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APPLICATION NUMBER:

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MEDICAL REVIEW(S)

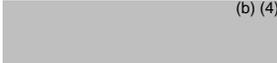
CLINICAL REVIEW

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Established Name Gabapentin enacarbil
(Proposed) Trade Name Horizant
Therapeutic Class Anti-convulsant
Applicant GSK

Formulation(s) 600 mg Tablet
Dosing Regimen Daily
Indication(s) RLS
Intended Population(s) Adult  (b) (4)

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Recommendations/Risk Benefit Assessment

On February 17, 2010, the Agency issued a Complete Response (CR) to the sponsor (GSK) for the New Drug Application for gabapentin enacarbil (GE) for treatment of moderate to severe symptoms of Restless Leg Syndrome (RLS) in adults. The Agency's primary reason, prompting the CR action, was that the NDA did not adequately address the potential serious unknown risk to patients with RLS, associated with a preclinical finding of pancreatic acinar cell carcinoma observed in carcinogenicity studies for both GE and Neurontin.

On October 6, 2010, the GlaxoSmithKline (GSK) resubmitted the application. The sponsor's resubmission includes new preclinical data, epidemiologic studies and new clinical safety data. The new clinical safety data is comprised of the Final Safety Update (FSU) for the RLS clinical development program as well as summary data on clinical safety from studies of GE used in other indications. The other indications for GE, include, RLS-associated sleep disturbances, Pain in Diabetic Peripheral Neuropathy, Post-Herpetic Neuralgia, Migraine Prophylaxis.

Overall, the adverse events profile in both RLS clinical development program as well as for other indications is consistent with that reported in the previous Clinical Review (2/10/2010). The most common adverse events are related to sedation, somnolence and dizziness, across all indications. There have been no significant new safety signals noted in the data submitted by the sponsor.

1.1 Recommendation on Regulatory Action

Approval of gabapentin enacarbil (GE) 600mg/day for moderate to severe RLS.

Review of the clinical data reveals evidence of efficacy of GE in moderate to severe RLS in the adult population. The basis for clinical efficacy is two pivotal trials of 12 weeks duration using co primary endpoints, change from baseline to week 12/early termination of 1) IRLSS scale, and internationally accepted and validated scale for RLS, 2) Clinical Global Impression by the Investigator (CGI-I).

(Source:FDA primary statistical reviewer)

Study	XP052		XP053		
Treatment	Placebo	1200	Placebo	1200	600
N	108	112	96	114	111
Change in IRLSS:baseline to week 12	-8.8	-13.2	-9.8	-13	-13.8
P-value		0.0003		0.0017	<0.0001

Proportion of responders on CGI-I at week 12	38.9%	76.1%	44.8%	77.5%	72.8%
Estimated odds ratio		5.1		4.29	3.32
p-value		<0.0001		<0.0001	<0.0001

Although, GE at 600mg a day of GE has similar efficacy to GE at 1200mg/day for moderate to severe symptoms of RLS, the most common adverse events of somnolence, sedation and dizziness are dose dependent. Treatment emergent adverse events in the safety population for GE at 600mg a day were dizziness (13%), somnolence (20%) and for sedation (<1 %) compared to GE 1200mg/day, which were dizziness (22 %), somnolence (23%) and sedation (4%).

Clinical Reviewer Table: Common Adverse Events

The number of events, grouped as indication impaired cognition/total number of AEs, is shown.

Preferred Term	Number (%) of Subjects		
	Placebo N=245	XP13512 600mg N=163	XP13512 1200mg N=269
Any event	182 (74)	132 (81)	226 (84)
Somnolence	12 (5)	32 (20)	61 (23)
Dizziness	11 (4)	22 (13)	59 (22)
Fatigue	11 (4)	9 (6)	18 (7)
Sedation	3 (1)	1(<1)	11 (4)
Feeling drunk	0	2 (1)	7 (3)
Feeling abnormal	1(<1)	1(<1)	9 (3)
Vertigo	0	2 (1)	7 (3)
Disorientation	1(<1)	2 (1)	4 (1)
Vision blurred	0	1(<1)	4 (1)
Disturbance in attention	1(<1)	3 (2)	2(<1)
Total	40	75	182
% Total number of AEs	7.09	17.94	22.39

The clinical efficacy of GE at 600mg/day for moderate to severe RLS provides the lowest rate of common, treatment emergent, adverse events.

1.2 Risk Benefit Assessment

The recommendation to approve GE at 600mg/day for patients with moderate to severe symptoms of RLS, also takes into account the preclinical finding of pancreatic acinar tumors in Wistar rats and its potential relevance to humans. In the 2-year carcinogenicity study, pancreatic acinar cell carcinoma was reported in high dose (both sexes) and male rats given the mid-dose. The results of this study were the basis for the Agency's CR letter dated 2/17/2010. In rat carcinogenicity study, there was an increased incidence of pancreatic acinar cell hyperplasia, adenomas and carcinomas in both sexes at doses of 5000mg/kg/d and in males at 2000mg/kg/d. The sponsor resubmitted the application, which includes three arguments for approval of 600mg/day for GE for moderate to severe RLS. The three arguments, presented by the sponsor, address the Agency's safety concern described in the CR action letter regarding GE 600mg/day.

THRESHOLD DOSE FOR CARCINOGENIC EFFECT

The sponsor states that the threshold dose for a carcinogenic effect is 2000mg/kg/day (in Wistar rats) of GE. At 2000mg/kg/day, there was no clear increase in hyperplasia or adenoma, and only one carcinoma reported for Wistar rats. The single male animal with reported carcinoma was considered to be consistent with the background rate of pancreatic carcinoma reported in the specific strain of rats (Wistar). The safety margin between the systemic exposure to gabapentin in the rat at 2000 mg/kg/day is 38 fold higher than the systemic exposure achieved clinically at the recommended human dose of 600mg/day of GE.

TISSUE CONCENTRATION VERSUS PLASMA CONCENTRATION

The sponsor states that gabapentin is accumulated 5-10x more in rat pancreas compared to human pancreas. Therefore, the concentration in the target tissue is more relevant than plasma levels in determining the response of the tissue to a potential carcinogen. The fact that rat pancreas accumulates the drug more than human pancreas would result in a safety margin of at least 50 times.

PUBLISHED RESULTS FROM A CARCINOGENICITY STUDY OF GABAPENTIN (NEURONTIN)

The sponsor proposes relying on published information of rat carcinogenicity study of gabapentin, Neurontin. The no effect dose was determined to be 1000mg/kg/day for gabapentin (considered the mid-dose). The plasma exposure in rats in the gabapentin study would be at least 25 times that provided by the recommended human dose of 600mg/day of GE.

The sponsor's first argument, setting the threshold dose for carcinogenic effect in the GE carcinogenicity study at 2000mg/kg of GE is reasonable. In the Toxicology review from the first review cycle (T. Peters, 1/2010), it was noted that there is a high background rate of pancreatic hyperplasia, adenoma and carcinoma in Wistar rats.

Therefore using the 2000mg/kg/day dose of GE in rats would provide approximately a 38 fold margin for a clinical dose of 600mg/day of GE.

However, the second and third arguments provided by the sponsor are dependent on the interpretation of the data. The high tissue concentration of GE in rat pancreas cannot alone explain the higher rate of pancreatic carcinomas. Mice are also reported to have high concentrations of GE in the pancreas; however, the carcinogenicity study performed in mice did not find an increase incidence of pancreatic carcinoma. Therefore, another mechanism in addition to elevated tissue concentration is needed to explain the rat findings.

Additionally, the sponsor has argued that since GE is a pro drug of gabapentin (nearly 100% converted to gabapentin once it crosses the intestinal lumen) the clinical experience with gabapentin would apply to GE as well. However there remains the concern of the relative systemic exposure of GE compared to Neurontin. The plasma concentration of GE is greater, at the recommended dose (600 mg/day), compared to gabapentin. After an oral dose of GE the resulting plasma concentration of gabapentin is greater compared to approved gabapentin products.. The systemic exposure of GE at 600mg/day is similar to the systemic exposure of Neurontin at approved doses of Neurontin (1200-1800mg/day) Please refer to Clinical Review, 02/10/2010.

To assess the relevance of the animal signal for pancreatic carcinoma to humans who take gabapentin chronically, the sponsor performed 2 case control epidemiologic studies using the United Kingdom General Practice Research Database (GPRD). The most important limitation of the study was that there were only a small number of patients in the GPRD database with long term use of gabapentin, causing protopathic bias. Although, the study had a limited ability to detect a small increased risk for cancer there was evidence of an increased risk for renal or pancreatic carcinoma in patients. The Agency performed a search of the AERS database (May 12, 2010). The search revealed three cases of pancreatic carcinoma in patients taking Neurontin. This number of cases of pancreatic cancer is not considered to be an increased rate in drug event combination compared to other drugs.

The additional studies submitted by the sponsor, preclinical and epidemiologic, taken in the context of the extensive clinical experience with Neurontin (>15years), the probability of the preclinical pancreatic cancer signal being relevant to humans appears to be low. .Approval of GE at a dose of 600mg/day for moderate to severe RLS is supported by clinical efficacy with the lowest incidence of adverse reactions and would provide the greatest safety margin of exposure in humans

1.3 Recommendations for Postmarket Risk Evaluation and Mitigation Strategies (REMS)

Initially, the Agency required a Medication Guide be included as part of a Risk Evaluation and Mitigation Strategy (REMS), however the Agency's thinking on the requirements for a REMS has changed since the time of the initial NDA review. The Agency's recent guidance permits a Medication Guide to be required without it necessarily being part of a REMS, in all cases. The Division of Neurology Products, in agreement with The Office of Surveillance and Epidemiology has determined that although a Medication guide is still required it should not be part of a REMS.

1.3 Recommendations for Postmarket Requirements and Commitments

RLS is classified as a sleep disorder as well as a movement disorder. Somnolence and sedation can be a consequence of poor sleep caused by RLS and it may also be caused by GE. Regardless of the cause, the Agency remains concerned about the effect GE may have on the ability to drive safely. The results of the efficacy trials did not demonstrate that the 1200 mg/day dose was superior to the 600 mg/day dose at relieving the symptoms of RLS. Additional dose response studies that include lower doses (300mg, 450mg) of GE are needed to define the maximally effective, lowest dose to relieve moderate to severe symptoms of RLS.

The Division recommends the dose response study be a PMR because the selection of the dose(s) that will be studied in the long-term safety study will depend on the results of the dose response study.

Post marketing Requirements and Commitments

- 1 Conduct a PK/PD trial in adolescents ages =13 years to 17 years with moderate to severe symptoms of primary Restless Legs Syndrome.

 Final Protocol Submission: 01/2015
 Study/Trial Completion: 06/2016
 Final Report Submission: 06/2017

- 2 Conduct a double-blind, randomized, placebo-controlled, parallel group efficacy and safety evaluation trial in adolescents =13 years to 17 years with moderate to severe symptoms of Primary Restless Legs Syndrome.

 Final Protocol Submission: 06/2105
 Study Completion: 10/2023
 Final Report Submission: 10/2024

- 3 Conduct a long-term safety trial of adolescents ages =13 years to 17 years with moderate to severe symptoms of primary Restless Legs Syndrome. The study must provide a descriptive analysis of safety data in pediatric patients during at least 12 months of continuous treatment with gabapentin enacarbil at individualized doses in association with the study described in PMR #2.

Final Protocol Submission: 01/2016
Study Completion: 07/2024
Final Report Submission: 07/2025

- 4 Conduct a driving trial in adolescent patients of legal driving age that has Restless Legs Syndrome, using diphenhydramine as active control.

Final Protocol Submission: 06/2017
Study Completion: 06/2021
Final Report Submission: 06/2022

5. A simulated driving trial in healthy adult subjects treated with 600 mg gabapentin enacarbil that includes active comparator and placebo arms.

The timetable you submitted on March 28, 2011 states that you will conduct this study according to the following schedule:

Final Protocol Submission: 05/2011
Study Completion: 10/2011
Final Report Submission: 02/2012

- 6 A simulated driving trials in healthy adult subjects treated with an appropriate dose of gabapentin enacarbil determined in PMR #8 that includes active comparator and placebo arms.

The timetable you submitted on March 28, 2011 states that you will conduct this study according to the following schedule:

Final Protocol Submission: 10/2014
Study Completion: 05/2015
Final Report Submission: 09/2015

- 7 An *in vitro* study to evaluate the potential for gabapentin enacarbil and gabapentin to be inhibitors of CYP2C8 and CYP2B6.

The timetable you submitted on March 28, 2011 states that you will conduct this study according to the following schedule:

Final Protocol Submission: 05/2011
Study Completion: 08/2011
Final Report Submission: 10/2011

- 8 A randomized, placebo-controlled, double-blind, parallel-group clinical trial of gabapentin enacarbil at *300 mg/day, 450 mg/day and 600 mg/day* in patients with moderate to severe symptoms of RLS. .

The timetable you submitted on March 28, 2011 states that you will conduct this study according to the following schedule:

Final Protocol Submission: 03/2012
Study Completion: 07/2014
Final Report Submission: 02/2015

- 9 An in vitro dissolution study to evaluate alcohol dose dumping using the final dissolution method, and evaluate different concentrations of alcohol up to 40% (0, 5, 10, 20, and 40%).

The timetable you submitted on March 28, 2011 states that you will conduct this study according to the following schedule:

Final Report Submission: 06/2011

- 10 An adequate, randomized, double-blind, placebo- and moxifloxacin-controlled trial to evaluate the effect of gabapentin enacarbil on cardiac repolarization in healthy adult subjects.

The timetable you submitted on March 28, 2011 states that you will conduct this study according to the following schedule:

Final Protocol Submission: 08/2011
Trial Completion: 05/2012
Final Report Submission: 11/2012

- 11 A clinical drug-drug interaction trial to evaluate the pharmacokinetic interaction between gabapentin enacarbil and morphine.

The timetable you submitted on April 1, 2011 states that you will conduct this study according to the following schedule:

Final Protocol Submission: 07/2011
Trial Completion: 12/2011
Final Report Submission: 04/2012

PMC

- 12 Develop a dosage form that will allow for a 300 mg dose that could be taken once daily in patients with severe renal impairment, including patients on hemodialysis.

The timetable you submitted on March 28, 2011 states that you will conduct this study according to the following schedule:

(b) (4)

2 Introduction and Regulatory Background

2.1 Product Information

Gabapentin enacarbil (GE) is an extended release pro-drug of gabapentin manufactured as a 600mg extended release (ER) oral tablet. It was originally submitted as a new molecular entity (NME), because of its structure (please refer to section 2.5). Compared to gabapentin molecule GE has a novel chemical structure which allows it to be more readily and completely absorbed from the G.I. tract.

2.2 Tables of Currently Available Treatments for Proposed Indications

There are three drugs approved for moderate to severe RLS; however, only two of the drugs, pramipexole and ropinirole, are currently available. (Table)

Drugs approved for Moderate to Severe RLS				
	Generic/Chemical Name	Brand Name	Sponsor(s)	Dosage Form
	Pramipexole HCL	Mirapex	Boehringer-Ingelheim	tablets

Clinical Review
 Susanne R. Goldstein, M.D.
 NDA 22399
 Horizant, gabapentin enacarbil

	Ropinirole	Requip	GSK	tablets
Drugs approved but not available for moderate to severe RLS				
	(b) (4)			

Drugs that are not currently approved for RLS, but are used off label are listed in the table below.

Generic/Chemical Name	Brand Name	Class	Dosage Form
L-dopa	Sinemet	Dopaminergic	Tablets
Bromocriptine	Parlodel	Dopaminergic	Tablets
Methadone		Opioid	Tablet
Hydrocodone		Opioid	Tablet
Gabapentin	Neurontin	Alpha 2 delta blocker	Tablet
Pregabalin	Lyrica	Alpha 2 delta blocker	Tablet
Clonazepam	Klonopin	Benzodiazepines	Tablet
Iron			Tablet
Iron dextran			IV

2.3 Availability of Proposed Active Ingredient in the United States

GE is a pro-drug of gabapentin, Neurontin. Neurontin (Pfizer) was first approved in the United States in December 1993 as an add-on medication for treatment of refractory partial epilepsy. In May 2004, Neurontin was approved for post-herpetic neuralgia. There is extensive postmarketing experience for prescribing over the past 17 years. There are several generic gabapentin products approved in the U.S. (17 approved generics, Orange Book 2/2011)

2.4 Important Safety Issues with Consideration to Related Drugs

ADVERSE EVENTS OF INTEREST

The most common adverse reactions/events reported in controlled trials with GE are sedation, somnolence and dizziness. Somnolence is of particular concern in patients with RLS who already have impaired sleep and may suffer from daytime sleepiness. A simulated driving study (XP083) compared the effects on lane position variability (LPV) and the frequency of simulated crashes in patients with RLS taking 1200mg, 1800mg, placebo or 50 mg of diphenhydramine (active control). The patients taking 1200mg of GE for 2-weeks had driving impairments that were very similar to patient tested at Tmax after receiving 50 mg of diphenhydramine. Patients who received 1800 mg/day of GE

for 2-weeks performed similar to patients who received placebo. 600mg/day of GE has not been studied in a simulated driving study; therefore its effects on driving are unknown. The conflicting effects of the 1200 mg and 1800 mg/day doses of GE on simulated driving performance emphasizes the need to study the effect of the 600 mg/days dose on driving.

