CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

202810Orig1s000

CLINICAL PHARMACOLOGY AND BIOPHARMACEUTICS REVIEW(S)

Clinical Pharmacology Review

NDA:	202810
Generic Name:	Oxcarbazepine (SPN-8040)
Trade Name:	Oxtellar XR™
Strength and Dosage Form	150 mg, 300 mg, 600 mg Extended Release Tablets
Sponsor:	Supernus Pharmaceuticals, Inc
Indication:	Adjunctive therapy for partial seizures
Submission Type:	Original NDA (505(b)(2))
Priority Classification:	Standard
Submission Date:	12/21/2011
OCP Division:	DCP1
OND Division:	DNDP
PM Reviewer:	Satjit Brar, Pharm.D., Ph.D.
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1. Executive Summary

The sponsor submitted oxcarbazepine (OXC) extended release (ER) tablets as a 505(b)(2) application using OXC immediate release (IR) (Trileptal™) as the reference product. The clinical program included (1) an adult study evaluating the efficacy and safety of 1200 and 2400 mg of OXC ER (adjunctive) in refractory epilepsy and (2) a pharmacokinetics study evaluating an initiation dose of 8-10 mg/kg in pediatrics with refractory epilepsy. The sponsor is seeking approval of OXC ER as adjunctive therapy in children (4-17 years) and adults suffering from partial onset seizures. Our findings are summarized as the follows:

- Patients should not be switched from OXC IR to OXC ER at the same dose. The active metabolite, 10-monohydroxy derivative (MHD) and the parent compound, oxcarbazepine (OXC) after administration of OXC ER were not bioequivalent to those after administration OXC IR (Trileptal™).

- OXC ER should be administered under fasting conditions (i.e. 1 hour before or 2-hours after meals). There was about 62% and 181% increase in peak concentration (Cmax) for MHD and OXC, respectively, when OXC ER was administered with food compared to under fasting conditions.

- The same dose of OXC ER can be administered by using combinations of different strengths. MHD pharmacokinetics were equivalent following administration of 4 x 150 mg, 2 x 300 mg, 1 x 600 mg OXC ER.

- A 1200 mg/day dosing appears to be effective. A concentration-response relationship was observed with percentage reduction in seizure frequency as a function of MHD Cmin concentrations. Similar concentration-response relationships were identified between 1200 mg/day dosing and 2400 mg/day dosing. In addition, the exposure-response relationship between the OXC-IR and OXC-ER formulations are similar. Based on the established concentration-response relationship, there appears to be a clinically meaningful decrease in seizure frequency at the dose of 1200 mg.

- The established exposure-response relationships support the use of OXC ER in pediatric patients up to 17 years of age, who require OXC ER as adjunctive therapy. The exposure-response relationship (MHD Cmin vs. seizure reduction) for both pediatrics and adults are significant and similar amongst the populations.

- Pediatric dose can be adjusted by body weight of the patient. Pharmacokinetics (PK) of oxcarbazepine has been adequately characterized in pediatric patients (4-16 years of age). PK in patients 17 years of age can be sufficiently derived based on existing pediatric and adult data. Based on PK simulations, dosing based on body weight in pediatric patients (4-17 years) will yield comparable MHD Cmin exposures to the adult population.

1.1 Recommendation

The Office of Clinical Pharmacology (OCP) supports a recommendation for approval of OXC-ER as adjunctive therapy in adult with refractory epilepsy at a dosing regimen of 1200 mg/day and 2400 mg/day. We recommend that the indication in pediatric patient population be approved. In pediatric patients, it is recommended that the initiation dose be 8-10 mg/kg/day. To achieve a target maintenance dose, the dose should be increased by no more than 600 mg/week, titrated to tolerability and effectiveness.

1.2 Post-Marketing Studies

No post-marketing studies are recommended by OCP.

1.3 Labeling Recommendations

1. The recommended initiation dose of OXC-ER is 8-10 mg/kg/day. To achieve a target maintenance dose, the dose should be increased by no more than 600 mg/week, titrated to tolerability and effectiveness. The dosing nomogram below only serves as a guide for target maintenance dosing in pediatrics.

Recommended OXC-ER Maintenance Dosing for the Pediatric Population targeting Adult median MHD Cmin exposures after 1200 and 2400 mg/day

Weight range	Dose (mg/day)
20 – 29 kg	900
29.1– 39 kg	1200
> 39 kg	1800

2. Oxcarbazepine extended release tablet should be administered as a single daily dose taken on an empty stomach, i.e., 1 hour before or 2-hour after meals.

3. OXC-ER administered as a once daily dose is not bioequivalent to the same total dose of OXC-IR given twice daily. Patients should not be switched from OXC IR to OXC ER at the same dose.

1.4 Summary of Clinical Pharmacology and Biopharmaceutics Findings

Relative Bioavailability Evaluation

The exposures of the active metabolite, 10-monohydroxy derivative (MHD), which is primarily responsible for pharmacological effect, and the parent compound, oxcarbazepine (OXC), after multiple dose administration of 1200 mg of OXC ER were not bioequivalent to those after administration of 1200 mg Oxcarbazepine IR (Trileptal™) for 7 days. AUC, Cmax and Cmin for MHD were about 19%, 19%, and 16%, respectively lower after administration of OXC ER compared to those after Trileptal (Table 1). Because the two formulations failed to demonstrate bioequivalence, the effectiveness of OXC XR was evaluated in a pivotal safety and efficacy study. In addition, the study results suggested that patients should not be switched from Trileptal to OXC ER at the same dose.

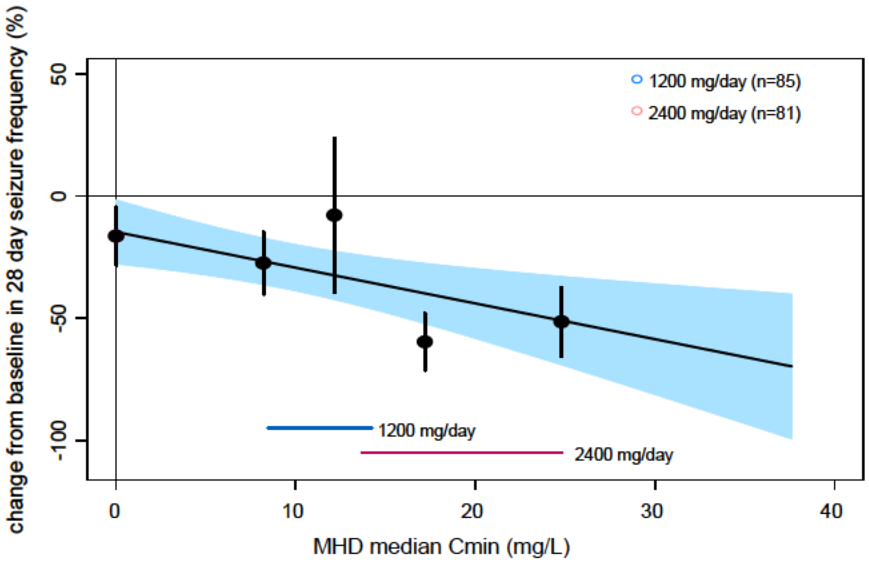
Table 1: Statistical Evaluation of Pharmacokinetic Parameters of MHD and OXC in Plasma

Pharmacokinetic Parameters	Ratios of LSM and 90% Confidence Intervals (CI)	
	MHD in Plasma OXC XR vs OXC IR	OXC in Plasma OXC XR vs OXC IR
AUC(0-24)	80.8% (77.5 -84.3%)	63.8% (59.6 -68.4%)
Cmax, ss	80.8% (77.0 – 84.9%)	38.6% (33.3 – 44.8%)
Cmin, ss	83.7% (78.8 – 88.9%)	104.2% (91.5 – 118.6%)

Exposure-Response

A significant dose-response and concentration-response relationship was observed for the OXC-ER formulation. A trend in dose-response was observed for the ER formulation, but only the 2400 mg/day showed a statistically significant difference from placebo (p-value ~0.003).
A concentration-response relationship was observed with percentage reduction in seizure frequency as a function of MHD (10-monohydroxy metabolite, the primary active metabolite) Cmin concentrations (slope= -1.47 [95% CI: -2.27, -0.663], p-value = 0.0003). A simple linear model was fit (Figure 1), pooling the responses from all analyzable patients.

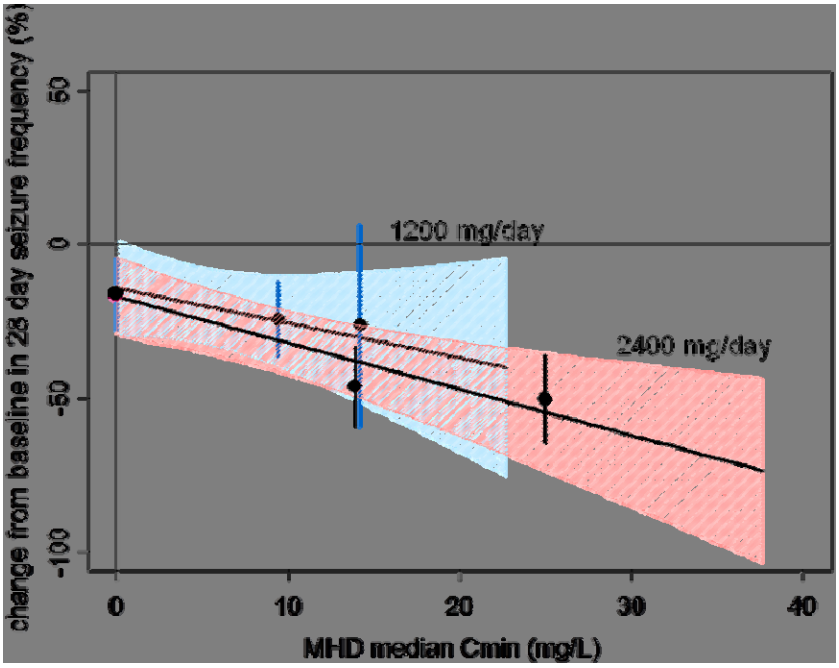
Figure 1: Placebo-anchored exposure-response for the OXC-ER formulations from the pivotal trial. Data includes placebo patients along with patients with PK and PD information from both the 1200 mg/day and 2400 mg/day groups.



Note: For exposure-response, solid symbols and bars represent the mean and 95% confidence interval of change from baseline in 28-day seizure frequency for each MHD concentration quantile. The interquartile ranges for the 1200 mg/day and 2400 mg/day doses are denoted by the horizontal lines. The solid line represents the mean prediction from the linear relationship and its corresponding 95% confidence interval (shaded region).

A significant and similar relationship was observed with percentage reduction in seizure frequency as a function of MHD Cmin concentrations for both the 1200 mg/day and 2400 mg/day doses.

Figure 2: Placebo-anchored exposure-response for the OXC-ER formulations (1200mg/day and 2400 mg/day modeled separately). Data includes placebo patients along with patients with PK and PD information from both the 1200 mg/day and 2400 mg/day groups.



Note: For exposure-response, solid symbols and bars represent the mean and 95% confidence interval of change from baseline in 28-day seizure frequency for each MHD concentration quantile. The solid line represents the mean prediction from the linear relationship and its corresponding 95% confidence interval for the 1200 mg/day group (blue shaded region) and 2400 mg/day group (red shaded region).

Based on an empiric linear model, the relationship between percentage reduction in seizure frequency and MHD Cmin is not different between the OXC-ER and OXC-IR formulations.

Pediatric vs Adult exposure after administration of OXC ER

In the pediatric PK study, MHD Cmin concentrations were evaluated after an initiation dosing regimen of 8-10 mg/kg to 17 pediatric patients. Absolute doses in the study included 150, 300, 450 and 600 mg/day. Although these actual doses were not evaluated in the pivotal trial, pharmacokinetic simulations in adults (administered equivalent doses) showed comparable MHD exposures to the pediatric population. The population PK model suggests that weight-based dosing would yield comparable MHD exposures to that found in the adult population.

The current label proposes initiation of OXC-ER at 8-10 mg/kg/day and target maintenance dose should be increase by no more than 600 mg/week and should be titrated to tolerability and effectiveness. The dosing nomogram below only serves as a guide for target maintenance dosing in pediatrics.

Table 2: Recommended OXC-ER Maintenance Dosing for the Pediatric Population targeting Adult median MHD Cmin exposures

Weight range	Dose (mg/day)
20 – 29 kg	900
29.1– 39 kg	1200
> 39 kg	1800

Dosage Equivalence and Dose linearity

MHD pharmacokinetics were equivalent following administration of 4 x 150 mg, 2 x 300 mg, 1 x 600 mg OXC XR. OXC pharmacokinetics was also comparable with respect to AUC but not Cmax. OXC Cmax was about 25% lower, which is not considered clinically meaningful, after administration of 4 x 150 mg compared to 1 x 600 mg OXC XR. Therefore, the same dose of OXC ER can be achieved by a combination of different strengths.

But when OXC XR formulation was administered as 1 x 150 mg, 1 x 300 mg or 1 x 600 mg tablets, under fasting conditions, a greater than proportional increase in AUCs and a less than proportional increase in Cmax over the 150mg to 600mg dose range for both MHD and OXC were observed (Table 3). Therefore, MHD and OXC concentrations were not linear after administration of higher strengths of OXC ER.

Table 3: Power model results (slope and 95% CI) for the Ln-Transformed PK Parameters for MHD

Statistical Analysis	Slope	95% CI
AUC_{0-t}	1.25	1.21 – 1.29
AUC_{∞}	1.24	1.20 – 1.28
Cmax	0.91	0.88 – 0.94

The approved dose can be achieved by giving different strengths of OXC XR. However, if a dose needs to be adjusted, using different strengths may not provide the needed reduction in exposure.

Effect of food

The extent of exposure (AUC) to MHD is not significantly affected when OXC ER is administered with high fat meal (1000 kcal) compared to when it is taken under fasting conditions. But the peak exposure (Cmax) of MHD is increased about 62% after administration with food compared to under fasting conditions. Tmax of MHD following the administration of OXC ER under fed conditions occurred approximately 2.5 hours earlier than under fasting conditions. OXC ER should be administered under fasting conditions.

2. Question Based Review (QBR)

2.1 General Attributes

What pertinent regulatory background or history contributes to the current assessment of the clinical pharmacology and biopharmaceutics of this drug?

The sponsor submitted oxcarbazepine (OXC) extended release (ER) tablets as a 505(b)(2) using OXC immediate release (Trileptal) as the reference product. Trileptal is approved in the United States for initial monotherapy and adjunctive therapy in children and adults suffering from partial onset seizures. The sponsor is seeking only the adjunctive therapy indication for OXC ER. The rationale for the development of OXC-ER included targeting an improved treatment adherence to a once daily regimen. Moreover, the ER formulation was developed to yield a "flatter" PK daily profile of OXC with the intent to yield an improved safety and tolerability profile when used as adjunctive antiepileptic drug (AED) therapy.

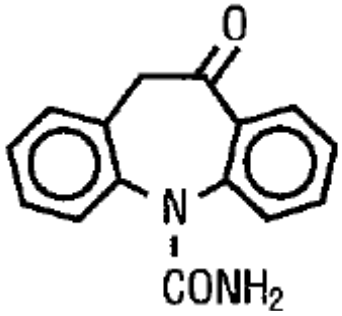
In addition to 7 pharmacokinetic studies and exposure response analysis, the sponsor submitted a single, randomized, placebo-controlled trial of OXC ER as adjunctive therapy in adults with partial epilepsy. The sponsor is also seeking the indication of adjunctive therapy in children based on a pharmacokinetic study conducted in children ages 4 to 16 years old. The sponsor is seeking a waiver for children from birth to age 4 years and age 17 years old.

The batches used in the clinical pharmacology studies were laboratory scale batches while that used in the pivotal safety and efficacy studies were commercial batches. The laboratory and commercial scale batches were manufactured at different sites. The sponsor requested and the Agency concurred at a meeting in April 2009 that there is no need to conduct a bridging BE study to prove equivalence between the laboratory scale and the commercial scale batches. The agency requested a multi-point dissolution test be conducted comparing the laboratory scale batches to the commercial scale batches in the following dissolution media: water with 1% sodium lauryl sulfate (SLS), 0.1N hydrochloric acid (HCl) with 1% SLS, United States Pharmacopeia (USP) buffer medium at pH 4.5 with 1% SLS, and USP buffer medium at pH 6.8 with 1% SLS. The results submitted indicate similarity between the laboratory and the commercial scale batches (Refer to ONDQA-Biopharm review).

What are the highlights of the chemistry and physical-chemical properties of the drug substance and the formulation of the drug product as they relate to clinical pharmacology and biopharmaceutics?

Oxcarbazepine chemically is 10,11-Dihydro-10-oxo-5*H*dibenz[b, *f*]azepine-5-carboxamide. It is currently approved in the U.S. as an immediate release dosage form (Trileptal) in strengths of 150 mg, 300 mg and 600 mg film coated tablets for oral administration. Trileptal is also available as a 300 mg/5 mL (60 mg/mL) oral suspension. The sponsor has developed an extended release oral tablet dosage formulation in strengths of 150 mg, 300 mg and 600 mg. Oxcarbazepine structure is provided in Figure 3.

Fig 3



Structure of Oxcarbazepine

What are the proposed mechanism (s) of action and therapeutic indication(s)?

The sponsor is seeking approval to use oxcarbazepine extended release tablets as once a day administration for adjunctive therapy in the treatment of partial onset seizures in adults and children with epilepsy. The precise mechanism by which oxcarbazepine and MHD exert their antiseizure effect is unknown; however, in vitro electrophysiological studies indicate that they produce blockade of voltage-sensitive sodium channels, resulting in stabilization of hyperexcited neural membranes, inhibition of repetitive neuronal firing, and diminution of propagation of synaptic impulses.

What are the proposed dosage and route of administration?

Oxcarbazepine should be initiated with a dose of 600 mg/day, given once daily in adults. The dose may be increased by a maximum of 600 mg/day at approximately weekly intervals. The proposed recommended daily dose is between 1200 – 2400 mg/day.

In pediatric patients aged 4-17 years, treatment should be initiated at a dose of 8-10 mg/kg every day (QD), generally not to exceed 600 mg QD. The target maintenance dose should be achieved by dose increases of no more than 600 mg/week.

2.2 General Clinical Pharmacology

What are the design features of the clinical pharmacology and clinical studies used to support dosing or claims?
Tables 4 and 5 contain clinical studies in support of OXC ER new drug application. Studies 804P101 and 804P102 were conducted only for formulation selection and therefore were not reviewed.

Table 4: Clinical Studies in Healthy Adult Subjects

Study	N	Objective	Oxcarbazepine (OXC) Test	Trileptal (Reference)
			Treatment QD (every day)	Treatment BID (twice daily)
804P101 (pilot-formulations exploration)	16	Evaluate BA of 3 ER formulations (Form)	1 x 600 mg Form A 1 x 600 mg Form B 1 x 600 mg Form C	300 mg bid
804P102 (pilot- Form exploration)	21	Evaluate steady state BA of two ER Form	1 x 600 Form A x 7days 1 x 600 mg Form B x 7 days	300 mg bid for 7 days
804P103	32	Evaluate steady state BA of OXC vs Trileptal	600 mg QD x 3, then 900 mg QD x3, then 1200 mg QD x 7	300 mg bid x 3 days, then 450 mg bid x 3 days, then 600 mg bid x 7 days
804P104	54	Evaluate dose proportionality	Single doses of 4 x 150 mg 2 x 300 mg 1 x 600 mg	Not applicable
804P104.5	54	Evaluate dose linearity	Single doses of 1 x 150 mg 1 x 300 mg 1 x 600 mg	Not applicable
804P105	62	Evaluate food effect	Single doses of 600 mg under fed and fasting conditions	Not applicable

Table 5: Clinical Studies in Subjects with Epilepsy

Study	N	Design	Treatments	Status
804P301	123 (2400 mg OXC ER) 122 (1200 mg OXC ER) 121 (Placebo)	Phase 3, randomized, blinded, placebo-controlled, in patients with refractory partial onset seizures	1:1:1 randomization to 1200 mg/day 2400 mg/day Placebo	Completed-Registration trial
804P302	21	Open-label safety follow-on of 804P301	600 – 2400 mg/day OXC ER	Ongoing
80P107	32 (18 completed)	PK at steady state in pediatric partial onset seizures	150 – 600 mg/day based on weight	Completed-submitted
804P303	54	Open-label, safety follow on of 804P107	As clinically indicated	CSR in progress

What is the basis for selecting the response endpoints (i.e. clinical or surrogate endpoints) or biomarkers and how are they measured in clinical pharmacology and clinical studies

The primary endpoint in the efficacy trials was percentage change (PCH) in seizure frequency per 28 day during the treatment phase relative to the baseline phase (PCHt) in the ITT population. All seizures up to the point of subject discontinuation (excluding the Tapering/Conversion Period) were included in the analysis.

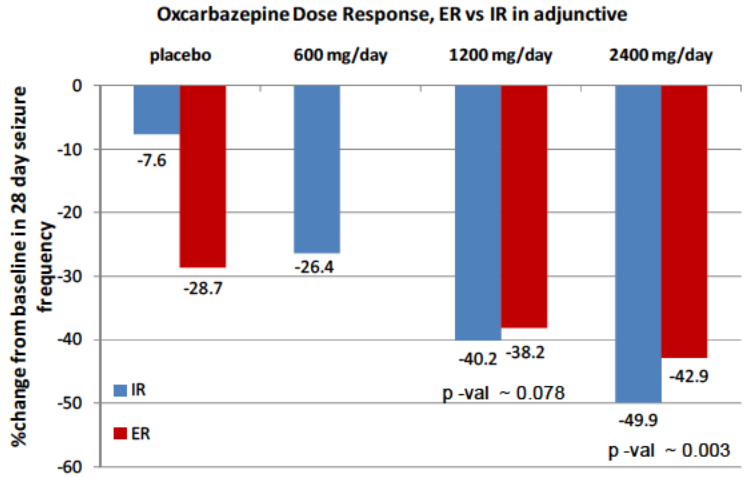
2.2.1 Exposure-Response

Is there evidence of an exposure-response relationship (dose-response, concentration-response) for efficacy of the OXC-ER formulation?

Yes. A significant dose-response and concentration-response relationship was observed for the OXC-ER formulation. Figure 4 below shows the results of the pivotal trial graphically, and makes comparison to the dose-response information from the IR formulation pivotal trial results. The results from the IR formulation pivotal trials were obtained from approved label. For the IR

formulation, a trend in dose-response was observed with all doses (600, 1200 and 2400 mg/day) being statistically different from placebo (all p-values <0.05). A trend in dose-response was observed for the ER formulation, but only the 2400 mg/day showed a statistically significant difference from placebo (p-value ~0.003). For further details please refer to the review by Dr. Ohid Siddiqui (Office of Biostatistics, OTS).

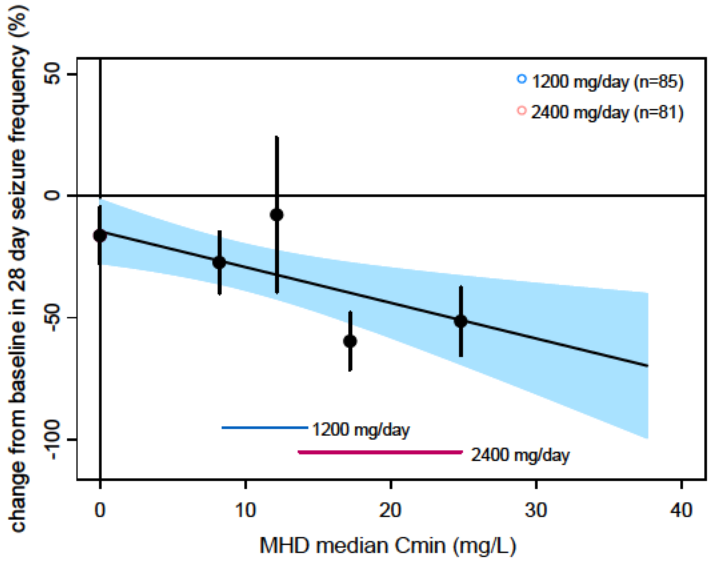
Figure 4: Dose-Response for the OXC-ER (red) and IR (blue) formulations from the pivotal trials.



Note: The p-values presented, contrasting each dose with placebo, are for the ER formulation for both the 1200 mg and 2400 mg/day. For the IR formulation, all doses were statistically different than placebo (all p-values <0.05)

A concentration-response relationship was observed with percentage reduction in seizure frequency as a function of MHD (Cmin concentrations (slope= -1.47 [95% CI: -2.27, -0.663], p-value = 0.0003). A simple linear model was fit (Figure 5), pooling the responses from all analyzable patients.

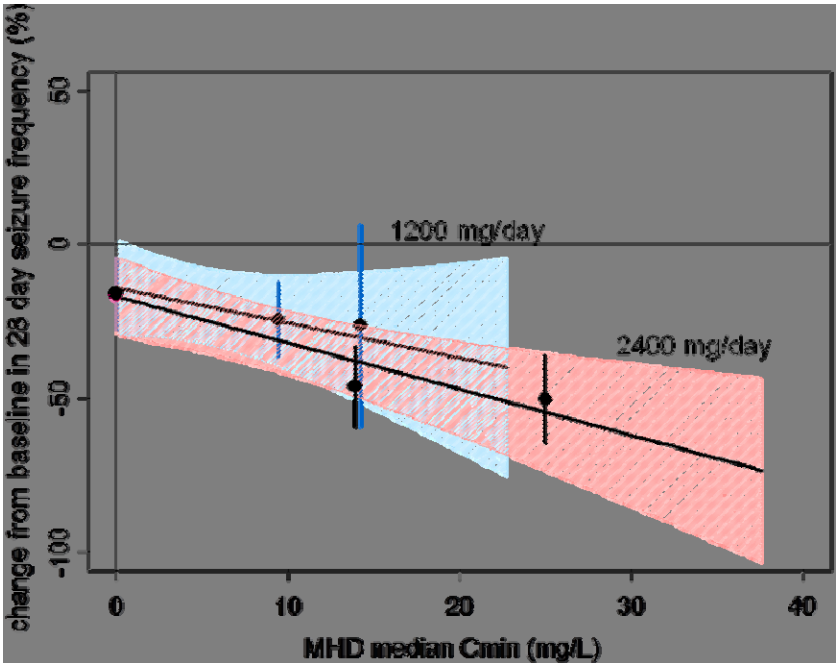
Figure 5: Placebo-anchored exposure-response for the OXC-ER formulations from the pivotal trial. Data includes placebo patients along with patients with PK and PD information from both the 1200 mg/day and 2400 mg/day groups.



