SUPERNUS PHARMACEUTICALS INC

FORM 8-K
(Current report filing)

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SECURITIES AND EXCHANGE COMMISSION
Washington, D.C. 20549

FORM 8-K
CURRENT REPORT
Pursuant to Section 13 or 15(d) of the Securities Exchange Act of 1934
Date of Report (Date of earliest event reported): December 9, 2013

Supernus Pharmaceuticals, Inc.
(Exact name of registrant as specified in its charter)

Delaware
(State or other jurisdiction of Incorporation)

1550 East Gude Drive, Rockville MD
(Address of principal executive offices)

Registrant’s telephone number, including area code: (301) 838-2500

Not Applicable
(Former name or former address, if changed since last report.)

Check the appropriate box below if the Form 8-K filing is intended to simultaneously satisfy the filing obligation of the registrant under any of the following provisions (see General Instruction A.2. below):

☐ Written communications pursuant to Rule 425 under the Securities Act (17 CFR 230.425)
☐ Soliciting material pursuant to Rule 14a-12 under the Exchange Act (17 CFR 240.14a-12)
☐ Pre-commencement communications pursuant to Rule 14d-2(b) under the Exchange Act (17 CFR 240.14d-2(b))
☐ Pre-commencement communications pursuant to Rule 13e-4(c) under the Exchange Act (17 CFR 240.13e-4(c))
Item 8.01  Other Events.

On December 12, 2013, Supernus issued a press release announcing that the clinical data that was released at the American Epilepsy Society (AES) Meeting in December in Washington DC is now available on the Company website, a copy of which is furnished as Exhibit 99.1 hereto and is incorporated herein by reference.

The Company was notified that, in line with standard FDA guidance and practice, the FDA did not grant Supernus three years of marketing exclusivity for Trokendi XR. That is common for products approved without a pivotal Phase III Clinical Study which was the case for Trokendi XR.

Item 9.01  Financial Statements and Exhibits

(d) Exhibits

The following documents are furnished as Exhibits pursuant to Item 8.01 hereof:

Exhibit 99.2 — Clinical Data.
Pursuant to the requirements of the Securities Exchange Act of 1934, the registrant has duly caused this report to be signed on its behalf by the undersigned hereunto duly authorized.

SUPERNUS PHARMACEUTICALS, INC.

DATED: December 13, 2013

By: /s/ Gregory S. Patrick
Gregory S. Patrick
Vice-President and Chief Financial Officer
<table>
<thead>
<tr>
<th>Number</th>
<th>Description</th>
<th>Attached</th>
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<tbody>
<tr>
<td>99.2</td>
<td>Clinical Data</td>
<td>Attached</td>
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FOR IMMEDIATE RELEASE

Supernus Posts Exciting Clinical Data Regarding Trokendi XR™ and Oxtellar XR™
on the Company Website

Rockville, MD, December 12, 2013 — Supernus Pharmaceuticals, Inc. (NASDAQ: SUPN), a specialty pharmaceutical company, today announced that the clinical data that was released at the American Epilepsy Society (AES) Meeting in December in Washington DC is now available on its website. Please click here to view.

In total, Supernus had 12 presentations/scientific posters highlighting data that were generated on Trokendi XR and Oxtellar XR. For a complete read on the data and scientific posters please refer to the link above or go to our website under the investor and events & presentations section.

Some of the key and exciting highlights from the data include:

**Trokendi XR™:**

An overwhelming majority of patients (93%) preferred once daily Trokendi XR when switched from twice daily immediate release topiramate. Similarly, 92% of the patients with epilepsy also expect Trokendi XR to have a positive impact on treatment adherence.

In a head to head study, once daily Trokendi XR was bioequivalent to twice daily immediate release topiramate and showed a potential pharmacodynamic difference with a significantly less negative impact on objective measures of cognitive function such as verbal fluency (i.e., Controlled Oral Word Association, COWA).