INTERCHANGEABILITY

GE is not interchangeable with other gabapentin products. GE is better absorbed from the G.I. tract resulting in a linear increase plasma concentration with increasing GE dose at doses up to 6000 mg. By comparison, the plasma concentration of gabapentin (Neurontin) reaches a plateau at approximately 1200-1800mg.

SUICIDALITY

Gabapentin, has a small increased risk for suicidality, gabapentin derived from GE, shares the same suicidality risk. Antiepileptic drugs have been associated with an increased risk for suicidality (Statistical Review and Evaluation: Antiepileptic Drugs and Suicidality, US Dept. Of HHS, FDA, 2009). The odds ratio (95% CI) for suicidality with gabapentin was 1.57 (0.12, 47.66). Clinical trials with gabapentin were included in the review, regardless of indication an duration, with at least a total of 30 patients.

PRECLINICAL CARCINOGENICITY

Carcinogenicity studies completed during the development programs for gabapentin (Neurontin) and gabapentin enacarbil, reported a dose related increase in the incidence of pancreatic acinar cell tumors in Wistar rats. The relevance of this finding to humans is uncertain. (Please refer to Section 4.3 for further details).

PEDIATRIC USE

Gabapentin is approved in children down to the age of 2. However, GE has not been studied in children.

2.5 Summary of Presubmission Regulatory Activity Related to Submission

The NDA was originally submitted on September 15, 2008. The submission was withdrawn due to statistical issues with the datasets from study XP060, a randomized withdrawal study to evaluate the maintenance of efficacy of GE in patients who tolerate the drug.

The NDA was resubmitted on January 9, 2009 with standard review status as a 505(b) (1) application. The review cycle was extended from a November 9, 2009 PDUFA goal date to February 9, 2010 due to the sponsor's submission of a Risk Evaluation and Mitigation Strategy (REMS) for suicidality. The sponsor submitted proposed REMS on October 9, 2009.

The Agency issued a Complete Response, on February 17, 2010; the NDA did not adequately address the potential unknown risk to patients with RLS associated with a preclinical finding of pancreatic acinar cell carcinoma observed in carcinogenicity studies for both GE and Neurontin. The preclinical animal signal (males at dose of 2000mg/kg/day, males and females at 5000mg/kg/day)

The Agency recognized that findings in laboratory animals are not necessarily translatable to risk in humans. Gabapentin products have been available for over 15 years, postmarketing safety data did not indicate a signal for pancreatic cancer, based on an analysis of reports contained in the AERS database. Although the agency recognized the limitations for signal detection associated with the analysis of AERS data.

Additionally, the Agency concluded that the sponsor's proposed recommended dose of 1200mg was effective for the treatment of moderate to severe RLS however; 1200mg/day did not provide additional benefit when compared to the 600mg/day dose. Adverse events were reported more frequently by patients treated with the 1200mg/day dose compared with the group receiving 600 mg/day. The agency concluded that if gabapentin enacarbil is ultimately approved, "...labeling should recommend a daily dose of 600mg or lower, to be given at 5pm."

Subsequently, the sponsor requested a Type A, End of Review meeting with the Agency to discuss key elements of their Resubmission. The face to face meeting occurred on May 18, 2010. The issues discussed at the meeting included the following:

- Conversion of NDA 22399 to a 505 (b)(2) submission in order to use Summary Basis of Approval (SBA) for Neurontin (1993) to support the current application. The Agency stated that any data in the SBA for Neurontin that had not been published could not be used to in support of the Sponsor's NDA.
- The Agency stated that it assumed the pancreatic acinar cell tumors produced by gabapentin enacarbil are due to gabapentin. The Division agreed to review the Sponsor's proposal that would base safety margins on pancreatic tissue concentrations rather than plasma exposures (AUC).

Possible approaches to address the relevance of pre-clinical carcinogenicity to humans were discussed. These included the following concepts:

- The Sponsor could further investigate potential mechanisms for the pancreatic acinar cell tumors which may explain occurrence in rats only.
- The sponsor could perform an epidemiological study using a database such as GPRD to see if there is an association between pancreatic cancer and exposure to gabapentin. The Agency and DEPI did note that the epidemiology study had its limitations (number of patients with long-term exposure to gabapentin), but in the context of other data (preclinical) may help support the application.

On August 30, 2010, the Agency sent the sponsor a letter confirming the sponsor's request to amend the application from a 505(b) (1) application to a 505(b) (2) application as part of the resubmission. The amendment allows the sponsor to rely on published literature and FDA's finding of safety and and/or effectiveness for Neurontin (the listed drug described in the published literature for the Complete Response Resubmission).

- *Identifying each listed drug(s) (in accordance with the Agency's regulations at 21 CFR 314.54) on which GSK intends to rely on the Agency's finding of safety and/or effectiveness or published literature describing the listed drug(s);*
- *Establishing that such reliance is scientifically appropriate (e.g., establishing a "bridge" between your proposed drug product and each listed drug(s) upon which you propose to rely);*
- *Submitting data necessary to support any aspects of the proposed drug product that represent modifications to the listed drug(s);*
- *Complying with applicable regulatory requirements, including but not limited to providing an appropriate patent certification or statement for each patent(s) listed in the Orange Book for the listed drug(s) on which GSK intends to rely.*

On October 6, 2010, the sponsor submitted a Complete Response Submission. On November 5, 2010, the Division sent a letter to the sponsor, acknowledging the resubmission to be a complete, Class 2 response.

3 Ethics and Good Clinical Practices

The sponsor's submission is in eCTD format. All sections/modules were completed appropriately. Financial disclosures and Debarment Certification were completed. The sponsor attested that all clinical trials were conducted in accordance with "good clinical

practices” GCP, all applicable regulatory requirements, and the guiding principles of the Declaration of Helsinki.

4 Significant Efficacy/Safety Issues Related to Other Review Disciplines

4.1 Chemistry Manufacturing and Controls

There was no new CMC data included in the company’s Complete Response submission. A review of key CMC information is mentioned here since there is no CMC review for this cycle.

The CMC review team recommended approval for NDA 22-399, Horizant (gabapentin enacarbil) ER Tablets.

[REDACTED] (b) (4)

4.2 Clinical Microbiology

N/A

4.3 Preclinical Pharmacology/Toxicology

Preclinical studies of GE show similar findings to gabapentin, Neurontin. In both GE and gabapentin there is a pancreatic cancer signal in Wistar rats. With gabapentin, tumors were seen only in male rats at the high dose. However, with GE, the tumors were seen in both male and female rats; male rats at moderate and high doses, female rats at high doses. The findings for Neurontin were associated with an increased incidence of pancreatic acinar carcinoma only in male rats given the highest dose group, 2000mg/kg (Neurontin label, 2009).

In order to better understand the relevance of this signal to humans, a search of the AERS database by the Agency (May 12, 2010) was performed. The search revealed three cases of pancreatic carcinoma in patients taking Neurontin. This number of cases of pancreatic cancer is not considered to be an increased rate in drug event combination compared to other drugs (Table 1, Courtesy DMEPA).

Table 1. Data mining (MGPS) results for the HLT Pancreatic neoplasms malignant (excl islet and carcinoid). AERS data is current as of 4/8/2010.*

Generic Name	PT	SOC	N	EB05	EB95	EBGM
Gabapentin	Pancreatic carcinoma	Neopl	5	0.321	1.29	0.675

* PT=MedDRA Preferred Term, SOC = System Organ Class, N = Number of reports

REVIEWER COMMENT: A drug event combination having an EB05=2 indicates a drug event combination occurs at least two times the “expected” rate, with 95% confidence. The preferred term (PT) pancreatic carcinoma had an EB05<2.

The sponsor was asked to provide evidence that the mechanism underlying the increased incidence of pancreatic and renal carcinoma reported in the 2-year carcinogenicity study is unique to the species or specifically to Wistar rats... The Agency recommended that the sponsor try to adopt a multifaceted approach to include animal and pharmaco-epidemiological data that seeks to demonstrate an increased risk for an all cancer term in addition to renal and pancreatic carcinoma.

 (b) (4)
The sponsor concluded that neither lab performed adequately when tested independently in two laboratories.

The Pharm-Tox Review Team (draft comments) stated the sponsor did not demonstrate that the signal for pancreatic carcinoma reported in the 2-year carcinogenicity study is not relevant to humans. The Pharm-Tox Review Team did not find the sponsor’s arguments of high tissue concentration of GE in rat pancreatic tissue as a mechanism for the increased susceptibility for developing acinar cell carcinoma convincing. However, on re-examination of the gabapentin 2-year carcinogenicity studies, the Pharm-Tox Review team concluded the no effect level for tumors in rats is at the mid-dose (1000mg/kg/day). This level provides a safety margin of 25 fold in patients treated with GE for symptoms of RLS (Please see Pharm-Tox review for details).

In addition, the sponsor performed epidemiologic studies using the GPRD database to see if there was an increased risk for reported pancreatic, renal and for any cancers in patients treated with gabapentin long-term. Although the results of these studies are limited due to the fact that there was only small number of patients with long term exposure to gabapentin, no clear association between gabapentin use and pancreatic tumors was found.

The sponsor has presented three arguments that the margin for safety for the proposed dose of GE in humans of 600mg/day is >25.

4.4 Clinical Pharmacology

One clinical pharmacology study, PXN110882, was completed and submitted with the application. Study PXN110882 is an open-label, randomized, single –dose, five-period, crossover study to evaluate relative bioavailability of different formulations of GE in 17 healthy volunteers. The study assessed two new 600mg and two new 900mg extended release formulations in comparison with the 600mg tablet of the current extended release formulation. All formulations were given at a dose of 1800mg.

According to the Clin Pharm reviewer (J. Cho, DARRTS 03/29/2011), analysis of pharmacokinetic profiles shows that AUC (0-infinity) and Cmax for all formulations are comparable with the exception of one formulation (Formula AK, 900mg test tablet). The Clin Pharm reviewer compared new formulations which had PK data for fed conditions only, to the proposed marketed formulation. Overall, values for AUC (0-infinity) and Cmax in Study PXN110882 are consistent with those in previous studies. (Please refer to Clin Pharm review for details).

The results of the study reviewed for the current NDA submission are only relevant at the 600mg dose of GE. The sponsor is not proposing to market the 900mg dose of GE.

REVIEWER COMMENT: Although, there have not been bioequivalence studies performed comparing GE ER, the proposed formulation for RLS, and Neurontin, the single dose study comparing GE IR and Neurontin have been performed (See Appendix I). GE IR 700mg is similar to Neurontin 1200mg, based upon AUC and Cmax. Garcia-Borreguero et al (Neurology 2009) conducted a double blind placebo controlled trial of gabapentin versus placebo in treatment of RLS. Efficacy was achieved at mean doses of 1300mg to 1800mg a day of gabapentin. However, RLS Medical Bulletin, 2005, published by the RLS Foundation, noted that many patients appear to benefit from lower doses. In addition, the RLS Foundation recommends that treatment with Neurontin should “...commence at 100 to 300mg per dose because of the tendency of the drug to cause somnolence and gait unsteadiness, especially in elderly patients.”

As part of PMR/PMCs, the division has recommended studying doses lower than 600mg in order to establish the minimally effective dosing for RLS.

DOSING IN RENAL IMPAIRMENT

GE is cleared by the kidneys. The sponsor has proposed (b) (4) Clinical Pharmacology Review team had recommended daily dosing with 300mg GE daily for patients with creatinine clearance of 15-29mL/min. Dosing renally impaired patients (creatinine clearance of 15-29mL/min) with (b) (4) as opposed to 300mg GE a day, would cause the plasma levels to drop below clinically therapeutic levels between dosing. In order to maintain a steady plasma level of GE, it is recommended that patients with creatinine clearance <30mL/min take 300mg GE a day.

FDA recommendations (courtesy Clinical Pharmacology)

Renal Function Creatinine Clearance (mL/min)	Titration Dose Regimen	Target Dose Regimen
≥60	600 mg per day for 3 days	600 mg per day starting day 4
30-59	300 mg per day for 3 days	600 mg per day starting day 4
15-29	no titration	300 mg per day

QT Studies

The sponsor conducted a QT study at 6000mg of GE. The IRT group found the study to be inconclusive. The moxifloxacin response failed to meet criteria for assay sensitivity. The agency recommended that the sponsor conduct a repeat TQT study.

5 Sources of Clinical Data

The sponsor submitted a complete response on October 6, 2010. There is **no new efficacy** data presented in the RLS clinical development program (CDP). The open-label extension trial, XP055, was fully enrolled during the previous review cycle (PDUFA February 17, 2010). Along with epidemiology data and preclinical data, the sponsor has submitted the Final Safety Update (FSU), cut off date June 18, 2010. The current submission includes new safety data on completed subjects in open label extension Study XP055. In addition, safety data for completed studies in **other indications, not previously reviewed**, are included in this submission.

The open-label extension Study XP055 is the only GSK-sponsored RLS study conducted as part of the Phase II and Phase III RLS CDP with **new safety data** available since the original NDA submission (1/09/2009). The data is presented in the Final Safety Update.

Since the 120-Day Safety Update (submitted on May 1, 2009) submission cut-off date January 16, 2009, 5 additional GSK-sponsored clinical studies and 3 Astellas-sponsored studies have been completed.

Other Indication Clinical Studies include:

- A Phase IIIb study for the treatment of RLS-associated sleep disturbance: RXP110908.
- A Phase IIb study for the treatment of pain associated with diabetic peripheral neuropathy (DPN): PXN110448
- 2 Phase II studies for the treatment of post-herpetic neuralgia (PHN): PXN110527 and PXN110748
- A Phase IIb study evaluating migraine headache prophylaxis: MPX111381

Deaths and SAEs are included for the following studies:

- 2 completed Astellas-sponsored studies were conducted in Japan for the treatment of primary RLS: 8825-CL-003 and 88825-CL-0005,
- 1 completed Astellas-sponsored study for neuropathic pain associated with DPN: 8825-CL-0007

5.1 Tables of Studies/Clinical Trials

TRIALS IN RLS CLINICAL DEVELOPMENT PROGRAM

Study Number	Phase	Design and Control	Primary Objectives	Duration	Regimens	Number of Subjects
XP021	II	DB, randomized, PBO controlled, 2 period crossover	Efficacy and Safety	14 days for each period	XP13512 1800mg/PBO PBO/XP13512 1800mg	34
XP045	II	DB, randomized, PBO-controlled, parallel group	Efficacy and Safety	14 days	PBO/XP13512 1800mg	29
					XP13512 1200mg	32
					PBO	33
XP081	II	DB, randomized, PBO-controlled, parallel group	Efficacy and safety, dose/exposure response	12 weeks	XP13512 600mg	47
					XP13512 1200mg	43
					XP13512 1800mg	37
					XP13512 2400mg	44
					PBO	40
XP083	II	DB, randomized, PBO-controlled	Simulated driving performance, cognition, efficacy and Safety	14 days (for efficacy)	XP13512 1200mg	28
					XP13512 1800mg	33
					PBO	33
					PBO+diphenhydramine 50mg (once on Day 16)	28

XP052	III	DB, randomized, PBO controlled, parallel group	Efficacy and Safety	12 weeks	XP13512 1200mg	112
					PBO	108
XP053	III	DB, randomized, PBO controlled, parallel group	Efficacy and Safety	12 weeks	XP13512 1200mg (primary comparison)	111
					XP13512 600mg	114
					PBO	96
XP060	III	24 wk single blind phase with responders entering 12 wk, DB, randomized, PBO controlled, parallel group phase	Maintenance of Efficacy and safety	36 weeks	Single-blind:XP13512 1200mg	311
					Double-blind:XP13512 1200mg	97
					Double-blind PBO	96
XP055	III	Long-Term Safety	Safety	52 weeks	XP13512 1200mg	583

Adapted from Xenoport Module 2.5

TRIALS IN OTHER INDICATIONS

The following Sponsor table outlines clinical studies for indications other than RLS that will be covered in the Safety section of this review (Section 7). **Study XP009**, Efficacy, Safety and PK study in PHN, was submitted during the previous review cycle and will not be discussed in detail, in the current review. Although GSK-sponsored Study **RXP110908**, included subjects with RLS, the primary endpoint was RLS-sleep associated disturbances and therefore, is not included in the RLS clinical development program. The 3 **Astellas** sponsored studies (2 in RLS and 1 in PHN) are included in the Exposures, Deaths and SAEs sections of this review. No further safety information was provided by the sponsor.

