CLINICAL REVIEW

Application Type	NDA
Application Number(s)	202810
Priority or Standard	S
Submit Date(s)	12/19/2011
Received Date(s)	12/19/2011
PDUFA Goal Date	10/19/2012
Division / Office	DNP / OND1
Reviewer Name(s)	Steven T. Dinsmore
Review Completion Date	9/22/2011
Established Name	Oxcarbazepine ER
(Proposed) Trade Name	OXTELLAR XR™
Therapeutic Class	Anti-epilepsy Drug
Applicant	Supernus Pharmaceuticals, Inc
Formulation(s)	Extended Release Tablet
Dosing Regimen	Once daily
Indication(s)	Adjunctive therapy in the treatment of partial seizures
Intended Population(s)	Adults, Children (b)(4) – 17 years

Template Version: March 6, 2009

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1 Recommendations/Risk Benefit Assessment

1.1 Recommendation on Regulatory Action

The review supports approval of oxcarbazepine XR in the framework of a 505(b)(2) application. The sponsor has adequately bridged to the reference (Trileptal) immediate release tablet formulation with one adequate and well controlled clinical study which demonstrates efficacy at the 2400mg dose. The 1200mg dose approached but did not achieve statistically significant separation from placebo. There is evidence, although Bayesian in quality, that therapeutic benefit may be seen beginning at a dose of 1200mg based on prior knowledge that the same API (active pharmaceutical ingredient), oxcarbazepine, in the immediate release form has demonstrated treatment benefit at 600mg /day[1]. Addition support for a dose range from 1200mg through 2400mg is provided by post hoc exposure response analysis performed by the clinical pharmacology team. This analysis showed a percentage reduction in seizure frequency as a function of MHD C_{min} concentrations adequate to indicate a clinically meaningful decrease in seizure frequency at the dose of 1200 mg. Some assurance of a continuum of efficacy in the 1200mg to 2400mg dose range is also provided by the observation in post hoc analysis of a notable treatment effect size by region. There is significant separation of treatment arm from placebo in both the 1200mg and 2400mg dose groups in the North American regional subset. This collective evidence supports adult labeling for the dose range of 1200mg to 2400mg, Appendix 9.2. Pediatric labeling may also be approved based on clinical pharmacology analysis of the pediatric PK study which demonstrates that effective adult exposures may be achieved with a weight based nomogram, Appendix 9.2. Due to tablet size tolerance in younger children, it is recommended that approved pediatric labeling begin at age 6 rather than age 4 with a resultant pediatric indication of age 6 to 17 years old.

Improved compliance with once daily treatment as well as some reduction of Cmax associated common adverse events provides a reasonable argument for the benefit of this preparation. The risk of oxcarbazepine has been identified through 12 years of use in the United States while still providing acceptable benefit for treatment of epilepsy. New risk of this extended release formulation exists in the potential for under treatment if patients on the IR form are converted to the extended release form under an assumption of mg to mg equality between formulations. This risk can be addressed by clear labeling of this differential in oxcarbazepine delivery.

1 Trileptal Label, Revised 03/2011, page 22, section 14.2, Table 8.

1.2 Risk Benefit Assessment

There is a benefit to this preparation due to the once daily dosing. This mode of delivery will likely enhance compliance and also attenuate adverse effects associated with Cmax. This is not a groundbreaking advance in epilepsy treatment but is a benefit of acceptable magnitude when weighted against the well characterized risk profile of the active pharmaceutical ingredient, oxcarbazepine, which has been available on the world market for 21 years. Oxcarbazepine has been used with an acceptable safety profile during this time period. The Oxcarbazepine XR form, as stated, may attenuated some of the Cmax associated adverse events but the more serious risks identified in the "Warnings and Precautions" section of the Trileptal label remain unchanged. Some additional risk to be considered is the AUC non- bioequivalence between the extended release form and the immediate release formulation. There is not a 1:1 correspondence between the immediate release and extended release formulations, therefore patients transitioning to the extended release form may not simply change from IR to XR on a mg to mg basis. Labeling must be clear that patients taking immediate release oxcarbazepine should not be converted on an assumption of mg to mg equality.

1.3 Recommendations for Postmarket Risk Evaluation and Mitigation Strategies

Medication guide

1.4 Recommendations for Postmarket Requirements and Commitments

none

2 Introduction and Regulatory Background

2.1 Product Information

Oxcarbazepine (OXC) is approved in the European Union and the United States for initial monotherapy, and adjunctive therapy in children and adults suffering from partial onset seizures

Supernus has developed SPN-804O as an extended-release version of OXC, based on a proprietary delivery technology, as a monolithic, controlled-release matrix tablet capable of generating a pharmacokinetic profile compatible with a once-daily (QD) dosing regimen. Available tablet strengths of SPN-804O are 150 mg, 300 mg and 600 mg.

The active ingredient of oxcarbazepine extended-release tablets is oxcarbazepine, commercially manufactured by (b) (4) The inactive ingredients are non-novel compendial and noncompendial excipients. Oxcarbazepine extended-release tablets are manufactured and packaged in either 100-

count bottles or 5-count blister packs by [redacted] (b) (4) .

SPN-804O utilizes a proprietary drug delivery technology, [redacted] (b) (4) which uses the solubility enhancement concept in an extended release matrix tablet to develop a release profile for the drug that is specifically tailored for the therapeutic application. One product has been successfully commercialized in the USA with this technology.

2.2 Tables of Currently Available Treatments for Proposed Indications

Anticonvulsants in common clinical use for the treatment of partial epilepsy

Carbamazepine
Gabapentin
Lacosamide
Lamotrigine
Levetiracetam
Oxcarbazepine
Phenobarbital
Phenytoin
Potiga
Pregabalin
primidone
Tiagabine
Topiramate
Valproic acid
Zonisamide

2.3 Availability of Proposed Active Ingredient in the United States

The active ingredient, oxcarbazepine, has been available in the United States since the approval of Trileptal in January 2000

2.4 Important Safety Issues with Consideration to Related Drugs

As an extended release form of an established API, oxcarbazepine, the important safety issues have been well characterized. The common adverse effects produced by oxcarbazepine were observed in study 804P301. Serious adverse effects noted for the reference product in warnings and precautions are hyponatremia, serious dermatologic reactions (toxic epidermal necrolysis (TEN) & Stevens-Johnson syndrome (SJS)), suicidal behavior and ideation (AED class effect) and multiorgan hypersensitivity. Some non-serious adverse effects are also well characterized for sodium channel active anticonvulsants. These are primarily the CNS effects of dizziness, sedation and impaired motor function.

2.5 Summary of Presubmission Regulatory Activity Related to Submission

Meetings to discuss, clarify development issues were conducted on 4 occasions. These included a Pre-IND meeting on June 29, 2007, a meeting to review the division responses to a special protocol assessment (SPA) on July 14, 2008, an EOP2 meeting to cover CMC issues on March 30, 2011 and a Pre-NDA meeting on May 18, 2011.

1. Pre IND May 29, 2007:

Notable points of discussion:

The pivotal clinical trial for oxcarbazepine XR should examine adjunctive use. A monotherapy study with pseudo-placebo has been deemed unethical by the general epilepsy research community.

The division indicated that pediatric development should proceed not with a comparison of controlled release oxcarbazepine to Trileptal but rather a comparison of the oxcarbazepine controlled release product between the adult and pediatric populations.

2. July 14, 2008: Discussion of responses to SPA of February 26, 2008.

Notable points of discussion:

The sponsor proposed only a 1200mg and 2400mg dose arm in the proposed pivotal study due to a decrease Cmax of both OXC and its active metabolite MHD, in the fasting state. The division indicted this was inconsistent with the plan to administer OXC XR with meals in the proposed study. Subsequently the sponsor agreed to conduct the study (804P301) with patients taking study drug in a fasting state.

Also the division recommended: “we believe that exposures with 1200 mg ER dose under fed conditions will give exposures close (about 33% higher) to the 1200 mg IR tablet. Given this we also feel that the 600 mg dose under fed conditions may not be an inefficacious dose either. Considering these issues we would like to additionally recommend that your study should examine a complete useful therapeutic range of dosages, which would include 600 mg fed.”

The division expressed concern that USP naming rules require that established names for all extended release preparation be the same (e.g. oxcarbazepine extended release). This creates the potential for medication dosing error if an identical dose but not bioequivalent ER preparation is developed, as in the case of your intended ER formulation, because they can both be freely interchanged when only the established name is written in the prescription.

3. May 23, 2011: Pre-NDA meeting

Notable points of discussion:

The sponsor indicated at initial plan they would not present safety data derived from the studies in healthy volunteers. The division recommended that all clinical safety data be submitted, including those from Phase I protocols conducted in healthy volunteers.

The division reminds the sponsor that a 505(b)(2) applicant that seeks to rely on the Agency's finding of safety and/or effectiveness for a listed drug may rely only on that finding as is reflected in the approved labeling for the listed drug.

The sponsor proposed inclusion of a conversion table in the label based on population PK approach. The division indicated that the acceptability of such a table would be a matter of review. Statements in labeling about any equivalency of dosing between the IR and ER preparations would not likely be included in labeling.

The division indicated that a REMS will not be required but a medication guide should be proposed.

The three participants in study 804P301 from site 115 may be excluded from the primary analysis due to suspected lack of data integrity.

Concerning the sponsor proposed waiver and deferral of pediatric studies, the sponsor is informed that PREA requires the development of an age appropriate formulation or documentation detailing why a pediatric formulation cannot be developed. Concerning the proposal to submit pediatric PK information for the pediatric population age 4-17 years of age the sponsor is advised that a pediatric assessment is sufficient to support dosing, efficacy and safety (using an age appropriate formulation) in all relevant pediatric populations. It is noted that the adequacy of PK data alone to fulfill PREA will be a review issue. If exposures related to the extended release product exceed exposures associated with immediate release formulations additional safety information may be required. In addition if an efficacy study is not conducted because of reliance on extrapolation of efficacy from adequate and well controlled studies in adults or other pediatric patients a scientific rational for the extrapolation must be provided.

2.6 Other Relevant Background Information

None

3 Ethics and Good Clinical Practices

3.1 Submission Quality and Integrity

The ISS was poorly developed (13 pages), there was no integrated discussion of exposure from the phase 1 trials, the pivotal trail 804P301 and open label extension 804P302. An additional information request was needed to insure that a comprehensive

presentation of exposure would be available in the 120 day safety update. There was also no discussion of laboratory values, the reviewer was dependent on reference to the pivotal trial (outside of the ISS) for this information and there was no central location for an integrated discussion of the laboratory observations from the phase 1 trials.

Labeling for the pediatric population was not supported by scientific rational. Although correspondence from the pre-NDA meeting of May 23, 2011 state "if you will not be conducting efficacy studies and will be relying on extrapolation of efficacy fro adequate and well controlled studies in adults or other pediatric patients, you must include the scientific rationale for this extrapolation. No such justification was provided, only the following statement in the Request for Partial Waiver of Pediatric Studies, "Supernus believes that conduct of Protocol 804P107 meets PREA requirements. Supernus' position is that the conduct of Protocol 804P107 in children ages 4 to 16 exceeds what is required based on FDA's own precedent for pediatric waiver when a product available as an immediate-release product is presented for approval in an extended-release form." It appears the sponsor believes this position supersedes the requested scientific rational noted in the pre-NDA meeting.

Labeling for the pediatric population was not supported by *pre-specified* scientific rationale, although requested in the pre NDA meeting as follows: "if you will not be conducting efficacy studies and will be relying on extrapolation of efficacy from adequate and well controlled studies in adults or other pediatric patients, you must include the scientific rationale for this extrapolation. The sponsor has provided no detailed scientific rational. The following statement is provided in module 1.9 of the NDA submission: "This protocol evaluates children ages 4 to16, inclusive, and is intended to provide pediatric pharmacokinetic information that parallels the adult information being provided in this New Drug Application" …"Supernus believes that conduct of Protocol 804P107 meets PREA requirements". Minimal language to support the use of PK data for use in the pediatric age range (b) (4) to 17 was provided in study 804P107 as follows: An important goal was to determine which metric for body size (*e.g.*, weight or weight raised to the 0.75 power) was most appropriate to select a dose for a pediatric patient that would yield exposure (a plasma concentration profile for OXC and/or MHD) comparable to that in adults.

3.2 Compliance with Good Clinical Practices

The sponsor identified that a site for study 804P301 was compromised by investigator misconduct. This site, 115, enrolled 3 patients. After this finding it was agreed these three subjects could be excluded from the study analysis.

The protocol deviation dataset for study 804P301 was examined. 185 protocol deviations entries were generated by 101 patients. The majority of deviations were "other/ Missing Seizure Diary Data" (see Table 1 Protocol Deviation Analysis).

Table 1 Protocol Deviation Analysis

Category	# occurrences	% of total deviations
Eligibility	27	15
Other / Missing Seizure Diary Data	130	70
Prohibited Medication	16	9
Treatment (Study Medication)	10	5
Withdrawal	2	1

A DSI consult was initiated for inspection of three sites as show in Table 2 Clinical Site Inspections:

Table 2 Clinical Site Inspections

Site # / Location	Protocol ID	Number of Subjects	Indication
Site #: 701 Sofia Bulgaria	804P301	11	1. site is greater than 90th percentile of enrollment, represents 3% of randomized subjects 2. One of top 7 sites driving efficacy outcome. 3. site had 18 non-serious adverse events, 10th most frequent of all sites 4. 10 protocol deviations, 4th most frequent of all sites 5. 45% subject discontinuation
Site #: 406 Krakow Poland	804P301	11	1. Large enrollment, 11 subjects is greater than the 90th percentile of enrollment, represents 3% of randomized subjects. 2. Unusually large placebo effect, 72 percent reduction in median seizure frequency with a maximum treatment effect of 75.4% reduction. 3. site had 75 non-serious adverse events, 2nd most frequent of all sites.
Site #:510 Zagreb, Croatia	804P301	9	1. Enrollment greater than 3rd quartile. 2. 44% subject discontinuations

DSI inspection results:

Site # 701: the clinical inspection summary report notes: a one item Form FDA 483 was issued to the clinical investigator for failing to report an adverse event. Subject #7 experienced dizziness and nausea, and this adverse event was not reported to the sponsor. The concluding "Assessment of Data Integrity" states: Although a single regulatory violation was noted at Dr. Shotekov's site, the finding is not likely to significantly affect overall data integrity or subject safety. The data from Dr. Shotekov's site are considered reliable in support of the application.

Site #406: the clinical inspection summary report notes: a one item Form FDA 483 was issued to Dr. Czapinski. Our investigation found two transcription errors in the e-CRF entries for the Quality of Life in Epilepsy (QOLIE). For Subject 406001, the source document showed for Visit 2, question 10, "Did you feel tired?" subject answered 3, "A good bit of time", and for Visit 7, question 30, "Mental effects of antiepileptic medication" subject answered 3, "Not very worried". The CRF reported a score of 2, "somewhat worried". The concluding "Assessment of Data Integrity" states: "Although regulatory deviations were noted, the minor discrepancies are not likely to critically impact primary efficacy and safety analyses; therefore, DSI does not consider the effect on overall data integrity to be significant. In general, the data in support of clinical efficacy and safety at Dr. Czapinski's site are considered reliable and appear acceptable in support of the pending application."

Site # 510: the clinical inspection summary report notes: no Form FDA 483 was issued to Dr. Basic. The medical records reviewed were found to be in order, organized and the data verifiable. There were no deaths and no evidence of underreporting of adverse events. There were no known limitations to the inspection. The concluding "Assessment of Data Integrity" states: "The data generated in support of the clinical efficacy and safety at Dr. Basic's site are considered reliable and appear acceptable in support of the pending application."

The clinical inspection summary overall assessment of findings indicated that the data submitted from all sites are considered acceptable in support of the pending application.

Reviewer Comment: the regulatory violations identified at sites 701 and 406 were limited in scope such that no overall impact on the assessment of safety resulted. The violations also do not involve data related to efficacy assessment therefore no action is indicated in the overall assessment of the application.

3.3 Financial Disclosures

A complete table containing investigator / subinvestigator by site is provided in section 1.3.4 Financial Disclosure in the administrative information section of the NDA. Seven sub-investigators from study 804P301 did not complete financial disclosure forms. In two cases the individuals did not participate in the study, in four cases the sub-investigators were no longer employed at the study sites, and could not be reached for completion of the forms and in one case there was a transfer of the CRO and the documentation was lost to follow up. There was 1 PI who did not sign a financial disclosure form; however the site was not activated and did not contribute to study 804P301. One sub investigator from a phase 1 study did not complete a financial disclosure form but her duration of employment at the site lasted only 10 days after form 1572 was completed.

Reviewer Comment: The seven instances where a financial disclosure form is not available for a subinvestigator in study 804P301 represents only 1.5% of all

investigative personnel in the study. In addition these subinvestigators were dispersed among 5 sites. Overall this lapse in financial disclosure information is not a threat to the study integrity.

4 Significant Efficacy/Safety Issues Related to Other Review Disciplines

4.1 Chemistry Manufacturing and Controls

Recommendation and Conclusion on Approvability: from CMC review 8-28-2012

The applicant has provided adequate responses to the FDA CMC IR letters. Additionally, the ONDQA Biopharm review has been satisfactorily completed and submitted into DARRTS; revised drug product dissolution specifications are recommended therein, which are acceptable to the applicant. There are no CMC pending issues. However, OC's overall acceptable recommendation based on site inspection is pending and when received will be entered into DARRTS as a Memoto-File. Once this acceptable recommendation is received the NDA will be recommended for approval from a CMC perspective.

The Office of Compliance Summary Report was received on 9/10/2012. The CMC review was updated with a statement that there were no other CMC pending issues and accordingly the NDA was recommended for approval from a CMC prospective.

4.2 Clinical Microbiology

None

4.3 Preclinical Pharmacology/Toxicology

No new preclinical studies were required in the development of this extended release formulation of oxcarbazepine. The reader is referred to section 13 “Nonclinical Toxicology” of the product label which is adapted from the March 2011 Trileptal label.

4.4 Clinical Pharmacology

The key conclusions and summary of Clinical Pharmacology and Biopharmaceutics Findings are provided in the following text, for the full text the reader is referred to the Clinical Pharmacology Review.

<u>Conclusions</u>

- 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.

Summary

Relative Bioavailability Evaluation

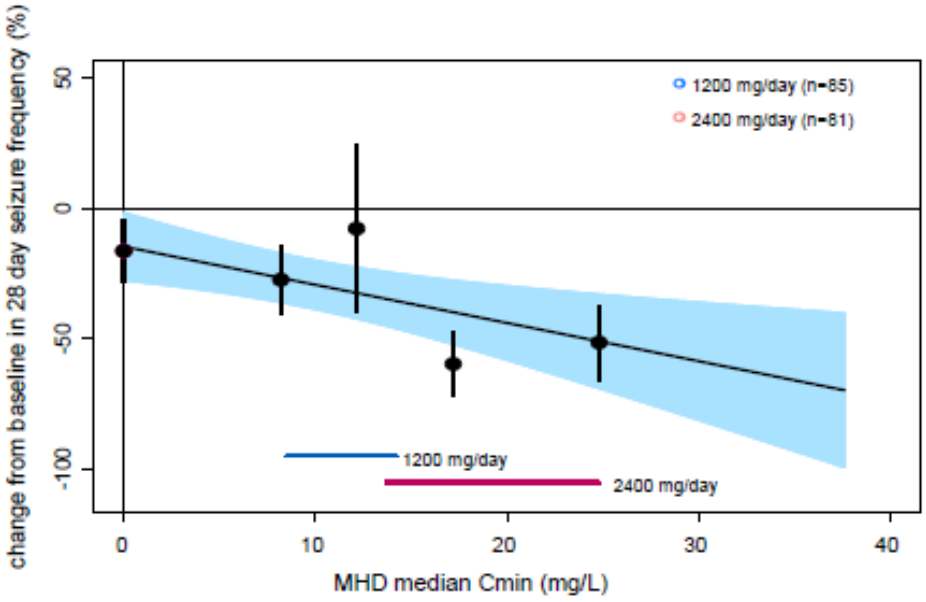
The exposures of the active metabolite, 10-monohydroxy derivative (MHD), which is primarily responsible for pharmacological effect, and the parent compound, oxcarbazepine (OXC), after multiple dose administration of 1200 mg of OXC ER were not bioequivalent to those after administration of 1200 mg Oxcarbazepine 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 24). 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.

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.

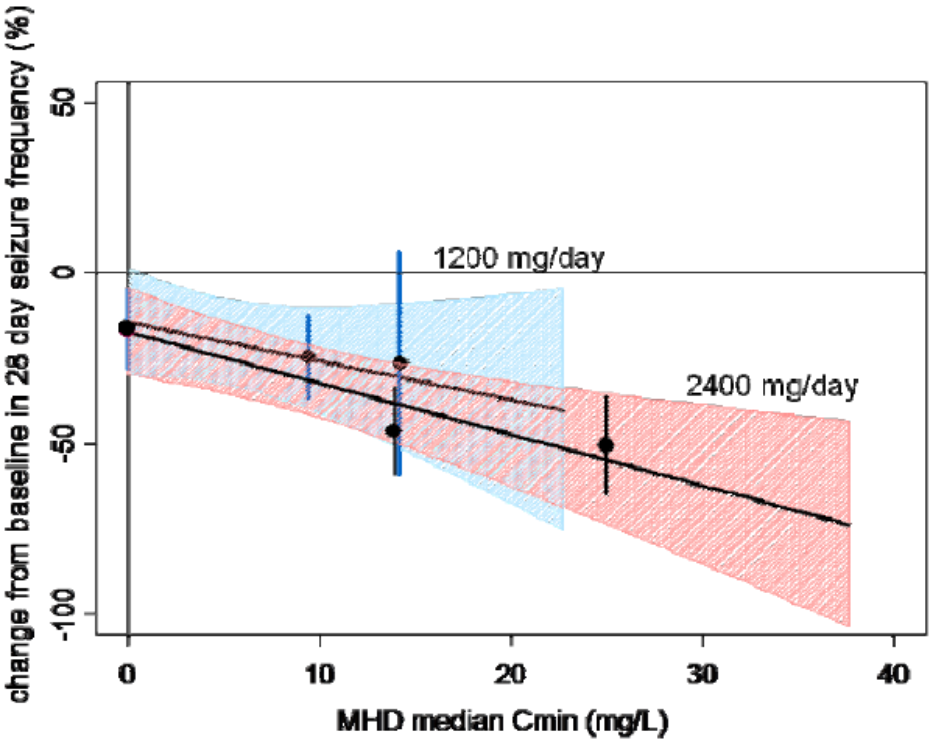
Figure 1 Placebo-anchored exposure-response for the OXC-ER formulations from the pivotal trial. Data includes placebo patients along with patients with PK and PD information from both the 1200 mg/day and 2400 mg/day groups.



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).

Figure 2 Placebo-anchored exposure-response for the OXC-ER formulations (1200mg/day and 2400mg/day modeled separately). Data includes placebo patients along with patients with PK and PD information from both the 1200mg/day and 2400mg/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 4).

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.

Clinical Pharmacology 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.

Table 4 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.

4.4.1 Mechanism of Action

Mechanism of action as currently presented in section 12.1 of the reference labeled product (Trileptal):

The pharmacological activity of Trileptal is primarily exerted through the 10-monohydroxy metabolite (MHD) of oxcarbazepine. 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. These actions are thought to be important in the prevention of seizure spread in the intact brain. In addition, increased potassium conductance and modulation of high-voltage activated calcium channels may contribute to the anticonvulsant effects of the drug. No significant interactions of oxcarbazepine or MHD with brain neurotransmitter or modulator receptor sites have been demonstrated.

4.4.2 Pharmacodynamics

Pharmacodynamics as currently presented in section 12.1 of the reference labeled product (Trileptal):

Oxcarbazepine and its active metabolite (MHD) exhibit anticonvulsant properties in animal seizure models. They protected rodents against electrically induced tonic extension seizures and, to a lesser degree, chemically induced clonic seizures, and abolished or reduced the frequency of chronically recurring focal seizures in Rhesus monkeys with aluminum implants. No development of tolerance (i.e., attenuation of anticonvulsive activity) was observed in the maximal electroshock test when mice and

rats were treated daily for five days and four weeks, respectively, with oxcarbazepine or MHD.

4.4.3 Pharmacokinetics

See Clinical Pharmacology summary, section 4.4 for discussion of salient features.

5 Sources of Clinical Data

5.1 Tables of Studies/Clinical Trials

NDA 202810 for Oxcarbazepine extended release is a 505(b)(2) application. The submission package contains a panel of phase 1 studies to examine bioavailability, steady state PK of formulations, relative bioavailability, dose proportionality, dose linearity, food effect, steady state PK study in children and one phase 3 efficacy and safety study. A table of studies providing additional detail on each study is provided in Table 5. Studies 804P302 and 804P303 are included in the ISS discussion but the study reports are not yet complete and the safety datasets are not provided.

Table 5 Table of Clinical Studies

Study ID	Study Design	Treatments/ Dose/ Regimen	Objective	# Subjects	Results
804P101	Four-way crossover, single administration in healthy adults	A: OXC CRe-F Tablet, 600mg QD B: OXC CRe-M Tablet, 600mg QD C: OXC CRe-S Tablet, 600mg QD D: Trileptal® Tablet, 300mg, BID	Relative bioavailability of different OXC CR formulation prototypes and Trilepta ®	Randomized: 16 Completed: 16	Formulation B produced AUC results closest to OXC IR.
804P102	Three-way crossover, multiple dose administration in healthy adults	A: OXC CRe-M Tablet, 600mg QD B: OXC CRe-S Tablet, 600mg QD C: Trileptal® Tablet 300mg, BID	Steady-state PK of two different OXC CR prototypes vs Trileptal	Randomized: 21 Completed: 18	Results support further development of OXC CRe-M.
804P103	Two-way crossover, multiple dose administration in healthy adults	A: OXC XR Tablets, 600mg x 2 QD B: Trileptal® 600mg, BID	Steady-state relative bioavailability	Randomized: 32 Completed: 28	The AUC0-24 and Cmax,ss of MHD of SPN-804O were about 19% lower than with OXC IR.
804P104	Three-way crossover, single-dose administration in healthy adults	A: OXC XR Tablet, 150mg x 4 B: OXC XR Tablet, 300mg x 2 C: OXC XR Tablet, 600mg x 1	Dose Proportionality	Randomized: 54 Completed: 53	The three SPN-804O strengths produced proportional PK parameters.
804P104.5	Three-way crossover, single dose administration in healthy adults	A: OXC XR Tablet, 150mg B: OXC XR Tablet, 300mg C: OXC XR Tablet, 600mg	Dose linearity	Randomized:54 Completed:52	The acceptance criteria were met for all comparisons for the dose-normalized (to 300mg) Cmax but not for AUC0-t (C vs A) and AUCinf (C vs B and C vs A).
804P105	Two-way crossover, single administration in healthy adults	A: OXC XR Tablet, 600mg (fasted) B: OXC XR Tablet, 600mg (fed)	Food effect	Randomized: 62 Completed:59	The AUCs of MHD did not change after a high fat meal, but Cmax presented a 63% increase.

804P107	Multicenter, open-label, multiple dose administration in pediatric patients	Subject Weight 15.0 to 29.9 Kg 30.0 to 44.9kg 45.0 to 59.9kg 60.0kg +	SPN-8040 Total 150mg/day 300mg/d 450mg/d 600mg/d	Steady state pharmacokinetics of adjunctive OXC XR in children with partial epilepsy	Randomized: 18 Completed: 18	Dosing of pediatric patients with SPN-804O can be determined based on body weight. Weight-normalized doses in pediatric patients should produce MHD exposures (AUC) comparable to that in typical adults.
804P301	Multicenter, double-blind, placebo-controlled, three-arm, parallel group in adult patients	A: 2400mg SPN-804O QD tablets B: 1200mg of SPN-804O QD tablets C: Placebo QD tablets		Efficacy of adjunctive SPN-804O therapy of partial-onset seizures in adults with refractory epilepsy on at 1-3p to three AEDs	Enrolled: 369 Completed: 248	SPN-804O was statistically superior to placebo in reducing the partial seizure frequency per 28 days for 2400mg/d (p=0.003) but not for 1200mg/d (p=0.078). Incidence and types of adverse events reported for the SPN-804O groups were consistent with those reported for IR formulation of OXC. No apparent safety concerns with SPN 804O were identified.
804P302	Multicenter, 12-month open-label extension study to 804P302	SPN-804O QD tablets, total daily dose between 600mg and 2400mg, per investigator discretion.		Safety and tolerability of long-term adjunctive SPN-804O in refractory partial onset epilepsy adults on multiple AEDs	214 enrolled	Study ongoing. Preliminary interim data support the safety and tolerability of long-term administration of SPN-804O.
804P303	Multicenter, 12-month, open-label extension study to 804P107	SPN-804O QD tablets, total daily dose between 150mg and 1800mg, based on subject weight, and per investigator discretion		Safety and tolerability of long term adjunctive SPN-804O therapy in pediatric subjects with partial seizures	Enrolled 10	Final Study Report in progress

5.2 Review Strategy

Seizure data analyses are utilized for the efficacy review as per the primary outcome measure. The seizure diary datasets are provided in the application in module 5 under study 804P301

All studies listed in Table 5 contribute to safety conclusions.

5.3 Discussion of Individual Studies/Clinical Trials

There was one pivotal clinical trial of efficacy, Study 804P301 described in section 6.1.1.

6 Review of Efficacy

Efficacy Summary

This is a 505b2 application. The RLD (reference listed drug) for this oxcarbazepine extended release formulation is Trileptal tabs approved January 14, 2000 (oxcarbazepine IR). This investigative product represents a new dosage form, a modification of the oral tablet to create an extended release behavior of the reference drug, Trileptal, API, oxcarbazepine. This application relies on agency finding of safety and efficacy for the immediate release formulation of oxcarbazepine. Additional support for the safety and efficacy of this modified formulation is also required. Bioequivalence data alone is insufficient, the divisions' position stated in the pre-IND meeting of May 29, 2007, is "that one can only assume efficacy of a comparator product if PK curves are superimposable". In the case of this formulation the Cmax will be lower than the reference drug (Trileptal) due to its controlled release formulation.

Study 804P102 was a multiple dose, three-way cross-over study in healthy volunteers, in which the two best-performing prototypes from study 804P101 (CRe-M and CRe-S prototypes) at doses of 600 mg/day for 7 days were compared at steady state to Trileptal given 300mg BID for 7 days. Formulation CRe-M in the fasting state was found to yield bioequivalence for the MHD moiety but not for oxcarbazepine, section 6.1.10. The CRe-M formulation was chosen for full development and designated SPN-804O (study drug). In the fed state this formulation has a 63% increase in Cmax and 2 hour shorter Tmax than in fasting state. This fed state food effect approximates the characteristics of the oxcarbazepine immediate release formulation.

There was a single clinical efficacy and safety trial 804P301conducted with study medication taken in a fasting state. This trial examined 1200mg and 2400mg and Placebo added as adjunctive therapy to patients on 1 to 3 AEDs as a stable regimen. The 1200mg dose did not separate with significance from placebo treatment. The 2400mg dose did separate significantly from placebo. Examination of the effect size reveals that the median 28 day percent reduction in seizure frequency over placebo was

-9.5% (p<0.078) for the 1200mg/day group and -14.2% (p<0.003) for the 2400mg/day group.