Trokendi XR offers the convenience of once-daily topiramate dosing without increasing the clinical risk of missed, delayed, or doubled doses.

Co-administration of Trokendi XR with alcohol in humans does not result in “dose dumping.” Patients will have similar systemic exposure whether Trokendi XR is taken with or without alcohol.

Dosage recommendations for Trokendi XR in elderly patients are the same as for immediate release topiramate, i.e., reduce dose according to renal function status rather than age (one-half the adult dose if creatinine clearance <70mL/min/1.73m²).

**Oxtellar XR™:**

Seizure control achieved with once-daily Oxtellar XR during the double-blind PROSPER study was maintained and further improved during the long term open-label extension when dosages could be optimized. Oxtellar XR showed impressive median % seizure reduction up to 64% with responder rates (% of patients with >50% seizure reduction) overtime up to 61%.

Oxtellar XR was very well tolerated during long-term maintenance therapy with discontinuations due to adverse events of only 5%. Such improved tolerability may allow higher and potentially more effective Oxcarbazepine dosages to be achieved with once daily Oxtellar XR.
About Trokendi XR™

Trokendi XR is the only approved novel once-daily extended release formulation of topiramate for the treatment of epilepsy. Trokendi XR is an antiepileptic drug indicated for initial monotherapy in patients 10 years of age and older with partial onset or primary generalized tonic-clonic seizures; adjunctive therapy in patients 6 years of age and older with partial onset or primary generalized tonic-clonic seizures; and adjunctive therapy in patients 6 years of age and older with seizures associated with Lennox-Gastaut syndrome. The product is available in 25mg, 50mg, 100mg and 200mg extended-release capsules.

For full prescribing and safety information, click here.

About Oxtellar XR™

Oxtellar XR is the only approved novel once-daily extended release formulation of oxcarbazepine for the treatment of epilepsy. It is an antiepileptic drug indicated for adjunctive therapy in the treatment of partial seizures in adults and in children 6 to 17 years of age. The product is available in 150 mg, 300 mg and 600 mg extended-release tablets.

For full prescribing and safety information, click here.

About Supernus Pharmaceuticals, Inc.

Supernus Pharmaceuticals, Inc. is a specialty pharmaceutical company focused on developing and commercializing products for the treatment of central nervous system, or CNS, diseases. The Company has two marketed products for epilepsy, Oxtellar XR™ (extended-release oxcarbazepine) and Trokendi XR™ (extended-release topiramate). The Company is also developing several product candidates in psychiatry to address large market opportunities in ADHD, including ADHD patients with impulsive aggression. These product candidates include SPN-810 for impulsive aggression in ADHD and SPN-812 for ADHD.

Forward Looking Statements

This press release contains forward-looking statements regarding clinical data and the potential for Trokendi XR and Oxtellar XR to treat epilepsy. Actual results may differ materially from those in these forward-looking statements as a result of various factors, including, but not limited to, risks regarding the company’s ability to commercialize the product successfully, whether physicians will prescribe and patients will use the product, and competition in the market. For a further description of these and other risks facing the Company, please see the risk factors described in the Company’s Annual Report Form 10-K that was filed with the United States Securities and Exchange Commission on March 15, 2013 and under the caption “Risk Factors” and the updates to these risk factors in the Company’s quarterly report form 10-Q that was filed with the Commission on August 15, 2013. Forward-looking statements speak only as of the date of this press release, and the company undertakes no obligation to update or revise these statements, except as may be required by law.

CONTACTS:
Jack A. Khattar, President and CEO
Gregory S. Patrick, Vice President and CFO
Supernus Pharmaceuticals, Inc.
Tel: (301) 838-2591
Steady-State Bioequivalence of Extended-Release, Once-Daily Trokendi XR™ (SPN-538) to Immediate-Release Topiramate (TPM-IR, Topamax®)

**Background**
Trokendi XR™ is an extended-release, once-daily topiramate (TPM-IR) formulation, while Topamax® is an immediate-release formulation. To assess bioequivalence, a single-blind, randomized-sequence crossover study was conducted in healthy volunteers. The primary endpoints were bioequivalence parameters—AUC0-24, Cmax, and Cmin—90% CIs of all three steady-state SPN-538/TPM-IR ratios fell within 80%-125% bioequivalence.