Clinical Review
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 NDA 22399
 Horizant, gabapentin enacarbil

XenoPort Study Number/ GSK Study Number	No. Study Centers Location(s)	Study Start; Enrollments Status and Date; Total Enrollment /Target Enrollment	Study Objectives	Study Design	Diagnosis; Key Inclusion Criteria	Treatment Details (Drug; Dose; Form; Route; Frequency; Duration)	No. of Subjects by Group Entered/ Completed	Gender M/F; Mean Age (Range)	Primary Endpoint(s)	Location of Study Report
Completed XenoPort-Sponsored Clinical Study – PHN										
XP009 / PXN111044	17 centers in US	21 Jun 2004/ 15 Mar 2005/ Target 160/ Total 116	Efficacy, safety, and PK in PHN	Double-blind, randomized, placebo-controlled, parallel group	Subjects with PHN	Gabapentin 600 mg TID (11 days) followed by a double-blind period with either GEn 1200 mg BID or Pbo/ Oral/ 14 days	Gabapentin 1800 mg: 115 received/ 101 completed GEn 2400 mg: 48 randomized/ 45 completed Placebo: 54 randomized/ 47 completed	Pbo 50% M 50% F 64.0 (23.0 – 87.2) GEn 2400 mg: 47%M 53%F 65.0 (33.7 – 82.1)	Change in average weekly pain scores from the 7-day baseline period compared to the final 7 days of the randomized treatment	NDA 022399, 09 January 2009, Sequence Number 0004, m5.3.5.4
Completed GSK-Sponsored Phase IIIb Study in RLS-Associated Sleep Disturbance										
NA / RXP110908	27 centers in US	01 Oct 2008/ 22 Jul 2009/ Completed Total: 136 Target: 114	Efficacy and safety, PSG study	Double-blind, randomized, placebo-controlled, crossover	Subjects with RLS	Treatment period 1 (titration to GEn 1200 mg or Pbo OD for 25 days); Oral; then taper (7 days) and wash-out (7 days), followed by crossover Treatment period 2 (titration to GEn 1200 mg or Pbo for 25 days), then taper (7 days)	136 entered into tx period 1 / 130 completed tx period 1 123 entered into tx period 2/ 114 completed tx period 2	42% M: 58%F 52.1 (18-77) years	WTDS (Wake Time During Sleep)	IND 71.352 (Serial No. 0216) GSK Document #2009/000 67/00

XenoPort Study Number/ GSK Study Number	No. Study Centers Location(s)	Study Start; Enrollments Status and Date; Total Enrollment /Target Enrollment	Study Objectives	Study Design	Diagnosis; Key Inclusion Criteria	Treatment Details (Drug; Dose; Form; Route; Frequency; Duration)	No. of Subjects by Group Entered/ Completed	Gender M/F; Mean Age (Range)	Primary Endpoint(s)	Location of Study Report
Completed XenoPort-Sponsored Clinical Study – PHN										
XP009 / PXN111044	17 centers in US	21 Jun 2004/ 15 Mar 2005/ Target 160/ Total 116	Efficacy, safety, and PK in PHN	Double-blind, randomized, placebo-controlled, parallel group	Subjects with PHN	Gabapentin 600 mg TID (11 days) followed by a double-blind period with either GEn 1200 mg BID or Pbo/ Oral/ 14 days	Gabapentin 1800 mg: 115 received/ 101 completed GEn 2400 mg: 48 randomized/ 45 completed Placebo: 54 randomized/ 47 completed	Pbo 50% M 50% F 64.0 (23.0 – 87.2) GEn 2400 mg: 47%M 53%F 65.0 (33.7 – 82.1)	Change in average weekly pain scores from the 7-day baseline period compared to the final 7 days of the randomized treatment	NDA 022399, 09 January 2009, Sequence Number 0004, m5.3.5.4
Completed GSK-Sponsored Phase IIIb Study in RLS-Associated Sleep Disturbance										
NA / RXP110908	27 centers in US	01 Oct 2008/ 22 Jul 2009/ Completed Total: 136 Target: 114	Efficacy and safety, PSG study	Double-blind, randomized, placebo-controlled, crossover	Subjects with RLS	Treatment period 1 (titration to GEn 1200 mg or Pbo OD for 25 days); Oral; then taper (7 days) and wash-out (7 days), followed by crossover Treatment period 2 (titration to GEn 1200 mg or Pbo for 25 days), then taper (7 days)	136 entered into tx period 1 / 130 completed tx period 1 123 entered into tx period 2/ 114 completed tx period 2	42% M: 58%F 52.1 (18-77) years	WTDS (Wake Time During Sleep)	IND 71.352 (Serial No. 0216) GSK Document #2009/000 67/00

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 NDA 22399
 Horizant, gabapentin enacarbil

XenoPort Study Number/ GSK Study Number	No. Study Centers Location(s)	Study Start; Enrollments Status and Date; Total Enrollment /Target Enrollment	Study Objectives	Study Design	Diagnosis; Key Inclusion Criteria	Treatment Details (Drug; Dose; Form; Route; Frequency; Duration)	No. of Subjects by Group Entered/ Completed	Gender M/F; Mean Age (Range)	Primary Endpoint(s)	Location of Study Report
Completed GSK-Sponsored Clinical Studies – Neuropathic Pain										
NA / PXN110448	85 centers in US	11 Mar 2008/ 17 Feb 2009/ Completed Target 392 Total: 421	Efficacy, safety, and dose-response	Double-blind, randomized, placebo- and active-controlled, parallel group	Subjects with NP associated with DPN	GEN 600 mg, 1200 mg, 1800 mg, Pbo, BID or pregabalin 100 mg TID/ Oral/ 1 week titration, with 12 weeks treatment maintenance; 1 week down-titration; up to 16 days follow-up	Placebo: 120 randomized/ 90 completed GEN 1200 mg: 62 randomized/ 47 completed GEN 2400 mg: 56 randomized/ 37 completed GEN 3600 mg: 117 randomized/ 79 completed Pregabalin: 66 randomized/ 47 completed	59% M: 41% F 58.7 (29-85 years)	Change from baseline to end of treatment with respect to the mean 24-hr average pain intensity score based on an 11-point PI-NRS	(b) (4) GSK Document # RM2009/00 018/00 Refer to Section 4.1.3.1 for description.

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XenoPort Study Number/ GSK Study Number	No. Study Centers Location(s)	Study Start; Enrollments Status and Date; Total Enrollment /Target Enrollment	Study Objectives	Study Design	Diagnosis; Key Inclusion Criteria	Treatment Details (Drug; Dose; Form; Route; Frequency; Duration)	No. of Subjects by Group Entered/ Completed	Gender M/F; Mean Age (Range)	Primary Endpoint(s)	Location of Study Report
NA / PXN110527	38 centers (29 centers in US; 9 centers in Germany)	14 Mar 2008/27 Jul 2009/ Completed/ Target: 98 Total: 96	Efficacy and safety	Double-blind, randomized, two-period, crossover	Subjects with PHN	Baseline treatment with gabapentin 600mg TID for 2 weeks, randomized to GEn 600 mg or 1800 mg BID; Oral; 28 days, then XO (all subjects take 1200 mg BID x 4 days) followed by 28 days (GEn 600 mg or 1800 mg BID), 1 week down- titration and up to 16 days follow-up	Baseline: 138 subjects Total: 96 randomized/ 76 completed GEn 1200 mg: 91 started/ 79 completed GEn 2400 mg: 82 started/ 81 completed GEn 3600 mg 85 started/ 82 completed	61% M: 39% F 63.1 (26- 87 years)	Change from baseline to end of treatment period with respect to mean 24-hr average pain intensity score for the last week of each treatment period based on an 11-point PI-NRS	(b) (4) GSK Document # RM2009/00 303/00 Refer to Section 4.1.3.2 for description.
NA / PXN110748	72 centers in North America (63 centers in US and 9 centers in Canada)	6 Feb 2008/ 29 Jul 2009/ Complete Target 368 Total: 376	Efficacy, safety, and dose- response	Double-blind, randomized, placebo- controlled, parallel group	Subjects with PHN	GEn 600 mg, 1200 mg, or 1800 mg BID; Oral; 1 week titration, with 12 weeks treatment maintenance; 1 week down-titration; up to 16 days follow-up	Placebo: 95 randomized/ 64 completed GEn 1200 mg: 107 randomized/ 85 completed GEn 2400 mg: 84 randomized/ 60 completed GEn 3600 mg: 90 randomized/ 56 completed	51% M 49% F 62.1 (18- 92 years)	Change from baseline to end of treatment with respect to the mean 24-hr average pain intensity score based on an 11- point PI-NRS	(b) (4) GSK Document # RM2009/00 240/00 Refer to Section 4.1.3.3 for description.

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 Horizant, gabapentin enacarbil

XenoPort Study Number/ GSK Study Number	No. Study Centers Location(s)	Study Start; Enrollments Status and Date; Total Enrollment /Target Enrollment	Study Objectives	Study Design	Diagnosis; Key Inclusion Criteria	Treatment Details (Drug; Dose; Form; Route; Frequency; Duration)	No. of Subjects by Group Entered/ Completed	Gender M/F; Mean Age (Range)	Primary Endpoint(s)	Location of Study Report
Completed GSK-Sponsored Clinical Study – Migraine Headache Prophylaxis										
NA / MPX111381	53 centers in US and Canada	26 Aug 2008/ 02 Jun 2010 Complete/ Target 528 Total 526	Efficacy, safety, and dose-response	Double-blind, randomized, placebo-controlled, parallel group	Migraine headache prophylaxis	GEn 1200 mg, 1800mg, 2400mg, 3000mg or placebo; Oral; 5 weeks flexible titration, 12-weeks treatment maintenance, 3 weeks taper	Placebo: 129 randomized/ 95 completed GEn 1200 mg: 67 randomized/ 49 completed GEn 1800 mg: 134 randomized/ 88 completed GEn 2400 mg: 134 randomized/ 97 completed GEn 3000 mg: 62 randomized/ 37 completed	18% M 82% F 39.2 (18 - 70 years)	Change from baseline in the number of migraine headache days during the last 4 weeks of treatment prior to taper	Complete (CSR in development) / Refer to Section 4.1.5.1 for description.
Non-GSK Sponsored Studies: Astellas-Sponsored Studies in Japan										
8825-CL-0003	Japan	NA/ Completed/ Target 400	Efficacy and safety	Double-blind, randomized, placebo-controlled	Subjects with RLS	GEn 600 mg, 900 mg, 1200 mg or placebo OD; Oral; NA	NA	NA	NA	Completed / Refer to Section 4.1.6.1 for description.
8825-CL-0005	Japan	NA / Completed/ NA	NA	Open-label	Subjects with RLS	GEn (dose NA); Oral	NA	NA	NA	Completed / Refer to Section 4.1.6.2 for description.

XenoPort Study Number/ GSK Study Number	No. Study Centers Location(s)	Study Start; Enrollments Status and Date; Total Enrollment /Target Enrollment	Study Objectives	Study Design	Diagnosis; Key Inclusion Criteria	Treatment Details (Drug; Dose; Form; Route; Frequency; Duration)	No. of Subjects by Group Entered/ Completed	Gender M/F; Mean Age (Range)	Primary Endpoint(s)	Location of Study Report
8825-CL-0007	Japan	NA / Study terminated/ Target 360	Efficacy and safety	Double-blind, randomized, placebo-controlled	Subjects with painful DPN	GEn (3 doses) or placebo; Oral; NA	NA	NA	NA	Study terminated / Refer to Section 4.1.6.3 for description.

AE = adverse event; BID = twice daily, Cauc = Caucasian, DPH = diphenhydramine, DPN = Diabetic peripheral neuropathy, CGI-I = Clinical Global Impression - Improvement, ECG = electrocardiogram, ER = extended release, ESRD = end stage renal disease, IR = immediate release, IRLS = International Restless Legs Syndrome, Jap = Japanese, OD = once daily, Pbo = Placebo, PK = pharmacokinetics, PSG = polysomnography, RLS = Restless Legs Syndrome, ER = extended release, TID = three times daily, Tx= treatment; XP = GEn, UK = United Kingdom, US = United States

6.0 Efficacy Summary

Gabapentin enacarbil, a pro-drug of gabapentin, has been studied for Restless Leg Syndrome (RLS) as well as neuropathic pain, post herpetic neuralgia and migraine. The review of efficacy will summarize the pivotal and supportive studies on moderate to severe, idiopathic RLS, the proposed indication for the drug in this application. There have been several trials in the US as well as outside of US (Japan through Astellas pharmaceuticals).

During the previous review cycle (CR letter 2/17/2010), the Agency acknowledged that the sponsor had established the efficacy of GE in the treatment of moderate to severe RLS. This was based upon the efficacy results of the pivotal trials, XP052 and XP053. Statistically significant improvement in co-primary endpoints and secondary endpoints was shown. (Please refer to Clinical Review, 02/10/2010).

7 Review of Safety

In this section, **new safety results** from clinical trials with GE will be reviewed. The new data includes:

- Final Safety Update for **RLS**, which incorporates the final safety data from open label extension Study XP055.
- Summary safety data from GSK-sponsored trials in **other indications** (RLS-associated sleep disorders, post-herpetic neuralgia, and migraine).
- **Astellas**-sponsored trials

In addition, safety data from cut off dates for ISS NDA 22399 (December 6, 2007), 120 Day Safety Update (July 31, 2008), and Final Safety Update (June 18, 2010) will be presented for comparison.

7.1 Methods

At the time of the original NDA submission, the only ongoing study from the Phase II and Phase III RLS development program was the Phase III open-label extension study XP055.

The sponsor states that “...With the exception of Study XP055, data from the Phase II and Phase III studies in the RLS CDP [clinical development program] are identical to those provided in the ISS in NDA 022399(09 January 2009, Sequence Number 0004)”.

The Final Safety Update (FSU) of all RLS trials has been submitted with the Complete Response. The FSU includes safety data for completed Phase II and Phase III RLS Clinical Development Program

CLINICAL TRIALS USED TO EVALUATE SAFETY IN RLS

All studies are complete and data in the FSU are presented with a data cut-off date of June 18, 2010. Sponsor Table 9 presents study groupings for RLS clinical development program used in the original NDA ISS and FSU.

Table 9 FSU and Original NDA 022399 ISS Study Groupings for Phase II and Phase III RLS Studies

Study Grouping	Studies	ISS ¹	120-Day SU ²	FSU ³
12-Week Placebo-Controlled RLS Studies (Integrated)	XP052, XP053, XP081	✓	-	-
All Placebo-Controlled Phase II & Phase III RLS Studies (Integrated)	12-Week Placebo-Controlled RLS Studies (XP052, XP053, XP081) plus: XP083, XP045	✓	-	-
All RLS Studies (Integrated and Individual)	XP052, XP053, XP081, XP083, XP060, XP021, XP045, XP055 ⁴	✓	✓	✓
RLS Long-Term Integration (Integrated)	12-Week Placebo-Controlled RLS Studies (XP052, XP053, XP081) plus: XP083, XP055 ⁴	✓	✓	✓

1. NDA 022399 ISS data cut-off date: 06 December 2007 (XP055 was the only ongoing study in the Phase II and III RLS CDP).
2. 120-Day SU data cut-off date: 31 July 2008 (XP055 was the only ongoing study in the Phase II and III RLS CDP)
3. All studies in the Phase II and III RLS CDP were complete as of the FSU data cut-off date of 18 June 2010.
4. XP055 is the only study contributing new safety information to the study groupings for the All RLS Studies and RLS Long-Term Integration grouping in this FSU.

The **All RLS Studies** grouping contains 12 weeks placebo controlled trials (XP052, XP053, XP081, XP060) 2 week placebo controlled trials (XP021, XP045, XP083) as well as open label extension trial XP055. The **All RLS Studies** grouping will be used to present Safety data in this review where possible. Although not all of the studies were of similar design and duration, this grouping captures all subjects with **RLS** exposed to gabapentin enacarbil at any dose and duration. If All RLS Study Grouping is not available, 12 week placebo controlled RLS studies which comprise **RLS Long-Term Integration** Study Grouping, will be presented.

CLINICAL TRIALS USED TO EVALUATE SAFETY IN OTHER INDICATIONS

Study #	N Total	N Exposed to drug	Design	Dosage	Duration (maintenance dose)	INDICATION
RXP110908	136	127	Phase IIIb, RCT, 2 period crossover	1200mg vs.PBO	8wks	RLS assoc. sleep disorder
PXN110448	421	234	Phase IIb, RCT, parallel group	1200mg, 2400mg,3600mg vs. PBO	12 wks	Pain assoc. DPN
PXN110527	138	258	Phase IIa, RCT, 2 period crossover	1200mgv3600mg vs. PBO	8 wks	PHN
PXN110748	376	276	Phase IIb RCT, parallel group	1200mg,2400mg,3600mg vs. PBO	12 wks	PHN
MPX111381	526	328	RCT, parallel group	1200mg, 1800mg, 2400mg flexible dosing vs.PBO	12 wks	Migraine prophylaxis
ASTELLAS SPONSORED						
8825-CL-0003	474		RCT, DB,	600mg, 900mg, 1200mg vs, PBO		RLS
8825-CL-0005	NA		Open label	NA	NA	RLS
8825-CL-0007	199		RCT, DB	NA	NA	PHN

NA = NOT AVAILABLE

REVIEWER COMMENT: The design of the GSK sponsored clinical trials for other indications includes 3 randomized controlled, parallel group studies and 2 two period crossover studies. The studies are all Phase II, except for RLS-associated sleep disturbance study, and include doses higher than the recommended dose of GE 600mg for RLS. Due to the differences in design and doses used, it is difficult to make direct comparisons to the RLS studies. However, it is useful to review overall summary safety findings in these studies for possible new safety signals.

DISPOSITION

Disposition of Subjects in RLS CDP

During the previous review cycle, the clinical review team noted that a significant number of subjects withdrew consent (WC), were lost to follow-up (LTFU) or were withdrawn due to investigator judgment (IJ). During the sponsor meeting held with the agency to discuss CR letter (May 18, 2010), the Agency recommended that the sponsor obtain further information on these subjects and include them as part of the resubmission package.

Significant adverse events occurring in $\geq 5\%$ of subjects are presented for the FSU in sponsor Table 128. The sponsor further subdivides these events into three groups; subjects who withdrew consent (WC), subjects who were lost to follow-up (LTFU), and subjects who terminated secondary to investigator judgment (IJ). The adverse events noted were not necessarily the cause for early termination, but rather are a list of treatment emergent adverse events reported.