6.1 Indication

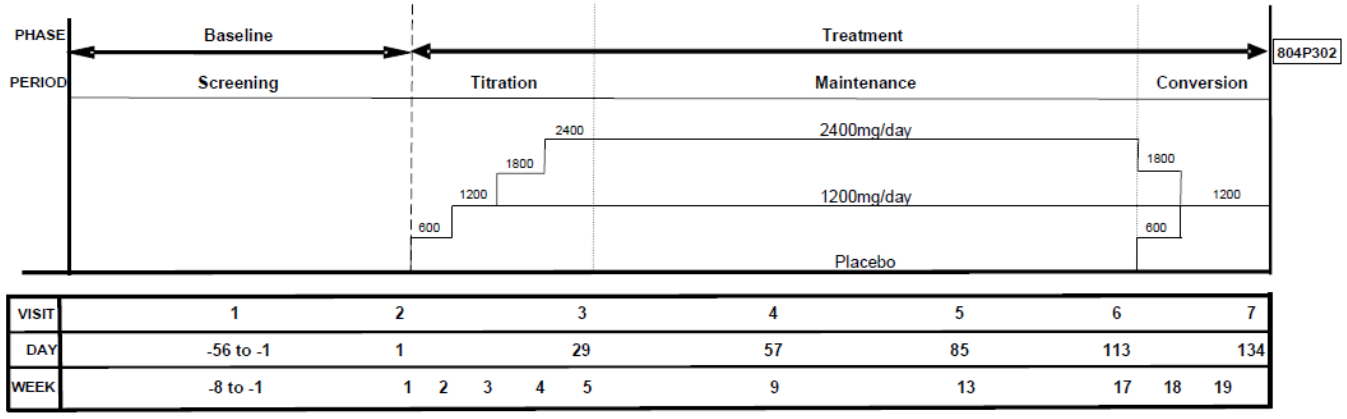
The requested indications for this extended release formulation of oxcarbazepine are:

- Adults: Adjunctive therapy in the treatment of partial seizures
- Children: Adjunctive therapy in the treatment of partial seizures in children (b) (4)-17 years (*1*)

6.1.1 Methods

Adults: Efficacy was tested in a single pivotal trial 804P301. This was a multicenter, double blind randomized 1:1:1, parallel group, placebo controlled study which evaluated oxcarbazepine ER as add on therapy in patients from age 18 to 65 years old who had refractory epilepsy. There were three arms to the study, a placebo, SPN-804O delivered as 2 x 600mg (1200mg / day) tablets daily or 4 x 600mg tablets (2400mg / day) daily. Patients must have been stable on regimens of at least one or up to three concomitant AEDs at baseline and maintained unchanged dose of these AEDs through the course of the study. Planned enrolment in the study was 360 subjects, 369 subjects were enrolled and 248 subjects completed the study. The study was conducted at 120 centers internationally.

Figure 3 Study 804P301 study Schematic



Pediatrics: The sponsor is seeking the indication for children aged (b) (4) to 16 based on pharmacokinetic information presented in study 804P107. This is a multiple dose, open label, multi center study to examine the steady state pharmacokinetics of SPN-804O and the safety and tolerability of repeated oral dosing in pediatric subjects with partial seizures. Forty subjects were planned and 18 subjects were enrolled and completed the study. Discussion of this trial is provided in section 6.1.7

6.1.2 Demographics

Table 6 through Table 13 shown below provide the study demographics for Ethnicity and Race, Age and Sex, Epilepsy history and duration, seizure type by treatment arm, number of AEDs by treatment arm, concomitant AEDs by treatment arm, baseline seizure frequency by treatment arm, and subject randomization by country and region.

Table 6 Study 804P301 Ethnicity & Race

Ethnicity and Race				
Parameter	SPN-804O 2400mg/day (N=123)	SPN-804O 1200mg/day (N=122)	Placebo (N=121)	Total (N=366)
Ethnicity n (%)				
Hispanic or Latino	21 (17.1)	16 (13.1)	17 (14.0)	54 (14.8)
Not Hispanic or Latino	102 (82.9)	106 (86.9)	104 (86.0)	312 (85.2)
Race				
African American	1 (1)	5 (4)	1 (1)	7 (2)
White	105 (85)	104 (85)	107 (88)	316 (86)
Asian	1 (1)	1 (1)	0	2 (0.5)
American Indian or Alaska Native	1 (1)	0	0	1 (0.3)
Other	15 (12.2)	12 (9.8)	13 (10.7)	40 (10.9)

Reviewer Comment: The distribution of Caucasian and Latino patients is balanced across treatment arms. There are insufficient African American and Asian subjects to generalize efficacy and safety specifically to these populations.

Table 7 Study 804P301 Age & Sex

Age and Sex				
Age (years)	SPN-804O 2400mg/day (N=123)	SPN-804O 1200mg/day (N=122)	Placebo (N=121)	Total (N=366)
Mean (SD)	38.5 (11.58)	39.1 (11.51)	39.1 (12.49)	38.9 (11.84)
Median	40.0	39.0	39.0	39.0
Min, Max	18, 64	18, 64	18, 66	18, 66
Sex, n (%)				
Male	59 (48.0)	51 (41.8)	54 (44.6)	164 (44.8)
Female	64 (52.0)	71 (58.2)	67 (55.4)	202 (55.2)

Reviewer Comment: There are more females than males randomized in the study by a margin of approximately 10%. The enrollment of males and females across treatment arms is balanced.

Epilepsy and Treatment History

Table 8 Study 804P301 Subject Epilepsy History- Duration of Epilepsy (years) by treatment arm

Epilepsy History- Duration of Epilepsy (years) by treatment arm				
	SPN-804O 2400mg/day (N=123)	SPN-804O 1200mg/day (N=122)	Placebo (N=121)	Total (N=366)
n	121	121	121	363
Mean (SD)	19.8 (12.96)	21.3 (14.47)	21.2 (13.91)	20.8 (13.77)
Median	19.1	19.8	19.7	19.5
Min, Max	0.3, 55.1	0.2, 55.4	0.3, 52.2	0.2, 55.4

Reviewer Comment: Mean and median subject duration of epilepsy is very close across treatment arms

Table 9 Study 804P301 Subject Seizure type by treatment arm

Occurrence of Seizure type by treatment arm				
	SPN-804O 2400mg/day (N=123)	SPN-804O 1200mg/day (N=122)	Placebo (N=121)	Total (N=366)
Simple partial seizures	44 (35.8)	37 (30.3)	45 (37.2)	126 (34.4)
Complex partial seizures	93 (75.6)	90 (73.8)	94 (77.7)	277 (75.7)
Secondarily generalized seizures	62 (50.4)	60 (49.2)	58 (47.9)	180 (49.2)
Other	7 (5.7)	9 (7.4)	10 (8.3)	26 (7.1)

Reviewer Comment: The predominant seizure type is complex partial seizures. All seizure types are balanced in distribution across treatment arms.

Table 10 Study 804P301 Subject Number of AEDs by Treatment Arm

Number of AEDs by treatment arm				
	SPN-804O 2400mg/day (N=123)	SPN-804O 1200mg/day (N=122)	Placebo (N=121)	Total (N=366)
1 AED	40 (32.5)	36 (29.5)	43 (35.5)	119 (32.5)
2 AEDs	67 (54.5)	68 (55.7)	61 (50.4)	196 (53.6)
3 AEDs	15 (12.2)	18 (14.8)	17 (14.0)	50 (13.7)
4 AEDs	1 (0.8)	0	0	1 (0.3)

Reviewer Comment: Number of AEDs is acceptably balanced across treatment arms,

Table 11 Study 804P301, Concomitant AEDs by Treatment Arm

	SPN-804O 2400mg/day (N=123)	SPN-804O 1200mg/day (N=122)	Placebo (N=121)	Total (N=366)	Max difference between treatment arms
Carbamazepine	49 (39.8)	53 (43.4)	44 (36.4)	146 (39.9)	1200mg – PBO = 7%

	SPN-804O 2400mg/day (N=123)	SPN-804O 1200mg/day (N=122)	Placebo (N=121)	Total (N=366)	Max difference between treatment arms
Valproate[a]	62 (50.4)	55 (45.1)	49 (37.2)	166 (45.4)	2400mg – PBO = 13.2%
Phenytoin	2 (1.6)	3 (2.5)	4 (3.3)	9 (2.4)	PBO – 2400mg = 1.6%
Lamotrigine	34 (27.6)	31 (25.4)	37 (30.6)	102 (27.9)	PBO – 1200mg = 5.2%
Levetiracetam[b]	28 (22.8)	20 (16.4)	27 (22.3)	75 (20.5)	2400mg – 1200mmg = 6.4%
Topiramate[b]	23 (18.7)	23 (18.8)	21 (17.3)	67 (18.3)	1200mg – PBO = 1.5%
Other[b]	18 (14.6)	29 (23.8)	26 (21.5)	73 (19.9)	1200mg – 2400mg = 7.2%

Reviewer Comment: The maximum difference between treatment arms for an AED is noted for VPA where the 2400mg treatment group has a 13.2% excess of VPA treatment compared to placebo. The second largest difference occurs in the "other' category with 7.2% between the 1200mg and 2400mg treatment arms. Overall most notable is the increase in VPA in the2400mg arm compared to PBO. It is uncertain if this over representation of VPA in the 2400mg group has an impact on the study endpoint.

Table 12 Study 804P301 Baseline Seizure Frequency (# episodes / 28 days) by Treatment Arm

Baseline Seizure Frequency (number of episodes / 28 days by treatment arm				
	SPN-804O 2400mg/day (N=123)	SPN-804O 1200mg/day (N=122)	Placebo (N=121)	Total (N=366)
Mean (SD)	37.4 (190.24)	18.5 (48.41)	13.0 (27.55)	23.1 (115.04)
Median	6	6	7	6.5
Min, Max	1.5, 2005.8	1.5, 462.2	2.2, 284.5	1.5, 2005.8

Reviewer Comment: The mean baseline seizure frequency is greatest in the 2400mg treatment arm; however this is driven by two outlier patients, one with a 28 day baseline seizure count of 2006 and a second with a count of 612. The median 28 day baseline seizure frequency is very similar between groups.

Table 13 Study 804P301, Subject Randomization by Country and Region

Patient Randomization by Country and Region				
Country	**# subjects**	**% by country**	**Region**	**n (%) by region**
US	72	19%	USA & Canada	74 (20%)
Canada	2	1%		
Mexico	45	12%	Mexico	45 (12%)
Poland	55	15%	Eastern Europe & Russia	251 (68%)
Croatia	29	8%		
Romania	24	6%		
Bulgaria	53	14%		
Russia	90	24%		

Table 14 Study 804P301, Country listing by number of subjects contributed

Country	# subjects	% by country
Russia	90	24%
US	72	19%
Poland	55	15%
Bulgaria	53	14%
Mexico	45	12%
Croatia	29	8%
Romania	24	6%
Canada	2	1%

Reviewer Comment: Table 13 and Table 14 reveal that Russia contributes the largest proportion of subjects (90, 24%) to study 804P301 followed by the United States (72, 19%) and Poland (55, 15%). The majority of patients are from the Eastern Europe and Russia region. The 74 (20%) patient participation by the United States and Canada provide evidence of generalizability of the results to the US population.

6.1.3 Subject Disposition

Table 15 Study 804P301 Subject disposition

Study 804P301, patient disposition				
	Placebo	**OXC XR 1200mg/day**	**OXC XR 2400mg/day**	**Total**
Population				
Randomized Total*				369
Randomized	121 (33.1)	122 (33.4)	123 (33.6)	366
Safety	121 (33.1)	122 (33.4)	123 (33.6)	366
ITT+	121 (100)	122 (100)	123 (100)	366
Per Protocol (PP)**	99 (81.8)	88 (72.1)	80 (65)	267 (73)
Patient Disposition				
N (safety population)	121	122	123	366
Completed	95 (78.5)	82 (67.2)	71 (57.7)	248 (67.8)
Discontinued	26 (21.5)	40 (32.8)	52 (42.3)	118 (32.2)
Reason for Discontinuation				
Adverse event	10 (8.3)	18 (14.8)	37 (30.1)	65 (17.8)
Subject withdrew consent	6 (5.0)	10 (8.2)	11 (8.9)	27 (7.4)
Pregnancy	0	0	0	0
Death	0	0	0	0
Non-compliance	4 (3.3)	6 (4.9)	1 (0.8)	11 (3.0)
Protocol violation	1 (0.8)	1 (0.8)	0	2 (0.5)
Lost to follow up	2 (1.7)	5 (4.1)	1 (0.8)	8 (2.2)
Investigator decision	1 (0.8)	0	0	1 (0.3)
other	2 (1.7)	0	2 (1.6)	4 (1.1)

* Three subjects from site 115 were not included in the analysis due to suspect lack of data integrity
+All randomized subjects who received at least one dose of study drug and had Baseline Seizure diary data and at least one visit during the Treatment Phase
** ITT subjects who completed at least four weeks of the Maintenance Period without significant protocol deviations

Reviewer Comment: Table 15 reveals that Fifty two (42%) of the 2400mg arm discontinued treatment, 71% due to adverse effect and 40 patients (33%) discontinued in the 1200mg treatment arm, 45% of these due to adverse event.

The discontinuation rate due to adverse event for the low and high dose treatment arms combined is 23%, this rate is the same as the discontinuation rate due to adverse event reported in the reference drug label (Trileptal). In the Clinical Studies Experience, section 6.1 of the RLD label, for Adjunctive therapy/Monotherapy in Adults Previously Treated with other AEDs" the label notes "Approximately 23% of these 1537 adult patients discontinued treatment because of an adverse experience"

6.1.4 Analysis of Primary Endpoint(s)

In order to support the extended release dose form of oxcarbazepine a clinical trial to support efficacy and safety was needed in addition to reliance on agency approval of oxcarbazepine immediate release. This requirement was fulfilled by study 804P301, a multicenter, double blind, randomized, placebo controlled, three arm, parallel group study to evaluate the efficacy and safety of oxcarbazepine XR as adjunctive therapy in subjects with refractory partial seizures due to epilepsy on up to three concomitant antiepileptic medications. The primary endpoint of this study was the percentage change in seizure frequency per 28 day during the treatment phase relative to the baseline phase in the intention to treat population (ITT). This has been the accepted endpoint by the division for development of adjunctive anticonvulsant drugs (AEDs). Examination of the **placebo treatment arm** revealed a difference in median 28 day seizure frequency from baseline to treatment phase of 2.0 with a resultant percent change in median 28 day baseline to treatment phase seizure frequency of -28.7%, Table 16 .

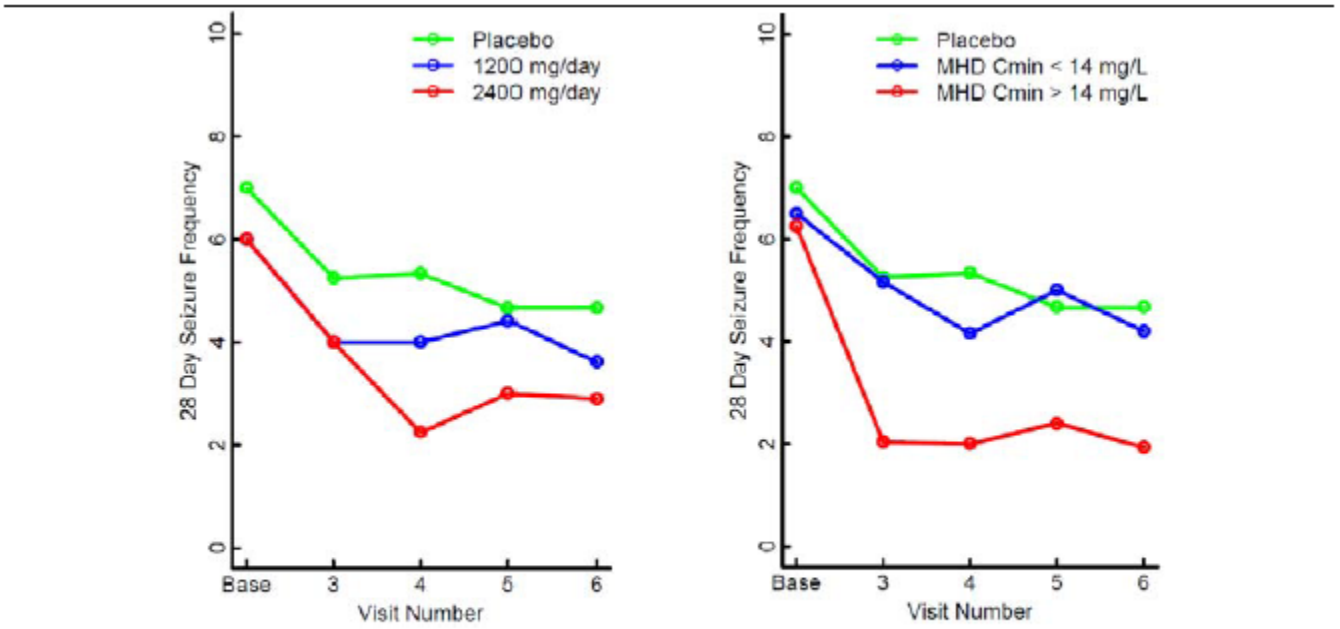
Examination of the **1200mg treatment arm** revealed a difference in median 28 day seizure frequency from baseline to treatment phase of 1.7 with a resultant percent change in median 28 day baseline to treatment phase seizure frequency of -38.2%. Examination of the difference in percent change in 28 day baseline to treatment phase seizure frequency between the 1200mg / day treatment arm and placebo revealed an effect size of 9.5% where the difference between groups has a significance of p=0.078 (Table 16).

Examination of the **2400mg treatment arm** revealed a difference in median 28 day seizure frequency from baseline to treatment phase of 2.3 with a resultant percent change in median 28 day baseline to treatment phase seizure frequency of -42.9%. Examination of the difference in percent change in 28 day baseline to treatment phase seizure frequency between the 2400mg / day treatment arm and placebo revealed an effect size of 14.2% where the difference between groups has a significance of p=0.003 (Table 16).

Table 16 Study 804P301 Primary Efficacy Results, ITT Population (sponsor table)

Statistics	Placebo (N=121)	SPN-804O 1200mg/day (N=122)	SPN-804O 2400mg/day (N=123)
n	117	109	111
Median baseline 28 day seizure frequency	7	6	6
Median treatment phase 28 day seizure frequency	5	4.3	3.7
Mean (SD)	-15.43 (67.34)	-29.14 (69.84)	-38.03 (53.11)
median	-28.7	-38.2	-42.9
Min, max	-100.0, 333.6	-100.0, 556.1	-100.0, 212.8
Effect size (median percent change treatment – placebo)	--	9.5%	14.2%
p value vs placebo*		0.078	0.003
* 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.			

Figure 4 Median 28 day seizure frequency at baseline and at each visit in the Treatment Phase



Data in the left panel are stratified by treatment group: placebo (n=121), green; 1200mg/day (n=122), blue; 2400mg/day (n=123), red. Data in the right panel are stratified by concentration group: placebo (n=121), green; Cmin < 14mg/L (n=84), blue; Cmin > 14mg/L (n=82), red.

Reviewer comment: The 2400mg dose separates from placebo with significance. The 1200mg dose does not significantly separate from placebo. There was a 28 day percent

seizure reduction of 42.9% in the 2400mg treatment group which had significant statistical separation from placebo. The effect size of both the 1200mg and 2400mg treatment arms was notably smaller than the effect size noted in the study of immediate release oxcarbazepine in adjunctive therapy trials[2]. This is due to a larger placebo group seizure reduction in the extended release study (804P301). It is noted that median percent seizure reduction from baseline to treatment for the placebo arm in study 804P301 was 28.7% compared to a 7.6% reduction in the adult adjunctive therapy trials of oxcarbazepine immediate release. This large placebo effect reduced the effect size of study 804P301.

6.1.5 Analysis of Secondary Endpoints(s)

Several secondary endpoints were explored in study 804P301 including the responder rate in the ITT population (Table 17). This represents the percentage of patients with a greater than 50% reduction in seizures compared to baseline.

Table 17 Study 804P301 Secondary Efficacy Endpoints

Statistics	SPN-804O 2400mg (N=123)	SPN-804O 1200mg (N=122)	Placebo (N=121)
Per Protocol Population			
PCH – Treatment Period			
n	80	88	99
Median	-43.95	-33.05	-30.30
p-value versus placebo[a]	*0.005*	*0.288*	
Hodges-Lehmann Estimate	-18.15	-6.40	
95% Confidence Interval	(-31.00, -5.60)	(-19.10, 6.00)	
ITT Population			
PCH – Maintenance Period Only			
n	123	122	121
Median	-49.15	-35.30	-32.90
p-value versus placebo[b]	*0.003*	*0.589*	
Hodges-Lehmann Estimate	-20.60	-3.30	
95% Confidence Interval	(-33.00, -6.30)	(-16.20, 9.70)	
Responder Rate – Treatment Phase			
n	123	122	121
Responder, n (%)	50 (40.7)	44 (36.1)	34 (28.1)
Non-responder, n (%)	61 (49.6)	65 (53.3)	83 (68.6)
p-value versus placebo[c]	*0.018*	*0.075*	
Odds Ratio	1.983	1.670	
95% Confidence Interval	(1.126, 3.494)	(0.950, 2.937)	
Seizure-Free Rates - Treatment Phase			
N	123	122	121
Subjects with valid diary data	111	109	117
Number (%) seizure free	14 (11.4)	6 (4.9)	4 (3.3)
p-value versus placebo[d]	*0.013*	*0.528*	

2 Trileptal Label, Revised 03/2011, page 22, section 14.2, Table 8.

Seizure-Free Rates - Maintenance Period Only			
N	123	122	121
Subjects with valid diary data	88	97	109
Number (%) seizure free	17 (13.8)	4 (3.3)	7 (5.8)
p-value versus placebo[d]	*0.008*	*0.546*	

[a]Wilcoxon rank-sum test of the median percentage change in partial seizure frequency per 28 days during the 16-week
Treatment Phase relative to the 8-week Baseline Phase.
[b]Wilcoxon rank-sum test of the median percentage change in partial seizure frequency per 28 days during the 8-week
Maintenance Period relative to the 8-week Baseline Phase
[c]P-value from logistic regression
[d]P-value from Fisher's exact test

Reviewer Comment: The secondary efficacy endpoints for the 2400mg treatment group are congruent with the findings in the primary endpoint. There is a statistically significant separation from placebo for the per protocol analysis of the 28 day percent seizure reduction in the treatment phase compared to baseline with a confidence interval that does not exceed zero. Similarly the percent seizure reduction, treatment phase responder rate, and seizure free rate during maintenance period also reveal significant separation from placebo for the 2400mg treatment group. The 1200mg group does not show a significant separation from placebo for any of these analyses. These findings reinforce those of the primary outcome endpoint analysis.

6.1.6 Other Endpoints

Subject Global Impression of Change (ITT Population)

This instrument utilizes a 7 point Likert scale which is the subjects self reported assessment of his/her epilepsy status compared to baseline. The subject is asked the following question regarding his or her condition: "How have you felt compared to before you started study medication?", The subject selects the response below that best describes his or her condition:

1. Very much improved
2. much improved
3. minimally improved
4 no change
5. minimally worse
6. much worse
7. very much worse

The Global Impression of Change revealed no difference between treatment groups as seen in Table 18.

Table 18 Study 804P301, Secondary Efficacy Results: Global Impression of Change, ITT population

Secondary Efficacy Results: Global Impression of Change, ITT Population							
	Treatment Group			p- value		Hodges-Lehmann Estimate and 95% CI	
Median Subject Global Impression of Change Score	OXC XR 2400mg/day (N=123)	OXC XR 1200mg/day (N=122)	Placebo (N=121)	OXC XR 2400mg/day vs. Placebo	OXC XR 1200mg/ day vs. Placebo	OXC XR 2400mg/day vs. Placebo	OXC XR 1200mg/day vs. Placebo
Visit 4	3.0	3.0	3.0	0.057	0.513	0.00 (-1.00, 0.00)	0.00 (0.00, 0.00)
Visit 6	2.0	3.0	3.0	0.087	0.301	0.00 (-1.00, 0.00)	0.00 (0.00, 0.00)
End of Study (Visit 7 or 9)	3.0	3.0	3.0	0.969	0.757	0.00 (0.00, 0.00)	0.00 (0.00, 0.00)

QOLIE-31

At Visits 2, 4, 6, 7, and 9 subjects completed the QOLIE-31, a survey of health-related quality of life for adults (18 years) with epilepsy, and contains seven multi-item scales: emotional well-being, social functioning, energy/fatigue, cognitive functioning, seizure worry, medication effects, and overall quality of life.

There was no difference from baseline in the QOLIE-31 overall quality of life measure at "End of Maintenance" or "End of Study" survey points between placebo and the oxcarbazepine XR treatment arms (1200mg & 2400mg) in the ITT population.

Secondary generalized seizure frequency: There was no significant difference from baseline to treatment in the median percent change in seizure frequency per 28 days in the ITT population.

6.1.7 Subpopulations

Pediatrics

Study 804P107 was performed to establish PK characteristics of oxcarbazepine XR in a population aged 4 to 17 years. The sponsor conducted analysis to determine if the typical values for systemic parameters obtained in adult patients could be applied to pediatric patients after scaling for body size.

The sponsor reports that the OXC analysis revealed that both weight normalized and allometric scaling yielded bias and required an additional scaling factor applied to clearance and apparent distribution clearance or to all systemic parameters. Once applied the scaling factor allowed fit of both allometric and weight normalized models.

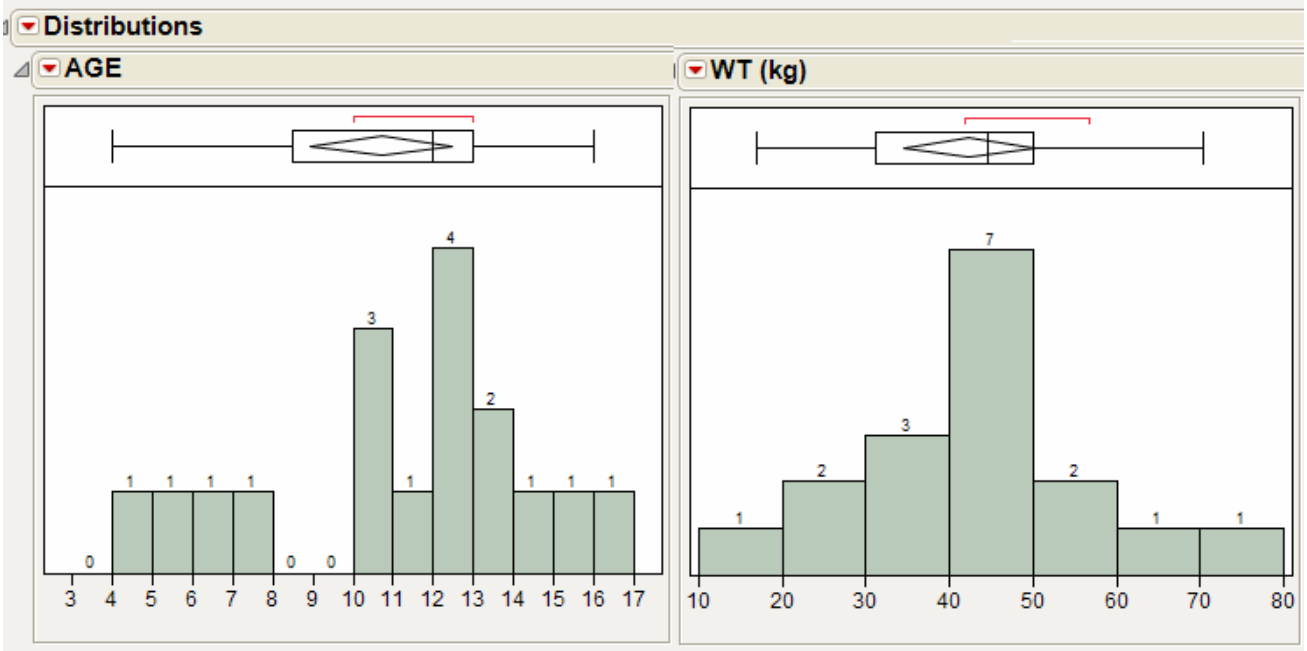
The sponsor reports that the MHD analysis revealed that weight normalized model for MHD did not require additional scaling. The weight normalization fit the data well and was preferred over the allometric model. The sponsor concludes that dosing of pediatric patients with OXC ER can be determined based on body weight. The weight based dosing in pediatric patients should produce MHD exposures (AUC) comparable to that in typical adults although these dosing regimens will produce OXC exposures approximately 40% higher than in adults.

The distribution of age, weight and body surface area (BSA) of the 17 patients who contributed to the analysis of study 804P107 is shown in Table 19 with a graphic representation of the distribution of age and weights. The mean and median ages are 10.7 years and 12 years respectively. The mean and median weights are 42.4kg and 44.5kg respectively. There is a skew in the sample toward children older than 8 years and heavier than 30kg. Figure 5 below provides a visual histogram of Table 19.

Table 19 Study 804P107 Age and Body metrics of Participants

	Age and body metrics of 17 patients contribution to analysis of 804P107			
	AGE (yr)	**WT (kg)**	**BSA (m^2)**	**Dose (mg)**
	4	17	0.7	150
	5	23.2	0.87	150
	6	20.5	0.81	150
	7	46.6	1.34	450
	10	30.9	1.06	300
	10	33.2	1.12	300
	10	31.3	1.1	300
	11	50.5	1.44	450
	12	46.5	1.44	450
	12	70.4	1.78	600
	12	41.9	1.36	300
	12	49.5	1.44	450
	13	44.5	1.41	300
	13	46.4	1.45	450
	14	56.8	1.61	450
	15	42.1	1.35	300
	16	69	1.71	600
mean	10.7	42.4	1.3	362
median	12	44.5	1.36	300

Figure 5 Histogram of Study 804P107 Subject Age & Weight



The comparability of adult Cmax and AUC at 600mg OXC ER to pediatric Cmax and AUC at 10mg/kg are shown in Table 20 for MHD and OXC. This cross study comparison of Cmax and AUC for OXC and MHD between the steady state data from Study 304P102 and 304P107 reveals the mean Cmax and AUC are notably lower for both OXC and MHD in the pediatric population at 10mg/kg compared to the adult means at 600mg/day.

Table 20 Cross Study 804P107 / 804P301, Pediatric to Adult Steady State Cmax & AUC for OXC and MHD moieties

Moiety	Pediatric, Study 804P107 -PK study report, Dose 10mg/kg, N=18*		Adult, Study 804P102 (Formulation CRe-M), N=18, Dose 600mg	
	Mean Cmax	Mean AUC 0-24	Mean Cmax (ng/ml)	Mean AUC 0-24 (ng.hr/ml)
OXC	571	5808	591	5271
MHD	8767	170616	11400	221278
* Cmax and AUC 0-24 are taken from sponsor tables 23 and 25. units which appear to be in error in tables 23 and 25 (pages 60 & 62 of study report) are corrected from ug to ng based on examination of sponsor figure 31 simulation of plasma concentration where Cmax can be seen to be in units of ng/ml.				

The relationship between weight and the exposure parameters Cmax and AUC reveals a decreasing trendline for OXC and an increasing trendline for MHD. This appears to indicate an uneven exposure across the spectrum of pediatric weights. Based on weight

alone the lower weight pediatric subjects have MHD under treatment whereas the higher weight subjects achieve exposures similar to adults, Figure 7.