Note: For exposure-response, solid symbols and bars represent the mean and 95% confidence interval of change from baseline in 28-day seizure frequency for each MHD concentration quantile. The interquartile ranges for the 1200 mg/day and 2400 mg/day doses are denoted by the horizontal lines. The solid line represents the mean prediction from the linear relationship and its corresponding 95% confidence interval (shaded region).

To further evaluate the effectiveness of the 1200 mg/day and 2400 mg/day doses, exposure-response analysis was performed by dose. A significant trend was observed with percentage reduction in seizure frequency as a function of MHD Cmin concentrations for both the 1200 mg/day and 2400 mg/day doses.

Figure 6: Placebo-anchored exposure-response for the OXC-ER formulations (1200mg/day and 2400 mg/day modeled separately). Data includes placebo patients along with patients with PK and PD information from both the 1200 mg/day and 2400 mg/day groups.



Note: For exposure-response, solid symbols and bars represent the mean and 95% confidence interval of change from baseline in 28-day seizure frequency for each MHD concentration quantile. The solid line represents the mean prediction from the linear relationship and its corresponding 95% confidence interval for the 1200 mg/day group (blue shaded region) and 2400 mg/day group (red shaded region).

Are the exposure-response relationships for the OXC-ER and IR formulations similar?

Yes. Based on an empiric linear model, the relationship between percentage reduction in seizure frequency and MHD Cmin is not different between the OXC-ER and OXC-IR formulations.

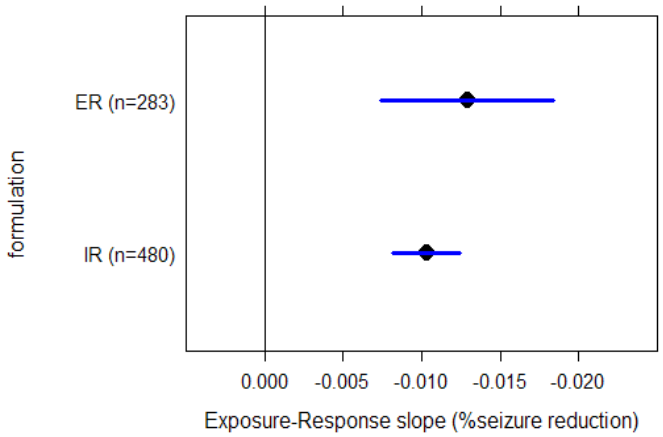
In the case for OXC-ER, a ~ 16-19% lower exposure (AUC and Cmax) of MHD was observed in the pivotal bioequivalence study, not meeting the pre-specified criteria for bioequivalence. Therefore, the intent of this analysis was to determine if, despite the differential MHD exposures seen between the OXC-ER and IR formulations, the exposure-response relationships were similar. For the evaluation, the model parameters of the exposure-response relationship for the IR formulation was obtained from publicly available information.[1] For the IR exposure response relationship, an empiric model was derived relating the percentage change from baseline in seizure frequency to MHD Cmin concentrations:

$$log\ (\%\ change\ from\ baseline\ in\ seizure\ frequency + 110) = \beta 0 + \beta 1 * Cmin + \varepsilon$$

where, β0 and β1 is the intercept and slope, respectively, or the linear relationship, ε is the residual error and Cmin is the MHD exposure metric (in µmol/L) used to assess the relationship. Using the same empiric model, the exposure-response relationship was derived for the OXC-ER formulation, and the slope parameter estimate was compared to the parameter (β1) published for

the OXC-IR relationship. Results for the comparison as seen in Figure 47 below show the exposure-response relationship between the formulations are similar.

Figure 7: Point estimate for the slope parameter (and corresponding 95% CI interval) for the OXC-ER and OXC-IR formulations (1200mg/day and 2400 mg/day inclusive). Data includes placebo patients along with patients with PK and PD information from both the 1200 mg/day and 2400 mg/day groups.



The slope parameter of exposure-response relationships for both formulations are both statistically significant (both relationships with p-values <0.05). Overlapping 95% confidence bounds infer that the point estimates are indistinguishable between the ER and IR formulations. The smaller 95% confidence bounds for the IR formulation exposure-response relationship may be due to the increased sample size used for the analysis.

([1] East Coast Population Analysis Group Conference, 2006. Workshop presentation by Joga Gobburu. http://www.ecpag.org/2006/6_JogaGobburu.)

Pediatric exposure-response

Are similar Cmin concentrations achieved in adults and pediatrics with the OXC-ER formulation?

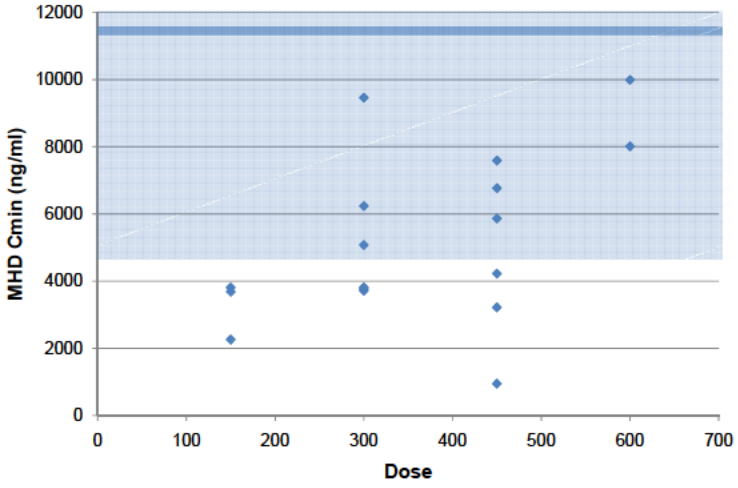
Yes. In the pediatric PK study, MHD Cmin concentrations were evaluated after an initiation dosing regimen of 8-10 mg/kg to 17 pediatric patients. An age range of 4-17 was supposed to be evaluated, but the sponsor did not obtain PK for patients who were >16 years old. Absolute doses in the study included 150, 300, 450 and 600 mg/day. Although these actual doses were not evaluated in the pivotal trial, pharmacokinetic simulations in adults (administered equivalent doses) showed comparable MHD exposures to the pediatric population.

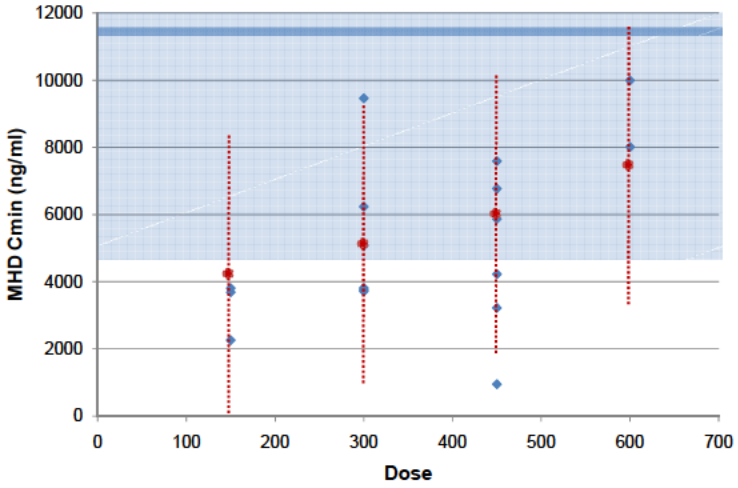
In the development of Trileptal®, both an adult and pediatric study was performed to determine the effectiveness of IR Oxcarbazepine in the adjunctive setting. Available public information infers that the exposure-response relationships between these populations are reasonably similar.* This notion suggests that the epilepsy disease between populations are reasonably similar as well. Under the assumption that the exposure-response relationships between the OXC-IR and OXC-ER formulations are similar in adults, bridging the pediatric approval would require a PK study in pediatrics to match MHD exposures in adults (as the sponsor attempted to perform).

In the pediatric study for OXC-ER, the PK of OXC and MHD were adequately characterized from 17 subjects. The population PK model suggests that weight-based dosing would yield comparable MHD exposures to that found in the adult population. MHD Cmin exposures, after an initiation regimen of 8-10 mg/kg (range 150 – 600 mg/day), are presented in Figure 8 (top graph). For reference, the blue shaded area represents the bottom 50 percentile of the range of MHD Cmin exposures for adult patients that were dosed *1200 mg/day* in the pivotal adult trial. In order to compare exposures between the adult and pediatric populations, PK simulations (n=1000) were performed in adults to determine whether the MHD Cmin exposures would yield comparable exposures to that found in the pediatric population. The sponsor's derived population PK model was used to determine ranges of MHD Cmin concentrations in adults after receiving 150, 300, 450 and 600 mg/day. The bottom plot depicts the median and range for the PK simulations in adults, superimposed on the observed pediatric MHD Cmin concentration. From graphical inspection, the simulated adult exposures reasonably overlap with the observed pediatric MHD exposures.

(* East Coast Population Analysis Group Conference, 2006. Workshop presentation by Joga Gobburu. http://www.ecpag.org/2006/6_JogaGobburu.pdf)

Figure 8: MHD Cmin exposures obtained from the Pediatric OXC-ER PK study (Top plot, n=17) and Superimposed simulated MHD Cmin concentrations if n=1000 adults were given an equivalent dose (median and range, Bottom plot).





Note: Blue shaded region represents the approximately the bottom 50 percentile of MHD Cmin exposures obtained after adult dosing of 1200 mg/day (from the pivotal adult study). The dark blue line represents the median Cmin exposure for adults given 1200 mg/day. Pediatric observations are in blue diamonds while the simulated adult exposures (n=1000), for the specified dose are in red circles (median and range).

The PK model was further employed to determine the pediatric maintenance dosing required to attain adult median MHD Cmin concentrations after dosing with 1200 mg/day and 2400 mg/day (Table 6). The current label proposes initiation of OXC-ER at 8-10 mg/kg/day and target maintenance dose should be increased by no more than 600 mg/week and should be titrated to tolerability and effectiveness. The dosing nomogram below only serves as a guide for target maintenance dosing in pediatrics.

Table 6: Recommended OXC-ER Maintenance Dosing for the Pediatric Population targeting Adult median MHD Cmin exposures

Weight range	Dose (mg/day)
20 – 29 kg	900
29.1– 39 kg	1200
> 39 kg	1800

Building on the information that, in the adjunctive epilepsy setting:

1) the exposure-response relationship (MHD Cmin vs. seizure reduction) for both pediatrics and adults are significant and similar amongst the populations.

2) the exposure-response relationship between the OXC-IR and OXC-ER formulations are similar, based on similar parameter estimates of the linear model.

3) and the PK model developed with adult and pediatric observations adequately describes MHD concentrations.

4) PK simulations show comparable exposures between adults and pediatric population, given the same absolute dose.

Dosing based on body weight will yield comparable MHD Cmin exposures to the adult population.

Is the dose and dosing regimen selected by the sponsor consistent with the known relationship between dose-concentration-response?

The dose selected is based on the results of the pivotal clinical efficacy trial and exposure-response analysis. This trial demonstrated that 2400 mg was statistically significantly better than placebo. Even though the 1200 mg was not statistically significantly better than placebo there appears to be a clinically meaningful decrease in seizure frequency. Exposure response analysis suggested a relationship between concentration/dose and decrease in frequency of exposure (refer to pharmacometric review).

What are the evidences of efficacy provided by the sponsor in support of the application?

Table 7 from the sponsor's analysis indicates the 2400 mg resulted in greater reduction in seizure frequency and this reduction was statistically significantly (P = 0.003) better than placebo. The 1200 mg dose also resulted in decrease in seizure frequency per 28 days relative to baseline but was not statistically significantly different from placebo (p=0.078). Refer to medical review for Agency's evaluation.

Table 7: Primary Efficacy Results

Statistics	SPN-804O 2400mg/day (N=123)	SPN-804O 1200mg/day (N=122)	Placebo (N=121)
n	111	109	117
Median Baseline 28-day Frequency	6	6	7
Median Treatment 28-day Frequency	3.7	4.3	5.0
Mean (SD)	-38.03 (53.11)	-29.14 (69.84)	-15.43 (67.34)
Median	-42.90	-38.20	-28.70
Min, Max	-100.0, 212.8	-100.0, 556.1	-100.0, 333.6
p-value versus placebo[a]	0.003	0.078	
Hodges-Lehmann Estimate	-18.30	-10.30	
95% Confidence Interval	(-30.40, -5.80)	(-22.30, 1.20)	

Sources: Tables 5.2.1.5 and 5.2.2.1, and Table A5.2.1.1.0
[a]Wilcoxon rank-sum test of the median percentage change in partial seizure frequency per 28 days during the 16-week Treatment Phase (Titration + Maintenance Periods) relative to the 8-week Baseline Phase.

What are the characteristics of the exposure-response relationships (dose-response, concentration-response) with regards to safety?

The sponsor reported that in the pivotal safety and efficacy study (study 301), overall, AEs were more frequently reported in subjects receiving 2400mg/day (69.1%) compared with 1200mg/day (56.6%) and placebo (55.4%). Dizziness, somnolence, headache, nausea, diplopia, and vomiting were the most frequently reported AEs (≥10%) in subjects treated with OXC XR. The incidence of dizziness, somnolence, headache, and diplopia appeared to be dose-related. The sponsor states that the occurrence and reporting frequency of AEs in Phase 3 oxcarbazepine treatment groups were consistent with the expected AE profile of immediate-release OXC. Incidence rates for

common, dose-limiting, OXC-associated AEs (dizziness, somnolence, headache, nausea, diplopia, and vomiting) in the OXC XR groups were no greater than the expected incidence rates reported for patients with partial seizures treated with Trileptal. The sponsor reported that the most common adverse events (AEs) in healthy volunteers were headache, somnolence, dizziness, and nausea, occurring in 17.8%, 13.1%, 4.7%, and 3.8% of subjects treated with oxcarbazepine XR and 16.7%, 13.6%, 18.2%, and 10.6% in subjects treated with Trileptal®, respectively (Refer to medical review for Agency evaluation of safety).

Does this drug prolong the QT or QTc interval?

A thorough QT study was not required and not conducted in support of this 505 (b)(2) NDA.

2.2.2. General Pharmacokinetics

Are the active moieties in the plasma (or other biological fluid) appropriately identified and measured to assess pharmacokinetic parameters and exposure response relationship?

Yes, the active moieties, MHD and OXC were appropriately measured in biological fluids. Oxcarbazepine is rapidly reduced by cytosolic enzymes in the liver to its 10-monohydroxy metabolite, MHD, which is primarily responsible for the pharmacological effect. MHD is metabolized further by conjugation with glucuronic acid. Minor amounts (4% of the dose) are oxidized to the pharmacologically inactive 10,11-dihydroxy metabolite (DHD).

What are the general ADME (Absorption, Distribution, Metabolism and Elimination) Characteristics of Oxcarbazepine?

Refer to Trileptal approved label for general ADME

Oxcarbazepine is cleared from the body mostly in the form of metabolites which are predominantly excreted by the kidneys. Fecal excretion accounts for less than 4% of the administered dose. Approximately 80% of the dose is excreted in the urine either as glucuronides of MHD (49%) or as unchanged MHD (27%); the inactive DHD accounts for approximately 3% and conjugates of MHD and oxcarbazepine account for 13% of the dose.

The half-life of the parent is about two hours, while the half-life of MHD is about nine hours.

Figure 8 below is the reported metabolic pathway of oxcarbazepine.

Oxcarbazepine Metabolic Pathway

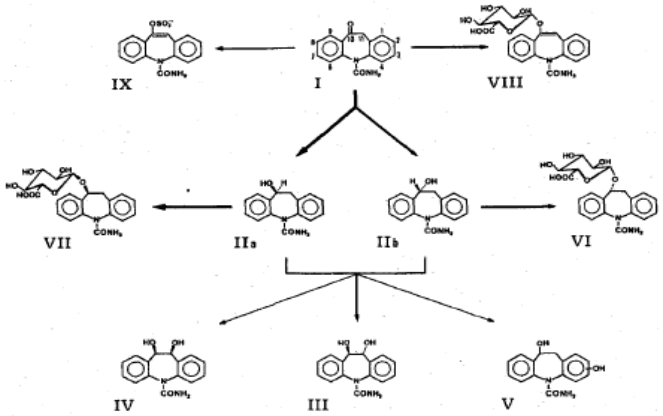


Figure 2. Urinary metabolites of oxcarbazepine isolated in this study and pathways of biotransformation in man after a single oral dose of 400 mg ^{14}C-oxcarbazepine.

Schutz et al: Xenobiotica, 16(8):769-778, 1986

I- oxcarbazepine, II- MHD (IIa S-enantiomer, IIb- R-enantiomer), VI and VII - glucuronide metabolites of MHD, VIII- glucuronide metabolite of oxcarbazepine, IX- sulphide metabolite of oxcarbazepine, III, IV and V minor metabolites of MHD

Intrinsic factors

Refer to Trileptal label.

Extrinsic Factors

Refer to Trileptal label for general drug-drug interaction information.

Did concomitant medications (carbamazepine, phenytoin, Phenobarbital, valproic acid) administered in the adjunctive therapy trial affect the exposure to MHD when administered together with OXC XR?

Based on population pharmacokinetic analysis evaluation in epileptic patients in the phase III study, co-administration of one or more of carbamazepine, phenytoin, phenobarbital or valproic acid increased the apparent clearance of MHD, typically by factor of 1.3. Studies conducted in support of Trileptal label show that there is 40% , 25%, 30% and 18% decrease in MHD concentration after administration of Trileptal with carbamazepine, phenobarbital, phenytoin and valproic acid, respectively. Dose adjustment for OXC-ER is not recommended when Valproic acid and Phenobarbital are co-administered. The dose of OXC-ER should be titrated to clinical response if there is a need to administer carbamazepine and phenytoin with OXC-ER.

Are exposures comparable and proportional after administration of equivalent doses of different strengths OXC ER?

The sponsor evaluated whether administration of the same dose of OXC ER by using different strengths produced similar exposures. The study evaluated the dosage form equivalence of oxcarbazepine extended release (OXC XR) formulation when administered as 4 x 150 mg tablets, 2 x 300 mg tablets, or 1 x 600 mg tablet, under fasting conditions. The following table provides the results of the comparison.

Table 8: Summary of the Ratios of LSMs and the 90% Confidence Interval for MHD

ANOVA	Treatment Comparisons*	Ratio of LS Means (%)	90% CI (%)	Intra-Subject CV (%)
AUC_{0-t}	B vs A	100.73	96.94 – 104.66	11.72
	C vs B	98.26	94.51 – 102.16	
	C vs A	98.97	95.22 – 102.88	
$AUC_{0-\infty}$	B vs A	100.59	96.70 – 104.64	12.06
	C vs B	98.45	94.59 – 102.47	
	C vs A	99.04	95.18 – 103.05	
Cmax	B vs A	97.93	94.46 – 101.52	11.01
	C vs B	97.23	93.74 – 100.85	
	C vs A	95.22	95.22 – 98.74	

A= OXC XR Tablet, 4 x 150 mg, B= OXC XR Tablet, 2 x 300 mg, C= OXC XR Tablet,

MHD pharmacokinetics were comparable following administration of 4 x 150 mg, 2 x 300 mg, 1 x 600 mg OXC XR. OXC pharmacokinetics was also comparable with respect to AUC but not Cmax. The difference in OXC Cmax comparison between 4 x 150 mg and 1 x 600 mg could be due to the multiple dosage units used for the 150 mg and should not be clinically relevant. Therefore, the doses of OXC ER can be administered by combinations of tablets with different strengths.

Based on PK, what is the degree of linearity or non-linearity in the dose concentration relationship?

The sponsor also evaluated the dosage form pharmacokinetic linearity of OXC XR formulation when administered as 1 x 150 mg tablets, 1 x 300 mg tablets, or 1 x 600 mg tablet, under fasting conditions. Table 9 provides the results of the power model used to evaluate dosage form linearity.

Table 9: Power model results (slope and 95% CI) for the Ln-Transformed PK Parameters for MHD

Statistical Analysis	Slope	95% CI
AUC_{0-t}	1.25	1.21 – 1.29
AUC_{∞}	1.24	1.20 – 1.28
Cmax	0.91	0.88 – 0.94

The lower and upper bounds of the 95% CI for the slope of the power model were greater than 1 for AUCs and lower than 1 for Cmax. These results indicate a greater than proportional increase in AUCs and a less than proportional increase in Cmax over the 150 mg to 600 mg dose range for MHD. Similar results were observed with the parent compound, OXC.

2.3 *General Biopharmaceutics*

Is Oxcarbazepine ER bioequivalent to the reference listed drug, Oxcarbazepine IR (Trileptal)?

The sponsor evaluated the bioequivalence between OXC ER and Trileptal after multiple dose, open-label, randomized two-way cross over study. Doses were titrated to the desired dose of 1200 mg daily. The ER dose was given once daily and the IR was administered twice daily. Figure 9 depicts the plasma concentration time profile after administration.

Figure 9: Mean Plasma MHD concentration over time

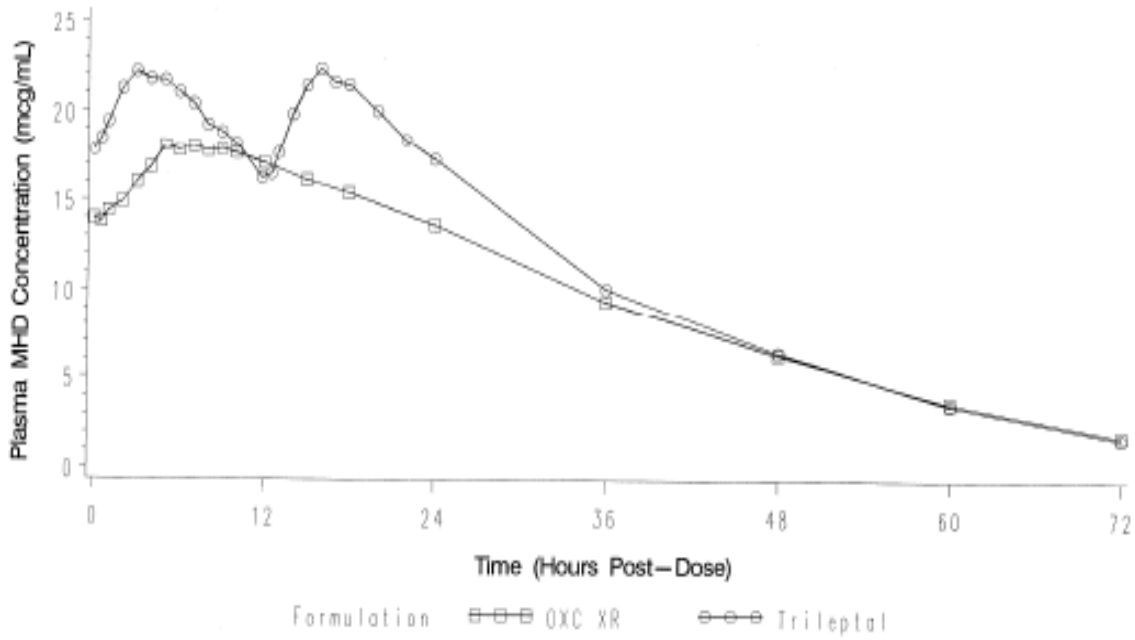


Table 10 contains the statistical evaluation of selected pharmacokinetic parameters of MHD and OXC in plasma.

Table 10: Statistical Evaluation of Pharmacokinetic Parameters of MHD and OXC in Plasma

Pharmacokinetic Parameters	Ratios of LSM and 90% Confidence Intervals (CI)	
	MHD in Plasma OXC XR vs OXC IR	OXC in Plasma OXC XR vs OXC IR
AUC(0-24)	80.8% (77.5 -84.3%)	63.8% (59.6 -68.4%)
Cmax, ss	80.8% (77.0 – 84.9%)	38.6% (33.3 – 44.8%)
Cmin, ss	83.7% (78.8 – 88.9%)	104.2% (91.5 – 118.6%)

The exposures of the active metabolite (MHD) and OXC after multiple dose administration of 1200 mg of OXC ER were not bioequivalent to that after administration of 1200 mg Trileptal. AUC, Cmax and Cmin for MHD were about 19%, 19%, and 16%, respectively lower after administration of OXC ER compared to that after Tripletal. The 90% confidence interval around

the point estimate for Cmax and AUC were not contained within the regulatory criteria of 80% to 125%.

Is the exposure to MHD significantly different after administration of OXC ER with or without food?

The sponsor evaluated the effect of food in a single center, single dose, open-label, randomized, 2-way (Fed versus Fasting) crossover study. The subjects were administered 600 mg of OXC ER under fed conditions (FDA recommended breakfast) and under fasting conditions. Table 11 provides the statistical results for MHD and oxcarbazepine (OXC).

Table 11: Statistical evaluation after administration of OXC ER with or without food

	Ratio of LSM and 90% Confidence Intervals	
Pharmacokinetics	OXC OXC XR Fed vs OXC XR Fasted	MHD OXC XR Fed vs OXC XR Fasted
AUC0-t	131.3 (126.1 – 136.7%)	113.5 (109.5 – 117.7%)
AUC∞	129.4 (124.4 – 134.5%)	112.0 (107.9 – 116.2%)
Cmax	281.7 (254.5 – 311.75%)	162.6 (156.7 – 168.7%)

The extent of exposure (AUC) to MHD is not significantly affected when OXC ER is administered with high fat meal (1000 kcal) compared to when it is taken under fasting conditions. But the peak exposure (Cmax) of MHD is increased about 62% after administration with food compared to under fasting conditions. The extent (AUC) and peak (Cmax) exposure to the parent compound, oxcarbazepine, are significantly increased when OXC ER is administered with food. Tmax of OXC following the administration of OXC ER under fed conditions occurred about 2 hours later than for OXC ER under fasting conditions (6.7 vs 4.6 hours). Tmax of MHD following the administration of OXC ER under fed conditions occurred approximately 2.5 hours earlier than under fasting conditions (9.7 vs 12.1 hours). Therefore, it is recommended that OXC ER be administered under fasting conditions because of the significant increase in peak exposure.

What is the composition of oxcarbazepine extended release formulations used in the bioavailability and clinical registration trials?

The sponsor has developed OXC as an extended-release (ER) version of OXC immediate release, based on a monolithic, controlled-release matrix tablet capable of a once-daily (QD) dosing regimen (Table 12). Available tablet strengths of OXC ER are 150 mg, 300 mg and 600 mg. The batches used in the clinical registration trials are commercial scale batches.