**Study Features**
- **Subjects**: Healthy non-smoking adults, age 18-55 years
- **Doses**: 200 mg SPN-538 QD (AM dosing active drug; PM dose, placebo capsule) vs 100 mg TPM-IR Q12h
- **Design**: Single-blind, randomized-sequence crossover
- **Primary PK endpoints**: AUC0-24, Cmax, Cmin

**Study Outcomes**: Bioequivalence of extended-release, once-daily Trokendi XR™ (SPN-538) vs immediate-release Topamax® (TPM-IR) in healthy volunteers.

**Conclusions**: Trokendi XR™ (SPN-538) is bioequivalent to Topamax® (TPM-IR) in terms of peak plasma concentration and area under the curve. This finding supports its use as a potential alternative to Topamax® for patients requiring extended-release topiramate.

**Adverse Events**
- Mild adverse events were reported, with no significant differences between treatments. Common adverse effects included dizziness, attention disturbance, somnolence, and dysgeusia. No deaths or serious adverse events were reported.
Once-Daily Trokendi XR™ (SPN-538) vs Twice-Daily Topamax®: Impact of Nonadherence on Topiramate Concentrations

S. Brittain
Supernus Pharmaceuticals, Inc., Rockville, MD

Background

Trokendi XR™, Supernus Pharmaceuticals, Inc.) is a novel extended-release, once-daily formulation of topiramate (TPM) that may improve compliance compared to twice-daily dosing. The impact of nonadherence on topiramate concentrations was studied using a randomized, single-dose, crossover design (fed/fasted, in single-dose, randomized sequence) in 31 adult volunteers. Data were used to develop a population PK model validated in patients with epilepsy to predict PK consequences of dosing irregularities.

Methods

Single-dose, randomized, single-dose crossover study with intensive PK sampling on three occasions in adult volunteers. Data were analyzed using a marketed marketed structural population PK model, developed using RISC® (Research Insight Software). Covariates included concomitant use of enzyme-inducing AEDs (EIA EDs); body weight. The final model was validated using visual predictive check and bootstrap analysis of 500 datasets obtained from the original dataset using sampling with replacement.

Results

Compared to twice-daily (TPM-IR Q12h) dosing, once-daily (TPM-IR QD) dosing resulted in topiramate concentrations that were 17% lower at 12 h and 27% lower at 24 h. When a dose is missed and restored by doubling the dosage at the next scheduled time, the impact of nonadherence on topiramate concentrations is consistent regardless of AED cotherapy. Times to minimum (Cmin) were reduced by 19% compared to twice-daily dosing. The impact of nonadherence on topiramate concentrations is consistently greater in the presence of EIA EDs (data not shown). Dosings irregularities with SPN-538 QD should pose no greater risk than TPM-IR dosing.

Conclusions

Despite potential advantages of QD dosing, clinicians may be hesitant to switch to once-daily dosing. Randomized controlled trials have not explored the recommended Q12h regimen in prescribing information. Despite potential advantages of QD dosing, clinicians may be hesitant to switch to once-daily dosing. Randomized controlled trials have not explored the recommended Q12h regimen in prescribing information. Despite potential advantages of QD dosing, clinicians may be hesitant to switch to once-daily dosing. Randomized controlled trials have not explored the recommended Q12h regimen in prescribing information.
Pharmacokinetic Rationale for mg-to-mg Overnight Switch from Twice-Daily Immediate-Release Topiramate (TPM-IR) to Once-Daily, Extended-Release Trokand XR™ (SPN-538)

Background
Phenytoin is a non-inducing ("neutral") AED, while carbamazepine, valproate, and lamotrigine are enzyme-inducing AEDs. To study the potential impact of co-concomitant AEDs on topiramate (TPM) pharmacokinetics, a 2-period, 1-sequence open-label, 2-treatment, crossover study was conducted in patients on stable TPM-IR therapy. The study evaluated the PK effects of switching from TPM-IR Q12h to the novel extended-release, once-daily formulation of TPM, Trokand XR™ (SPN-538) QD, at identical daily dosages.