Figure 6 Study 804P107, OXC Trendlines for Cmax and AUC vs Weight

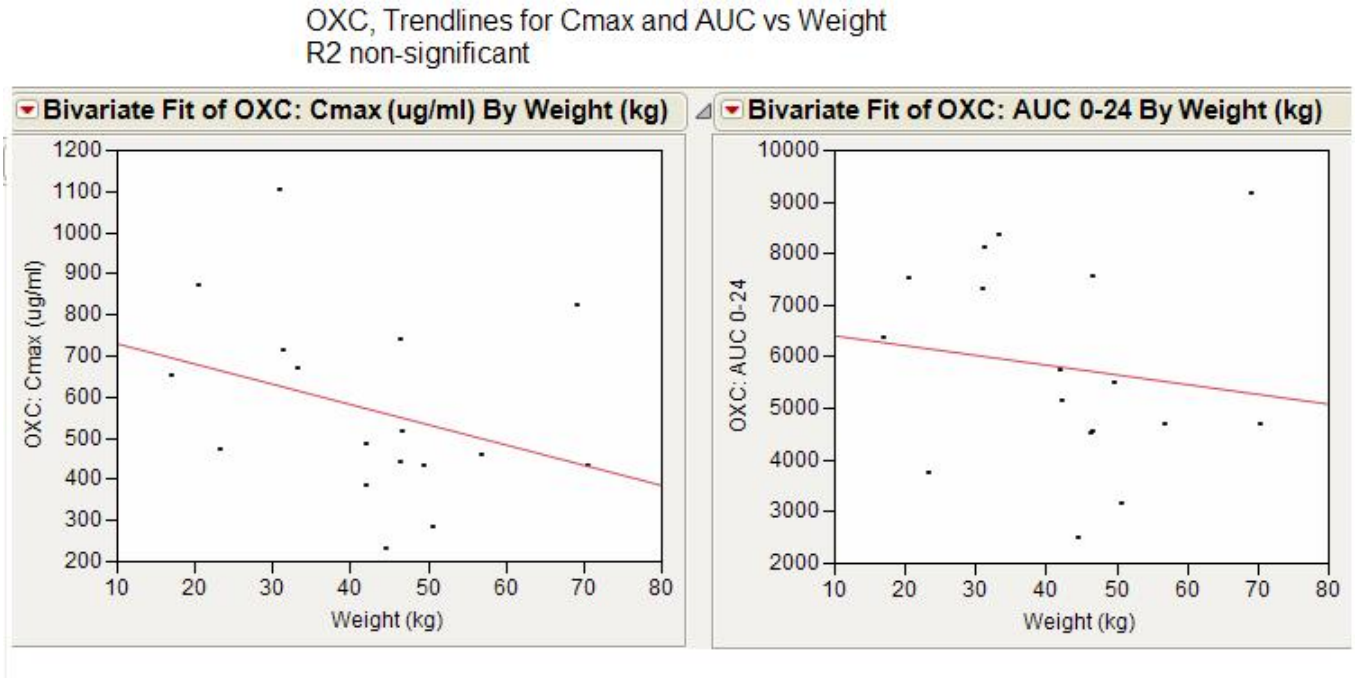
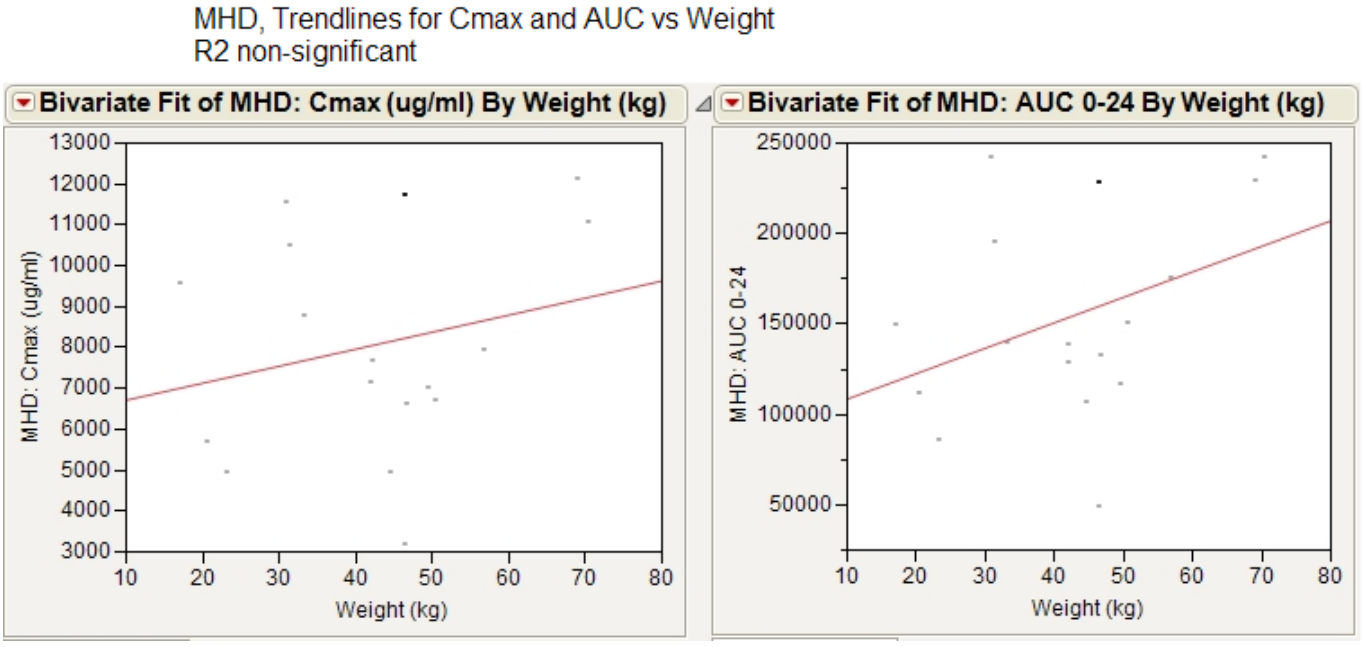


Figure 7 Study 804P107, MHD Trendlines for Cmax and AUC vs Weight



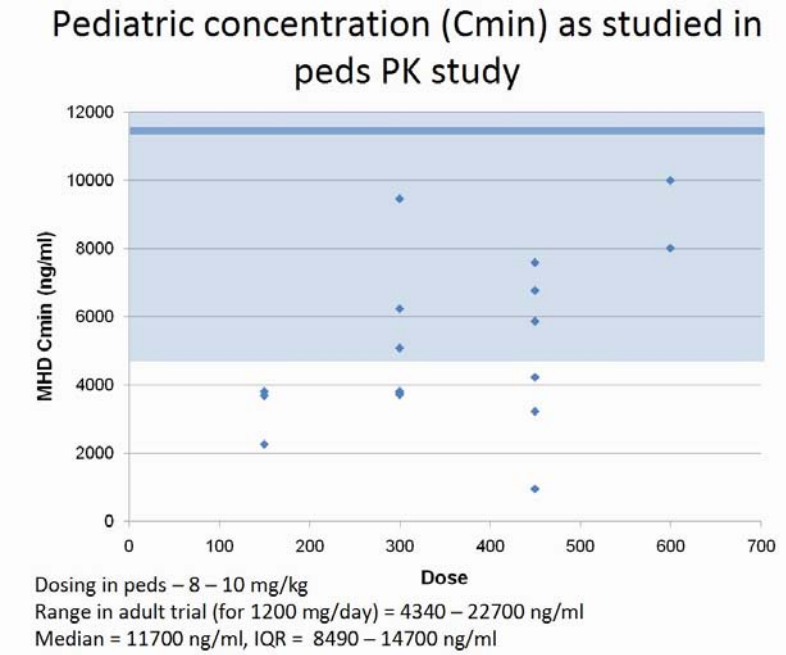
RLD Pediatric dosing: Trileptal, oxcarbazepine IR, has labeling for adjunctive treatment of partial seizures in the age range 2 to 16 years and initial monotherapy in the age range 4 to 16 years. Both have a weight based dose recommendation beginning at 8-10mg/kg/day.

Sponsor conclusion from study 804P107 (final paragraph, p 43- study report body): 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. In addition, daily doses used in the present study, 8-10 mg/kg, are smaller than the daily doses of OXC ER studied in the phase 3 study 804P301 (1200 and 2400 mg; approximately 17 and 34 mg/kg for a typical 70-kg adult).

Proposed labeling: there is a recommendation to start dosing at 8-10mg/ kg daily with target maintenance dose achieved by increases not greater than 600mg/week. However the proposed labeling does not provide guidance for target maintenance dose. The Clinical Pharmacology team presents an argument that a population PK model suggests that weight-based dosing would yield comparable MHD exposures to that found in the adult population.

Clinical Pharmacology: the clinical pharmacology reviewer has examined the pediatric Cmin from study 804P107 and found a portion of the patients achieve Cmin below the range achieved by those in the adult study, see Figure 8. The clinical pharmacology team recommends scaling the weight based dose to achieve adult Cmin concentration by creating a weight based nomogram.

Figure 8 Clinical Pharmacology Analysis, Pediatric (804P107) compared to Adult (804P301) Cmin



Reviewer Comment: Proposed labeling provides no direction on target maintenance does for adjunctive therapy in pediatric treatment. Based on an examination of the PK data from study 804P107 there is a trend to achieve adult range AUC and Cmax for MHD only in the approximately 70kg weight range when dosing at 10mg/kg/day while the clinical pharmacology analysis reveals that a portion of subject have MHD Cmin below any achieved by adult patient. After deliberation, the review team found an acceptable path forward which was proposed by the Clinical Pharmacology team. This solution is a weight based nomogram designed to yield a target pediatric maintenance dose which will achieve adult range $C_{min,}$ see section 4.4 and Table 4.

6.1.8 Analysis of Clinical Information Relevant to Dosing Recommendations

Food Effect

The food effect study examined the impact of a standard high fat breakfast on PK parameters of a single 600mg dose of SPN-804O. This study revealed that in the fed state there was a 63% increase Cmax and 2 hour shorter Tmax. The full spectrum of PK parameters in the fed and fasting state of study 804P105 as well as the PK parameters for the immediate release (RLD) from study 804P101 are shown in Table 21 and Table 22 below.

Table 21 Immediate Release OXC (804P101) Compared to Fed and Fasting OXC XR (804P105) Cmax, Tmax AUC_{0-t}

	IR study 804P101 (300mg Q12)			XR Study 804P105 (Fed) (600mg single dose)			XR Study 804P105 (Fasting) (600mg single dose)		
	Cmax (ng/ml)	Tmax (hr)	AUC 0-t (ng.hr/ml)	Cmax (ng/ml)	Tmax (hr)	AUC 0-t (ng.hr/ml)	Cmax (ng/ml)	Tmax (hr)	AUC 0-t (ng.hr/ml)
OXC	829	13.75	4848	1409	6.74	6776	507	4.58	5233
MHD	6131	16.4	165220	7914	9.66	188503	4926	12.1	167493
Values for IR from study 804P101 (table 2.1). Values for Fed / Fasting from study 804P105 (table 11.2.1.3:1)									

Table 22 PK Parameters, Cmax and AUC. Fed Compared to Fasting and Fed Compared to Immediate Release (IR), Difference Between Fed and Fasting and Fed / IR expressed as Percent Increase

	Fed parameter compared to Fasting (within study)		**Fed Parameters compared to IR (cross study)**	
	% Cmax : [(Fed – Fast)/fast] *100	**% AUC** [(Fed – Fast)/fast] *100	**% Cmax**: [(Fed – IR)/IR] *100	**% AUC** [(Fed – IR)/IR] *100
OXC	177	24.5	70	40
MHD	61	12.5	29	14
Values for IR from study 804P101 (table 2.1). Values for Fed / Fasting from study 804P105 (table 11.2.1.3:1)				

Reviewer Comment: the MHD values for study drug oxcarbazepine XR when taken in the fed state approximate the immediate release formulation with an earlier Tmax. This result is observed when the values from the food effect study (804P105) are compared to the values for the RLD observed in study 804P101. This phenomenon may produce peak level toxic adverse effects in patients who have accommodated to the lower Cmax of the fasting state. Labeling should reflect this possibility.

Figure 9 Study 804P301, 28 day Seizure Frequency at Each Visit by Treatment Arm

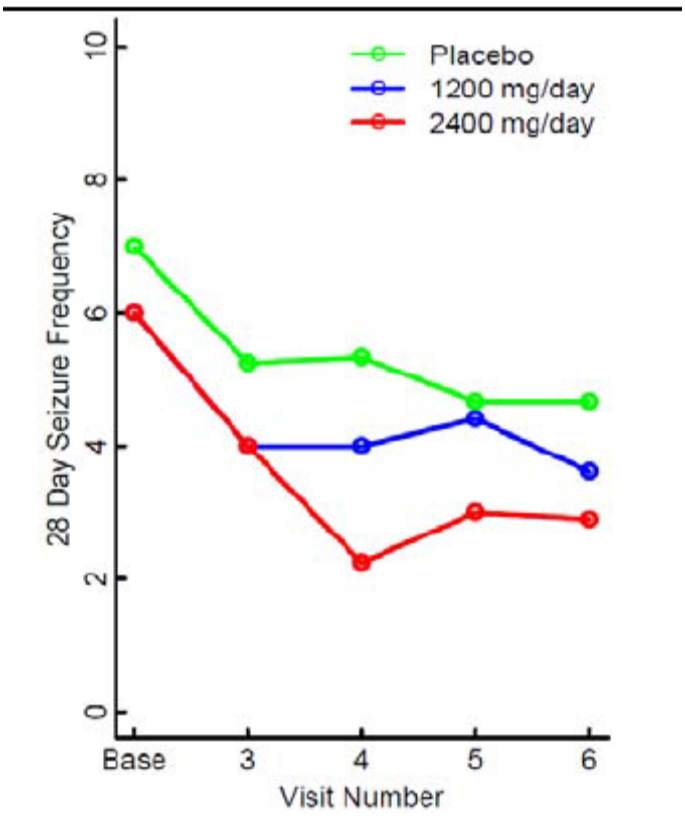


Figure 9 above illustrates the median 28 day seizure frequency at baseline and each treatment phase visit. This graphic reveals that at visit 5 there is no separation from placebo in the 1200mg/day dose group and only small separation from placebo at visit 6. This is commensurate with the outcome of the study (804P301) where there was significant separation from placebo for the 2400mg / day group only.

Reviewer Comment: The observation of significant separation from placebo for the 1200mg / day group in the North American subset of the study cohort provides support for a meaningful clinical effect of the 1200mg /day which may serve as the low end of treatment range in labeling.

6.1.9 Discussion of Persistence of Efficacy and/or Tolerance Effects

Clinical Pharmacology labeling in the RLD section 12.2 indicates “No development of tolerance (i.e., attenuation of anticonvulsive activity) was observed in the maximal electroshock test when mice and rats were treated daily for five days and four weeks, respectively, with oxcarbazepine or MHD.

6.1.10 Additional Efficacy Issues/Analyses

505(b)(2) Bridge to RLD and labeling window (1200mg to 2400mg)

Clinical study 804P301 is an adequate and well controlled clinical trial to support the efficacy of 2400mg daily dose of oxcarbazepine XR for the adjunctive treatment of partial seizures. The results are presented in primary endpoints, section 6.1.4. This study also provided PK data to evaluate exposure response which is discussed below. The primary endpoint did not achieve significant separation from placebo in the overall study for the 1200mg dose. A post-hoc examination for significant efficacy by region revealed the North American sub-population to have a much larger effect size compared to the total study effect size which conveys significant separation from placebo for both the 2400mg and 1200mg dose, Table 23.

Table 23 Primary Endpoint Analysis by Regional Clusters

Primary variable analysis by regional clusters							
	Treatment Group PCH (N)			**p-value (vs Placebo)**		**Hodges-Lehman Estimate and 95% CI**	
Cluster	**SPN-8040**						
	2400mg	**1200mg**	**PBO**	**2400mg**	**1200mg**	**2400mg**	**1200mg**
North America	***-52.6 (35)***	***-34.5 (40)***	***-13.3 (41)***	***0.006***	***0.022***	***-35.25 -59.1, -12.5***	***-26.10 -47.9, -4.1***
US/Canada	-52.0 (20)	-34.5 (24)	-13.3 (27)	0.044	0.140	-30.00 -65.3, -2.5	-18.70 -46.0, 10.0
Mexico	-53.3 (15)	-45.6 (16)	-6.7 (14)	0.076	0.085	-48.50 -85.9, 2.5	-39.75- 81.7, 8.2
All Other	***-41.2 (88)***	***-38.4 (82)***	***-33.2 (80)***	***0.130***	***0.596***	***-9.55 -24.0, 2.9***	***-3.70 -17.3, 10.3***
Poland	-50.0 (25)	-35.2 (16)	-49.5 (13)	0.882	0.584	2.00 -27.6, 33.9	11.55 -17.3 ,35.5
Croatia/ Romania/ Bulgaria	-44.5 (35)	-40.0 (35)	-47.4 (36)	0.536	0.390	-6.70 -29.4, 14.0	8.65 -13.3, 31.4
Russia	-39.3 (38)	-43.4 (31)	-18.9 (31)	0.082	0.053	-15.10 -37.2, 2.7	-20.80 -41.7, 0.80

Steady State Bioequivalence

This 505(b)(2) application is based on a single efficacy trial of an established active pharmaceutical ingredient (oxcarbazepine) of the reference listed product (RLD)

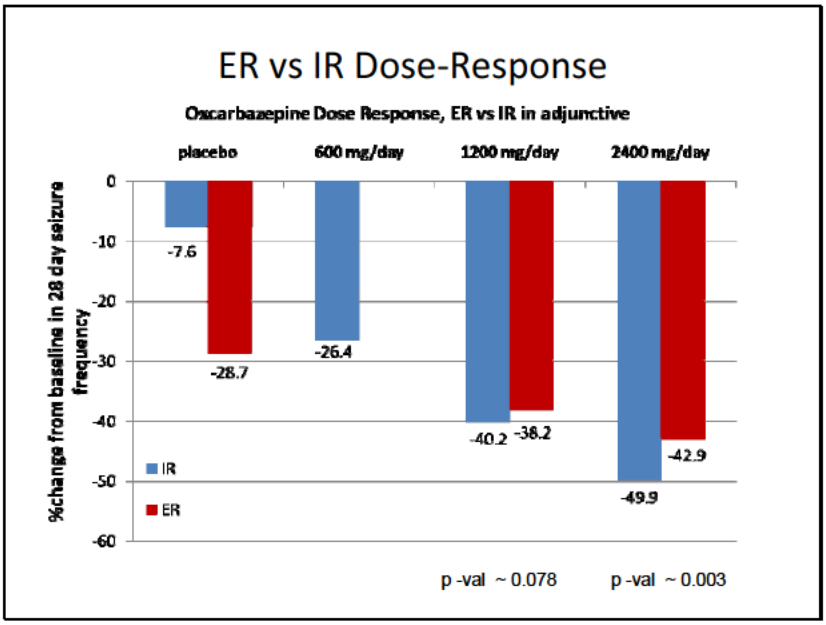
Trileptal. The bridge between this extended release formulation oxcarbazepine and the RLD is a single efficacy trial of the new formulation and a steady state bioavailability study comparing the new formulation to Trileptal. The results of the clinical trial (804P301) have been discussed in the preceding sections. The bioavailability at steady state analysis reveals the results for the oxcarbazepine and MHD moiety fall outside of bioequivalence limits. The results are shown in Table 24 below.

Table 24 ANOVA of PK metrics MHD and OXC in Plasma (steady state, Day 13)

Results of ANOVA on Pharmacokinetic Metrics of MHD and OXC in Plasma* (steady state, day 13)		
	Ratios of LSM and 90% Confidence Intervals*	
Pharmacokinetic metrics	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%)
$C_{max,ss}$	80.8% (77.0 – 84.9%)	38.6% (33.3 – 44.8%)
$C_{min,ss}$	83.7% (78.8 – 88.9%)	104.2% (91.5 – 118.6%)
*Table 3, P12 (synopsis) study 804P103- Single Center, Multiple Dose, Open Label, Randomized, 2-Treatment Crossover Study to Compare a Daily Administration of Oxcarbazepine Extended-Release (OXC XR) Tablet and a Twice a Day Administration of Trileptal® Tablets in Health Adult Volunteers under Fasting Conditions.		

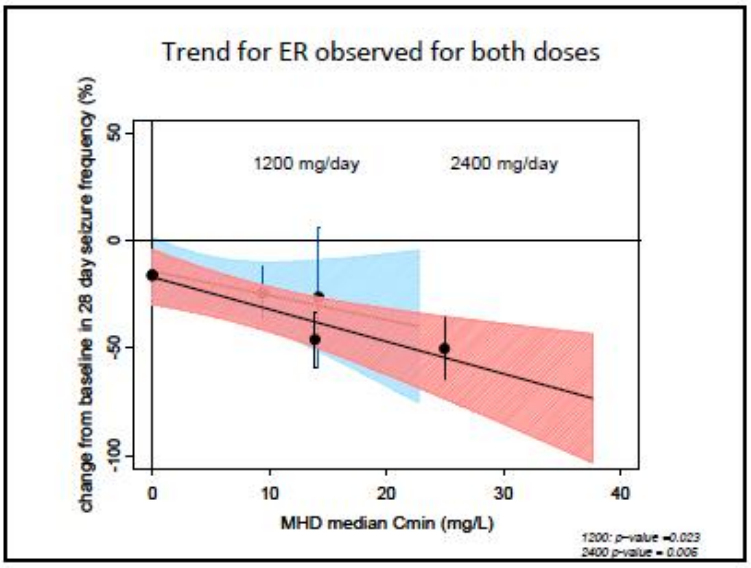
Dose response: The dose response for oxcarbazepine XR is similar at the 1200mg and 2400mg dose to that seen in the oxcarbazepine IR study with the IR study showing a 2.6% and 16% larger response respectively. The placebo response in the IR and XR studies is quite different with a 277% larger placebo response in the XR study, Figure 10 below. This observation supports the proposition that the large placebo response in trial 804P301 contributed to the lack of 1200mg dose significance.

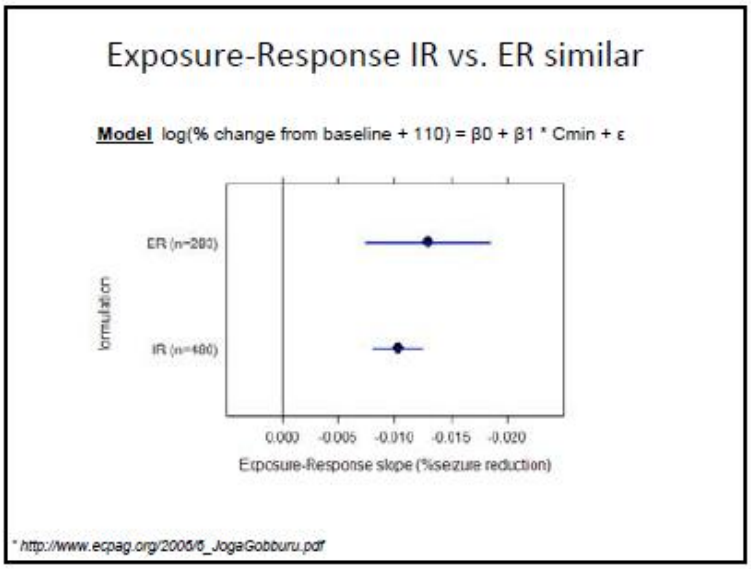
Figure 10, ER vs IR Dose – Response Bar Chart comparison, Clin-Pharm Review



Exposure response: the clinical pharmacology team examined exposure response of the 1200mg and 2400mg dose groups for Cmin. Figure 11 below reveals similar slopes for both fit lines with a significant exposure – response correlation for both. This observation indicates that the floor of exposure achieved for the XR formulation delivers a reduction in seizure frequency through the continuum from the 1200mg dose to the 2400mg dose. The mean of the slopes of the exposure response of the IR formulation are found to be similar. The CI for the XR formulation are wider, which may be due to the smaller sample size, however all but a very small fraction of the CI of the XR formulation falls below (larger negative slope) the CI of the IR formulation, Figure 11 below. This analysis supports labeling the range from 1200mg to a target of 2400mg.

Figure 11 Clinical Pharmacology Analysis, Study 804P301- Exposure Response by Treatment. / Exposure - Response IR vs ER by slope





Reviewer Comment: The study drug, oxcarbazepine XR formulation, fell short of AUC bioequivalence at steady state for both the MHD and oxcarbazepine moieties. The MHD moiety is the most clinically meaningful because it is the primary circulating product. Clinical study 804P301 identified efficacy for the 2400mg but not the 1200mg dose of oxcarbazepine XR. Examination of study results by region revealed a notably high placebo response in Poland, Romania, Croatia, and Bulgaria with no significant separation from placebo for 1200mg or 2400mg treatment arm. The North American region had a more typical placebo response and a significant separation from placebo in both the 1200mg and 2400mg treatment arms. This post hoc analysis lends some support to effectiveness of 1200mg dose. Utility of the 1200mg dose is further supported by subsequent analysis by the clinical pharmacology reviewers who examined exposure response of the 1200mg and 2400mg dose groups as well as the dose response and exposure response relationships of the XR formulations compared to the IR formulations. The exposure response analysis indicates a continuum of

exposure response for Cmin from the 1200mg group through the 2400mg group with significant correlation between exposure and treatment effect for both dose groups. The dose response of the oxcarbazepine IR study is found to be similar to that of the XR study with the placebo response showing a large divergence between the two studies, much larger in the XR study. The slopes of the exposure response trends of the XR study are found to be similarly negative to the IR study.

Summary Comment: overall the profile of clinical study results, post hoc analysis of regional variation in the study and exposure response analysis provide and adequate bridge from the reference product and support inclusion of 1200mg as the low side of a 1200mg to 2400mg treatment window in labeling, see section 9.2, labeling recommendations.

7 Review of Safety

Safety Summary

Safety Summary

The oxcarbazepine XR development program was comprised of seven pharmacokinetic studies in healthy adults which were performed to establish dose linearity, proportionality, food effect, single-dose and steady-state pharmacokinetics and bioavailability compared to the immediate-release formulation. A single Phase 3, double-blind, randomized, placebo-controlled study was conducted in 369 subjects with refractory epilepsy; 214 of these subjects also enrolled in the ongoing open-label follow-on study. Eighteen pediatric subjects with epilepsy were given SPN-804O for two weeks in a study of PK parameters.

Exposure to this oxcarbazepine XR formulation is examined by pooling all studies, including healthy volunteer studies. This analysis reveals that 206 subjects have exposure greater than 3 months and less than 6 months and 109 subjects have exposure for an interval greater than 9 months and less than 12 months with a total of 289 patient years of exposure. The exposures do not reach the guidelines set in ICH E1, however SPN-804O is a new formulation of an established API. The primary risk of the new formulation is expected to be carried by the API and explored in the reference product. The exposures identified for SPN-804O appear adequate for the circumstance of a new formulation.

The routine clinical testing during the pivotal trial 804P301 was appropriate for this drug. The sponsor obtained a full profile of hematologic and biochemistry parameters at baseline and periodically through the study. There was also baseline and periodic monitoring of physical and neurologic exam. Vital signs and ECG studies were performed on a regular basis. Overall there clinical and laboratory safety monitoring was adequate.

The metabolic clearance and interaction evaluation reveals 2% of the parent API in circulation and 70% of the parent is circulating as the mon-hydroxy metabolite (MHD) which is the primary anticonvulsant moiety of this drug. The MHD has a Tmax of 4.5 hours, T1/2 of 9 hours and reaches steady state plasma concentrations in 2-3 days. Oxcarbazepine has a t1/2 of 2 hours. The volume of distribution is 49 L.

Examination of major safety results reveals there were no deaths in the phase 1 development program. There was one death in study 804P301 however this patient was diagnosed with ovarian cancer 2 days after entering the study. A second death occurred in the open label follow on study. This event occurred 147 days after the patient began taking his open label dose of oxcarbazepine XR. The cause of death is unclear but may have been due to complications of status epilepticus although this is speculative.

Examination of non fatal serious adverse events reveals the occurrence of all serious adverse events (SAEs) from combined oxcarbazepine XR (OXC XR) treatment arms were 1% in excess of placebo. The occurrence of SAEs in the 1200mg treatment arm was equal to placebo, 7% SAEs in each, while the 2400mg treatment arm had an occurrence of SAEs in 10% of the group which was 3% greater than placebo. The most frequent SAEs were injury (4), followed by ischemic stroke (2) and drug intolerance (2). The occurrence of ischemic stroke stands out as somewhat unusual. In both patients there was pre-existing cerebrovascular disease, both cases occurred in Romania, in the second case there was temporal relation with onset of drug treatment (the event occurred in titration phase). In summary, concerning these two stroke events, there is insufficient evidence to support causality, there is treatment association only, no clear explanatory mechanism, both are confounded by evidence of pre-existing cerebrovascular disease, there is temporal association in one case only and in both events the patients were maintained on study drug. Overall the profile of SAEs in the controlled and open label extension data do not suggest a signal for new safety events which are not seen in the oxcarbazepine IR label.

Discontinuations due to adverse events are seen to be maximum for the 2400mg treatment arm with an occurrence in 30% of the group, while 16.4% of the 1200mg treatment arm discontinued due to an adverse event. The AE related discontinuation rate of the 1200mg treatment arm exceeds placebo by only 4% while the 2400mg arm exceeds the placebo arm by 17.6%. The reference drug label (Trileptal) indicates a discontinuation rate from subjects in all Trileptal adjunctive and monotherapy adult trials of 23%. This number is not fully comparable since it is a pooled multiple study discontinuation rate and not from a single similar study. Nonetheless it provides a framework for expectations and it is almost identical to the combined discontinuation due to adverse events from both OXC XR treatment arms (1200mg & 2400mg) of study 804P301which is seen to be 23%.

There are submission specific primary safety concerns based on the known safety profile of the reference drug. These items are suicidality (class effect), serious skin reaction rash, and hyponatremia. The adverse event dataset did not reveal a profile of

SAEs in these categories in excess of placebo treatment in the double blind interval of 804P301.

Common adverse events (non-SAE) from all system organ class “es” (SOCs) occurred in 69% of the 2400mg treatment group, 57% of the 1200mg treatment group and 55% of the placebo group. Adverse events were seen most commonly in the “Nervous System Disorders” and “Gastrointestinal Disorders” SOCs. The most common adverse event (AE) seen was dizziness followed by somnolence, this pattern was found in all treatment arms. Dizziness, somnolence, headache, vomiting, and asthenia were dose related. This profile of adverse events was similar to that seen in the reference drug (Trileptal) labeling in section 6.1, clinical studies.

Review of laboratory data is divided into “hematology” and “clinical chemistry”. The hematology review examined change from baseline, outlier profile, and shift tables. The change from baseline focus was directed to “change from baseline –high” or “change from baseline- low” according to the know risk profile of the parameter under examination. The shift analysis was directed similarly. These analyses were performed for hemoglobin, white blood cell (WBC) count, absolute lymphocyte count, and platelet count, Taken together the results of the analysis of notable change from baseline, outlier analysis and shift analysis do not indicate a need to strengthen or add to proposed labeling (derived from reference drug) for hematopoietic events.

Clinical chemistry analysis examined change from baseline, outlier profile, and shift tables. The change from baseline focus was directed to “change from baseline –high” or “change from baseline- low” according to the know risk profile of the parameter under examination. The shift analysis was directed similarly. These analyses were performed for ALT, AST, total bilirubin, urea nitrogen, CO2, creatinine, potassium, and sodium. Only examination of sodium values revealed a conclusive signal for induction of hyponatremia associated with OXC XR treatment. This safety signal is presently addressed in section 5.1, “Warnings and Precautions” of the reference drug and proposed oxcarbazepine XR labeling.

