tablets are active drug each containing 600mg OXC XR and are identical to non-active tablets.	
Reporting group title	1200mg/day SPN-804
Reporting group description: Subjects take four identical tablets orally once daily. Two tablets are active drug each containing 600mg OXC XR and the other two tablets are non-active.	

Primary: Percent change from baseline in seizure frequency during Treatment Phase (Primary Efficacy Endpoint)

End point title	Percent change from baseline in seizure frequency during Treatment Phase (Primary Efficacy Endpoint)
End point description: The primary efficacy endpoint is the median percent change from baseline in seizure frequency per 28 days during Treatment Phase (4 weeks Titration Period + 12 weeks Maintenance Period). This analysis included randomized subjects who took at least one dose of study medication, had seizure diary data during the Baseline Phase, and completed at least one study visit during the Treatment Phase.	
End point type	Primary
End point timeframe: Change at 16 weeks (4 weeks Titration + 12 weeks Maintenance) compared to Baseline	

End point values	Placebo	2400mg/day SPN-804	1200mg/day SPN-804	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	117	111	109	
Units: percent				
median (full range (min-max))	-28.70 (-100.0 to 333.6)	-42.90 (-100.0 to 212.8)	-38.20 (-100.0 to 556.1)	

Statistical analyses

Statistical analysis title	Statistical Analysis 1: 2400mg SPN-804 vs Placebo
Statistical analysis description: A Wilcoxon rank-sum test was used to test hypothesis that there is no difference in the median percent change from baseline in seizure frequency per 28 days during Treatment Phase between SPN-804 and placebo. The sample size of 120 patients per treatment arm provides over 95% power to detect a difference of 31% to 42% between placebo and 2400mg SPN-804 at a two-sided 0.025 level for an overall Type I error rate of 0.050.	
Comparison groups	2400mg/day SPN-804 v Placebo

Number of subjects included in analysis	228
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.003 ^[1]
Method	Wilcoxon (Mann-Whitney)
Parameter estimate	Mean difference (net)
Point estimate	-18.3
Confidence interval	
level	95 %
sides	2-sided
lower limit	-30.4
upper limit	-5.8

Notes:

[1] - P-values reported are not adjusted for multiple comparisons. To preserve the overall Type I error-rate at 0.050, a step-up Hochberg procedure was used for the pair-wise comparisons.

Statistical analysis title	Statistical Analysis 2: 1200mg SPN-804 vs Placebo
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Statistical analysis description:

A Wilcoxon rank-sum test was used to test hypothesis that there is no difference in the median percent change from baseline in seizure frequency per 28 days during Treatment Phase between SPN-804 and placebo. The sample size of 120 patients per treatment arm provides over 95% power to detect a difference of 24% to 32% between placebo and 1200mg SPN-804 at a two-sided 0.025 level for an overall Type I error rate of 0.050.

Comparison groups	1200mg/day SPN-804 v Placebo
Number of subjects included in analysis	226
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.078 ^[2]
Method	Wilcoxon (Mann-Whitney)
Parameter estimate	Mean difference (net)
Point estimate	-10.3
Confidence interval	
level	95 %
sides	2-sided
lower limit	-22.3
upper limit	1.2

Notes:

[2] - P values reported are not adjusted for multiple comparisons. To preserve the overall Type I error-rate at 0.050, a step-up Hochberg procedure was used for the pair-wise comparisons.

Secondary: Percent change from baseline in seizure frequency during Maintenance Period (Secondary Efficacy Endpoint)

End point title	Percent change from baseline in seizure frequency during Maintenance Period (Secondary Efficacy Endpoint)
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End point description:

A secondary efficacy endpoint is the median percent change (PCH) from baseline in seizure frequency per 28 days during Maintenance Period (12 weeks) of the Treatment Phase. This analysis included randomized subjects who took at least one dose of study medication, had seizure diary data during the Baseline Phase, and completed at least one study visit during the Titration Period and one study visit during the Maintenance Period of the Treatment Phase.

