UNITED STATES
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)

0-50440	**20-2590184**
(Commission File Number)	(IRS Employer Identification No.)
1550 East Gude Drive, Rockville MD	**20850**
(Address of principal executive offices)	(Zip Code)

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 99.1 — Press Release dated December 12, 2013.
Exhibit 99.2 — Clinical Data.

SIGNATURES

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

EXHIBIT INDEX

Number	Description	
99.1	Press Release dated December 12, 2013.	Attached
99.2	Clinical Data.	Attached

Exhibit 99.1

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/1.73m^2).

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

Exhibit 99.2

Steady-State Bioequivalence of Extended-Release, Once-Daily Trokendi XR™ (SPN-538) to Immediate-Release Topiramate (TPM-IR, Topamax®)

J. Johnson[1], S. Brittain[1], J. Stocks[1], P. Baroldi[2]
[1]Supernus Pharmaceuticals, Inc., Rockville, MD; [2]formerly with Supernus

Background

The clinical usefulness of topiramate (TPM) as a broad-spectrum antiepileptic drug (AED) is well established, with a safety profile based on more than 4 million exposures.

Tolerability issues with immediate-release topiramate (TPM-IR), especially distinctive neurocognitive effects, as well as b.i.d. dosing may adversely affect patient adherence.

SPN-538 (Trokendi XR™, Supernus Pharmaceuticals, Inc.) is a novel extended-release, once-daily capsule formulation of TPM that uses the Microtrol® drug delivery system. Trokendi XR may improve tolerability and enhance adherence.

This study compared the relative bioavailability of once-daily SPN-538 and b.i.d. TPM-IR (Topamax®, Janssen Pharmaceuticals) to assess steady-state bioequivalence.

Study Features

Design	Single-blind, randomized-sequence crossover
Subjects	Healthy non-smoking adults, age 18-55 yrs
Drugs	• 200 mg SPN-538 QD (AM dose active drug; PM dose, placebo capsule) • 100 mg TPM-IR Q12h
Titration	50-mg weekly increments to 200 mg/day
Treatment duration	21 days (10-day maintenance)
Washout between treatments	22 days

PK Parameters/Analyses

Pre-dose (trough) samples	• Each titration step • Steady-state (last 3 days of maintenance phase)
Post-dose samples	Multiple time points for 1 wk after last dose
Primary PK endpoints	AUC_{0-24}, C_{max}, C_{min}
Bioequivalence definition	90% CIs of SPN-538/TPM-IR ratios <u>for all three</u> primary PK endpoints within 80%-125% limits
Partial AUC (post-hoc analysis)	AUCs from time 0-t hrs (0.5, 1, 1.5, 2, 3, 4, 6, 8, 12, 16, 24 hrs post-dose)
PK Population	All subjects completing both treatment periods with adequate PK profile (sufficient number of blood draws with no missing samples around steady-state C_{max})
PK bioequivalence statistical analysis	Analysis of variance (ANOVA) performed by fitting linear mixed model with fixed effects for sequence, period, and treatment, and random effects model for subject nested within sequence to log-transformed values of AUC_{0-24}, C_{max}, C_{min}, AUC_{0-t} and untransformed FL%. Least-squares (LS) means, LS treatment differences, and 90% CIs on log scale obtained for AUC_{0-24}, C_{max}, C_{min}, and AUC_{0-t}. Results transformed back to original scale by exponentiation for treatment geometric LS means, point estimates of geometric LS mean SPN-538/TPM-IR ratios, and 90% CIs.

Cognitive Assessments (Secondary Endpoints)

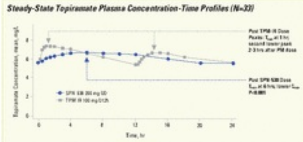
Cognitive tests	• Controlled Oral Word Association (COWA) • Digit Symbol Substitution Test (DSST)
Test times	Pre-AM dose (trough)
Test days	• Baseline (Day 1) • End of each titration step: Days 8 (50 mg/day), 15 (100 mg/day), 22 (150 mg/day) • End of maintenance, Day 31 (200 mg/day)

Results

Subject Disposition (N=39)

Randomized, n (%)	39 (100%)
Completed, n (%)	33 (85%)
Discontinuations, n (%)	6 (15%)
Adverse event	2
Non-adherence	1
Protocol deviation	1
Withdrew consent	2

Steady-State Topiramate Plasma Concentration-Time Profiles (N=33)



Steady-State Pharmacokinetics (N=33)

PK Parameter, mean (SD)	SPN-538 200 mg QD	TPM-IR 100 mg Q12h
AUC_{0-24}, mg•hr/L	147 (28)	151 (28)
$C_{avg(0-24)}$, mg/L	6.12 (1.15)	6.28 (1.09)
$C_{max(0-24)}$, mg/L	6.83 (1.25)	7.88 (1.25)
$C_{min(0-24)}$, mg/L	5.25 (1.07)	5.22 (0.99)
$C_{trough(0-24)}$, mg/L	5.58 (1.20)	5.81 (1.07)
T_{max}, hr[a]	6.00 (4.00-24.00)	1.00 (0.25-3.00)[b]
$t_{1/2}$, hr	21.4 (2.8)	20.9 (3.1)
k_{el}, 1/hr	0.0324 (0.0027)	0.0336 (0.0032)
FL, %	25.9 (8.4)	39.8 (8.4)

[a] T_{max} presented as median (range)
[b] T_{max} for morning TPM-IR dose ($T_{max,1}$)

SPN-538 TPM plasma concentrations more consistent than with TPM-IR, with less fluctuation

Pharmacokinetic Bioequivalence at Steady State (N=33)

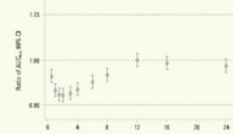
Parameter	Geometric LS Mean: SPN-538 200 mg QD	Geometric LS Mean: TPM-IR 100 mg Q12h	Ratio	90% CIs	Within-Subject Variability (%)	Between-Subject Variability (%)
AUC_{0-24}, mg•hr/L	144	149	97.1%	94.0, 100.2	7.8	17.5
$C_{max(0-24)}$, mg/L	6.69	7.60	88.0%	85.1, 91.0	8.0	17.5
$C_{min(0-24)}$, mg/L	5.12	5.13	99.9%	95.9, 104.1	9.8	19.4
FL, %	26.1	40.1	-14.1%*	-16.7, -11.5	NR	NR

LS, least squares
*Fluctuation presented as absolute difference

- For traditional PK parameters (AUC_{0-24}, C_{max}, C_{min}), 90% CIs of all three steady-state SPN-538/TPM-IR ratios fell within 80%-125% bioequivalence limits.
- Within-subject variability was <10% and between-subject variability was <20%.
- Fluctuation between steady-state plasma peak and trough concentrations was significantly lower (P<0.001) with once-daily SPN-538 than with TPM-IR Q12h (relative difference: 35%; absolute difference, -14.1%).

Once-daily SPN-538 is bioequivalent to TPM-IR Q12h

Partial AUCs: SPN-538/TPM-IR Ratios



Time point dose, hrs	0-0.5	0-1	0-1.5	0-2	0-3	0-4	0-6	0-8	0-12	0-16	0-24
SPN-538 pAUC (mg•hr/L)	2.8	5.5	8.6	11.6	17.8	24.2	37.2	50.1	75.5	99.8	144.3
TPM-IR pAUC (mg•hr/L)	3.0	6.6	10.2	13.9	21.1	28.1	41.3	54.0	75.7	101.4	148.6
Ratio	0.92	0.86	0.84	0.84	0.85	0.86	0.90	0.93	1.00	0.99	0.97

SPN-538 was bioequivalent to TPM-IR throughout 24-hr dosing interval, as determined by partial AUCs

Cognitive Assessments*

Controlled Oral Word Association (COWA, verbal fluency): In subjects completing both treatment arms (n=33), COWA change scores favoring SPN-538 QD were significant over the entire treatment period (P=0.03) and at 100 mg/day (P<0.001). Subjects with meaningful (>1 within-subject SD) negative changes: TPM-IR, 38%; SPN-538, 12% (P=0.04).

Digit Symbol Substitution Test (DSST, working memory): Score changes favoring SPN-538 over TPM-IR did not reach statistical significance.

Adverse Events

- Most commonly reported adverse events (AEs): paresthesia, headache, attention disturbance, somnolence, and dysgeusia.
- AE incidences were generally similar across treatments, although certain CNS/cognitive AEs (dizziness, attention disorder, aphasia, speech disorder) were reported by more subjects during TPM-IR treatment.
- Most treatment-related AEs were mild and transient.
- Eight (21%) of 38 subjects experienced dizziness or postural dizziness during TPM-IR exposure vs 0/34 during SPN-538 treatment.
- Of two subjects who discontinued due to AEs, AEs were considered study drug-related in one subject and occurred during SPN-538 exposure (50 mg/day, decreased concentration and attention; 100 mg/day, somnolence, memory impairment, forgetfulness, aphasia, apathy, and transient blurred vision). Subject withdrew from study without crossover to TPM-IR.
- No deaths or other serious adverse events were recorded.

Overall, the range and severity of adverse events were consistent with those expected for TPM

Conclusions

- At steady state, once-daily SPN-538 is bioequivalent to b.i.d. TPM-IR based on conventional criteria and on more rigorous measure of partial AUCs throughout a 24-hr dosing period.
- Slower drug absorption with SPN-538 delivers more constant plasma TPM concentrations over the 24-hr dosing period.
- Despite PK bioequivalence, a signal of a potential pharmacodynamic difference was observed in the form of a significantly less negative impact of once-daily SPN-538 than TPM-IR b.i.d. on objective measures of cognitive function.*
- Once-daily SPN-538 may improve tolerability and adherence for potentially greater retention and effectiveness in epilepsy patients.

* Details of cognitive assessments presented in AES Poster 1.325. Schwabe S, Brittain S. Cognitive effects of extended-release, once-daily Trokendi XR™ vs b.i.d. immediate-release topiramate (Topamax®) in healthy volunteers. *Epilepsy Curr.* 2014; 14 (Suppl. 1): 1.325.

Study funded by Supernus Pharmaceuticals, Inc.

For questions about the data presented above, please contact the Medical Affairs Department of Supernus Pharmaceuticals via Prosar Corp. at medinfo@prosarcorp.com.

Johnson J, Brittain S, Stocks J, Baroldi P. Steady-state bioequivalence of extended-release, once-daily Trokendi XR™ (SPN-538) to immediate-release topiramate (TPM-IR, Topamax®). *Epilepsy Curr.* 2014; 14 (Suppl. 1): 2.119.

Once-Daily Trokendi XR™ (SPN-538) vs. Twice-Daily Topamax®: Impact of Nonadherence on Topiramate Concentrations

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

Background

Extended-release (ER) antiepileptic drugs (AEDs) offer potential advantages over immediate-release (IR) AEDs, particularly when dosing can be simplified from BID/TID to once-daily dosing. SPN-538 (Trokendi XR™, Supernus Pharmaceuticals, Inc.) is a novel extended-release, once-daily topiramate formulation of topiramate (TPM) that may improve tolerability and enhance adherence. SPN-538 QD is bioequivalent to TPM-IR (Topamax®, Janssen Pharmaceutica) dosed per the recommended BID regimen in prescribing information.

Despite potential advantages of QD dosing, clinicians may be hesitant to switch patients with refractory epilepsy from an IR AED/BID dosing to its ER counterpart and QD dosing. Intuitively, a missed QD dose that represents 50% of the total daily dose would seemingly have a greater impact on AED plasma concentrations than a missed QD dose that represents 100% of the total daily dose. Likewise, restoring a delayed/missed QD dose would seemingly represent less risk of drug toxicity than restoring a delayed/missed QD dose. This view fails to consider that IR and ER AEDs have very different pharmacokinetic (PK) profiles that may make ER AEDs more "forgiving" with nonadherent dosing.

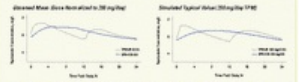
Randomized controlled trials have not explored the consequences of dosing irregularities for an ER AED and its QD IR counterpart. Because they can be powerful predictive tools, population PK modeling and simulation were used to compare the potential PK consequences of dosing irregularities during steady-state AED treatment with SPN-538 QD and BID TPM-IR.