Vital sign examination included blood pressure and body temperature. The examination of body temperature revealed a small negative shift in the body temperature in the 2400mg group. This observation does not appear to be clinically meaningful based on the magnitude of the change and examination of adverse effects in the 2400mg group, however current Trileptal labeling does note a decrease in T_4, unrelated to clinical hypothyroidism. The observed decline in body temperature, although subtle, raises the possibility of a connection with the observed depression of T4 in current Trileptal labeling. The observed body temperature change in the oxcarbazepine XR treatment groups in this application support a need for continued pharmacovigilance of this issue.

Electrocardiogram (ECG) examination is performed on the QT interval, heart rate, PR interval, QRS interval, and reveals no signal for treatment associated adverse effect on the electrocardiogram.

Immunogenicity of this small molecule agent is not seen as in development of antibodies, however current Trileptal labeling contains warning for “Anaphylactic Reactions and Angioedema”, “Serious Dermatological Reactions”, and “Multi-Organ Hypersensitivity”. These reactions are dysimmune disorders which may be induced by oxcarbazepine.

Dose dependency of AEs is seen when all events for all SOCs are combined. Dose dependency for AEs of the “Nervous System Disorders” SOC is also noted. There is also clear time dependency for adverse events. The frequency of AEs from all SOCs is high during titration then decreases during the maintenance interval. There were on average four times (4x) as many AEs during each 10 day interval of titration phase compare to the average of any 10 day blocked occurrence rate of AEs during the maintenance phase, see Figure 15 and Figure 16.

Analysis of drug demographic interaction reveals a trend of AEs to increase with rise in patient age for all SOCs, see Figure 17. Drug – sex interaction reveals a small excess of AEs in females compared to males for all SOCs. The frequency of adverse events for all SOCs is noticeably greater in patients of Hispanic origin than white subjects but there are insufficient numbers of other ethnic / racial groups for meaningful comparison. A drug- drug interaction analysis which examined AEs according to top ten concomitant medications did not reveal a spike in adverse events which differed notably from the overall profile of AEs seen with OXC-XR.

Examination of the adverse events, laboratory datasets, vital sign datasets and ECG datasets of pediatric PK study 804P107 did not reveals evidence of a risk profile which differs from the reference product, overall no new safety signal is identified in the pediatric population.

In conclusion the safety analysis of OXC-XR development did not reveal a significant divergence from the safety profile of the reference drug label.

7.1 Methods

All available safety datasets studies listed in the table of clinical studies are evaluated for the safety. Datasets are not submitted for ongoing trials 804P302 and 804P303 so the narrative information present in the ISS are the data source for these studies, this is also true for the 120 day safety update. Dataset pooling was not requested at the Pre-NDA meetings so the datasets of the healthy human subjects of the phase 1 studies and the Phase 3 clinical trial are reviewed separately.

7.1.1 Studies/Clinical Trials Used to Evaluate Safety

Studies from the panel of phase 1 investigations and the single phase 3 pivotal efficacy and safety study are used for evaluation of safety.

7.1.2 Categorization of Adverse Events

In Table 25 below the dataset columns for verbatim terms are compared to the preferred term to check for splitting of adverse event splitting.

Table 25 Evaluation of Verbatim Term / Preferred Term for Evidence of Category Splitting

Study	MedDRA version	Evaluation for verbatim to MedDRA splitting	Total subjects	Study type	Duration / exposure
804P101	9.0	30 adverse events occurred among 10 patients. There was no evidence of splitting safety terms in the transition from verbatim to MedDRA coding	16	Four-way crossover, single administration in healthy adults. Relative bioavailability of different OXC CR formulation prototypes and Trileptal ®	16 subjects each had 3 individual doses of an XR formulation. Total 16 subjects x 1800mg (3 doses) of an XR form.
804P102	9.1	101 adverse events among 17 patients. There was no evidence of splitting safety terms in the transition from verbatim to MedDRA coding	R-21 C-18	Three-way crossover, multiple dose administration in healthy adults. Steady-state PK of two different OXC CR prototypes vs Trileptal	20 subjects received 600mg XR for 7 days, 18 of these received 600mg XR (different formulation) for 7 days. Approximates 18 subject x 14 days of XR (but 2 different formulations)
804P103	10.1	There were 349 adverse events listed among 32 patients. There was no evidence of splitting safety terms in the transition from verbatim to MedDRA coding	R-32 C-28	Two-way crossover, multiple dose administration in healthy adults. Steady-state relative bioavailability	Total = 13 days a. 7 days titration to 1200mg b. 7 days 1200mg maintained
804P104	9.1	157 adverse events among 42 patients. There was no evidence of splitting safety terms in the transition from verbatim to MedDRA coding	R-54 C-53	Three-way crossover, single-dose administration in healthy adults. Dose proportionality	50 patients (approximate) received 3 dosages of OXC XR, 1 formulation XR, 600mg, delivered as 3 different dose strengths. This represents final choice of XR formulation. Longest duration exposure 19 days
804P104.5	Not found	52 adverse events among 27 patients.	R-54	Three-way crossover, single	53 patients each

Study	MedDRA version	Evaluation for verbatim to MedDRA splitting	Total subjects	Study type	Duration / exposure
		The dataset had no entries for MedDRA terms.	C-53	dose administration in healthy adults. Dose linearity.	exposed to 3 doses of OXC XR delivered as a single dose of 150mg, 300mg and 600mg, thus each total exposure was 1050mg. The exposure occurred over a 14 day interval.
804P105	11.0	32 adverse events among 15 patients. There was no evidence of splitting safety terms in the transition from verbatim to MedDRA coding	R-62 C-59	Two-way crossover, single administration in healthy adults. Food Effect	59 subjects received 2 single dosages of OXC ER during an interval of 10 days. Thus total exposure of 1200mg over 10 days.
804P107	11.0	There were 4 adverse events among 3 patients	R-18 C-18	Multicenter, open-label, multiple dose administration in pediatric patients. Steady state pharmacokinetics.	Pediatric patients with epilepsy, 18 patients, a 7 day treatment, dose based on weight.
804p109 (available at 120 day update)		Dataset unavailable, AEs available only in group summary of all phase 1 studies	18 patients anticipated in provided synopsis	This is a two-center, single-dose, open-label, parallel-group PK study of 600mg OXC XR administered to two populations of healthy subjects, young adults (Group 1 at Center 1) and elderly (Group 2 at Center 2).	
804P301	11.1	There were 827 adverse events listed in the study 804P301 dataset among 226 patients. The verbatim and PTs (preferred terms) for this study were examined. There was no evidence of splitting safety terms in the transition from verbatim to MedDRA coding	R-369 C-248	Multicenter, double-blind, placebo-controlled, three-arm, parallel group in adult patients. Efficacy and Safety	

7.1.3 Pooling of Data Across Studies/Clinical Trials to Estimate and Compare Incidence

This NDA submission was comprised of a single pivotal clinical trial with a follow up open label extension. The 120 day safety update contains a table of pooled adverse effects of the placebo controlled study and the available open label extension adverse event data.

7.2 Adequacy of Safety Assessments

7.2.1 Overall Exposure at Appropriate Doses/Durations and Demographics of Target Populations

Oxcarbazepine is not a new molecular entity rather a new formulation of an established active pharmaceutical ingredient. Oxcarbazepine was first approved as Trileptal on January 14, 2000. The current submission is a 505(b)(2) referencing the Trileptal New Drug Application 021014 [oxcarbazepine oral tablet (Novartis)]. It is implicit that the ICH E1 population exposure guidelines were achieved in the reference application.

Safety exposure requirements for change in formulation / excepient: The bulk of risk is considered to be carried by the API. There are no clear guidelines for appropriate exposures of new formulations of an established API.

A single Phase 3 efficacy study (Study 804P301) of SPN-804O as adjunctive treatment of seizures in adults with refractory epilepsy was conducted. A total of 369 patients were enrolled at 88 sites in eight countries; one site (three patients) was not included in the analysis due to suspected lack of integrity of the data. After four weeks titration and 12 weeks maintenance therapy, patients who qualified were given the option to enroll in the open-label follow-on study, Study 804P302, for up to one year. A total of 214 enrolled in the follow-on study, which allowed modification of SPN-804O dosing from 600- 2400mg/day.

The demographics of the target population may be seen in section 6.1.2 above.

7.2.2 Explorations for Dose Response

In the pivotal trial there was a maximum exposure to all doses of 123 patients for a duration of greater than 3 months and less than 6 months (>3, ≤6 months). In this same trial there were 31451 patient days of exposure with 15293 patient days

of exposure at 1200mg and 6334 patient days of exposure at 2400mg. Patients at each dose and number of subject days are shown in Table 26.

Table 26 Study 804P301 Subject Exposure by Dose and Duration in Weeks and Days

804P301	600	1200	1800	2400	Total*
Total N =332					
<= 1 wk	280	53	30	18	*381*
>1w, ≤1m	29	168	61	22	*280*
>1m, ≤3m	18	27	12	35	*92*
>3, ≤6m	5	76	10	32	*123*
>6, ≤9m		1			1
Total subjects	332	325	114	107	*878*
Total subject days	4136	15293	5688	6334	31451
Mean	12.5	47.1	24.9	59.2	
SD	18.11	49.23	29.67	41.59	
Median	7	22	14	89	
Min	2	1	1	1	
Max	121	183	105	166	
Total subject years	11.33	41.90	15.58	17.35	86.17

Exposure is pooled for the double blind and open label extension studies 804P301 and 804P302 – completed p6 ISS, 120 day safety update. This analysis reveals 107 patients achieved an exposure for an interval greater than 6 months but less than 9 months (>9, ≤ 12 months). 8 patients had an exposure greater than 1 year. There were 101828 total patient days of exposure with 9434 of these at 2400mg and 51800 at 1200mg. Patients at each dose and number of subject days are shown in Table 27.

Table 27 Pooled Exposure, Studies 804P301- 804P302 by Dose and Duration in Weeks / Days

Subjects at each dose								
301 and 302	600	900	1200	1500	1800	2100	2400	Total*
N=215								
<= 1 wk	378	29	56	9	34	4	21	*531*
>1w, ≤1m	62	5	201	7	70	2	22	*369*

Subjects at each dose								
301 and 302	**600**	**900**	**1200**	**1500**	**1800**	**2100**	**2400**	**Total***
>1m, ≤3m	25	6	90	17	27	8	37	*210*
>3, ≤6m	10	1	98	18	32	4	41	*204*
>6, ≤9m	4	2	14	14	11	3	6	*54*
>9m, ≤12m	12	8	70	3	12	1	1	*107*
>12m, ≤18m	0	0	8	0	0	0	0	*8*
>18m, ≤24m	0	0	0	0	0	0	0	
>24m, ≤36m	0	0	0	0	0	0	0	
>36m	0	0	0	0	0	0	0	
Total subjects	491	51	537	68	187	22	128	
Days at each dose								
Total subject days	11047	3784	51800	7504	16114	2145	9434	101828
Mean	22.50	74.20	96.46	110.35	86.17	97.50	73.70	
SD	91.90	115.95	140.22	91.97	102.28	92.90	90.69	
Median	7	7	103	91	123	83	156	
Min	3	7	1	1	1	1	3	
Max	354	318	394	353	334	323	343	
Total subject years	30.27	10.37	141.92	20.56	44.15	5.88	25.85	278.98
* contains duplicate subjects								

Exposure is pooled for all studies, including healthy volunteer studies. This analysis reveals that 206 subjects have exposure greater than 3 months and less than 6 months and 109 subjects have exposure for an interval greater than 9 months and less than 12 months with a total of 289 patient years of exposure. Patients at each dose and number of subject days are shown in Table 28.

Table 28 Pooled Exposure of All Adult Studies- Healthy Volunteer, 804P301 and 804P302 by Dose and Weeks

	Number of subjects at each dose												
All subjects, N=623	**150**	**300**	**450**	**600**	**750**	**900**	**1050**	**1200**	**1500**	**1800**	**2100**	**2400**	**TOTALS***
<= 1 wk	52	52	1	630	0	60	1	86	9	34	4	21	*950*
>1w, <1m	6	8	7	83	1	5	0	201	7	70	2	22	*412*
>1m, <3m	0	0	1	25	1	6	0	91	17	27	8	37	*213*

	Number of subjects at each dose												
All subjects, N=623	**150**	**300**	**450**	**600**	**750**	**900**	**1050**	**1200**	**1500**	**1800**	**2100**	**2400**	**TOTALS***
>3, <6m	0	0	1	10	0	1	0	99	18	32	4	41	*206*
>6, <9m	0	0	1	4	0	3	0	14	14	11	3	6	*56*
>9m, <12m	0	0	1	13	0	8	0	70	3	12	1	1	*109*
>12m, <18m	0	1	0	0	0	1	0	8	0	0	0	0	*10*
>18m, <24m	0	0	0	0	0	0	0	0	0	0	0	0	*0*
>24m, <36m	0	0	0	0	0	0	0	0	0	0	0	0	*0*
>36m	0	0	0	0	0	0	0	0	0	0	0	0	*0*
Totals*	*58*	*61*	*12*	*765*	*2*	*84*	*1*	*569*	*68*	*186*	*22*	*128*	
	Number of days at each dose												**TOTAL**
Total subject days	123	503	848	12149	52	4471	7	52118	7504	16114	2145	9434	105468
Total subject years	0.34	1.38	2.32	33.28	0.14	12.25	0.02	142.79	20.56	44.15	5.88	25.85	288.95
* contains duplicate subjects													

Reviewer Comment: The exposures do not reach the guidelines set in ICH E1, however SPN-804O is a new formulation of an established API. The primary risk of the new formulation is expected to be carried by the API and explored in the reference product. The exposures identified for SPN-804O appear adequate for the circumstance of a new formulation.

7.2.3 Special Animal and/or In Vitro Testing

none

7.2.4 Routine Clinical Testing

Study 804P301

This study is the pivotal clinical trial to examine efficacy and safety. In review, it has a 16 week titration plus maintenance period with a 3 week tapering / conversion to open label period.

In this study routine clinical testing included the following (see Table 29 to map study visits to week):

1. Physical examination performed at screening (visit 1) and end of study (visit 7 or 9)

2. Neurologic examination performed at screening (visit 1), baseline (visit 2), visit 6, 8 and end of study (visit 7 or 9).

3. Vital Signs: are obtained at screening then at each visit. Blood pressure and heart rate were measured with subjects in a seated position for five minutes unless supine due to study related event such as an AE of nausea or dizziness or if deemed necessary by the investigator.

4. 12 lead ECG: ECG was obtained at screening (visit 1), visit 3, visit 6, end of study.

5. Hematology / biochemistry (
Table 30): these laboratory studies were obtained at screening (visit 1), visit 2, visit 6, end of study (visit 7).

Table 29 Study 804P301 Procedure / Visit timeline key

Period	Screening	Titration	Maintenance			Tapering or conversion		Additional tapering	
Visit #	1	2	3	4	5	6	7	8	9
Day	-1 through -28 or -56	1	29	57	85	113	134 / end of study	134	141
Weeks		1	4	8	12	16	19		

Table 30 Study 804P301 hematology / biochemistry parameters obtained

HEMATOLOGY	BIOCHEMISTRY
NEUTROPHILS ABSOLUTE	CHLORIDE
LYMPHOCYTES ABSOLUTE	GLUCOSE, FAST SERUM
MONOCYTES ABSOLUTE	CREATININE
EOSINOPHILS ABSOLUTE	CALCIUM
BASOPHILS ABSOLUTE	ALBUMIN
NEUTROPHIL, SEGS	BILIRUBIN, TOTAL
LYMPHOCYTES	BILIRUBIN, DIRECT
MONOCYTES	LACTIC DEHYDROGENASE
EOSINOPHILS	GLOBULIN
BASOPHILS	ASAT (SGOT)
HEMATOCRIT	ALAT (SGPT)
HEMOGLOBIN	POTASSIUM
PLATELET COUNT	ALKALINE PHOSPHATASE
RED CELL COUNT	SODIUM
WHITE CELL COUNT	CARBON DIOXIDE (CO2)
	PHOSPHORUS INORGANIC

	PROTEIN, TOTAL SERUM
	URIC ACID
	UREA NITROGEN

Reviewer Comment: the content and frequency of the clinical testing through the course of the trial was appropriate for the known risks of oxcarbazepine.

7.2.5 Metabolic, Clearance, and Interaction Workup

This 505(b)(2) New Drug Application references the Trileptal® New Drug Application 021014 [oxcarbazepine oral tablet (Novartis)] and Trileptal® New Drug Application 021285 [oxcarbazepine oral suspension (Novartis)], although no suspension formulation is present in this application.

Brief summary of Reference product (immediate release) label:

> **Pharmacokinetics**: oxcarbazepine is completely absorbed and extensively metabolized to its pharmacologically active 10-monohydroxy metabolite (MHD). In a mass balance study in people, only 2% of total radioactivity in plasma was due to unchanged oxcarbazepine, wit approximately 70% present as MHD, and the remainder attributable to minor metabolites.
>
> **Absorption**: After single-dose administration of Trileptal tablets to healthy male volunteers under fasted conditions, the median tmax was 4.5 (range 3 to 13) hours. Steady-state plasma concentrations of MHD are reached within 2-3 days in patients when Trileptal is given twice a day. At steady state the pharmacokinetics of MHD are linear and show dose proportionality over the dose range of 300 to 2400 mg/day.
>
> Effect of Food: Food has no effect on the rate and extent of absorption of oxcarbazepine from Trileptal tablets. Although not directly studied, the oral bioavailability of the Trileptal suspension is unlikely to be affected under fed conditions. Therefore, Trileptal tablets and suspension can be taken with or without food.
>
> **Distribution:**
>
> The apparent volume of distribution of MHD is 49L.
>
> Approximately 40% of MHD is bound to serum proteins, predominantly to albumin. Binding is independent of the serum concentration within the therapeutically relevant range. Oxcarbazepine and MHD do not bind to alpha-1-acid glycoprotein.
>
> **Metabolism and Excretion:**

Oxcarbazepine is rapidly reduced by cytosolic enzymes in the liver to its 10-monohydroxy metabolite, MHD, which is primarily responsible for the pharmacological effect of Trileptal. MHD is metabolized further by conjugation with glucouronic acid. Minor amounts (4% of the dose) are oxidized to the pharmacologically inactive 10,11- dihydroxy metabolite (DHD).

Oxcarbazepine is cleared from the body mostly in the form of metabolites which are predominantly excreted by the kidneys. More than 95% of the dose appears in the urine, with less than 1% as unchanged oxcarbazepine. Fecal excretion accounts for less than 4% of the administered dose. Approximately 80% of the dose is excreted in the urine either as glucuronides or 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 he parent is about two hours, while the half-life of MHD is about nine hours.

SPN-804O (oxcarbazepine extended release)

Pharmacokinetics: after SPN-804O traverses the absorption phase of pharmacokinetics the distribution, metabolism and excretion of the active pharmaceutical ingredient, oxcarbazepine, must exhibit the properties of the reference product noted above.

Absorption (SPN-804O): following single dose administration of SPN-804O, peak plasma concentrations for oxcarbazepine are observed between 4 and 5 hours post dose, while peak plasma concentrations of MHD are observed between 11 and 13 hours post dose. When SPN-804O was administered as a single 150mg, 300mg, and 600mg oral dose under fasting conditions, the Cmax of MHD increased in proportion to the dose. However, the AUC of MHD increased approximately 2.4-fold with a 2-fold increase in dose

Single dose administration of 600mg SPN-804O following a high-fat meal produced overall MHD exposure (plasma AUC) equivalent to that produced under fasting conditions (804P105). Peak plasma concentrations (Cmax) of MHD, however, were ***63% higher and occurred 2 hours earlier*** under fed conditions than under fasting conditions.

7.2.6 Evaluation for Potential Adverse Events for Similar Drugs in Drug Class

The adverse event profile is expected to be the same as the reference product. There may be some attenuation of adverse events related to the Cmax of SPN-804O (in fasting state) due to the lower Cmax of the extended release formulation.

7.3 Major Safety Results

7.3.1 Deaths

Healthy Adult subjects, phase 1 studies: in six completed pharmacokinetic studies there were no deaths.

Studies 804P301 and 804P302: one death occurred in each study.

Study 804P301 subject 707003 was diagnosed with ovarian cancer (b) (6) days after randomization into the study. The patient had multiple metastases and died within (b) (6) weeks of diagnosis.

Study 804P302 five months after beginning treatment in the open label study, subject 815009 a 33 yo male patient from a Russian site, assigned to the 1200mg / day treatment arm in the controlled trial. The patient was in the open label extension on 1800mg/day when, after (b) (6) days of treatment in the open label trial, a change in mental status was noted. The patient's relative (uncle) informed the investigator that a change in mental status had developed. The patient was subsequently hospitalized with a diagnosis of "Encephalopathy of mixes genesis, state after multiple seizures". The patient died (b) (6) days later with cause of death listed after autopsy as bilateral pulmonary thromboemboli.

Reviewer Comment: The death in study 804P301 is unrelated to study drug. The death in study 804P302 is of uncertain relationship. The history of "multiple seizures" may have been an interval of status epilepticus which if severe could result in disseminated intravascular coagulation and pulmonary embolism. This is speculative but provides a possible link between an epileptiform event and cause of death. Status epilepticus may have occurred as a precedent event to death, nonetheless the relationship to study drug remains uncertain.

7.3.2 Nonfatal Serious Adverse Events

Healthy Adult subjects, phase 1 studies: in six completed pharmacokinetic studies there were no SAEs.

Clinical Trials:

Study 804P301: There were 20 serious adverse events in those treated with SPN-804O and 8 serious adverse events in placebo treated patients. The number and percent of SAEs in each treatment arm are shown in Table 31.

Table 31 Study 804P301 Patients by treatment arm with any SAE

Study 804P301 Patients by treatment arm with any SAE				
	SPN-804O 2400mg/day (N=123)	**SPN-804O 1200mg/day (N=122)**	**All SPN-804O Treatment (N=245)**	**Placebo (N=121)**
SAE	12 (10%)	8 (7%)	20 (8%)	8 (7%)

The occurrence of SAEs by preferred term and treatment arm reveals that the only hepatic related SAE occurred in the placebo treatment arm while 7 events occurred in 7 preferred terms in the 1200mg arm and 12 events occurred in 10 preferred terms in the 2400mg treatment arm. These are shown in Table 32.

Table 32 Occurrence of Serious Adverse Events by Treatment Arm

Occurrence of Serious Adverse Events by Treatment Arm

2400		1200		PBO	
Preferred Term	**# Events**	**Preferred Term**	**# Events**	**Preferred Term**	**# Events**
DRUG INTOLERANCE	2	ACUTE MYOCARDIAL INFARCTION	1	ALANINE AMINOTRANSFERASE INCREASED	1
ISCHAEMIC STROKE	2	HEAD INJURY	1	ASPARTATE AMINOTRANSFERASE INCREASED	1
ARTHROPOD BITE	1	PITYRIASIS ROSEA	1	BLOOD LACTATE DEHYDROGENASE INCREASED	1
CONVULSION	1	POSTICTAL STATE	1	COMPLEX PARTIAL SEIZURES	1
DIZZINESS	1	SKIN LACERATION	1	DEEP VEIN THROMBOSIS	1
HYPONATRAEMIA	1	SKULL FRACTURED BASE	1	DEHYDRATION	1
NYSTAGMUS	1	STATUS EPILEPTICUS	1	DIZZINESS	1
PITUITARY TUMOUR BENIGN	1			GASTROENTERITIS	1
RASH GENERALISED	1			OVARIAN CANCER	1
VOMITING	1			RASH ERYTHEMATOUS	1
				STEVENS-JOHNSON SYNDROME	1
Totals	**12**		**7**		**11**

In Table 33 all SAEs from the 1200mg and 2400mg treatment arms are summed and compared to the occurrence in placebo.

Table 33 804P301 Serious Adverse events, All OXC XR treatment arms vs Placebo

804P301 Serious Adverse events, All OXC XR treatment arms vs Placebo				
	RX (1200 / 2400mg)		Placebo	
Preferred term	**N**	**%**	**N**	**%**
Acute Myocardial Infarction	1	0.4	0	0
Convulsions / CP seizure	1	0.4	0	0
Dehydration	0	0	1	0.8
Dizziness	1	0.4	1	0.8
Drug intolerance	2	0.8	0	0
Deep venous thrombosis	0	0	1	0.8
Gastroenteritis	0	0	1	0.8
Hyponatraemia	1	0.4	0	0
injury	4	1.6	0	0
ischemic stroke, 603008, 606004	2	0.8	0	0
LFT increase	0	0	1	0.8
neoplasm	1	0.4	1	0.8
Nystagmus	1	0.4	0	0
Post ictal state	1	0.4	0	0
Rash	2	0.8	1	0.8
Status epilepticus	1	0.4	1	0.8
Steven-Johnson Syndrome	0	0	1	0.8
Vomiting	1	0.4	0	0
Total	**19**		**9**	

Reviewer Comment: The SAE by preferred term shown in Table 33 reveals an unusual occurrence of two events of ischemic stroke. Both cases occurred in Romania at two different sites. Case 606004 was a 52 year old female with a past medical history of stroke and a dislipidemia. The patient experienced sudden onset right hemiplegia and language disorder (b) (6) days after beginning study medication. The patient was hospitalized for (b) (6) days but maintained on study medication. The degree of resolution of the hemiplegia and language disorder is not provided in detail. It is reported that on (b) (6) the event resolved and patient was discharged. The second case, 603008, occurred in a 64 year old mail with a history of atherosclerotic disease and a transient ischemic attack 1 year before study entry. The patient suffered symptoms of a posterior circulation ischemic event (b) (6) days after beginning study medication. The patient was hospitalized for (b) (6) days and discharged after “favorable resolution of symptoms” In both cases there was a preexisting history of cerebrovascular disease. In case 606004 there

is not a compelling temporal relationship between initiation of study drug treatment and onset of stroke. This is not likely related to oxcarbazepine XR. In case 603008 there is a temporal relationship between cerebrovascular event and onset of study drug treatment, however there is also pre-existing cerebrovascular disease. This occurrence of cerebrovascular events in a study of this size, in the same country is unusual but there is insufficient data to suggest a signal for cerebrovascular risk related to this oxcarbazepine XR formulation.

Reviewer Comment Overall SAEs 804P301: The serious adverse event (SAE) occurrence for combined OXC-XR treatment arms of study 804P301 was 1% greater than the placebo rate while the 1200mg treatment arm was equal to placebo and the 2400mg treatment arm was 2% greater than placebo, see Table 31. The adverse event profile within study 804P301 does not indicate a signal of unexpected excess SAEs over the placebo group.

Studies 804P301 and 804P302:

At the 120 day safety update there were 38 serious adverse events reported from the double blind and open label studies combined. This represents an additional 6 serious adverse events which occurred during the interval since initial submission. The SAE tables from the initial submission and 120 day update (paper tables, xpt datasets not provided) are examined for number of events in submission specific categories of hyponatremia, seizures / convulsions, serious skin reactions, suicidality and bone marrow suppression. Adverse events occurring in the 120 day update interval are also examined. This analysis reveals a sum of 7 epilepsy term events, one event of hyponatremia, no serious skin reactions, one suicidality event, and no bone marrow related events. There were six new events in the 120 day update interval. One event of cholangitis, 1 gastroenteritis, 1 new epilepsy related preferred term, 1 humerus fracture, 1 event of nephrolithiasis and one event of non- cardiac chest pain. The analysis can be seen in Table 34.

Table 34 Serious Adverse Events from Pooled Studies 804P301 & 804P302 at 120 day Safety Update

Analysis Table; SAE from initial submission and 120 day update								
	Initial NDA Submission			120 day update	Update minus initial	Comment, negative Δ from initial count	Change from initial submission PT's to more specific PT in 120 day update	Negative delta original categories (initial submission PTs)
Preferred Term (PT)	804P301	804P302	sum 301 + 302	301 / 302 combined	Δ			
Group sum	**19**	**13**	**32**	**38**	**6**			
AMI	1		1	1	0			
arthropod bite			0	1	1		1	injury
Ataxia		1	1	1	0			
cholangitis			0	1	1			
Convulsions / CP seizure	1	4	5	2	-3	3 shift to alt MedDRA terms		
Dizziness	1		1	1	0			
Drug intolerance	2		2	2	0			
DVT		1	1	1	0			
Encephalopathys		1	1	1	0			
Epilepsy			0	2	2		2	Convulsions / CP
Gastroenteritis			0	1	1			
Grand mal convulsion			0	2	2		1	Convulsions / CP, 3 redistributed, 1 new
head injury			0	1	1		1	injury
humerus fx			0	1	1			
Hyponatraemia	1		1	1	0			
hypothermia		1	1	1	0			
injury	4	1	5	0	-5	5 shift to alt MedDRA terms		
ischemic stroke	2		2	2	0			
neoplasm	1		1	0	-1	1 shift to alt MedDRA term		
nephrolithiasis			0	1	1			
non-cardiac chest pain			0	1	1			
Nystagmus	1		1	1	0			
pituitary tumor			0	1	1		1	neoplasm
Pityriasis rosea			0	1	1		1	Rash

Analysis Table; SAE from initial submission and 120 day update								
	Initial NDA Submission			120 day update	Update minus initial	Comment, negative Δ from initial count	Change from initial submission PT's to more specific PT in 120 day update	Negative delta original categories (initial submission PTs)
Preferred Term (PT)	804P301	804P302	sum 301 + 302	301 / 302 combined	Δ			
Post ictal state	1		1	1	0			
PSA increase		1	1	1	0			
Pyelonephritis		1	1	1	0			
Rash		2	2	0	-2	2 shift to alternate MedDRA terms		
Rash generalized			0	1	1		1	Rash
skin laceration			0	1	1		1	injury
skull fx base			0	1	1		1	injury
spinal fx			0	1	1		1	injury
Status epilepticus	1		1	1	0			
Suicidal behavior		1	1	1	0			
TIA		1	1	1	0			
Vomiting	1		1	1	0			
Total	19	13		38	6	11	11	

Reviewer Comment: There are 6 new serious adverse events added at the 120 day update, these originate from the open label extension study 804P302. These events were two "Grand mal convulsions", 1 "injury", 1 "nephrolithiasis", 1 "non-cardiac chest pain", and 1 "gastroenteritis". These events do not indicate emergence of a new safety signal.

SAE Narrative reports review, study 804P302:

Table 35 Study 804P302, 120 day Safety Update- Analysis of Relatedness to Study Drug Based on Narrative Report

SAE	Report term	comment
103-002	hypothermia	Patient in 2400mg arm developed hypothermia (94.3 F) after (b)(6) months on study drug. No sepsis identified. Study drug temporarily stopped then restarted at 1200mg day, Negative rechallenge. Unrelated
107-001	fall , spine fx	unrelated
110-003	oxcarbazepine toxicity	unrelated, occurred on stable dose
118-001	TIA	unrelated, on stable Rx for seven months
122-022	Increased seizure activity	on stable dose study medication for 8 months, also correlated with reduction titration of Vimpat. unrelated
143-005	prostatitis, hyperplasia	unrelated
170-002	Kidney stones	unrelated, 5 mo stable dose
172-004	grand mal seizure	grand mal seizure on stable dose of 1200mg/day
177-003 narrative #1	non cardiac chest pain	unrelated
177-003 narrative #2	non cardiac chest pain	unrelated
312-006	seizure worsening, several tonic - clonic seizures	Insufficient data does not provided.
312-012	seizure worsening, possibly non-compliance with concomitant medication, inappropriate supply of study medication	insufficient data
510-005	suicidal behavior	suicidal on maintenance phase. class labeling
801-011	worsening seizure	medication non-compliance
815-009 (consolidation of 2 AE reports)	pulmonary emboli	Death, status epilepticus? Possible relationship
816-004 narrative #1	pyelonephritis	on stable dose
816-004 narrative #2	pyelonephritis	stable dose, unrelated

The narrative reports of SAEs from 804P302 are reviewed (Table 35). There are 17 reports from 15 patients which yielded 19 adverse events. Review reveals that in 10 of the 15 patients the event was unrelated to the oxcarbazepine XR. In two of the five remaining reports there was insufficient data for determination of relatedness. In one of the remaining 3 cases the event was suicidal behavior which is currently part of class labeling. There are two remaining reports, one is a case of a grand mal seizure where cause is undetermined and the final is an SAE - death due to pulmonary embolus possibly preceded by status epilepticus. The latter two cases fall in the category of seizure worsening; however the controlled study data does not suggest a signal for seizure worsening or pro-convulsant potential.