The sponsor reported that oxcarbazepine is a BCS class II drug. The drug substance is poorly water soluble with an aqueous solubility of approximately 0.07mg/mL at room temperature, and shows similar solubility throughout the physiological pH range in the gastrointestinal tract. The solubility of oxcarbazepine increases in the presence of sodium lauryl sulfate (SLS). Oxcarbazepine is reported to exhibit high permeability across the Caco-2 cell monolayer.
The following table contains the quantitative composition of the 150 mg, 300 mg and 600 mg oxcarbazepine extended release tablets.

Table 12: Composition of commercial scale oxcarbazepine extended release tablets

Component	Function	Amount per tablet (mg)		
		150 mg	300 mg	600 mg
Oxcarbazepine	Drug Substance	150	300	600
Silicified Microcrystalline Cellulose, NF (Prosolv SMCC50)	Tableting aid	11.25	35	95
Methacrylic Acid Copolymer (Type C), NF (Eudragit L 100-55)	Enteric Polymer	25	50	100
Sodium Lauryl Sulfate, NF (Texapon K 12 P PH)	Solubilizer	12.5	25	50
Hypromellose (Type 2208), USP (Methocel K4M Premium CR)	Release controlling agent	37.5	62.5	100
Povidone, USP (Kollidon 25 Polymer)	Binder	12.5	25	50
Magnesium Stearate, NF (Non-Bovine, HyQual Code 5712)	Lubricant	1.25	2.5	5
Opadry II Yellow 85F12383	Coloring agent and nonfunctional cosmetic coat	7.5	15	30
Ink Black , Opacode S-1-17823	Printing ink	Trace	Trace	Trace
Purified water, USP	Granulation fluid	Removed during processing	Removed during processing	Removed during processing
Purified water, USP	Coating solvent	Removed during processing	Removed during processing	Removed during processing
Total		257.5	515	1030

2.4 Analytical Methods

What bioanalytical methods are used to assess concentrations of OXC and MHD and is the validation complete and acceptable?

A sensitive, accurate, and reproducible bioanalytical method for the determination of oxcarbazepine and 10-hydroxycarbazpine (MHD) in human plasma was developed and validated using liquid chromatography with tandem mass spectrometry (LC/MS/MS). The method was validated over a concentration range of 0.005-1.0 µg/mL for oxcarbazepine and 0.05-10.0 µg/mL for MHD in human plasma. The overall absolute recovery for all analytes was 86.8 % or greater. Interference from blank human plasma and carryover from the highest standard were less than or equal to 7.5% of the lower limit of quantitation (LLOQ) for both analytes. The acceptance criteria were met and the method has been validated successfully. The analytical method is acceptable.

Table 13: Analytical Method Summary

Element	SPE Method	Table	Result		Specification
			Oxcarbazepine	10-Hydroxycarbazepine	
Calibration Standard Precision & Accuracy	Cartridge	7	Prec. 2.1 to 5.7% Accu. 94.5 to 112.0%	Prec. 0.5 to 6.8% Accu. 97.7 to 106.7%	< ±15.0% < ±20.0% at LLOQ
	96-well	8	Prec. 0.6 to 6.9% Accu. 95.2 to 106.7%	Prec. 0.2 to 4.5% Accu. 98.0 to 101.2%	< ±15.0% < ±20.0% at LLOQ
Intra-Assay Precision & Accuracy (n=5)	Cartridge	11, 12	Prec. 0.9 to 4.2% Accu. 100.2 to 106.1%	Prec. 1.7 to 5.4% Accu. 94.7 to 104.5%	< ±15.0%
	96-well	13, 14	Prec. 1.8 to 3.7% Accu. 95.8 to 105.2%	Prec. 0.7 to 2.8% Accu. 98.0 to 103.4%	< ±15.0%
Inter-Assay Precision & Accuracy (n=15)	Cartridge	15, 16	Prec. 2.1 to 3.6% Accu. 102.3 to 104.6%	Prec. 4.6 to 5.4% Accu. 99.6 to 100.5%	< ±15.0%
	96-well	17, 18	Prec. 2.9 to 3.8% Accu. 100.0to 103.5%	Prec. 2.1 to 3.8% Accu. 98.9 to 99.7%	< ±15.0%
Specificity (n=6)	Cartridge	19, 20	6.5% of LLOQ 0.3% of IS	1.7% of LLOQ 0.2% of IS	< 20.0% of LLOQ < 5.0% of IS
	96-well	21, 22	7.5% of LLOQ 0.5% of IS	1.6% of LLOQ 0.2% of IS	< 20.0% of LLOQ < 5.0% of IS
Sensitivity / LLOQ (n=6)	Cartridge	23	Precision 2.1% Accuracy 110.3%	Precision 3.0% Accuracy 90.8%	< ±20.0%
	96-well	24	Precision 5.5% Accuracy 113.3%	Precision 1.8% Accuracy 99.2%	< ±20.0%
Dilution (DF=10)	Cartridge	25	Precision 1.5% Accuracy 100.8%	Precision 3.1% Accuracy 95.9%	< ±15.0%
Absolute Recovery	Cartridge	26	86.8 to 95.3% OXC 87.8 to 94.6% OXC-d4	89.6 to 104.8% MHD 92.8 to 100.4% MHD-d4	No sig. diff. from levels or lots
	96-well	27	93.6 to 103.0% OXC 96.1 to 105.7% OXC-d4	91.1 to 101.1% MHD 95.9 to 101.8% MHD-d4	No sig. diff. from levels or lots
Re-injection Stability (72 Hrs @ 6°C)	Cartridge	28	Prec. 0.9 to 3.2% Accu. 98.8 to 105.5%	Prec. 1.7 to 5.3% Accu. 97.3 to 101.8%	Mean Prec & Acc < ±15.0%
Extract Stability (72 Hrs @ 6°C)	Cartridge	29	0.5 to 1.7% Diff	0.2 to 0.7% Diff	< 15.0% diff from fresh QCs
Short-Term Matrix Stability (4 Hrs @ RT)	Cartridge	30	-3.2 to -1.8% Diff	-7.5 to -2.3% Diff	< 15.0% diff from fresh QCs
Freeze-Thaw Stability (3 x F/T Cycles)	Cartridge	31	-3.7 to 0.1% Diff	0.0 to 1.9% Diff	< 15.0% diff from fresh QCs
Long-Term Matrix Stability (6 wks @ -70°C)	Cartridge	32	-9.6 to -4.4% Diff	-5.7 to -5.1% Diff	< 15.0% diff from time zero
Stock Solution Stability (-20°C)	N/A	33	-0.2% Diff OXC (6wk) -1.4% Diff OXC-d4 (4 wk)	2.9% Diff MHD (6 wk) 2.8% Diff MHD-d4 (4wk)	< 5.0% diff from fresh
Wrk Soln Stability	N/A	34, 35	2.3% Diff (4 days @ 6°C) 2.3% Diff (6 Hr @ RT)	-0.6% Diff (4 days @ 6°C) 1.7% Dif (6 Hr @ RT)	< 5.0% diff from fresh
IS Spk Soln Stability	N/A	36, 37	0.8% Diff (1 mo @ 6°C) -1.9% Diff (6 Hr @ RT)	-3.6% Diff (1 mo @ 6°C) -1.0% Diff (6 Hr @ RT)	< 5.0% diff from fresh
Carry-over Limit (Blank after ULOQ)	Both	38	0.0 to 0.1%	0.0 to 0.1%	< 20.0% of LLOQ
Batch Size (b) (4)	Cartridge	39	Prec: 2.1 to 5.0% Accu: 103.8 to 110.2%	Prec: 5.4 to 7.6% Accu: 108.2 to 113.3%	Meet acceptance criteria for run

3. Individual Studies

3.1 Clinical Pharmacology Review

Pharmacokinetics- Multiple Dose Study

Report #: 804P103	**Study Period**: 1/2	EDR Link: \\Cdsesub1\evsprod\nda202810\0000\m5
Title	A single-center, multiple dose, open-label, randomized, 2-treatment crossover study to compare a daily administration of oxcarbazepine extended-release (OXC XR) tablet and twice a day administration of Trileptal (Novartis Pharmaceuticals Corporation) tablets in healthy adult volunteers under fasting conditions	
Objective	Primary Objective: To evaluate the steady-state relative bioavailability of 10-hydroxycarbazepine (MHD) assessed by using AUC(0-24) and Cmax,ss for two different oral formulations of OXC following up-titration to 1200 mg a day.	

Study Design: Multiple dose, open label, randomized, two-way, crossover. Healthy subjects were randomized to 2 treatments. Subjects were administered study drug after overnight fast. OXC XR was administered daily for 13 days. OXC immediate release (IR) was administered twice daily for 13 days. Treatments were separated by at least 7 days washout periods.

Number of Subjects/ dose group	**OXC XR**	16	**OXC IR**	16

Doses by Group
OXC XR
Days 1-3: 600 mg dose given orally QD in the morning
Days 4-6: 900 mg dose given orally QD in the morning
Days 7-13: 1200 mg dose given orally QD in the morning

OXC IR
Days 1-3: 300 mg dose given orally Q12h
Days 4-6: 450 mg dose given orally Q12h
Days 7-13: 600 mg dose given orally Q12h

PK Sampling Times: OXC XR: 0.5, 1, 2, 3, 4, 5, 6, 7, 8, 9, 10, 12, 13, 14, 15, 16, 17, 18, 20, 22, 24, 48, 60, 72 hours post morning dose
OXC IR: 0.5, 1, 2, 3, 4, 5, 6, 7, 8, 9, 10, 11.83, 12.5, 13, 14, 15, 16, 17, 18, 20, 22, 24, 36, 48, 60, 72 hours post morning dose

PD measurements collected prior to morning dose and 2.25 (OXC IR) or 5.25 (OXC XR) hours post dose. PD measurement: CogState test battery (Untimed and Timed Groton Maze Chase Tasks, Groton Maze Learning Task, Simple Reaction Time (Detection Task), Choice Reaction Time (Identification Task), One Card Learning Task). The tests were used to access visuomotor processing, executive function, psychomotor function, visual attention and visual learning.

Pharmacokinetic parameters for OXC and MHD, relative to dose administration on day 13 (at steady state) were calculated using non-compartmental methods. FL = (Cmax,ss – Cmin,ss)/Cavg, Swing = (Cmax,ss – Cmin,ss)/Cmin,ss

Analytical Method:

Type	LC/MS/MS	**Range**	OXC: 0.005 – 1 µg/mL MHD: 0.05 – 10 µg/mL
The performance of the analytical method is acceptable. Standard Curve Precision (%RSD): OXC: 2 – 14%, MHD: 1-3%. Accuracy: OXC : 98- 105%, MHD: 99 -100% Quality Control Samples Precision: OXC (%RSD): 5 -8%, MHD: 4% Accuracy: OXC 95- 97%, MHD: 105 -108%			☑ Yes ☐ No

Study Population :

Randomized/Completed/ Discontinued Due to AE	32/28/0
Age [Mean (range)]	40 (24- 55years)
Male/Female	20/12
Race (Caucasian/Black/Asian/other)	31/1/0/0

Results

- Pharmacokinetics Parameters for active metabolite (MHD) Per Treatment Group, Mean (±SD)

Treatment	AUC_{0-24} (µg.h/mL)	$C_{max,ss}$ (µg/mL)	$C_{min,ss}$ (µg/mL)	$t_{1/2}$ (h)	FL(%)	Swing (%)
OXC XR	387±74	19.4 ± 3.9	12.9 ± 2.76	15.4 ± 3.90	40.8 ± 9.09	51.7 ± 13.4
OXC IR	476 ± 74.2	23.8 ± 3.49	15.3 ± 2.71	14.4 ± 2.97	43.2 ± 8.70	57.3 ± 17.2

- Was the pharmacokinetics dose proportional? ☐ Yes ☐ No ☑ NA

- Pharmacokinetics Parameters for OXC Per Treatment Group, Mean (±SD)

Treatment	AUC_{0-24} (µg.h/mL)	$C_{max,ss}$ (µg/mL)	$C_{min,ss}$ (µg/mL)	$t_{1/2}$ (h)	FL(%)	Swing (%)
OXC XR	10.9 ± 3.81	1.10 ± 0.59	0.21 ± 0.08	13.0 ± 3.34	191 ± 66.4	459 ± 277
OXC IR	16.8 ± 4.73	2.72 ± 0.82	0.19 ± 0.06	13.4 ± 2.66	364 ± 102	1361 ± 565

Statistical Evaluation of Pharmacokinetic Parameters of MHD and OXC in Plasma

Pharmacokinetic Parameters	Ratio of LSM and 90% Confidence Intervals (CI)	
	MHD in Plasma OXC XR vs OXC IR	OXC in Plasma OXC XR vs OXC IR
AUC(0-24)	80.8% (77.5 -84.3%)	63.8% (59.6 -68.4%)
Cmax, ss	80.8% (77.0 – 84.9%)	38.6% (33.3 – 44.8%)
Cmin, ss	83.7% (78.8 – 88.9%)	104.2% (91.5 – 118.6%)
FL	94.3% (85.1 – 103.5%) -2.5(-6.4, 1.5)	52.4% (41.8 – 63.0%) -173(-211.5, -134.5)
Swing	90.3% (78.2 – 102.4%) -5.6 (-12.5, 1.4)	33.7% (19.1-48.3%) -902 (-1101, -703)

- The pharmacokinetics is best described by:

☐ Mono-exponential decay, ☑ Bi-exponential decay, ☐ Tri-Exponential Decay

- Was there a lag time in absorption? ☐ Yes ☑No

Safety

- Was there any death or serious adverse events? ☐Yes ☑ No ☐ NA
- The sponsor reported that overall, adverse events were more frequently reported in subjects receiving OXC IR (190 AEs, 61.3% of total AEs) than in subjects receiving OXC XR (120 AEs, 38.7% of total AEs). Most of the AEs were mild or moderate in intensity. Four subjects were discontinued due to AE - 2 after due to papular rash or hyponatremia after taking OXC XR or OXC IR. No deaths were reported. The most AEs (>10%) were dizziness, headache, constipation, hypoaesthesia oral, nausea, pollakiuria and euphoric mood. No dizziness was reported after taking OXC XR.
- The sponsor reported that no apparent safety concerns of treatment with multiple oral doses of OXC XR 600mg, 900mg or 1200mg extended-release formulations were identified.

Comments

AUC(0-24) and Cmax,ss of MHD following the administration of OXC XR were approximately 19% lower than with OXC IR. Mean Cmin of MHD was about 16% lower after administration of OXC XR compared to OXC IR. The AUC(0-24) of OXC following the administration of OXC XR was approximately 36% lower than with OXC IR. The Cmax,ss of OXC following the administration of OXC XR was approximately 61% lower than with OXC IR. Steady state was reached by day 11 for both MHD and OXC in these studies.
There was no change in the PD parameters evaluated after administration of OXC XR compared to OXC IR.

The reviewer agrees with the conclusions of the sponsor.

Pharmacokinetics- Dose Proportionality

Report # 804P104	**Study Period**: 1/2	EDR Link\\Cdsesub1\evsprod\nda202810\0000\m5

Title	A Randomized open-label, 3-way crossover, single center study evaluating the dosage form proportionality of three different strengths of oxcarbazepine extended release tablets (150, 300, and 600 mg) administered as a single 600 mg oral dose to healthy subjects under fasting conditions
Objective	To evaluate the dosage form proportionality of a Supernus extended release oxcarbazepine (OXC XR) formulation when administered as 4 x 150 mg tablets, 2 x 300 mg tablets, or 1 x 600 mg tablet, under fasting conditions

Study Design:

Single center, open-label, randomized, 3-period, 6-sequence, crossover 7-day washout between periods. The design does not include a placebo arm.

Number of Subjects/ dose group	**Drug**		**Placebo**	
	A: 52 B: 51 C: 50		N/A	

Doses by Group: A: OXC XR, 4 x 150 mg, single dose, Batch/Lot No: B07034B
B: OXC XR, 2 x 300 mg, single dose, Batch/Lot No.: B07035C
C: OXC XR, 1 x 600 mg, single dose, Batch/Lot No.: B07033C

PK Sampling Times: 0 (pre-dose), 1, 2, 4, 5, 6, 8, 10, 12, 15, 18, 24, 36, 48, 60, 72 hours post-dose.

Analytical Method:

Type	LC/MS/MS	**Range**	0.05 – 10 µg/mL for MHD, 0.005 – 1.0 µg/mL for OXC
The performance of the analytical method is acceptable.		☑ Yes ☐ No	

Study Population :

Randomized/Completed/ Discontinued Due to AE	54/53/1
Age [Median (range)]	39 (19 – 55) years
Male/Female	20/34
Race (Caucasian/Black/Asian/other)	51/1/0/2

Results

- Pharmacokinetics Parameters Per Dose Group, Mean (%CV)

Summary of the Pharmacokinetic Parameters for MHD

Dose	$AUC_{0-\infty}$	C_{max}	T_{max}	$t_{1/2}$	AUC_{0-t}	
OXC 4 x 150 mg	166.40 (23.85)	4.92 (21.95)	11.7 (33.46)	10.19 (21.01)	162.49 (23.01)	
OXC 2 x 300 mg	166.45 (21.45)	4.81 (19.96)	13.3 (38.75)	10.11 (17.81)	162.80 (20.82)	
OXC 1 x 600 mg	164.63 (23.92)	4.70 (19.19)	12.4 (43.25)	10.24 (20.08)	160.78 (23.04)	

Summary of Pharmacokinetic Parameters for OXC

Dose	$AUC_{0-\infty}$	Cmax	Tmax	T ½	AUC_{0-t}	
OXC 4 x 150 mg	5.39 (32.61)	0.50 (53.91)	4.79 (33.17)	10.67 (16.27)	5.23 (33.78)	
OXC 2 x 300 mg	5.40 (32.97)	0.43 (52.49)	4.63 (36.61)	10.57 (16.21)	5.27 (33.92)	
OXC 1 x 600 mg	5.36 (36.31)	0.42 (42.04)	4.69 (31.16)	10.69 (20.63)	5.21 (37.84)	

- Was the pharmacokinetics dose proportional? ☐Yes ☐ No ☑NA
- Dosage strength equivalence was demonstrated.

Summary of the Ratios of LSMs and the 90% Confidence Interval for MHD

ANOVA	Treatment Comparisons*	Ratio of LS Means (%)	90% CI (%)	Intra-Subject CV (%)
AUC_{0-t}	B vs A C vs B C vs A	100.73 98.26 98.97	96.94 – 104.66 94.51 – 102.16 95.22 – 102.88	11.72
$AUC_{0-\infty}$	B vs A C vs B C vs A	100.59 98.45 99.04	96.70 – 104.64 94.59 – 102.47 95.18 – 103.05	12.06
Cmax	B vs A C vs B C vs A	97.93 97.23 95.22	94.46 – 101.52 93.74 – 100.85 91.82 – 98.74	11.01

*A= OXC XR Tablet, 4 x 150 mg, B= OXC XR Tablet, 2 x 300 mg, C= OXC XR Tablet, 1 x 600 mg

Summary of the Ratios of LSMs and the 90% Confidence Intervals for OXC

ANOVA	Treatment Comparisons*	Ratio of LS Means (%)	90% Confidence Interval (CI) (%)	Intra-Subject CV (%)
AUC_{0-t}	B vs A C vs B C vs A	101.78 97.69 99.44	97.45 – 106.31 93.48 – 102.10 95.17 – 103.69	13.31
$AUC_{0-\infty}$	B vs A C vs B C vs A	101.12 98.31 99.41	96.98 – 105.43 94.23 – 102.57 95.31 – 103.89	12.78
C_{max}	B vs A C vs B C vs A	87.70 98.26 86.17	80.60 – 95.42 90.19 – 107.04 79.14 – 93.83	26.14

*A= OXC XR Tablet, 4 x 150 mg, B= OXC XR Tablet, 2 x 300 mg, C= OXC XR Tablet, 1 x 600 mg

- The pharmacokinetics is best described by:

☐ Mono-exponential decay, ☑ Bi-exponential decay, ☐ Tri-Exponential Decay

- Was there a lag time in absorption? ☐ Yes ☑ No

Safety

- Was there any death or serious adverse events? ☐ Yes ☑ No ☐ NA
- The sponsor reported a total of 157 treatment-emergent adverse events (TEAEs) were reported by 42 of the 54 subjects who received at least one dose of the study medication (safety population). The breakdown by treatment group is as follows: 55 AEs reported by 45.3% (n=24) of the 53 subjects who received Treatment A, 57 AEs reported by 49.1% (n=26) of the 53 subjects who received Treatment B, and 45 AEs reported by 37.3% (n=19) of the 51 subjects who received Treatment C.

The sponsor reported the most frequent AEs for the subjects who received the study medication were: headache, somnolence, catheter site pain, and fatigue. The most commonly observed adverse events with Treatment A were Nervous System Disorders: headache and somnolence, observed in 10 (18.9%) and 8 (15.1%) of subjects, respectively.

The most commonly observed adverse events with Treatment B were Nervous System Disorders: headache and somnolence, observed in 7 (13.2%) and 5 (9.4%) of subjects, respectively. The most commonly observed adverse events with Treatment C were Nervous System Disorders: somnolence, headache and dizziness (8 [15.7%], 6 [11.8%], and 2 [3.9%] subjects experienced these adverse events, respectively). The sponsor reported that abnormalities were only observed for QTcF interval greater than 450msec. One subject (subject No. 51) presented a QTcF interval of 456msec with a corrected QTcF change from baseline of 42 msec. However, the Principal Investigator judged it to be not clinically significant since there was not a significant change from baseline (not over 60msec).

Comments

The 90% CI for the ratios (B/A, C/B and C/B) were contained within 80% to 125% for both MHD and OXC parameters of AUC and Cmax except the Cmax comparison of OXC XR, 1 x 600 mg vs OXC XR 4 x 150 mg (C/A) for OXC which was 79.14 to 93.83. Therefore, MHD exposures were comparable following administration of 4 x 150 mg, 2 x 300 mg, 1 x 600 mg OXC XR. OXC pharmacokinetics was also comparable with respective to AUC. The difference in OXC Cmax comparison between 4 x 150 mg and 1 x 600 mg could be due to the multiple dosage units used for the 150 mg and should not be clinically relevant.

The reviewer agrees with the sponsor's conclusion that the 4 x 150 mg, 2 x 300 mg and 1 x 600 mg strengths are comparable. No serious safety event was reported.

Pharmacokinetics- Dose Proportionality

Report # 804P104.5	**Study Period**:	EDR Link
Title	A randomized open-label, 3-way crossover, single center study evaluating the dosage form pharmacokinetic linearity of three different strengths of oxcarbazepine extended release tablets (150, 300, and 600 mg) administered as a single 600 mg oral dose to healthy subjects under fasting conditions	
Objective	To evaluate the dosage form pharmacokinetic (PK) linearity of a Supernus extended release oxcarbazepine (OXC XR) formulation when administered as 1 x 150 mg tablets, 1 x 300 mg tablets, or 1 x 600 mg tablet, under fasting conditions	

Study Design:

Single center, open-label, randomized, 3-period, 6-sequence, crossover.
Minimum of 7-day washout between periods. The design does not include a placebo arm
Criteria for PK dose linearity:
For MHD, 90% geometric CIs for the ratio of geometric LSM (1 x 300mg vs 1 x 150mg, 1 x 600mg vs 1 x 300mg and 1 x 600mg vs 1 x 150mg) for AUC(0-t), AUC∞ and Cmax should be within 80% to 125%.
Linearity was also assessed for each parameter (P) using the power model, i.e.
$P = a \times Dose^b$, where "a" is a multiplicative coefficient of the power model (it is related to the intercept when the model is log-transformed) and "b" is the exponential coefficient of the power model (it corresponds to the slope when the model is log-transformed); if the 95% confidence interval (CI) for b contained 1, then linearity was to be concluded.

Number of Subjects/ dose group	**Drug**	**PK Pop**	**Placebo**	
	A: 52 B: 54 C: 53	A: 51 B: 52 C:52	N/A	

Doses by Group: A: OXC XR, 1 x 150 mg, single dose, Batch/Lot No: B07034C
B: OXC XR, 1 x 300 mg, single dose, Batch/Lot No.: B07035D
C: OXC XR, 1 x 600 mg, single dose, Batch/Lot No.: B07033D

PK Sampling Times: 0 (pre-dose), 1, 2, 4, 5, 6, 8, 10, 12, 15, 18, 24, 36, 48, 60, 72 hours post-dose.