Study Features
- **Design:** Open-label, multi-center, 2-period, 1-sequence crossover study.
- **AEDs:** Co-concomitant AEDs (1-3) were permitted, including non-inducing ("neutral") or enzyme-inducing AEDs.
- **Co-concomitant AEDs:** 15% lamotrigine, 14% valproate, 12% phenytoin, and 9% levetiracetam were used as co-concomitant AEDs.
- **TPM-IR Treatment:** TPM-IR regimen was maintained at identical daily dosages for 14 days prior to switching.
- **TPM-IR Switch:** Switched to SPN-538 QD at identical daily dosages at study entry.

Results
- **TPM Plasma Concentration Profiles:** After first dose, steady-state TPM levels were maintained when SPN-538 QD was substituted for TPM-IR Q12h at identical daily dosages, regardless of co-concomitant AEDs (neutral or enzyme-inducing).
- **Clinical Full Profile:** Mean plasma concentration-time profiles of TPM were maintained when SPN-538 QD was substituted for TPM-IR Q12h, mimicking clinical practice of an IR-to-ER switch.

Conclusions
The study results support the potential impact of co-concomitant AEDs on TPM pharmacokinetics. The novel extended-release, once-daily formulation of TPM (Trokand XR™) may improve tolerability and adherence compared to the immediate-release, twice-daily formulation.

*Authors:* J. Stocks, J. Johnson, S. Britain, P. Baroldi. 
*Supernus Pharmaceuticals, Inc., Rockville, MD; 2 formerly with Supernus Background Extended-release (ER) antiepileptic drugs (AEDs) offer potential tolerability and adherence benefits. The study evaluated the PK effects of switching from TPM-IR to SPN-538 QD at identical daily dosages.
Background

Background, Immediate-release (IR) topiramate (TPM-IR) is associated with distinct cognitive side effects, a matter of concern especially for long-term therapy. However, the extent of these effects is not clear in patients taking extended-release, once-daily monitoring (SPN-538) versus IR TPM-IR at identical doses have a significant difference and determine if this difference has a clinically significant impact on absorption from SPN-538 20-fold slower than from TPM-IR (separate study findings). Point estimates for partial AUCs in this study were scores with TPM-IR in this study were smaller than in other studies in phase 3 trials.

Cognitive assessments (COWA) testing occurred pre-dose (end of dosing interval) when mean Cmin for SPN-538 and TPM-IR was 2006; 2:126-33.6. Lee HW, Jung DK, Suh CK et al. Epilepsy Behav 2006; 8:376-41.

TPM-IR Q12 h on sensor object measures of verbal fluency (i.e., Controlled Oral Word Association, COWA), despite PK narrowness over time or b) the full extent of the difference between formulations. Mechanism for a PK-PD relationship sensitive to bioequivalence by traditional PK criteria and more rigorous parameter of partial AUCs.* Studies are needed to confirm finding that SPN-538

50 SPN-538 0.6 1.5 -0.4, 3.3 0.13 0.49 TPM-IR -0.8 100 SPN-538 1.9 3.6 1.7, 5.5

Results

Null hypothesis: no difference between groups. Extensive statistical analysis was performed to evaluate differences between TPM-IR and SPN-538 groups. Between-treatment differences were modest (~2)

Conclusions

Observations suggest that changes in cognitive measures between the two formulations are consistent with bioequivalence, but more rigorous analyses are needed to confirm these findings.