In addition, simulations compared QD dosing of SPN-538 and TPM-IR to address the perception that, due to the long half-life of TPM, QD dosing produces relatively constant TPM concentrations regardless of formulation.

Methods

Data analysis (modeling and simulation)	Nonlinear mixed effects modeling program (NONMEM, ICON Development Solutions; PLTools, P Less Than Company)
Primary structural model development	• Linear two-compartment model • TPM plasma concentration data for healthy adult volunteers in single-dose, randomized sequence (fed/fasted) crossover study (N=31 with intensive PK sampling for 168hrs post-dose)
Final model development	• Primary structural model • TPM plasma concentration data from intensive PK sampling on three occasions in adult epilepsy patients (N=40) on stable maintenance TPM-IR Q12h as monotherapy or adjunctive therapy switched to identical SPN-538 QD doses • Covariates incorporated into model: Concomitant use of enzyme-inducing AED s (EIAEDs); Body weight
Model validation	• Visual inspection of model graphics for goodness of fit • Bootstrap analysis of 500 datasets obtained from original dataset using sampling with replacement
Dosing simulations	• Separate simulations for monotherapy/non-inducing AED no therapy (shown) and for EIAED no therapy (not shown) • Predicted concentrations for each dosing scenario (e.g., delayed dose) compared with predicted concentrations for adherent dosing

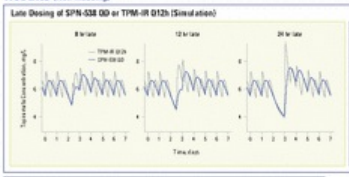
Population PK Model: Steady-State TPM Plasma Concentration-Time Profiles



Simulations based on typical values (monotherapy/not EIAEDs) of PK parameters (e.g., CL/F, V/F) estimated with the final model compared favorably with mean dose-normalized data (250 mg/day total daily dose) observed in non-induced epilepsy patients, illustrating high predictability of the population PK model

Results (Non-inducing)

Late Dosing of SPN-538 QD or TPM-IR Q12h (Simulation)

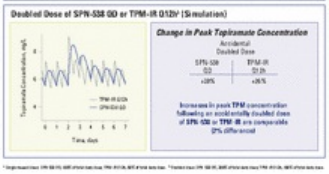


Changes in Trough and Peak Topiramate Plasma Concentrations vs. Time of Late Dose

Late Dosing	C_{min} Change: SPN-538 QD	C_{min} Change: TPM-IR Q12h	C_{max} Change: SPN-538 QD	C_{max} Change: TPM-IR Q12h
8 hr	-12%	-16%	+6%	+6%
12 hr	-17%	-21%	+16%	+12%
24 hr	-31%	-31%	+14%	+26%

For both trough and peak TPM concentrations following a late dose, SPN-538 QD is more "forgiving" than TPM-IR Q12h, regardless of AED co-therapy

Missed Dose of SPN-538 QD or TPM-IR Q12h† (Simulation)



Change in Topiramate Concentration

C_{min} Change: SPN-538 QD	C_{min} Change: TPM-IR Q12h	C_{max} Change: SPN-538 QD	C_{max} Change: TPM-IR Q12h
-21%	-21%	+14%	+12%

When a dose is missed and restored by doubling the dosage at the next scheduled dosing, the reduction in trough TPM concentration and the subsequent increase in peak TPM concentration are similar for SPN-538 QD and TPM-IR Q12h

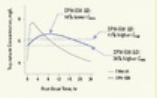
Doubled Dose of SPN-538 QD or TPM-IR Q12h† (Simulation)

Change in Peak Topiramate Concentration

Accidental Doubled Dose: SPN-538 QD	Accidental Doubled Dose: TPM-IR Q12h
+28%	+26%

Increases in peak TPM concentration following an accidentally doubled dose of SPN-538 or TPM-IR are comparable (2% difference)

QD Dosing at Steady State (Simulation)



PK Parameters

	SPN-538 QD	TPM-IR QD
AUC, hrmg/L	140	134
C_{max}, mg/L	4.6	7.3
C_{min}, mg/L	3.5	4.1
C_{avg}, mg/L	4.2	5.6
t_{max}, hr	6.0	1.0

Conclusions

- Validated population PK model based on data collected in patients with epilepsy is highly predictive of clinical observations
- Population PK modeling and simulation is a valuable predictive tool to quantify potential PK consequences of dosing irregularities
- Simulations using population PK model predict that the slower and more prolonged absorption with SPN-538 QD vs. BPM-IR (QD or Q12h) will produce more constant BPM plasma concentrations and mitigate impact of dosing irregularities

Based on simulations:

- SPN-538 QD is generally more forgiving than BPM-IR Q12h when dosing is late, regardless of AED co-therapy
  - C_{min} reductions tend to be less with delayed SPN-538 QD dose than with BPM-IR Q12h
  - With dose restoration, C_{min} increases are similar or lower with SPN-538 QD vs. BPM-IR Q12h
  - When a dose is missed and doubled at the subsequent scheduled dosing period, C_{min} and C_{max} changes vs. adherent dosing are similar for SPN-538 QD and BPM-IR Q12h
- After a missed SPN-538 QD dose, BPM concentrations can be restored by taking the next dose at any time or doubling the next scheduled dose
- C_{max} increases following an accidentally doubled dose of SPN-538 or BPM-IR are comparable (2% difference between formulations)
- For SPN-538 and BPM-IR, the impact of non-adherent dosing is consistently greater in the presence of EIAEDs (data not shown)
- Dosing irregularities with SPN-538 QD should pose no greater risk than with BPM-IR Q12h
- SPN-538 offers the convenience of once-daily BPM dosing without increasing the clinical risk of missed, delayed, or doubled doses

Study funded by Supernus Pharmaceuticals, Inc.

For questions about the data presented above, please contact the Medical Affairs Department of Supernus Pharmaceuticals via Prosar Corp. at medinfo@prosarcorp.com.

Brittain S. Once-daily Trokendi XR™ (SPN-538) vs. twice-daily Topamax™: Impact of nonadherence on topiramate concentrations. *Epilepsy Curr* 2004; 4i (Suppl. 1): 3 A12.

Pharmacokinetic Rationale for mg-to-mg Overnight Switch from Twice-Daily Immediate-Release Topiramate (TPM-IR) to Once-Daily, Extended-Release Trokendi XR™ (SPN-538)

J. Stocks[1], J. Johnson[1], S. Brittain[1], P. Baroldi[2]
[1]Supernus Pharmaceuticals, Inc., Rockville, MD; [2]formerly with Supernus

Background

Extended-release (ER) antiepileptic drugs (AEDs) offer potential tolerability and adherence advantages over immediate-release (IR) formulations. Clinicians need practical dosing guidance for an IR-to-ER AED switch in epilepsy patients, particularly for patients receiving concomitant therapy with enzyme-inducing AEDs.

SPN-538 (Trokendi XR, Supernus Pharmaceuticals, Inc.) is a novel extended-release, once-daily capsule formulation of topiramate (TPM) that may improve tolerability and enhance adherence. Based on a study in healthy volunteers, once-daily SPN-538 is pharmacokinetically bioequivalent to immediate-release topiramate (TPM-IR, Topamax®, Janssen Pharmaceuticals).

The study reported here evaluated PK effects of substituting SPN-538 QD for identical daily dosages of TPM-IR Q12h in epilepsy patients on stable TPM-IR therapy, thereby mimicking clinical practice of an IR-to-ER AED switch.

Study Features

Patients	• Adults (18-65 yrs) • Partial-onset or primary generalized seizures • Seizures: 0-3 seizures/month (30-day average) • TPM-IR treatment duration: ≥4 wks (stable TPM-IR dose ≥2 wks before study entry) – Monotherapy or adjunctive therapy – Concomitant AEDs (1-3): Non-inducing ("neutral") or inducing
Study design	Open label, multicenter, 2-period, 1-sequence conversion study • Period 1 (14 days): TPM-IR b.i.d. (Topamax tablets) • Period 2 (14 days): SPN-538 after immediate substitution of identical total daily dose (i.e., overnight mg-to-mg conversion with no washout)
TPM dosage	200, 250, 300, 350, or 400 mg/day (dosage in Period 1 and Period 2 identical to stabilized total daily dosage at study entry)
PK samples	• TPM-IR last dose (Day 14, Period 1) – Pre-dose – Post-dose: 0.5, 1, 2, 3, 4, 6, 8, 11.75, 12.5, 13, 14, 15, 16, 18, 20, 24 hrs • SPN-538 first dose (Day 1, Period 2); SPN-538 last dose (Day 14, Period 2) – Pre-dose – Post-dose: 0.5, 1, 2, 3, 4, 5, 6, 8, 10, 12, 16, 20, 24 hrs
Primary PK endpoints	Steady-state AUC_{0-24}, C_{max}, C_{min} normalized to 200-mg dose
Other endpoints of interest	• First dose AUC_{0-24}, C_{max}, C_{min} normalized to 200-mg dose • Steady-state PK parameters C_{avg}, T_{max}, FL% normalized to 200-mg dose • Patient survey (administered at study end)
Analysis	ANOVA model with subject as a random component calculated ratios of geometric least squares means (LSMs) for each treatment
Study populations	• Safety: All patients receiving ≥1 dose of study medication • PK: Patients with adequate PK profile (e.g., no missing plasma samples around C_{max}) – Induced: Carbamazepine or phenytoin as concomitant AED – Neutral: TPM monotherapy or no enzyme-inducing AEDs

Results

Patient Profile at Baseline

	Safety Population (N = 66)
Gender, male/female	29%/71%
Age, mean (SD)	38.6 yrs (10.8)
Race	
White	70%
Black/African American	27%
American Indian/Alaska Native	1.5%
Asian	1.5%
Epilepsy duration, median	20 yrs
Seizure type	
Partial onset	62%
Primary generalized	36%
Mixed	2%
Concomitant AEDs	
0	46%
1	33%
2	14%
≥3	5%
Concomitant AEDs	
Lamotrigine	15%
Valproate	14%
Phenytoin	12%
Levetiracetam	9%
Carbamazepine	8%
Other*	18%
Enzyme inducing co-therapy	20%
Neutral	80%
TPM-IR treatment duration, median	3.5 mo
TPM dosage	
200 mg/day	48%
400 mg/day	33%
Other	18%

*[illegible]

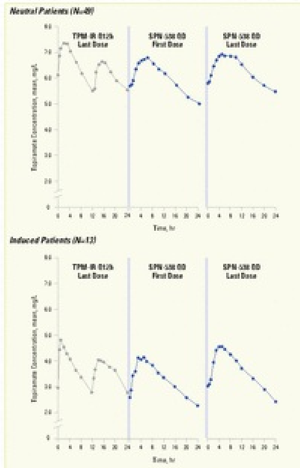
Steady-State† Pharmacokinetics, PK Population (N=62)

Parameter	TPM-IR LSM	SPN-538 LSM	SPN-538 / TPM-IR Ratio
	Neutral (n=49)		
AUC_{0-24} (hr•mg/L)	150	150	100%
C_{max} (mg/L)	7.8	7.7	98%
C_{min} (mg/L)	5.1	5.3	103%
	Induced (n=13)		
AUC_{0-24} (hr•mg/L)	93.1	94.8	102%
C_{max} (mg/L)	5.2	5.0	96%
C_{min} (mg/L)	2.4	2.2	90%

†[illegible]

Steady-state TPM PK profile maintained when SPN-538 QD substituted for TPM-IR Q12h at identical daily dosages, regardless of concomitant AEDs (neutral or enzyme-inducing)

Mean Plasma Concentration-Time Profiles (normalized to 200 mg total daily dose)



TPM plasma concentration profile after first dose of SPN-538 was consistent with steady-state profile

Other Key Observations

Steady-State PK Parameters of Interest (PK Population)

Dose normalized parameter	TPM-IR	SPN-538
C_{avg} mean, mg/L	5.6	5.6
T_{max} median, hr	1.0	5.0
%FL median	46%	34%

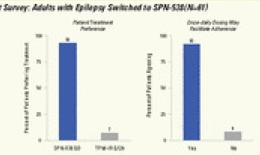
Clinical Observations

- Substitution of SPN-538 QD for TPM-IR Q12h at identical dosages was not associated with deterioration of seizure control.
- Adverse events (AEs) were mild to moderate in severity.
- Only AEs reported by >1 patient: fatigue (n=3), headache (n=4) during SPN-538 treatment.
- One AE-related discontinuation unrelated to study drug (valproate toxicity) during TPM-IR treatment.