Reviewer Comment: the analysis of SAE occurrence reveals only a 3% increase over the placebo rate for the 2400mg arm of study 804P301. In addition the occurrence of SAEs is 1% greater for the sum of all treatment arms of study 804P301 compared to placebo. There was an unusual occurrence of two ischemic strokes in the Romanian treatment population; however these events do not rise to the level of evidence that suggests a safety signal for cerebrovascular events. Overall the profile of SAEs in the controlled study do not reveal a notable increase over the occurrence of SAEs seen in the placebo treatment arm.

7.3.3 Dropouts and/or Discontinuations

Healthy Adult subjects, phase 1 studies: Five subjects in two studies discontinued due to adverse events:
Study 804P104.5 Subject number 42 received the first two treatments, dose 1 was 300mg, dose 2 600mg, this patient experienced mild dermatitis the day following the second treatment and discontinued. The event resolved within two days.

Study 804P103: two subjects discontinued from the study due to experiencing moderate hyponatremia after receiving SPN804O (Subject 10) and OXC IR (Subject 28). Two other subjects discontinued due to the occurrence of a papular rash after receiving SPN-804O (Subject 21) and OXC IR (Subject 18).

Study 804P301

Table 36 Study 804P301 Subject Discontinuation by Cause and Treatment Arm

Study discontinuation, by cause and treatment group				
	SPN-804O 2400mg/day (N=123)	**SPN-804O 1200mg/day (N=122)**	**All SPN-804O Treatment (N=245)**	**Placebo (N=121)**
Reason for discontinuation				
Adverse Event	37	18	55	10
Lost to follow-up	1	5	6	2
Non-compliance	1	6	7	4

Study discontinuation, by cause and treatment group				
	SPN-804O 2400mg/day (N=123)	**SPN-804O 1200mg/day (N=122)**	**All SPN-804O Treatment (N=245)**	**Placebo (N=121)**
Protocol Violation	0	1	1	1
Investigator decision	0	0	0	1
Other	2	0	2	2
subject withdrew consent	11	10	21	6
Total	**52 (42%)**	**40 (33%)**	**92 (38%)**	**26 (22%)**

Table 36 shows the three top causes of discontinuation in order of magnitude were “adverse event”, “non-compliance” and “lost to follow up”.

Study discontinuation due to Adverse Events

Table 37, Study 804P301				
	SPN-804O 2400mg/day (N=123) n (%)	SPN-804O 1200mg/day (N=122) n (%)	All SPN-804O Treatment (N=245) n (%)	Placebo (N=121) n (%)
Discontinuation	37 (30.0)	20 (16.4)	57 (23.3)	15 (12.4)

Table 37 Study 804P301, Discontinuations by Treatment Arm n (%)

Table 37 above reveals the 1200mg treatment arm of study 804P301 has 4% greater discontinuations due to adverse effects than the placebo group and the 2400mg arm has an occurrence 17.6% greater than placebo. This rate of discontinuation is not unusual in anticonvulsant trials.

The combined oxcarbazepine XR treatment arms (1200mg & 2400mg) have a total of 57 discontinuations due to adverse events out of 245 patients. This represents 23% of patients which compares favorably with discontinuations from the combined 1537 patients of the oxcarbazepine IR adjunctive and monotherapy studies shown in section 6.1, “Clinical Studies Experience” of the Trileptal label where there were 23% discontinuations due to adverse events.

Table 38 Study 804P301, Adverse Events Leading to Discontinuation, Preferred Terms (#) by Dose Group

DISC4 frequency of adverse events leading to discontinuations by dose group					
2400mg		**1200mg**		**PBO**	
preferred term	**# events**	**preferred term**	**# events**	**preferred term**	**# events**
dizziness	19	dizziness	5	dizziness	6
vomiting	11	nausea	4	somnolence	4
diplopia	7	balance disorder	2	nausea	3
headache	6	dyspepsia	2	vomiting	3
nausea	6	somnolence	2	diplopia	2
somnolence	4	vomiting	2	alanine aminotransferase increased	1
drug intolerance	3	agitation	1	anorexia	1
asthenia	2	anorexia	1	aspartate aminotransferase increased	1
balance disorder	2	chest pain	1	asthenia	1
rash generalised	2	convulsion	1	balance disorder	1
ataxia	1	depression	1	blood lactate dehydrogenase increased	1
convulsion	1	diarrhoea	1	fear	1
dermatitis allergic	1	diplopia	1	headache	1
erectile dysfunction	1	gait disturbance	1	lower limb fracture	1
fatigue	1	gastritis	1	ovarian cancer	1
head titubation	1	haematemesis	1	rash erythematous	1
hyponatraemia	1	headache	1	stevens-johnson syndrome	1
leukopenia	1	hyponatraemia	1		
memory impairment	1	lethargy	1		
musculoskeletal chest pain	1	melaena	1		
nystagmus	1	mental disorder due to a general medical condition	1		
pituitary tumour benign	1	mood altered	1		
stomach discomfort	1	palpitations	1		
tachycardia	1	personality disorder	1		
urticaria	1	rash erythematous	1		
vision blurred	1	rash generalised	1		
		rash pruritic	1		
		status epilepticus	1		
		vision blurred	1		

DISC4 frequency of adverse events leading to discontinuations by dose group					
2400mg		**1200mg**		**PBO**	
preferred term	**# events**	**preferred term**	**# events**	**preferred term**	**# events**
		visual impairment	1		

Table 39 Study 804P302, 120 day update, Adverse Events Leading to Discontinuation, Analysis of Narratives for Relatededness of Study Drug

DISC5 Discontinue	804P302	
143-008	diarrhea	related, + dechallenge
145-003	disequilibrium	related + dechallenge
301-001	Nausea, vomiting	probably related
510-002	diplopia, vertigo	Probably related
801-008	dizziness, somnolence	unrelated
817-004	nausea, vomiting, fear	related + dechallenge
818-008	vomiting, gastritis, esophagitis	possibly related

The examination of overall discontinuations for study 804P301 reveals that “adverse event”, “lost to follow up” and “non compliance” are the most frequent causes of discontinuation with adverse event accounting for 22% of discontinuations and the categories “lost to follow up” and “non compliance” together account for 5%, Table 36. Discontinuation due to adverse events as seen in

Table 37, Study 804P301				
	SPN-804O 2400mg/day (N=123) n (%)	SPN-804O 1200mg/day (N=122) n (%)	All SPN-804O Treatment (N=245) n (%)	Placebo (N=121) n (%)
Discontinuation	37 (30.0)	20 (16.4)	57 (23.3)	15 (12.4)

Table 37 is highest in the 2400mg group, at 30% and 23% in the combined discontinuations of the 1200mg and 2400mg treatment arms. The combined discontinuation rate for the 1200mg and 2400mg treatment arms is the same as the discontinuation rate seen in the clinical trials section, “Adjunctive Therapy/Monotherapy in Adults Previously Treated with other AEDs” where it is noted that “approximately 23% of these 1537 patients discontinued treatment because of an adverse experience” This is within the bounds of the discontinuation rate also seen in other AED

development programs. Table 38, frequency of adverse events leading to discontinuation reveals a notable increase in discontinuations in the 2400mg group due to dizziness, vomiting, diplopia, headache, and nausea compared to placebo while these same discontinuations in the 1200mg group occur at a similar rate as placebo. These events are common dose related toxicities of the AEDs. Study 804P302 (Table 39), the open label continuation of 804P301 had 7 discontinuations due to adverse events, analysis

revealed most were related to study drug but the adverse events were again clustered in those seen as common central nervous system and gastroenterologic toxicities of AEDs.

Reviewer Comment: The frequency of discontinuations due to adverse events in the treatment arms compared to placebo does not signal a new level of toxicity when compared to the clinical trials adverse experience in the Trileptal label. The profile of adverse events leading to discontinuations in study 804P301 is similar to the profile of adverse experiences leading to discontinuation in the RLD labeling (Trileptal).

7.3.4 Significant Adverse Events

Healthy Adult subjects, phase 1 studies: no events of increased or unusual significance occurred in the phase 1 study subjects.

Study 804P301: no events of increased or unusual significance occurred.

7.3.5 Submission Specific Primary Safety Concerns

Submission specific safety concerns are directed by the know safety concerns of the reference listed drug product which are identified by the reviewer as suicidality (class effect), serious skin rash, and hyponatremia. Seizure worsening is examined on a precautionary basis.

In Table 40, adverse events of special interests, the occurrence of these events in each treatment arm of study 804P301 are presented. Seizure related terms occur in approximately the same frequency as placebo. There are no completed suicides or suicidal ideation terms in the oxcarbazepine XR treatment arms. There is one entry each for the terms depression and mood disorder which exceeds the rate in placebo (0). There was one event of angioedema in the treatment group, representing approximately the same frequency as placebo. There was one event of Stevens-Johnson syndrome, in placebo only.

Table 40 Study 804P301, Adverse Events of Special Interest for Evaluation of Seizure Worsening, Suicidality, Serious Skin Reactions and Hyponatremia

Adverse events of special interest for evaluation of Seizure Worsening, Suicidal Ideation, Serious Skin reactions, and Hyponatremia				
SOC / PreferredTerm	**OXC XR 2400mg/day**	**OXC XR 1200mg/day**	**OXC XR All treatment**	**Placebo**
Nervous system disorders				
Post ictal state	0	1 (0.8)	1 (0.4)	1 (0.3)
Status epilepticus	0	1 (0.8)	1 (0.4)	1 (0.3)
complex partial seizures	0	0	0	1 (0.8)

Partial Seizures	0	0	0	1 (0.8)
Psychiatric disorders				
Suicidal Ideation	0	0	0	1 (0.3)
Mood altered	0	1 (0.8)	1 (0.4)	0
Depressed Mood	1 (0.8)	0	1 (0.4)	0
Skin and Subcutaneious tissue Disorders				
Rash Generalized	2 (1.6)	1 (0.8)	3(1.2)	0
Rash	1 (0.8)	1(0.8)	2(0.8)	1 (0.8)
Angioedema	1 (0.8)	0	1 (0.4)	1 (0.3)
Stevens-Johnson Syndrome	0	0	0	1 (0.8)
Metabolism and Nutritional disorders				
Hyponatraemia	1 (0.8)	2 (1.6)	3 (1.2)	2 (1.7)

Seizure worsening

There were two epilepsy related adverse event leading to discontinuation identified in the safety review, see Table 41. Subject 101006 is a 35 year old female enrolled in study 804P301 assigned to the 1200mg / day treatment arm who developed worsening seizures on day 106 of the study. This event occurred in the late maintenance interval of the study. Subject 418003 had an increase in seizure frequency and pattern of seizures as well as dizziness, diplopia, nausea, vomiting, abdominal pain, headache and nervousness. This event occurred on day 18 during titration to 2400mg. The event may be drug toxicity with a related increase in seizures.

Table 41 Study 804P301, Epilepsy Related Serious Adverse Events- All OXC XR Treatment vs Placebo

SW1 804P301 Epilepsy related Serious Adverse events, All OXC XR treatment arms vs Placebo		
	RX (1200 / 2400mg) (245)	**Placebo**
Convulsion/CP seizure/ Status epilepticus	**2**	**1**
%	**0.8**	**0.8**

Reviewer Comment: Examination of serious adverse events in the categories which are considered submission specific safety concerns do not reveal a profile of these events in excess of placebo in the double blind interval of the pivotal clinical trial.

7.4 Supportive Safety Results

7.4.1 Common Adverse Events

Healthy Adult Subjects: Studies 804P10, 804P102, 804P103, 804P104, 804P104.5, 804P105, 804P109

Overall Adverse events: The most common AEs were headache, somnolence, dizziness, nausea, and fatigue occurring in 16%, 12%, 4.4%, 3.6% and 3.3% of subjects treated with SPN-804O and 16.7%, 13.6%, 18.2%, and 10.6% and 1.5% in subjects treated with OXC IR, respectively, these data may be seen in tabular form in Table 42.

Table 42 Phase 1, PK studies, Composite of Adverse Events with Frequency > or equal to 2%, any treatment

Composite of 7 phase 1 PK studies, Adverse events of greatest frequency (≥2% for any treatment)		
Adverse Event	SPN-804O* n (%)	OXC-IR n (%)
	N=275†	N=66
Vision blurred	5 (1.8)	3 (4.5)
Nausea	10 (3.6)	7 (10.6)
Fatigue	9 (3.3)	1 (1.5)
Dizziness	12(4.4)	12 (18.2)
Headache	44 (16.0)	11 (16.7)
Somnolence	33 (12.0)	9 (13.6)
*All formulations included. Each subject was counted separately for each exposure. †Three of the 275 randomized subjects did not receive any SPN-804O		

Study 804P301

There is an increase in total adverse events (sum of adverse events in each SOC) as dose advances from 0 (placebo), through 1200mg/day to 2400mg/ day. The change from 0 to 1200mg/day is shallow, only changing from 55% to 57% of patient experiencing an adverse event. There is a larger change in the interval from 1200mg/day to 2400mg/day, increasing from 57% to 69% in the 1200mg and 2400mg respectively. The adverse events in the System Organ Class (SOC) of Nervous System Disorders, General disorders, administration site disorders, and Musculoskeletal and connective tissue disorders, show a dose response from placebo to the 2400mg dose group, although the frequency of events in the musculoskeletal SOC is low.

The occurrence of adverse events by system organ class is seen in Table 43. For all system organ classes 69% of subjects in the 2400mg dose arm experienced an adverse event, 57% in the 1200mg dose group and 55% in the placebo group. There was a dose response seen for all (total) SOCs. The SOC with the greatest number of adverse events was "Nervous System disorders". This SOC had a dose response with 31% of placebo group, 38.5% of the 1200mg group and 56% of the 2400mg group experiencing an adverse event. The most frequent events within "Nervous system disorders" and those also driving the dose response were Dizziness, Somnolence, and Headache, seen in Table 44. The most frequent events within "General disorders and administration site conditions" were Asthenia and Fatigue with the term Asthenia showing a dose response, seen in Table 44.

Table 43 Study 804P301, Adverse Events by SOC and Treatment Group

Table SOC				
MedDRA System Organ Class (SOC)	**OXC XR 2400mg/d (N=123)**	**OXC XR 1200mg/d (N=122)**	**All OXC XR (N=245)**	**Placebo (N=121)**
All SOCs	**85 (69.1)**	**69 (56.6)**	**154 (62.9)**	**67 (55.4)**
Nervous system disorders	69 (56.1)	47 (38.5)	116 (47.3)	38 (31.4)
Gastrointestinal disorders	31 (25.2)	28 (23.0)	59 (24.1)	28 (23.1)
Eye disorders	18 (14.6)	18 (14.8)	36 (14.7)	7 (5.8)
General disorders and administration site disorders	19 (15.4)	17 (13.9)	36 (14.7)	7 (5.8)
Infections and infestations	4 (3.3)	14 (11.5)	18 (7.3)	12 (9.9)
Injury, poisoning and procedural complications	5 (4.1)	7 (5.7)	12 (4.9)	10 (8.3)
Psychiatric disorders	7 (5.7)	9 (7.4)	16 (6.5)	8 (6.6)
Skin and subcutaneous tissue disorders	7 (5.7)	7 (5.7)	14 (5.7)	6 (5.0)
Metabolism and nutrition disorders	3 (2.4)	4 (3.3)	7 (2.9)	7 (5.8)
Musculoskeletal and connective tissue disorders	6 (4.9)	3 (2.5)	9 (3.7)	2 (1.7)
Investigations	2 (1.6)	3 (2.5)	5 (2.0)	5 (4.1)
Respiratory, thoracic, and mediastinal disorders	1 (0.8)	4 (3.3)	5 (2.0)	4 (3.3)
Cardiac disorders	2 (1.6)	4 (3.3)	6 (2.4)	2 (1.7)
Renal and urinary disorders	4 (3.3)	1 (0.8)	5 (2.0)	3 (2.5)
Vascular disorders	0	3 (2.5)	3 (1.2)	3 (2.5)
Reproductive system and breast disorders	2 (1.6)	0	2 (0.8)	3 (2.5)
Blood and lymphatic system disorders	2 (1.6)	1 (0.8)	3 (1.2)	1 (0.8)
Ear and labyrinth disorders	0	1 (0.8)	1 (0.8)	1 (0.8)
Immune system disorders	0	2 (1.6)	2 (0.8)	0
Neoplasms, benign, malignant, and unspecified	1 (0.8)	0	1 (0.4)	1 (0.8)
Hepatobiliary disorders	1 (0.8)	0	1 (0.4)	0
For each row category, a subject with two or more adverse events in that category is counted only once.				

The SOCs with incidence of individual adverse events occurring in ≥ 2% of subjects, in order of frequency, were Nervous System Disorder, Gastrointestinal Disorders, Eye Disorders, General disorders and administration site disorders, and infections and infestations, Table 44.

A dose response was noted for the preferred terms “Dizziness”, Somnolence”, “Headache”, “Diplopia”, and “Asthenia”. The incidence of dizziness ranged from 15% in the placebo group to 41% in the 2400mg treatment arm. The occurrence of somnolence, next in frequency, ranged from 9% in placebo to 14% in the 2400mg treatment arm. Headache had a dose response from 7% in the placebo group to 15% in the 2400mg treatment arm. Nausea with no dose response occurred in 12% of the placebo group and 2400mg treatment arm. Diplopia had a treatment response ranging from 4% in the placebo group to 13% in the 2400mg treatment arm. Vomiting, with no dose response occurred in 9% of the placebo group and 15% of the 2400mg treatment arm. Balance disorder with no treatment response, occurred in 5% of the placebo group and 7% in the 2400mg treatment arm. Asthenia, with a dose response, occurred in 1% of the placebo group and 7% of the 2400mg treatment arm. Fatigue, with no dose response, occurred in 1% of the placebo group and 3% of the 2400mg treatment arm. These data are show graphically in the Percent Adverse Events in study 804P301, Figure 12 and Table 44.

Figure 12 Adverse Event percent, by High Dose Group (2400mg), Combined Dose Groups, and Placebo

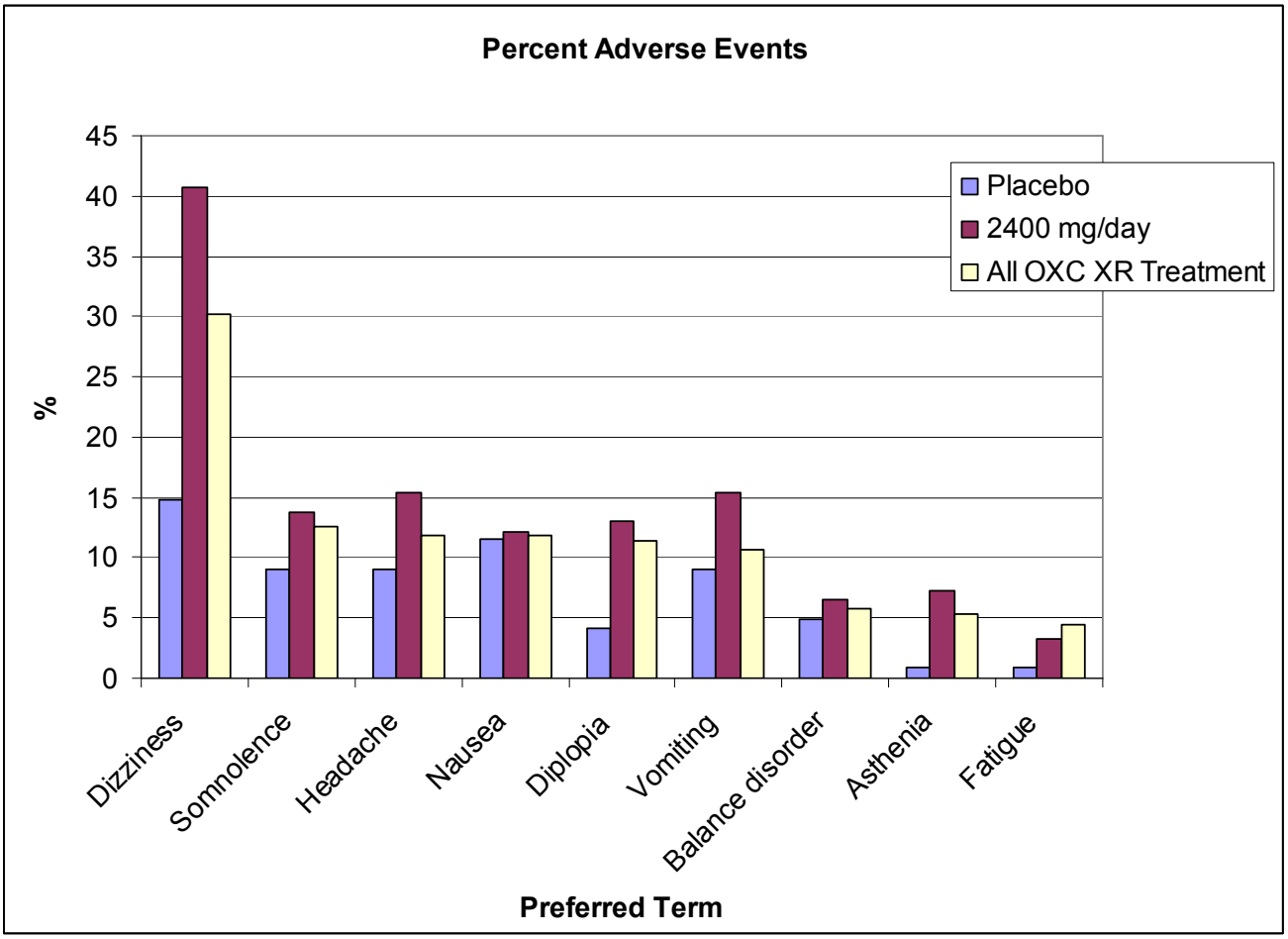


Table 44 Study 804P301, Adverse Event Preferred Terms by Dose Group, Occurring in ≥2% of Patients

Table adverse events by preferred term.				
Incidence of Adverse Events occurring in ≥2% of patients in any preferred term.				
SOC / Preferred Term	**OXC XR 2400mg/day**	**OXC XR 1200mg/day**	**OXC XR All treatment**	**Placebo**
Nervous system disorders	69 (56.1)	47 (38.5)	116 (47.3)	38 (31.4)
Dizziness	50 (40.7)	24 (19.7)	74 (30.2)	18 (14.9)
Somnolence	17 (13.8)	14 (11.5)	31 (12.7)	11 (9.1)
Headache	19 (15.4)	10 (8.2)	29 (11.8)	9 (7.4)
Balance disorder	8 (6.5)	6 (4.9)	14 (5.7)	6 (5.0)
Tremor	1 (0.8)	6 (4.9)	7 (2.9)	2 (1.7)
Nystagmus	4 (3.3)	3 (2.5)	7 (2.9)	1 (0.8)
Ataxia	1 (0.8)	3 (2.5)	4 (1.6)	1 (0.8)
Speech disorder	3 (2.4)	1 (0.8)	4 (1.6)	0

Table adverse events by preferred term.				
Incidence of Adverse Events occurring in ≥2% of patients in any preferred term.				
SOC / Preferred Term	**OXC XR 2400mg/day**	**OXC XR 1200mg/day**	**OXC XR All treatment**	**Placebo**
Gastrointestinal disorders	31 (25.2)	28 (23.0)	59 (24.1)	28 (23.1)
Nausea	15 (12.2)	14 (11.5)	29 (11.8)	14 (11.6)
Vomiting	19 (15.4)	7 (5.7)	26 (10.6)	11 (9.1
Diarrhea	1 (0.8)	3 (2.5)	4 (1.6)	4 (3.3)
Abdominal pain upper	0	4 (3.3)	4 (1.6)	1 (0.8)
Dyspepsia	0	4 (3.3)	4 (1.6)	1 (0.8)
Gastritis	0	3 (2.5)	3 (1.2)	2 (1.7)
Eye Disorders	18 (14.6)	18 (14.8)	36 (14.7)	7 (5.8)
Diplopia	16 (13.0)	12 (9.8)	28 (11.4)	5 (4.1)
Vision blurred	1 (0.8)	5 (4.1)	6 (2.4)	3 (2.5)
Visual Impairment	1 (0.8	3 (2.5)	4 (1.6)	0
General disorders and administration site conditions	19 (15.4)	17 (13.9)	36 (14.7)	7 (5.8)
Asthenia	9 (7.3)	4 (3.3)	13 (5.3)	1 (0.8)
Fatigue	4 (3.3)	7 (5.7)	11 (4.5)	1 (0.8)
Gait disturbance	0	3 (2.5)	3 (1.2)	1 (0.8)
Drug intolerance	3 (2.4)	0	3 (1.2)	0
Infections and infestations	4 (3.3)	14 (11.5)	18 (7.3)	12 (9.9)
Sinusitis	0	3 (2.5)	3 (1.2)	2 (1.7)
Nasopharyngitis	0	4 (3.3)	4 (1.6)	0

Study 804P302

The frequency and type of common adverse effects seen in the open label continuation study were similar to those occurring in the blinded study. There was an increase in the occurrence of respiratory infection seen in the follow on group. The sponsor proposes this variation may be due to the difference in seasonal interval of participation between the two studies. At the initial submission there were two occurrences of hyponatremia in study 302 and at the time of the 120 day safety update there were four additional cases of hyponatremia. No action was taken regarding oxcarbazepine XR treatment in these reports of hyponatremia.

Reviewer Comment: The common adverse event profile reveals that the incidence of the most frequent events in the 2400mg dose arm to be lower than those noted for the same events in the Adjunctive therapy trial of oxcarbazepine IR presented in the Trileptal (RLD) label. Several cases of hyponatremia were seen to accrue in the open label extension study 804P302; however this is a known adverse effect of oxcarbazepine which is present in the “Warnings and Precautions” section of the

Trileptal label. The label indicates hyponatremia was seen in 2.3% of Trileptal treated patients in 14 controlled epilepsy trials, thus this does not represent a new safety signal.

7.4.2 Laboratory Findings

Study 804P301

Hematology

Mean changes: The ISS indicates statistically significant decline in mean values for RBC count, hemoglobin, hematocrit, white cell count and absolute lymphocyte count. Although of interest, the mean change did not leave the normal range. Because these mean changes may be driven by outliers representing individual patients with clinically meaningful changes the laboratory dataset is examined for values outside of the defined reference range. Those patients who were found to have a change which placed the laboratory value out of reference range at a treatment phase visit were subsequently examined to determine the magnitude of the change. These same patients (subject ID's) are examined in the adverse event dataset to determine if there is an adverse event term that is relevant to the laboratory abnormality and also determine if there is a serious adverse event associated with the laboratory abnormality.

Because these mean changes in myeloid and lymphoid cell lines may be driven by outliers with clinically meaningful change in their laboratory values during study drug treatment interval, further evaluation is performed on the hematology laboratory datasets. Decline outliers, individuals with a drop in hemoglobin, WBC count, absolute lymphocyte count, and platelet count will be captured and examined. The range of decline will be examined to determine if there are very serious outliers and the frequency of occurrence of outliers will be examined to determine if there are a notably large number of outliers or a dose response to the outlier frequency.

Analysis of Change from Baseline To Visit 6: Hemoglobin, WBC count, Absolute Lymphocytes, Platelet Count and Examination of Outliers

Outlier Parameters (Reviewers chosen threshold)

Table 45 Hematology Outlier Parameters

Parameter	Low	High
Hemoglobin	≤ 100 G/dl (10g/dl)	≥
WBC count	≤ 2.8 k/ul	≥16k/ul
Platelet count	≤100k/ul	≥500k/ul
Absolute lymphocyte count	≤2.0k/ul	

Hemoglobin: Patients with a decline in hemoglobin ≥ 1 gram are captured from visits number 6.. Visit number six represents end of maintenance interval. A total of 35 cases

are identified in all treatment arms where there was a drop in hemoglobin greater than or equal to 1 gram. There were 10, 10 and 15 incidents of drop greater than 1 gram in the placebo, 1200mg OXC XR , and 2400mg/day OXC XR groups respectively. The average drop in hemoglobin in this subset was 1.5 grams, 1.8 grams and 1.4 grams in the placebo, 1200mg/day OXC XR, and 2400mg/day OXC XR groups respectively. There was a maximum decline of 2.5 grams, 4.2 grams and 2.6 grams seen in the placebo, 1200mg/day OXC XR, and 2400mg/day OXC XR groups respectively, see Table 46.

Table 46 Maximum Hemoglobin Decline of 1 gram or Greater, Identified at Visit 6 or 7- All Treatment Groups.

Max Hb decline 1 gram or greater drop identified at visit 6 or 7, all treatment groups						
Treatment group	N	Patient with drop > 1gm Hb	%	Average Hb drop	Maximum decline	Patients Below reference range
Placebo	121	10	8	1.5	2.5	4
OXC XR 1200mg/day	123	10	8	1.8	4.2	5
OXC XR 2400mg/day	122	15	12	1.4	2.6	7

The adverse events dataset is matched to the subject ID of patients treated with oxcarbazepine who had a decline in hemoglobin greater than or equal to 1 gram to determine if events related to bone marrow suppression or blood loss occurred in this group.

In the oxcarbazepine treated group serious adverse events are recorded for two of the patients with a decline in hemoglobin ≥ 1 gram. In one patient (118001) the adverse event was a non-ST elevation myocardial infarction, treatment assignment was 1200mg/day of oxcarbazepine XR. The narrative report reveals no discussion of anemia or blood loss. This patient did have a decline in hemoglobin of 4.2 g/dl from baseline (16.9 to 12.7), however the hemoglobin remained in the reference range and the patient remained on study drug.

The second patient (603003) with a serious AE had an event identified as “skull fracture base”; this 52 yo male patient was assigned to the 1200mg/day treatment group. Hemoglobin declined 1.5g/dl (14.3g/dl to 12.8g/dl). The adverse event occurred during maintenance phase of the study. Narrative report indicates the patient was on concomitant topiramate 200mg/day and phenobarbital 100mg/day. The patient experienced a seizure with secondary generalization on his return home from clinic visit 5 and fell to the ground and struck his head. There were no obvious neurologic deficit in the emergency room. A skull base fracture was not confirmed. Ethmoid and sphenoid

sinusitis developed and were treated with antibiotic therapy. The duration of hospitalization was 8 days. The SAE which occurred on 6/17/10 is unrelated to the drop in hemoglobin which occurred on 8/12/10.