Sponsor Table

Table 128 TEAEs (>=5% and occurring in >1 subject in a column) in the GEn All Doses Group (Safety Population: All RLS Studies) and for Subjects who discontinued due to WC, LTFU or IJ (All Subjects: All RLS Studies)

Preferred Term	Number (%) of Subjects			
	FSU: GEn All Doses ¹ (N=1201)	WC GEn All Doses ² (N=112)	LTFU GEn All Doses ² (N=70)	IJ GEn All Doses ² (N=5)
Any event	1024 (85)	90 (80)	46 (66)	5 (100)
Somnolence	358 (30)	35 (31)	13 (19)	1 (20)
Dizziness	268 (22)	28 (25)	7 (10)	3 (60)
Headache	160 (13)	11 (10)	6 (9)	1 (20)
Nasopharyngitis	97 (8)	9 (8)	2 (3)	2 (40)
Nausea	90 (7)	11 (10)	6 (9)	1 (20)
Fatigue	83 (7)	11 (10)	7 (10)	1 (20)
Insomnia	52 (4)	2 (2)	0 (0)	1 (20)
Upper respiratory tract infection	58 (5)	2 (2)	3 (4)	0 (0)
Diarrhea	56 (5)	4 (4)	2 (3)	0 (0)
Back pain	41 (3)	7 (6)	2 (3)	1 (20)
Dry mouth	52 (4)	7 (6)	2 (3)	0 (0)
Muscle strain	0 (0)	7 (6)	0 (0)	0 (0)
Sinusitis	53 (4)	7 (6)	0 (0)	0 (0)
Myalgia	28 (2)	6 (5)	0 (0)	1 (20)
Irritability	0 (0)	3 (3)	0 (0)	2 (40)

Data Source: Table 1.36, Table 8.3, Table 8.5, Table 8.10, Table 8.12, Table 8.17 and Table 8.19

1. From the All RLS Studies grouping (Phase II and Phase III RLS CDP).
2. All Subjects Population is comprised of all randomized subjects who were in one of the 8 RLS studies (All RLS Studies grouping) who discontinued due to WC, LTFU, or IJ

REVIEWER COMMENT: It is notable that the majority of subjects who withdrew consent (WC) and/or were lost to follow-up (LTFU) experienced adverse events of somnolence and dizziness. It is not clear at this time whether these subjects were accounted for in the adverse events dataset. The sponsor was queried for further information on the subjects who discontinued due to WC, LTFU or IJ as to whether these subjects were in fact included in the adverse events dataset.

Subsequently, the sponsor submitted a response (Amendment 50, 3/4/2011). The sponsor stated that the adverse events noted in the subjects who WC, LTFU or IJ, were accounted for in the original AE dataset. Additionally, the sponsor submitted a line listing by trial of subjects who WC, LTFU, IJ, with further information. There were still 47 subjects who WC without a known reason. The Table below summarizes the subjects who WC, by study and dose (where known).

REASONS FOR WITHDRAWAL OF CONSENT (Reviewer Table)

Study #	GE Dose	Total subje	Total WC	AE	Transport ation/Movi	Job related	Other Illness	UNK	Protocol violation	Lack of efficacy	Sxs resolved
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		cts	N (%)		ng						
XP052											
	PBO	108	3 (3)		2	1					
	1200mg	112	4 (4)		2	2					
XP053											
	PBO	96	8 (8)		1	2	2	3			
	600mg	114	3 (3)		1	2					
	1200mg	111	4 (4)		1	1		2			
XP055											
	GE	583	57 (10)	2	10	5	6	24	4	3	3
XP060											
	SB only	311	27 (9)	2	6	6	2	9	1	1	
	DB (includes PBO)	193	6 (3)		4	1		1			
XP081											
	PBO	40	6 (15)			2	2	2			
	600mg	47	5 (11)			3			2		
	1200mg	43	4 (10)					2	1	1	
	1800mg	37	1 (3)					1			
	2400mg	44	0 (0)								
XP083											
	PBO/DPH	61	2 (3)					2			
	1200mg	28	1 (4)					1			
	1800mg	33	0 (0)								

REVIEWER COMMENT: There is no clear pattern of reasons for WC by study. The largest number of withdrawals is from XP055, open label extension trial. However, this would not be unexpected due to the length of the study and time commitment involved for subjects. It is difficult to know if there is a dose dependent pattern for WC with the data provided.

Disposition-Other Indications

RXP110908 – RLS-Associated Sleep Disturbance

RXP11908 was a phase III-b, multi-center, double-blind, placebo-controlled, 2 period crossover polysomnography study of GE versus placebo in patients with moderate to severe primary RLS and associated sleep disturbance. The study consisted of 7 study periods: Screening/Washout (2-5 weeks), Baseline (2 days), Treatment Period 1 (4 weeks), Taper and Washout (2 weeks), Treatment Period 2 (4 weeks), Taper (1 week) and Follow-up (1 week). 136 subjects were enrolled in the study; 67 of the subjects

received GE 1200mg followed by placebo and 69 subjects received placebo followed by GE1200mg. All randomized subjects took at least one dose of GE.

Sponsor Table 17 presents number of subjects completed, number of subjects prematurely withdrawn as well as reasons for withdrawal.

Table 17 Summary of Subject Disposition (Safety Population: Study RXP110908)

Subject Status	Number (%) of Subjects
	N=136
Completed	114 (84)
Prematurely withdrawn	22 (16)
Primary Reason for Withdrawal¹	
Withdrew consent	8 (6)
Adverse event	8 (6)
Lost to follow-up	3 (2)
Protocol deviation ²	2 (1)
Subject reached protocol defined stopping criteria ³	1 (<1)

Data Source: [Table 2.1](#).

1. Primary reason for withdrawal is the reason for early withdrawal reported by the investigator on the End of Study record in the eCRF.
2. Includes Subject 53 whose primary reason for withdrawal on the End of Study record was a protocol deviation (wrong bottle dispensed). Subject reported AEs of dizziness and influenza-like illness which are reported on the AE page as resulting in an action taken of 'investigational product withdrawn' which is not reflected in this table.
3. Subject 1265 whose primary reason for withdrawal on the End of Study record was meeting the liver safety stopping criteria due to elevated liver enzymes. The elevated LFTs are also noted on the AE page with an action taken of 'investigational product withdrawn' which is not reflected in this table.

REVIEWER COMMENT: The primary reason for withdrawal given by the sponsor is "Withdrew Consent". An equal number of subjects withdrew due to adverse events. These results are similar to disposition results in RLS clinical development program.

PXN110448- Pain associated with DPN

Study PXN110448 was a multicenter, randomized, double-blind, double-dummy, parallel group, placebo-controlled study. Comparing dose response of GE in subjects with neuropathic pain associated with DPN. Pregabalin (PGB) was used as an active control. Subjects were randomized in a ratio of 2:1:1:1:2 to receive either oral GE 3600mg/day, GE 2400mg/day, GE 1200mg/day, PGB 300mg/day or matching placebo, respectively. The study consisted of a screening phase of up to 4 weeks, a 1 week baseline phase, a 14 week treatment phase, and a follow-up phase (up to 16 days post-treatment).

Sponsor Table 18 presents summary of subject disposition with primary reason for withdrawal, by dose.

Table 18 Summary of Subject Disposition and Primary Reason for Premature Withdrawal (Randomized Population: Study PXN110448)

	Number (%) of Subjects					
	PBO N=120	GEn 1200 mg N=62	GEn 2400 mg N=56	GEn 3600 mg N=117	PGB 300 mg N=66	Total N=421
Completed	90 (75)	47 (76)	37 (66)	79 (68)	47 (71)	300 (71)
Withdrawn	30 (25)	15 (24)	19 (34)	38 (32)	19 (29)	121 (29)
Adverse event	11 (9)	5 (8)	12 (21)	21 (18)	6 (9)	55 (13)
Protocol Deviation	7 (6)	6 (10)	4 (7)	4 (3)	6 (9)	27 (6)
Lost to follow-up	6 (5)	2 (3)	1 (2)	3 (3)	3 (5)	15 (4)
Lack of efficacy	3 (3)	1 (2)	0	4 (3)	3 (5)	11 (3)
Withdrew consent	3 (3)	1 (2)	2 (4)	4 (3)	1 (2)	11 (3)
Investigator Discretion	0	0	0	2 (2)	0	2 (<1)

Data Source: [Table 3.2](#)

PBO=placebo; PGB=pregabalin

REVIEWER COMMENT: The primary reason for withdrawal in this study is secondary to an adverse event. The 1200mg GE cohort is similar to placebo and pregabalin. The 2400mg and 3600mg cohorts have higher adverse event rates than placebo. This data is suggestive of a dose response for adverse events.

PXN110527- PHN

Study PXN110527 was a multi-center, randomized, double-blind, and two-period crossover study comparing the efficacy of a high dose (3600mg/day) versus a low dose (1200mg/day) of oral GE in adult subjects with post-herpetic neuralgia. Of note, subjects were first enrolled in a two week baseline period, which included treatment with **1800mg/day of gabapentin**. Subjects who had a partial response (pain scale score, PI-NRS, of ≥ 4) were then randomized to receive GE (either 1200mg/day or 3600mg/day in a 1:1 ratio) for Treatment Period 1 (28 days). Following completion of Treatment Period 1, all subjects received a dose of GE 2400mg/day for 4 days during the Crossover Period, followed by an alternate fixed dose of GE (either 3600mg/day or 1200mg/day in a 1:1 ratio) for Treatment Period 2 (28 days).

Summary disposition and primary reason for withdrawal are presented for subjects in sponsor Table 19.

Table 19 Summary of Subject Disposition and Primary Reason for Premature Withdrawal (Randomized Population: Study PXN110527)

Subject Status	Number (%) of Subjects					
	GEn 1200 mg N=91	GEn 2400 mg ¹ N=82	GEn 3600 mg N=85	Down- titration N=76	Post- treatment N=76	Total N=96
Completed	79 (87)	81 (99) ²	82 (96)	74 (97)	75 (99)	76 (79)
Withdrawn	12 (13)	1 (1)	3 (4)	1 (1)	1 (1)	20 (21) ³
Withdrew Consent	3 (3)	1 (1)	0	1 (1)	1 (1)	7 (7) ⁴
Lack of efficacy	4 (4)	0	0	0	0	4 (4)
Adverse event	3 (3)	0	0	0	0	3 (3)
Protocol deviation	2 (2)	0	1 (1)	0	0	3 (3)
Investigator discretion	0	0	1 (1)	0	0	2 (2) ⁵
Lost to Follow-up	0	0	1 (1)	0	0	1 (1)

Data Source: [Table 4.2](#)

1. Crossover period treatment with GEn 2400mg.
2. One subject (1201) was not withdrawn from the study, but did not participate in the Crossover period prior to GEn dosing in Treatment Period 2. At week 4, subject was provided 2 Medisets and initiated treatment with the Mediset for Treatment Period 2, rather than for the Crossover period. The error was noted by the site and sponsor and IRB were notified.
3. The Total column includes 2 subjects who withdrew during the Down-titration and Post-treatment periods and 2 subjects who were randomized but withdrew prior to dosing with GEn study treatment.
4. 1 additional subject withdrew consent during the down-titration phase; 1 additional subject withdrew consent during the post-treatment phase; and, 1 subject withdrew after being randomized but prior to taking investigational product.
5. 1 subject withdrew after randomization, but prior to taking investigational product

REVIEWER COMMENT: Study PXN110527 is a randomized, crossover design, making the results more difficult to interpret and to compare to the RLS studies. In addition, the subjects had been exposed to gabapentin 1800mg/day for 2 weeks prior to randomization. The previous exposure to gabapentin may have affected the disposition and adverse events experienced in this population. The fact that patients were able to

tolerate 1800mg/day of gabapentin would theoretically, make them more likely to tolerate gabapentin enacarbil, particular the lower dose of GE (1200mg/day).

PXN110748 – PHN

Study PXN110748 was a multicenter, randomized, double-blind, parallel-group, placebo-controlled study, to evaluate efficacy and safety of three maintenance doses of GE (1200mg/day, 2400mg/day, and 3600mg/day) to treat peripheral neuropathic pain associate with PHN. The study consisted of a screening period, a one-week baseline period, a one-week up titration period, a 12 week maintenance treatment phase, a one-week down-titration period and a follow-up post-treatment phase of up to 16 days.

Summary of subject disposition and primary reason for withdrawal are presented in sponsor Table 20.

Table 20 Summary of Subject Disposition and Primary Reason for Premature Withdrawal (Randomized Population: Study PXN110748)

	Number (%) of Subjects				
	PBO N=95	GEn 1200 mg N=107	GEn 2400 mg N=84	GEn 3600 mg N=90	Total N=376
Completed	64 (67)	85 (79)	60 (71)	56 (62)	265 (70)
Withdrawn	31 (33)	22 (21)	24 (29)	34 (38)	111 (30)
Adverse event	12 (13)	6 (6)	12 (14)	16 (18)	46 (12)
Protocol Deviation	5 (5)	4 (4)	4 (5)	9 (10)	22 (6)
Withdrew consent	5 (5)	7 (7)	5 (6)	4 (4)	21 (6)
Lack of efficacy	6 (6)	1 (<1)	1 (1)	4 (4)	12 (3)
Lost to follow-up	1 (1)	2 (2)	0	1 (1)	4 (1)
Investigator Discretion	2 (2)	2 (2)	2 (2)	0	6 (2)

Data Source: [Table 5.2](#)

REVIEWER COMMENT: The majority of subjects withdrew from the study secondary to an adverse event, which appears to be dose dependent.

MPX111381 – Migraine Headache Prophylaxis

Study MPX111381 was a multicenter, randomized, double-blind, placebo-controlled, parallel group, flexible-dose evaluation of GE 1200mg, 1800mg/day, 2400mg/day and 3000mg/day compared with placebo in the prophylactic treatment of migraine headache. Because of the flexible titration period, subjects may not have reached the treatment dose they were assigned due to adverse events (AEs) and therefore, stopped titration at their maximum tolerated dose (MTD).

Subjects were randomized in a 2:1:2:2:1 ratio to the following treatment groups: placebo, GE 1200mg/day, 1800mg/day, 2400mg/day, and 3000mg/day.

Summary of subject disposition and primary reason for withdrawal is presented in sponsor Table 21.

Table 21 Summary of Subject Disposition and Primary Reason for Premature Withdrawal (Randomized Population: Study MPX111381)

	Number (%) of Subjects
Randomized	526
Completed	366 (70)
Withdrawn	160 (30)
Primary Reason for Withdrawal¹	
Adverse event	61 (12)
Withdrew consent	37 (7)
Protocol deviation	23 (4)
Lost to follow-up	20 (4)
Lack of efficacy	12 (2)
Investigator discretion	7 (1)

Data Source: [Table 7.2](#)

1. Subject may have only one primary reason for withdrawal.

REVIEWER COMMENT: Similar to the other studies, the primary reason for withdrawal is secondary to an adverse event. The number of withdrawals, particularly due to an adverse event, may have been affected by the flexible dosing schedule. As noted by the sponsor, subjects who were experiencing an AE were allowed to adjust the dose of GE, theoretically making it less likely to withdraw. The sponsor did not provide data for disposition by dose.

SUMMARY:

Across all studies, all indications, the most common reason for withdrawal is secondary to an adverse event. It is difficult to make further comparisons (dose response) since the studies were of varying designs and treated a variety of disorders.

7.2 EXPOSURE

NEWLY REPORTED EXPOSURE DATA- All Indications

Since the March 31, 2008 cut off date, an additional 1,142 subjects exposed to GE have been reported. (Sponsor Table 22)

Table 22 Enumeration of Unique Subjects Exposed to Investigational Product

	Number of Subjects		
	Placebo	GEn	Blinded Treatment
Unique Exposures in Clinical Pharmacology Studies	39¹	382	-
Individual Phase II and Phase III RLS CDP			
XP052	108	113	-
XP053	96	226	-
XP081	41	176	-
XP083	64 ¹	65	-
XP060	98	326	-
XP045	33	62	-
XP021	36	36	-
XP055 (GEn naïve subjects only) ²	-	197	-
Total Phase II and Phase III RLS CDP	476²	1201	-
Completed GSK-Sponsored Phase IIIb RLS-Associated Sleep Disturbance Study			
RXP110908 (Polysomnography)	132	127	
Completed Neuropathic Pain Studies (XenoPort-Sponsored)			
XP009 (PXN111044) (PHN)	54	47	-
Completed GSK-Sponsored Studies in Neuropathic Pain			
PXN110448 (DPN)	120	234	-
PXN110527 (PHN)	0	94	-
PXN110748 (PHN)	95	276	-
Completed GSK-Sponsored Study in Migraine Headache Prophylaxis			
MPX111381 (Migraine Headache Prophylaxis)	128	395	
Completed/Terminated Astellas -Sponsored Studies			
Astellas Study 8825-CL-0003 (CTR ID No. NCT00530530)	-	-	474 ³
Astellas Study 8825-CL-0005	-	-	NA ⁴
Astellas Study 8825-CL-0007 (CTR ID No. NCT00508430)	-	-	199 ³
Total Exposures in Other Indications	529	1173	673
Total Unique Exposures	1044	2756	(b) (4)

Data Source: Table 1.2, Table 2.4, Table 3.1, Table 4.1, Table 5.1, Table 6.2, Table 7.1 and individual clinical pharmacology CSRs

NA=not available

Data cut-off: 18 June 2010

- Subjects may have received placebo only or placebo and another investigational product.
- The 197 GEn naïve subjects in XP055 contribute to both the All RLS Studies total numbers of placebo and GEn subjects, as they participated in a parent study where they received placebo or placebo plus diphenhydramine, and in the open-label extension Study XP055 where they received GEn.
- Number of subjects enrolled.
- The number of subjects enrolled is unavailable.