Patient Survey

- Treatment/dosing preference: 51/61 (93%) preferred SPN-538 QD
- Adherence: 56/61 (92%) expected once-daily dosing to facilitate treatment adherence.

Patient Survey: Adults with Epilepsy Switched to SPN-538 (N=61)



Conclusions

- At steady state, SPN-538 QD bioavailability is comparable to TPM-IR Q12h.
- When transitioning from TPM-IR to SPN-538, an overnight mg-to-mg conversion can be undertaken, regardless of concomitant AED.
- Patients with epilepsy preferred SPN-538 QD to TPM-IR Q12h and expect a positive impact on treatment adherence.

Study funded by Supernus Pharmaceuticals, Inc.

For questions about the data presented above, please contact the Medical Affairs Department of Supernus Pharmaceuticals via Prosar Corp. at medinfo@prosarcorp.com.

Stocks J, Johnson J, Brittain S, Baroldi P. Pharmacokinetic rationale for mg-to-mg overnight switch from twice-daily immediate-release topiramate (TPM-IR) to once-daily extended-release Trokendi XR™ (SPN-538). *Epilepsy Curr.* 2014;14 (Suppl 1): 2.135.

Cognitive Effects of Extended-Release, Once-Daily Trokendi XR™ (SPN-538) vs b.i.d. Immediate-Release Topiramate (TPM-IR, Topamax®) in Healthy Volunteers

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

Background

Immediate-release topiramate (TPM-IR) is regarded as one of the more effective antiepileptic drugs (AEDs) in terms of seizure control. However, it has also been associated with distinctive cognitive symptoms (e.g., word-finding difficulty, slowed mental processing) that have limited its clinical usefulness in some patients.

- Neurocognitive effects are reportedly the most common reason for discontinuing TPM-IR therapy in clinical practice.[1,2]
- In some patients, these effects occur early, during titration at low dosages.[3,4]
- Objective measures of cognitive function have confirmed distinctive neurocognitive effects of TPM.[5-12]
- Negative cognitive effects have also demonstrated sensitivity to TPM-IR dose, titration speed, and plasma TPM concentrations,[7-9] suggesting a likely pharmacokinetic-pharmacodynamic (PK-PD) relationship.
- Cognitive/CNS tolerability may be improved with an extended-release TPM formulation that has a slower absorption rate and lower plasma peak concentration.[8]

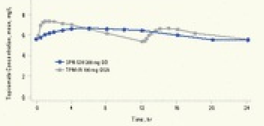
SPN-538 (Trokendi XR, Supernus Pharmaceuticals, Inc.) is a novel extended-release, once-daily capsule formulation of TPM that may improve tolerability and adherence.

In a single-blind crossover study in healthy volunteers, SPN-538 200 mg QD was shown to be bioequivalent to TPM-IR 100 mg Q12h (Topamax®, Janssen Pharmaceuticals). A secondary endpoint was to compare the two formulations' effect on objective measures of cognitive function.

Study Features

Design	Single-blind, randomized-sequence crossover
Subjects	Healthy non-smoking adults, age 18-55 yrs
Drugs	• 200 mg SPN-538 QD (AM dose active drug, PM dose, placebo capsule) • 100 mg TPM-IR Q12h
Titration	50 mg weekly increments to 200 mg/day
Treatment duration	29 days (10 day maintenance)
Washout between treatments	33 days
Primary endpoint	Relative bioavailability to determine bioequivalence
Secondary endpoint	Objective assessments of cognitive function

Steady-State Topiramate Concentration-Time Profiles



Primary endpoint: SPN-538 200 mg QD is bioequivalent to TPM-IR 100 mg Q12h

Cognitive Assessments

Cognitive tests	• Controlled Oral Word Association (COWA): Subjects name as many different words as possible beginning with a specific letter (e.g., F or S) in 1 min (different letter at each visit but same letter sequence for each subject) • Digit Symbol Substitution Test (DSST): Subjects match symbols with corresponding numbers using look-up table (different digit/symbol combinations used at each visit)
Test times	Pre AM dose (trough)
Test days	• Baseline (Day 0) • End of each titration step: Days 8 (50 mg/day), 15 (100 mg/day), 22 (150 mg/day) • End of maintenance, Day 29 (200 mg/day)
Endpoints	• Between-treatment differences in change scores at each on-treatment visit and across visits with a composite score (average of change scores across all on-treatment tests) • Distribution of composite change scores expressed as within-subject SD change scores • Post hoc: Proportion of subjects displaying meaningful negative change (≥1 within-subject SD) determined for each treatment (compared with Chi-square test)
Statistical analysis	• Between-treatment comparisons evaluated by fitting a repeated measures linear mixed model with fixed effects for treatment, sequence, period, day, and treatment by day • Treatment LS means, point estimate of the LS mean difference, and 95% CI for difference determined • Magnitude of the difference (effect size) in standardized change scores used Cohen's d statistic: difference of mean score changes (SPN-538 minus TPM-IR)/within-subject SD. Cohen's d effect size: – Mild: 0.2 - <0.5 – Moderate: 0.5 - <0.8 – Large: ≥0.8
Analysis population	Subjects completing both treatment periods (protocol-defined population was all subjects with ≥1 test score but the more appropriate and conservative analysis was to analyze the study completer population due to study dropouts that created an imbalance in drug exposure)

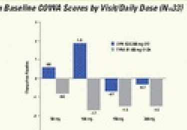
Results

Controlled Oral Word Association (COWA): Change from Baseline Score (N=32)

Dose, mg/day	Treatment	LSM Score	LSM Difference	95% CI	P-value	Effect Size
50	SPN-538 TPM-IR	0.6 -0.8	1.5	-0.4, 3.3	0.13	0.45
100	SPN-538 TPM-IR	1.9 -1.7	3.6	1.7, 5.5	<0.001	1.22
150	SPN-538 TPM-IR	-0.7 -1.6	0.8	-1.5, 2.7	0.41	0.27
200	SPN-538 TPM-IR	-0.3 -1.5	1.1	-0.7, 3.0	0.23	0.35
Composite	SPN-538 TPM-IR	0.4 -1.4	1.8	0.2, 3.3	0.03	0.59

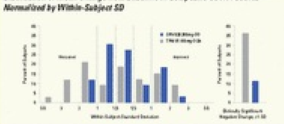
LSM = least squares mean

Change from Baseline COWA Scores by Visit/Daily Dose (N=32)



- COWA change scores significantly favored SPN-538 200 mg QD over TPM-IR 100 mg Q12h over entire treatment period (P=0.03) and at 100 mg/day (P<0.001) in subjects exposed to both formulations
- Pattern of changes in DSST scores favoring SPN-538 QD over TPM-IR Q12h was similar to that observed in COWA testing but differences were not statistically significant

Distribution of Mean Change from Baseline in Composite COWA Scores Normalized by Within-Subject SD



Discussion

Signal in this study suggests pharmacodynamic (PD) difference between SPN-538 200 mg QD and TPM-IR 100 mg Q12h despite PK bioequivalence by traditional criteria (AUC_{0-24}, C_{max}, C_{min}) and more rigorous criteria of partial AUC at multiple post-dose intervals (e.g., during absorption/distribution phase).*

- Significant between-treatment difference cannot be explained by differences in plasma TPM concentrations at the time of testing:
  - COWA testing occurred pre-dose (end of the dosing interval) when mean C_{min} for SPN-538 and TPM-IR was virtually identical.
  - Exploratory analyses of individual subject responses found no relationship between C_{min} and COWA score changes (data not shown).
  - Point estimate difference between SPN-538 and TPM-IR for AUC_{0-24} was 3% – relatively small difference an unlikely cause of change score differences between formulations.
- Does absorption rate account for signal of potential cognitive tolerability difference between SPN-538 and TPM-IR?
  - TPM absorption rate: Most notable PK difference between products.
  - Declines in baseline COWA scores with TPM-IR in this study were smaller than in other studies in which COWA tests performed within 3 hrs of TPM-IR dosing (100-200 mg), i.e., early in post-dose phase of drug absorption and distribution.[5,6,9]
  - Rate of TPM absorption from SPN-538 30 fold slower than from TPM-IR (separate study findings).
  - Point estimates for partial AUCs in this study were ~8%-16% lower with SPN-538 vs. TPM-IR during the first 4 hrs post dose, but remained within 80%-125% bioequivalence limits.
  - Because cognitive function testing was performed at the end of the dosing interval, between-treatment difference, which was modest (~2 word difference on COWA) but significant, could have reflected a) the residual effect of a larger difference earlier in the dosing period that narrowed over time or b) the full extent of the difference between formulations.
  - Mechanism for a PK-PD relationship sensitive to absorption rate that could explain a signal measured long after plasma concentration has peaked is unclear.

Study limitations include: single-blind design in which personnel administering neuropsychometric tests were unblinded to treatment; generalizability of short-term exposure in healthy volunteers to chronic therapy in patients with epilepsy; and unclear clinical implications of a significant difference in objective verbal fluency tests in terms of cognitive tolerability clinically.

Conclusions

- SPN-538 QD is associated with significantly less impact than TPM-IR Q12h on sensitive objective measures of verbal fluency (i.e., Controlled Oral Word Association, COWA), despite PK bioequivalence by traditional PK criteria and more rigorous parameter of partial AUCs.*
- Studies are needed to confirm finding that SPN-538 and TPM-IR at identical doses have a significant PD difference and determine if this difference has a clinically significant impact on tolerability.

* Details of bioequivalence analysis presented in: Porter J, 111, Johnson J et al. Steady-State Bioequivalence of Extended-Release, Once-Daily SPN-538™ (SPN-538) to Immediate-Release Topiramate (TPM-IR, Topamax®).

Study funded by Supernus Pharmaceuticals, Inc.

For questions about the data presented above, please contact the Medical Affairs Department of Supernus Pharmaceuticals via Prosar Corp. at medinfo@prosarcorp.com

Schwabe S, Brittain S. Cognitive effects of extended-release, once-daily Trokendi XR™ (SPN-538) vs b.i.d. immediate-release topiramate (TPM-IR, Topamax®) in healthy volunteers. *Epilepsy Curr* 2014; 14 (Suppl 1): 1.225.

Linearity and Dose Strength Equivalence of Once-Daily, Extended-Release Topiramate (Trokendi XR™, SPN-538)

E. Roers[1], S. Brittain[1], J. Stocks[1], P. Baroldi[1]
[1]Supernus Pharmaceuticals, Inc., Rockville, MD; [2]formerly with Supernus

Background

When managing patients with epilepsy, clinicians must often make multiple dosage adjustments to achieve an optimal individualized dose. Clinicians need to be confident that 1) different dosage strengths are equivalent and 2) dosage adjustments will produce predictable changes in AED plasma concentrations.

SPN-538 (Trokendi XR, Supernus Pharmaceuticals, Inc.) is a novel extended-release, once-daily capsule formulation of topiramate (TPM) that is bioequivalent to b.i.d. immediate-release TPM (TPM-IR) and may improve tolerability and enhance adherence.

The clinical profile of TPM-IR is well-established, encompassing more than 30 double-blind, randomized controlled trials in patients with epilepsy and with a safety profile based on over 4 million patient exposures.

SPN-538 has been approved on the basis of a bridging clinical development program that demonstrated pharmacokinetic (PK) bioequivalence of once-daily SPN-538 to b.i.d. TPM-IR (Topamax®, Janssen Pharmaceuticals).