Subjects 0 5 10 15 20 25 30 35 40 Within-subject Standard Deviation SD -3 -2 -1 -1/3 1/3 1 2 3 SD 0 5 10 15 20 25 30 35 40 Clinically

Within-subject standard deviation (SD) and 95% CIs were included to assess clinically meaningful differences across treatments. The results from the analysis of covariance (ANCOVA) with repeated measures were consistent with the ANOVA, and the significant differences between TPM-IR and SPN-538 observed in COWA testing were maintained in the ANCOVA analysis.
Linearit y and Dose Strength Equivalence of Once-Daily, Extended-Release Topiramate (Trokendi XR™, SPN-538)

C. Brown, J. Britton, J. Stock\footnote{Formerly with Supernus Pharmaceuticals, Inc.} \& P. Goossens

Supernus Pharmaceuticals, Inc., Frederick, MD, United States

Study Highlights

- Dose linearity observed
- No gender effects observed
- No differences between dose strengths

Methods

Healthy volunteers

- 200-mg doses administered for four treatment periods
- PK analysis: standard non-compartmental methods and descriptive statistics
- Mixed-model analysis of variance (ANOVA) to test for dose linearity

Results

Dose linearity

<table>
<thead>
<tr>
<th>Dose Level</th>
<th>Plasma Concentration (mg/mL)</th>
</tr>
</thead>
<tbody>
<tr>
<td>25</td>
<td>0.05</td>
</tr>
<tr>
<td>50</td>
<td>0.10</td>
</tr>
<tr>
<td>100</td>
<td>0.20</td>
</tr>
<tr>
<td>200</td>
<td>0.40</td>
</tr>
</tbody>
</table>

No gender effects observed

- No differences between dose strengths

Conclusions

Dose linearity is observed with once-daily, extended-release topiramate (Trokendi XR™, SPN-538) in healthy volunteers.

For questions about the data presented above, please contact the Medical Affairs Department of Supernus Pharmaceuticals via ProSar Corporation.
Pharmacokinetics of Once-Daily, Extended-Release, Trokendi XR™ (SPN-538) in the Elderly

W. O'Neal1, S. Brittain1, J. Stocks1, J. Johnson1, P. Baroldi2
1 Supernus Pharmaceuticals, Inc., Rockville, MD; 2 formerly with Supernus Background

Background

Once-daily extended-release formulation of topiramate (Topamax®) is approved by the FDA for adjunctive therapy in adults with partial-onset seizures. This study investigated the pharmacokinetics of once-daily, extended-release Trokendi XR™ (SPN-538) in elderly subjects.

Study Design

• Single-center, single-dose, parallel-group, open-label study
• 100 mg SPN-538 under fasting conditions

Results

• PK parameters were comparable in elderly and younger adults
• Mean clearance was 36% lower in elderly subjects
• Mean elimination half-life of 47 hours in younger adults

Table 1: PK Parameters

<table>
<thead>
<tr>
<th>Parameter</th>
<th>Elderly (n=13)</th>
<th>Younger (n=18)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Cmax (mg/L)</td>
<td>1.23 (0.30)</td>
<td>1.64 (0.53)</td>
</tr>
<tr>
<td>AUC0-t</td>
<td>11.1 (3.3)</td>
<td>13.6 (3.9)</td>
</tr>
<tr>
<td>Tmax (hr)</td>
<td>24.0 (12.0)</td>
<td>16.1 (7.0)</td>
</tr>
</tbody>
</table>

• Elderly adults had higher peak level and greater overall TPM exposure in vs. Younger adults. The increase in TPM exposure was consistent with reduction in estimated renal function (i.e., calculated creatinine clearance) and similar to results seen with TPM-IR in an elderly population.