As of the cut off date of the FSU, June 18, 2010, there have been a total of **2,756** subjects exposed to GE, any dose, all indications. A total of **1,201** subjects with **RLS**

have been exposed to gabapentin enacarbil inclusive of all doses (unchanged from 120-day safety update, July 31, 2008).

EXPOSURE BY INDICATION-RLS

A comparison of unique exposures is presented in Sponsor Table 24, by cut off date.

Sponsor Table 24 presents UNIQUE Subject Exposures to GE for ALL RLS as well as RLS Long-Term Integration Safety Groupings.

Table 24 Duration of Unique Subject Exposures to GEn by Mutually Exclusive Time Interval for the All RLS Studies and RLS Long-Term Integration Groupings (Safety Populations)

Duration of exposure in months (days)	All RLS			RLS Long-Term Integration		
	NDA Data Cut-off: 06 Dec 07	120-Day SU Data Cut-off: 31 July 08	FSU: 18 June 10 Studies Complete	NDA Data Cut-off: 06 Dec 07	120-Day SU Data Cut-off: 31 July 08	FSU: 18 June 10 Studies Complete
	GEn All Doses (N=1201)	GEn All Doses (N=1201)	GEn All Doses (N=1201)	GEn All Doses (N=777)	GEn All Doses (N=777)	GEn All Doses (N=777)
<3 (<91 days)	389 (32)	378 (31)	375 (31)	214 (28)	203 (26)	200 (26)
3 to <6 (91-181 days)	317 (26)	221 (18)	213 (18)	234 (30)	138 (18)	130 (17)
6 to <9 (182-272 days)	303 (25)	204 (17)	199 (17)	137 (18)	38 (5)	33 (4)
9 to <12 (273-364 days)	72 (6)	85 (7)	43 (4)	72 (9)	85 (11)	43 (6)
≥12 (≥365 days)	120 (10)	313 (26)	371 (31)	120 (15)	313 (40)	371 (48)

Data Source: Table 1.17, Table 1.19; NDA 022399 01 May 2009, Sequence Number 0011, m5.3.5.3, 120-Day SU Appendix, Table 1.35, Table 1.37, Table 4.59, and Table 4.61.

The maximum length of exposure is included for each subject (including on-treatment and taper).

Note: For subjects who entered Study XP055, their extent of exposure in the parent study and in the follow-up study is combined. Exposure may not be continuous.

For Study XP060, duration of exposure from the SB and DB phase is combined.

REVIEWER COMMENT: As of the FSU, June 18, 2010, 371 subjects have been exposed to GE (any dose) for 12 months or greater. The increase from 313 subjects in the 120 day SU reflects the completion of the open-label extension trial, XP055.

DURATION OF EXPOSURE TO GE BY DOSE FOR RLS

Duration of Exposure to Gabapentin Enacarbil by Dose

Sponsor Table 31 presents duration of Exposure by Randomized Dose (Parent Studies XP052, XP053, XP081, and XP083) and Modal Dose (Open-label Extension Study, XP055) for Mutually Exclusive Time Intervals.

Table 31 Duration of Subject Exposures by Randomized (Parent Studies) and Modal Dose (for XP055) for Mutually Exclusive Time Intervals (Safety Population: All RLS Studies)

Duration of exposure in months (days)	FSU: 18 June 2010				
	Number (%) of Subjects				
	GEN 600 mg (n=191)	GEN 1200 mg (n=770)	GEN 1800 mg (n=218)	GEN 2400 mg (n=21)	GEN All Doses (N=1201)
<3 (<91 days)	85 (45)	214 (28)	62 (28)	13 (62)	375 (31)
3 to <6 (91-181 days)	44 (23)	143 (19)	18 (8)	8 (38)	213 (18)
6 to <9 (182-272 days)	10 (5)	177 (23)	12 (6)	0	199 (17)
9 to <12 (273-364 days)	15 (8)	18 (2)	10 (5)	0	43 (4)
≥12 (≥365 days)	37 (19)	218 (28)	116 (53)	0	371 (31)

Data Source: Table 1.16.

The maximum length of exposure is included for each subject (including on-treatment and taper).

Note: For subjects who entered Study XP055, their extent of exposure in the parent study and in the follow-up study is combined. Exposure may not be continuous. For Study XP060, duration of exposure from the single-blind and double-blind phases are combined.

One subject had a modal dose of 0 and is not included in the above table. This subject was randomized to placebo plus diphenhydramine in parent Study XP083 prior to Study XP055 where the subject missed treatment for 4 of the 8 days while enrolled in the open-label extension study.

As of June 18, 2010, FSU cut off date, 191 subjects were exposed to 600mg GE. 37 (19%) were exposed to GE 600mg/day for ≥ 1 year.

REVIEWER COMMENT: ICH guidelines require at least 100 subjects to be exposed at the proposed dose (600 mg/d) or greater for at least one year. The sponsor meets these criteria for all exposure to all doses, 371 subjects for greater than 1 year.

EXPOSURE BY DOSE OF GE IN OTHER INDICATIONS:

Study RXP 110908- RLS-associated Sleep Disturbance

A summary of exposure is presented in Table 39. The mean duration of exposure was 34.2 days for GEn. The mean daily dose of GEn during treatment was 1015.7mg, based on a randomized dose of GEn 1200 mg.

Table 39 Summary of Exposure (Safety Population: Study RXP110908)

	GEn N=127	Placebo N=132
Average Total Daily Dose (mg)		
n	125	132
Mean (SD)	1015.7 (67.72)	0
Median (Min-Max)	1028.6 (600-1114)	0
Days on Investigational Product		
n	125	132
Mean (SD)	34.2 (6.36)	34.6 (4.94)
Median (Min-Max)	35.0 (3-55)	35.0 (4-46)

Data Source: Table 2.5

REVIEWER COMMENT: All subjects on active treatment were assigned to 1200mg GE.

Study PXN110448- Pain Associated with DPN

Duration of exposure by treatment group is presented in sponsor table 42.

Table 42 Duration of Exposure by GEn Treatment Group (1200, 2400 and 3600 mg) (Safety Population: Study PXN110448)

Duration of Exposure in days	Number (%) of Subjects			
	GEn 1200mg	GEn 2400 mg	GEn 3600mg	TOTAL
N	61	56	116	233
1-30 days	3 (4.9)	12 (21.4)	16 (13.8)	31 (13.3)
31-60 days	5 (8.2)	4 (7.1)	13 (11.2)	22 (9.4)
61-90 days	6 (9.8)	1 (1.8)	7 (6.0)	14 (6.0)
>90 days	47 (77.0)	39 (69.6)	80 (69.0)	166 (71.2)

Data Source: Table 3.6

Note: Duration includes Up-Titration, Maintenance and Down-Titration.

REVIEWER COMMENT: GE 1200mg cohort had the **greatest proportion** (77%) of subjects exposed for >90days. Overall, GE 3600mg cohort had the **greatest number** of patients exposed for >90days.

Study PXN110527- Post Herpetic Neuralgia

Duration of exposure to GE by treatment dose is presented in sponsor Table 48.

Table 48 Duration of Exposure to GEn Treatment by Dose (Safety Population: Study PXN110748)

Duration of Exposure in days ¹	Number (%) of Subjects			
	GEn 1200 mg	GEn 2400 mg	GEn 3600 mg	TOTAL
N	104	82	86	272
1-30 days	5 (4.8)	13 (15.9)	16 (18.6)	34 (12.5)
31-60 days	8 (7.7)	5 (6.1)	7 (8.1)	20 (7.4)
61-90 days	4 (3.8)	2 (2.4)	7 (8.1)	13 (4.8)
>90 days	87 (83.7)	62 (75.6)	56 (65.1)	205 (75.4)

Data Source: Table 5.6

1. Includes Up-titration, Maintenance and Down-titration periods.

REVIEWER COMMENT: The **greatest number** (87) and **proportion** (83.7%) of subjects exposed for >90days were in GE 1200mg cohort.

Study MPX111381- Migraine Headache Prophylaxis

Duration of exposure by dose is presented in sponsor Table 54.

Table 54 Duration of Exposure by GEn Dose (Safety Population: Study MPX111381)

Duration of Exposure during Maintenance Period (days)	Number (%) of Subjects				
	GEn 600 mg	GEn 1200 mg	GEn 1800 mg	GEn 2400 mg	GEn 3000 mg
N	19	66	106	94	43
1-30 days	0	1 (2)	8 (8)	6 (6)	6 (14)
31-60 days	0	2 (3)	5 (5)	3 (3)	3 (7)
61-90 days	19 (100)	58 (88)	85 (80)	82 (87)	33 (77)
>90 days	0	5 (8)	8 (8)	3 (3)	1 (2)

Data Source: Table 7.6

REVIEWER COMMENT: The **greatest proportion** of subjects exposed to GE for >90days was in 1200mg and 2400mg cohorts. The **greatest number of subjects** (8) exposed to GE for >90days is in the 1800mg cohort.

SUMMARY: Overall there is limited data for exposure to GE at 600mg/day. Only in the RLS CDP, were subjects exposed to GE 600mg/day for an extended period. Exposure data for other indications are not necessarily relevant to RLS, since significantly higher doses were used.

7.3 Major Safety Results

DEATHS

In the FSU, the June 18, 2010 cut-off date, there have been a **total of 6 deaths** in clinical trials with gabapentin enacarbil. **A total of 3 deaths have been previously reported in the RLS clinical development program;** 1 in Phase I clinical pharmacology trial, 2 in Phase II and III RLS trials. There have been no new deaths in the RLS clinical development program reported, since 120-day safety update (July 31, 2008)

DEATHS NEWLY REPORTED IN FSU, CUT OFF JUNE 18, 2010

No new deaths have been reported in RLS clinical development program.

Deaths- Other Indications:

Three additional deaths have been reported in the FSU (June 18, 2010), all in studies of gabapentin enacarbil for **other indications**.

MPX111381- Migraine Prophylaxis Study

Two of the deaths occurred in the migraine prophylaxis study, MPX11381 (Sponsor Table 81).

Table 81 Deaths Reported in Study MPX111381 as of 18 June 2010

Subject (age [yr], gender)	Fatal SAE (PT)	GEn Dose	Related?
00526 (42, F)	bronchopneumonia	1800 mg ¹	No
10801 (31, M)	Accidental overdose	2400 mg ¹	undetermined

Data cut-off: 18 June 2010,

Data Source: Listing 7.1, m5.3.5.3 Narratives

1. Randomized dose, SAE occurred during the down-titration phase of the study.

1. MPX111381 Migraine Prophylaxis Study/Subject 00526

The subject had "Sudden Death (Unknown Etiology)" on (b) (6)
(b) (6) Final results of the autopsy received by sponsor on May 10, 2010, listed the cause of death as bronchopneumonia due to drug use.

Toxicology results indicated the presence of cocaine metabolites, and low levels of acetaminophen, oxycodone, alprazolam, carisoprodol, meprobamate, citalopram, clonazepam and mirtazapine.

2. MPX111381 Migraine Prophylaxis Study/Subject 10801

The subject died due to accidental overdose. A police report (received by the sponsor July 7, 2010) included the medical examiner diagnosis. The pathological diagnosis listed cause of death as “combined toxicity of multiple drugs”. The death was listed as accidental. The subject’s wife stated that the subject had been taking Percocet and alprazolam as well as study drug.

Astellas-sponsored RLS study

3. RLS STUDY 8825-CL-0005/Subject CL05-207-38

Table 82 Deaths in Astellas-Sponsored Studies

Study	Subject (age [yr], gender)	Fatal SAE (PT)	GEn Dose	Related?
RLS Study 8825-CL-0005 Data cut-off: 18 June 2010	CL05-207-38 (57, M)	Lymphoma	1200 mg	Possibly

The subject was a 57 year old male enrolled in Astellas open-label study for long term administration of gabapentin enacarbil for the treatment of RLS. On [REDACTED]^{(b) (6)}, 171 days after starting gabapentin enacarbil, the subject developed suspected malignant lymphoma. The subject was admitted to the hospital. The subject died [REDACTED]^{(b) (6)}. Follow-up reports from the investigator (April 2 and 20, 2009) stated that the subject had complained of physical deconditioning from June 17, 2008. An autopsy was performed approximately 29 weeks after start of study drug, confirming diagnosis of malignant lymphoma.

REVIEWER COMMENT: The three additional deaths reported in the FSU, cut off date June 18, 2010, were on drug treatment. In total, all 6 deaths which occurred with GE (all doses, all indications), have been on drug treatment.

NON-FATAL SERIOUS ADVERSE EVENTS (SAEs)

SAEs- RLS

Sponsor Table 85 lists Treatment Emergent Serious Adverse Events (TESAEs) for the safety population of **All RLS studies**.

Table 85 TESAEs and Follow-up Phase SAEs (Safety Population: All RLS Studies)

Study	Subject	Treatment ¹	Preferred Term	Related	Withdrawn	Outcome
XP052	1042009	Placebo	Appendicitis	No	No	Recovered
XP053	1873002	Placebo	Cholelithiasis	No	No	Recovered
XP060	1204023	Placebo	Diverticulitis	No	No	Recovered
	1864009	Placebo	Anaphylactic reaction	No	Yes	Recovered
XP081	1445004	Placebo	Peripheral vascular disorder ²	No	Yes	Unknown (LTFU)
GEn						
XP053	1143025	600 mg	Cellulitis	No	No	Recovered
	1873005	600 mg	Intervertebral disc protrusion	No	No	Resolved/w Sequelae
XP081	1115011	2400 mg	Rotator cuff syndrome	No	No	Recovered
	1285001	1200 mg	Cholelithiasis ²	No	Yes	Recovered
XP060	1354008	1200 mg	Angina pectoris	No	No	Recovered
	1514021	1200 mg	Chest pain	No	No	Recovered
	1864008	1200mg	Asphyxia	No	Yes	Death
	2064019	1200 mg	Convulsion (taper)	Possibly	Yes	Recovered
XP055	2003004	600 mg	Pulmonary embolism	No	No	Recovered
	2287001	600 mg	Lumbar vertebral fracture	No	No	Resolved/w Sequelae
	2287008	0 mg	Exostosis ² , Nerve Compression ²	No	No	Resolved/w Sequelae
	1337012	1200 mg	Meningitis viral	No	No	Recovered
	1332018	1800 mg	Cholecystitis acute	No	No	Recovered
	1503004	1800 mg	Non-cardiac chest pain	No	No	Recovered
	1047003	0 mg	Intervertebral disc protrusion ²	No	Yes	Recovered
	1282015	600 mg	Cerebrovascular accident	No	No	Recovered
	1285006	600 mg	Back pain	No	No	Recovered
			Drug withdrawal syndrome ³	No	No	Recovered
	1232021	0 mg	Lumbar spinal stenosis	No	Yes	Resolved/w Sequelae
	1292009	1200 mg	Angina unstable	No	No	Recovered
	1295014	1200 mg	Transient ischemic attack	No	Yes	Recovered
	1922026	1200 mg	Chest pain	No	No	Recovered
	1415010	1200 mg	Mental status changes	Possibly	Yes	Recovered
	9033017	1200 mg	Colitis	No	No	Recovered
	1425006	1800 mg	Road traffic accident	No	No	Recovered
			Myocardial infarction	No	No	Recovered
	2065010	1800 mg	Non-small cell lung cancer	No	Yes	Recovered
			Herpes zoster	No	No	Resolved/w sequelae
	2033010	1200 mg	Herpes zoster	No	No	Resolved/w sequelae
	1143022	0 mg	Rectal haemorrhage ^{2,4}	No	No	Recovered
	1813027	0 mg	Fall ²	No	No	Death
2115007	1800 mg	Appendicitis	No	No	Recovered	
		Post procedural Infection	No	No	Recovered	

Data Source: Listing 1.4, Individual Subject Narratives (m5.3.5.3, Narratives)

1. Actual dose of investigational product the subject received the day the SAE emerged is provided in Listing 1.4, current treatment dose was obtained from Individual Subject Narratives for interrupted treatment.
2. Events classified in Listing 1.4 as occurring during the follow-up phase.
3. Withdrawal syndrome secondary to discontinuation of pain medication.
4. Event occurred more than 30 days after the last dose of investigational product.

There is no clear pattern of treatment emergent serious adverse events in the All RLS safety population across the clinical development program.

REVIEWER COMMENT: Adverse events involving motor vehicles accidents are a safety concern for GE. A simulated driving study (XP083), in RLS subjects, has been completed using GE 1200mg, 1800mg, versus placebo or diphenhydramine (50mg). The subjects taking GE (1200mg and 1800mg) performed as poorly as subjects taking diphenhydramine. All groups performed worse than placebo.

There was one TESAЕ involving a road traffic accident (red arrow) in the open label extension trial XP055. Subject 1425006 is a 53 year old female enrolled in open-label extension study for the treatment of RLS. She was a **passenger** in a motor vehicle accident. Therefore, it is unlikely that the study drug was related to the motor vehicle accident.

Sponsor Table 84 shows TESAEs for safety population, RLS Long-Term Integration, for NDA cutoff December 6, 2001, 120 Day Safety Update cut off July 31, 2008 and FSU cut off June 18 2010.