Analytical Method:

Type	LC/MS/MS	**Range**	0.05 – 10 µg/mL for MHD, 0.005 – 1.0 µg/mL for OXC
The performance of the analytical method is acceptable.	☑ Yes ☐ No		

Study Population :

Randomized/Completed/ Discontinued Due to AE/protocol violation	54/52/1/1
Age [Median (range)]	38(19 – 55) years
Male/Female	20/34
Race (Caucasian/Black/Asian/Hispanics)	37/2//0/11

Results

-
-
-
-

- Pharmacokinetics Parameters Per Dose Group, Mean (%CV)

Summary of the Pharmacokinetic Parameters for MHD

Dose	$AUC_{0-\infty}$	C_{max}	T_{max}	$t_{1/2}$	AUC_{0-t}	
OXC 150 mg (A)	28.39 (22.14)	1.23 (24.77)	9.24 (34.95)	9.52 (14.09)	27.22 (22.96)	
OXC 300 mg (B)	67.32 (25.84)	2.32 (22.70)	10 (34.11)	9.65 (13.39)	65.92 (26.29)	
OXC 600 mg (C)	159.39 (23.71)	4.37 (23.19)	15.2 (36.53)	11.09 (23.35)	154.60 (23.25)	

Summary of Pharmacokinetic Parameters for OXC

Dose	$AUC_{0-\infty}$	Cmax	Tmax	T ½	AUC_{0-t}	
OXC 150 mg	0.95 (30.24)	0.13 (49.82)	4.99 (28.79)	7.44 (33.19)	0.86 (32.10)	
OXC 300 mg	2.13 (33.02)	0.23 (43.90)	4.81 (20.18)	10.26 (20.33)	2.10 (34.32)	
OXC 600 mg	4.76 (29.94)	0.38 (39.73)	4.54 (35.29)	11.16 (18.05)	4.62 (30.43)	

Summary of the Dose-Normalized to the 300 mg Dose Pharmacokinetic Parameters for MHD

Parameter	*Treatment A Mean (%CV)	Treatment B Mean (%CV)	Treatment C Mean (%CV)	
AUC_{0-t} (μg*h/mL)	54.45 (22.96)	65.92 (26.29)	77.30 (23.25)	
$AUC_{0-\infty}$ (μg*h/mL)	56.76 (22.14)	67.32 (25.84)	79.69 (23.71)	
C_{max} (μg/h)	2.47 (24.77)	2.32 (22.70)	2.19 (23.19)	

*A= OXC XR Tablet, 1 x 150 mg, B= OXC XR Tablet, 1 x 300 mg, C= OXC XR Tablet, 1 x 600 mg

Summary of the Dose-Normalized to the 300 mg Dose Pharmacokinetic Parameters for OXC

Parameter	*Treatment A Mean (%CV)	Treatment B Mean (%CV)	Treatment C Mean (%CV)	
AUC_{0-t} (μg*h/mL)	1.71 (32.01)	2.01 (34.32)	2.31 (30.43)	
$AUC_{0-\infty}$ (μg*h/mL)	1.90 (30.24)	2.13 (33.02)	2.38 (29.94)	
C_{max} (μg/h)	0.257 (49.82)	0.23 (43.90)	0.19 (39.73)	

*A= OXC XR Tablet, 1 x 150 mg, B= OXC XR Tablet, 1 x 300 mg, C= OXC XR Tablet, 1 x 600 mg

Summary of the Ratios of LSMs and the 90% Confidence Interval for Dose Normalized (to 300 mg) for MHD

ANOVA	Treatment Comparisons*	Ratio of LS Means (%)	90% CI (%)	Intra-Subject CV (%)
AUC_{0-t}	B vs A	118.27	112.62 – 124.20	15.00
	C vs B	118.93	113.29 – 124.85	
	C vs A	140.66	133.7 – 147.7	
$AUC_{0-\infty}$	B vs A	115.82	110.42 – 121.48	14.63
	C vs B	119.75	114.21 – 125.56	
	C vs A	138.69	132.23 – 145.48	
Cmax	B vs A	93.36	89.80 – 97.07	11.90
	C vs B	94.28	90.71 – 98.00	
	C vs A	88.03	84.67 – 91.52	

*A= OXC XR Tablet, 1 x 150 mg, B= OXC XR Tablet, 1 x 300 mg, C= OXC XR Tablet, 1 x 600 mg

Summary of the Ratios of LSMs and the 90% Confidence Interval for Dose Normalized (to 300 mg) for OXC

ANOVA	Treatment Comparisons*	Ratio of LS Means (%)	90% CI (%)	Intra-Subject CV (%)
AUC_{0-t}	B vs A	114.50	108.83 – 120.68	15.85
	C vs B	116.78	110.93 – 122.92	
	C vs A	133.83	127.08 – 140.93	
$AUC_{0-\infty}$	B vs A	110.12	104.78 – 115.73	15.12
	C vs B	113.07	107.66 – 118.74	
	C vs A	124.50	118.47 – 130.84	
Cmax	B vs A	89.79	82.85 – 97.32	24.88
	C vs B	83.69	77.27 – 90.64	
	C vs A	75.15	69.34 – 81.44	

*A= OXC XR Tablet, 1 x 150 mg, B= OXC XR Tablet, 1 x 300 mg, C= OXC XR Tablet, 1 x 600 mg

Power model Results (slope and 95% CI) for the Ln-Transformed PK Parameters for MHD

Statistical Analysis	Slope	95% CI
AUC_{0-t}	1.25	1.21 – 1.29
AUC_{∞}	1.24	1.20 – 1.28
Cmax	0.91	0.88 – 0.94

Power model Results (slope and 95% CI) for the Ln-Transformed PK Parameters for OXC

Statistical Analysis	Slope	95% CI
AUC_{0-t}	1.21	1.18 – 1.26
AUC_{∞}	1.16	1.12 – 1.20
Cmax	0.80	0.73 – 0.87

- Was the pharmacokinetics Linear? ☐Yes ☑ No

Safety

- Was there any death or serious adverse events? ☐ Yes ☑ No ☐ NA

A total of 51 TEAEs were reported by 25 of the 54 subjects who received at least one dose of the study medication. Fifteen (15) AEs reported by 19.2% (n=10) of the 52 subjects who received Treatment A, 12 AEs reported by 11.1% (n=6) of the 54 subjects who received Treatment

B, and 24 AEs reported by 30.2% (n=16) of the 53 subjects who received Treatment C.
The most commonly observed AEs with Treatment A were catheter site pain recorded for 4 (7.7%) of subjects. The next most frequently observed AEs were headache, observed in 3 (5.8%) of subjects. The most commonly observed AEs with Treatment C were headache and somnolence, observed in 3 (5.7%) and 2 (3.8%) of subjects, respectively. The next most frequently observed AEs were vomiting observed in 2 (3.8%) of subjects. More AEs were observed in Treatment C (n = 24) than in Treatments A (n = 15) and B (n = 12).

Comments

In accordance with the study protocol, dose linearity was to be concluded if the 90% geometric CI for the ratios of geometric LSM (1 x 300mg (B) vs 1 x 150mg (A), 1 x 600mg (C) vs 1 x 300mg (B) and 1 x 600mg (C) vs 1 x 150mg(A)) for AUC0-t, AUC∞ and Cmax were within 80.00% to 125.00% for MHD. The acceptance criteria were met for all comparisons for the dose-normalized Cmax but not for AUC0-t and AUC∞.
For both MHD and OXC, the lower and upper bounds of the 95% CI for the slope of the power model were greater than 1 for AUCs and lower than 1 for Cmax. These results indicate a greater than proportional increase in AUCs and a less than proportional increase in Cmax over the 150mg to 600mg dose range for both the parent and the metabolite.
In conclusion, when OXC XR is administered under fasting conditions as 150mg, 300mg, and 600mg tablets, AUC of MHD and OXC increases more than proportional with an increase in dose.
The reviewer agrees with the sponsor's conclusion that when OXC ER is administered as 150 mg, 300 mg and 600 mg dose, there is greater than proportional increase in total exposure to the active metabolite and parent drug. AUC for MHD increase by approximately 20 to 40%. Dose linearity was not demonstrated in this study by either method the sponsor used to evaluate linearity.

Biopharmaceutics- Food Effect

Report # 804P105	**Study Period**: 1/2	EDR Link \\Cdsesub1\evsprod\nda202810\0000\m

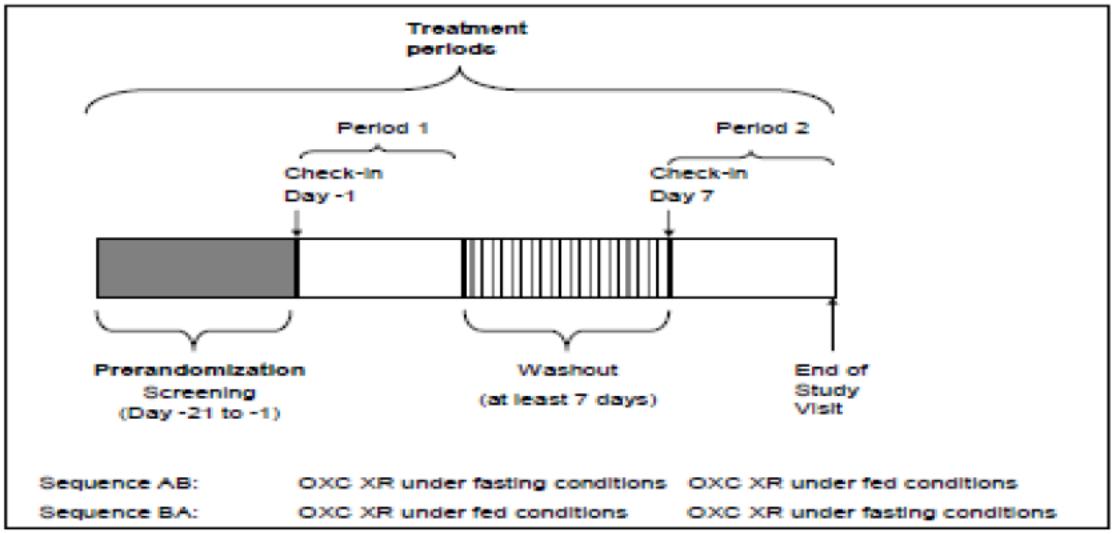
Title	A single center, single dose, open-label, randomized, 2-way (Fed versus Fasting) crossover study to evaluate the effect of food on the bioavailability of oxcarbazepine extended release tablets in healthy adul volunteers
Objective	The primary objective of this study was to compare the pharmacokinetics (PK) of a single dose of OXC X 600 mg tablet administered under fed and fasting conditions

Study Design

☑ Food Effect

Single-Center Single-Dose Randomized Open-Label Cross-Over 2-Period 2-CohortHealthy Vonuteers

Eligible subjects were then checked in to the study unit on the evening before dosing in each study period (Day -1 and Day 7). Subjects were randomized into 2 treatment sequences. Each dose was separated by a 7-day washout period. Subjects were administered the study medication (SM) on day 1 and day 8, either under fasted conditions (Treatment A or 30 minutes after administration of a high fat breakfast (Treatment B). PK blood samples were taken for 72 hours aft administration of SM in each study period, and subjects were discharged after the 36-hour blood sample. Subjects returned to the study unit to provide the 48-, 60- and 72-hour PK blood samples. Throughout the study, vital signs were monitored and AEs
recorded.



Screening: ≤ 21 days	**Washout:** 7 days between doses (fed and fasted states) outpatient
Period 1/2	☑Y ☐ N:

Treatments: (Active Ingredient: MHD)

Formulation	**Formulation**
Dosage Form/Strength	Tablet/600 mg
Dose Used in the Study	600 mg
Batch #.	B07033F
To be Marketed Formulation	Yes ☑ No ☐
Highest Strength Available	Yes ☑ No ☐

Meal used meets the FDA Guidance Recommendations: Yes ☑ No ☐
2 slices of buttered toast, 2 fried eggs, 2 strips of bacon, 1 serving of hash brown potatoes, and 240 mL of whole milk (1000 total kcal).

Sampling Times (PK, plasma) : pre-dose (0), and at 1, 2, 3, 3.5, 4, 4.5, 5, 6, 6.5, 8, 9, 9.5, 10, 10.5, 11, 12, 15, 18, 24, 36, 48, 60 and 72 hours post dose

Analytical Method: The performance of the analytical method is acceptable Yes ☑ No ☐
LC/MS/MS. Range 0.005 – 1.0 μg/mL for OXC and 0.05 – 10 μg/mL for MHD.

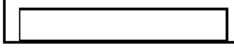
Statistical Method: ANOVA on ln transformed AUCt, AUC∞ and Cmax fitting for sequence, period, and treatment. LS mean and 90% CI for the difference were constructed.

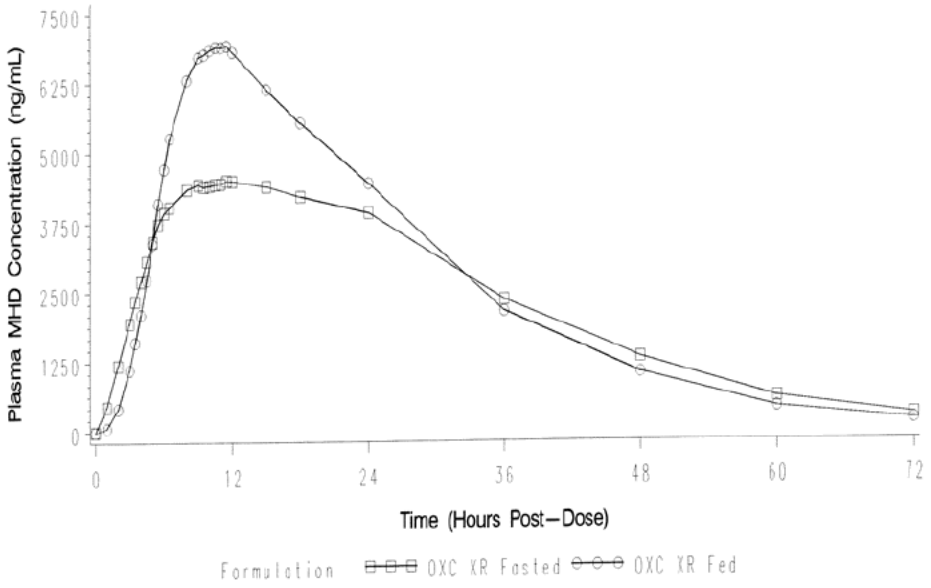
Study Population :

Formulation	**Formulation**
Randomized/Completed/ Discontinued Due to AE/other	62/59/0/3
Age [Median (range)]	41 (21-55) years
Male/Female	40/22
Race (Caucasian/Black/Asian/other)	61/1/0
Hispanic or Latino/Not Hispanic or Latino (Ethnicity)	13/49

Results

The mean plasma concentration time profile for MHD after administration of OXC XR 600 mg under fasting and fed conditions is presented in the following graph





Summary of Plasma OXC and MHD Pharmacokinetics by treatment

Parameter	Measurement	OXC		MHD	
		OXC XR Fasted (A)	OXC XR Fed (B)	OXC XR Fasted (A)	OXC XR Fed (B)
AUC0-t (ng*h/mL)	Mean (±SD)	5233 (1760)	6776 (1963)	167493 (34165)	188503 (29487)
AUC∞ (ng*h/mL)	Mean (±SD)	5405 (1769)	6911 (1957)	172173 (35839)	191098 (30265)
Cmax (ng/mL)	Mean (±SD)	507 (291)	1409 (601)	4926 (1087)	7914 (1175)
Tmax (h)	Mean (±SD)	4.58 (0.977)	6.74 (2.26)	12.1 (4.76)	9.66 (2.69)
T ½ (h)	Mean ± SD	11.4 ± 3.09	11.1 ± 1.64	10.8 ± 2.69	9.43 ± 1.84

Results of the ANOVA on Pharmacokinetics of OXC and MHD in Plasma

	Ratio of LSM and 90% Confidence Intervals	
Pharmacokinetics	OXC OXC XR Fed vs OXC XR Fasted	MHD OXC XR Fed vs OXC XR Fasted
AUC0-t	131.3 (126.1 – 136.7%)	113.5 (109.5 – 117.7%)
AUC∞	129.4 (124.4 – 134.5%)	112.0 (107.9 – 116.2%)
Cmax	281.7 (254.5 – 311.75%)	162.6 (156.7 – 168.7%)

Site Inspected

Requested: Yes☐ No ☑	**Performed:** Yes☐ No ☐ N/A ☑

Safety

- Was there any death or serious adverse events? ☐ Yes ☑ No ☐ NA

The sponsor reported adverse events were more frequently reported (23 AEs, 71.9% of total AEs) in subjects receiving

Treatment B under fed conditions than in subjects receiving Treatment A under fasting conditions (9 AEs reported {28.1% of total AEs}). The most frequently reported AE was headache (9.7% of all subjects), followed by dizziness, feeling hot, venipuncture site swelling and nausea (each reported in 3.2% of all subjects). All other AEs occurred in 1.7% or fewer subjects per treatment group.
Summary and Conclusion
The 90% confidence intervals of the AUC0-t, AUC∞ and Cmax for OXC in plasma were outside 80-125%, indicating that following the administration of a high fat meal, the exposure to OXC is significantly increased compared to the fasted state. The 90% confidence intervals of the AUC0-t and AUC∞ for MHD in plasma were within 80-125%, however, the confidence interval of the Cmax for MHD in plasma were outside 80-125%. The administration of a high fat meal does not affect the extent of bioavailability of MHD, however the peak plasma concentration of MHD is significantly increased compared to the fasted state. The mean T½ of OXC and MHD were comparable under fasted ar fed conditions. However, the mean T ½ of OXC following the administration of OXC XR under fed conditions was about 2 hours longer than for OXC XR under fasting conditions. The mean Tmax of MHD following the administratio of OXC XR under fed conditions was about 2.5 hours shorter than under fasting conditions .
Comments
The reviewer agrees with the sponsor's conclusions. It is recommended oxcarbazepine be given under fasting conditions.

Validation of Bioanalytical Method for Determination of Oxcarbazepine and 10-hydroxycarbazepine (MHD) in Human Plasma by LC/MS/MS

Report No. TR-04-32

A sensitive, accurate, and reproducible bioanalytical method for the determination of oxcarbazepine and 10-hydroxycarbazpine in human plasma has been developed and validated using high pressure liquid chromatography (HPLC) with tandem mass spectrometry (MS/MS). The assay uses solid phase extraction (SPE) and isotopically labeled internal standards. The concentrations of oxcarbazepine and 10-hydroxycarbazepine are determined by comparing the peak area ratio of each analyte to its respective internal standard with a standard curve defined by calibration standards at eight levels.

The method was validated over a concentration range of 0.005-1.0 µg/mL oxcarbazepine and 0.05-10.0 µg/mL 10-hydroxycarbazepine in human plasma using two different SPE platforms, single SPE cartridges, and 96-well SPE plates. The overall absolute recovery for all analytes was 86.8 % or greater. Interference from blank human plasma and carryover from the highest standard were less than or equal to 7.5% of the lower limit of quantitation (LLOQ) for both analytes. Stability was determined for stock solutions, spiking solutions, and sample extracts. Matrix stability was established at room temperature for 6 hours, at –70°C for six weeks, and following three freeze/thaw cycles. Dilution accuracy and precision and batch size also were established. The sponsor reported that the acceptance criteria were met and the method has been validated successfully. In addition, each extraction method was validated and shown to be statistically similar in regards to the performance elements tested. The attached table contains the performance statistics for the analytical method.

Reviewer comment: The analytical method is adequately validated and acceptable.

Analytical Method Validation Summary

Element	SPE Method	Table	Result		Specification
			Oxcarbazepine	10-Hydroxycarbazepine	
Calibration Standard Precision & Accuracy	Cartridge	7	Prec. 2.1 to 5.7% Accu. 94.5 to 112.0%	Prec. 0.5 to 6.6% Accu. 97.7 to 106.7%	< ±15.0% < ±20.0% at LLOQ
	96-well	8	Prec. 0.6 to 6.9% Accu. 95.2 to 106.7%	Prec. 0.2 to 4.5% Accu. 98.0 to 101.2%	< ±15.0% < ±20.0% at LLOQ
Intra-Assay Precision & Accuracy (n=5)	Cartridge	11,12	Prec. 0.9 to 4.2% Accu. 100.2 to 106.1%	Prec. 1.7 to 5.4% Accu. 94.7 to 104.5%	< ±15.0%
	96-well	13,14	Prec. 1.6 to 3.7% Accu. 95.8 to 105.2%	Prec. 0.7 to 2.6% Accu. 96.0 to 103.4%	< ±15.0%
Inter-Assay Precision & Accuracy (n=15)	Cartridge	15,16	Prec. 2.1 to 3.6% Accu. 102.3 to 104.6%	Prec. 4.6 to 5.4% Accu. 99.6 to 100.5%	< ±15.0%
	96-well	17,18	Prec. 2.9 to 3.8% Accu. 100.0to 103.5%	Prec. 2.1 to 3.8% Accu. 98.9 to 99.7%	< ±15.0%
Specificity (n=6)	Cartridge	19,20	6.5% of LLOQ 0.3% of IS	1.7% of LLOQ 0.2% of IS	< 20.0% of LLOQ < 5.0% of IS
	96-well	21,22	7.5% of LLOQ 0.5% of IS	1.6% of LLOQ 0.2% of IS	< 20.0% of LLOQ < 5.0% of IS
Sensitivity / LLOQ (n=6)	Cartridge	23	Precision 2.1% Accuracy 110.3%	Precision 3.0% Accuracy 90.8%	< ±20.0%
	96-well	24	Precision 5.5% Accuracy 113.3%	Precision 1.6% Accuracy 99.2%	< ±20.0%
Dilution (DF=10)	Cartridge	25	Precision 1.5% Accuracy 100.8%	Precision 3.1% Accuracy 95.9%	< ±15.0%
Absolute Recovery	Cartridge	26	86.8 to 95.3% OXC 87.8 to 94.6% OXC-d4	89.6 to 104.8% MHD 92.6 to 100.4% MHD-d4	No sig. diff. from levels or lots
	96-well	27	93.6 to 103.0% OXC 96.1 to 105.7% OXC-d4	91.1 to 101.1% MHD 95.9 to 101.8% MHD-d4	No sig. diff. from levels or lots
Re-Injection Stability (72 Hrs @ 6°C)	Cartridge	28	Prec. 0.9 to 3.2% Accu. 98.8 to 105.5%	Prec. 1.7 to 5.3% Accu. 97.3 to 101.8%	Mean Prec & Acc < ±15.0%
Extract Stability (72 Hrs @ 6°C)	Cartridge	29	0.5 to 1.7% Diff	0.2 to 0.7% Diff	< 15.0% diff from fresh QCs
Short-Term Matrix Stability (4 Hrs @ RT)	Cartridge	30	-3.2 to -1.8% Diff	-7.5 to -2.3% Diff	< 15.0% diff from fresh QCs
Freeze-Thaw Stability (3 x F/T Cycles)	Cartridge	31	-3.7 to 0.1% Diff	0.0 to 1.9% Diff	< 15.0% diff from fresh QCs
Long-Term Matrix Stability (6 wks @ -70°C)	Cartridge	32	-9.6 to -4.4% Diff	-5.7 to -5.1% Diff	< 15.0% diff from time zero
Stock Solution Stability (-20°C)	N/A	33	-0.2% Diff OXC (6wk) -1.4% Diff OXC-d4 (4 wk)	2.9% Diff MHD (6 wk) 2.8% Diff MHD-d4 (4wk)	< 5.0% diff from fresh
Wrk Soln Stability	N/A	34,35	2.3% Diff (4 days @ 6°C) 2.3% Diff (6 Hr @ RT)	-0.6% Diff (4 days @ 6°C) 1.7% Dif (6 Hr @ RT)	< 5.0% diff from fresh
IS Spk Soln Stability	N/A	36,37	0.8% Diff (1 mo @ 6°C) -1.9% Diff (6 Hr @ RT)	-3.6% Diff (1 mo @ 6°C) -1.0% Diff (6 Hr @ RT)	< 5.0% diff from fresh
Carry-over Limit (Blank after ULOQ)	Both	38	0.0 to 0.1%	0.0 to 0.1%	< 20.0% of LLOQ
Batch Size (b) (4)	Cartridge	39	Prec: 2.1 to 5.0% Accu: 103.8 to 110.2%	Prec: 5.4 to 7.6% Accu: 108.2 to 113.3%	Meet acceptance criteria for run

3.2 Pharmacometric Review

OFFICE OF CLINICAL PHARMACOLOGY:

PHARMACOMETRIC REVIEW

SUMMARY OF FINDINGS

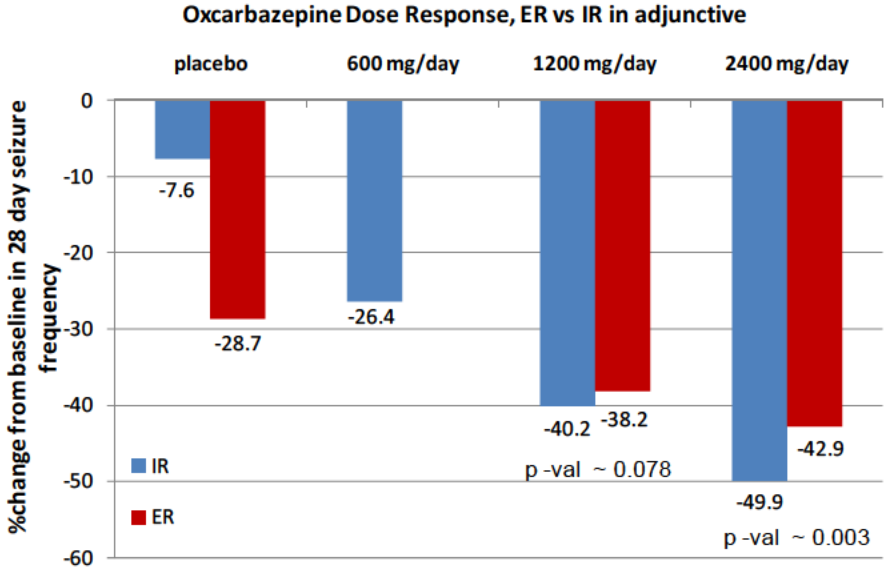
Key Review Questions

The purpose of this review is to address the following key questions.

Is there evidence of an exposure-response relationship (dose-response, concentration-response) for efficacy of the OXC-ER formulation?

Yes. A significant dose-response and concentration-response relationship was observed for the OXC-ER formulation. Figure 1 below shows the results of the pivotal trial graphically, and makes comparison to the dose-response information from the IR formulation pivotal trial results. The results from the IR formulation pivotal trials were obtained from approved label. For the IR formulation, a trend in dose-response was observed with all doses (600, 1200 and 2400 mg/day) being statistically different from placebo (all p-values <0.05). A trend in dose-response was observed for the ER formulation, but only the 2400 mg/day showed a statistically significant difference from placebo (p-value ~0.003). For further details please refer to the review by Dr. Ohid Siddiqui (Office of Biostatistics, OTS).

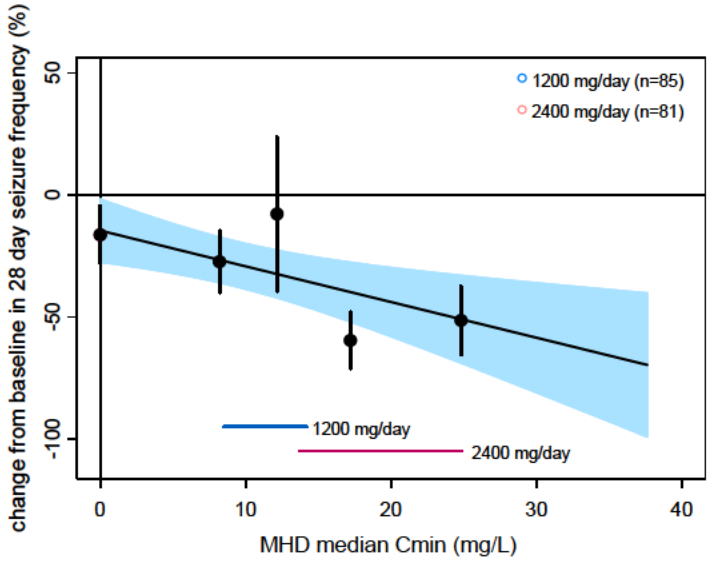
Figure 1. Dose-Response for the OXC-ER (red) and IR (blue) formulations from the pivotal trials.



Note: The p-values presented, contrasting each dose with placebo, are for the ER formulation for both the 1200 mg and 2400 mg/day. For the IR formulation, all doses were statistically different than placebo (all p-values <0.05)

With respect to a concentration-response relationship, a trend was observed with % reduction is seizure frequency as a function of MHD (10-monohydroxy metabolite, the primary active metabolite) Cmin concentrations (slope= -1.47 [95% CI: -2.27, -0.663], p-value = 0.0003). A simple linear model was fit (Figure 2), pooling the responses from all analyzable patients.