End point type	Secondary
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End point timeframe:

Change at 12 weeks (Maintenance Period) compared to Baseline

End point values	Placebo	2400mg/day SPN-804	1200mg/day SPN-804	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	109	88	97	
Units: percent				
median (full range (min-max))	-32.90 (-100.0 to 212.6)	-49.15 (-100.0 to 158.0)	-35.30 (-100.0 to 690.5)	

Statistical analyses

Statistical analysis title	Statistical Analysis 1: 2400mg SPN-804 vs Placebo
Statistical analysis description:	
A Wilcoxon rank-sum test was used to test hypothesis that there is no difference in the median percent change from baseline in seizure frequency per 28 days during Maintenance between SPN-804 and placebo. The sample size of 120 patients per treatment arm provides over 95% power to detect a difference of 31% to 42% between placebo and 2400mg SPN-804 at a two-sided 0.025 level for an overall Type I error rate of 0.050.	
Comparison groups	Placebo v 2400mg/day SPN-804
Number of subjects included in analysis	197
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.004 ^[3]
Method	Wilcoxon (Mann-Whitney)
Parameter estimate	Mean difference (net)
Point estimate	-20.6
Confidence interval	
level	95 %
sides	2-sided
lower limit	-33
upper limit	-6.3

Notes:

[3] - P-values reported are not adjusted for multiple comparisons. To preserve the overall Type I error-rate at 0.050, a step-up Hochberg procedure was used for the pair-wise comparisons.

Statistical analysis title	Statistical Analysis 2: 1200mg SPN-804 vs Placebo
Statistical analysis description:	
A Wilcoxon rank-sum test was used to test hypothesis that there is no difference in the median percent change from baseline in seizure frequency per 28 days during Maintenance between SPN-804 and placebo. The sample size of 120 patients per treatment arm provides over 95% power to detect a difference of 24% to 32% between placebo and 1200mg SPN-804 at a two-sided 0.025 level for an overall Type I error rate of 0.050.	
Comparison groups	1200mg/day SPN-804 v Placebo
Number of subjects included in analysis	206
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.589 ^[4]
Method	Wilcoxon (Mann-Whitney)
Parameter estimate	Mean difference (net)
Point estimate	-3.3

Confidence interval	
level	95 %
sides	2-sided
lower limit	-16.2
upper limit	9.7

Notes:

[4] - P-values reported are not adjusted for multiple comparisons. To preserve the overall Type I error-rate at 0.050, a step-up Hochberg procedure was used for the pair-wise comparisons.

Secondary: Responder Rate at end of Treatment Phase (Secondary Efficacy Endpoint)

End point title	Responder Rate at end of Treatment Phase (Secondary Efficacy Endpoint)
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End point description:

A secondary efficacy endpoint is the percentage of subjects with a positive response (defined as a 50% or greater reduction in the change from baseline seizure frequency per 28 days) at end of Treatment Phase. This analysis included randomized subjects who took at least one dose of study medication, had seizure diary data during the Baseline Phase, and completed at least one study visit during the Treatment Phase.

End point type	Secondary
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End point timeframe:

At the end of 16 weeks (4 wks Titration + 12 wks Maintenance)

End point values	Placebo	2400mg/day SPN-804	1200mg/day SPN-804	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	121	123	122	
Units: percent				
number (not applicable)	28.1	40.7	36.1	

Statistical analyses

Statistical analysis title	Statistical Analysis 1: 2400mg SPN-804 vs Placebo
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Statistical analysis description:

The treatment response was analyzed using a logistic regression model with treatment group as a factor and country (or cluster), age, sex, and baseline seizure frequency per 28 days as explanatory variables.

Comparison groups	Placebo v 2400mg/day SPN-804
Number of subjects included in analysis	244
Analysis specification	Pre-specified
Analysis type	superiority ^[5]
P-value	= 0.018
Method	Regression, Logistic
Parameter estimate	Odds ratio (OR)
Point estimate	1.983
Confidence interval	
level	95 %
sides	2-sided
lower limit	1.126
upper limit	3.494

Notes:

[5] - The treatment response was analyzed using a logistic regression model with treatment group as a factor and country (or cluster), age, sex, and baseline seizure frequency per 28 days as explanatory variables.