Table 84 Any TESAEs (Safety Population: RLS Long-Term Integration)

Preferred Term	Number (%) of Subjects					
	NDA Data Cut-off: 06 December 2007		120-Day SU Data Cut-off: 31 July 2008		FSU: 18 June 2010 Studies Complete	
	Total GEn (N=777)	Time since first dose (Days)	Total GEn (N=777)	Time since first dose (Days)	Total GEn (N=777)	Time since first dose (Days)
Any event	13 (2)	-	19 (2)	-	20 (3)	-
Back pain	0	-	2 (<1)	263 & 135	1 (<1)	135
Colitis	1 (<1)	8	1 (<1)	8	1 (<1)	8
Rotator cuff syndrome	1 (<1)	27	1 (<1)	27	1 (<1)	27
Intervertebral disc protrusion	1 (<1)	31	1 (<1)	31	1 (<1)	31
Cellulitis	1 (<1)	36	1 (<1)	36	1 (<1)	36
Meningitis viral	1 (<1)	38	1 (<1)	38	1 (<1)	38
Myocardial infarction	1 (<1)	41	1 (<1)	41	1 (<1)	41
Non-small cell lung cancer	1 (<1)	41	1 (<1)	41	1 (<1)	41
Angina unstable	1 (<1)	84	1 (<1)	84	1 (<1)	84
Cholecystitis acute	1 (<1)	111	1 (<1)	111	1 (<1)	111
Chest pain	1 (<1)	132	1 (<1)	132	1 (<1)	132
Lumbar spinal stenosis	1 (<1)	190	1 (<1)	190	1 (<1)	190
Pulmonary embolism	1 (<1)	263	1 (<1)	263	1 (<1)	263
Non-cardiac chest pain	1 (<1)	318	1 (<1)	320 ²	1 (<1)	320
Cerebrovascular accident	1 (<1)	321	1 (<1)	321	1 (<1)	321
Drug withdrawal syndrome	0	-	1 (<1)	147	1 (<1)	147
Appendicitis	0	-	1 (<1)	370	1 (<1)	370
Post procedural infection	0	-	1 (<1)	379	1 (<1)	379
Lumbar vertebral fracture	0	-	1 (<1)	263	1 (<1)	263
Road traffic accident	0	-	1 (<1)	182	1 (<1)	182
Transient ischemic attack	0	-	1 (<1)	235	1 (<1)	235
Mental status changes	0	-	1 (<1)	165	1 (<1)	165
Cholelithiasis	0	-	0	-	1 (<1)	56
Peripheral vascular disorder	0	-	0	-	1 (<1)	10
Herpes Zoster	0	-	0	-	1 (<1)	284
Exostosis	0	-	0	-	1 (<1)	168
Nerve root compression	0	-	0	-	1 (<1)	168
Rectal hemorrhage	0	-	0	-	1 (<1)	107
Fall	0	-	0	-	1 (<1)	389

Data Source: Table 1.42, Listing 1.4; NDA 022399, 09 January 2009, Sequence Number 0004, m5.3.5.3 ISS, Table 2.28, Listing 2.4; NDA 022399, 01 May 2009, Sequence Number 0011, m5.3.5.3 120-Day SU, Table 4.30, Listing 4.4
 Note: TEAEs with an onset date in the on-treatment and taper medication phases are included.

REVIEWER COMMENT: Since the 120-day safety update cut off, there are 7 additional TESAEs noted. These events are of varying etiology with no clear pattern. Overall there is no notable difference in numbers of subjects experiencing TESAEs or particular pattern of adverse events.

NON FATAL SAEs- Other Indications

RLS-Associated Sleep Disturbance Study RXP110908

Two SAEs were reported during the treatment periods both subjects were on 1200mg a day.

Table 86 TESAEs and Follow-up Phase SAEs (Safety Population: RXP110908)

Subject	Treatment	Preferred Term	Related	Withdrawn	Outcome
00052	GEn 1200mg	Cellulitis	No	No	Recovered
00563	GEn 1200mg	Transient Ischemic attack	No	Yes	Recovered

Data Source: [Table 2.11](#) and [Listing 2.2](#)

Study PXN110448- Neuropathic Pain

Twenty-two SAEs were reported in subjects on study drug; **7** were on placebo, **3** were on 1200mg GE, **4** were on 2400mg GE, **5** were on 3600mg GE and **3** were on pregabalin (active control).

Table 87 Cumulative TESAEs and Post-treatment SAEs (Safety Population: Study PXN110448)

Subject	Treatment	Preferred Term	Related	Withdrawn	Outcome
1103	Placebo	Chronic lymphocytic leukaemia	No	Yes	Not Resolved
2114	Placebo	Renal failure acute ¹	No	NA	Resolved
2301	GEn 2400 mg	Partial seizures	Yes	Yes	Resolved
2502	Placebo	Supraventricular tachycardia	Yes	Yes	Resolved
2601	Pregabalin	Affective Disorder	No	Yes	Resolved
3009	GEn 3600 mg	Hypoglycaemia	No	No	Resolved
3010	GEn 1200 mg	Cellulitis	No	Yes	Resolved
		Skin ulcer	No	Yes	Resolved
		Diabetic ketoacidosis ^{1,2}	No	NA	Resolved
3416	GEn 2400 mg	Ankle fracture	No	Yes	Resolved
3606	GEn 1200 mg	Infected skin ulcer	No	No	Resolved
3607	GEn 2400 mg	Diabetic ketoacidosis	No	No	Resolved
4516	GEn 3600 mg	Oedema	Yes	Yes	Resolved
5525	Pregabalin	Cholecystitis ²	No	No	Resolved
		Pneumonia ^{1,2}	No	NA	Resolved
6005	GEn 3600 mg	Coronary artery stenosis	No	Yes	Resolving
6213	Placebo	Sinus tachycardia	Yes	Yes	Resolved
6702	Placebo	Dizziness	Yes	No	Resolved
7201	GEn 2400 mg	Hyperkalaemia	No	NA ³	Resolved
		Renal failure	No	NA ³	Resolved
		Respiratory failure	No	NA ³	Resolved
7728	GEn 3600 mg	Angina pectoris	No	No	Resolved
		Rhabdomyolysis	No	No	Resolved
8802	Pregabalin	Acute myocardial infarction ^{1,2}	Yes	NA	Resolved
8917	GEn 1200 mg	Benign prostatic hyperplasia	No	No	Resolved
9802	Placebo	Chest pain ²	No	NA ⁴	Resolved
10312	Placebo	Syncope	No	No	Resolved
10408	GEn 3600 mg	Ataxia	No	No	Resolved
		Ataxia	No	Yes	Resolved

Source Data: [Listing 3.2](#) and [m5.3.3.3, Narratives](#)

NA=not applicable due to occurrence during post-treatment period.

- SAE occurred post-treatment
- Includes updates from the 120-Day SU
- Subject was withdrawn from the study as they had missed 3 consecutive days of investigational product.
- Subject not considered withdrawn because the event occurred on the day of last dose of investigational product.

Study PXN110527-PHN

Two SAEs were reported in the study. One subject had TESAEs during down titration at 1200mg GE, the other was on 3600mg GE.

Table 88 Cumulative TESAEs and Post-treatment SAEs (Safety Population: Study PXN110527)

Subject	Treatment/Phase	Preferred Term	Related	Withdrawn	Outcome
1504	GEn 1200 mg Down-titration	Hallucination auditory	No	No	Resolved
		Depression ¹	No	NA	Resolved
3207	GEn 3600 mg	Chest pain ¹	No	NA	Resolved

Source Data: [Listing 4.2](#) and [m5.3.5.3, Narratives](#)

NA=not applicable due to occurrence during post-treatment

1. SAE occurred post-treatment.

Study PXN110748-PHN

There were a total of 9 TESAEs in the study. Two subjects were on placebo, one subject was on 1200mg GE, 4 subjects were on 2400mg GE and 2 subjects were on 3600mg GE.

Table 89 Cumulative TESAEs and Post-treatment SAEs (Safety Population: Study PXN110748)

Subject	Treatment	Preferred Term	Related	Withdrawn	Outcome
10	Placebo	Atrial fibrillation	No	No	Resolved
875	GEn 2400 mg	Intracranial aneurysm	No	Yes	Resolved
1355	GEn 2400 mg	Blood pressure increased	No	No	Resolved
1769	GEn 1200 mg	Coronary artery disease ¹	No	NA	Resolved
2652	GEn 3600 mg	Gastritis	Yes	Yes	Resolved
4258	Placebo	Vascular injury	No	Yes	Resolved
4264	GEn 2400 mg	Anxiety	No	Yes	Resolved
		Chest pain	No	Yes	Resolved
6051	GEn 2400 mg	Multiple sclerosis ²	No	No	Resolved
		Sinusitis	No	No	Resolved
		Multiple Sclerosis ³	No	Yes	Resolved
7557	GEn 3600 mg	Cystocele	No	No	Resolving

Source Data: [Listing 5.2](#) and [m5.3.5.3, Narratives](#)

NA=not applicable due to occurrence during post-treatment

1. SAE occurred post-treatment.

2. Verbatim term is advanced multiple sclerosis.

3. Verbatim term is exacerbation of multiple sclerosis

Study MPX111381- Migraine Headache Prophylaxis

Eight subjects experienced SAEs during treatment with study drug. Two were on placebo, 1 was on 600mg GE, 2 were on 1200mg GE, 1 was on 1800mg GE, and 2 were on 3000mg GE.

Table 90 **TESAEs and Post-treatment SAEs (Safety Population: Study MPX111381)**

Subject	Treatment	Preferred Term	Related	Withdrawn	Outcome
3101	GEn 1200 mg	Appendicitis	No	No	Resolved
3305	GEn 600 mg	Cholecystitis	No	No	Resolved
		Cholelithiasis	No	No	Resolved
708	GEn 3000 mg	Metastatic malignant melanoma	No	No	Unresolved
5923	Placebo	Muscle Spasms	No	No	Resolved
309	GEn 1200 mg	Convulsion	No	Yes	Resolved
3729 ¹	GEn 1800 mg	Conversion disorder	Yes	Yes	Resolved
1454	GEn 3000 mg	Pneumonia	No	No	Resolved
5574	Placebo	Pharyngitis	No	No	Resolved

Data Source: [Listing 7.2](#), Individual subject narratives ([m5.3.5.3, Narratives](#))

ASTELLAS SPONSORED STUDIES

Cumulative SAEs for Astellas-sponsored studies are presented in sponsor Table 91. Information on drug dosage is not available.

Table 91 Cumulative SAEs Received from Astellas-Sponsored Studies as of 18 June 2010

Subject	Treatment	Preferred Term	Related
RLS Study 8825-CL-0003			
CL03-001-22	GEn	Pneumonia	No
CL03-004-09	GEn	Angina pectoris	Yes
CL03-004-18	GEn	Aortic dilatation	No
CL03-051-04	GEn	Nephritis	No
RLS Study 8825-CL-0005			
CL05-20-02	GEn	Prostate cancer	No
CL05-207-38 ¹	GEn	Lymphoma ³	Yes
CL05-215-01	GEn	Neck injury	No
CL05-215-03	GEn	Subileus	No
CL05-208-09	GEn	Gastroenteritis viral	No
DPN Study 8825-CL-0007			
B0511189A	GEn	Cardiac failure	No
		Edema peripheral	No
		Back pain	Yes
701	GEn	Vomiting ²	No
306 ¹	GEn	Pollakiuria	No
4703	GEn	Loss of consciousness	No
703	GEn	Dizziness	No
1217	GEn	Muscle injury	Yes
		Contusion	Yes
		Depressed level of consciousness	Yes
		Dizziness	Yes
		Fall	Yes

Data Source: [m5.3.5.3, Narratives](#) (Narratives not updated were provided in NDA 022399, 09 January 2009, Sequence Number 0004, m5.3.5.3 m5.3.5.3, Narratives or -Day SU, NDA022399, May 1, 2009, Sequence Number 0011)

NA=not applicable

1. Narrative was provided in the 120-Day SU, NDA022399, May 1, 2009, Sequence Number 0011, and has been subsequently updated.
2. SAE onset was 30 days after the last dose of investigational product.
3. SAE had a fatal outcome.

REVIEWER COMMENT: There is no clear pattern of SAEs across study indications.

TREATMENT EMERGENT ADVERSE EVENTS (TEAEs) LEADING TO WITHDRAWAL

RLS

Treatment Emergent Adverse Events leading to withdrawal are presented for Safety Population (RLS Long-Term Integration) in sponsor Table 93.

Table 93 TEAEs Leading to Withdrawal in More than One Subject (Safety Population: RLS Long-Term Integration)

Preferred Term	Number (%) of Subjects		
	NDA Data Cut-off: 06 December 2007	120-Day SU Data Cut-off: 31 July 2008	FSU: 18 June 2010 Studies Complete
	GEn All Doses (N=777)	GEn All Doses (N=777)	GEn All Doses (N=777)
Any event	100 (13)	106 (14)	104 (13)
Somnolence	18 (2)	18 (2)	18 (2)
Dizziness	17 (2)	17 (2)	18 (2)
Sedation	7 (<1)	7 (<1)	7 (<1)
Nausea	5 (<1)	5 (<1)	6 (<1)
Depression	5 (<1)	5 (<1)	5 (<1)
Feeling abnormal	4 (<1)	4 (<1)	4 (<1)
Hepatic enzyme increased	3 (<1)	4 (<1)	3 (<1)
Weight increased	3 (<1)	4 (<1)	4 (<1)
Fatigue	3 (<1)	3 (<1)	3 (<1)
Irritability	3 (<1)	3 (<1)	3 (<1)
Rash	2 (<1)	3 (<1)	3 (<1)
Vertigo	3 (<1)	3 (<1)	3 (<1)
Vision blurred	3 (<1)	3 (<1)	3 (<1)
Balance disorder	2 (<1)	2 (<1)	2 (<1)
Headache	2 (<1)	2 (<1)	2 (<1)
Lethargy	2 (<1)	2 (<1)	2 (<1)
Oedema peripheral	2 (<1)	2 (<1)	2 (<1)
Disorientation	1 (<1)	1 (<1)	2 (<1)
Anxiety	3 (<1)	2 (<1)	2 (<1)
Libido decreased	2 (<1)	2 (<1)	2 (<1)
Alanine aminotransferase increased	2 (<1)	2 (<1)	2 (<1)
Blood creatine phosphokinase increased	2 (<1)	2 (<1)	2 (<1)
Abdominal pain upper	2 (<1)	2 (<1)	2 (<1)
Dyspnoea	1 (<1)	2 (<1)	2 (<1)

Data Source: Table 1.45; NDA 022399, 09 January 2009, Sequence Number 0004, m5.3.5.3 ISS, Table 2.32; NDA 022399, 01 May 2009, Sequence Number 0011, m5.3.5.3 120-Day SU, Table 4.32

Note: TEAEs with an onset date in the on-treatment and taper medication phases are included.

The most common TEAEs leading to withdrawal are due to somnolence, dizziness and sedation. The FSU, compared to the 120 Day safety update of June 18, 2010, shows

one additional subject withdrawal due to dizziness, one to nausea and one to disorientation.

REVIEWER COMMENT: The overall trend in TEAEs leading to withdrawal is unchanged compared to the previous review (submitted to DARRTS 2/10/2010).

TEAEs LEADING TO WITHDRAWAL-

Other Indications

The sponsor provided summary data on TEAEs leading to withdrawal, for each of the indications separately. The individual datasets were not provided with the submission. Therefore, an independent review of the data could not be performed.

STUDY PXN110448- Pain Associated with Diabetic Peripheral Neuropathy

In study for Pain Associated with Diabetic Peripheral Neuropathy (DPN), study PXN110448, the most common adverse events are dizziness and somnolence, which appear to be dose related (Table 96).

Table 96 TEAEs Leading to Withdrawal (>=2%) in Any GEn Treatment Group (Safety Population: Study PXN110448)

Preferred Term	Number (%) of Subjects		
	GEn 1200 mg N=62	GEn 2400 mg N=56	GEn 3600 mg N=116
Any event	5 (8)	12 (21)	21 (18)
Dizziness	0	1 (2)	4 (3)
Somnolence	0	1 (2)	4 (3)
Headache	0	1 (2)	2 (2)
Balance disorder	0	1 (2)	0
Lethargy	1 (2)	1 (2)	0
Hypoaesthesia	0	1(2)	0
Memory impairment	1 (2)	0	0
Partial seizures	0	1 (2)	0
Constipation	0	1(2)	2 (2)
Nausea	1 (2)	0	2 (2)
Abdominal pain	0	2 (4)	0
Dry mouth	0	1 (2)	0
Toothache	0	1 (2)	0
Oedema peripheral	0	0	2 (2)
Confusional state	1 (2)	1 (2)	0
Bipolar disorder	0	1 (2)	0
Vision blurred	0	2 (4)	1 (<1)
Blood creatinine increased	1 (2)	0	0
Blood potassium increased	1 (2)	0	0
Blood urea increased	1 (2)	0	0
Arthralgia	0	1 (2)	0
Cellulitis	1 (2)	0	0
Ankle fracture	0	1 (2)	0
Stress fracture	0	1 (2)	0
Cough	1 (2)	0	0
Increased appetite	0	1 (2)	0
Skin ulcer	1 (2)	0	0

Data Source: Table 3.12

Placebo group was not presented in the summary table (Table 96). The sponsor provided an Appendix of line listing adverse events leading to withdrawal for placebo patients in study PXN110448. Twelve subjects in the placebo group withdrew for TEAEs. Adverse events included anorexia, anxiety, insomnia, hyperhidrosis, hypoesthesia, dizziness, somnolence, chest pain, blisters, broken blood vessel on nose, worsening hypertension, depression, increase in CPK and vaginal cyst. Only **somnolence, dizziness, anxiety and increase in blood pressure** occurred in more than one subject in the placebo group.