Study Highlights

Subjects	Fasting healthy volunteers
Study Design	• Open-label crossover design • Four treatment periods in randomized sequence • 28-day washout between treatments
PK Sampling	Pre-dose and at specified times for 1 wk post-dose
PK Analysis	Standard non-compartmental methods and descriptive statistics; mixed-model analysis of variance (ANOVA) to test for equivalence
Safety Population	Subjects who received ≥1 dose of study drug provided safety/tolerability data
PK Population	Subjects who completed ≥2 treatment periods included in PK analysis

Dose Linearity Study

25, 50, 100, 200 mg administered as single SPN-538 capsules:

- 1 x 25 mg
- 1 x 50 mg
- 1 x 100 mg
- 1 x 200 mg

Dose-Strength Equivalence Study

Single 200-mg doses of SPN-538 administered by capsule strength:

- 8 x 25 mg
- 4 x 50 mg
- 2 x 100 mg
- 1 x 200 mg

Results

Dose Linearity Study

Safety Population, N	36
PK Population, N	33
Gender, M/F, N	12/24
Age, mean (range)	30 yrs (18-51)

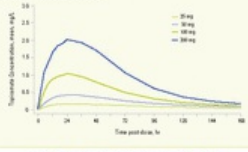
Dose Linearity: Pharmacokinetic Parameters with Single-Dose Administration

PK Parameter, Mean*	25 mg (n=33)	50 mg (n=30)	100 mg (n=31)	200 mg (n=32)
AUC_{0-t}, hr•mg/L (%CV)	16.3 (33.8)	36.4 (21.5)	77.6 (17.1)	153 (16.8)
$AUC_{0-\infty}$, hr•mg/L (%CV)	20.8 (32.3)	42.1 (18.6)	82.7 (17.9)	162 (16.8)
C_{max}, mg/L (%CV)	0.169 (32.6)	0.401 (36.9)	1.086 (24.1)	2.038 (26.1)
T_{max}, hr† (range)	24 (12-72)	24 (12-48)	24 (10-48)	36 (16-48)
$t_{1/2}$, hr (SD)	70 (15)	53 (8)	43 (7)	35 (5)
k_{el}, 1/hr (SD)	0.0104 (0.0022)	0.0134 (0.0021)	0.0178 (0.0036)	0.0210 (0.0029)

*AUC, C_{max} presented as geometric mean; $t_{1/2}$ and k_{el} presented as arithmetic mean
†T_{max} presented as median

- Dose-normalized ratios for AUC_{0-t} and $AUC_{0-\infty}$ 25–200 mg for all treatment comparisons demonstrated dose linearity; 90% CIs for ratios were within 80%-125% limits.
- C_{max} exhibited linearity across 50-200 mg as single dose. C_{max} of 25-mg dose was disproportionately lower, possibly due to TPM binding to carbonic anhydrase in red blood cells.

Dose Linearity: Mean Plasma TPM Concentration vs Time After Single-Dose Administration



SPN-538 pharmacokinetics: Linear across 50-200 mg

Dose-Strength Equivalence Study

Safety Population, N	34
PK Population, N	26
Gender, M/F, N	18/15
Age, mean (range)	30 yrs (18-55)

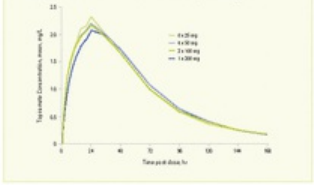
Dose-Strength Equivalence: Pharmacokinetic Parameters with 200-mg Dose Administered as Different Capsule Strengths

PK Parameter, Mean*	8 x 25 mg (n=24)	4 x 50 mg (n=25)	2 x 100 mg (n=25)	1 x 200 mg (n=22)
AUC_{0-t}, hr•mg/L (%CV)	160 (15.1)	165 (12.9)	157 (15.1)	159 (14.0)
$AUC_{0-\infty}$, hr•mg/L (%CV)	168 (16.1)	174 (13.7)	166 (16.5)	168 (14.4)
C_{max}, mg/L (%CV)	2.34 (18.7)	2.25 (16.1)	2.22 (13.9)	2.13 (18.4)
T_{max}, hr† (range)	24 (16-36)	24 (16-48)	24 (12-36)	24 (16-48)
$t_{1/2}$, hr (SD)	35 (4)	36 (4)	36 (5)	36 (4)
k_{el}, 1/hr (SD)	0.0199 (0.0022)	0.0196 (0.0022)	0.0196 (0.0025)	0.0194 (0.0021)

*AUC, C_{max} presented as geometric mean; $t_{1/2}$ and k_{el} presented as arithmetic mean
†T_{max} presented as median

- 90% CIs for ratios (AUC_{0-t}, $AUC_{0-\infty}$, C_{max}) fell within 80%-125% range, demonstrating no difference between identical doses delivered via different dose strengths.

Dose-Strength Equivalence: Mean Plasma TPM Concentration vs Time After 200 mg Administered with Different SPN-538 Capsule Strengths



All four 200-mg doses of SPN-538 are equivalent, regardless of capsule strength

Safety and Tolerability

- SPN-538 well tolerated; most adverse events (AEs) were mild to moderate.
- No unexpected tolerability/safety signals were observed. Most frequently reported AEs were headache, dizziness, and paresthesia. Paresthesia was associated with higher SPN-538 doses.

Conclusions

Dose Linearity

Pharmacokinetics of SPN-538 are linear across the 50-200 mg dosage range; nonlinearity at 25 mg may reflect TPM binding to carbonic anhydrase in red blood cells.

Dose Strength Equivalence

TPM exposure is equivalent for 200 mg administered as 25-, 50-, 100-, and 200-mg SPN-538 capsules.

Study funded by Supernus Pharmaceuticals, Inc.

For questions about the data presented above, please contact the Medical Affairs Department of Supernus Pharmaceuticals via Prosar Corp. at medinfo@prosarcorp.com.

Roers E, Brittain S, Stocks J, Baroldi P. Linearity and dose strength equivalence of once-daily, extended-release topiramate (Trokendi XR™, SPN-538). *Epilepsy Curr.* 2014; 14 (Suppl. 1): 2121.

Pharmacokinetics of Once-Daily, Extended-Release, Trokendi XR™ (SPN-538) in the Elderly

W. O'Neal[1], S. Brittain[1], J. Stocks[1], J. Johnson[1], P. Barold[2]
[1]Supernus Pharmaceuticals, Inc., Rockville, MD; [2]formerly with Supernus

Background

Aging is characterized by a progressive decline in the functional capacity of multiple organ systems, which may impact the pharmacokinetic (PK) profile of medications taken by elderly adults.

- Age-related functional declines affecting drug clearance are particularly common for drugs largely or primarily cleared renally.
- Topiramate (TPM) is not extensively metabolized, with ~70% of an administered dose eliminated unchanged in the urine.
- In elderly subjects receiving the original immediate-release TPM (TPM-IR) formulation (Topamax®, Janssen Pharmaceuticals), TPM clearance was reduced in elderly vs. younger adults only to the extent that renal function was reduced. In patients with reduced renal function, lower TPM-IR doses are recommended.*

SPN-538 (Trokendi XR™, Supernus Pharmaceuticals, Inc.) is a novel extended-release, once-daily formulation of TPM that may improve tolerability and enhance adherence. A single-dose PK study evaluated the effect of subject age on TPM PK in healthy adults receiving SPN-538.

*Topamax Prescribing Information, Janssen Pharmaceuticals, Inc., Titusville, NJ. Revised October 2012

Study Design

- Single-center, single-dose, parallel-group, open-label study.
- 100 mg SPN-538 under fasting conditions in healthy volunteers.
  - Younger adults: 18-45 yrs
  - Elderly adults: ≥65 yrs
- PK sampling pre-dose and at specified time points through 1 wk post-dose.
- Primary PK parameters:
  - TPM exposure from dosing to last measurable concentration (AUC_{last})
  - Total TPM exposure (AUC_{inf})
  - Peak TPM plasma concentration (C_{max})
- Additional PK analyses: time of observed maximum concentration (T_{max}), apparent first-order elimination constant (k_{el}), apparent first-order elimination half-life ($t_{1/2}$).
- Statistical analysis for primary PK parameters: Analysis of variance (ANOVA) model with age group as a fixed effect using natural log-transformed values. ANOVA included calculation of geometric least-squares (LS) mean, difference between LS means, standard error (SE), and 90% confidence interval (CI) for difference. The ratio (Elderly/Younger) and 90% CIs were obtained by back transformation.
- Creatinine clearance calculated from serum creatinine using Cockcroft-Gault equations.

Results

Subject Characteristics

	Younger Adults (n=18)	Elderly Adults (n=13)
Gender, M/F	11/7	3/10
Age, mean (range)	33 (19-45) yrs	75 (71-84) yrs
Race		
White	10 (56%)	12 (92%)
African American	8 (44%)	1 (8%)
Weight, mean (SD)	74.6 (14.9) kg	76.0 (14.5) kg

Topiramate Pharmacokinetics Following 100 mg SPN-538 (Single Dose)

Pharmacokinetic Parameters

PK Parameter	Younger Adults (n=18)	Elderly Adults (n=13)
C_{max} (mg/L), mean (SD)	1.33 (0.30)	1.64 (0.53)
AUC_{inf} (hr•mg/L), mean (SD)	79.1 (18.1)	113 (32)
AUC_{0-tau} (hr•mg/L), mean (SD)	86.1 (18.2)	127 (36)
T_{max} (hr), median (min, max)	24.0 (12.0, 26.0)	16.1 (12.0, 26.0)
$t_{1/2}$ (hr), mean (SD)	47.0 (6.6)	49.6 (7.1)

- C_{max}, AUC_{0-tau} and AUC_{inf} were higher in elderly vs. younger adults.
- T_{max} occurred earlier in elderly adults.

Relative Bioavailability

PK Parameter*	Younger Adults (n=18)	Elderly Adults (n=13)	Elderly/Younger Ratio (95% CI)
C_{max} (mg/L)	1.20	1.56	130% (109–156)
AUC_{inf} (hr•mg/L)	77.2	109	141% (120–166)
AUC_{0-tau} (hr•mg/L)	84.3	122	144% (124–169)

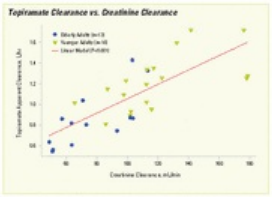
*Geometric LSM

- C_{max}: ~30% higher in elderly vs. younger adults.
- AUC: 41%-44% higher in elderly adults.
- 90% CIs for PK parameters fell partially outside the 80%-125% equivalence limits.

TPM clearance was 29% lower in elderly subjects, resulting in higher C_{max}, AUC_{0-tau} and AUC_{inf} (30%, 41%, and 44%, respectively) in elderly vs. younger adults.

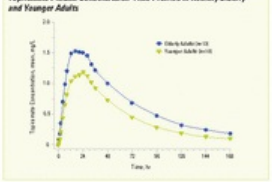
TPM clearance was highly correlated with creatinine clearance (calculated). Creatinine clearance was 36% lower in elderly subjects.

Topiramate Clearance vs. Creatinine Clearance



Although C_{max} and AUC in elderly adults were both higher than in younger adults, the rate of decline in plasma concentration appeared similar in both age groups, with an apparent elimination half-life of 47 hrs in younger subjects and 49 hrs in older subjects.

Topiramate Plasma Concentration-Time Profiles in Healthy Elderly and Younger Adults



Safety and Tolerability

	Younger Adults (n=18)	Elderly Adults (n=13)
Adverse Events		
Overall	8 (44%)	10 (78%)
Treatment-related	7 (39%)	3 (23%)
In >1 subject	Headache 3 (17%)	Puncture site hemorrhage 4 (31%)
	Somnolence 3 (17%)	Headache 3 (23%)
	Dysgeusia 2 (11%)	

- Treatment-related adverse events (AEs) were mild in severity and more frequent in younger vs. older adults.
- No serious AEs, deaths, or discontinuations due to AEs occurred during the study.
- Mean creatinine clearance (calculated) was 35% lower in elderly (77 mL/min/1.73m²) vs. younger (119 mL/min/1.73m²) adults.
- No new or unexpected safety or tolerability signals were observed.

Conclusions

- A single 100-mg dose of SPN-538 resulted in higher peak level and greater overall TPM exposure in elderly vs. younger adults.
- The increase in TPM exposure was consistent with reductions in estimated renal function (i.e., calculated creatinine clearance) and similar to results seen with TPM-IR in an elderly population.
- Dosage recommendations for SPN-538 in elderly patients are the same as for TPM-IR, i.e., reduce dose according to renal function status rather than age (one-half the adult dose if creatinine clearance <70mL/min/1.73m²).

Study funded by Supernus Pharmaceuticals, Inc.

For questions about the data presented above, please contact the Medical Affairs Department of Supernus Pharmaceuticals via Prosar Corp. at medinfo@prosarcorp.com.