There were 33 non-serious adverse events experienced by 9 remaining patients who experienced a decline in Hb > 1gm from baseline. None of these adverse events were in the SOC of "Blood and lymphatic system disorders". None of the preferred terms were clearly related to anemia or blood loss although there were 6 events of "dizziness", 1 of "fatigue", and 1 of "asthenia" which may be associated with the state of anemia.

Hemoglobin outliers: 3 patients are identified who have hemoglobin less than 11g/dl at visit 6, not present at baseline. Two of these are in the placebo arm and one in the treatment arm. The single patient (0.8%) from the treatment arm had a change from baseline of 0.7 g/dl with a result of 10.9 g/dl.

Reviewer Comment: analysis does not reveal a dose response for decline in Hb, Low value outliers in the placebo treatment arm exceed the treatment arm. Exam of adverse events of patients with decline in Hb >1g did not reveal preferred terms in the SOC ""Blood and lymphatic system disorders". These observations do not provide evidence of a safety signal for anemia or bone marrow suppression.

WBC count:
Patients with a decline in WBC count≥ 2000 cells/ul are captured from visits number 6. Visit number six represents end of maintenance interval. A total of **29** cases are identified in all treatment arms where there was a drop in WBC count greater than or equal to 2000 cells/ul from baseline. There were 7, 10 and 12 incidents of drop greater than or equal to 2000 cells/ul in the placebo, 1200mg OXC XR, and 2400mg/day OXC XR groups respectively. The average drop in WBC count was 2.6k/ul, 2.9k/ul and 2.9k/ul in the placebo, 1200mg/day OXC XR, and 2400mg/day OXC XR groups respectively. There was a maximum decline of 3.6k/ul, 4.0k/ul and 3.7k/ul seen in the placebo, 1200mg/day OXC XR, and 2400mg/day OXC XR groups respectively, Table 47.

The adverse events dataset is matched to the subject ID of patients treated with oxcarbazepine who had a decline in WBC count greater than or equal to 2000 cells/ul to determine if events related to bone marrow suppression or leukocytopenia occurred in this group. Thirty seven adverse events were captured in this manner, none were SAEs. One was in the SOC of "Infections and Infestations", the preferred term was "Nasopharyngitis". None the remaining terms were related to an infectious process.

Table 47 Maximum WBC decline of 2000 cells/ul or greater drop identified at visit 6 or 7, all treatment groups

Max WBC decline 2000 cells/ul or greater drop identified at visit 6 or 7, all treatment groups						
Treatment group	N	Patient with drop > 2000 cells/ul	%	Average count drop in thousands of those who met drop > 2000 criteria	Maximum decline	Below Ref
Placebo	121	7	6	2.6	3.6	2
OXC XR 1200mg/day	123	10	8	2.9	4.0	1
OXC XR 2400mg/day	122	12	10	2.9	3.7	3

Total Leukocyte outliers (WBC): Two patients are identified with WBC count less than 2.8k/ul not present at baseline. These were both in the oxcarbazepine treatment group. One patient had a decline from 4.9k/ul at baseline to 2.8k/ul at visit six, the second had a baseline value of 4.1k/ul which decreased to a value of 2.5k/ul at visit six. Both patients were in the 1200mg/day treatment group (1.6%).

Absolute Lymphocytes:

Patients with a decline in absolute lymphocyte count ≥1000 cells/ul are captured from visit number 6. Visit number six represents end of maintenance interval. A total of 46 cases are identified in all treatment arms where there was a drop in absolute lymphocyte count greater than or equal to 1000 cells/ul. There were 13, 15 and 18 incidents of drop greater than or equal to 1000 cells/ul in the placebo, 1200mg OXC XR, and 2400mg/day OXC XR groups respectively. The average drop in lymphocyte count in was 1.7k/ul, 2.8k/ul and 2.2k/ul in the placebo, 1200mg/day OXC XR, and 2400mg/day OXC XR groups respectively. There was a maximum decline of 2.9k/ul, 4.6k/ul and 5.0k/ul seen in the placebo, 1200mg/day OXC XR, and 2400mg/day OXC XR groups respectively, Table 48.

As a subsequent step in the analysis, the adverse events dataset is matched to the subject ID of patients treated with oxcarbazepine who had a decline in absolute lymphocyte count greater than or equal to 1000 cells/ul to determine if events related to bone marrow suppression or lymphopenia occurred in this group. Forty nine adverse events were captured in this manner; two were SAEs, one “Skull Fractured Base” (SUBJID 603003) and one “Ischaemic Stroke” (606004). Both of the SAEs preceded visit 6 by a minimum of 25 days. Among the remaining 47 adverse events there were 5 events which occurred in 4 patients under the SOC “Infections and Infestations”, none of these was an SAE. There were no preferred terms in the remaining adverse events which were related to infection or bone marrow suppression. The “infections and infestations” adverse events represent a minority of the 47 identified AEs, and because these were not SAEs, there is no case report data to explore in detail if there is causality related to low absolute count. Infection resulting from the observed decline in lymphocyte count is not supported by examination of outliers, next paragraph, where only one patient each in the 1200mg and 2400mg groups had values below 1k and no SAE was noted in these patients.

Table 48 Maximum absolute lymphocyte decline 1000 cells/ul or greater drop identified at visit 6, all treatment groups

Maximum absolute lymphocyte decline 1000 cells/ul or greater drop identified at visit 6, all treatment groups						
Treatment group	N	Patient with drop ≥ 1000 cells/ul	%	Average count drop in thousands of subject who meet ≥ 1000 criteria	Maximum decline	Below Ref
Placebo	121	13	11	1.7	2.9	2
OXC XR 1200mg/day	123	15	12	2.8	4.6	0
OXC XR 2400mg/day	122	18	15	2.2	5	5

Absolute Lymphocyte outliers: Three patients are identified with an absolute lymphocyte count less than 1k/ul not present at a baseline value. One of these occurs in the placebo group, one in the 1200mg /day group (0.8%) and one in the 2400mg/day treatment group (0.8%). The patient from the 1200mg/day group had a baseline value of 1.15k/ul which declined to .86k/ul. The patient in the 2400mg/day group had a baseline value of 4.28k/ul which declined to.84k/ul.

Reviewer Comment: the analysis of absolute lymphocyte counts from study 804P301 reveals a dose relationship between lymphocyte count decline greater than 1000, maximum decline from baseline (among those with a decline greater than 1000) and there is no dose relation between the average drop of those in this category nor is there

a dose relation noted for the occurrence of absolute lymphopenia (count <1000/ul). There were two patients fell into the group of lymphocyte count <1000 and one of these had a baseline lymphocyte value below reference range. This data suggests a weak signal for an effect of study drug on lymphocyte count but does not provide a level of evidence to add lymphocyte drop or absolute lymphopenia to labeling.

Platelet Count

Patients with a decline in platelet count≥ 50,000 cells/ul are captured from visit number 6. Visit number six represents end of maintenance interval. A total of 9 cases are identified in all treatment arms where there was a drop in platelet count greater than or equal to 50,000 cells/ul. There were 3, 5 and 1 incidents of drop greater than or equal to 50,000 cells/ul in the placebo, 1200mg OXC XR, and 2400mg/day OXC XR groups respectively. The average drop in platelet count was 71k/ul, 86k/ul and 83k/ul in the placebo, 1200mg/day OXC XR, and 2400mg/day OXC XR groups respectively. There was a maximum decline of 90k/ul, 116k/ul and 83k/ul seen in the placebo, 1200mg/day OXC XR, and 2400mg/day OXC XR groups respectively, Table 49.

Table 49 Maximum platelet count decline 50,000 cells/ul or greater drop identified at visit 6, all treatment groups

Max platelet count decline 50,000 cells/ul or greater drop identified at visit 6, all treatment groups	Column A					
Treatment group	N	Patient with drop ≥ 50,000 cells/ul	%	Average count drop in thousands of those who met column A criteria	Maximum decline	Below Ref
Placebo	121	3	2.5	71	90	0
OXC XR 1200mg/day	123	5	4.1	86	116	2
OXC XR 2400mg/day	122	1	0.8	83	83	0

The adverse events dataset is matched to the subject ID of patients treated with oxcarbazepine who had a decline in platelet count greater than or equal to 50,000 cells/ul to determine if events related to bone marrow suppression or bleeding occurred in this group. Eleven adverse events were captured in this manner. These 11 events occurred in 2 patients. One was an SAE, which occurred in the SOC “Injury, Poisoning And Procedural Complications”. The PT for this entry was “Humerus Fracture”. This SAE occurred in the screening interval. None of the remaining 10 AEs was related to bleeding or bone marrow suppression.

Platelet outliers: one patient in the 1200mg/day group (0.8%) is identified with a platelet count of ≤100k/ul not present at baseline. This patient had a beeline value of 168k/ul that dropped to 100k/ul at visit 6.

Reviewer Comment: There is no evidence of a signal for thrombocytopenia.

APPEARS THIS WAY ON ORIGINAL

Table 50 Summary Hematology Shift Table by Dose Group, Examination of Normal to Low, Normal to High

	2400mg/day	1200mg/day	PBO	Comment	
Parameter	Normal to Low	Normal to Low	Normal to Low	Normal to high	Low to normal
RBC count	11 (8.9)	9 (7.4)	6 (5.0)	No normal to high	50% of Normal to low effect of 2400mg group, 1 patient in 1200mg, 8 in PBO.
Hemoglobin	8 (6.5)	7 (5.7)	3 (2.5)	1 normal to high in 1200mg/day group	Some change seen but in treated patients max 25% of effect seen in Normal to low.
Hematocrit	6 (4.9)	7 (5.7)	2 (1.7)	None in 2400mg, 2 in 1200mg, 5 in PBO	Max. of 30% of normal to low effect seen in 2400mg group,
Platelet Count	1 (0.8)	2 (1.6)	0	No normal to high	Overall magnitude of change up to 2x normal to low direction in 2400mg/day
WBC count	6 (4.9)	3 (2.5)	3 (2.5)	No normal to high	Overall magnitude of change 50% of normal to low in 2400mg/day and equal in 1200mg/day,
Neutrophils	4 (3.3)	2 (1.6)	6 (5.0)	Equal magnitude for PBO, 2x for 1200mg /day and similar for 2400mg.	Similar magnitude in 2400mg group, 64% greater effect than normal to low in 1200mg/group, 50%of change seen in PBO
Absolute lymphocyte count	0	0	0	1 normal to high in each treatment arm	2 patients in 1200mg/day, 0 in remaining treatments

Reviewer Summary and Comment. Trends of notable decline from baseline values and low outlier values were examined due to the reports of pancytopenia, agranulocytosis and leukopenia in Trileptal[3] post marketing reports. Examination of hemoglobin revealed decline from baseline in up to 12% of patients in the highest dose group and 8% of placebo patients, there was no dose response in the numbers affected or the average decline or maximum decline. The examination of the total leukocyte (WBC) count revealed up to 10% of treated patients and 6% of placebo patients experienced a decline in WBC count. There was a dose response noted in the percent of patients affected but no dose response seen in the average decline or maximum decline per group. The examination of absolute lymphocyte count revealed a decline in up to 15% of patients in the highest dose group and 11% in the placebo group. There was a dose response in percent affected but not in average decline in each group. Maximum decline also revealed a dose response. Examination of the platelet count revealed a maximum of 4.1% of patients affected but no dose response in percent affected, average decline by group or maximum decline.

Shift tables reveal a dose response for hemoglobin normal to low shift and the related parameters of RBC count and hematocrit. There was a consistent dose response among the hemoglobin and RBC related parameters. The shift from normal to low for hemoglobin was 2.6 times the placebo value for the 2400mg dose group. Hemoglobin revealed minimal shift in the opposite direction (normal to high). Platelet count revealed minimal normal to low shift. WBC had no dose response in normal to low shift; separation from placebo was 200% in the 2400mg/day group. Neutrophils had less normal to low shift than placebo in both oxcarbazepine treatment groups. Normal to high shift was similar in the 2400mg / day group and two times as great for the 1200mg/day group.

In the examination of change from baseline there was no separation from placebo greater than 4%. There was dose response seen in the leukocyte parameters, there was no large average decline in any of the hematologic parameters. The shift table reveals a more consistent change from normal to low for hemoglobin, RBC count and hematocrit as well as a dose response. There is also a predominance of shift from normal to low compared to low to normal or normal to high. The leukocyte parameters reveal the normal to low shift is less consistent than noted for red cell related parameters, and less consistent separation from placebo. Taken together, the results of the analysis of notable decline from baseline, outlier analysis and shift analysis do not indicate a need to strengthen the language for hematopoietic adverse effects in the oxcarbazepine XR label.

Clinical Chemistry (804P301)

The sponsor reports that using the Kruskal Wallis test to compare the active treatment arms to placebo statistically significant changes were observed for alkaline

3 Trileptal Prescribing information, Drugs at FDA 3/3/2011

phosphatase, total bilirubin, urea nitrogen, creatinine, calcium and uric acid among the biochemistry tests.

Increase from Baseline, Outlier to out of range.

ALT

AE

Examination of the adverse event dataset reveal three patients were discontinued due to elevated ALT, two of these patients were in the placebo treatment arm and the third patient was found to have ALT elevation at screening and baseline.

Increase from baseline

Two patients treated with oxcarbazepine are found to have an increase in ALT greater than 40U/L from baseline to visit 6. One patient (204002) is in the 1200mg treatment group. This patient had an increase of 70U/L from a baseline of 16U/L (result 86 U/L, 1.8 ULN), the second patient had an increase of 41U/L from a baseline of 32U/L (result 73 U/L, 1.5 ULN). There is no AE or discontinuation reported for either patient.

Out of Reference Range (ULN=48 U/L)

There were 9 patients with ALT values above reference range at visit 6; two were in the placebo group, 3 in the 1200mg/day group and 4 in the 2400mg/day group.

7 patients in the oxcarbazepine treatment arms are found to have values for ALT elevated above reference range at visit 6, three of these patients had elevated values at baseline. Among the patients with new elevation, the highest ALT value was 86U/L (1.8 x ULN) (204002) due to an increase of 70U/L. There is no adverse event entry for this patient and no indication of discontinuation. The remaining three have values of 52, 53 and 55 U/L.

Abbreviated Shift Table:

Table 51 ALT High / Low Shift by Dose Group

ALT shift	OXC XR 2400mg/day n(%)	OXC XR 1200mg/day n(%)	PBO n(%)
Normal to High	2 (1.6)	2 (1.6)	1 (0.8)
Normal to Low	0	0	0

Reviewer Comment *ALT*: The numbers of patients with notable increase from baseline or out of reference range at visit 6 were not high and those in this category 3 were elevated at baseline. Of those which were normal at baseline the maximum elevation did not exceed 1.8 times upper limit of normal. The shift table analysis (Table 51) did

not reveal a notable increase in shift from normal to high over that seen in placebo (gradient = 0.8%).

AST

Increase from baseline

The laboratory dataset is examined for entries with an increase AST from baseline to visit 6 of ≥40U/L. The search reveals 3 entries for one each of three patients in the placebo group. None are found in the oxcarbazepine treatment group.

Shift Table

Table 52 AST High / Low Shift by Dose Group

AST shift	OXC XR 2400mg/day n(%)	OXC XR 1200mg/day n(%)	PBO n(%)
Normal to High	1 (0.8)	1 (0.8)	4 (3.3)
Normal to Low	0	0	0

Reviewer Comment *AST*: There are no subjects with notable increase from baseline in the oxcarbazepine treatment group. The shift table analysis (Table 52) reveals notably greater shift from normal to high values in the placebo group than in the oxcarbazepine treatment groups.

Total Bilirubin

Out of Reference Range (22 umol/L = ULN)

The laboratory database is examined for patients with a total bilirubin out of reference range. The search reveals 2 patients in an oxcarbazepine treatment arm. One patient has a total bilirubin elevation which is out of reference range at baseline and has no change in value at visit 6. The second patient (821008) had a normal baseline value with an elevation to 39 umol/l at visit 6, an increase of 30umol/l. Patient number 821008 total bilirubin value at visit 6 reaches 1.8 x ULN, however the ALT is normal, therefore this patient does not meet criteria for a HY's law case. Alkaline Phosphatase also remains in the normal limit but does reveal an increase from 62 u/l at baseline to 85 u/l at visit 6.

Increase from baseline

The laboratory dataset is examined for patients with increase from baseline to visit 6 bilirubin greater than two standard deviations of the mean of all patient baseline values, 6.0umol/l. This search identifies 6 patients; five of these patients are placebo. The remaining patient (821008) has an increase of 30umol/l. The adverse event database reveals this patient had three adverse events, none SAEs. These events were a single entry for general weakness and two entries for somnolence. These events occurred on

study days 11 (asthenia, somnolence) and 37 (somnolence), notably none present for hepatic dysfunction.

Shift table

Table 53 Total Bilirubin High / Low Shift by Dose Group

Total Bilirubin Umol/L	OXC XR 2400mg/day n(%)	OXC XR 1200mg/day n(%)	PBO n(%)
Normal to High	1 (0.8)	0	1 (0.8)
Normal to Low	0	0	0

Reviewer Comment (*Total Bilirubin)*: One subject has a notable elevation of total bilirubin from baseline which equals 1.8 ULN. This subject has no elevation of ALT and no adverse event related to hepatic dysfunction, the patient continues in the study. The shift table (Table 53) reveals a shift from normal to high total bilirubin values which is equal in the placebo and oxcarbazepine treatment groups.

Reviewer Comment *hepatic dysfunction*: Examination of ALT, AST and total bilirubin values reveals no evidence of a hepatic dysfunction signal in study 804P301

Urea Nitrogen

Out of reference range (9 mmol/L = ULN)

Two patients are identified with urea nitrogen out of reference range at visit 6. One of these subjects was in the placebo treatment arm; the remaining patient (103002) was in the 2400mg/day oxcarbazepine treatment arm. The dataset reveals the urea nitrogen value increased by 150% from baseline to visit 6 (4mmol/L to 10mmol/L). The adverse event database reveals this patient had one adverse event on study day 29 of pain in extremity. This was not entered as an SAE and did not lead to study discontinuation.

Increase from baseline

The laboratory dataset is examined for patients with increase from baseline to visit 6 bilirubin greater than two standard deviations from the mean of all patient baseline values, 3.0mmol/l. Three patients are identified in this manner. One patient is in the placebo treatment arm. A second patient in the 2400mg/day treatment group had an increase from 4mmol/l at baseline to 10 mmol/l at visit 6. The result at visit 6 was 1 mmol/L beyond the reference limit. The third patient identified (103002) was identified in the “out of reference range” analysis above.

Shift Table

Table 54 Urea Nitrogen High / Low Shift by Dose Group

Urea Nitrogen	OXC XR	OXC XR	PBO

mmol/L	2400mg/day n(%)	1200mg/day n(%)	n(%)
Normal to High	1 (0.8)	0	1 (0.8)
Normal to Low	0	0	0

Reviewer Comment *urea nitrogen*: two patients are identified in the out of reference range and increase from baseline analysis, there is only a small elevation above ULN (1.1 x ULN). The shift table (Table 54) analysis reveals equal placebo and oxcarbazepine shifts from normal to high, one patient in each.

Carbon Dioxide

Out of reference range

The laboratory database is examined for patients with CO2 out of reference range. The search reveals 36 patients with an entry of low CO2, reference range 20-32 mmol/l. There were no visit entries with high CO2. Fourteen of the 36 patients with a low visit 6 value had low CO2 at baseline. Among the 22 patients with normal baseline CO2 there were 6, 8 and 8 patients with low CO2 values in the 2400mg/day, 1200mg/day and placebo groups respectively. The percent change from baseline for each of these patients is calculated to determine if there is a difference between the treatment and non treatment groups and also if there is a dose response within the oxcarbazepine treatment groups. This analysis is shown in Table 55. The greatest mean and median change from baseline was noted in the placebo group with no dose response noted for mean decrease in the oxcarbazepine treatment groups. The range of percent decline from baseline was also similar.

No adverse events indicating respiratory or renal disorders are identified among the adverse events experienced by the 22 visit 6 patients with CO2 below reference range and not low at baseline.

Table 55 CO_2 Percent Decline From Baseline in Patients not Low at Baseline

CO2 Percent decline from baseline in patients not low at baseline	OXC XR 2400mg/day	OXC XR 1200mg/day	PBO
n	6	8	8
Mean % decline	14.3	14.3	16.7
Median % decline	14.60	12.5	15.5
Range of % decline	9.5 – 18.2	5-22.7	9.5 – 28.6

Decrease from baseline

All CO2 values from visit 2 are utilized to calculate mean baseline CO2 value with standard deviation. The mean is found to be 22.5 with an SD of 2.9. Normal SI range is 20 to 32 mmol/l. All visit 6 values are examined for a decline from baseline greater than 5.8 mmol/l (2 SD from mean), four patients are identified using this method. One patient

is in the placebo group and 3 in the 2400mg /day group. Only the placebo group patient has a visit 6 result that is below reference range. Although there was a 2 SD or greater decline in CO2 among the treatment patients the visit 6 result remains within reference range.

Shift table

Table 56 CO2 High / Low Shift by Dose Group

CO2 mmol/L	OXC XR 2400mg/day n(%)	OXC XR 1200mg/day n(%)	PBO n(%)
Normal to High	0	0	0
Normal to Low	3 (2.4)	7 (5.7)	4 (3.3)

Reviewer Comment, *carbon dioxide*: There are 22 patients who are out of reference range low, there is no dose response in number of patients by dose group. In each oxcarbazepine treatment arm taken alone, the number of patients with an out of reference range low value does not exceed placebo. There were no adverse events among these patients which were related to renal or respiratory disorders. The examination of patients with a decline from baseline > 2 SD from mean identifies 3 patients which fulfill this criteria but none has a resultant value below reference range. The shift table (Table 56) analysis reveals no dose response in shift from normal to low. There is an excess over placebo of 2.4% in shift from normal to low in the 1200mg treatment arm. Taken overall this analysis does not identify a safety signal for decline in CO2 values.

Creatinine

Out of Reference Range

No oxcarbazepine treated patients are identified with a creatinine value out of reference range at visit 6.

Increase from baseline

All creatinine values from visit 2 are utilized to calculate mean baseline creatinine value with standard deviation. The mean is found to be 71 umol/l with a SD of 15 umol/l. Normal SI unit range is 44 to 124 umol/l. All visit 6 values are examined for an increase from baseline greater than 30 umol/l. Two patients are identified with an increase in creatinine ≥30 umol/l, both of these patients are in the placebo treatment arm.

Shift table

Table 57 Creatinine High / Low Shift by Dose Group

Creatinine umol/L	OXC XR 2400mg/day n(%)	OXC XR 1200mg/day n(%)	PBO n(%)

Creatinine umol/L	OXC XR 2400mg/day n(%)	OXC XR 1200mg/day n(%)	PBO n(%)
Normal to High	1 (0.8)	0	1 (0.8)
Normal to Low	4 (3.3)	0	1 (0.8)

Reviewer Comment, *creatinine*: no subject is identified with creatinine laboratory abnormalities in the examination of patients out of reference range or increase from baseline. The shift table (Table 57) analysis reveals a normal to high shift in which is equal in the placebo and OXC-XR treatment arms. There is an excess of patients in the 2400mg treatment arm with a shift from normal to low, however the clinical significance is uncertain and unlikely related to a physiologic safety signal.

Glucose

Out of reference range

Table 58 Glucose: Patients Out of Reference Range at Visit 6 with Normal Range Value at Baseline

Patients out of reference range at Visit 6 with normal range values at baseline.	Out of Reference Range High			Out of reference range Low		
Out of reference range – high / low (OORR)	N	Mean Glucose value	Mean change from baseline	N	Mean Glucose value	Mean change from baseline
OXC XR 2400mg/day	5 (4%)	132	32	5 (4%)	63	-19
OXC XR 1200mg/day	4 (3.3%)	122	28	6 (5%)	63	-26
Placebo	5 (4.1%)	119	31	2 (1.7%)	68	-20

Increase from baseline

All glucose values from visit 2 are utilized to calculate a mean baseline glucose value with standard deviation. The mean is found to be 94 mg/dl with a SD of 25mg/dl. Normal mg/dl range is 70 to 125mg/dll. All visit 6 values are examined for an increase from baseline greater than 50mg/dl. No patients met the test for an increase from baseline greater than 50mg/dl (2x standard deviation of this cohort baseline). A more conservative test for increase glucose from baseline was subsequently performed. All visit 6 values were examined for an increase from baseline greater than 30mg/dl. A total of 8 patients are identified, 2 from the placebo group, 2 from the 1200mg/ day treatment arm and 4 from the 2400mg/day treatment arm. There was little difference between the mean visit 6 glucose values among the three treatment arms. The mean change (increase) from baseline was 40mg/dl, 39mg/dl and 37mg/dl in the placebo, 1200mg/day and 2400mg/day respectively.

Table 59 Glucose: Patients with Increase from Baseline > 30mg/dl

Patients with Increase from baseline >30mg/dl	N	Mean Glucose value	Mean change from baseline
OXC XR 2400mg/day	4	130	37
OXC XR 1200mg/day	2	130	39
Placebo	2	133	40

Decrease from Baseline

The visit 2 values were utilized to calculate the mean and standard deviation baseline glucose values as noted above. All visit 6 values were examined for a decrease from baseline greater than 50mg/dl. Six patients are identified with a decline from baseline ≤-50mg/dl, one from the placebo treatment group and the remaining 5 from the 1200mg/day treatment arm. The visit six value results were below reference range in one patient from the 1200mg/day treatment group. One of the 1200mg/day treatment patients had a decline from baseline of 171mg/dl, however the baseline value was well above reference range at 300mg/dl.

Table 60 Glucose: Patients with Decrease from Baseline ≤-50mg/dl

Patients with Decrease Glucose from baseline ≤-50mg/dl	N	Mean Glucose value	Mean change from baseline	Mean change from baseline with elimination of the 300 to 129mg/dl outlier
OXC XR 2400mg/day	-	-	-	
OXC XR 1200mg/day	5	97	-79	-56
Placebo	1	78	-80	

Abbreviated Shift table

Table 61 Glucose High / Low Shift by Dose Group

Glucose at visit 6	OXC XR 2400mg/day n(%)	OXC XR 1200mg/day n(%)	PBO n(%)
Normal to High	5 (4.1)	3 (2.5)	3 (2.5)
Normal to Low	4 (3.3)	3 (2.5)	2 (1.7)

Reviewer Comment: examination of glucose values out of reference range at visit 6 reveal similar numbers of patients whose values are out of reference range high and out of reference range low. In those patients whose values are out of reference range high,

the numbers in placebo group are similar to those in the 1200mg and 2400mg treatment arm. In those subjects with values out of reference range low there are greater numbers in the treatment group than in the placebo group although the decline from baseline value is similar in all treatment arms. Examination of those with increase in glucose greater than 30mg/dl from baseline reveals a small increase in this positive movement from baseline compared with placebo. There was no meaningful difference between the mean glucose values or mean change from baseline in those with an increase value. In those with a decrease from baseline less than -50mg/dl there was a single outlier case with a baseline value of 300mg/dl that declined to 129mg/dl. Only one of the remaining four incidents of decline from baseline resulted in a value that was out of reference range. The abbreviated shift table reveals roughly equal numbers of shift from normal to low and normal to high in each treatment arm. All of these analyses taken together reveal no signal for hypo or hyper glycemia due to oxcarbazepine XR.

Potassium

Out of Reference Range (V6, normal at baseline)

Examination of the visit 6 potassium values reveals a total of 5 patients with values out of reference range which were normal at baseline. Two of these values are above reference range and one each occurs in the placebo and 2400mg/day treatment arm. The maximum difference between upper limit of normal and those above reference is 0.3mmol/l. There were three patients below reference range at visit 6. One of these incidents was in the placebo group while two were in the 1200mg treatment arm. The maximum difference between the low value and reference value was 0.3mmol/l.

Increase from baseline

All potassium values from visit 2 are utilized to calculate a mean baseline potassium value with standard deviation. The mean is found to be 4.4mmol/l with a SD of 0.42mmol/l. Normal range is 3.5mmol/l to 5.5mmol/l. all potassium values from visit 6 are examined to identify change from baseline greater than .084mmol/l. Six patients are identified who fulfill this criteria, 2 in the placebo group, 2 in the 1200mg/day group and 2 in the 2400mg/day group. None of the resultant (visit 6) values are above reference range.

Decrease from baseline

All potassium values from visit 6 are examined to identify change from baseline larger than -0.84mmol/l. A total of 11 patients are identified who meet these criteria. There are 4, 6 and 1 patients in the placebo, 1200mg and 2400mg groups respectively, with a decline in potassium value between baseline and visit 6 greater than -0.84mmol/l. The mean potassium value is 4.2mmol/l in the placebo group and 3.7mmol/l in the oxcarbazepine treated groups. The mean decline in potassium value is -1.2mmol/l in both the placebo and 1200mg/day treatment groups as seen in Table 62.

Table 62 Decrease from baseline K+ less than -0.84mmol/liter

Decrease from baseline K+ less than -0.84mmol/liter	N	Mean Potassium value	Mean change from baseline potassium
OXC XR 2400mg/day	1 (0.8%)	3.7	-0.9
OXC XR 1200mg/day	6 (4.9%)	3.7	-1.2
Placebo	4 (3.3%)	4.2	-1.2

Abbreviated shift table

Table 63 Potassium (K+) High / Low Shift by Dose Group

Potassium visit 6	OXC XR 2400mg/day n(%)	OXC XR 1200mg/day n(%)	PBO n(%)
Normal to High	1 (0.8)	0	1 (0.8)
Normal to Low	0	2 (1.6)	1 (0.8)

Reviewer Comment: The frequency and relative potassium value deviations above and below reference range at visit 6 was similar. Examination of the increase and decrease from baseline greater than (*absolute value*)│0.84mmol/l│did not reveal notable differences between placebo and treatment groups. None of those with an increase from baseline greater than 0.84mmol/l had a resulting value outside of reference range. Two of the 11 patients with a decrease from baseline to visit 6 larger than -0.84mmol/l reveal a resulting value below the reference range. Both of these were in the 1200mg/day group. The shift table (Table 63) does not reveal a notable difference in number of patients changing from normal to low or normal to high, nor is there a notable difference between normal to low or high in the treatment compared to the placebo groups. There is no signal that oxcarbazepine XR treatment is associated with hyperkalemia or hypokalemia.

Sodium

Out of Reference Range (V6, normal at baseline, Table 64)

High: there are two patients identified with a sodium value normal at baseline and above reference range at visit 6. These occurred one each in the 1200mg/day and 2400mg/day group. The average of these high values was 148mmol/l with an increase of 3 mmol/l in both instances.

Low: There were 22 patients identified with sodium values normal at baseline and below reference range at visit six.

Table 64 Patients out of reference range Na^+ at Visit 6 with normal range values at baseline.

Patients out of reference range Na^+ at Visit 6 with normal range values at baseline.	Na^+ Out of Reference Range High			Na^+ Out of reference range Low		
Out of reference range – high / low (OORR)	N	Mean Na^+ value	Mean change from baseline	N	Mean Na^+ value	Mean change from baseline Na^+
OXC XR 2400mg/day	1 (0.8%)	149	3	8 (7%)	128	-12.6
OXC XR 1200mg/day	1 (0.8%)	147	3	12 (10%)	131	-8.4
Placebo	0	0	0	2 (2%)	132	-5.5

Increase from baseline

Visit 2: Mean 140mmol/l, SD= 2.5mmol/l, range = 131 to 153

There are 4 patients identified with an increase from baseline greater than 5 mol/l. Three of these patients are in the placebo treatment group. There is one patient in the 2400mg/day treatment group who had a 7mmol/l increase from baseline but the resultant Na^+ remained within normal limits.