REVIEWER COMMENT: The most common adverse events leading to withdrawal are somnolence and dizziness. The numbers are small, but there appears to be a dose response.

STUDY PXN110748 Post Herpetic Neuralgia

Studies of gabapentin enacarbil for Post Herpetic Neuralgia (PHN), PXN110748 leading to withdrawal reveal somnolence and dizziness to be the most common, with somnolence showing a dose response.

Table 98 TEAEs Leading to Withdrawal ($\geq 2\%$) in Any GEn Treatment Group (Safety Population: Study PXN110748)

Preferred Term	Number (%) of Subjects		
	GEn 1200 mg N=107	GEn 2400 mg N=82	GEn 3600 mg N=87
Any event	6 (6)	12 (15)	16 (18)
Dizziness	2 (2)	3 (4)	1 (1)
Somnolence	1 (<1)	1 (1)	3 (3)
Headache	0	2 (2)	0
Nausea	2 (2)	0	2 (2)
Fatigue	3 (3)	0	1 (1)
Oedema peripheral	0	2 (2)	0

Data Source: Table 5.12

Similarly to the previous study, the sponsor did not provide a column for the placebo group; the data was presented in a separate line listing. In the placebo group, there were 17 events leading to withdrawal; 3 for dizziness, 2 for somnolence, 1 for hypoesthesia, 2 for anxiety, 1 for depression, 1 for chest pain, 1 for increase in CPK, 1 for increase in blood pressure, 1 for blister, 1 for hyperhidrosis, 1 for anorexia, 1 for vascular injury, 1 for vaginal cyst.

REVIEWER COMMENT: Although dizziness and somnolence are among the more common adverse events leading to withdrawal, fatigue and nausea are also frequent. There is not a clear dose response notable in the data presented.

STUDY MPX11381 Migraine Prophylaxis

TEAEs leading to withdrawal are presented in Sponsor Table 99.

Table 99 TEAEs Leading to Withdrawal (>=2%) in Any GEn Treatment Group (Safety Population: Study MPX11381)

Preferred Term	Number (%) of Subjects				
	PBO	GEn 1200 mg	GEn 1800 mg	GEn 2400 mg	GEn 3000 mg
	N=128	N=66	N=134	N=133	N=62
Any event	11 (9)	4 (6)	16 (12)	15 (11)	13 (21)
Dizziness	1 (<1)	0	4 (3)	3 (2)	0
Nausea	2 (2)	0	3 (2)	2 (2)	1 (2)
Somnolence	0	0	1 (<1)	1 (<1)	1 (2)
Fatigue	1 (<1)	0	2 (1)	3 (2)	1 (2)
Depression	0	1 (2)	1 (<1)	0	1 (2)
Edema peripheral	0	0	1 (<1)	1 (<1)	1 (2)
Anxiety	0	1 (2)	0	0	2 (3)
Headache	1 (<1)	1 (2)	0	0	0
Convulsion	0	0	0	0	1 (2)
Coordination abnormal	0	0	0	0	1 (2)
Hypoaesthesia	0	0	0	0	1 (2)
Abdominal pain	0	1 (2)	0	0	1 (2)
Abdominal discomfort	0	0	0	0	1 (2)
Vomiting	0	0	0	0	1 (2)
Chills	0	0	0	0	1 (2)
Anorgasmia	0	0	0	0	1 (2)
Conversion disorder	0	0	0	0	1 (2)
Insomnia	0	0	0	0	1 (2)
Intentional self-injury	0	0	0	0	1 (2)
Nervousness	0	0	0	0	1 (2)
Sleep disorder	0	0	0	0	1 (2)
Blood creatine phosphokinase	0	0	0	1 (<1)	1 (2)
Alanine aminotransferase increased	0	1 (2)	0	0	0
Aspartate aminotransferase abnormal	0	1 (2)	0	0	0
Gamma-glutamyltransferase	0	1 (2)	0	0	0
Rash	0	1 (2)	0	1 (<1)	0
Joint swelling	0	0	0	2 (2)	0
Vertigo	0	0	3 (2)	0	0
Metastatic malignant melanoma	0	0	0	0	1 (2)

Data Source: Table 7.13

REVIEWER COMMENT In the study on migraine prophylaxis, MPX111381, the most common adverse event was dizziness, although this was not clearly dose responsive.

SUMMARY: Although dizziness and somnolence were the most common reasons for withdrawal in other indications (PHN, migraine), the overall frequency of these adverse events was lower than in RLS. Higher doses of GE were used in studies for other indications. In RLS subjects, somnolence and dizziness occurred as low as GE 600mg and increased with increasing dose. In the studies for other indications, the dose range was 1200mg to 3600mg; dizziness and somnolence did not always occur until doses greater than 1200mg were achieved. The etiology of the differences in frequency of TEAEs by indication is unclear and difficult to interpret, given differences in trial design, sample size, dosing and disease itself.

7.4 COMMON ADVERSE EVENTS

The common adverse events noted in the original NDA submission, January 9, 2009, were somnolence and dizziness. Treatment Emergent Adverse Events of somnolence and sedation are dose dependent. The FSU included the completed subjects from the open label study XP055. As seen in sponsor Table 67 (ALL RLS safety population), the proportion of treatment emergent adverse events did not significantly change from the NDA cut off of December 2007 or 120-Day cut off of July 2008.

Table 67 TEAEs Reported in at least 5% of Subjects in the GEn All Doses Group (Safety Population: All RLS Studies)

Preferred Term	Number (%) of Subjects		
	NDA Data Cut-off: 06 December 2007	120-Day SU Data Cut-off: 31 July 2008	FSU: 18 June 2010 Studies Complete
	GEn All Doses (N=1201)	GEn All Doses (N=1201)	GEn All Doses (N=1201)
Any event	1009 (84)	1019 (85)	1024 (85)
Somnolence	355 (30)	358 (30)	358 (30)
Dizziness	265 (22)	267 (22)	268 (22)
Headache	154 (13)	159 (13)	160 (13)
Nasopharyngitis	91 (8)	96 (8)	97 (8)
Nausea	87 (7)	92 (8)	90 (7)
Fatigue	79 (7)	83 (7)	83 (7)
Upper respiratory tract infection	47 (4)	56 (5)	58 (5)
Diarrhea	52 (4)	55 (5)	56 (5)

Data Source: Table 1.36; 1.32 NDA 022399, 09 January 2009, Sequence Number 0004, m5.3.5.3 ISS, Table 2.8 and Table 2.12; NDA 022399, 01 May 2009, Sequence Number 0011, m5.3.5.3 120-Day SU, Table 4.25

Note: TEAEs with an onset date in the on-treatment and taper medication phases are included.

REVIEWER COMMENT: Somnolence and dizziness (30% and 22% respectively) account for more than half of the treatment emergent adverse events in ALL RLS safety population, which remains unchanged from previous safety updates.

COMMON ADVERSE EVENTS-

Other Indications

Study RXP110908 RLS-Associated Sleep Disturbance

Sponsor Table 69 presents treatment emergent adverse events reported in at least 5% of subjects in Study RXP110908. The GE group was taking 1200mg gabapentin enacarbil/day.

Table 69 TEAEs Reported in at least 5% of Subjects (Safety Population: Study RXP110908)

Preferred Term	Number (%) of Subjects	
	GEn N= 127	Placebo N= 132
Any event	86 (68)	70 (53)
Dizziness	26 (20)	3 (2)
Somnolence	16 (13)	2 (2)
Headache	11 (9)	9 (7)
Constipation	6 (5)	4 (3)
Dry mouth	6 (5)	5 (4)
Nausea	6 (5)	5 (4)
Nasopharyngitis	6 (5)	4 (3)

Data Source: [Table 2.9](#)

AEs are assigned to a treatment based on the event start date and the treatment taken during or immediately prior to the AE start. AEs that started during the Washout or Follow-Up periods were assigned to the subject's last treatment.

REVIEWER COMMENT: Dizziness and somnolence are the most common adverse events reported for GE compared to placebo.

Study PXN110448 Pain Associated with DPN

Sponsor Table 70 presents TEAEs which occurred in at least 5% of subjects.

Table 70 TEAEs Reported in at least 5% of Subjects (Safety Population: Study PXN110448)

Preferred Term	Number (%) of Subjects				
	PBO N=120	GEN 1200mg N=62	GEN 2400mg N=56	GEN 3600mg N=116	PGB 300mg N=66
Any event	79 (66)	45 (73)	38 (68)	86 (74)	47 (71)
Dizziness	7 (6)	9 (15)	8 (14)	16 (14)	9 (14)
Somnolence	5 (4)	2 (3)	7 (13)	14 (12)	9 (14)
Nausea	9 (8)	7 (11)	4 (7)	7 (6)	3 (5)
Peripheral edema	5 (4)	2 (3)	0	11 (9)	11 (17)
Headache	9 (8)	3 (5)	4 (7)	4 (3)	6 (9)
Muscle spasms	4 (3)	6 (10)	0	11 (9)	3 (5)
Diarrhea	6 (5)	3 (5)	2 (4)	6 (5)	5 (8)
Urinary tract infection	5 (4)	3 (5)	4 (7)	6 (5)	4 (6)
Constipation	4 (3)	3 (5)	4 (7)	4 (3)	6 (9)
Fatigue	3 (3)	3 (5)	3 (5)	5 (4)	4 (6)
Arthralgia	5 (4)	1 (2)	2 (4)	5 (4)	3 (5)
Nasopharyngitis	5 (4)	1 (2)	2 (4)	4 (3)	3 (5)
Pain in extremity	2 (2)	1 (2)	4 (7)	6 (5)	2 (3)
Vision blurred	5 (4)	0	3 (5)	2 (2)	3 (5)
Weight increased	1 (<1)	0	2 (4)	5 (4)	5 (8)
Back pain	3 (3)	1 (2)	1 (2)	3 (3)	3 (5)
Increased appetite	4 (3)	0	3 (5)	1 (<1)	3 (5)
Dry mouth	4 (3)	0	4 (7)	1 (<1)	1 (2)
Disturbance in attention	2 (2)	2 (3)	0	2 (2)	3 (5)
Vomiting	3 (3)	3 (5)	1 (2)	2 (2)	0
Bronchitis	1 (<1)	3 (5)	1 (2)	0	1 (2)
Excoriation	0	1 (2)	1 (2)	1 (<1)	3 (5)
Hypoaesthesia	1 (<1)	1 (2)	1 (2)	0	3 (5)
Paraesthesia	0	2 (3)	1 (2)	0	3 (5)
Fall	0	3 (5)	1 (2)	1 (<1)	0

Source Data: [Table 3.9](#)

All AEs occur more frequently than placebo in at least one active treatment arm.

REVIEWER COMMENT: Dizziness is the most common adverse event reported for GE at 1200mg and 2400mg. At 3600mg GE, peripheral edema is reported more commonly than dizziness. Peripheral edema has been reported with gabapentin and is part of the Neurontin Labeling (2009).

Study PXN110527 PHN

Sponsor Table 71 presents treatment emergent adverse events in at least 5% of subjects.

Table 71 TEAEs Reported in at least 5% of Subjects (Safety Population: Study PXN110527)

	Number (%) of Subjects				
	GEN 1200 mg	Crossover GEN 2400 mg	GEN 3600 mg	Down- Titration	GEN Subtotal
N	91	82	85	80	94
Any Event	27 (30)	5 (6)	21 (25)	7 (9%)	42 (45)
Nasopharyngitis	4 (4)	0	1 (1)	0	5 (5)

Source Data: Table 4.9

The summary table (Sponsor Table 71) only provides information on TEAEs occurring in more than 5% of subjects, nasopharyngitis. However, in the data source table more information is provided on TEAEs of interest, specifically Nervous System and GI, but which occurred in less than 5% of subjects.

Protocol: PXN110527 RXPPSU GEN (GSK1838262 / XP13512)
 Population: Safety

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Table 4.10
 Summary of Drug Related Treatment-Emergent Adverse Events

System Organ Class Preferred Term	Baseline GBP 1800 (N=94)	GEN 1200 (N=91)	Crossover GEN 2400 (N=82)	GEN 3600 (N=85)	Down- titration (N=80)	GEN Subtotal (N=94)
ANY EVENT	1 (1%)	10 (11%)	4 (5%)	10 (12%)	2 (3%)	20 (21%)
Nervous system disorders						
Any event	0	3 (3%)	1 (1%)	6 (7%)	1 (1%)	9 (10%)
Dizziness	0	0	1 (1%)	2 (2%)	0	3 (3%)
Somnolence	0	1 (1%)	0	2 (2%)	0	3 (3%)
Headache	0	1 (1%)	0	1 (1%)	0	2 (2%)
Post herpetic neuralgia	0	2 (2%)	0	0	0	2 (2%)
Balance disorder	0	0	0	1 (1%)	0	1 (1%)
Migraine	0	0	0	0	1 (1%)	1 (1%)
Paraesthesia	0	0	0	1 (1%)	0	1 (1%)
Tremor	0	0	0	1 (1%)	0	1 (1%)
Gastrointestinal disorders						
Any event	0	6 (7%)	0	2 (2%)	0	8 (9%)
Nausea	0	3 (3%)	0	0	0	3 (3%)
Constipation	0	2 (2%)	0	0	0	2 (2%)
Dyspepsia	0	0	0	2 (2%)	0	2 (2%)
Abdominal pain upper	0	1 (1%)	0	0	0	1 (1%)
Abdominal distension	0	1 (1%)	0	0	0	1 (1%)

Note: Drug related is as judged by the investigator.

Note: Drug related adverse events with date of onset/date of increase in severity, which is on or after the dose of study medication and within one day of last dose are included. Pre-treatment (date of onset/date of increase in severity, which is on or after screening and prior to first dose) adverse events are not summarized in this table but are included in the listing of all adverse events.

ksr25778: /arenv/arprod/gsk1838262/pxn110527/rxpfsu/drivers/t_ae_rel.sas 23JUN2010 12:09

REVIEWER COMMENT: Dizziness and somnolence did occur in subjects; however the frequency was low (1-2%) and not clearly dose dependent.

Study PXN110748 PHN

Sponsor Table 72 presents TEAEs reported in at least 5% of subjects.

Table 72 TEAEs Reported in at least 5% of Subjects (Safety Population: Study PXN110748)

Preferred Term	Number (%) of Subjects			
	PBO N = 95	GEn 1200 mg N = 107	GEn 2400 mg N = 82	GEn 3600 mg N = 87
Any Event	63 (66)	75 (70)	64 (78)	71 (82)
Dizziness	14 (15)	18 (17)	21 (26)	26 (30)
Somnolence	8 (8)	11 (10)	9 (11)	12 (14)
Headache	9 (9)	11 (10)	8 (10)	6 (7)
Nausea	5 (5)	9 (8)	3 (4)	8 (9)
Constipation	5 (5)	7 (7)	4 (5)	4 (5)
Diarrhea	5 (5)	6 (6)	2 (2)	6 (7)
Fatigue	1 (1)	5 (5)	4 (5)	9 (10)
Nasopharyngitis	5 (5)	5 (5)	3 (4)	5 (6)
Edema peripheral	0	6 (6)	6 (7)	5 (6)
Arthralgia	3 (3)	6 (6)	4 (5)	3 (3)
Insomnia	2 (2)	3 (3)	4 (5)	6 (7)
Urinary Tract Infection	3 (3)	8 (7)	2 (2)	1 (1)
Back Pain	3 (3)	4 (4)	4 (5)	2 (2)
Weight Increased	1 (1)	3 (3)	4 (5)	4 (5)
Dry Mouth	2 (2)	1 (<1)	4 (5)	4 (5)
Hypertension	1 (1)	2 (2)	4 (5)	2 (2)
Nasal congestion	1 (1)	2 (2)	0	5 (6)
Vision blurred	0	2 (2)	4 (5)	2 (2)
Flatulence	0	1 (<1)	1 (1)	4 (5)
Joint sprain	0	2 (2)	0	4 (5)
Tremor	0	0	0	4 (5)

Data Source: [Table 5.9](#)

All AEs occur more frequently than placebo in at least one active treatment arm.

REVIEWER COMMENT: Similar to the RLS studies, dizziness and somnolence were the most common adverse events, and appear to be dose dependent.

Study MPX11381- Migraine Headache Prophylaxis

Sponsor Table 73 presents TEAEs reported in at least 5% of subjects.