O'Neal W, Brittain S, Stocks J, Johnson J, Barold P. Pharmacokinetics of once-daily, extended-release, Trokendi XR™ (SPN-538) in the elderly. *Epilepsy Curr.* 2014; 14 (Suppl. 1): 3.396.

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

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Background

Oxcarbazepine (OXC), via its active metabolite 10-monohydroxy derivative (MHD), is similar to carbamazepine in efficacy but has more favorable metabolism and pharmacokinetics. However, the therapeutic success of immediate-release OXC (OXC-IR) has often been limited by dose-related toxicity.[1-3] Several of the side effects most frequently associated with OXC-IR Q12h (e.g., dizziness, coordination difficulties, blurred vision) are among those shown to be most deleterious to quality of life.[4]

SPN-804 (Oxtellar XR™; Supernus Pharmaceuticals) is an extended-release OXC tablet using a novel matrix delivery (Solutrol®) technology. SPN-804 slows OXC absorption and reduces plasma MHD exposure ~19% (AUC, C_{min}) to ~15% (C_{max}) relative to OXC-IR 600 mg Q12h.[5] A crossover PK study of 1200 mg SPN-804 QD vs OXC-IR (Trileptal) 600 mg Q12h in healthy volunteers (N=30) suggested the potential for improved tolerability with SPN-804; dizziness was not reported during the SPN-804 period whereas 11/30 (37%) reported dizziness with OXC-IR Q12h exposure.

The efficacy, tolerability, and safety of SPN-804 QD (1200 and 2400 mg) was evaluated in a 16-wk double-blind, placebo-controlled trial (Prospective, Randomized Study of OXC XR in Subjects with Partial Epilepsy Refractory, PROSPER; ClinicalTrials.gov identifier: NCT00772603). This Phase 3 study led to FDA approval in October 2012 of Oxtellar XR as once-daily adjunctive therapy for partial-onset seizures with or without secondary generalization in adults and children ≥6 yrs.

Study Design

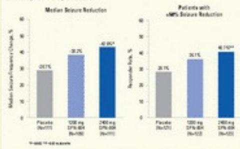
Study design	Multinational, multicenter, randomized, double-blind, parallel-group study
Randomization (1:1:1)	• Placebo QD • 1200 mg SPN-804 QD • 2400 mg SPN-804 QD (blinded down-titration to 1800 mg allowed)
Double-blind Treatment Duration	16 wks (titration, 4 wks; maintenance, 12 wks)
Titration	600 mg increments at 2-wk intervals
Patients	• 18-65 yrs of age with inadequately controlled partial-onset seizures with/without secondary generalization • ≥3 seizures/28 days in baseline (partial-onset seizures without discognitive features, i.e., simple partial seizures, had to have observable motor component to be counted) • 1-3 concominant AEDs at stable doses (VNS allowed but not counted as AED; current OXC use or history of being refractory to OXC 1200 mg/day not allowed)
Primary Efficacy Endpoint	Median percent change from baseline 28-day seizure frequency
Other Efficacy Measures	Responder rate (proportion of patients with ≥50% seizure frequency reduction), proportion of patients seizure-free 16 wks
Statistical Analysis	Wilcoxon rank-sum test with overall Type I error rate α=0.050 using step-up Hochberg procedures: If both observed p-values were ≤0.050 in favor of both SPN-804 groups, then differences for both groups were declared significant. If the observed p-value was >0.050 for only one SPN-804 group, then the other SPN-804 group was significantly superior to placebo only if p≤0.025.
Intent-to-Treat (ITT) Population	All randomized patients who received ≥1 dose of study drug, had baseline seizure diary data, and ≥1 visit during double-blind treatment. For primary efficacy analysis, patients had to have analyzable seizure diary data, i.e., for ≥21 consecutive days in baseline and ≥14 consecutive days after study drug receipt. Patients down-titrated to 1800 mg SPN-804 were included in 2400 mg group for all analyses.
Safety Population	All randomized patients who received ≥1 dose of study drug

Results

Demographics and Baseline Characteristics (Safety Population)

Characteristic	Placebo (N = 121)	SPN-804, mg/day 1200 (N = 122)	SPN-804, mg/day 2400 (N = 123)
Age (yrs), mean	39.1	39.1	38.5
Female, %	55.4	58.2	52.0
Race, %			
White	80.4	85.2	85.4
Black	9.0	4.1	0.8
Other	10.7	10.7	13.8
Epilepsy duration (yrs), mean	21.2	21.3	19.8
Baseline seizure frequency (seizures/28 days), median	7.0	6.0	6.0
Concomitant AEDs, %			
1 AED	35.5	29.5	32.5
2 AEDs	50.4	55.7	54.5
3 AEDs	14.0	14.8	13.0
Valproate	37.2	45.1	50.4
Carbamazepine	35.4	43.4	39.8
Lamotrigine	30.5	25.4	27.6
Levetiracetam	22.3	16.4	22.8
Topiramate	17.3	18.0	18.7
Phenytoin	3.3	2.5	1.6
Other	21.5	23.0	14.6

Efficacy (ITT Population)



Pre-specified Pragmatic ITT Analysis of Seizure Freedom[a]

	Placebo (N=121)	SPN-804, mg/day 1200 (N=122)	SPN-804, mg/day 2400 (N=123)
Patients seizure-free 16 wks	3.3%	4.9%	11.4%
p-value vs placebo[b]		0.52	0.006

[a]Overall ITT population as denominator; patients only considered seizure free if they completed double-blind treatment; patients discontinuing early counted as non-responders[6]
[b]Fisher's exact test

- SPN-804 2400 mg QD statistically superior to placebo in key efficacy measures
  - Median % seizure reduction
  - Response rate (% patients with ≥50% seizure reduction)
  - Seizure-free rate
- Although efficacy outcomes were numerically superior to placebo, SPN-804 1200 mg/day failed to separate statistically from placebo in the primary endpoint analysis. Other analyses, including a sensitivity analysis (regional differences showing differences favoring both SPN-804 doses over placebo in median seizure frequency reduction) and a concentration-response analysis, documented the efficacy of 1200 mg SPN-804, which was approved by FDA as a target dose when initiating therapy with Oxtellar XR.

Treatment-Emergent Adverse Events (Safety Population)

	% Patients Placebo (N=121)	SPN-804, mg/day 1200 (N=122)	SPN-804, mg/day 2400 (N=123)
Any adverse event	55.4	56.6	69.1
Serious adverse events	5.8	5.7	8.1
Adverse events leading to discontinuation	12.4	14.8	30.1
Incidence			
Dizziness	14.9	19.7	40.7
Vomiting	9.1	5.7	15.4
Headache	7.4	8.2	15.4
Somnolence	9.1	11.5	13.8
Diplopia	4.1	9.8	13.0
Nausea	11.6	11.5	12.2
Asthenia	0.8	3.3	7.3
Balance disorder	5.0	4.9	6.5
Fatigue	0.8	5.7	3.3

- Overall adverse event (AE) incidence was similar in placebo and SPN-804 1200 mg groups
- Most frequently reported AEs – dizziness, nausea, somnolence, vomiting, headache, and diplopia – were typically dose-related
- In SPN-804 groups, AEs resulting in discontinuation occurred primarily during forced-titration phase (1200 mg: 13/18, 65%; 2400 mg: 26/37, 70%); 23 (19%) patients were down-titrated from 2400 mg to 1800 mg
- Serious AEs considered study drug-related: SPN-804 1200 mg group, n=0; placebo group, n=3 (one patient each with erythematous rash, Stevens-Johnson syndrome, or dizziness); SPN-804 2400 mg, n=6 (one patient each with symptomatic hyponatremia, generalized rash, dizziness, vomiting; 2 patients with general drug intolerance characterized by other non-serious AEs, e.g., dizziness, diplopia, nausea, vomiting, abdominal pain, and/or headache). Study drug discontinued in all patients with serious AEs
- No new safety concerns identified with SPN-804 1200 and 2400 mg QD

Discussion

In the PROSPER study, median percent seizure reductions with SPN-804 1200 mg (-38%) and 2400 mg (-43%) were similar to those observed with 600 mg Q12h (-40%) and 1200 mg Q12h (-50%) OXC-IR in a similarly designed study[6] that was used to determine sample sizes for the PROSPER study. However, given the magnitude of the placebo response in the PROSPER study (nearly 4-fold higher than OXC-IR study), the number of randomized patients in the PROSPER study may have been too low to demonstrate a significant effect favoring SPN-804 1200 mg QD over placebo. Other analyses of PROSPER study data documented a significant treatment effect for SPN-804 1200 mg QD (results summarized separately in companion posters), resulting in FDA approval of 1200 mg QD as an initial target dose in adults for Oxtellar XR as adjunctive therapy.

In a similarly designed study of OXC-IR Q12h, 36% of patients assigned to OXC-IR 600 mg Q12h discontinued due to AEs.[6] The most common AEs with OXC-IR 600 mg Q12h – dizziness, 32%; diplopia, 30%; somnolence, 26%; vomiting, 25%; nausea, 25%; ataxia, 17% – were reported less frequently in patients receiving 1200 mg SPN-804 QD while discontinuations due to AEs was 15%. Similar differences were observed for OXC-IR and SPN-804 at 2400 mg. Although indirect comparisons of the OXC-IR study[6] and PROSPER study with SPN-804 are somewhat confounded by differences in study design (e.g., treatment duration, titration rate), the results are suggestive of the potential for improved tolerability with SPN-804. Seizure-free rates in the two studies hint at the potential therapeutic benefit if tolerability and retention can be improved with once-daily SPN-804. In the pragmatic ITT analysis of seizure-free rates in the PROSPER study, 11.4% of patients assigned to SPN-804 2400 mg were seizure-free for 16 wks; with the higher discontinuation rates in the OXC-IR study (treatment-limiting adverse events: 600 mg Q12h, 36%; 1200 mg Q12h, 67%), the pragmatic ITT seizure-free rate was 1.2%.[6]

Conclusions

- Adjunctive once-daily SPN-804 improves seizure control in patients with inadequately controlled partial-onset seizures with or without secondary generalization
- Once-daily 1200 mg and 2400 mg SPN-804 are generally well tolerated
- Adverse event frequency, as observed in the PROSPER study, is consistent with the pharmacokinetic profile of SPN-804 which produces lower peak plasma concentrations vs OXC-IR

Study funded by Supernus Pharmaceuticals, Inc.

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For questions about the data presented above, please contact the Medical Affairs Department of Supernus Pharmaceuticals via Prosar Corp. at medinfo@prosarcorp.com.

French JA, Baroldi P, Brittain ST, Johnson JK for PROSPER Investigators. Efficacy and safety of extended-release oxcarbazepine (Oxtellar XR™) as adjunctive therapy in patients with refractory partial-onset seizures: A randomized controlled trial. *Acta Neurol Scand* (in press).

Efficacy and Tolerability of Oxtellar XR™, A Novel Once-Daily, Extended-Release Formulation of Oxcarbazepine, As Adjunctive Treatment of Refractory Partial Seizures in a North American Subpopulation

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Background

Although oxcarbazepine (OXC), via its active moiety 10-monohydroxy derivative (MHD), is similar to carbamazepine in efficacy[1] and has more favorable metabolism and pharmacokinetics, the therapeutic success of immediate-release OXC (OXC-IR) has often been hampered by:

- Dose-related toxicity limiting the ability to achieve dosages >1200 mg/day OXC-IR that can offer potentially greater activity against seizures[1,2]
- Frequent occurrence of intermittent and/or persistent side effects most deleterious to quality of life (eg, dizziness, coordination difficulties, blurred vision)[3] as well as patient adherence.

Oxtellar XR™ (Supernus Pharmaceuticals) is a novel extended-release OXC tablet using a matrix delivery technology that delivers a unique plasma MHD concentration profile, allowing once-daily dosing and improving OXC tolerability vs. OXC-IR.

Approved by the FDA as once-daily adjunctive therapy for partial-onset seizures (adults and children aged ≥6 years), Oxtellar XR (1200 mg and 2400 mg once daily) was evaluated in a 18-week multinational, double-blind, placebo-controlled trial (INCT00772603).