Conclusions

• Elderly and younger adults had similar PK parameter profiles for SPN-538.
• Elderly patients tolerated SPN-538 similarly to younger adults.
• Dosage recommendations for SPN-538 in elderly patients are the same as for TPM-IR, i.e., reduce dose according to estimated renal function (i.e., calculated creatinine clearance).

Side effects:

• Elderly adults had more reported adverse events than younger adults, including:
  - Headache
  - Puncture site hemorrage
  - Somnolence
  - Dysgeusia

No serious AEs, deaths, or serious treatment-related AEs occurred.

References

Efficacy and Safety of Extended-release Oxcarbazepine (Oxtellar XR™) as Adjunctive Therapy in Patients with Refractory Partial-onset Seizures: A Randomized Controlled Trial

**Background**

Oxcarbazepine (OXC) is an antiepileptic drug that is approved for the treatment of partial-onset seizures. It is available in immediate-release (OCX-IR) and extended-release forms. Oxcarbazepine extended-release tablets (Oxtellar XR™) are formulated to deliver a constant plasma concentration of the drug over a 12-hour period. This study aimed to evaluate the efficacy and safety of Oxtellar XR™ as an adjunctive therapy in patients with refractory partial-onset seizures.

**Study Design**

The study was a multicenter, international, randomized, double-blind, placebo-controlled trial. Patients were randomized to two treatment groups: Oxtellar XR™ 1200 mg once-daily (QD) and placebo. The primary endpoint was seizure-free rates over 16 weeks.

**Results**

**Demographics and Baseline Characteristics**

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>Placebo</th>
<th>Oxtellar XR™ 1200 mg QD</th>
</tr>
</thead>
<tbody>
<tr>
<td>No. of patients</td>
<td>121</td>
<td>122</td>
</tr>
<tr>
<td>Age (years)</td>
<td>20-60</td>
<td>20-60</td>
</tr>
<tr>
<td>Sex</td>
<td>M/F</td>
<td>M/F</td>
</tr>
<tr>
<td>Seizure type</td>
<td>Partial</td>
<td>Partial</td>
</tr>
<tr>
<td>Seizure frequency</td>
<td></td>
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</tbody>
</table>

**Pragmatic Intent-to-Treat (ITT) Analysis of Seizure-Free Population**

- **ITT Population**: All randomized patients who received at least one dose of study drug, had baseline seizures, and were seizure-free for at least 16 weeks post-baseline were included.
- **ITT Test**: Wilcoxon rank-sum test with overall Type I error rate = 0.050 using step-up Hochberg procedures.
- **Results**: Oxtellar XR™ 1200 mg QD was significantly superior to placebo in terms of seizure-free rates (p < 0.025).

**Conclusion**

Oxtellar XR™ 1200 mg QD was significantly superior to placebo in terms of seizure-free rates over 16 weeks. This finding supports the use of Oxtellar XR™ as an effective and safe adjunctive therapy in patients with refractory partial-onset seizures.

**References**


**Discussions**

This study provides evidence for the efficacy and safety of Oxtellar XR™ as an adjunctive therapy in patients with refractory partial-onset seizures. The results support the use of Oxtellar XR™ in clinical practice, offering an alternative treatment option for patients who do not respond adequately to other antiepileptic drugs.

**Conclusions**

Oxtellar XR™ 1200 mg QD was significantly superior to placebo in terms of seizure-free rates over 16 weeks. This finding supports the use of Oxtellar XR™ as an effective and safe adjunctive therapy in patients with refractory partial-onset seizures.
**Background**

Oxcarbazepine monotherapy (OX-C) is the standard of care for refractory partial-onset seizures (PTE) in adults and children aged 6 years or older. However, due to its narrow therapeutic index, monotherapy may not be sufficient for all patients. Oxcarbazepine extended release (XR) is a once-daily, extended-release formulation of oxcarbazepine that provides a novel therapeutic option for the treatment of refractory PTE. Compared to conventional oxcarbazepine immediate-release formulations (OX C), oxcarbazepine XR may have the potential to be more effective therapy, as it increases the opportunities for seizure control by allowing for higher, more consistent levels of therapeutic plasma concentrations. Oxcarbazepine XR is approved by the FDA as an adjunctive therapy for the treatment of partial-onset seizures in adults and children aged 6 years or older. This study evaluated the efficacy and tolerability of oxcarbazepine XR in a North American subset of patients with refractory partial-onset seizures.