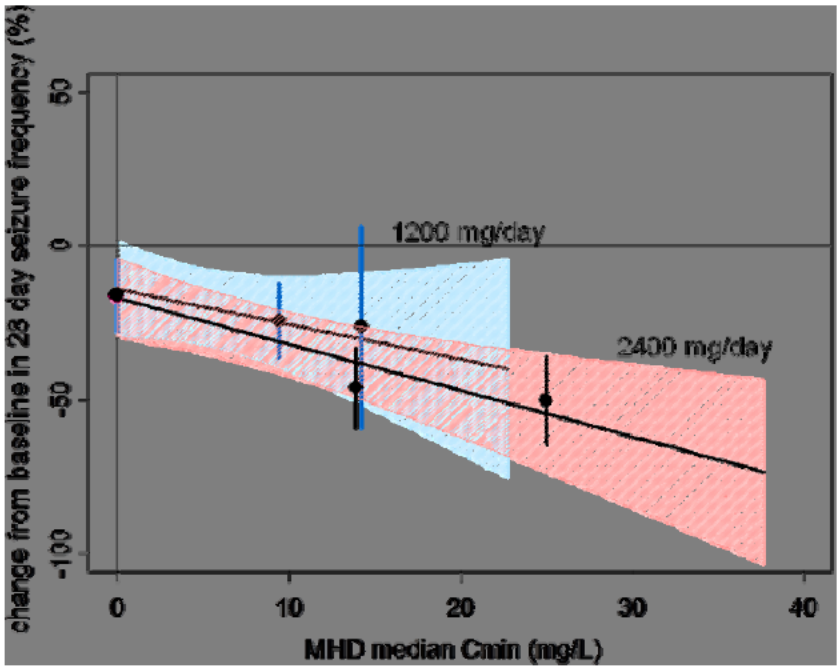
Figure 2. Placebo-anchored exposure-response for the OXC-ER formulations from the pivotal trial. Data includes placebo patients along with patients with PK and PD information from both the 1200 mg/day and 2400 mg/day groups.



Note: For exposure-response, solid symbols and bars represent the mean and 95% confidence interval of change from baseline in 28-day seizure frequency for each MHD concentration quantile. The interquartile ranges for the 1200 mg/day and 2400 mg/day doses are denoted by the horizontal lines. The solid line represents the mean prediction from the linear relationship and its corresponding 95% confidence interval (shaded region).

To further evaluate the effectiveness of the 1200 mg/day and 2400 mg/day doses, exposure-response analysis was performed by dose (Table 1 and Figure 3). A significant trend was observed with % reduction is seizure frequency as a function of MHD Cmin concentrations for both the 1200 mg/day and 2400 mg/day doses.

Figure 3. Placebo-anchored exposure-response for the OXC-ER formulations (1200mg/day and 2400 mg/day modeled separately). Data includes placebo patients along with patients with PK and PD information from both the 1200 mg/day and 2400 mg/day groups.



Note: For exposure-response, solid symbols and bars represent the mean and 95% confidence interval of change from baseline in 28-day seizure frequency for each MHD concentration quantile. The solid line represents the mean prediction from the linear relationship and its corresponding 95% confidence interval for the 1200 mg/day group (blue shaded region) and 2400 mg/day group (red shaded region).

Table 1. Slope Parameter estimates for the Exposure-Response relationships of both 1200 mg/day and 2400 mg/day

Dose group	Slope (95% CI)	p-value
1200 mg/day	-1.14 (-2.06 – -0.216)	0.014
2400 mg/day	-1.50 (-2.47 – -0.732)	<0.001

Although the relationship is slightly steeper for the 2400 mg/day dose level, overlapping 95% confidence intervals for both doses suggest that the slope estimates are indistinguishable from one another.

In the pivotal trial for the OXC-ER formulation, a marked placebo effect was observed. Since the exposure-response relationships for both dose-groups were significant and similar (i.e., increasing MHD Cmin concentration yielding reduction in seizure frequency for both doses), this analysis provides evidence that both the 1200 mg/day and 2400 mg/day are effective over placebo.

Are the exposure-response relationships for the OXC-ER and IR formulations similar?

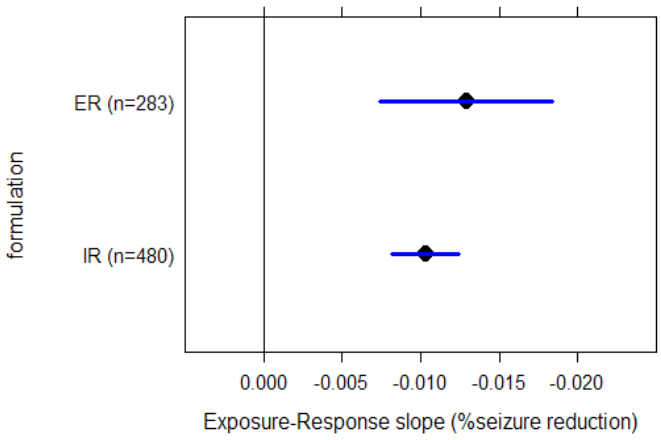
Yes. Based on an empiric linear model, the relationship between % reduction in seizure frequency and MHD Cmin is not different between the OXC-ER and OXC-IR formulations.

In the case for OXC-ER, a ~ 16-19% lower exposure (AUC and Cmax) of MHD was observed in the pivotal bioequivalence study, not meeting the prespecified criteria for bioequivalence. Therefore, the intent of this analysis was to determine if, despite the differential MHD exposures seen between the OXC-ER and IR formulations, the exposure-response relationships were similar. For the evaluation, the model parameters of the exposure-response relationship for the IR formulation was obtained from publicly available information.* For the IR exposure response relationship, an empiric model was derived relating the % change from baseline in seizure frequency to MHD Cmin concentrations:

$$log\ (\%\ change\ from\ baseline\ in\ seizure\ frequency + 110) = \beta 0 + \beta 1 * Cmin + \varepsilon$$

where, β0 and β1 is the intercept and slope, respectively, or the linear relationship, ε is the residual error and Cmin is the MHD exposure metric (in µmol/L) used to assess the relationship. Using the same empiric model, the exposure-response relationship was derived for the OXC-ER formulation, and the slope parameter estimate was compared to the parameter (β1) published for the OXC-IR relationship. Results for the comparison as seen in Figure 4 below show the exposure-response relationship between the formulations are similar.

Figure 4. Point estimate for the slope parameter (and corresponding 95% CI interval) for the OXC-ER and OXC-IR formulations (1200mg/day and 2400 mg/day inclusive). Data includes placebo patients along with patients with PK and PD information from both the 1200 mg/day and 2400 mg/day groups.



The slope parameter of exposure-response relationships for both formulations are both statistically significant (both relationships with p-values <0.05). Overlapping 95% confidence bounds infer that the point estimates are indistinguishable between the ER and IR formulations. The smaller 95% confidence bounds for the IR formulation exposure-response relationship may be due to the increased sample size used for the analysis.

[1] East Coast Population Analysis Group Conference, 2006. Workshop presentation by Joga Gobburu. http://www.ecpag.org/2006/6_JogaGobburu.

Is there an influence of geographical region on the exposure-response relationship?

Yes. A marked placebo effect was observed in the pivotal trial for the ER formulation (-28.7% seizure reduction). Table 2 tabulates the primary efficacy variable results by regional cluster.

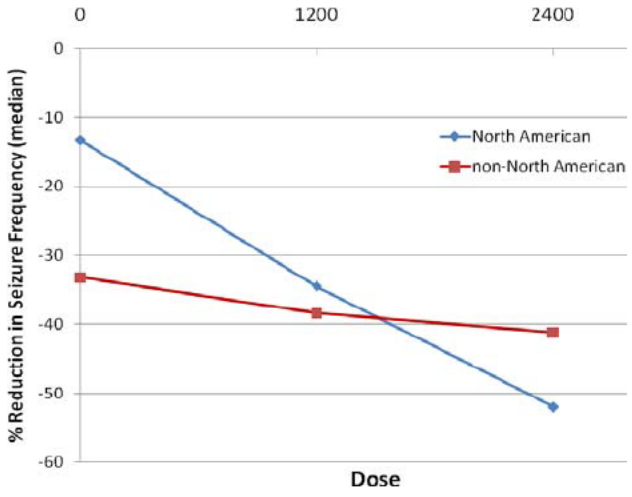
Table 2. Primary Efficacy results by Regional Cluster (median)

	Treatment Group (% change from baseline, N)			p-value (vs. placebo)	
Cluster	OXC-ER		Placebo		
	2400 mg	1200 mg		2400 mg	1200 mg
North America[1]	-52.6 (35)	-34.5 (40)	-13.3 (41)	***0.006***	***0.022***
All other[2]	-41.2 (88)	-38.4 (82)	-33.2 (80)	0.130	0.596

[1] includes US/Canada and Mexico; [2] Includes Poland, Croatia, Romania, Bulgaria and Russia (Non-north America)

The analysis by regional cluster shows that the placebo effect in non-North America sites was approximately 20% greater that the North American sites, whereas the response for the 2400 mg/day was numerically more effective on North America (11.4%) and the response for 1200 mg/day was slightly more effective in the non-North American sites (~3.9%). Post-hoc statistical comparison shows that both the 2400 mg/day and 1200 mg/day doses are significantly better than placebo, whereas neither dose was statistically different from placebo in the non-North American sites. The dose-response relationships for both geographical regions are exemplified in Figure 5 below.

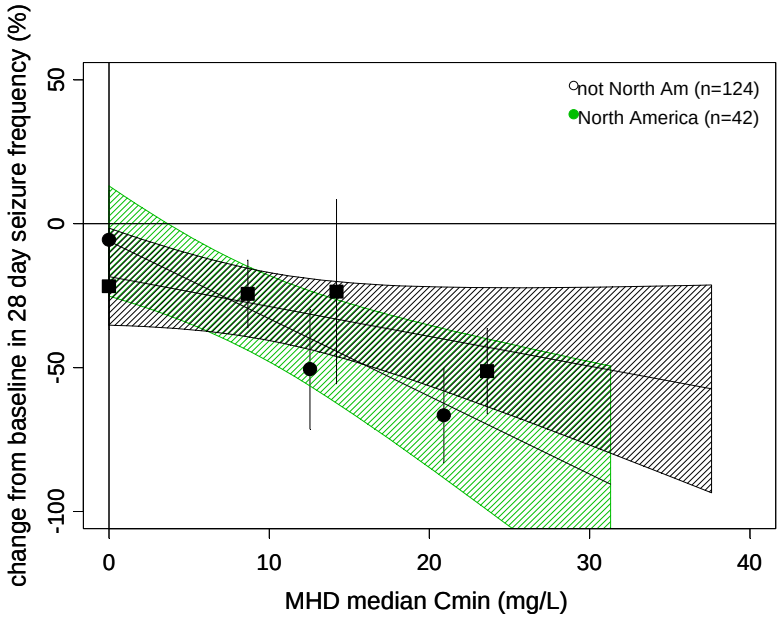
Figure 5. Dose-Response for the OXC-ER Pivotal Trial by Regional Cluster (red: non-North American, blue: North-American).



To further evaluate the discrepancy between geographical regions, MHD concentration- response analysis was performed using similar sub-grouping of patients that had PK/PD date (Figure 6). A significant trend was observed with % reduction is seizure frequency as a function of MHD Cmin concentrations for both the geographical regions. The exposure-response relationship was more pronounced in the North-American group (p-value <0.0001) compared to the non-North American group (p-value = 0.012), which coincides with what observed for the dose-response relationship observed in Figure 5 above.

The collected information suggests that the pronounced placebo effect in the non-North American sites may be driving the lack of statistical significance for the 1200 mg/day dose level in the pooled analysis. Dose-response information for the North-American sites suggest both the 1200 mg/day and 2400 mg/day doses are effective and is corroborates with the exposure-response information obtained for the different geographical regions.

Figure 6. Placebo-anchored exposure-response of the OXC-ER formulations for the North American and non-North American geographical regions. Data includes placebo patients along with patients with PK and PD information from both the 1200 mg/day and 2400 mg/day groups.



Note:

For exposure-response, solid symbols and bars represent the mean and 95% confidence interval of %change from baseline in 28-day seizure frequency for each MHD concentration quantile (squares = non North American, circles = American). The solid lines represent the mean prediction from the linear relationship and its corresponding 95% confidence interval for the North America group (green shaded region) and non-North American group (grey shaded region).

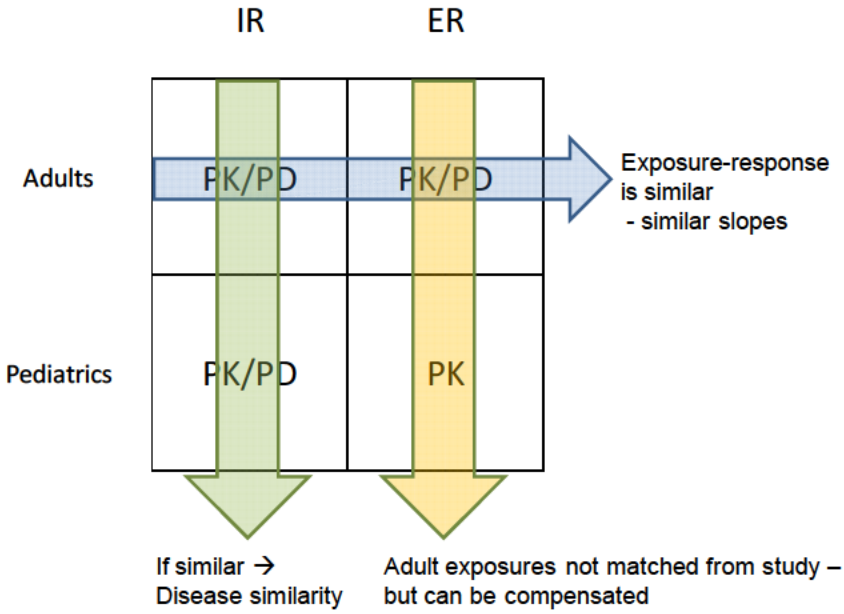
Are similar Cmin concentrations achieved in adults and pediatrics with the OXC-ER formulation?

Yes. In the pediatric PK study, MHD Cmin concentrations were evaluated after an initiation dosing regimen of 8-10 mg/kg to n=17 pediatric patients. Absolute doses in the study included 150, 300, 450 and 600 mg/day. Although these actual doses were not evaluated in the pivotal trial, pharmacokinetic simulations in adults (administered equivalent doses) showed comparable MHD exposures to the pediatric population.

In the development of Trileptal®, both an adult and pediatric study was performed to determine the effectiveness of IR Oxcarbazepine in the adjunctive setting. Available public information infers that the exposure-response relationships between these populations are reasonably similar.* This notion suggests that the epilepsy disease between populations is reasonably similar as well. Under the assumption that the exposure-response relationships between the OXC-IR and OXC-ER formulations are similar in adults, bridging the pediatric approval would require a PK study in pediatrics to match MHD exposures in adults (as the sponsor attempted to perform). A schematic outlining the overall development paradigm for approval of ER-OXC in the pediatric population is depicted in Figure 7.

* East Coast Population Analysis Group Conference, 2006. Workshop presentation by Joga Gobburu. http://www.ecpag.org/2006/6_JogaGobburu.pdf

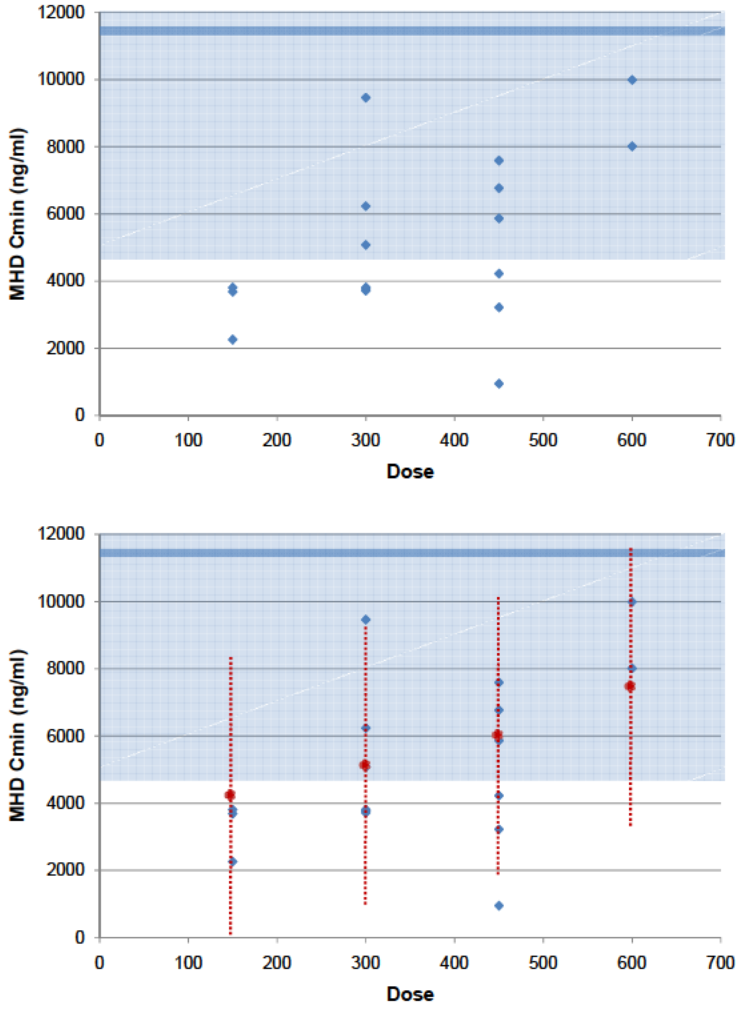
Figure 7. Schematic Outlining the Drug Development of IR and ER Oxcarbazepine formulations in the Adult and Pediatric Populations.



In the pediatric study for OXC-ER, the PK of OXC and MHD were adequately characterized from n=17 subjects. The population PK model suggests that weight-based dosing would yield comparable MHD exposures to that found in the adult population. MHD Cmin exposures, after

an initiation regimen of 8-10 mg/kg (range 150 – 600 mg/day), are presented in Figure 8 below (top graph). For reference, the blue shaded area represents the bottom 50 percentile of the range of MHD Cmin exposures for adult patients that were dosed *1200 mg/day* in the pivotal adult trial. In order to compare exposures between the adult and pediatric populations, PK simulations (n=1000) were performed in adults to determine whether the MHD Cmin exposures would yield comparable exposures to that found in the pediatric population. The sponsor's derived population PK model was used to determine ranges of MHD Cmin concentrations in adults after receiving 150, 300, 450 and 600 mg/day. The bottom plot depicts the median and range for the PK simulations in adults, superimposed on the observed pediatric MHD Cmin concentration. From graphical inspection, the simulated adult exposures reasonably overlap with the observed pediatric MHD exposures.

Figure 8. MHD Cmin exposures obtained from the Pediatric OXC-ER PK study (Top plot, n=17) and Superimposed simulated MHD Cmin concentrations if n=1000 adults were given an equivalent dose (median and range, Bottom plot).



Note: Blue shaded region represents the approximately the bottom 50 percentile of MHD Cmin exposures obtained after adult dosing of 1200 mg/day (from the pivotal adult study). The dark blue line represents the

median Cmin exposure for adults given 1200 mg/day. Pediatric observations are in blue diamonds while the simulated adult exposures (n=1000), for the specified dose are in red circles (median and range).

The PK model was further employed to determine the pediatric maintenance dosing required to attain adult median MHD Cmin concentrations after dosing with 1200 mg/day and 2400 mg/day (Table 3). The current label proposes initiation of OXC-ER at 8-10 mg/kg/day and target maintenance dose should be increase by no more than 600 mg/week and should be titrated to tolerability and effectiveness. The dosing nomogram below only serves as a guide for target maintenance dosing in pediatrics.

Table 3. Recommended OXC-ER Maintenance Dosing for the Pediatric Population targeting Adult median MHD Cmin exposures after 1200 and 2400 mg/day

	MHD plasma concentration; Adjunctive: Cmin (mg/ml)			
Weight (kg)	11.7 (median in 1200 mg/day in adults)		19.4 (median in 2400 mg/day in adults)	
	Dose (mg/day)	Dose (mg/kg/day)	Dose (mg/day)	Dose (mg/kg/day)
20	600	30.0	900	45.0
25	900	36.0	1200	48.0
30	900	30.0	1200	40.0
35	900	25.7	1500	42.8
40	900	22.5	1500	37.5
45	1200	26.7	1500	33.3
50	1200	24.0	1800	36.0
60	1200	20.0	2100	35.0
70	1200	21.4	2100	30.0

Building on the information that, in the adjunctive epilepsy setting:

1) the exposure-response relationship (MHD Cmin vs. seizure reduction) for both pediatrics and adults are significant and similar amongst the populations.

2) the exposure-response relationship between the OXC-IR and OXC-ER formulations are similar, based on similar parameter estimates of the linear model.

3) and the PK model developed with adult and pediatric observations adequately describes MHD concentrations.

4) PK simulations show comparable exposures between adults and pediatric population, given the same absolute dose.

Dosing based on body weight will yield comparable MHD Cmin exposures to the adult population.

Recommendations

Building on the totality of information that, in the adjunctive epilepsy setting:

- the exposure-response relationship (MHD Cmin vs. seizure reduction) for both pediatrics and adults are significant. Moreover, the relationships are similar amongst the populations.
- the exposure-response relationship between the OXC-IR and OXC-ER formulations are similar, based on similar parameter estimates of the linear model.
- the PK model developed with adult and pediatric observations adequately describes MHD concentrations.
- PK simulations show comparable exposures between adults and pediatric population, given the same absolute dose.

The Pharmacometrics reviewer recommends approval of OXC-ER for both the 1200 mg/day and 2400 mg/day dosing regimens in adult and pediatric patients with refractory epilepsy.

Label Statements

Labeling statements to be removed are shown in ~~red strikethrough font~~ and suggested labeling to be included is shown in underline blue font.
For the label, a recommended maintenance dose for the pediatric population should be supplied (see table below)

Recommended OXC-ER Maintenance Dosing for the Pediatric Population targeting Adult median MHD Cmin exposures after 1200 and 2400 mg/day

	MHD plasma concentration; Adjunctive: Cmin (mg/ml)			
Weight (kg)	11.7 (median in 1200 mg/day in adults)		19.4 (median in 2400 mg/day in adults)	
	Dose (mg/day)	Dose (mg/kg/day)	Dose (mg/day)	Dose (mg/kg/day)
20	600	30.0	900	45.0
25	900	36.0	1200	48.0
30	900	30.0	1200	40.0
35	900	25.7	1500	42.8
40	900	22.5	1500	37.5
45	1200	26.7	1500	33.3
50	1200	24.0	1800	36.0
60	1200	20.0	2100	35.0
70	1200	21.4	2100	30.0

PERTINENT REGULATORY BACKGROUND

Oxcarbazepine (OXC, Trileptal®) is currently approved in the Europe and the United States for monotherapy and adjunctive therapy in children and adults with partial onset seizures. The effectiveness of Trileptal was previously established for adjunctive and monotherapy for partial seizures in adults, and as adjunctive therapy in children aged 2-16 years in seven multicenter,

randomized, controlled trials. With respect to monotherapy for pediatrics, the effectiveness of Trileptal for partial seizures in children aged 4-16 years was determined from data obtained from prior studies, as well as results from pharmacokinetic/pharmacodynamic analyses.

Supernus Pharmaceuticals has developed an extended-release (ER) version of OXC as a controlled-release matrix tablet for the intent of dosing as a once-daily regimen. Available tablet strengths of OXC-ER are 150 mg, 300 mg and 600 mg. The rationale for the development of OXC-ER included targeting an improved treatment adherence with a once-daily regimen. Moreover, the ER formulation was developed to yield a "flatter" PK daily profile of OXC with the intent to yield an improved safety and tolerability profile when used as adjunctive antiepileptic drug (AED) therapy.

RESULTS OF SPONSOR'S ANALYSIS

Summary of Clinical Study Report SPN-804P301

Clinical efficacy of OXC-ER was tested in a single pivotal trial, SPN-804P301. This study was a multicenter, double-blind, randomized (1:1:1), parallel group, placebo-controlled study evaluating add-on therapy with OXC-ER in patients from 18 to 65 years with refractory epilepsy (simple partial seizures, complex partial seizures, or partial seizures with secondarily generalized seizures). The aim of the study was to evaluate the efficacy and safety of OXC-ER as add-on therapy compared to placebo, with OXC-ER administered either as 2 x 600 mg tablets QD or 4 x 600 mg tablets QD. Patients must have been on stable regimens of at least one or up to three concomitant AEDs at baseline and continued those regimens during the study. Randomized patients were to have had a mean of at least three recorded partial seizures every 28 days during the 8-week Baseline Phase.

Three hundred sixty-six subjects were randomized, including 164 men (44.8%) and 202 women (55.2%) with a mean age of 38.9 years. Subjects were treated with OXC-ER 2400 mg/day (n=123), OXC-ER 1200 mg/day (n=122), or placebo (n=121) as part of adjunctive therapy. The types and frequencies of seizures experienced by subjects during the baseline phase were similar across treatment groups, with median seizure frequency per 28 days of 6 in both OXC-ER groups, and 7 in the placebo group. The majority of patients were receiving either one AED (32.5%) or two AEDs (53.6%), with 50 patients (13.7%) receiving three AEDs. The three treatment groups were comparable with respect to the types of concomitant AEDs taken.

Active subjects initiated treatment at 600 mg/day and escalated to their maintenance dose. Subjects in the 1200 mg/day treatment group reached their target dose by week 2 of the Titration Period. Subjects in the 2400 mg/day treatment group reached their target dose by week 4 of the Titration Period. In the Maintenance Period (beginning at Visit 3 and continuing through Visits 4 and 5) subjects were maintained at their target dose. Subjects in the 2400 mg/day treatment group were permitted one blinded dose reduction to 1800 mg/day beginning at week 4 of the Titration Period and at any time during the Maintenance Period.

The primary endpoint for this study was the median percent change (PCH) in seizure frequency between the Baseline and Treatment phases (Titration plus Maintenance Periods) for each OXC-ER dose compared to placebo for the ITT population. Analysis of primary and secondary endpoints included examination of the Per Protocol (PP) population. Overall, 267 (73%) subjects were included in the PP population, with the lowest percentage (65%) in the 2400mg group and the highest (82%) in the placebo group; 72% of the 1200mg group met the criteria for the PP population.