- Key efficacy endpoints showed significant differences favoring 2400 mg/day Oxtellar XR over placebo. However, unexpectedly high placebo response may have compromised the study's ability to demonstrate that the numerical differences favoring 1200 mg/day Oxtellar XR over placebo were statistically significant.
- Because responses in multinational clinical trials can exhibit geographic differences, eg, influence of racial/genetic factors, local practice patterns, and cultural factors, a cluster analysis of study centers in the United States, Mexico, and Canada evaluated study outcomes in a population most relevant to the U.S. healthcare system.

Study Design

Multinational, multicenter, double-blind, 3-arm, parallel-group study:
1:1:1 randomization to placebo, Oxtellar XR 1200 mg/day, Oxtellar XR 2400 mg/day*

- 6-wk baseline
- 18-wk double-blind study: 4-wk titration (600-mg increments at weekly intervals) followed by 12-wk maintenance phase

Key Patient Characteristics

- 18-65 yrs of age
- Inadequately controlled partial-onset seizures with/without secondary generalization
- ≥3 seizures/28 days in baseline
- Receiving 1-3 AEDs at stable doses (VNS allowed but not counted as AED)

Assessments

- Primary efficacy endpoint: Median percent change in 28-day seizure frequency for 18-wk double-blind treatment period vs baseline
- Other efficacy measures: Treatment response (proportion of patients with ≥50% seizure frequency reduction from baseline during 18-wk double-blind treatment period) and seizure freedom
- Statistical analysis: Wilcoxon rank sum test with overall Type I error rate $\alpha = 0.050$ using step-up Hochberg procedure: if $P \leq 0.050$ in favor of both Oxtellar XR groups, both groups are statistically superior to placebo. If $P > 0.050$ for one Oxtellar group, the other group is statistically superior to placebo only if $P \leq 0.025$ for that group
- Intent to Treat population (ITT): All randomized patients who received ≥1 dose of study drug, had baseline seizure diary data, and ≥1 visit during double-blind treatment
- Safety population: All randomized patients who received ≥1 dose of study drug
- North American subset: 116/288 (32%) ITT patients at study centers in U.S., Canada, and Mexico

*Blinded down titration to 1800 mg/day allowed

For questions about the data presented above, please contact the Medical Affairs Department of Supernus Pharmaceuticals via Prosar Corp. at medinfo@prosarcorp.com.

Results

Patient Demographics and Baseline Characteristics: North American Subset (ITT, N=116)

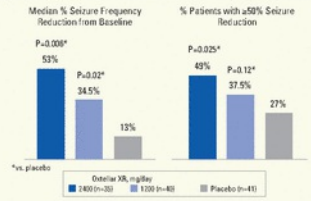
	Placebo (n=41)	Oxtellar XR, mg/day 1200 (n=40)	2400 (n=35)
Age, mean (SD), yrs	39 (13)	41 (11)	37 (12)
Gender, M/F, %	41/59	42.5/57.5	54/46
Race, %			
White	78	85	57
Black	2	12.5	3
Other	20	22.5	40
Concomitant AEDs, %			
1 AED	34	37.5	29
2 AEDs	51	45	54
≥3 AEDs	15	17.5	17
Carbamazepine	32	42.5	31
Lamotrigine	22	30	34
Levetiracetam	32	22.5	34
Topiramate	17	12.5	17
Valproate	24	32.5	37

Tolerability and Safety: North American Safety Subset (N=119)

	% (n) Patients		
	Placebo (n=43)	Oxtellar XR, mg/day 1200 (n=40)	2400 (n=36)
Any adverse event	86 (37)	77.5 (31)	89 (32)
Treatment-related adverse event	63 (27)	60 (24)	69 (25)
Any serious adverse event*	9 (4)	10 (4)	6 (2)
Adverse event leading to discontinuation	9 (4)	27.5 (11)	28 (10)
Most common adverse events			
Dizziness	28 (12)	30 (12)	25 (9)
Headache	14 (6)	7.5 (3)	17 (6)
Diplopia	0	10 (4)	11 (4)
Fatigue	2 (1)	7.5 (3)	6 (2)
Nausea	9 (4)	17.5 (7)	6 (2)
Somnolence	5 (2)	12.5 (5)	3 (1)
Vomiting	5 (2)	12.5 (5)	0

*One death occurred in a patient on placebo

Efficacy Outcomes for 16-Week Treatment Period (ITT): North American Subset (N=116)



- Seizure-free rates for 18-week treatment period: Placebo 1/41 (2%); Oxtellar XR 1200 3/40 (7.5%, P=0.33); Oxtellar XR 2400 4/35 (11%, P=0.19)
- Seizure-free rates for 12-week maintenance period: Placebo 1/41 (2%); Oxtellar XR 1200 2/40 (5%, P=0.58); Oxtellar XR 2400 6/35 (17%, P=0.01)

Conclusions

- Once-daily Oxtellar XR exhibited dose-related efficacy in the North American subset with both 1200 mg/day and 2400 mg/day doses significantly reducing partial-onset seizure frequency.
- Once-daily Oxtellar XR 2400 mg/day also demonstrated significant superiority vs placebo in responder rate and seizure-free rate during the maintenance phase.
  - Both Oxtellar XR dosages were generally well tolerated; no new safety signals were observed.
  - Incidences of adverse events were lower than in a similarly designed placebo-controlled study of 1200 mg/day and 2400 mg/day administered as b.i.d. OXC-IR.[3]
  - Fewer patients receiving Oxtellar XR discontinued due to adverse events (Oxtellar XR 1200, 27.5%; Oxtellar XR 2400, 28%) when compared with similarly designed placebo-controlled study (placebo, 9%; OXC-IR 1200, 32%; OXC-IR 2400, 61%).[3]
- Because better tolerated therapy has the potential to be more effective therapy, Oxtellar XR may increase the opportunities for seizure control by allowing higher, more effective dosages to be achieved.
- Simplified dosing and improved tolerability of once-daily Oxtellar XR facilitates patient adherence which may have a potentially positive impact on outcomes.

Study funded by Supernus Pharmaceuticals, Inc.

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Pharmacokinetic/Pharmacodynamic Analysis of Extended-Release Once-Daily SPN-804 (Oxtellar XR™) in Adults with Epilepsy: Correlation of MHD Concentrations and Seizure Reduction

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Background

Oxcarbazepine (OXC) is almost completely converted to its 10-monohydroxy derivative (MHD), the active metabolite primarily responsible for the drug's antiseizure activity. As an immediate-release (IR) formulation, OXC requires twice-daily dosing due to the rapid absorption and conversion to MHD and to the relatively short half-life (~9 hrs) of MHD. The plasma MHD concentration profile following OXC-IR administration is characterized by considerable fluctuation during the dosing interval. MHD concentrations, particularly at the post-dose peak and at higher OXC-IR dosages, have been associated with intermittent and/or persistent adverse events (e.g., dizziness, coordination difficulties, blurred vision) that can negatively impact quality of life.

SPN-804 (Oxtellar XR™, Supernus Pharmaceuticals) is an extended-release OXC tablet using a novel matrix delivery (Solutrol™) technology. Its plasma MHD concentration profile allows once-daily dosing and may improve tolerability. Oxtellar XR is approved by the FDA as once-daily adjunctive therapy for partial-onset seizures (adults and children ≥6 yrs) at a recommended dose of 1200-2400 mg once-daily for adults.

SPN-804 (1200 mg QD, 2400 mg QD) was evaluated in a 16-week double-blind, placebo-controlled trial (Prospective Randomized Study of OXC-XR in Subjects with Partial Epilepsy Refractory, PROSPER, NCT00772603).[1] In this study, significant differences favored 2400 mg SPN-804 QD over placebo in key efficacy endpoints (e.g., median percent reduction from baseline 28-day seizure frequency) whereas numerical differences favoring 1200 mg over placebo did not achieve statistical significance. Although the treatment effects achieved with both SPN-804 doses were similar to those observed with OXC-IR in a similarly designed trial,[2] the effect size in the PROSPER study was smaller due to a nearly four-fold higher placebo response, perhaps reflecting a "placebo drift" that has been especially notable over the last 5 years in AED adjunctive trials.[3] In light of the established efficacy of 1200-2400 mg OXC-IR, an analysis was undertaken to examine the concentration-response relationship in the PROSPER study.

Methods

PROSPER Study

Study design	Multinational, multicenter, randomized, double-blind, parallel-group study
Randomization (1:1:1)	Placebo QD; 1200 mg SPN-804 QD; 2400 mg SPN-804 QD (blinded down-titration to 1800 mg allowed before maintenance)
Double-blind Treatment Duration	16 wks (titration, 4 wks; maintenance, 12 wks)
Patients	• 18-65 yrs of age with inadequately controlled partial-onset seizures with/without secondary generalization • ≥3 seizures/28 days in baseline despite 1-3 AEDs at stable doses
Primary Efficacy Endpoint	Median percent change from baseline 28-day seizure frequency
PK Samples	Per PROSPER protocol, 5 samples per patient were to be drawn over the course of maintenance (n=3) and taper/conversion periods at pre-dose and 1, 2, 4, 7 hr post-dose

Population PK Model

The primary structural population pharmacokinetic (PK) model for OXC and MHD was developed from a randomized-sequence crossover study of SPN-804 QD and OXC-IR Q12h with intensive PK sampling at steady state in healthy volunteers. When applied to data from the PROSPER study, the primary structural model fit the PROSPER patient data well. Release of OXC from SPN-804 and its subsequent gastric absorption were modeled as a single first-order process. Pharmacokinetics of OXC followed a two-compartment model; PK of MHD followed a one-compartment model with MHD produced by a first-order process from the central OXC compartment. Three covariates were included in the model: weight, dose, and AED co-therapy. Apparent clearance of OXC and MHD increased with weight; production of MHD from OXC was larger when the administered dose was smaller; and co-therapy with carbamazepine, phenytoin, phenobarbital or valproate increased apparent clearance of MHD.

Using the validated population PK model, PK variables were derived for each subject at each visit for which there was a valid PK observation. MHD C_{min} was derived by inspection of the individual predicted (patient-specific) concentration-time profile for that visit. A single representative value for C_{min} was calculated for each patient in the PK analysis dataset by taking the median across visits. Results of this analysis were applied to the analysis of pharmacodynamic (PD) data, i.e., percent change (PCH) in 28-day seizure frequency.

PK/PD (Emax) Model

A sigmoidal Emax model was fit to the C_{min} and PCH data for patients with estimated C_{min} values:

$$PCH = PCH_0 - Emax\left[\frac{1}{1+(C_{50}/C_{min})^{\gamma}}\right]$$

where PCH_0 is the intercept (upper asymptote), Emax is the maximum effect size, C_{50} is the concentration producing 50% of Emax, and γ is the shape factor; γ was fixed to a series of values and the remaining parameters were estimated. For each value of γ, the fit of the model to the data was evaluated graphically.

Results

The population PK subgroup comprised 186 patients from SPN-804 treatment groups (1200 mg/day, n=85; 2400 mg/day, n=101) for whom a representative C_{min} value over the Treatment Phase (titration + maintenance) could be estimated in the population PK analysis. Estimated median C_{min}: 1200 mg, 11.7 mg/L; 2400 mg, 19.4 mg/L; overall, 13.9 mg/L.

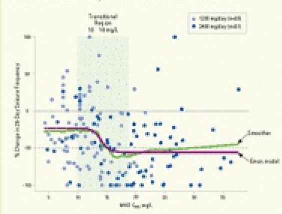
PK/PD Modeling

For the concentration-response analysis, percent change from baseline 28-day seizure frequency (PCH) was plotted against MHD C_{min} for each patient in the population PK subgroup (Fig. 1).

Key Observations

- PCH values for majority of patients, regardless of group, were associated with improvements (PCH < 0) and few patients demonstrated worsening PCH (PCH > 50).
- Smoothers drawn through data demonstrated strong relationship between PCH and MHD C_{min}.
- Sharpest transition from non-responsive (PCH < -50) to responsive (PCH > -50) occurred at C_{min} > 14 mg/L.