Statistical analysis title	Statistical Analysis 2: 1200mg SPN-804 vs Placebo
Statistical analysis description: The treatment response was analyzed using a logistic regression model with treatment group as a factor and country (or cluster), age, sex, and baseline seizure frequency per 28 days as explanatory variables.	
Comparison groups	1200mg/day SPN-804 v Placebo
Number of subjects included in analysis	243
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.075
Method	Regression, Logistic
Parameter estimate	Odds ratio (OR)
Point estimate	1.67
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.95
upper limit	2.937

Secondary: Seizure-Free Rates during the Treatment Phase (Secondary Efficacy Endpoint)

End point title	Seizure-Free Rates during the Treatment Phase (Secondary Efficacy Endpoint)
End point description: A secondary efficacy endpoint is the percentage of subjects who did not experience a seizure during the Treatment Phase. This analysis included randomized subjects who took at least one dose of study medication, had seizure diary data during the Baseline Phase, and completed at least one study visit during the Treatment Phase.	
End point type	Secondary
End point timeframe: At the end of 16 weeks (4 wks Titration + 12 wks Maintenance)	

End point values	Placebo	2400mg/day SPN-804	1200mg/day SPN-804	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	121	123	122	
Units: percent				
number (not applicable)	3.3	11.4	4.9	

Statistical analyses

Statistical analysis title	Statistical Analysis 1: 2400mg SPN-804 vs Placebo
Statistical analysis description: Pairwise comparisons of OXC XR 2400mg/day vs. placebo seizure-free rates during the Treatment Phase were made by means of Fisher's exact test for the ITT population.	
Comparison groups	Placebo v 2400mg/day SPN-804
Number of subjects included in analysis	244
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.013
Method	Fisher exact

Statistical analysis title	Statistical Analysis 2: 1200mg SPN-804 vs Placebo
Statistical analysis description: Pairwise comparisons of OXC XR 1200mg/day vs. placebo seizure-free rates during the Treatment Phase were made by means of Fisher's exact test for the ITT population.	
Comparison groups	Placebo v 1200mg/day SPN-804
Number of subjects included in analysis	243
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.528
Method	Fisher exact

Secondary: Seizure Free Rate during Maintenance Period (Secondary Efficacy Endpoint)

End point title	Seizure Free Rate during Maintenance Period (Secondary Efficacy Endpoint)
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End point description:

A secondary efficacy endpoint is the percentage of subjects who did not experience a seizure during Maintenance Period of Treatment Phase. This analysis included randomized subjects who took at least one dose of study medication, had seizure diary data during the Baseline Phase, and completed at least one study visit during the Titration Period and one study visit during the Maintenance Period of the Treatment Phase.

End point type	Secondary
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End point timeframe:

At the end of 12 weeks (Maintenance Period)

End point values	Placebo	2400mg/day SPN-804	1200mg/day SPN-804	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	121	123	122	
Units: percent				
number (not applicable)	5.8	13.8	3.3	

Statistical analyses

Statistical analysis title	Statistical Analysis 1: 2400mg SPN-804 vs Placebo
Statistical analysis description: Pairwise comparisons of OXC XR 2400mg/day vs. placebo seizure-free rates during the Maintenance Period were made by means of Fisher's exact test for the ITT population.	
Comparison groups	Placebo v 2400mg/day SPN-804
Number of subjects included in analysis	244
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.008
Method	Fisher exact

Statistical analysis title	Statistical Analysis 2: 1200mg SPN-804 vs Placebo
Statistical analysis description: Pairwise comparisons of OXC XR 1200mg/day vs. placebo seizure-free rates during the Maintenance Period were made by means of Fisher's exact test for the ITT population.	
Comparison groups	1200mg/day SPN-804 v Placebo
Number of subjects included in analysis	243
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.546
Method	Fisher exact

Adverse events

Adverse events information

Timeframe for reporting adverse events:

Up to 20 weeks (4 weeks Titration + 12 Weeks Maintenance + up to 4 weeks Tapering/Conversion)

Adverse event reporting additional description:

The number of subjects reported in each treatment arm for serious adverse events and non-serious adverse events is based on the Safety Population, defined as all randomized subjects who took at least one dose of study medication.