The results of the study showed that adjunctive therapy with OXC-ER at 2400mg, administered once-a-day, was statistically significant (median percentage seizure reduction of 42.9%, p=0.003). The 1200 mg/daily dose, in spite of a decrease in seizure frequency per 28 days relative

to baseline (-38.2%), failed to separate from the placebo arm (p=0.078), for which the median seizure frequency decrease was -28.7%. The percentage of treatment responders (defined as patients experiencing more than 50% reduction in their seizure frequency compared to baseline) were 40.7% for the 2400mg group, 36.1% for the 1200mg group, and 28.1%, for the placebo group.
Overall, AEs were more frequently reported in subjects receiving 2400mg/day (69.1%) compared with 1200mg/day (56.6%) and placebo (55.4%). Dizziness, somnolence, headache, nausea, diplopia, and vomiting were the most frequently reported AEs (≥10%) in subjects treated with OXC-ER. The incidence of dizziness, somnolence, headache, and diplopia appeared to be dose-related..

Summary of Population PK Report SPN-804P301

A population pharmacokinetic model for OXC-ER was developed in healthy normal adults (Study 804P103) and applied to the pharmacokinetic data from patients with epilepsy in the pivotal phase III study (804P301).
For each subject in the pivotal trial, a total of five plasma samples were planned for PK analysis. Samples were to be collected during the Maintenance Period (Visits 3, 4, and 5) and also during the Tapering or Conversion Periods (Visits 6 and 7). One sample was to be taken pre-dose; the other four samples were to be taken post-dose at 1h, 2h, 4h and 7h (±30 min). Each sample was to be obtained at a separate visit, if possible. Plasma concentrations for OXC and MHD (10-monohydroxy metabolite, the primary active metabolite) were determined for all samples collected. The final analysis dataset included 189 subjects: placebo-converted (n=22), 1200 mg/day (n=85), and 2400 mg/day (n=82).
The structural model for OXC was based on analysis from a previous study (Study 804P103). It included two systemic compartments and first-order elimination from the central compartment. OXC was presumed to be released at a constant rate from the formulation until available drug was fully released; absorption of OXC into the central circulation was quantified by a first-order process. The structural model for MHD was based on analysis from a previous study (804P103): MHD was formed by a first-order process, driven by the central compartment concentration of OXC. For MHD, a one compartment with first-order elimination characterized the PK well. Based on previous analysis, MHD was also formed during absorption of OXC, presumably due to first-pass metabolism. To prevent issues related to identifiability, it was assumed that 10% of OXC was converted to MHD. For both OXC and MHD, relationships between covariates and post hoc etas were evaluated and incorporated into the model.

Population PK of OXC

A linear two-compartment model developed in healthy normal subjects fit the patient data well. Only one covariate – body weight – was incorporated into the model. Allometric scaling of systemic parameters was determined to yield the best fit. Parameter estimates for the optimal model are displayed in Table 4 and diagnostic plots are presented in Figure 9.

Table 4. Parameter Estimates for OXC Population PK Model

Parameter	Typical Value	Inter-Individual Variability*
CL / F (L / hour) †	$93.5 \cdot (WT/70)^{0.75}$	48.4%
V_1 / F (L) †	74.0 • (WT/70)	106%
$CL_{distribution}$ / F (L / hour) †	$97.1 \cdot (WT/70)^{0.75}$	89.4%
V_2/F (L) †	3820 • (WT/70)	35.4%
k_a (/ hour) §	0.174	57.0%
Relative bioavailability**	0.68	0.2%
Duration of infusion component of release profile (hours)	2.93	49.6%

* Calculated as sqrt(*omega*^{2}) where *omega*^{2} is the variance of the corresponding *eta* term; sixty-eight % of the population lies within this range of the typical value.

** Relative bioavailability compared to the immediate-release formulation of oxcarbazepine, fixed to the value obtained in Study 804P103

§ This term includes both release of OXC from the ER formulation and absorption.

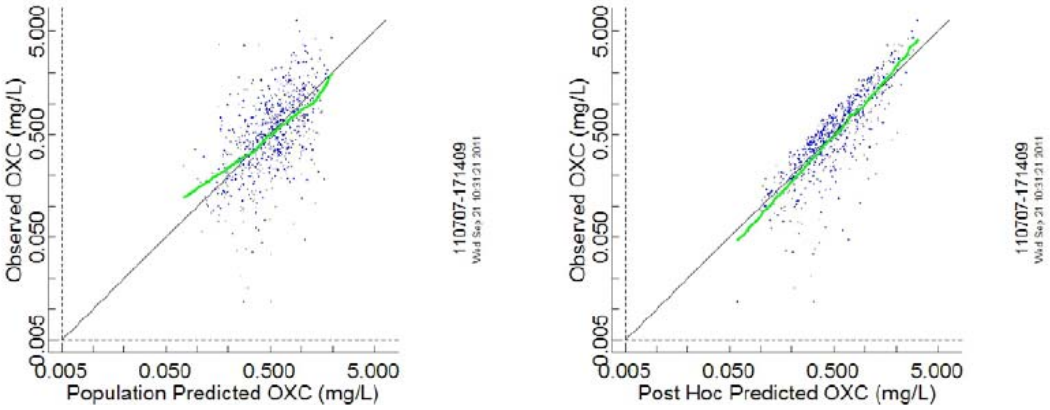
† In the absence of an intravenous dose of OXC, all systemic parameters are normalized by an unknown bioavailability factor (F).

	Variance
Proportional Error	0.2032
Additive Error	0*

* Variance of the additive component of error was fixed to 0 in the optimal model.

Source: Population PK Report SPN-804P301, page 5 (table 1 and 2)

Figure 9. Diagnostic Plots for OXC Population PK Model



Source: Population PK Report SPN-804P301, pg 43

Population PK of MHD

The linear one-compartment model developed and validated in healthy normal subjects fit the patient data well. Three covariates were incorporated into the model: an effect of weight on apparent clearance; a factor to describe the effect of treatment on production of MHD from OXC; and a factor to describe the effect of co-administration of carbamazepine, phenytoin,

phenobarbital or valproic acid on apparent clearance. Parameter estimates for the optimal model are displayed in **Table 5** and diagnostic plots are presented in Figure 10.

Table 5. Parameter Estimates for MHD Population PK Model

Parameter	Typical Value	Standard Error	Inter-Individual Variability*
AEDFACTOR (Factor for effect of concomitant influencing AEDs on CL/Fm)	1.31	0.0844	—‡
CL / Fm (L / hour) §	AEDFACTOR • 0.372 • (WT/70)$^{0.395}$	0.0239 0.0804**	34.7%
V / Fm (L) §	8.34	1.07	83.9%
Factor for conversion of OXC to MHD for placebo-converted and 1200 mg/day treatment groups††	1.52	0.136	—‡
Fraction of administered dose absorbed directly to MHD***	0.0650†	—†	—‡

* Calculated as sqrt(*omega*^{2}) where *omega*^{2} is the variance of the corresponding *eta* term; sixty-eight % of the population lies within this range of the typical value.

** 0.0239 applies to the value 0.372; 0.0804 applies to the value 0.395.

*** Determined previously in healthy normal subjects

§ To avoid issues related to identifiably of parameters for a metabolite model when the metabolite has not been administered separately, the model for MHD assumed that 10% of the administered dose (15.2% for 1200 mg/day and placebo-converted groups) was metabolized to MHD. Actual values for CL/F require correction for the (unknown) fraction of OXC metabolized to MHD and the ratio of molecular weights for the two compounds. The term Fm in these parameters is a composite term that includes these factors.

† Parameter value was fixed in the optimal model.

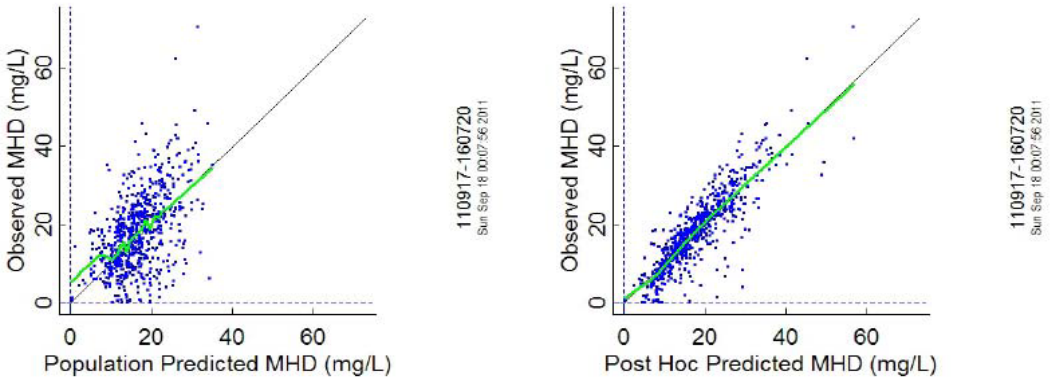
‡ Inter-individual variability was not permitted in the optimal model.

†† This factor applies to the fraction of OXC converted to MHD (at lower doses, more OXC is converted to MHD)

	Variance
Proportional Error	0.04053
Additive Error	12.06

Source: Population PK Report SPN-804P301, page 7 (table 5 and 6)

Figure 10. Diagnostic Plots for MHD Population PK Model



Source: Population PK Report SPN-804P301, pg 58

Reviewer's comments:
The sponsor's population PK models adequately describe the OXC and MHD PK observations after OXC-ER administration.

Summary of Population PK/PD Report SPN-804P301

Results of the population pharmacokinetic analysis were applied to the analysis of pharmacodynamic (PD) data (28-day seizure frequency) collected in the pivotal study. Analysis included graphical and statistical comparisons of the efficacy variables among treatment groups (placebo, 1200 mg/day, and 2400 mg/day) and among low (MHD Cmin < 14 mg/L) and high (MHD Cmin ≥ 14 mg/L) concentration groups. Additionally, a pharmacokinetic/pharmacodynamic (PK/PD) model was fit to the data.

PK variables were derived from simulated data for each subject (in an active treatment group) in the NONMEM analysis dataset at each visit for which there was a valid PK observation based on the individual post hoc predicted concentration vs. time profile at that visit. For each subject in the analysis dataset, a median value for Cmin was calculated by taking the median of values across visits for which Cmin was derived for that subject.

For each subject, a value for 28-day partial seizure frequency and percent change from baseline (PCH) in 28-day partial seizure frequency at each visit and overall for the Treatment Phase of the study:

$$\text{28-day partial seizure frequency} = 28 \times \frac{\text{(\# partial seizures during the specified interval)}}{\text{(\# days during the specified interval)}}$$

$$\text{PCH} = 100\% \times \frac{\text{[28-day seizure frequency (on study) – 28-day seizure frequency (baseline)]}}{\text{[28-day seizure frequency (baseline)]}}$$

A sigmoidal Emax model was fit to the Cmin and PCH data for the Treatment Phase for the 166 subjects with Cmin estimated.

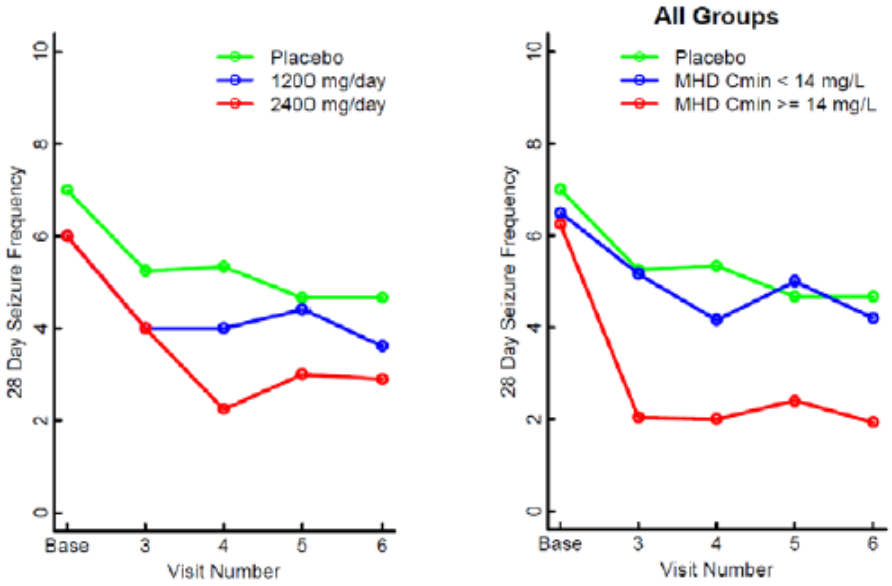
$$PCH = PCH_0 - Emax\left[\frac{1}{1+(C_{50}/Cmin)^{\gamma}}\right]$$

Where PCH0 is the intercept (upper asymptote), Emax is the maximum effect size, and γ is the shape factor. Due to difficulty estimating γ simultaneously with PCH0, Emax, and C50, 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.

Comparison among concentration groups and the placebo group showed a different pattern than comparisons among treatment groups (Figure 11). The high concentration group (Cmin ≥ 14 mg/L) was distinguished from both placebo (P < 0.00003) and the low concentration group (Cmin < 14 mg/L, P = 0.0024) as early as Visit 3 (end of Titration). This distinction continued through Visit 6. In contrast, the low concentration group and the placebo group demonstrated similar median seizure frequency throughout the study (see Figure 11). **Table 6** summarizes the results by concentration group. This dichotomous result above and below the median concentration for the study indicated that a strong concentration-response relationship might exist that could not be explained by dose alone.

Figure 11. Median 28-day Seizure Frequency at each visit in the treatment phase. Left panel stratified by treatment group: placebo (green, n=121), 1200 mg/day (blue, n=122), 2400 mg/day (red, n=123). Right panel stratified by concentration group: placebo (green, n=121); Cmin < 14 mg/L (blue, n=84); Cmin ≥ 14 mg/L (red, n=82).



Source: Population PK/PD Report SPN-804P301, pg 21

Table 6. Primary Efficacy Results for Concentration Groups

Concentration Group:	Placebo	Low (< 14 mg/L)	High (≥ 14 mg/L)
n	117	84	82
Baseline 28-day Frequency			
Mean (SD)	13 (27.5)	14.4 (24.6)	50.7 (234.5)
Median	7	6.5	6.3
Min, Max	2.2, 285	2.3, 150	1.5, 2006
Treatment 28-day Frequency			
Mean (SD)	10.4 (22.0)	11.8 (22.5)	20.9 (85.9)
Median	5.0	4.7	2.8
Min, Max	0, 175	0, 131	0, 630
Percent Change From Baseline			
Mean (SD)	-15.43 (67.34)	-18.74 (74.16)	-55.55 (40.98)
Median	-28.70	-29.95	-65.75
Min, Max	-100.0, 333.6	-100.0, 556.1	-100.0, 103.6
P value* *vs.* placebo		0.97	<0.000001
P value* *vs.* low concentration			<0.000001

*Wilcoxon rank-sum test

Source: Population PK/PD Report SPN-804P301, pg 27

The Sponsor modeled 28-day seizure frequency as a function of MHD Cmin for the population subgroup (

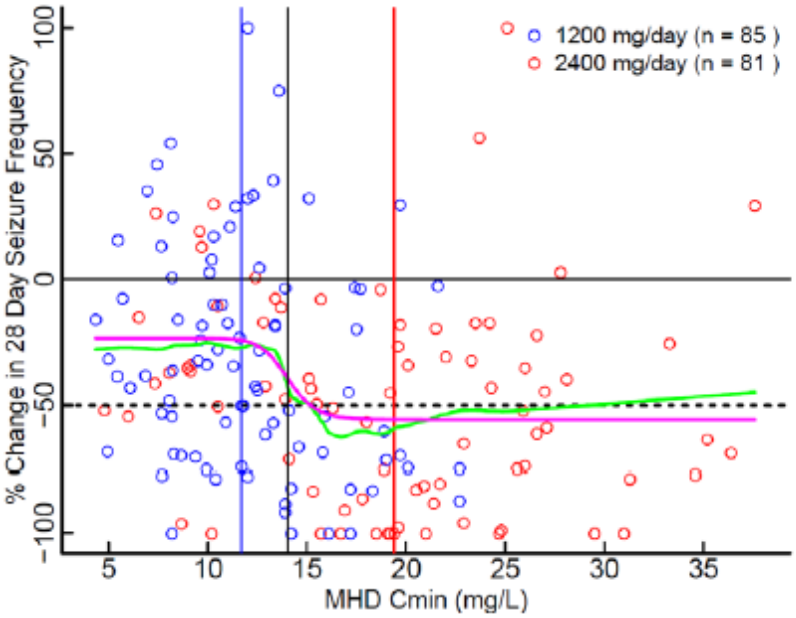
Table 7). The results of the Emax model shows that plasma levels of MHD above 14 mg/L are associated with better clinical outcome than levels below 14 mg/L (Figure 12). There exists a transitional region from 10 to 18 mg/L over which increased plasma concentration results in increased efficacy. Above 18 mg/L, increase in plasma concentration is not likely to result in further clinical improvement. The sponsor states that the effective plasma concentration range determined in the present analysis agrees with efficacious levels for MHD observed and reported elsewhere.

Table 7. Parameter estimates for the Emax model (final model incorporated γ = 20)

γ	PCH_0	Emax	PCH_0 - Emax	C_{50}
10	-23.15	33.14	-56.29	14.18
20	-23.45	32.28	-55.73	14.04
40	-23.29	32.19	-55.48	13.86
80	-23.01	32.71	-55.72	13.83
160	-22.67	33.19	-55.86	13.82
320	-22.50	33.29	-55.80	13.80
640	-22.49	33.22	-55.71	13.80

Source: Population PK/PD Report SPN-804P301, pg 31

Figure 12. Percent change from baseline in 28-day seizure frequency (PCH) vs. Cmin for the Treatment Phase. Plotted are data for 166 subjects in the population PK subgroup (for whom both Cmin and PCH were obtained).



Source: Population PK/PD Report SPN-804P301, pg 32

Notes: Data for subjects in the 1200mg/day treatment group (n = 85) are plotted as blue circles; data for subjects in the 2400mg/day treatment group (n=81) are plotted as red circles. Group median values for Cmin are plotted as vertical lines: 1200 mg/day (11.7 mg/L, blue) and 2400 mg/day (19.4 mg/L, red). PCH is stratified by levels of improvement (horizontal lines). For one subject with PCH > 100 (PCH = 556.1), PCH was set to 100. The magenta line is the fit of a sigmoidal Emax model to the data when $\gamma = 20$. The value of C50 estimated with the model (14.0 mg/L) is plotted as a vertical black line. The green line is a smoother.

Of 84 subjects with Cmin < 14 mg/L, 29% demonstrated PCH ≤ -50 (responsive); in contrast, of 82 subjects with Cmin ≥ 14 mg/L, 62% were responsive (**Table 8**). The ratios of responders to non-responders who had MHD Cmin above and below 14 mg/L were compared statistically using a chi-square test. The difference in response ratio was found to be significant (P = 0.000027).

Table 8. Responder Analysis for Subjects in the Population PK Subgroup (n=166) Above and Below Critical Value of MHD Cmin (14 mg/L)

	Responders (PCH ≤ -50)	Non-Responders (PCH > -50)	Ratio (Responders/Non-Responders)
Cmin ≥ 14 mg/L	51	31	1.65
Cmin < 14 mg/L	24	60	0.400

P = 0.000027 by chi-square analysis.

Source: Population PK/PD Report SPN-804P301, pg 30

The sponsor concludes that the PK/PD results of the study are supportive of the efficacy results, showing a significant correlation between MHD trough plasma concentrations and clinical response, with "optimal" trough plasma concentrations above 14mg/L.

Reviewer's comments:
The reviewer concurs with the sponsor's PK/PD characterization of MHD Cmin vs. % change from baseline in seizure frequency.

Summary of Clinical Study Report SPN-804P107

The pharmacokinetics of multiple-dose OXC-ER was assessed in a small population of pediatric patients (4 to 16 years of age) with partial onset seizures (Study 804P107). The population pharmacokinetic model developed in adult patients with epilepsy was applied to the pharmacokinetic data from pediatric patients.

Eighteen subjects participated in and completed the study. OXC-ER, 10 mg/kg/day, was administered for seven days (8 days in two subjects). All subjects received open-label, once-daily doses of OXC-ER as adjunctive therapy during the six consecutive days of the Dosing Period; at Day 7 the dose was taken on-site and blood samples were drawn for PK analysis. On the final day of dosing, dosing was observed in the clinic and plasma was sampled pre-dose and 1, 2, 4, and 7 hours post-dose. At Visit 1, eligible subjects were assigned to one of four treatment groups (150, 300, 450, or 600mg/day) based on weight.\

Each subject received OXC-ER following the 10mg/kg/day weight-based dosing guidance for OXC as follows (Subject Weight, Total Daily Dose): 15.0 to 29.9kg 150mg/day; 30.0 to 44.9kg 300mg/day; 45.0 to 59.9kg 450mg/day and 60.0kg and above 600mg/day.

Samples were assayed for OXC and MHD. For one subject, all OXC samples were reported as BQL; this subject was excluded from the pharmacokinetic analysis for each of OXC and MHD. Thus, seventeen subjects were included in the analysis. A population pharmacokinetic model was developed, incorporating knowledge gained from previous adult studies (in which sampling per subject was more extensive than in the present study).

Rather than estimating a new set of pharmacokinetic parameters in pediatric patients, the analysis was initially based on the assumption that the pharmacokinetic parameters in adults, scaled to the body size of children, applied to pediatric patients. This was accomplished by fixing the systemic parameters to values obtained in adult patients (Study 804P301). Then, various scaling approaches were evaluated.

The structural model for OXC was based on analyses of previous studies. It included two systemic compartments and first-order elimination from the central compartment. OXC was presumed to be released at a constant rate from the formulation until available drug was fully released; absorption of OXC into the central circulation was quantified by a first-order process.

The structural model for MHD was based on analyses from previous studies: MHD was formed by a first-order process, driven by the central compartment concentration of OXC. Based on previous analyses, MHD was also formed during absorption of OXC, presumably due to first-pass metabolism. There was one compartment for MHD with first-order elimination. To prevent issues related to identifiability, it was assumed that 10% of OXC was converted to MHD. For both OXC and MHD, relationships between covariates and post hoc etas were evaluated and incorporated into the model if appropriate.

Simulations were performed based on daily dosing for seven weeks and post hoc values obtained from the weight-normalized models for each of OXC and MHD. Graphics were prepared to confirm that steady state conditions were attained. Simulated plasma concentrations for the 24 hours at steady state were extracted from the NONMEM output table. Cmin and Cmax were determined by examination of the data. AUC was determined using linear trapezoids; Cmean was calculated as AUC / 24.

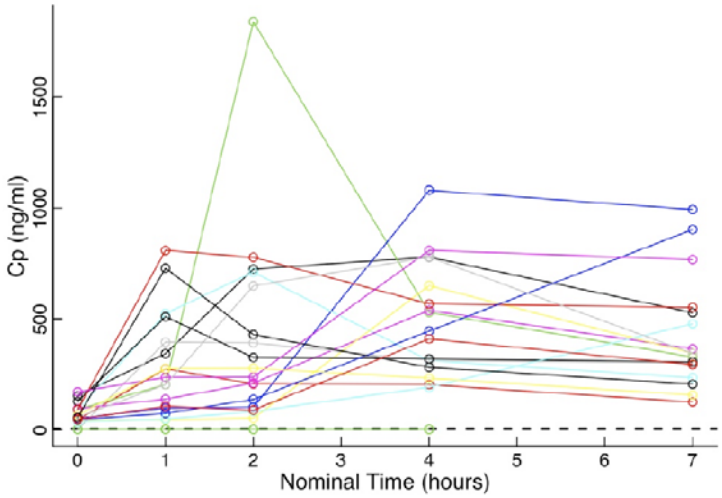
Pediatric Population PK of OXC

The PK profiles of OXC are presented in Figure 13. Allometric and weight-normalized models were evaluated. Other than body size, no covariates were incorporated into the model. The allometric model yielded the best objective function; however, the weight-normalized model

Figure 14.

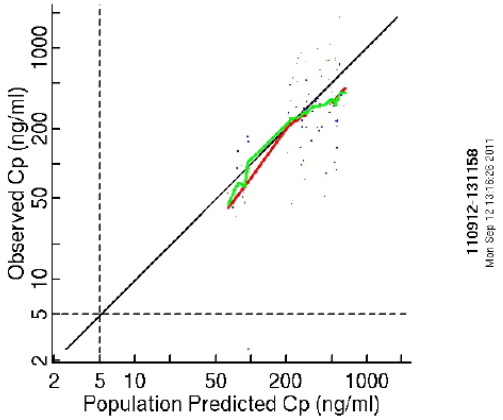
The base model for OXC generally fit the data well; however, ratios of observed-to population predicted concentrations were centered at slightly less than unity. This was addressed by applying an allomteric scaling factor, either to apparent clearance and apparent distribution clearance or to all systemic parameters. Both of these models were justified statistically compared to the model without scaling. The model in which both clearance terms were scaled had the lowest objective function and was adopted as the final model.

Figure 13. Plasma OXC Concentrations for all Pediatric Subjects.



Source: Population PK Report SPN-804P107, pg 32

Figure 14. Diagnostic Plot for OXC PK in Pediatrics.



Source: Population PK Report SPN-804P107, pg 36

PK metrics at steady state (simulated) for OXC are presented in Table 9.