Figure 1. Plot of Individual MHD C_{min} Estimated from Population PK Model and Percent Seizure Change (PCH) for PROSPER Treatment Phase

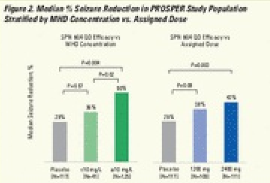


Sensitivity analyses were performed to examine the concentration-response relationship above and below critical values of C_{min} and PCH. At all C_{min} critical values between 10 and 18 mg/L (transitional region, Fig. 1), the responder/nonresponder ratio (i.e., number of patients above/below critical PCH) was significantly (P < 0.05) higher for concentrations above the critical C_{min} than for concentrations below, demonstrating that MHD C_{min} values as low as 10 mg/L were significantly linked to clinical improvement.

The shape of smoothers through the plot of PCH vs C_{min} data indicated that an Emax model could best describe the PK/PD data. A sigmoidal Emax model with γ = 20 most closely matched the shape of the smoother (Fig. 1). The value of C_{50} (14.04 mg/L) estimated in this model was also a highly significant critical C_{min} value in the sensitivity analyses; the lower asymptote (PCH_0 – Emax = -55.73) was better than the responder definition of PCH ≤ -50.

Overall, the results of the Emax model reinforced the graphical and statistical analyses demonstrating that the efficacy of SPN-804 QD increases as MHD C_{min} increases from 10 to 18 mg/L. Above 18 mg/L, an increase in plasma MHD concentration was 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



Conclusions

- Following OXC administration and absorption, OXC is almost completely converted to the MHD active metabolite. A population PK model was used to estimate MHD C_{min} for 186 patients receiving SPN-804 treatment in the PROSPER study.
- Values for estimated MHD C_{min} were compared with clinical outcome, i.e., percent change from baseline 28-day seizure frequency (PCH), and demonstrated a highly significant relationship. C_{min} values as low as 10 mg/L MHD significantly improved seizure control.
- Results suggest a continuum of efficacy in the 1200 mg to 2400 mg dose range, with a concentration-response relationship observed between MHD C_{min} concentration ≥10 mg/L and seizure reduction. However, above 18 mg/L, increases in MHD plasma concentrations are unlikely to result in further clinical improvement.
- Although it failed to separate statistically from placebo in the primary analysis, 1200 mg SPN-804 was shown to be an efficacious dose in the concentration-response analysis. Most patients (69%) receiving SPN-804 1200 mg/day achieved trough MHD concentrations associated with a significant clinical effect.

Study funded by Supernus Pharmaceuticals, Inc.

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1. French JA, Baroldi P, Brittain ST, Johnson JK for PROSPER Investigators. Efficacy and safety of extended-release oxcarbazepine (Oxtellar XR™) as adjunctive therapy in patients with refractory partial-onset seizures: A randomized controlled trial. Acta Neurol Scand. In press.
2. Barcs G, Walker E, Elger C et al. Oxcarbazepine placebo-controlled, dose-ranging trial in refractory partial epilepsy. Epilepsia 2000;41:1597-607.
3. Rheims S, Perucca E, Cucherat M et al. Factors determining response to antiepileptic drugs in randomized controlled trials. A systematic review and meta-analysis. Epilepsia 2011;52:219-33.

For questions about the data presented above, please contact the Medical Affairs Department of Supernus Pharmaceuticals via Prosar Corp. at medinfo@prosarcorp.com.

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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

J.K. Johnson[1]; J.A. French[2]; S.T. Brittain[1]; D. Louro[1]
[1]Supernus Pharmaceuticals, Inc., Rockville, MD; [2]NYU Comprehensive Epilepsy Center, New York, NY

Background

Dosing recommendations for immediate-release oxcarbazepine (OXC-IR) as adjunctive therapy – 600 mg b.i.d. – reflect the ~9 hr half-life of the active metabolite (10-monohydroxy derivative, MHD) and results of a double-blind, placebo-controlled trial in which most patients (67%) receiving 1200-2400 mg/day OXC-IR discontinued due to intolerable side effects.[1,2]

- In clinical practice conditions, nearly 30% of patients discontinued OXC-IR due to treatment- or dose-limiting side effects – more than twice the proportion discontinuing due to inadequate seizure control.[3]
- Intermittent and/or persistent side effects especially deleterious to quality of life (eg, dizziness, coordination difficulties, blurred vision)[4] correlate with plasma MHD concentrations, particularly MHD concentrations >30 μg/mL.[5,6]
- Oxtellar XR™ (Supernus Pharmaceuticals) is a novel extended-release OXC tablet that uses Solutrol™ delivery technology to produce a unique plasma MHD concentration profile that may improve tolerability vs. OXC-IR.
- Oxtellar XR is approved by the FDA as once-daily adjunctive therapy in partial-onset seizures (adults and children aged ≥6 yrs), with recommended daily dose of 1200-2400 mg once-daily for adults.
- Oxtellar XR QD (1200 mg, 2400 mg) was evaluated in a 16-week, double-blind, placebo-controlled trial (Prospective Randomized Study of OXC-XR in Subjects with Partial Epilepsy Refractory, PROSPER; NCT00772603).[7] Patients completing double-blind treatment were eligible to participate in the open-label extension study; results for 1 year of open-label treatment are reported here.

Study Design

- Key inclusion criteria for initial double-blind, placebo-controlled trial: adults (age, 18-65 yrs) with inadequately controlled partial-onset seizures (baseline frequency: ≥3 seizures/28 days) despite 1-3 concomitant antiepileptic drugs (AEDs) at stable doses.
- All patients entered the open-label study receiving 1200 mg Oxtellar XR QD after a blinded conversion phase, with doses adjusted as clinically indicated to achieve optimal response (increments/decrements, 600 mg QD; maximum, 2400 mg QD).
- Key open-label assessments: Median % reduction from baseline 28-day seizure frequency; proportion of patients with ≥50% seizure reduction; proportion of patients seizure-free; tolerability/safety.

For questions about the data presented above, please contact the Medical Affairs Department of Supernus Pharmaceuticals via Prosar Corp. at medinfo@prosarcorp.com.

Results

Open-Label Extension: Patient Characteristics (N=214)

Age, mean (SD)	37 (9.9) yrs
Male/female	48%/52%
Race	
White	83%
Black	3%
Native American/Alaskan	<0.5%
Asian	<0.5%
Other	14%
Concomitant AEDs (≥10% of patients)	
Valproate	32%
Carbamazepine	34%
Lamotrigine	25%
Topiramate	20%
Levetiracetam	16%

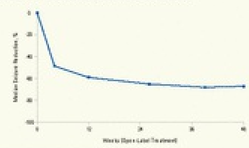
Median % Seizure Reduction vs Assignment in Initial Double-Blind Study (N=214)

Initial Assignment in Double-Blind Study	Double-Blind Study: n	Double-Blind Study: Median % Seizure Reduction	Open-Label Extension: n	Open-Label Extension: Additional Seizure Reduction	Double-Blind + Open-Label: n	Double-Blind + Open-Label: Total Seizure Reduction
1200 mg Oxtellar XR	109	-32%	76	-19%	76	-50%
2400 mg Oxtellar XR	111	-43%	49	-12%	49	-56%
Placebo	117	-28%	72	-39%*	72	-64%*

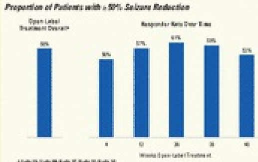
* Improvement following addition of Oxtellar XR

- Regardless of initial treatment assignment in the double-blind study, incremental benefit of once-daily Oxtellar XR was observed during open-label treatment.
  - Patients initially receiving placebo in double-blind trial exhibited expected improvements when Oxtellar XR was added.
  - Additional improvement was observed in open-label treatment when Oxtellar XR dosages could be adjusted according to clinical response in patients initially randomized to double-blind treatment with Oxtellar XR forced titrated to assigned fixed dose in the double-blind study.

Open-Label ITT Population (N=214): Median % Seizure Frequency Reduction from Baseline



Proportion of Patients with ≥50% Seizure Reduction



- Treatment effect – i.e., median % reduction from baseline seizure frequency; patients with clinically significant treatment response (≥50% seizure reduction) – was sustained with continued once-daily Oxtellar XR treatment.

Patients Seizure-Free During Open-Label Treatment

Seizure-free for at least one 8-wk interval[a]	13% - 50%
Seizure-free ≥1 yr (last observation carried forward)	7%
Seizure-free ≥1 yr (pragmatic ITT[b])	4%

[a]Initial study entry required ≥3 seizures per 28 days (8 wks), on average
[b]Completers seizure free at all open-label visits/ITT population (dropouts not considered seizure free)

- A subset of patients became seizure free at least 1 year with addition of once-daily Oxtellar XR despite refractory partial-onset seizures inadequately controlled with 1-3 concomitant AEDs.

Long-Term Tolerability and Safety: 1-Year Open-Label Treatment (N=214)

Any adverse event (AE)	58%
Treatment-related AEs	33%
Serious AEs	7%
AE-related actions	
Dose modification	16%
Temporary interruption	4%
Discontinuation	5%
Most common AEs (≥5% incidence)	
Dizziness	15%
Headache	11%
Diplopia	9%
Nausea	7%
Vomiting	6%
Somnolence	6%
Balance disorder	5%
Upper respiratory tract infection	5%

- Discontinuations due to AEs: 5% (n=10) in the overall open-label population; 8% among patients in whom Oxtellar XR therapy was initiated after receiving placebo in the double-blind trial.
- Patients converted from double-blind placebo to open-label Oxtellar XR (N=77; 36% of open-label population) accounted for:
  - ~50-75% of most common AEs (i.e., dizziness, headache, diplopia, nausea, vomiting, balance disorder, vision blurred)
  - 60% of discontinuations due to treatment-limiting AEs
- No new safety signals; no clinically significant changes from baseline in vital signs, ECGs, laboratory values with 1 year open-label treatment.
- No deaths attributed to study medication were reported. (One patient died following thrombosis, which the investigator considered unlikely related to study medication.)

Conclusions

- Seizure control achieved with once-daily Oxtellar XR during the double-blind PROSPER study was maintained and further improved during the open-label extension when dosages could be optimized according to clinical response.
- Patients converted from double-blind placebo to open-label Oxtellar XR contributed disproportionate share of the most common CNS AEs as well as discontinuations due to AEs during the 1-year open-label extension. However, with flexible dosing, the discontinuation rate in former placebo patients (8%) was substantially lower than in patients force-titrated to once-daily 1200 mg in the double-blind trial (19%).
- Oxtellar XR was well tolerated during long-term maintenance therapy. Improved tolerability with once-daily Oxtellar XR may allow higher and potentially more effective OXC dosages to be achieved.
- Once-daily Oxtellar XR may be a suitable alternative to OXC-IR when tolerability and/or nonadherence jeopardize seizure control.

Study funded by Supernus Pharmaceuticals, Inc.

References:
1. Trileptal Prescribing Information. Novartis Pharmaceuticals Corp. [illegible]
2. [illegible]
3. [illegible]
4. [illegible]
5. [illegible]
6. [illegible]
7. [illegible]
8. [illegible]
9. [illegible]

Presented at the Supernus-sponsored Scientific Exhibit, 67th Annual American Epilepsy Society Meeting, December 6-10, Washington, DC.

Effect of Alcohol on Bioavailability of Extended-Release, Once-Daily SPN-538 (Trokendi XR™) in Healthy Adult Males

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Supernus Pharmaceuticals, Inc., Rockville, MD

Background

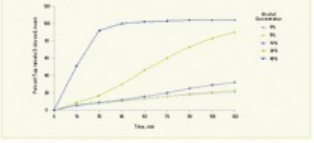
Modified-release drugs may contain excipients that are more soluble in alcohol than water. "Dose dumping" may result if drug release is accelerated in the presence of alcohol, increasing the risk of toxicity or sub-therapeutic effects.

SPN-538 (Trokendi XR®, Supernus Pharmaceuticals, Inc.) is a novel extended-release, once-daily capsule formulation of topiramate (TPM) that is pharmacokinetically bioequivalent to immediate-release TPM (Topamax®, Janssen Pharmaceutical) administered twice daily.

In vitro data showed that, in the presence of alcohol, the pattern of TPM release from SPN-538 capsules is significantly altered. Dissolution profiles were compared in dilute HCl solutions containing 0%-40% alcohol. While the dissolution rates for 0% and 5% alcohol were similar, higher alcohol concentrations were associated with increasingly faster release of TPM, indicating early drug release in the presence of alcohol.