**Study Design**

A multinational, multicenter, double-blind, 3-arm, parallel-group study: 1:1:1 randomization to placebo, Oxcarbazepine XR (1200 mg once-daily) and Oxcarbazepine XR (2400 mg once-daily). Results: In the North American subset with both 1200 mg/day and 2400 mg/day dosing, median percentage change in seizure frequency from baseline to week 16 was significantly lower with Oxcarbazepine XR 2400 mg/day compared to placebo. Oxcarbazepine XR 1200 mg/day was also significantly better than placebo.

**Key Patient Characteristics**

- Age: Mean 39 years
- Gender: M/F 41%/59%
- Mean dose: Oxcarbazepine XR 1200 mg once-daily
- Mean dose: Oxcarbazepine XR 2400 mg once-daily

**Assessments**

- Efficacy outcomes: Median percentage change from baseline to week 16 in seizure frequency
- Safety outcomes: Adverse events

**Results**

<table>
<thead>
<tr>
<th>PCT</th>
<th>Median % Seizure Frequency Reduction from Baseline</th>
<th>Placebo vs. Oxcarbazepine XR 1200 mg/day</th>
<th>Oxcarbazepine XR 1200 mg/day vs. 2400 mg/day</th>
</tr>
</thead>
<tbody>
<tr>
<td>Mean</td>
<td>39.5%</td>
<td>44.5%</td>
<td>50.6%</td>
</tr>
<tr>
<td>SD</td>
<td>13.1</td>
<td>14.4</td>
<td>15.4</td>
</tr>
</tbody>
</table>

**Conclusion**

Oxcarbazepine XR, a well-tolerated extended-release formulation of oxcarbazepine, is an effective and well-tolerated treatment option for the treatment of refractory partial-onset seizures. The results of this study support the use of Oxcarbazepine XR as an effective and well-tolerated treatment option for the treatment of refractory partial-onset seizures.
Pharmacokinetic/Pharmacodynamic Analysis of Extended-Release Once-Daily SPN-804 (DexOlor XR™) in Adults with Epilepsy: Correlation of MHD Concentrations and Seizure Reduction

Methods

Background

Oxcarbazepine (OXC) is almost completely absorbed after oral administration. However, there is large interpatient variability in oxcarbazepine plasma concentration, which is influenced by polymorphisms in the cytochrome P450 enzymes CYP2C9 and CYP2C19. We used the validated population pharmacokinetic (PK) model and population pharmacodynamic (PD) model to determine the impact of MHD on OXC exposure.

Results

A sigmoidal Emax model with = 20 most closely matched the shape of the smoother (Fig. 1). The value of C50 (14.04 mg/L) estimated in this model was also unlikely to result in further clinical improvement in a population of epilepsy patients treated with SPN-804 QD. Figure 2. Median % Seizure Reduction in PROSPER Study Population Stratified by MHD Concentration vs. Assigned Dose PK/PD (Emax) Model A sigmoidal Emax model was fitted to the Cmin and PCH data for patients with estimated Cmin values: where PCH 0 is the intercept (upper asymptote), Emax is the maximum effect, and C50 is the concentration at which half-maximal effect is observed. In this study, the primary structural model fit the PROSPER patient data well. Release of OXC from SPN-804 and its subsequent gastric absorption across visits. Results of this analysis were applied to the analysis of pharmacodynamic (PD) data, i.e., percent change (PCH) in 28-day profile for that visit. A single representative value for Cmin was calculated for each patient in the PK analysis dataset by taking the median apparent clearance of MHD. Using the validated population PK model, PK variables were derived for each subject at each visit for which the model was fit to the Cmin and PCH data for patients with estimated Cmin values: where PCH 0 is the intercept (upper asymptote), Emax is the maximum effect, and C50 is the concentration at which half-maximal effect is observed.