Table 9. Values for OXC for Apparent Clearance, Cmean, Cmin, and Cmax for Each Subject at Steady State

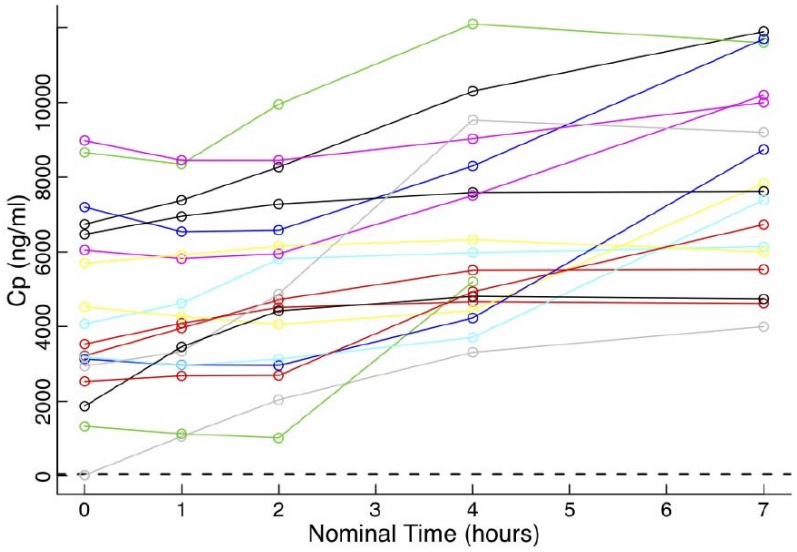
ID	Weight (kg)	Dose (mg)	CL / F (L/hour)	C_{mean} (µg / mL)	C_{min} (µg / mL)	C_{max} (µg / mL)
2001	46.5	450	0.19622	10285.94	7591.8	12519
3001	44.5	300	0.30083	4470.64	3716.6	4982.9
3002	30.9	300	0.11869	11335.76	9464.1	12885
3003	69	600	0.23835	11171.35	8014.4	13745
3004	46.6	450	0.35875	5618.88	4226.5	6727.2
3005	70.4	600	0.23855	11293.22	9994.2	12283
5001	41.9	300	0.1968	6803.96	5081.6	8164.4
6001	46.4	450	0.98472	2038.39	951.14	3204.9
6003	56.8	450	0.26189	7708.49	6772.5	8337.8
7001	20.5	150	0.12884	5215.57	3809.6	6282
7003	33.2	300	0.19541	6818.95	3768.6	9750.2
7004	42.1	300	0.21482	6233.83	3814.8	8537.5
8001	31.3	300	0.15196	8860.03	6236.2	11218
9001	50.5	450	0.30833	6545.32	5869.3	6984.6
10001	17	150	0.094402	7106.1	3688.9	10488
10002	23.2	150	0.18032	3721.52	2262.3	5096.9
10003	49.5	450	0.35774	5631.14	3223	7829.5
Mean	42.371	361.765	0.266	7109.358	5205.032	8766.818
SD	15.214	140.9	0.201	2724.792	2509.238	3080.503
Median	44.5	300	0.21482	6803.96	4226.5	8337.8
Minimum	17	150	0.094402	2038.39	951.14	3204.9
Maximum	70.4	600	0.98472	11335.76	9994.2	13745

Source: Population PK Report SPN-804P107, pg 38

Pediatric Population PK of MHD

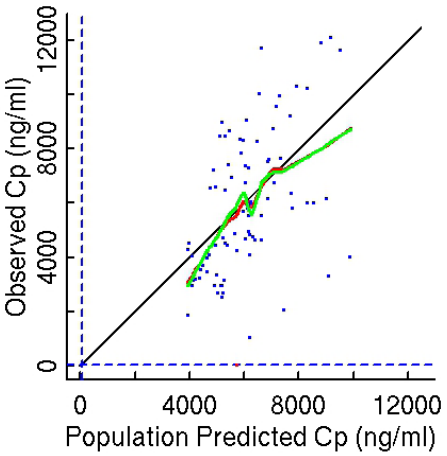
The PK profiles of MHD are presented in Figure 15. Allometric and weight-normalized models were evaluated. The weight-normalized model fit better than the allometric model as judged by the objective function and quality-of-fit graphics (Figure 16). There was no evidence of bias for the weight-normalized model; as a result, the additional scaling required for OXC was not required for MHD. Other than body size, no covariates were incorporated into the model. The weight-normalized model was adopted as the optimal model.

Figure 15. Plasma MHD Concentrations for all Pediatric Subjects.



Source: Population PK Report SPN-804P107, pg 49

Figure 16. Diagnostic Plot for MHD PK in Pediatrics.



Source: Population PK Report SPN-804P107, pg 37

PK metrics at steady state (simulated) for MHD are presented in Table 10.

Table 10. Values for MHD for Apparent Clearance, Cmean, Cmin, and Cmax for Each Subject at Steady State

ID	Weight (kg)	Dose (mg)	CL / F (L/hour)	C_{mean} (µg / mL)	C_{min} (µg / mL)	C_{max} (µg / mL)
2001	46.5	450	0.19622	10285.94	7591.8	12519
3001	44.5	300	0.30083	4470.64	3716.6	4982.9
3002	30.9	300	0.11869	11335.76	9464.1	12885
3003	69	600	0.23835	11171.35	8014.4	13745
3004	46.6	450	0.35875	5618.88	4226.5	6727.2
3005	70.4	600	0.23855	11293.22	9994.2	12283
5001	41.9	300	0.1968	6803.96	5081.6	8164.4
6001	46.4	450	0.98472	2038.39	951.14	3204.9
6003	56.8	450	0.26189	7708.49	6772.5	8337.8
7001	20.5	150	0.12884	5215.57	3809.6	6282
7003	33.2	300	0.19541	6818.95	3768.6	9750.2
7004	42.1	300	0.21482	6233.83	3814.8	8537.5
8001	31.3	300	0.15196	8860.03	6236.2	11218
9001	50.5	450	0.30833	6545.32	5869.3	6984.6
10001	17	150	0.094402	7106.1	3688.9	10488
10002	23.2	150	0.18032	3721.52	2262.3	5096.9
10003	49.5	450	0.35774	5631.14	3223	7829.5
Mean	42.371	361.765	0.266	7109.358	5205.032	8766.818
SD	15.214	140.9	0.201	2724.792	2509.238	3080.503
Median	44.5	300	0.21482	6803.96	4226.5	8337.8
Minimum	17	150	0.094402	2038.39	951.14	3204.9
Maximum	70.4	600	0.98472	11335.76	9994.2	13745

Source: Population PK/PD Report SPN-804P107, pg 39

The sponsor's analysis evaluated whether the typical values for systemic parameters obtained in adult patients could be applied to pediatric patients, after scaling for body size. They conclude that dosing of pediatric patients with OXC-ER can be determined based on body weight. Weight-normalized doses in pediatric patients should produce MHD exposures (AUC) comparable to that in typical adults, with OXC exposures ~40% higher in children than in adults. No other covariates appeared to influence the pharmacokinetic characteristics of OXC ER. However, this finding and the claim that doses in pediatric patients should be weight-based should be considered with caution because the number of patients in the present study and the quantity of data available from each subject were both small.

Reviewer's comments:
The reviewer concurs with the sponsor's PK characterization of MHD exposures in the pediatric population. The Sponsor explored the OXC and MHD concentrations at a dose that would be used for initiation of therapy but did not explore the PK maintenance doses. Moreover, PK plots of MHD suggested that week of dosing did not attain steady state conditions, rendering the assessment of MHD clearance to be based on simulation results. The sponsor rightfully explains that the combination of a small number of subjects and sparse sampling prevented independent analysis of the pediatric data from this study. Data were analyzed using the assumption that the systemic pharmacokinetic parameters obtained in adults applied to children (scaled for body size). The reviewer accepts this approach in characterizing the PK of MHD in the pediatric population.

REVIEWER'S ANALYSIS

Introduction

An independent analysis was performed to further explore the exposure-response relationship in adults. Moreover, further analysis was performed to determine whether the pediatric exposures are comparable to exposures to adults.

Objectives

Analysis objectives are to:

1. Assess if there is an overall relationship between MHD exposure and reduction in seizure frequency for the OXC-ER formulation.
2. Compare and contrast the exposure-response information with the OXC-ER formulation to that of the IR formulation.
3. Explore the influence of geographical region on the exposure-response relationship.
4. Determine if similar concentrations in adults and pediatrics be achieved with the OXC-ER formulation.

Methods

Exposure-response assessment was performed using MHD Cmin as an exposure metric and % change from baseline in 28 day seizure frequency that was collected in the pivotal study. MHD minimum concentration (Cmin) was derived directly by inspection. For each subject in the analysis dataset, a median value for Cmin was calculated by taking the median of values across visits for which Cmin was derived for that subject.

Analysis included graphical and statistical comparisons of the efficacy variables among treatment groups (placebo, 1200 mg/day, and 2400 mg/day) and among geographical regions, namely North American (NoAm) and Non-North American (Non-NoAm) sites.

The comparison of the exposure-response relationship between the IR and ER formulations was performed to provide confirmation of effectiveness of the ER formulation. The exposure-response model information for the IR formulation from publically available information[1] was obtained and the model parameters were contrasted to that found in the ER formulation.

[1] East Coast Population Analysis Group Conference, 2006. Workshop presentation by Joga Gobburu, Ph.D.. http://www.ecpag.org/2006/6_JogaGobburu.pdf

In the assessment of whether similar concentrations in adults and pediatrics can be achieved with the ER formulation, MHD Cmin concentrations from pediatrics were contrasted Cmin concentrations from the adult pivotal study. Furthermore, target concentrations were established based on the adult exposures obtained from the pivotal study (median MHD concentration for 1200 mg/day and 2400 mg/day). Simulations were performed to ascertain what the recommended maintenance dose for the pediatric populations would be, accounting for body-weight.

Further details of each analysis are presented below.

Data Sets

Data sets used are summarized in **Error! Reference source not found.**.

Table 11. Analysis Data Sets

Study Number	Name	Link to EDR
804p107	Pediatric PK	\\Cdsnas\pharmacometrics\Reviews\Ongoing PM Reviews\OxcarbazepineER_NDA202810_SSB\Sponsor Data and Reports\804p107-pk\analysis\legacy\datasets
804p301	Pivotal Trial efficacy	\\Cdsnas\pharmacometrics\Reviews\Ongoing PM Reviews\OxcarbazepineER_NDA202810_SSB\Sponsor Data and Reports\804p301\analysis\legacy\datasets
804p301pk	Pivotal Trial PK	\\Cdsnas\pharmacometrics\Reviews\Ongoing PM Reviews\OxcarbazepineER_NDA202810_SSB\Sponsor Data and Reports\804p301-pk\analysis\legacy\datasets

Software

NONMEM 6.1.0 (Globomax, Inc) was used for population PK analysis and simulations. Graphical and statistical analysis was performed via Tibco Spotfire S+ 8.1.

Models

The reviewer utilized the Sponsor's population PK model and final PK parameters to perform simulations.

Results

Refer to Section 1: Summary of Findings

LISTING OF ANALYSES CODES AND OUTPUT FILES

File Name	Description	Location in \\cdsnas\pharmacometrics\
Study301_er_bysite_ANCHORED	All Exposure response analysis	\\Cdsnas\pharmacometrics\Reviews\Ongoing PM Reviews\OxcarbazepineER_NDA202810_SSB\ER Analyses\ER_bysite
control-110919-102508.txt	MHD PopPK	\\Cdsnas\pharmacometrics\Reviews\Ongoing PM Reviews\OxcarbazepineER_NDA202810_SSB\PPK Analyses\FinalModels\MHD
control-110912-131158.txt	OXC PopPK	\\Cdsnas\pharmacometrics\Reviews\Ongoing PM Reviews\OxcarbazepineER_NDA202810_SSB\PPK Analyses\FinalModels\OXC

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/s/

KOFI A KUMI
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SATJIT S BRAR
09/19/2012

VENKATESH A BHATTARAM
09/19/2012

HAO ZHU
09/19/2012

BIOPHARMACEUTICS REVIEW Office of New Drug Quality Assessment			
Application No.:	NDA 202810	**Reviewer:** Sandra Suarez Sharp, PhD	
Division:	DNP		
Applicant:	Supernus Pharmaceuticals	**Biopharmaceutics Team Leader:** Angelica Dorantes, PhD	
Trade Name:	(b) (4)	**Biopharmaceutics Supervisory Lead (acting)**: Richard Lostritto, Ph.D.	
Generic Name:	Oxcarbazepine ER Tablets	**Date Assigned:**	Dec 22, 2011
Indication	Adjunctive therapy for partial seizures in epilepsy	**Date of Review:**	Aug 23, 2012
Formulation/ Strength	Extended Release Tablet/ 150 mg, 300 mg and 600 mg		
Route of Administration	Oral		

SUBMISSIONS REVIEWED IN THIS DOCUMENT

Submission Dates	CDER Stamp/Received Date	Date of informal/Formal Consult	Primary Review due in DARRTS
Dec 19, 2011 Aug 06, 2012 Aug 22, 2012	Dec 19, 2011 Aug 06, 2012 Aug 22, 2012	Dec 22, 2011	Aug 24, 2012
Type of Submission:	Original 505 (b)(2) Application		
Type of Consult:	Dissolution method and specifications/IVIVC/in vitro alcohol dose-dumping		

SUMMARY OF BIOPHARMACEUTICS FINDINGS:

Supernus Pharmaceuticals, Inc. seeks approval to market oxcarbazepine ER tablets for the once-daily treatment of partial onset seizures in adults and children with epilepsy. This 505 (b) (2) NDA submission for OXC makes reference to two approved drugs: Tripental (oxcarbazepine IR tablet) and Tripental (oxcarbazepine oral suspension) which were approved by the Agency on Jan 2000 and May 2001, respectively, for the initial monotherapy, and adjunctive therapy in children and adults suffering from partial onset seizures.

Oxcarbazepine ER Tablets, 150mg, 300mg, and 600mg, are matrix tablet formulations. The three product strengths use the same excipients but differ in the quantitative composition of the excipients in the formulations.

The development program supporting this submission consisted of six pharmacokinetic studies (dose linearity, proportionality, food effect, single-dose and steady-state pharmacokinetics, and bioavailability compared to the immediate-release formulation) and four efficacy/safety trials. All the PK studies are being reviewed by OCP.

The Biopharmaceutics review is focused on the acceptability of the dissolution method and acceptance criteria, the in vitro alcohol-dose dumping study, the acceptability of the IVIVC model, and the acceptability of the data provided to support several manufacturing

changes between the clinical and the commercial batches.. Note that the approval of the lower strengths (150 mg and 300 mg) is based on the results of a PK dose-proportionally study, which is being reviewed by OCP.

1) Dissolution Method and Acceptance Criteria

The following dissolution method and acceptance criteria proposed by the Applicant during the review cycle (refer to submission dated Aug 6, 2012) for Oxcarbazepine ER tablets, 150 mg, 300 mg and 600 mg are deemed acceptable:

USP Apparatus/RPM	Medium	Volume	Acceptance Criteria
II/75 rpm	De-ionized water with 1% (w/v) SLS	900 mL	2 hrs: (b) (4) 4 hrs: 8 hrs:

The discriminating ability of the method was demonstrated using BA/BE data. The dissolution acceptance criteria were based on the results of PK study 804P101 which evaluated the BA/BE of formulations with a wide range of release rates and on the performance of the pivotal clinical phase 3 and stability batches.

2) Assessment of the In Vitro Alcohol Dose-Dumping

No dose-dumping from the Oxcarbazepine ER Tablets was observed with a dissolution medium (the proposed QC medium and HCL 0.1 N, App II/75 rpm) containing up to 40% ethanol. On the contrary, the release profiles became slower in the presence of alcohol.

3) Evaluation of the IVIVC Model

The model was found not acceptable as it did not meet the acceptance criteria for internal and external validation, which has been acknowledged by the Applicant. The no acceptability of this IVIVC does not have any impact on the approvability of the NDA since the model was not used in this submission as a surrogate for BE studies or to set the dissolution acceptance criteria.

4) Evaluation of the Data Provided to Support the Manufacturing Changes

Laboratory scale batches were manufactured in a cGMP compliant facility at Supernus, Inc. Commercial scale batches were manufactured at (b) (4) The laboratory scale batches were different from the commercial scale batches with respect to composition, film coating, printing, and scale. The FDA concurred with the Applicant (refer to meeting minutes dated May 2, 2011) that there was no need to conduct a bridging BE study to prove equivalence between the laboratory scale and the commercial scale batches as the changes in the nonrelease and release controlling excipients were considered as Level 2 (the total additive effect of such changes was no more than 5% by weight). However, the agency requested a multi-point dissolution test be conducted comparing the laboratory scale batches to the commercial scale batches in four different media. The f2 values calculated for all the strengths ranged from 58 to 85, indicating similar in vitro performance between the batches manufactured at Supernus vs. those manufactured at (b) (4).

RECOMMENDATION:

The ONDQA/Biopharmaceutics team has reviewed NDA 202-810 and its amendments submitted on Dec 19, 2011, Aug 06, 2012, and Aug 22, 2012. The following dissolution method and dissolution acceptance criteria for Oxcarbazepine ER tablets, 150 mg, 300 mg and 600 mg have been agreed upon with the Applicant (refer to submission dated Aug 22, 2012) :

USP Apparatus/RPM	Medium	Volume	Acceptance Criteria
II/75 rpm	De-ionized water with 1% (w/v) SLS	900 mL	2 hrs: (b) (4) 4 hrs: 8 hrs:

The setting of the dissolution acceptance criteria were based on the results of PK study 804P101 which evaluated the BA/BE of formulations with a wide range of release rates and on the performance of the pivotal clinical and stability batches (refer to submission dated Aug 06, 2012).

From the Biopharmaceutics perspective, NDA 202-810 for Oxcarbazepine ER Tablets, 150 mg, 300 mg, and 600 mg is recommended for APPROVAL.

Sandra Suarez Sharp, Ph. D.
Biopharmaceutics Reviewer
Office of New Drug Quality Assessment

Angelica Dorantes, Ph. D.
Biopharmaceutics Team Leader
Office of New Drug Quality Assessment

cc: NDA 202-810/DARRTS cc block, R Lostritto;

BIOPHARMACEUTICS ASSESSMENT

BACKGROUND

Submission: Supernus is seeking approval to market oxcarbazepine ER tablets for the once-daily treatment of partial onset seizures in adults and children with epilepsy under NDA 202-810. This 505 (b) (2) NDA submission for OXC makes reference two approved drugs: Tripental (oxcarbazepine IR tablet) and Tripental (oxcarbazepine oral suspension). Tripental (oxcarbazepine IR tablet) and Tripental (oxcarbazepine oral suspension) were approved by the Agency on Jan 2000 and May 2001, respectively, for the initial monotherapy, and adjunctive therapy in children and adults suffering from partial onset seizures.

The development program supporting this submission consisted of six pharmacokinetic studies (dose linearity, proportionality, food effect, single-dose and steady-state pharmacokinetics and bioavailability compared to the immediate-release formulation) and four efficacy/safety trials. All the PK studies are being reviewed by OCP.

Review: The Biopharmaceutics review is focused on the acceptability of the dissolution method and acceptance criteria, the in vitro alcohol-dose dumping study, the acceptability of the IVIVC model, and the acceptability of the data provided to support several manufacturing changes between the clinical and the commercial batches.

Drug Substance

Oxcarbazepine is practically insoluble in water. The aqueous solubility of oxcarbazepine was found to be approximately (b) (4), to be pH independent, and to increase in a linear fashion with addition of solubilizers/surfactants.

Drug Product

Oxcarbazepine Extended-Release Tablets, 150 mg, 300 mg and 600mg, are extended-release matrix film coated tablets intended to deliver oxcarbazepine to the patient at a rate that allows for once-a-day administration up to a maximum daily dose of 2400mg. The three strengths of oxcarbazepine extended-release tablets use the same excipients but differ **(not compositionally proportional)** in the quantitative composition (on a % w/w basis) of two excipients in the formulations, (b) (4) and hypromellose. The three strengths of the coated tablets are distinguished by tablet size, color and imprinted code. The coated tablets are brownish red modified oval shaped tablets printed "600" on one side, along the long axis, with black ink. Table 1 summarizes the formulation of OXC ER tablets.

Table 1: Theoretical Formulation Composition of Oxcarbazepine Extended-Release Tablets, 150 mg, 300 mg, and 600 mg

Component and Quality Standard	Oxcarbazepine Extended-Release (% w/w)		
	150mg	300 mg	600 mg
Oxcarbazepine	58.25	58.25	58.25
Silicified Microcrystalline Cellulose, NF (b) (4)	(b) (4)		
Methacrylic Acid Copolymer (b) (4)			
Sodium Lauryl Sulfate, NF (b) (4)			
Hypromellose (b) (4) USP (b) (4)			
Povidone, USP (b) (4)			
Magnesium Stearate, NF (b) (4)			
(b) (4) Red (b) (4)			
Ink, Black (b) (4)			
Purified Water, USP			
Purified Water, USP			
Total	100.0	100.0	100.0

[a] (b) (4) color change depending on strength. Red is for the 600mg tablet.

Development Program

Figure 1 summarizes the development program for the proposed product. It also shows the Biopharmaceutics information available to establish a bridge between formulations used through out development. It is noted that the commercial and the phase 3 formulations are the same and therefore, not bridging was necessary.

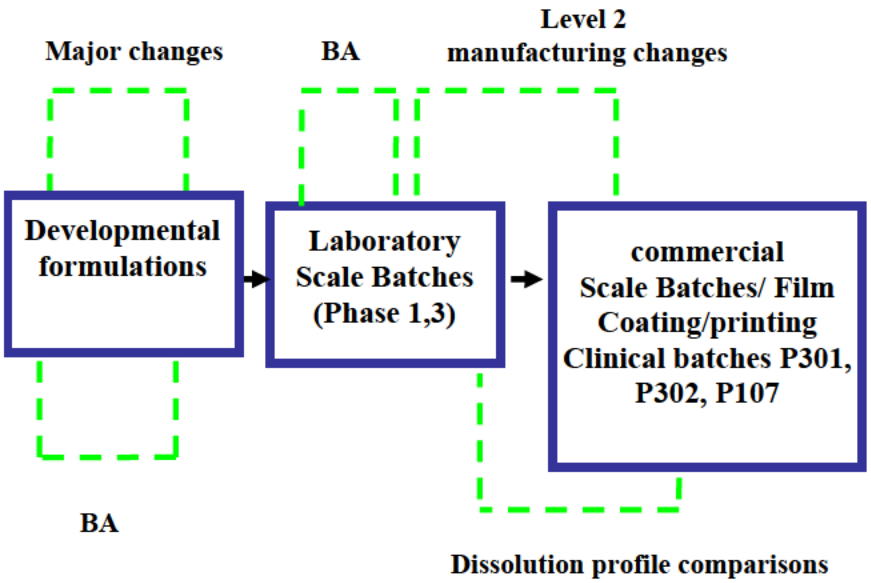

Figure 1. Schematic Overview of the Oxcarbazepine ER Tablets Formulation Development (generated using Applicant information).

DISSOLUTION METHOD

Dissolution testing is performed at release and on stability. The dissolution method being proposed for all the strengths of OXC ER tablets is summarized below:

USP Apparatus	Agitation Speed	Medium	Volume
II	75 rpm	De-ionized water with 1% (w/v) SLS	900 mL

Dissolution Method Development

Evaluation of Dissolution Media

Characterization of drug release from oxcarbazepine extended-release tablets in media with pH values ranging from 1.1 to 6.8 was performed. Mean dissolution profiles in each dissolution medium for batches manufactured at (b) (4) Supernus are shown in Figure 2 for the 600 mg strength.

Evaluation of SLS Amount in the Media

According to the Applicant, the aqueous solubility of oxcarbazepine was found to be approximately (b) (4) and to increase in a linear fashion with addition of solubilizers/surfactants. To simulate *in vivo* conditions, additional solubility experiments were conducted using de-ionized water as a medium with different percentages of various surfactants. Sodium lauryl sulfate (SLS) was found to be the best solubilizer for the oxcarbazepine drug substance (data not submitted). Solubility of oxcarbazepine in 1% SLS solution at 37°C is (b) (4) times higher, respectively, than the theoretical concentration of oxcarbazepine in 900mL of medium for 150mg tablets (b) (4), 300mg (b) (4), and 600mg tablets (b) (4).

The effect of SLS amount on the dissolution of OXC ER tablets 150 mg and 300 mg was evaluated. For this purpose the drug release profiles of OXC ER tablets, 150mg and 300mg in de-ionized water with (b) (4) SLS and (b) (4) SLS, respectively, were compared

with the profiles in de-ionized water with 1% SLS. The results of this study are shown in Figures 3 and 4, for the 150 mg and 300 mg strengths, respectively.

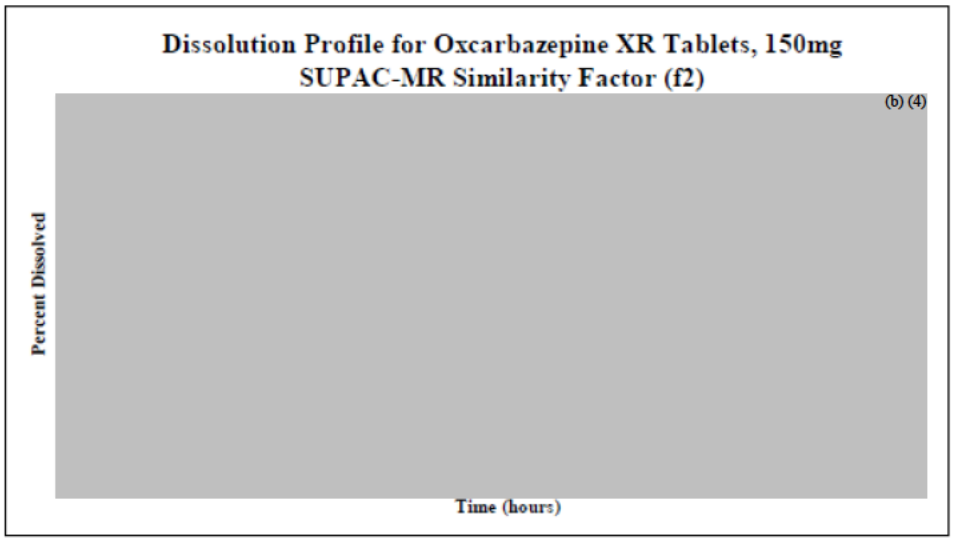

Figure 3. Mean Dissolution Profiles for Oxcarbazepine XR Tablets, 150mg for DI Water with 1% SLS Media vs. DI Water with (b) (4) SLS Media

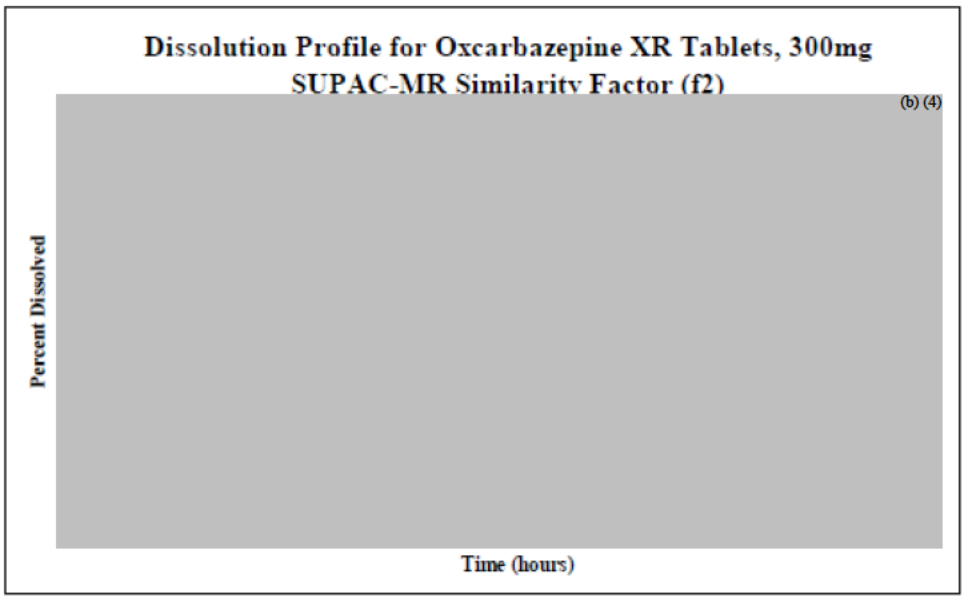

Figure 4. Mean Dissolution Profiles for Oxcarbazepine XR Tablets, 300mg for DI Water with 1% SLS Media vs. DI Water with (b) (4) SLS Media

The Applicant concludes that the selected dissolution medium is appropriate for use for the following reasons:

- The calculated dissolution similarity factors ((b) (4) for 150mg and (b) (4) for 300mg) showed that the profiles were similar in both media,

- A common dissolution method is desired for all three tablet strengths, and therefore the medium of de-ionized water with 1% SLS is necessary to accommodate solubility requirements for the 600mg dose strength.