However, because *in vitro* dissolution experiments are not necessarily predictive of *in vivo* behavior, a PK study in healthy volunteers was conducted to evaluate the dose-related effects of alcohol co-administration on the bioavailability of 200 mg SPN-538.

***In vitro* Dissolution Profile: Mean Percentage of Topiramate Released from 200-mg SPN-538 Capsules vs. Time in Solutions Containing 0%-40% Alcohol (N=12)**

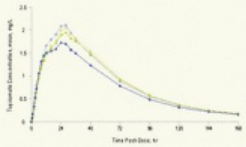


Study Highlights

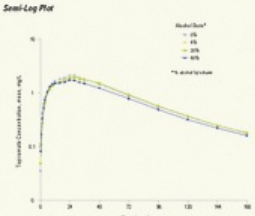
Subjects	Fasting healthy volunteers (males, 21-55 yr)
Study Design	• Open-label, crossover • Single dose • Four treatment periods with varying alcohol doses in randomized sequence • 30-day washout between treatments
SPN-538 Dose	200-mg SPN-538 capsule as a single dose
Alcohol Doses	0%, 4%, 20%, 40% (% alcohol by volume with orange juice to total 240 mL, ~8 oz)
PK Sampling	Pre-dose and at specified post-dose intervals for 6 wk (960 hrs)
Primary PK Parameters	• TPM exposure from dosing to last measurable concentration (AUC_{last}) • Total TPM exposure (AUC_{inf}) • Peak TPM plasma concentration (C_{max})
Statistical PK Analysis	Mixed model analysis of variance (ANOVA) with subject nested within sequence as a random factor and sequence, period, and treatment as fixed factors was performed for TPM AUC_{last}, AUC_{inf}, and C_{max}. All PK parameter data were analyzed using the natural logarithm (Ln). Treatment ratios (alcoholic/no alcohol) were calculated by taking the anti-logarithm of differences between treatment least-squares (LS) means, corresponding 90% confidence intervals (CIs) for ratios were obtained by taking anti-logarithm of 90% CIs for mean differences. Absence of alcohol effect demonstrated if 90% CIs for alcoholic/no alcohol ratios were within 80%-125% equivalence limits for all three PK parameters.
Safety Population	All subjects who received ≥ 1 SPN-538 dose
PK Population	All subjects who received SPN-538/0% alcohol plus ≥ 1 one other test treatment and had an adequate PK profile to determine TPM AUC_{last}, AUC_{inf}, and C_{max}

Results

***Topiramate* Plasma Concentration–Time Profiles vs Alcohol Dose: Linear Plot**



Semi-Log Plot



- Mean TPM plasma concentration profiles were similar across all alcohol doses.
- Slopes of semi-log plots were highly similar during both absorption and elimination phases, suggesting no effect of alcohol on TPM absorption or elimination if SPN-538 is co-administered with alcohol.

***Pharmacokinetic Parameters*, PK Population**

Parameter	Alcohol Dose* 0%	4%	20%	40%
n	27	25	25	22
AUC_{last}, mean (SD), h•mg/L	944 (225)	946 (250)	941 (220)	934 (223)
AUC_{inf}, mean (SD), h•mg/L	996 (251)	992 (263)	984 (240)	971 (228)
C_{max}, mean (SD), mg/L	2.2 (0.5)	2.1 (0.4)	2.0 (0.4)	1.8 (0.3)
T_{max}, median (range), hr	10 (10-10)	10 (10-10)	10 (10-10)	24 (10-24)
$t_{1/2}$, mean (SD), hr	43.3 (7.0)	42.6 (4.45)	42.3 (7.67)	43.1 (7.57)

*Calculated by volume

- PK parameters (AUC_{last}, AUC_{inf}, C_{max}) for SPN-538 co-administered with 4% and 20% alcohol were similar to SPN-538 administered without alcohol.
- Co-administration of SPN-538 with 40% alcohol slightly decreased primary exposure parameters (AUC_{last}, AUC_{inf}, C_{max}).
- Mean $t_{1/2}$ and median T_{max} were similar for all treatments.

Pairwise Comparisons of Relative TPM Bioavailability (Alcohol vs No Alcohol): PK Population (N=27)

Parameter	Alcohol Dose*	Pairwise Comparison Geometric LSM	Ratio (90% Confidence Interval)
C_{max}, mg/L	0%	2.12	--
	4%	2.02	94% (92-96)
	20%	1.89	94% (92-96)
	40%	1.70	80% (79-90)
AUC_{last}, h•mg/L	0%	940	--
	4%	944	100% (97-103)
	20%	918	98% (95-100)
	40%	926	98% (95-99)
AUC_{inf}, h•mg/L	0%	992	--
	4%	1005	101% (97-105)
	20%	1002	101% (96-106)
	40%	1011	102% (98-106)

*Calculated by volume

- Co-administration of SPN-538 with 4% and 20% alcohol had no effect on TPM exposure, i.e., LS means ratios and 90% CIs were contained entirely within equivalence limits (80%-125%) for all three primary PK parameters.
- Co-administration of SPN-538 with 40% alcohol had no effect on overall TPM exposure, i.e., LS means ratios and 90% CIs for AUC_{last} and AUC_{inf} were within equivalence limits.
- For C_{max}, co-administration of SPN-538 with 40% alcohol reduced LS means ratio by 18%.

Tolerability

- SPN-538 was generally well tolerated. Most adverse events (AEs) were mild.
- Most frequently reported AEs related to SPN-538: headache (n=4), oral paresthesia, cognitive disorder, dysgeusia, paresthesia, and sedation (each, n=3).
- Alcohol poisoning (n=24) and headache (n=10) were the most frequently reported AEs overall.
- AEs were more frequently reported during exposure to 240 mL (~8 oz) 40% alcohol.

Conclusions

- *In vitro* dissolution experiments were not predictive of *in vivo* performance when SPN-538 is co-administered with up to 40% alcohol.
- Co-administration of SPN-538 with alcohol in humans does not result in "dose dumping."
- Patients will have similar systemic exposure whether SPN-538 is taken with or without alcohol.
- Even at very high alcohol intake (240 mL or 8 oz of 40% alcohol), a decrease in peak concentration of the magnitude observed in this study (~14%) with a single dose is unlikely to be clinically relevant at steady state due to TPM accumulation associated with chronic dosing.

Study funded by Supernus Pharmaceuticals, Inc.

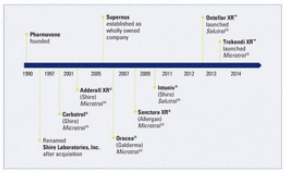
This research was conducted following the official FDA filing for market approval of Trokendi XR® and was not part of the marketing application review. Thus, the data do not appear in the package insert for Trokendi XR®. For questions, please contact the Medical Affairs Department of Supernus Pharmaceuticals via Prosar Corp. at medinfo@prosarcorp.com.

Presented at the Supernus sponsored Scientific Exhibit, 67th Annual American Epilepsy Society Meeting, December 8-10, Washington, DC.

Supernus Pharmaceuticals: Novel Extended-Release Technology Concepts Advancing Patient Therapy in Epilepsy

20+ Year History

Founded in 1990 as Pharmavene and acquired in 1997 by Shire, Supernus was established in 2005 as a wholly owned pharmaceutical company to leverage a 20+ year history of developing novel drug-delivery platforms and commercialize its own product portfolio using innovative extended-release (XR) technologies.



Proven Technology Concepts to Solve Oral Drug Delivery Challenges

- Clinical success of oral drug therapy depends on efficient drug delivery and overcoming physicochemical and physiologic barriers in order to achieve a desired pharmacokinetic (PK) profile.
- Complex array of factors must be considered when engineering oral drug formulations that achieve desired dosing frequency and shape of PK profile:
  - Solubility
  - Permeability
  - Active transport
  - Efflux
  - pH and enzyme-mediated degradation
  - Region-specific absorption
  - Bioavailability
  - Inter-patient variability
  - Food effect
- Supernus' expertise in commercial dosage form design has produced innovative technologies that enhance oral bioavailability and allow controlled drug release with drug delivery platforms tailored to the distinct characteristics of each drug.

Supernus' Innovative Controlled Release Platforms

Solutrol® Matrix tablet	Delivers soluble compounds or combines solubility enhancers with matrix release to enable delivery of compounds that are poorly soluble or have pH-dependent solubility profiles
Microtrol® Multiparticulate-filled capsule	Delivers an array of soluble and insoluble compounds, tailoring drug release profile to drug characteristics and desired release capsule profile by altering ratio of coated/uncoated multiparticulates
EnSoTrol® Osmotic tablet	Solubility enhanced core surrounded by semi-permeable membrane with laser-drilled hole through which core contents are released to yield surface-area controlled constant release profile

Extended-release products with established records of improving clinical performance using Supernus technologies:

- Carbatrol® (carbamazepine extended-release capsules)
- Adderall XR® (mixed salts of a single-entity amphetamine extended-release capsules)
- Oracea® (doxycycline delayed-release capsules)
- Sanctura XR® (trospium extended-release capsules)
- Intuniv® (guanfacine extended-release tablets)
- Oxtellar XR™ (oxcarbazepine extended-release tablets)
- Trokendi XR™ (topiramate extended-release capsules)

Commitment to Better Therapeutic Outcomes in Epilepsy

By improving the PK of proven antiepileptic drugs (AEDs), Supernus XR technologies offer the potential for:

- Improved drug tolerability
- Increased dosing convenience
- Enhanced patient acceptance and adherence
- Improved seizure control and therapeutic effectiveness
- Reduced seizure-related costs

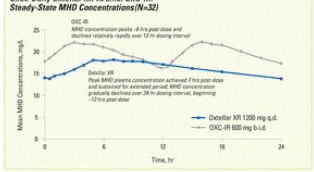
For questions, please contact the Medical Affairs Department of Supernus Pharmaceuticals via Prosar Corp. at medinfo@prosarcorp.com.

Oxtellar XR™: Extended Release Oxcarbazepine via Solutrol® Matrix Delivery

Oxtellar XR was specifically designed as an XR formulation of oxcarbazepine (OXC) to optimize plasma MHD concentrations and OXC clinical performance.

- Solutrol® matrix delivery technology overcomes OXC pH-dependent solubility and provides PK profile compatible with once-daily dosing.
- Plasma MHD concentration profiles at steady state are distinctly different for once-daily Oxtellar XR and b.i.d. immediate-release OXC (OXC-IR).

Once-Daily Oxtellar XR vs b.i.d. OXC-IR: Steady-State MHD Concentrations (N=32)



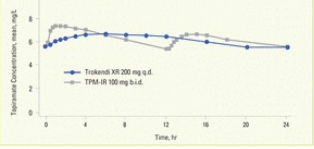
Solutrol® Matrix Delivery

Trokendi XR™: Extended Release Topiramate via Microtrol® Multiparticulate Delivery

Trokendi XR™ is a once-daily, XR formulation of topiramate (TPM) that is pharmacokinetically bioequivalent to the original immediate-release TPM formulation (Topamax®) administered twice daily.

- Capsule formulation contains three different type of beads – immediate-release beads and two types of extended-release beads.
- When administered at the same total daily dose, once-daily Trokendi XR provides steady-state plasma levels comparable to TPM-IR taken every 12 hrs.
- Trokendi XR once-daily is associated with relatively constant TPM plasma concentrations at steady-state, reflecting a 24-fold slower absorption rate when compared with TPM-IR administered twice-daily.
- Trokendi XR once-daily is associated with relatively constant TPM plasma concentrations at steady-state, reflecting a 24-fold slower absorption rate when compared with TPM-IR administered twice-daily.
- A single-blind, crossover, randomized sequence bioequivalence study in healthy volunteers (N=33) detected a potential signal that 200 mg Trokendi XR may have a less negative impact on verbal fluency ($p<0.05$) despite PK bioequivalence.
- In a conversion study, 93% of epilepsy patients (N=61) preferred Trokendi XR over TPM-IR and 92% believed that once-daily dosing would facilitate adherence.

Once-Daily Trokendi XR vs b.i.d. TPM-IR: Steady-State Topiramate Concentrations (N=33)



Microtrol® Multiparticulate Delivery: Specific ratios of coated and uncoated beads achieve desired release profile