Figure 1. Plot of Individual MHD Cmin Estimated from Population PK Model and Supernus Pharmacokinetics, Inc.

Conclusions

In this study, the MHD concentrations were found to be significantly related to the reduction in seizures in PROSPER study patients. The correlation between MHD concentrations and seizure reduction was stronger in patients with higher Cmin values. The results suggest that MHD concentrations play a critical role in the efficacy of SPN-804 QD in treating epilepsy patients.
Long-Term, Open-Label Safety and Tolerability Study of Oxtellar XR™, A Novel Once-Daily, Extended-Release Oxcarbazepine Formulation, as Adjunctive Therapy in Patients with Refractory Partial-Onset Seizures

Background

Studies have shown that once-daily extended-release oxcarbazepine (Oxtellar XR™) provides flexible dosing with improved adherence compared to 3- or 4-times daily dosing regimens. Due to the once-daily dosing regimen, patients may experience fewer treatment interruptions, reducing the risk of treatment discontinuation.

Study Design

This study was an open-label extension of a double-blind placebo-controlled trial. Patients were randomized to receive placebo, 1200 mg QD, or 2400 mg QD of Oxtellar XR™. The trial aimed to evaluate the safety and tolerability of Oxtellar XR™ in patients with refractory partial-onset seizures.

Results

Seizure response was assessed using the median reduction from baseline in seizure frequency. The reduction in seizure frequency was observed in all groups, with the highest reduction seen in the group receiving 2400 mg QD. The tolerability and safety profile of Oxtellar XR™ were consistent with previous studies, indicating minimal adverse effects.}

Conclusion

Oxtellar XR™ demonstrated effective seizure control and acceptable safety in patients with refractory partial-onset seizures. The once-daily dosing regimen provided better adherence compared to multiple daily dosing, highlighting the benefits of this formulation.
Effect of Alcohol on Bioavailability of Extended-Release, Once-Daily SPN-538 (Trakendi XR™) in Healthy Adult Males

S Schwabe, J Dost, S Brittain
Supernus Pharmaceuticals Inc., Rockville, MD

Background

Background

Bioavailability of tramadol extended-release capsules was assessed in a randomized, single-dose, open-label, four-period, four-sequence, four-way crossover study. The study included 30 healthy male subjects. Subjects received 200 mg of SPN-538, a modified-release formulation of tramadol, as capsules in the presence of 0%, 4%, 20%, and 40% alcohol by volume. The effects of alcohol on the primary pharmacokinetic parameter area under the curve (AUC) were analyzed using a mixed-effects model of variance (ANOVA) with subject nested within sequence as a random factor and sequence, period, and treatment as fixed factors.

Study Highlights

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- Study Design: Open-label, four-period, four-sequence, four-way crossover design
- Subjects: 30 healthy male subjects
- Dose: 200 mg of SPN-538 capsules
- Conditions: 0%, 4%, 20%, and 40% alcohol by volume
- Pharmacokinetic Parameters: Area under the curve (AUC)

Results

Results

- No significant effect of alcohol on overall TPM exposure (LS means; corresponding 90% confidence intervals (CIs) for ratios were obtained by taking antilogarithm of 90% CIs for mean concentrations).

Conclusions

Conclusions

- Alcohol did not affect the pharmacokinetics of TPM from SPN-538.

Additional Information

Additional Information

- Data were analyzed using a mixed-effects model of variance (ANOVA) with subject nested within sequence as a random factor and sequence, period, and treatment as fixed factors.
- Alcohol did not affect the pharmacokinetics of TPM from SPN-538.