Decrease from Baseline

There were 35 patients identified with normal baseline Na^+ and a decrease from baseline at visit 6 ≥ 5mmol/l. There were notably greater numbers of patients with a decrease from baseline in the oxcarbazepine treatment groups than in the placebo group. The mean Na^+ was higher in the placebo group in those with a decline from baseline than in the oxcarbazepine XR treatment groups and the mean decline from baseline was larger in the treatment groups than in the placebo group. These values are displayed in Table 65.

Table 65 Decline from baseline Na^+ at Visit 6 by more than 5mmol/liter

Decrease from baseline Na^+ less than 5mmol/liter	N	Mean Na^+ value	Mean change from baseline Na^+
OXC XR 2400mg/day	12 (10%)	130	-10.5
OXC XR 1200mg/day	17 (14%)	133	-8.1
Placebo	6 (5%)	136	-6.5

Abbreviate shift table

Table 66 Sodium (Na+) High / Low Shift by Dose Group

Na^+	OXC XR 2400mg/day n(%)	OXC XR 1200mg/day n(%)	PBO n(%)
Normal to High	1 (0.8)	1 (0.8)	0
Normal to Low	8 (6.5)	12 (9.8)	2 (1.7)

Reviewer comment: The examination of normal to high values of Na^+ revealed no meaningful tendency toward induction of high sodium values in the out of reference range, increase values from baseline or shift table data. The examination of Na+ values in the data for out of reference range at visit 6 revealed a notable separation between number of incidents which occurred in placebo compared to the oxcarbazepine XR treatment groups as well as the mean decline in Na+ values. The magnitude of incident number and mean decline in sodium for those below reference range was smaller in the placebo group. There were also notably more incidents of decrease Na+ from baseline in the oxcarbazepine XR treated groups compared to placebo as well as a larger mean change from baseline in the oxcarbazepine XR group. There was no dose response observed in the frequency of sodium below reference range or decline in sodium from baseline. The abbreviated shift table (Table 66) revealed a notably greater number of normal to low shift compared to normal to high shift as well as notably greater frequency of normal to low shift in the oxcarbazepine XR treatment groups compared to placebo. All of the analyses; out of reference range low at visit 6, decrease from baseline at visit 6 and shift from normal to low reveal a signal for induction of decline in sodium in the oxcarbazepine treatment groups. Hyponatremia is present in the current labeling, section 5.1 of “Warnings and Precautions” of the reference listed drug, Trileptal. The analysis of change in sodium here does not indicate additional need to strengthen the proposed oxcarbazepine XR label.

Clinical Chemistry conclusion: Among the clinical chemistry parameters ALT, AST, Total Bilirubin, urea nitrogen, carbon dioxide (CO2), creatinine, glucose, potassium and sodium, only examination of sodium values reveal a conclusive signal for induction of decline in sodium values associated with oxcarbazepine XR treatment. This safety

signal is presently addressed in section 5.1, “Warnings and Precautions” of the RLD and proposed oxcarbazepine XR labeling.

7.4.3 Vital Signs

The sponsor reports “the mean values for systolic blood pressure, diastolic blood pressure, heart rate, respiratory rate and temperature were within the normal range at baseline and end point in all treatment groups. There were non-clinically important changes in mean vital signs from baseline to end point for any treatment group.”

The vital sign datasets for temperature and blood pressure were further examined in the discussions below to corroborate the sponsor conclusion.

Blood Pressure

Reference Range

Table 67 Vital Sign Reference Range

Reference Range derived from Protocol 804P301 exclusion criteria	Systolic	Diastolic
Normal	≤140	40≤
High	>140	>90
Low	<90	<40

Out of Reference Range

High

Systolic Blood pressure: one patient (0.4%) in the oxcarbazepine XR treatment group had an elevated systolic blood pressure of 168mmHg at visit 6. no patient in the placebo group had an elevated systolic blood pressure.

Diastolic Blood pressure: eight patients (3.3%) in the oxcarbazepine XR treatment group had elevated diastolic blood pressure. Three patients (2.5%) in the placebo group had elevated diastolic pressure.

Low

Systolic blood pressure: two patients at visit 6, one each in the oxcarbazepine XR 2400mg/day group and one in the placebo treatment group had a low systolic blood pressure; the values were 86mmHg and 79mmHg respectively.

Diastolic blood pressure. Two patients at visit 6 in the oxcarbazepine XR treatment group and one patient in the placebo treatment group have a diastolic blood pressure less than 60mmHg. The patient in the treatment group had a low diastolic blood pressure (50mmHg) at baseline. The patient in the placebo group with low diastolic blood pressure had a normal range measurement at baseline.

Mean Blood Pressure

At visit 6 the mean systolic blood pressure of the Oxcarbazepine XR treatment group is 1.3mmHg greater than the placebo group and the median of the Oxcarbazepine group is 2mmHg greater than the treatment group. Mean and median diastolic blood pressure also reveals the oxcarbazepine XR treatment group to be slightly higher than placebo, Table 68. Baseline and Visit 6 group means and medians are examined for the oxcarbazepine XR group in Table 69. The mean at visit 6 is 1mmHg lower than baseline while the medians are the same at 120mmHg.

Table 68 Placebo and Oxcarbazepine XR Treatment groups, Systolic and Diastolic Blood pressure at Visit 6: means, median, range

Placebo and Oxcarbazepine XR Treatment groups, Systolic and Diastolic Blood pressure at Visit 6- means, median, range		
Statistic	Placebo, n=107	Oxcarbazepine, n= 170
	Systolic	
Mean	117.7	119
Median	118	120
range	79, 159	86, 168
	Diastolic	
Mean	74.1	75
Median	74	75
range	59, 100	50, 106

Table 69 Oxcarbazepine XR Systolic Blood Pressure at Baseline and Visit 6: means, medians and range

Oxcarbazepine XR Systolic Blood Pressure at Baseline and Visit 6- means, medians and range		
Oxcarbazepine XR, Systolic	Baseline	Visit 6
Mean	120	119
Median	120	120
range	90, 157	86, 168

Change from Baseline

Increase in systolic blood pressure greater than 10mmHg from baseline to Visit 6. There were 20 patients in the oxcarbazepine XR treatment group and 20 patients in the placebo treatment group with systolic blood pressure increase noted between baseline and visit 6. The average increase in the 20 placebo patients was 17mmHg while the average increase in the oxcarbazepine XR treatment group was 21mmHg. Among the 20 oxcarbazepine XR treated patients with a change from baseline greater than 10mmHg the highest resulting systolic blood pressure was 168mmHg following an increase of 36mmHg from a baseline of 132mmHg an additional three of these 20 patients had a systolic blood pressure result greater than 140mmHg following the increase from baseline.

Decrease in systolic blood pressure greater than 10mmHg from baseline to visit 6. There were 17 patients with a systolic blood pressure at visit 6 noted to have a value less than -10mmHg compared to the baseline visit and 10 patients in the placebo group with a decline from baseline less than -10mmHg. The mean decline of the 17 oxcarbazepine XR treatment patients was -21mmHg. The mean decline of the 10 placebo treated patients with systolic blood pressure decline less than -10mmHg was -19mmHg.

Increase in diastolic blood pressure greater than 10mmHg from baseline to visit 6: There were 15 oxcarbazepine XR treatment patients with a change of more than 10mmHg diastolic blood pressure from baseline to visit 6 and 10 patients in the placebo group with a change of more than 10mmHg in diastolic blood pressure from baseline to visit 6. The mean increase of the 15 oxcarbazepine XR treatment patients was 13.5mmHg while the mean increase of the 10 placebo treatment patients was 17mmHg. Among the 10 placebo patients who experienced a greater than 10mmHg increase from baseline the resultant diastolic blood pressure was greater than 90 in two patients. Among the 15 patients in the oxcarbazepine treatment patients who experienced an increase in diastolic blood pressure greater than 10mmHg three patients had a resultant blood pressure greater than 90mmHg.

Decrease in diastolic blood pressure to less than -10mmHg from baseline to visit 6: There were 13 oxcarbazepine XR treatment patients with a diastolic blood pressure measurement which declined by more than -10mmHg from baseline to visit 6 and 12 patients in the placebo group that had a measurement which declined by more than -10mmHg at visit 6. The mean change from baseline in the 13 oxcarbazepine XR treatment patients was -16mmHg while the mean decline from baseline in the 12 placebo treatment patients was -18mmHg. Among the 13 oxcarbazepine XR treated patients who experienced a larger than -10mmHg decline in diastolic blood pressure, one patient had a resultant diastolic blood pressure less than 60mmHg. Among the 12 placebo treated patients with a larger than -10mmHg decline from baseline in diastolic blood pressure one had a resultant diastolic blood pressure less than 60mmHg.

Reviewer Comment: The blood pressure dataset was explored by examination of values out of reference range at visit 6, examination of group means at baseline and visit 6 and increase or decrease from baseline at visit 6. There was no consisted

tendency for an increase or decline in systolic or diastolic blood pressure associated with oxcarbazepine XR treatment in these analyses.

Temperature

The vital signs dataset was examined for change in body temperature. Treatment group mean change from baseline body temperature was examined at visit 6 in Table 70. Visit 6 is selected as the comparator to baseline because it captures exposure to the study drug for the 12 week maintenance interval. There was a mean 0.1 degree F decrease of body temperature in the oxcarbazepine XR treatment groups with a mean increase of 0.05 degree F in the placebo group. The ranges of change from baseline are similar between groups with a somewhat greater minimum in the 2400mg/day group.

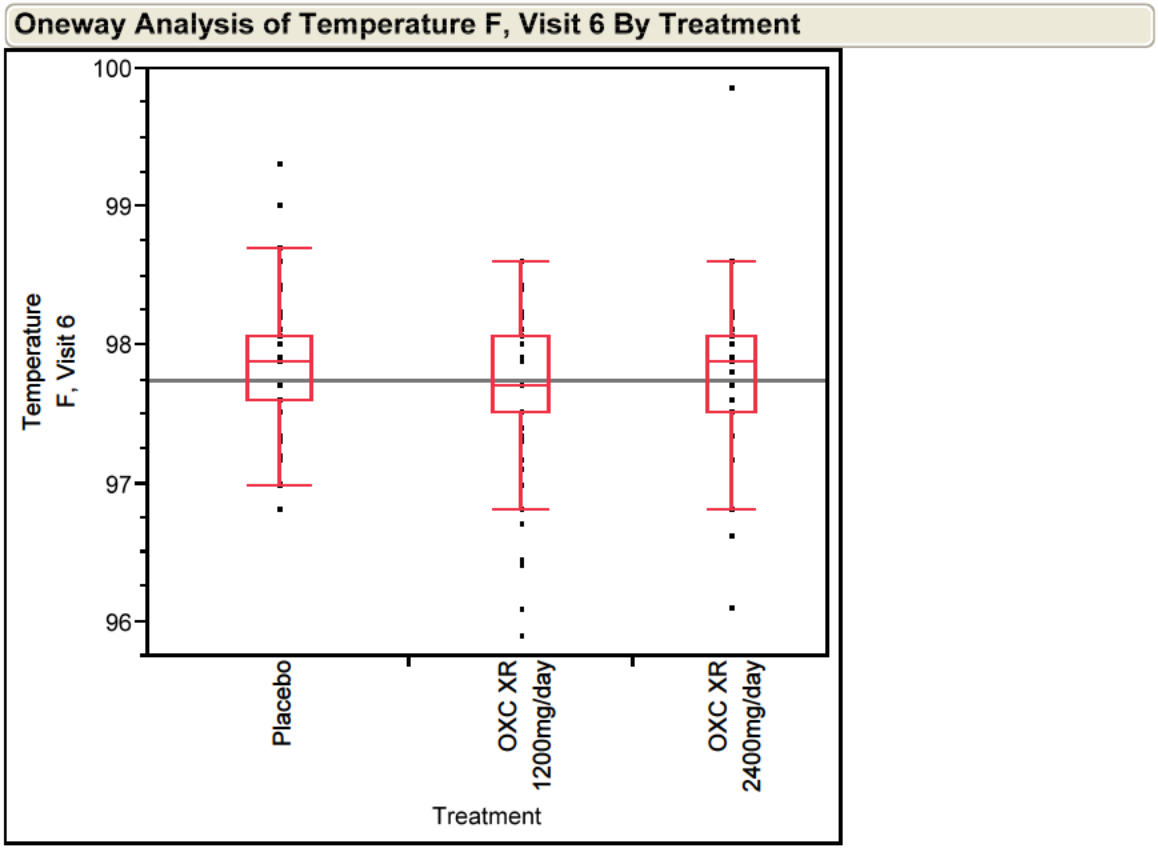
Table 70 Change from Baseline F^0, all patients at Visit 6

Change from Baseline F^0, all patients at Visit 6	PBO N=107	1200mg/day	2400mg/day
Mean	0.045	-0.098	-0.088
Median	0	0	0
range	-1.78, 1.6	-2, 1.26	-2.52, 1.98

In Figure 13 below, body temperature measurements are examined by treatment group at visit 6 in the table below. There are more frequent low body temperature outliers in the treatment groups, 1200mg/day > 2400mg/day, than in the placebo group.

In the table of descriptive statistics attached to Figure 13 there are no differences noted between placebo and the 2400mg treatment group at the median and 3rd quartiles of body temperature. There is a small decrease of .08 F^0 noted between placebo and both treatment groups in the 1st quartile of body temperature. The 1200mg treatment group reveals a small decrease of 0.18 degree F compared to the median placebo value for body temperature. There is no difference between the placebo and 1200mg treatment group at the 3rd quartile value for body temperature.

Figure 13 Mean Temperature at Visit 6 by Dose Group



Quantiles

Level	Minimum	10%	25%	Median	75%	90%	Maximum
Placebo	96.8	97.16	97.6	97.88	98.06	98.24	99.3
OXC XR 1200mg/day	95.9	96.8	97.52	97.7	98.06	98.232	98.6
OXC XR 2400mg/day	96.1	97.16	97.52	97.88	98.06	98.06	99.86

Reviewer Comment: There is a subtle trend toward decrease body temperature in the oxcarbazepine XR treatment groups noted in the change from baseline analysis and the low temperature outliers at visit 6. A very small negative shift in the mean of body temperature from all treatment visits of all patients in the 2400mg/day group can be seen in appendix 9.4. The subject ID of all oxcarbazepine XR treated patients with a body temperature less than 97 degrees F was matched to the adverse event dataset to determine if there were events related to hypothyroidism or metabolic dysfunction. There was one (preferred term) PT of feeling cold, however this patient had an equally low body temperature at baseline (312005), there were several events related to fatigue but these are too non-specific and more likely related to typical CNS adverse events seen with oxcarbazepine. The observation of a subtle shift to lower body temperature does not appear to be clinically meaningful based on adverse effects seen in the application.

Current Trileptal labeling does note a decrease in T_4, unrelated to clinical hypothyroidism, with the following language "*Laboratory data from clinical trials suggest that Trileptal use was associated with decreases in T4, without changes in T3 or TSH*"[4]. The observed decline in body temperature, although subtle, raises the possibility of a connection with the observed depression of T4 in current labeling. The observed body temperature change in the oxcarbazepine XR treatment groups in this application support a need for continued pharmacovigilance on this issue.

7.4.4 Electrocardiograms (ECGs)

The sponsor states "Vital sign and ECG changes were isolated and not considered clinically important by the Investigators. Based on the vital sign data available in this study, no vital sign abnormality was directly attributable to study drug."

In order to confirm this conclusion the ECG dataset was examined for out of reference range values during treatment visits, median change from baseline values, and change from normal at baseline to abnormal during treatment for QT, corrected QT interval, heart rate, PR interval and QRS interval.

QT

Examination of absolute QT in Table 71 below reveals no QT interval greater than 500ms. There were 2 patients with QT >450ms at visit 1 in the placebo group and 3 at each subsequent visit. In the 1200mg/day group there were none at the screening visit and 4 at visits 3 and 6 in the maintenance interval. In the 2400mg group there were 3 patients with QT > 450ms at screening, visit 3 and visit 6 in the maintenance interval. Overall the 1200mg/day group reveals an increase over placebo but in the 2400mg/day group there is no difference from placebo at any visit. There is also no difference between the 2400mg/day group and placebo at the maintenance visits 3 and 6. There were no occurrences of QT>500ms at any measurement.

Table 71 QT Value: Out of Reference Range, High > 450ms and > 500ms

QT Out of Reference Range, High >450ms	Visit 1 (screening)	Visit 3	Visit 6
Placebo	2	3	3
1200mg/day	0	4	4
2400mg/day	3	3	3
QT Out of Reference Range, High >500ms			
Placebo	0	0	0
1200mg/day	0	0	0
2400mg/day	0	0	0

4 Section 5.11 "Laboratory Tests", Trileptal Prescribing information, Drugs at FDA 3/3/2011

The change from baseline for QTcF (Fridericia's correction) is examined in Table 72 below at maintenance visits 3 and visit 6 for each treatment group. There is a median of -1.6ms decrease in the placebo group at visit 3 compared to -0.35ms at visit 3 in the 1200mg/day group and -0.3ms in the 2400mg/day group. At visit 6 there is some divergence between the median of the placebo group and 1200mg/day group with a +2.6ms median increase in the 1200mg/day group. The 2400mg/day group does not continue this trend and a median -0.95ms decline in QTcF is seen at visit 6. In the oxcarbazepine XR treatment groups the values for the 25th and 75th percentile, flanking the median are roughly similar in magnitude but are of opposite sign (negative / positive) at both visits 3 and visit 6.

Table 72 QTcF Change from Baseline at Visits 3 and 6 (Maintenance), median, range, and percentiles by Dose Group

QTcF Change from Baseline at Visits 3 and 6 (Maintenance), median, range, and percentiles								
Treatment	Visit #	Minimum	10%	25%	Median	75%	90%	Maximum
Placebo	3	-135.2	-45.28	-15	-1.6	10.2	22	82.5
	6	-126.8	-36.66	-18.3	-1.9	9.9	25.38	88.9
OXC XR 1200mg/day	3	-83.6	-27.55	-14.175	-0.35	16.25	28.77	81.4
	6	-94.9	-29.1	-14.2	2.6	15.3	38.8	112.1
OXC XR 2400mg/day	3	-123.7	-41.28	-14.3	-0.3	14.6	31.02	126.5
	6	-111	-29.7	-11.525	-0.95	13.575	33.43	87.9

The measured values of QTcF at screening and maintenance visits for each treatment group are examined. There is a shortening of median QTcF between screening and visit 6 in all treatment groups. The median QTcF in the 1200mg group at visit 6 is 3.6ms shorter than at screening visit. The median QTcF in the 2400mg/day group at visit 6 is 5.85ms shorter than at screening visit, Table 73 below.

Table 73 QTcF at Baseline (visit 1) and Maintenance (Visit 3, 6), median, range, and percentiles for each treatment group (outliers)

QTcF at Baseline (visit 1) and Maintenance (Visit 3, 6), median, range, and percentiles for each treatment group (outliers)								
Treatment	Visit #	Minimum	10%	25%	Median	75%	90%	Maximum
Placebo	1	270	368.68	386.2	402.1	413.1	433.54	496.2
	3	283.1	364.36	379	395.6	413.8	433.94	519.9
	6	293.2	362.02	380.8	397.8	411.1	432.32	458.7
OXC XR 1200mg/day	1	319.2	368.44	382.55	399.3	414.7	426.8	465
	3	291.4	367.7	378.9	394.6	408.3	430.9	463.3
	6	298.4	364	380.775	395.7	414.4	433.7	504
OXC XR 2400mg/day	1	297.5	356.15	382.075	401.1	417.175	429.8	465.5
	3	263.2	356.3	383.9	399.3	417	433.46	491.1
	6	284.2	357.48	381.325	395.25	410.85	429.2	458.6

Reviewer Comment: The analysis of QT out of reference range, and QTcF measured during exposure and change from baseline do not reveal evidence of QT prolongation.

Heart Rate

Out of reference range: Heart rate that is out of reference range is shown in Table 74 at screening and maintenance visits for each treatment group. The treatment groups reveal no separation from placebo for incidents above or below reference range. There is no dose response noted for occurrences of heart rate above or below reference range at any maintenance visit.

Table 74 Heart rate outliers, by visit and treatment group

Heart rate outliers, by visit and treatment group						
	V1 (screening)		V3		V6	
Out of Reference Range	<50	>100	<50	>100	<50	>100
PBO	2	2	2	1	2	1
1200	3	2	3	1	1	0
2400	3	3	1	0	1	1

Change from Baseline: Heart rate change from baseline is examined at maintenance visits 3 and visit 6 in Table 75 below. The median change in heart rate at visit 3 in the placebo group is seen to be -2 BPM and no change from baseline at visit 6. The 1200mg/day treatment group shows a no change from baseline at visit 3 and a 1.5 beat / minute increase at visit 6. The 2400mg group has a 1 beat per minute increase at both visit 3 and 6. The maximum and minimum changes from baseline heart rate are similar in all treatment arms while there is a somewhat symmetric distribution of decrease heart rate below the median and increase heart rate above the median. This is consistent with random variability rather than a systematic shift in the direction of change from baseline.

Table 75 Change From Baseline Heart Rate At Maintenance Visits 3 And 6- Median, Range And Percentiles For Each Treatment Group

Change From Baseline Heart Rate At Maintenance Visits 3 And 6								
Treatment	Visit # (n)	Minimum	10%	25%	Median	75%	90%	Maximum
Placebo	3 (112)	-26	-15	-7	-2	5	10.8	30
	6 (108)	-34	-11.2	-7	0	7	13	32
OXC XR 1200mg/day	3 (102)	-34	-11	-6	0	7	11	19
	6 (90)	-34	-15.6	-7.25	1.5	8.25	13	36
OXC XR 2400mg/day	3 (96)	-30	-12	-6	1	7	14	21
	6 (79)	-27	-16.1	-5	1	7.25	13.1	31

Heart rate at Screening and Maintenance: Heart rate at screening, mid maintenance and end of the maintenance interval is examined in Table 76. The median heart rate in the 1200mg/day group is very close to placebo at visits 3 and 6. There is a small decline in the median heart rate in the 2400mg/day group at visits 3 and 6 compared to placebo and the 1200mg/day group. The 2400mg/ day group has a 2 beat per minute median increase at visits 3 and 6 compared to screening. The maximum and minimum heart rate values are similar in treatment and placebo groups and there is no consistent change in the heart rate values as the maintenance interval progresses.

Table 76 Heart Rate Measurement At Screening, Maintenance Visits 3 And 6, Median, Range And Percentiles For Each Treatment Group

Heart Rate Measurement At Screening, Maintenance Visits 3 And 6								
Treatment	Visit # (n)	Minimum	10%	25%	Median	75%	90%	Maximum
Placebo	1 (123)	46	55	63	69	78	86.6	109
	3 (112)	40	55.2	62	70	76	83	103
	6 (108)	44	56.8	61	71	78	85	117
OXC XR 1200mg/day	1 (122)	43	55.3	60	68.5	76	85	112
	3 (102)	38	54	62	69	76	82	100
	6 (90)	44	60	64.75	70	77	83.9	97
OXC XR 2400mg/day	1 (124)	44	54.5	59	66	74	82	103
	3 (96)	43	57	61	68	74	79.4	92
	6 (79)	43	57	63	68	74.25	80	107

Reviewer Comment: There is no evidence of treatment related change in heart rate.

PR Interval

Out of reference Range: PR interval greater than 200ms at screening and maintenance visits 3 and 6 in placebo and treatment groups is examined in Table 77. The occurrences of patients out of reference range (>200ms) is similar in placebo, visit 6 of the 1200mg/day group and both maintenance visits of the 2400mg/day group. The numbers of patients in the 1200mg/day group at visit 6 and both maintenance visits of the 2400mg/day group are less than the number of occurrences at screening visit. The exception is visit 3 in the 1200mg/day group where there are 12 occurrences out of reference range, a notable divergence from both the 1200mg/day screening visit and the frequency in placebo. This higher frequency does not likely indicate a study drug effect because there is no dose response seen in either the 1200mg/day or 2400mg/day group nor did this larger magnitude effect persist to visit 6 in the 1200mg/day group.

Change from normal baseline to out of reference range is also examined in columns 3 and 4 of Table 77 below. The occurrence of this shift is greater in the 1200mg/day group at visit 3 and at both maintenance visits in the 2400mg/day group. As in the absolute number of out of reference range patients noted at visit 3 in the 1200mg/day

group, the largest number of patients with shift from normal to high occurs at visit 3 in the 1200mg/day group. The longest PR interval, 240ms, is seen in visit 3 of the 2400mg/day group, however as noted in column 5 (most left), all heart rates in this group were less than 60, which may result in a longer PR interval.

Table 77 PR Interval: Out Of Reference Range High at Visits 1, 3, 6. Change from Normal Baseline to High with Resulting PR interval

PR Interval: Out Of Reference Range High at Visits 1, 3, 6. Change From Normal Baseline To High with Resulting PR interval					
Column #	**1**	**2**	**3**	**4**	**5**
Treatment	**Visit # (n)**	**PR> 200ms**	**Change from normal baseline to > 200ms**	**PR interval (ms) of resultant change from baseline**	**Heart Rate**
Placebo	1 (123)	4			
	3 (112)	5	2 (1.8%)	202, 220	
	6 (108)	4	2 (1.9%)	226, 203	
OXC XR 1200mg/day	1 (122)	7			
	3 (102)	12	6 (5.9%)	202, 206, 232, 205 217, 230	
	6 (90)	5	2 (2.2%)	210, 204	
OXC XR 2400mg/day	1 (124)	8			
	3 (96)	4	4 (4.2%)	205, 212, 240, 220	All rates for this group < 60
	6 (79)	3	3 (3.8%)	206, 227, 220	

Reviewer Comment: examination of the PR interval in the ECG dataset does not reveal a consistent study drug related association with the occurrence of values outside the reference range. There is some separation from placebo noted with examination of those cases which shift from normal at baseline to high at visit 3 or 6. There is no clear dose response and the PR intervals identified at visit 3 of the 2400mg/ day group are associated with heart rate under 60 beats per minute. Overall there is insufficient evidence to conclude there is a signal for abnormal PR interval associated with study drug treatment.

QRS Interval

QRS interval is examined for out of reference range at visits 1,3 and 6 as well as change from normal at baseline to high at maintenance visits 3 and 6 with resulting QRS. The results are displayed in Table 78. The out of reference range high (>120ms) reveal no difference at any visit between placebo and treatment. There is also no difference in the treatment groups between screening and maintenance visits. The change from normal to high at visits 3 and 6 analyses reveal four instances of this occurrence in the 1200mg/day treatment group at visit 6. The 2400mg/day treatment group reveals small increase over placebo occurrence. No dose response for the

occurrence of widening QRS interval is noted. One case in visit 6 of the 1200mg/day group has a marked change of QRS duration of 166ms from baseline to visit 6. The adverse event database is of this subject is examined and no cardiac related term is identified. The patient did have 6 adverse event, 5 were entered as rash and one as pruritus.

Table 78 QRS interval: Out of Reference Range High at Visits 1,3,6, Change from Normal at Baseline to High with Resulting QRS Interval.

QRS interval: Out of Reference Range High at Visits 1,3,6, Change from Normal at Baseline to High with Resulting QRS Interval.				
Treatment	**Visit # (n)**	**QRS >120ms**	**Change from normal baseline to > 120ms**	**QRS interval (ms) of resultant change from baseline**
Placebo	1 (123)	3		
	3 (112)	4		
	6 (108)	3	1	124
OXC XR 1200mg/day	1 (122)	3		
	3 (102)	3	1	130
	6 (90)	1	4	246*, 122, 122, 123
OXC XR 2400mg/day	1 (124)	4		
	3 (96)	2	1	122
	6 (79)	2	2	150, 122
* subject 172005, heart rate 60, Δ from baseline 166ms, no SAE, 6 AEs (5 x rash, 1 x Pruritus). Subject did discontinue study due to non-compliance.				

Reviewer Comment: The examination of QRS out of reference range and change from normal at baseline to abnormal does not reveal a signal for study drug related effect on ventricular depolarization. There are only small numbers of patients with change from normal baseline to abnormal.

Reviewer ECG summary: no signal was identified for study drug associated adverse effect on the electrocardiogram.

7.4.5 Special Safety Studies/Clinical Trials

No special safety studies are performed in this submission

7.4.6 Immunogenicity

Although Oxcarbazepine is a small molecule drug, less likely than a therapeutic protein to elicit an antibody response, immunogenic action has been established. Current Trileptal labeling contains warning for “Anaphylactic Reactions and Angioedema”, “Serious Dermatological Reactions”, and “Multi-Organ Hypersensitivity”. These reactions are dysimmune disorders which may be induced by oxcarbazepine.

7.5 Other Safety Explorations

None in this submission

7.5.1 Dose Dependency for Adverse Events

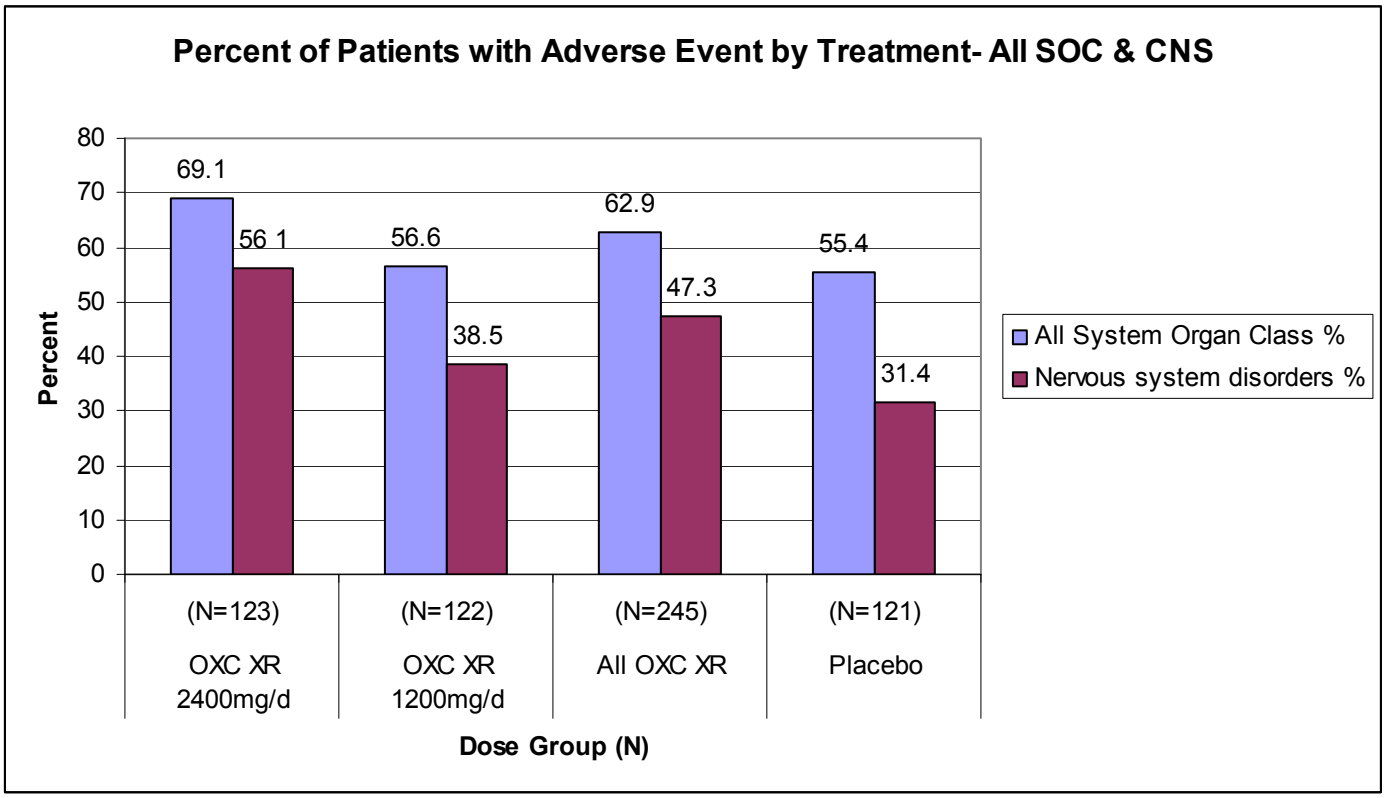
Central Nervous system related adverse effects appear dose related in the current Trileptal labeling where the highest discontinuation rate was seen in the 2400mg/day dose group and central nervous system adverse events were most common.