Assessment type	Systematic
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Dictionary used

Dictionary name	MedDRA
Dictionary version	11.1

Reporting groups

Reporting group title	Placebo
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Reporting group description:

Subjects take four identical tablets orally once daily. All four tablets are non-active and are identical to active tablets.

Reporting group title	2400mg/day SPN-804
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Reporting group description:

Subjects take four identical tablets orally once daily. All four tablets are active drug each containing 600mg OXC XR and are identical to non-active tablets.

Reporting group title	1200mg/day SPN-804
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Reporting group description:

Subjects take four identical tablets orally once daily. Two tablets are active drug each containing 600mg OXC XR and the other two tablets are non-active.

Serious adverse events	Placebo	2400mg/day SPN-804	1200mg/day SPN-804
Total subjects affected by serious adverse events			
subjects affected / exposed	7 / 121 (5.79%)	10 / 123 (8.13%)	7 / 122 (5.74%)
number of deaths (all causes)	0	0	0
number of deaths resulting from adverse events			
Investigations			
Alanine aminotransferase increased			
subjects affected / exposed	1 / 121 (0.83%)	0 / 123 (0.00%)	0 / 122 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Aspartate aminotransferase increased			
subjects affected / exposed	1 / 121 (0.83%)	0 / 123 (0.00%)	0 / 122 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Lactate dehydrogenase increased			

subjects affected / exposed	1 / 121 (0.83%)	0 / 123 (0.00%)	0 / 122 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Neoplasms benign, malignant and unspecified (incl cysts and polyps)			
Ovarian cancer			
subjects affected / exposed	1 / 121 (0.83%)	0 / 123 (0.00%)	0 / 122 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Pituitary tumour benign			
subjects affected / exposed	0 / 121 (0.00%)	1 / 123 (0.81%)	0 / 122 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Injury, poisoning and procedural complications			
Arthropod bite			
subjects affected / exposed	0 / 121 (0.00%)	1 / 123 (0.81%)	0 / 122 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Head injury			
subjects affected / exposed	0 / 121 (0.00%)	1 / 123 (0.81%)	0 / 122 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Skin laceration			
subjects affected / exposed	0 / 121 (0.00%)	0 / 123 (0.00%)	1 / 122 (0.82%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Skull fractured base			
subjects affected / exposed	0 / 121 (0.00%)	0 / 123 (0.00%)	1 / 122 (0.82%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Vascular disorders			
Deep vein thrombosis			

subjects affected / exposed	1 / 121 (0.83%)	0 / 123 (0.00%)	0 / 122 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Cardiac disorders			
Acute myocardial infarction			
subjects affected / exposed	0 / 121 (0.00%)	0 / 123 (0.00%)	1 / 122 (0.82%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Nervous system disorders			
Convulsions/complex partial seizures			
subjects affected / exposed	1 / 121 (0.83%)	1 / 123 (0.81%)	0 / 122 (0.00%)
occurrences causally related to treatment / all	0 / 1	1 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Dizziness			
subjects affected / exposed	1 / 121 (0.83%)	1 / 123 (0.81%)	0 / 122 (0.00%)
occurrences causally related to treatment / all	1 / 1	1 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Ischaemic stroke			
subjects affected / exposed	0 / 121 (0.00%)	2 / 123 (1.63%)	0 / 122 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 2	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Nystagmus			
subjects affected / exposed	0 / 121 (0.00%)	1 / 123 (0.81%)	0 / 122 (0.00%)
occurrences causally related to treatment / all	0 / 0	1 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Post-ictal state			
subjects affected / exposed	0 / 121 (0.00%)	0 / 123 (0.00%)	1 / 122 (0.82%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Status epilepticus			
subjects affected / exposed	0 / 121 (0.00%)	0 / 123 (0.00%)	1 / 122 (0.82%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
General disorders and administration			