(b) (4)

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Dissolution Acceptance Criteria

(b) (4)

Newly Proposed Acceptance Criteria	
2 hrs:	(b) (4)
4 hrs:	
8 hrs	

Reviewer's Comments

This reviewer acknowledges that the recommended acceptance criteria conveyed to the Applicant on Jun 6, 2012, will be rejecting batches that have the same performance as the clinical batches. The new data provided by the Applicant on Aug 6, 2012, (refer to

Module 1.11.1, Tables 2-4) support the Applicant's newly proposed dissolution acceptance criteria shown in the above table and these criteria are found acceptable.

It should be noted that the Agency's originally recommended acceptance criteria was based purely on data provided in the original submission, namely data from the BA/BE study 804P101 which are the data that the Applicant used originally to support their proposed specification ranges.

IVIVC DEVELOPMENT

An IVIVC model for OCX ER tablets was developed and evaluated. The model correlated OXC *in vitro* fraction released (Figure 7) with the active metabolite MHD *in vivo* fraction absorbed (Figure 8). The development and internal validation were conducted with two OXC extended-release formulations evaluated in study 804P101. The external validation was conducted with a third formulation evaluated in studies 804P104 and 804P104.5. (Table 9)

(b) (4)

IN VITRO EVALUATION OF THE POTENTIAL FOR ALCOHOL DOSE-DUMPING

The dissolution profiles of OXC ER tablets, 150 mg, 300 mg, and 600 mg were evaluated in 0.1N HCl, pH 1.1 with 1% SLS dissolution medium and the proposed QC medium both containing 0%, 4%, 10%, 20%, and 40% alcohol. The dissolution profiles of OXC ER tablets, 600 mg in the presence of several concentration of alcohol using the acid media, apparatus II/75 rpm are shown in Figure 10. The dissolution profiles of OXC ER tablets, 600 mg in the presence of several concentration of alcohol using the proposed QC media are shown in Figure 11.

The dissolution of OXC ER tablets in the presence of alcohol results in slower release profiles compared to the profile with no alcohol.

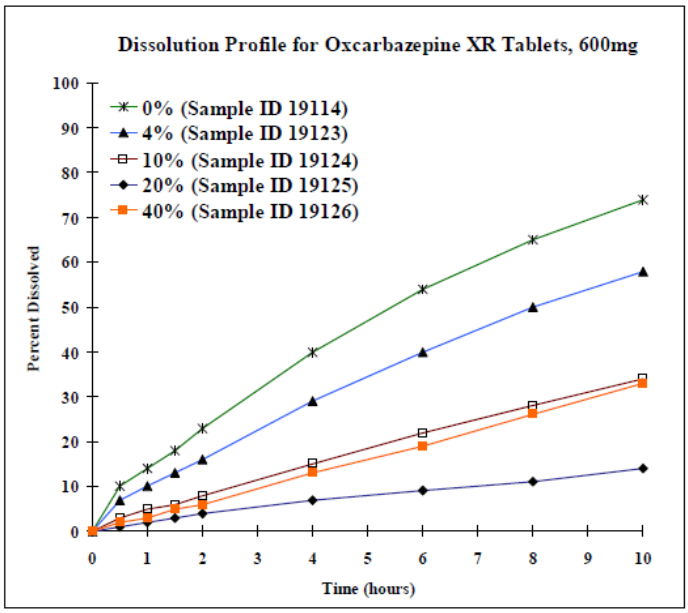

Figure 10. Dissolution Profiles for the 600 mg with 0%, 4%, 10%, 20%, and 40% Ethanol in 0.1N HCl with 1% SLS Media.

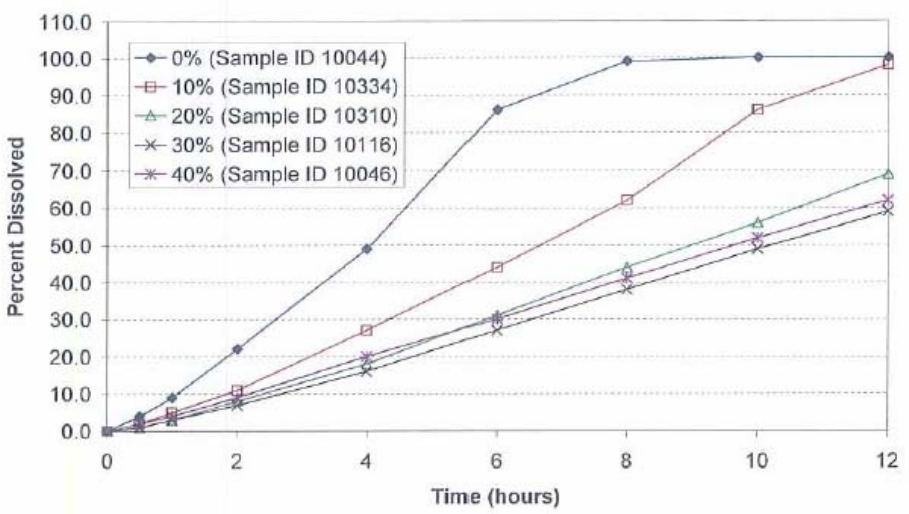

Figure 11. Dissolution Profiles for the 600 mg with 0%, 4%, 10%, 20%, and 40% Ethanol in DI water with 1% SLS Media

Reviewer's Conclusion/ In Vitro Alcohol Dose-Dumping

No dose-dumping from the Oxcarbazepine ER Tablets was observed with dissolution media containing up to 40% ethanol. On the contrary, the release profiles became slower in the presence of alcohol.

EVALUATION OF THE DATA PROVIDED TO SUPPORT THE MANUFACTURING CHANGES

Laboratory scale batches manufactured in a cGMP compliant facility at Supernus, Inc. were used in the following clinical studies: 804P101, 804P102, 804P103, 804P104, 804P104.5 and 804P105. Commercial scale batches manufactured at (b) (4) were used in the following clinical studies: 804P107, 804P301, 804P302. The laboratory scale batches were different from the commercial scale batches with respect to composition, film coating, printing, and scale.

The FDA concurred with the Applicant (refer to meeting minutes dated May 2, 2011) that there was no need to conduct a bridging BE study to prove equivalence between the laboratory scale and the commercial scale batches as the changes in the nonrelease and release controlling excipients were considered as Level 2 (the total additive effect of such changes was no more than 5% by weight). However, the agency requested a multi-point dissolution test be conducted comparing the laboratory scale batches to the commercial scale batches in the following dissolution media: water with 1% sodium lauryl sulfate (SLS), 0.1N hydrochloric acid (HCl) with 1% SLS, United States Pharmacopeia (USP) buffer medium at pH 4.5 with 1% SLS, and USP buffer medium at pH 6.8 with 1% SLS. On meeting minutes dated May 5, 2011 the reviewer concluded that "*The multipoint dissolution profile comparisons in three different media seem adequate to support a Level*

2 change as defined by the SUPAC ER guidance. Therefore, these data is sufficient to support this Level 2 change and the conduct of an in vivo BA/BE study is not necessary"

Figure 12 (same as Figure 2 above) shows the dissolution profiles for the 600 mg strength only in three different media for batches manufactured in Supernus and (b) (4). The f2 values calculated for all the strengths ranged from 58 to 85 (refer to report SPN-8040 under IND 77417-hyperlinked through 2.3.P.2.2.1.6)

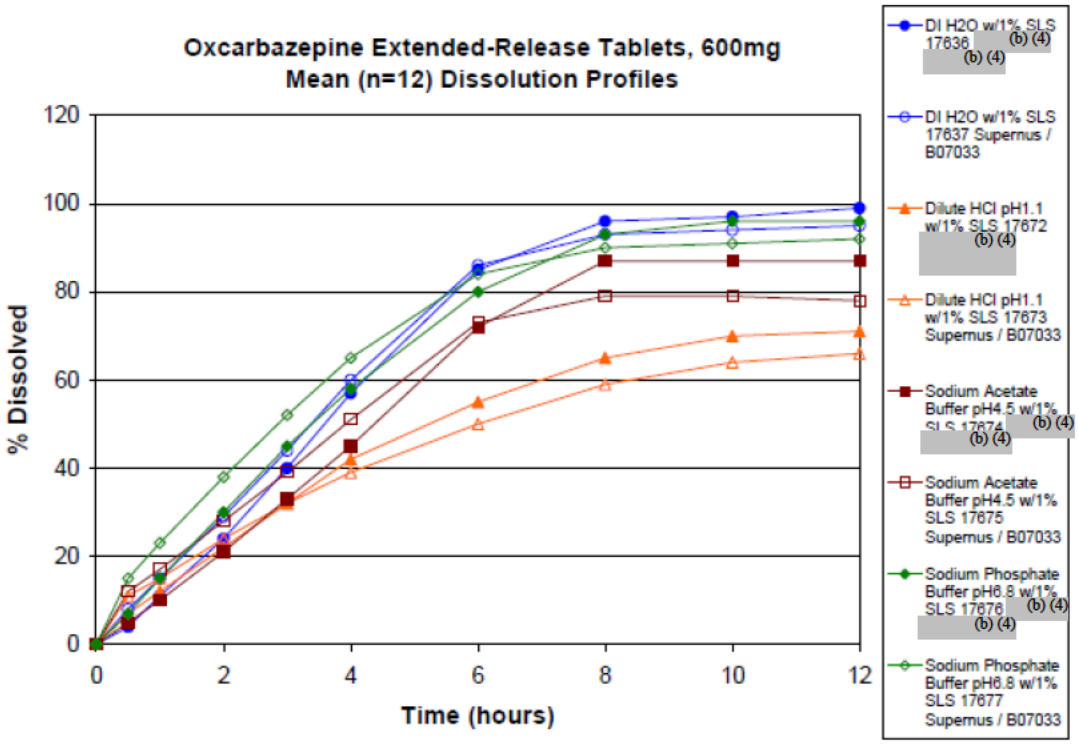

Figure 12. Mean Dissolution Profiles for SPN-804O Extended Release Tablets, 300mg, for Supernus and (b) (4) Lots in Various Media.

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/s/

SANDRA SUAREZ
08/24/2012

ANGELICA DORANTES
08/24/2012

PRODUCT QUALITY - BIOPHARMACEUTICS
FILING REVIEW

NDA Number	202-810
Product name, generic name of the active, and dosage form and strength	Oxcarbazepine ER Tablets, 150-, 300-, and 600 mg
Submission date	Dec 19, 2011
Applicant	Supernus Pharmaceuticals, Inc.
Medical Division	DNP
Type of Submission	Original NDA
Biopharmaceutics Reviewer	Sandra Suarez Sharp, Ph.D.
Biopharmaceutics Lead	Angelica Dorantes. Ph.D.

The following parameters from the ONDQA Quality (CMC and Biopharmaceutics) joint filing checklist are necessary in order to initiate a full Biopharmaceutics review, i.e., complete enough to review but may have deficiencies. On **initial** overview of the NDA application for filing:

A. BIOPHARMACEUTICS				
	Parameter	**Yes**	**No**	**Comment**
1.	Does the application contain dissolution data?	X		The following dissolution method is proposed for routine testing: Medium: De-ionized water with 1% (w/v) SLS Apparatus: USP 2 (paddle) Speed: 75 rpm Temperature: 37°C ± 0.5°C.
2.	Is the dissolution test part of the DP specifications?	X		(b) (4) 2 hrs: 4 hrs: 8 hrs: Note: The proposed Q values were set based on the slowing dissolved batch which showed to be Bioequivalent to the clinical batch. The acceptability of the proposed acceptance criteria will be a review issue.
3.	Does the application contain the dissolution method development report?	X		The Applicant submitted enough information to support the proposed method. The acceptability of this method will be a review issue.
4.	Is there a validation package for the analytical method and dissolution methodology?	X		The analytical method (HPLC/UV) used for analysis of samples collected during dissolution testing is included in 3.2.P.5.3.
5.	Does the application include a biowaiver request?	X		Dissolution profiles comparisons in three different media were submitted to support a Level 2 change implemented to the commercial formulation.

6.	Does the application include an IVIVC model?	X		A report including the development and validation of a Level A IVIVC was included. However, the applicant is not claiming it since they acknowledged that validation was not successful. Therefore, it will not be part of this review.
7.	Does the application include information/data on in vitro alcohol dose-dumping potential?	X		The provided information on the in vitro alcohol interaction study for Oxcarbazepine ER tablets was obtained using only the HCl medium. Note: the Applicant will be requested to provide additional information to rule out the potential for dose-dumping.
8.	Is there any in *vivo* BA or BE information in the submission?	X		A PK dose proportionally and dose linearity studies were conducted. These studies will be reviewed by OCP. The qualification of these studies is needed to support the approval of lower strengths since their chemical composition is not proportionally similar (see attached power point slides).
B. filing conclusion				
	Parameter	**Yes**	**No**	**Comment**
9.	**IS THE PRODUCT QUALITY AND BIOPHARMACEUTICS SECTIONS OF THE APPLICATION FILEABLE?**	X		➢ The NDA is filable from Biopharmaceutics Perspective ➢ The acceptability of the proposed dissolution method and acceptance criteria will be a review issue. ➢ The adequacy of the data provided to support the bridging between the Phase 1/early Phase 3 and the commercial formulations will be a review issue.
10.	If the NDA is not fileable from the product quality perspective, state the reasons and provide **filing** comments to be sent to the Applicant.			Not applicable.
11.	If the NDA is not fileable from the biopharmaceutics perspective, state the reasons and provide **filing** comments to be sent to the Applicant.			Not applicable.
12.	Are there any potential review issues identified?	X		There is not data on potential of alcohol dose-dumping in the QC media

13.	Are there any comments to be sent to the Applicant as part of the 74-Day letter?			• It was noted that the provided information on the in vitro alcohol interaction study for Oxcarbazepine ER tablets was obtained using only the HCl medium. Therefore, in order to rule out a possible dose-dumping (DD) effect in the presence of alcohol, we recommend that you conduct a drug-alcohol interaction study with your ER product using the proposed QC medium. The following alcohol concentrations for the in vitro dissolution studies (using 12 units each) are recommended: 0 %, 4 %, 10 %, 20 %, and 40 %. Please also include the following information as part of your report: o f2 values to assess the similarity (or lack thereof) in the dissolution profiles. o Compare the shape of the dissolution profile to see if the modified release characteristics are maintained, especially in the first 2 hour.

{See appended electronic signature page}

Sandra Suarez Sharp, Ph.D.
Biopharmaceutics Reviewer
Office of New Drug Quality Assessment

{See appended electronic signature page}

Angelica Dorantes, Ph.D.
Acting Biopharmaceutics Lead Date
Office of New Drug Quality Assessment

PRODUCT QUALITY - BIOPHARMACEUTICS
FILING REVIEW

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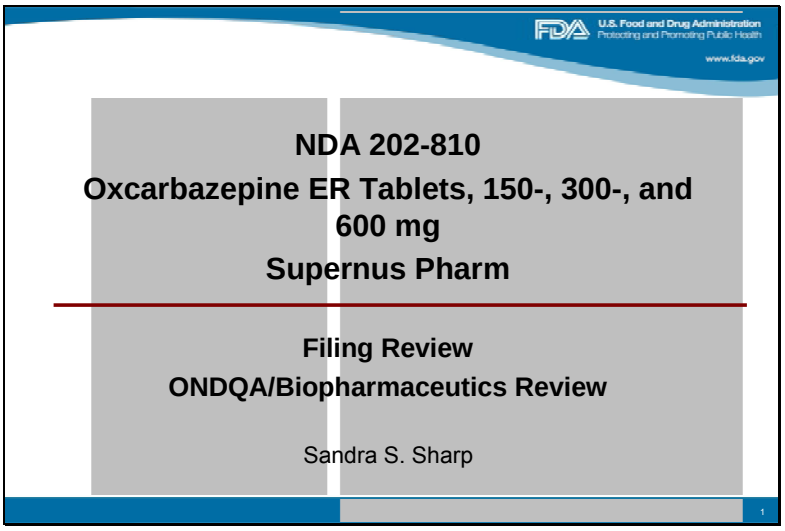

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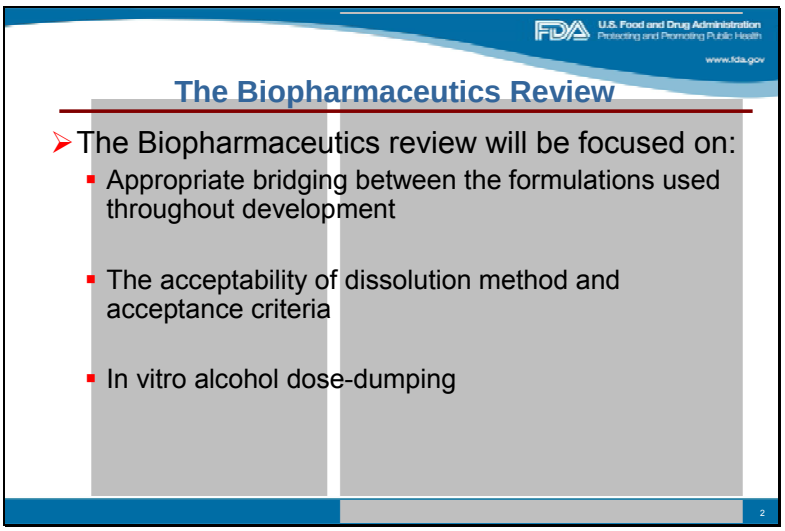

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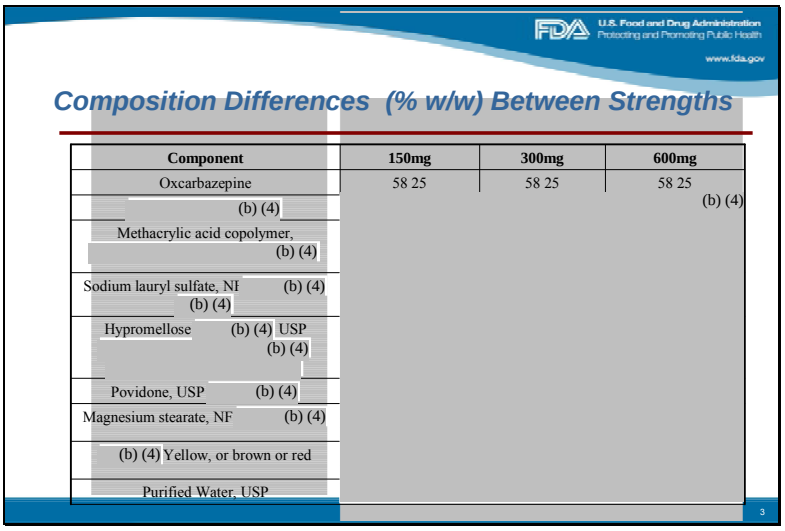

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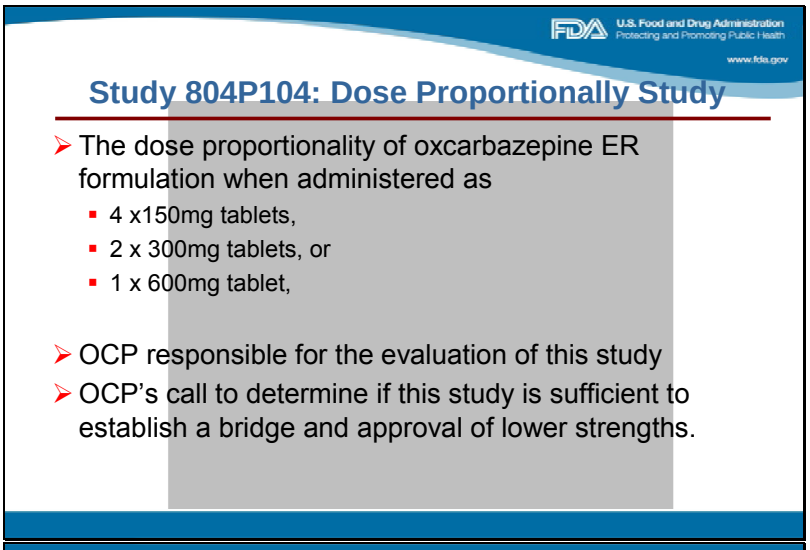

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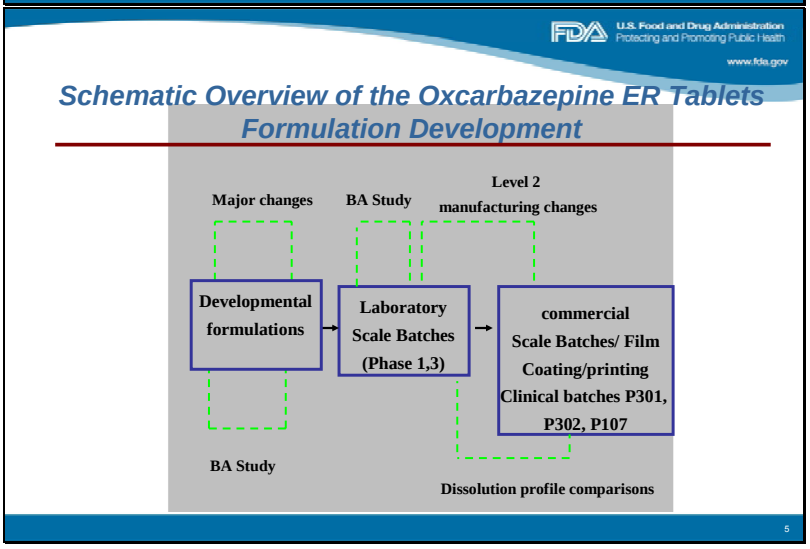

Slide 6

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Proposed Dissolution Method

Dosage Form	Apparatus	Speed	Medium	Volume (mL)
ER Tablet	II	75 rpm	De-ionized water with 1% (w/v) SLS	900 mL

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Proposed Dissolution Acceptance Criteria

Acceptance Criteria for all Strengths (% Dissolved)	
2 hrs:	(b) (4)
4 hrs:	
8 hrs	

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Slide 8

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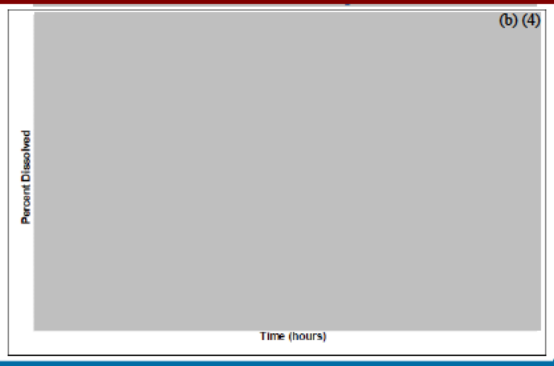
Mean Dissolution Profiles Study 804P101 and Proposed Dissolution Acceptance Criteria



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Slide 9

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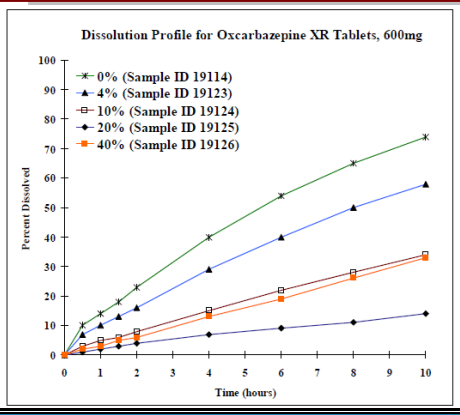
Dissolution Profiles for the 600 mg with 0%, 4%, 10%, 20%, and 40% Ethanol in 0.1N HCl with 1% SLS Media



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Slide 10

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Conclusions

- The acceptability of the proposed dissolution method and acceptance criteria will be a review issue.
- The adequacy of the data provided to support the bridging between the Phase 1/early Phase 3 and the commercial formulations will be a review issue.
- The NDA is filable from Biopharmaceutics Perspective

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Slide 11

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Potential Review Issues

- There is not data on potential of alcohol dose-dumping in the QC media

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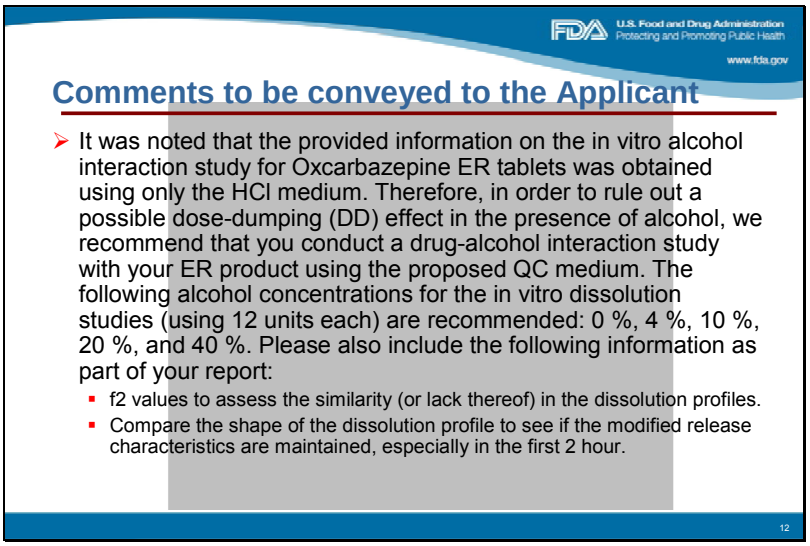
Slide 12



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/s/

SANDRA SUAREZ
02/15/2012

ANGELICA DORANTES
02/16/2012