Reviewer Comment: In the pivotal controlled trial of the current submission, study 804P301, there was a dose relationship to the category of "all" common adverse events (∑ adverse in all SOCs). Nervous system disorders were the most common of the adverse events and also had a dose relationship which is shown in Table 79 and Figure 14, (taken from section 7.4).

Table 79 Dose Dependency of Adverse Events: All SOCs and Nervous System Disorders by Dose Group

MedDRA System Organ Class (SOC)	OXC XR 2400mg/d (N=123)	OXC XR 1200mg/d (N=122)	All OXC XR (N=245)	Placebo (N=121)
All SOCs	**85 (69.1)**	**69 (56.6)**	**154 (62.9)**	**67 (55.4)**
Nervous system disorders	69 (56.1)	47 (38.5)	116 (47.3)	38 (31.4)

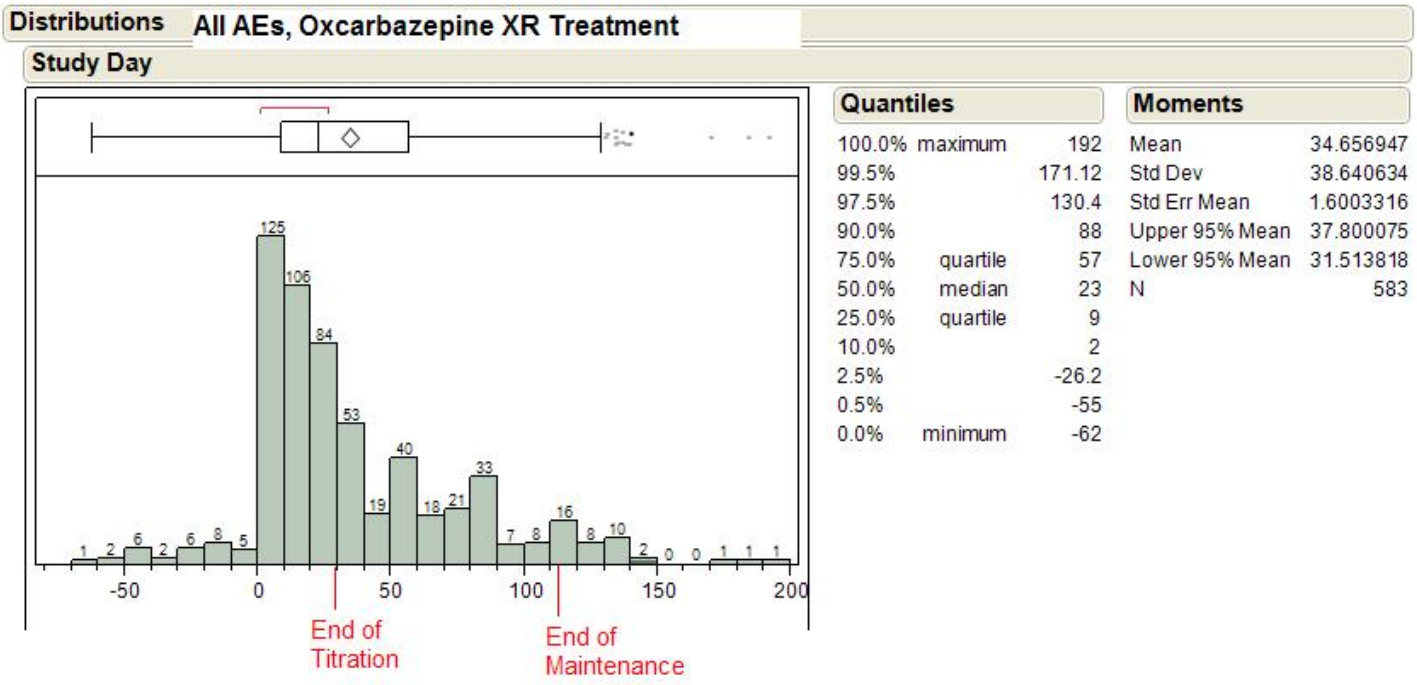
Figure 14 Histogram: Percent of Patients with Adverse Events by Treatment- All SOCs and Nervous System Disorders



7.5.2 Time Dependency for Adverse Events

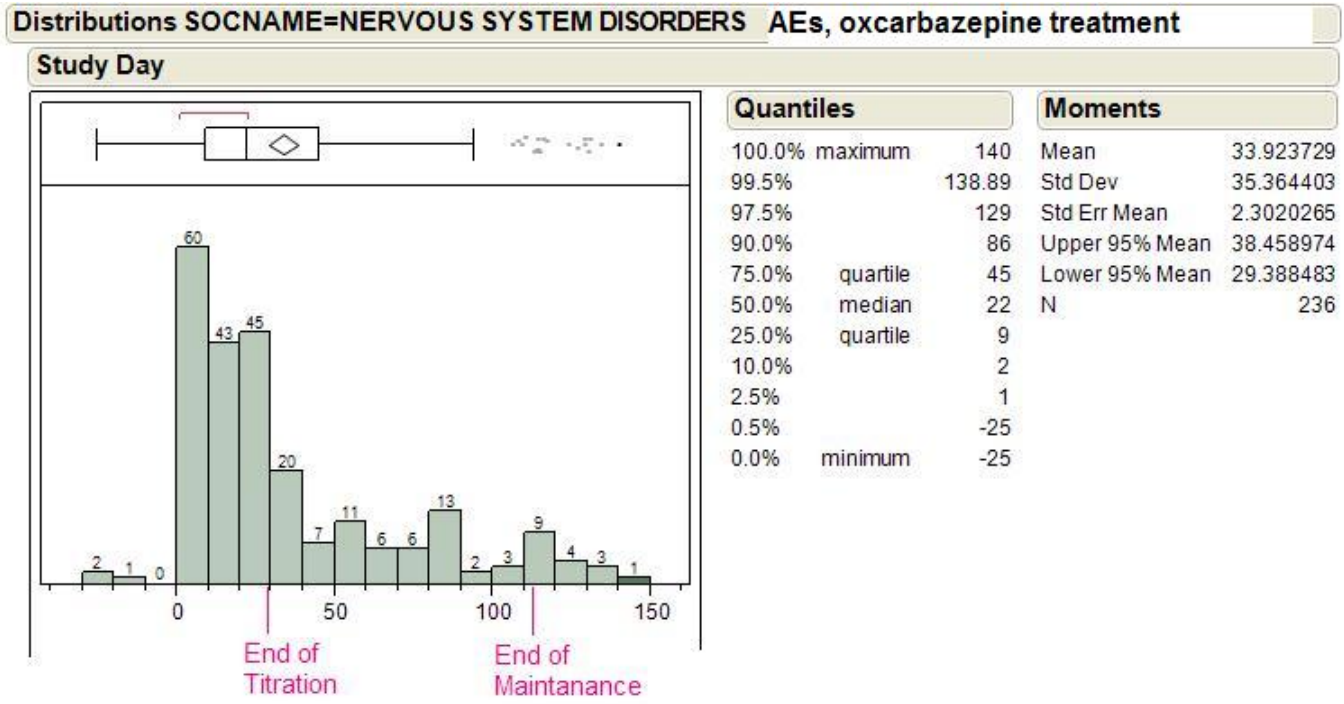
All adverse events in oxcarbazepine treatment patients showed a decreasing frequency over time from start of study. This can be seen in Figure 15 below, where end of titration occurs at day 29 and end of maintenance interval occurs at day 113. The median, 1st and 3rd quartile of events occur on day 23, 9 and 57 respectively. The interval of most frequent adverse events occurs during study drug titration then decreases and levels off during the maintenance interval.

Figure 15 Time Dependency of Adverse Events: Number of Adverse Events (any) by Study Day with Indicator for End of Titration and End of Maintenance



Central nervous system events follow a similar profile as overall adverse events, this is shown in Figure 16. The median, 1st quartile and 3rd quartile of events are captured by days 22, 9 and 45 respectively. The maximum rate of adverse events occurs during the titration interval.

Figure 16 Time Dependency of Adverse Events: Number of "Nervous System Disorder" (SOC) Adverse Events by Study Day with Indicator for End of Titration and End of Maintenance

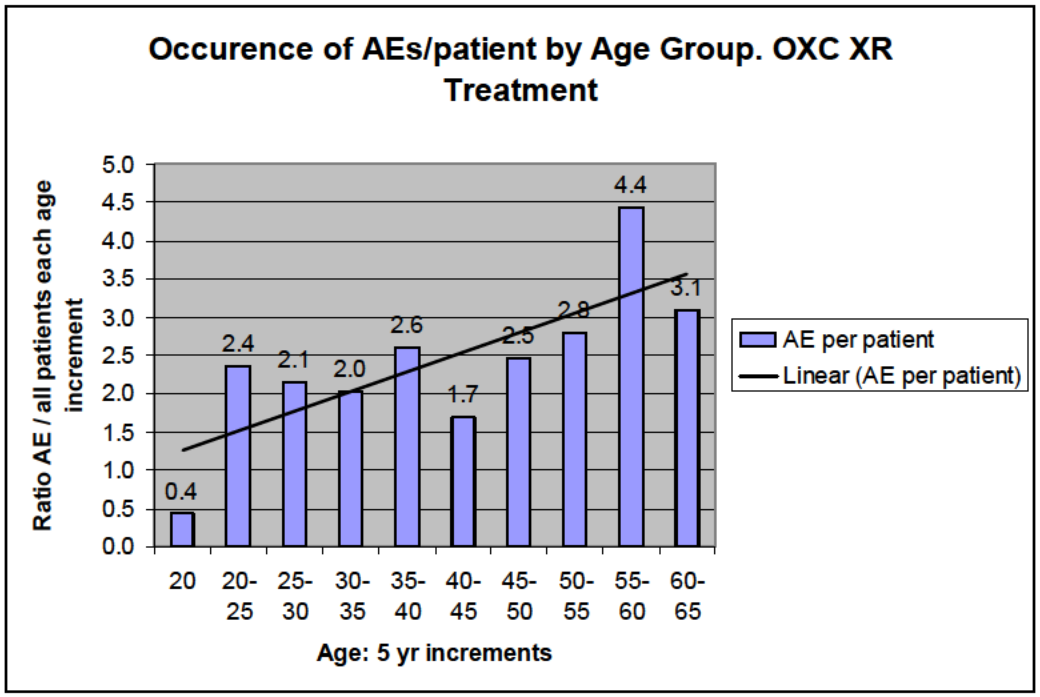


Reviewer Comment: There is a notable time dependency of adverse events. The frequency of adverse events from all SOCs is high during the titration interval then decreases and levels off during the maintenance interval. There were on average 105 adverse events in each 10 day interval during the titration phase of the study while there were on average 25 adverse events during each 10 days of the maintenance interval for events occurring under any SOC. There were 33 patients who discontinued (all treatment groups) due to adverse effects in the titration interval. An analysis of adverse events per patient/time would show a somewhat larger adverse event rate per patient time in the maintenance interval (this would normalized for dropouts) but would still be notably lower than the occurrence in the titration interval. This profile of adverse events is not uncommon in antiepilepsy drug treatment where tolerance to adverse effects, especially the central nervous system adverse effects is often seen over time.

7.5.3 Drug-Demographic Interactions

Drug age interaction: Examination of the occurrence of adverse events from all SOCs by patient age reveal a trend toward increasing adverse events with rise in patient age, noted in Figure 17 below. A change in medication tolerance is not unexpected with increase in age.

Figure 17 Drug-Demographic Interactions: Occurrence of AEs per Patient by Age Group, All OXC XR Treatment (1200mg + 2400mg)



Drug – Sex interaction: There is a small excess of adverse events in females compared to males for all SOCs. Table 80 displays the ratio of AEs to number of all males and females in both OXC XR treatment arms combined. A similar trend is noted upon examination of only the SOC "Nervous System Disorders", Table 81.

Table 80 Drug- Sex Interaction: Adverse Events from All SOCs by Sex

Adverse Events from All SOCs			
Sex	Total Patients All OXC XR Treatment	Adverse events	Ratio of AE to total in OXC XR Treatment
male	110	241	2.2
Female	136	342	2.5

Table 81 Drug- Sex Interaction: Adverse Events from "Nervous System Disorder" SOC by Sex

Nervous system disorders			
Sex	Total Patients All OXC XR Treatment	Adverse events	Ratio of AE to total in OXC XR Treatment
male	110	91	0.8
female	136	145	1.1

Drug Ethnicity interaction: The frequency of adverse events of all SOCs is notably greater in those patients of Hispanic origin than white, shown in Table 82. There are insufficient numbers of other ethnic / racial groups for meaningful comparison.

Table 82 Drug- Ethnicity Interaction: Adverse Events from All SOCs by Ethnicity

Adverse Events from All SOCs			
Ethnic Group	Total Patients All OXC XR Treatment	Adverse events	Ratio of AE to total in OXC XR Treatment
White	209	447	2.1
Hispanic	27	105	3.9

7.5.4 Drug-Disease Interactions

There is no formal dataset to capture medical co-morbidities. Study protocol 804P301 excludes “History or presence of clinically significant, chronic medical condition, including hyponatremia, especially those contraindicating antiseizure medication, (e.g., any neurological, gastrointestinal, endocrine, cardiovascular, pulmonary, hematological, immunologic, renal, hepatic, or metabolic disease) that may affect the safety of the subject in the opinion of the Investigator.”

The only mechanism to capture medical co-morbidities is from the indication column of the concomitant medications dataset. This is not used to perform a drug – disease interaction analysis because this is not a field that was specified to accurately capture co-morbid medical history.

7.5.5 Drug-Drug Interactions

Seventy patients who were taking the top 10 (by frequency) concomitant medications experienced adverse events, 40 of these patients were in the oxcarbazepine XR treatment group and 30 were in the placebo group. Examination of the adverse events associated with each of the ten medications, in those patients treated with oxcarbazepine XR did not reveal any spike in adverse events that differed notably from the overall profile of adverse events of the overall treatment population. There does not appear to be an adverse event due to a concomitant medication – study drug interaction.

7.6 Additional Safety Evaluations

None

7.6.1 Human Carcinogenicity

Formal human carcinogenicity study has not been performed. The current reference product labeling does not indicate a risk of human cancer. The sponsor ISS has no report of neoplastic adverse effects. Two subjects in study 804P301 have adverse event entries under the SOC “Neoplasms benign, malignant and unspecified (incl cysts and polyps)”. Subject 302005, a 26 year old female, had an episode of dizziness and was subsequently found to have a pituitary microadenoma. At the time of the discovery the patient had approximately 6 weeks of oxcarbazepine XR exposure. The second patient with an adverse event in the SOC “Neoplasms benign, malignant and unspecified (incl cysts and polyps)” was in the placebo treatment arm of the study and had not received oxcarbazepine XR.

7.6.2 Human Reproduction and Pregnancy Data

In section 8.1 the current reference product labeling indicates a pregnancy category C and Trileptal (oxcarbazepine) is closely related structurally to carbamazepine, which is considered to be teratogenic in humans. It is also noted oxcarbazepine levels may decrease during pregnancy.

7.6.3 Pediatrics and Assessment of Effects on Growth

Study 804P107

Adverse events

In this submission there was one pediatric PK study 804P107. Eighteen subjects were enrolled in the study entitled “Multiple Dose, Open-Label, Multi-Center Study to Evaluate the Pharmacokinetics, Safety, and Tolerability of OXC-ER as Adjunctive Therapy in Pediatric Subjects with Refractory Partial Epilepsy”. Safety data for the study was limited to the seven days the subjects were receiving OXC-XR. Subjects were treated with between 150mg and 600mg of oxcarbazepine XR per day for 6 consecutive days. There were no deaths, SAEs, or adverse events leading to discontinuation. There were four adverse events in the study, Table 83, all mild intensity, reported by three subjects. Three of the AEs were dizziness, lethargy, Influenza and paraesthesia.

Table 83 Adverse events by OXC-XR treatment arm in study 804P107

Dose Group	150mg	300mg	450mg	600mg	Total
Sample size / %	**(N = 4) n (%)**	**(N = 6) n (%)**	**(N = 6) n (%)**	**(N = 2) n (%)**	**(N = 18) n (%)**
Any AE	1 (25.0)	1 (16.7)	1 (16.7)	0	3 (16.7)
Infections and Infestations	**1 (25.0)**	**0**	**0**	**0**	**1 (5.6)**
Influenza	1 (25.0)	0	0	0	1 (5.6)
Nervous System Disorders	**0**	**1 (16.7)**	**(16.7)**	**0**	**2 (11.1)**
Dizziness	0	1 (16.7)	0	0	1 (5.6)
Lethargy	0	0	1 (16.7)	0	1 (5.6)

Dose Group	150mg	300mg	450mg	600mg	Total
Sample size / %	**(N = 4) n (%)**	**(N = 6) n (%)**	**(N = 6) n (%)**	**(N = 2) n (%)**	**(N = 18) n (%)**
Paresthesia	0	0	1 (16.7)	0	1 (5.6)
For each row category, a subject with two or more adverse events in that category is counted only once					

Laboratory Studies

The sponsor reports: No clinically significant values or changes in values, whether or not related to dose, were noted during the study

All out of reference range laboratory results are examined by the reviewer and compared to screening values when those were within reference range. Subject 07-001 had declines from normal reference range for HCT, hemoglobin, percent lymphocytes, and RBC count. The remainder of the subjects did not have notable changes in laboratory values. No safety signal is identified upon examination of clinical chemistry and hematology laboratory values.

Vital Signs

Systolic blood pressure (SBP)

Systolic blood pressure high outliers are examined (>122mmhg* 95th percentile for 90th percentile height, age 10, low <90mmhg). 14 measurments are found in seven patients with a value greater than 122mmhg. The maximum value was 136mmhg noted in a 16 year old patient with a change from baseline of 21mmhg. The most notable value for age was 128mmhg observed in a 4 year old patient with a change from baseline of only 1mmhg, this patient was noted to have an adverse event of “influenza”, see Table 84 .

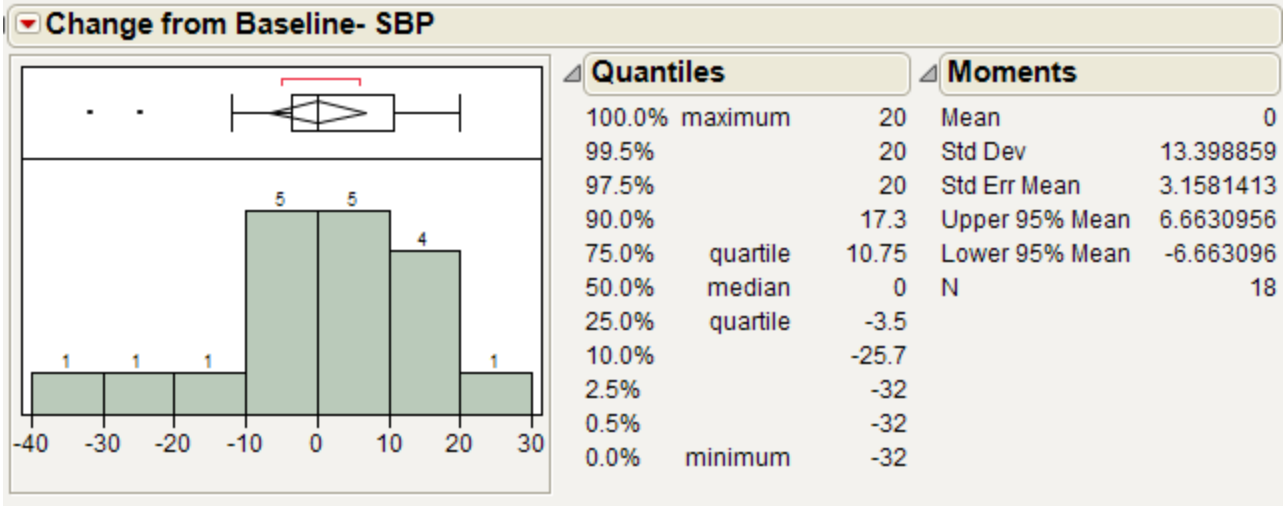
Table 84 Pediatric Systolic BP high outliers

AGE	Subject ID	Systolic BP mmhg, max	Change from Baseline	Baseline systolic BP
16	03-003	136	21	115
12	03-005	124	21	103
13	06-001	128	9	119
14	06-003	134	10	124
4*	10-001	128	1	127
5	10-002	123	17	106
12	10-003	130	14	116

Systolic blood pressure low (<90mmhg) outliers are examined. 4 measurements are found in a single patient. Three of the four values were the same as baseline while the remaining value declined by 1mmhg.

Change from baseline systolic blood pressures at 4 hours post dose are examined and reveal a similar distribution of high and low shift from baseline as well as a mean and median change of zero, Figure 18 .

Figure 18 Distribution of Pediatric Systolic Blood Pressure, Change from Baseline



ECG:

Heart Rate

High and low heart rate outliers are examined. One heart rate is identified below 60 BPM, this value of 55 BP occurs at screening. Two heart rate values are found greater than 120; these values are 121 and 122 BPM occurring in the same 6 yo male patient with change from baseline of 5 and 6 beats/min respectively. No adverse event is identified in these patients.

ECG is obtained at baseline and “End of Study”. End of study is the day of final day (day 7) of OXC-XR administration.
QT

Post baseline QT values are available from 16 patients while post baseline QTcF are only available in the ECG dataset from 11 patients, the same dataset reveals the RR interval absent for these same 11 patients. The maximum treatment QT interval is 401msec with a change from baseline of +12msec. The maximum postivie change from baseline QT interval is 40 msec resulting in a QT value of 400msec. No RR interval or corrected QTcF is available for this patient. Aside from this patient none of the remaining patients have a positive change from baseline QT value greater than 20msec. No other on treatment QT values exceed 400msec. The minimum on treatment QT interval is 296msec with a QTcF value of 358msec. The largest negative change

from baseline QT value is -54msec with a resultant QT value of 328msec, this patient does not have an RR interval or QTcF value in the dataset.

Reviewer comment: Examination of the QT values does not reveal a signal for QT prolongation. There is no evidence of an OXC-XR effect on heart rate. Four adverse events occurred in 3 patients during the study 804P107 treatment interval. Two of these adverse events, dizziness and lethargy were among the most common adverse events in the reference listed drug label (lethargy ≈ (somnolence or fatigue)). An infection, influenza, occurred in patient 10-001, a four year old individual. This infection event parallels the observations in adverse events in "*Adjunctive Therapy/Monotherapy in Pediatric Patients 1 Month to <4 Years Old Previously Treated or Not Previously Treated with other AEDs"* of the reference listed drug label (Trileptal) where it is noted that *"the most commonly observed adverse reactions seen in association with Trileptal in these patients were similar to those seen in older children and adults except for infections and infestations which were more frequently seen in these younger children."* Overall there is no evidence of a new safety signal in this small pediatric population which differs from the risk profile of the reference product.

Reference Product Labeling

In section 8.3 the current reference product labeling indicates "oxcarbazepine and its active metabolite (MHD) are excreted in human milk. A milk-to-plasma concentration ratio of 0.5 was found for both. Because of the potential for serious adverse reactions to Trileptal in nursing infants, a decision should be made about whether to discontinue nursing or to discontinue the drug in nursing women, taking into account the importance of the drug to the mother."

In addition section 8.4 of reference product labeling indicates that "Trileptal is indicated for use as adjunctive therapy for partial seizures in patients aged 2-16 years. Trileptal is also indicated as monotherapy for partial seizures in patients aged 4-16 years." The reader is referred to section 6.1 of this label for a description of the adverse events.

7.6.4 Overdose, Drug Abuse Potential, Withdrawal and Rebound

This submission does not contain an abuse potential study. The reference labeled product indicates in section 9.2 "The abuse potential of Trileptal has not been evaluated in human studies". Section 9.3 states "Intragastric injections of oxcarbazepine to four cynomolgus monkeys demonstrated no signs of physical dependence as measured by the desire to self-administer oxcarbazepine by lever pressing activity."

The reference product label indicates in section 10 "Isolated cases of overdose with Trileptal have been reported. The maximum dose taken was approximately 24,000 mg. All patients recovered with symptomatic treatment."

7.7 Additional Submissions / Safety Issues

No additional safety issues

8 Postmarket Experience

Oxcarbazepine extended release tablets have not been previously marketed.

9 Appendices

9.1 Literature Review/References

none

9.2 Labeling Recommendations

Food Effect: the MHD values for study drug oxcarbazepine XR when taken in the fed state approximate the immediate release formulation with an earlier Tmax. The full discussion is presented in section 6.1.8 "food effect"

Current proposed labeling addresses this issue with the following language:

"Single dose administration of 600mg TRADENAME following a high fat meal produced (b) (4) MHD exposure equivalent to that produced under fasting conditions. Peak MHD exposure (C_{max}) was (b) (4)% higher and occurred 2 hours earlier under fed conditions than under fasting conditions [see *Clinical Pharmacology* (*12.3*)].

(b) (4) The increase in C_{max} (b) (4) even without a significant change in the overall exposure, should be considered by the prescriber [see *Clinical Pharmacology* (*12.3*)]."

This language should be strengthened as follows to express that fed conditions result in Cmax which approximate the immediate release dosage form.

Reviewer Proposal in Red:

Single dose administration of 600mg TRADENAME following a high fat meal produced (b) (4) MHD exposure equivalent to that produced under fasting conditions. Peak MHD exposure (C_{max}) was (b) (4)% higher and occurred 2 hours earlier under fed conditions than under fasting conditions. (b) (4)

(b) (4)

The increase in C_{max} (b) (4) even without a significant change in the overall exposure, should alert the prescriber (b) (4)

(b) (4)

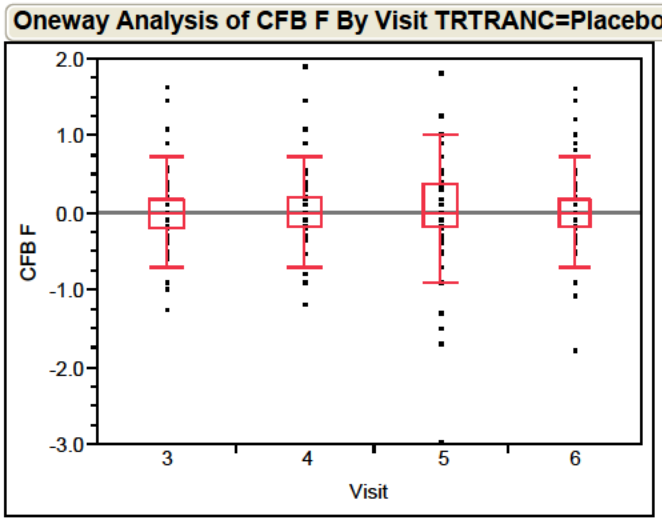
Recommended OXC-ER Maintenance Dosing for the Pediatric Population targeting Adult median MHD Cmin exposures after 1200 and 2400 mg/day

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

9.3 Advisory Committee Meeting

No advisory committee was convened for this product.

9.4 Temperature

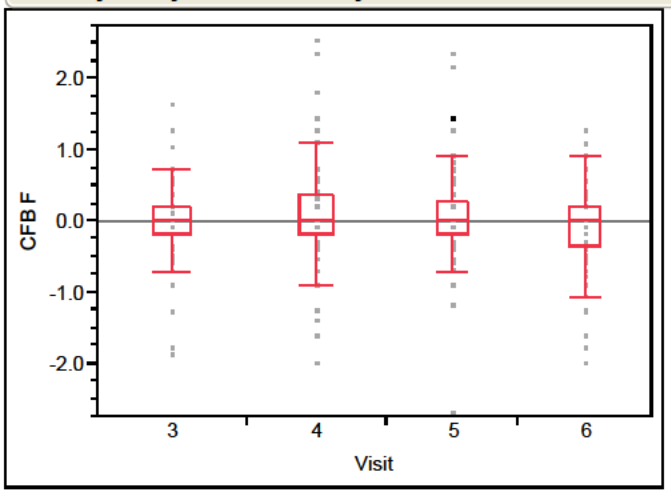


Missing Rows 245

Quantiles

Level	Minimum	10%	25%	Median	75%	90%	Maximum
3	-1.26	-0.576	-0.2	0	0.18	0.484	1.62
4	-1.2	-0.54	-0.18	0	0.2	0.54	1.900002
5	-2.97992	-0.54	-0.185	0	0.36	0.54	1.8
6	-1.77992	-0.54	-0.18	0	0.18	0.72	1.600001

Oneway Analysis of CFB F By Visit TRTRANC=OXC XR 1200mg/day



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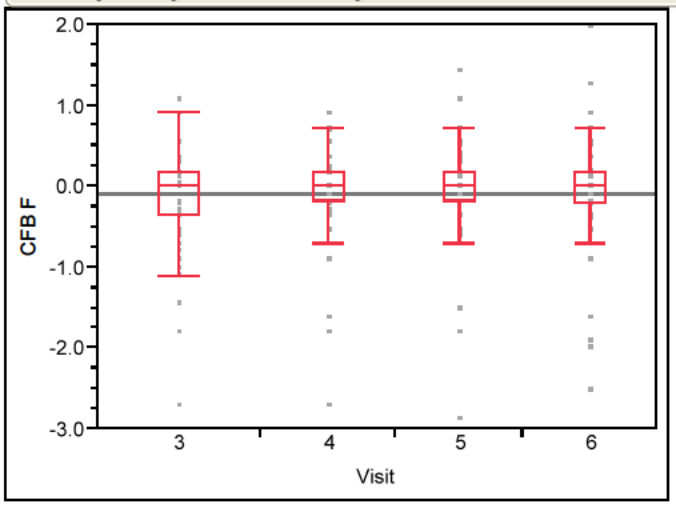
Quantiles

Level	Minimum	10%	25%	Median	75%	90%	Maximum
3	-1.9	-0.54	-0.18	0	0.185	0.54	1.62
4	-2	-0.54	-0.18	0	0.36	0.66	2.540078
5	-2.7	-0.72	-0.19	0	0.27	0.700001	2.34
6	-2	-0.72	-0.36	0	0.18	0.684	1.26

Oneway Analysis of CFB F By Visit TRTRANC=OXC XR 2400mg/day



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Quantiles

Level	Minimum	10%	25%	Median	75%	90%	Maximum
3	-2.7	-0.83	-0.36	0	0.18	0.36	1.08
4	-2.7	-0.36	-0.18	0	0.18	0.54	0.9
5	-2.88	-0.6	-0.18	0	0.18	0.36	1.44
6	-2.52	-0.7	-0.2	0	0.18	0.36	1.98

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/s/

STEVEN T DINSMORE
10/17/2012

NORMAN HERSHKOWITZ
10/19/2012