site conditions			
Drug intolerance			
subjects affected / exposed	0 / 121 (0.00%)	2 / 123 (1.63%)	0 / 122 (0.00%)
occurrences causally related to treatment / all	0 / 0	2 / 2	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Gastrointestinal disorders			
Vomiting			
subjects affected / exposed	0 / 121 (0.00%)	1 / 123 (0.81%)	0 / 122 (0.00%)
occurrences causally related to treatment / all	0 / 0	1 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Skin and subcutaneous tissue disorders			
Pityriasis rosea			
subjects affected / exposed	0 / 121 (0.00%)	0 / 123 (0.00%)	1 / 122 (0.82%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Rash erythematous			
subjects affected / exposed	1 / 121 (0.83%)	0 / 123 (0.00%)	0 / 122 (0.00%)
occurrences causally related to treatment / all	1 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Rash generalized			
subjects affected / exposed	0 / 121 (0.00%)	1 / 123 (0.81%)	0 / 122 (0.00%)
occurrences causally related to treatment / all	0 / 0	1 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Stevens-Johnson Syndrome			
subjects affected / exposed	1 / 121 (0.83%)	0 / 123 (0.00%)	0 / 122 (0.00%)
occurrences causally related to treatment / all	1 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Infections and infestations			
Gastroenteritis			
subjects affected / exposed	1 / 121 (0.83%)	0 / 123 (0.00%)	0 / 122 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Metabolism and nutrition disorders			
Dehydration			

subjects affected / exposed	1 / 121 (0.83%)	0 / 123 (0.00%)	0 / 122 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Hyponatremia			
subjects affected / exposed	0 / 121 (0.00%)	1 / 123 (0.81%)	0 / 122 (0.00%)
occurrences causally related to treatment / all	0 / 0	1 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0

Frequency threshold for reporting non-serious adverse events: 0.05 %

Non-serious adverse events	Placebo	2400mg/day SPN-804	1200mg/day SPN-804
Total subjects affected by non-serious adverse events			
subjects affected / exposed	55 / 121 (45.45%)	69 / 123 (56.10%)	57 / 122 (46.72%)
Nervous system disorders			
Balance disorder			
subjects affected / exposed	6 / 121 (4.96%)	8 / 123 (6.50%)	6 / 122 (4.92%)
occurrences (all)	7	12	11
Dizziness			
subjects affected / exposed	18 / 121 (14.88%)	50 / 123 (40.65%)	24 / 122 (19.67%)
occurrences (all)	21	60	30
Headache			
subjects affected / exposed	9 / 121 (7.44%)	19 / 123 (15.45%)	10 / 122 (8.20%)
occurrences (all)	12	21	10
Somnolence			
subjects affected / exposed	11 / 121 (9.09%)	17 / 123 (13.82%)	14 / 122 (11.48%)
occurrences (all)	12	19	14
General disorders and administration site conditions			
Asthenia			
subjects affected / exposed	1 / 121 (0.83%)	9 / 123 (7.32%)	4 / 122 (3.28%)
occurrences (all)	2	9	4
Fatigue			
subjects affected / exposed	1 / 121 (0.83%)	4 / 123 (3.25%)	7 / 122 (5.74%)
occurrences (all)	1	5	7
Eye disorders			

Diplopia subjects affected / exposed occurrences (all)	5 / 121 (4.13%) 5	16 / 123 (13.01%) 21	12 / 122 (9.84%) 15
Gastrointestinal disorders Vomiting subjects affected / exposed occurrences (all)	11 / 121 (9.09%) 11	19 / 123 (15.45%) 20	7 / 122 (5.74%) 10

More information

Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? No

Interruptions (globally)

Were there any global interruptions to the trial? No

Limitations and caveats

None reported