Table 73 TEAEs Reported in at least 5% of Subjects (Safety Population: Study MPX111381)

Preferred Term	Number (%) of Subjects				
	PBO N=128	GEn 1200 mg N=66	GEn 1800 mg N=134	GEn 2400 mg N=133	GEn 3000 mg N=62
Any event	87 (68)	44 (67)	99 (74)	101 (76)	49 (79)
Dizziness	8 (6)	16 (24)	43 (32)	35 (26)	11 (18)
Fatigue	9 (7)	10 (15)	12 (9)	14 (11)	3 (5)
Nausea	12 (9)	3 (5)	15 (11)	12 (9)	6 (10)
Somnolence	6 (5)	6 (9)	7 (5)	14 (11)	9 (15)
Weight increased	7 (5)	4 (6)	8 (6)	9 (7)	4 (6)
Upper respiratory tract infection	9 (7)	4 (6)	4 (3)	9 (7)	5 (8)
Constipation	3 (2)	4 (6)	7 (5)	8 (6)	5 (8)
Dry Mouth	3 (2)	4 (6)	6 (4)	5 (4)	3 (5)
Nasopharyngitis	8 (6)	3 (5)	4 (3)	4 (3)	2 (3)
Diarrhea	8 (6)	1 (2)	1 (<1)	7 (5)	1 (2)
Vomiting	5 (4)	1 (2)	3 (2)	7 (5)	2 (3)
Influenza	4 (3)	1 (2)	3 (2)	4 (3)	3 (5)
Insomnia	1 (<1)	4 (6)	1 (<1)	6 (5)	2 (3)
Edema peripheral	4 (3)	4 (6)	1 (<1)	3 (2)	2 (3)
Sinusitis	3 (2)	4 (6)	3 (2)	3 (2)	1 (2)
Balance disorder	1 (<1)	2 (3)	2 (1)	6 (5)	1 (2)
Abdominal Pain	1 (<1)	2 (3)	2 (1)	3 (2)	3 (5)
Back pain	0	1 (2)	6 (4)	1 (<1)	3 (5)
Cough	0	3 (5)	1 (<1)	0	0

Source Data: [Table 7.9](#)

Note: TEAEs have been determined to be any AEs beginning during treatment (including up to 1 day after the last dose). AEs beginning prior to first dose of investigational product but worsening after first dose of investigational product are also considered to be TEAEs.

REVIEWER COMMENT: Dizziness and fatigue are the most common adverse events noted in the Migraine Prophylaxis population. Dizziness appears to be dose dependent.

SUMMARY: Overall the most common treatment emergent adverse events are similar across indications. In other indications (not RLS) dizziness is usually the most common followed by somnolence. Unlike RLS population, the adverse events occur at higher doses and are not clearly dose dependent.

LABORATORY FINDINGS

RLS

The sponsor included datasets as well as tabulated reports for clinical chemistry and hematology. There were no new trends seen in these data compared to previous review. The sponsor also included markedly abnormal lab reports for studies of OTHER INDICATIONS, RLS-associated sleep disturbance, Post Herpetic Neuralgia and Migraine Prophylaxis. Narratives for significant lab abnormalities are presented below.

Other Indications

STUDY RXP110908-RLS associated sleep disorders

One subject from GSK-sponsored Phase IIIb RLS-associated sleep disturbance, Study RXP110908, met protocol-defined liver safety stopping criteria.

Subject 1265/RXP110908 is a 43 year old female, randomized to gabapentin enacarbil: PBO. At Week 4, visit, 28 days after starting study drug, the subject met stopping criteria of ALT>5X ULN. The lab values are presented in sponsor Table 112. The subject was tapered off study drug over 6 days. Hepatitis serologies were negative. The subject had positive history of alcohol use and was taking naproxen sodium during the study. In addition, the subject admitted to taking Tylenol PM and Percocet. The subject was clinically asymptomatic.

Table 112 Liver Function Test Results for Subject 1265

Visit Date	ALT (IU/L) ¹	AST (IU/L) ²	Alkaline Phosphatase (IU/L) ³	Total Bilirubin (umol/L) ⁴	GGT (IU/L) ⁵
Screen 01 Dec 2008	16	19	53	6	31
Week 4 31 Jan 2009	391	214	124	10	388
06 Feb 2009	333	213	126	10	ND
16 Feb 2009	241	149	98	12	ND
23 Feb 2009	223	126	104	6	ND
02 Mar 2009	164	114	93	8	ND
12 Mar 2009	129	92	76	10	ND
20 Mar 2009	70	47	67	6	ND
27 Mar 2009	59	51	67	6	100
03 Apr 2009	44	33	59	12	ND

Source data: Listing 2.4

ND=not done

1. ALT normal range: 0-48 IU/L
2. AST normal range: 20-125 IU/L
3. Alkaline phosphatase normal range: 20-125 IU/L
4. Total bilirubin normal range: 0-22 umol/L
5. GGT normal range: 0-45 IU/L

REVIEWER COMMENT: After discontinuation of study drug, the subjects LFTs improved. The improvement of LFTs after stopping the drug suggests a possible relationship between GE and increase in LFTs.

STUDY PXN110748- Post-Herpetic Neuralgia

In GSK sponsored study on Neuropathic Pain, Study PXN110748 (PHN), and a significantly abnormal liver chemistry result was noted in Subject 2654, a 43 year old white female, randomized to 3600mg gabapentin enacarbil. Thirty-six days following start of treatment with drug, the subject had an ALT of 163 IU/L. This did not meet GSK protocol defined liver stopping criteria; however, more intensive laboratory monitoring was performed. Hepatitis serologies were negative, and the subject was clinically asymptomatic. The subject remained on investigational product.

Table 1 Liver Function Test Results for Subject 2654

Visit Date	ALT (IU/L) ¹	AST (IU/L) ²	Alkaline Phosphatase (IU/L) ³	Total Bilirubin (umol/L) ⁴	GGT (IU/L) ⁵
Screen 20 Aug 2008	26	19	112	6	ND
Week 2 24 Sept 2008	58	40	100	6	ND
Week 5 15 Oct 2008	163	100	132	6	ND
Week 6 (unscheduled) 20 Oct 2008	147	50	127	6	ND
Week 7 (unscheduled) 27 Oct 2008	58	28	111	6	ND
Week 8 (unscheduled) 05 Nov 2008	32	22	109	6	ND
Week 9 12 Nov 2008	29	23	103	6	ND
Week 13 10 Dec 2008	20	19	86	6	ND

Source data: Table 5.20 and Listing 5.4

ND=not done

1. ALT normal range: 0-48 IU/L
2. AST normal range: 0-42 IU/L
3. Alkaline phosphatase normal range: 20-125 IU/L
4. Total bilirubin normal range: 0-22 umol/L
5. GGT normal range: 0-45 IU/L

REVIEWER COMMENT: The subjects LFTs are mildly elevated and resolve despite continuing study medication. It is not known whether the subject changed (decreased) the dose of study drug.

STUDY MPX111381- Migraine prophylaxis

In Study MPX111381, migraine headache prophylaxis, two subjects met protocol defined criteria for a liver event, one of whom met the protocol defined liver safety stopping criteria.

1. **Subject 3002**, a 56 year old white female, was randomized to gabapentin enacarbil 1200mg/day. At Week 17 visit, 119 days following start of treatment, the subject presented with abdominal pain and nausea. Alt was 200 IU/L, which met protocol defined liver stopping criteria of ALT>3X ULN, associated with symptoms of hepatitis. (Sponsor Table 2).

Table 2 Liver Function Test Results for Subject 3002

Visit Date	ALT (IU/L) ¹	AST (IU/L) ²	Alkaline Phosphatase (IU/L) ³	Total Bilirubin (umol/L) ⁴	GGT (IU/L) ⁵
Screen 6 Oct 2008	22	24	79	8	24
Baseline 19 Nov 2008	26	27	85	6	30
Week 5 24 Dec 2008	22	25	84	6	25
Week 9 21 Jan 2009	17	21	76	8	22
Week 13 18 Feb 2009	30	26	83	6	36
Early Withdrawal/End of Maintenance 18 Mar 2009	200	145	123	10	88
20 Mar 2009	147	61	148	8	ND
23 Mar 2009	69	31	118	6	ND
25 Mar 2009	51	26	115	8	ND
1 Apr 2009	32	27	94	10	ND
8 Apr 2009	19	20	81	8	ND
15 Apr 2009	18	22	81	6	24

Source data: Listing 7.5 and Listing 7.6

ND=not done

6. ALT normal range: 0-48 IU/L

7. AST normal range: 0-42 IU/L

8. Alkaline phosphatase normal range: 20-125 IU/L

9. Total bilirubin normal range: 0-22 umol/L

10. GGT normal range: 0-45 IU/L

Investigational drug product was discontinued two days later. Concomitant medications included acetylsalicylic acid, cyclosporine, hydroxychloroquine, hydroxyzine, naproxen sodium/sumatriptan (TREXIMET), paracetamol, and rizatriptan. Hepatitis serologies were negative. The subject's symptoms resolved 5 days after discontinuing investigational drug product. The case was reviewed by internal, independent safety review committee who did not think the study should be discontinued.

2. **Subject 3364**, a 31 year old white female was randomized to gabapentin enacarbil 2400mg/day. At the Week 5 visit, 35 days following the start of drug treatment, the subject was noted to have an ALT of 145 IU/L. This lab value did not meet protocol-defined liver stopping criteria, but warranted more intensive monitoring based on ALT > 3X ULN. (Sponsor Table 3)

Table 3 Liver Function Test Results for Subject 3364

Visit Date	ALT (IU/L) ¹	AST (IU/L) ²	Alkaline Phosphatase (IU/L) ³	Total Bilirubin (umol/L) ⁴	GGT (IU/L) ⁵
Screen 04 Sept 2009	41	42	111	6	51
Baseline 28 Oct 2009	35	45	75	12	36
Week 5 02 Dec 2009	145	80	74	8	90
Week 6 ⁶ 07 Dec 2009	87	41	82	6	N/D
Week 7 11 Dec 2009	55	40	76	8	N/D
Week 8 15 Dec 2009	44	37	73	8	N/D
Week 9 21 Dec 2009	36	39	67	6	N/D
Week 10 28 Dec 2009 (Early Withdrawal)	34	34	70	8	57
Week 10 Repeat Lab 28 Dec 2009	33	36	72	8	ND

Source data: Listing 7.5 and Listing 7.6

ND=not done; W/D=withdraw

1. ALT normal range: 0-48 IU/L

2. AST normal range: 0-42 IU/L

3. Alkaline phosphatase normal range: 20-125 IU/L

4. Total bilirubin normal range: 0-22 umol/L

5. GGT normal range: 0-45 IU/L

6. Also reported elevated lactic dehydrogenase = 333 (normal range 0-250)

The subject remained on investigational drug; hepatitis serologies were negative. Concomitant medications included Singular, Allegra D, levoxyl and lybrel. The subject was clinically asymptomatic.

In the first subject, LFTs improved after discontinuation of the study drug, while the second subject improved while being maintained on study drug.

VITAL SIGNS

RLS Clinical Development Program

A summary of markedly abnormal, post-baseline, values for blood pressure and pulse in RLS Long Integration safety population is presented in sponsor Table 117.

Table 117 Summary of Markedly Abnormal Values for Blood Pressure and Pulse at Any Post-Baseline Visit (Safety Population: RLS Long-Term Integration)

Vital Sign Change Relative to Baseline	Number (%) Subjects		
	NDA Data Cut-off: 06 December 2007	120-Day SU Data Cut-off: 31 July 2008	FSU: 18 June 2010 Studies Complete
	GEn All Doses (N=777)	GEn All Doses (N=777)	GEn All Doses (N=777)
N	762	762	762
SBP increment			
≥20 mmHg	137 (18.0)	157 (21)	163 (21)
≥40 mmHg (Severe)	13 (1.7)	14 (2)	14 (2)
SBP decrement			
≥20 mmHg	118 (15.5)	127 (17)	130 (17)
≥40 mmHg (Severe)	6 (0.8)	7 (<1)	7 (<1)
DBP increment			
≥10 mmHg	245 (32.2)	278 (36)	278 (36)
≥20 mmHg (Severe)	63 (8.3)	73 (10)	75 (10)
DBP decrement			
≥10 mmHg	226 (29.7)	238 (31)	239 (31)
≥20 mmHg (Severe)	48 (6.3)	53 (7)	54 (7)
Pulse increment			
≥15 bpm	229 (30.1)	255 (33)	255 (33)
≥30 bpm (Severe)	19 (2.5)	24 (3)	26 (3)
Pulse decrement			
≥15 bpm	98 (12.9)	107 (14)	109 (14)
≥30 bpm (Severe)	3 (0.4)	3 (<1)	3 (<1)

Data Source: Table 1.62; NDA 022399, 09 January 2009, Sequence Number 0004, m5.3.5.3 ISS, Table 4.8; NDA 022399, 01 May 2009, Sequence Number 0011, m5.3.5.3 120-Day SU, Table 4.49

Note: The final visit may be included with any post-baseline visit.

Comparing NDA cut off of December 2007, 120 Day cut off July 2008 and FSU, no new trends are noted.

Electrocardiograms (ECGs)

The percentages of subjects in RLS Long-Term Integration studies grouping with a QT interval change from baseline ≥ 30 and ≥ 60 msec are presented in sponsor Table 123.

Table 123 Summary of Change from Baseline for QT Interval Data Meeting the Outlier Criteria at Any Post-Baseline Visit (Safety Population: RLS Long-Term Integration)

ECG Parameter	Change from Baseline (msec)	Number (%) of Subjects		
		NDA Data Cut-off: 06 December 2007	120-Day SU Data Cut-off: 31 July 2008	FSU: 18 June 2010 Studies Complete
		GE _n All Doses (N=777)	GE _n All Doses (N=777)	GE _n All Doses (N=777)
Uncorrected QT interval, n		758	761	761
	≥30	144 (19)	152 (20)	166 (22)
	≥60	10 (1)	12 (2)	13 (2)
QTcB, n		760	761	761
	≥30	130 (17)	146 (19)	152 (20)
	≥60	8 (1)	8 (1)	8 (1)
QTcF, n		760	761	761
	≥30	74 (10)	80 (11)	86 (11)
	≥60	5 (<1)	5 (<1)	5 (<1)

Data Source: Table 1.67, Listing 1.10; NDA 022399, 09 January 2009, Sequence Number 0004, m5.3.5.3 ISS, Table 4.22, Listing 4.4; NDA 022399, 01 May 2009, Sequence Number 0011, m5.3.5.3 120-Day SU, Table 4.54, Listing 4.10

Across all cut off dates, the corrected QTc (QTcB or QTcF) no more than 1% of the RLS Long-Term Integration population have a ≥60msec change from baseline. Thirteen subjects with uncorrected QT interval change ≥60 are reported compared to 10 subjects in ISS in NDA 022399.

The sponsor provided a summary table for the 13 subjects reported in FSU with uncorrected QT interval of ≥60 msec change from baseline. (Table 124)

Table 124 Summary of Subjects with QTc change from Baseline greater than or equal to 60 msec or post-Baseline QTc Value greater than or equal to 500 msec (Safety Population: RLS Long-Term Integration)

Study	Subject	Age/ Gender	Treatment	Week	QTcB (msec) & Change from Baseline		QTcF (msec) & Change from Baseline		Comment
XP052	1112008	72/F	Placebo	Screen	449	-	436	-	No additional pertinent information.
				Baseline	368	-	357	-	
				1	418	50	407	50	
				4	426	58	410	53	
				8	412	44	421	64	
				12/ET	440	72	445	88	
XP053	1073014	42/F	1200 mg	Screen	441	-	415	-	Irregular sinus mechanism, Wandering pacemaker
				Baseline	369	-	372	-	
					381	-	376	-	
					365	-	368	-	
				1	417	52	390	22	
				4	414	49	389	21	
				8	393	28	398	30	
12/ET	453	88	427	59					
XP053	1493034	74/F	1200 mg	Screen	455	-	452	-	No additional pertinent information.
				Baseline	445	-	440	-	
					437	-	435	-	
					432	-	430	-	
				1	486	54	491	61	
				4	451	19	447	17	
				8	461	29	463	33	
12/ET	456	24	464	34					
XP053	2103003	47/M	1200 mg	Screen	411	-	401	-	No additional pertinent information.
				Baseline	393	-	389	-	
					388	-	385	-	
					378	-	377	-	
				1	421	43	416	39	
				4	449	71	446	69	
8	385	7	392	15					
12/ET	407	29	403	26					
XP081	1285006	65/M	1800 mg	Screen	350	-	352	-	Complete Left Bundle Branch Block (LBBB)
				Baseline	365	-	368	-	
					346	-	352	-	
				Baseline mean	356	-	360	-	
				1	405	50	400	40	
				1	408	53	408	48	
				4	440	85	437	77	
				8	421	66	419	59	
				12/ET	417	62	416	56	

Continued

Table 124 (Continued) Summary of Subjects with QTc change from Baseline greater than or equal to 60 msec or post-Baseline QTc Value greater than or equal to 500 msec (Safety Population: RLS Long-Term Integration)

Study	Subject	Age/ Gender	Treatment	Week	QTcB (msec) & Change from Baseline		QTcF (msec) & Change from Baseline		Comment
XP081	1115011	28/F	2400 mg	Screen	398	-	399	-	No additional pertinent information.
				Baseline	379	-	381	-	
					396	-	401	-	
					397	-	401	-	
				Baseline mean	391	-	394	-	
				1	410	19	409	15	
				4	421	30	386	-8	
XP055	1032014	47/M	600 mg	Baseline	367	-	352	-	No additional pertinent information.
				1	382	15	366	14	
				4	390	23	364	12	
				12	405	38	383	31	
				24	437	70	415	63	
XP055	1083015	74/M	1200 mg	Baseline	379	-	382	-	Premature ventricular systoles (Wks 4 and 36) and prolonged QT interval (Wk 36)
				1	379	0	381	-1	
				4	364	-15	366	-16	
				12	369	-10	367	-15	
				24	385	6	378	-4	
				36	472	93	460	78	
XP055	1222003	51/F	1200 mg	Baseline	393	-	394	-	QT read from Lead III at Wk 52, all others from Lead II
				1	402	9	399	5	
				4	418	25	417	23	
				12	398	5	396	2	
				24	418	25	412	18	
				36	420	27	416	22	
XP055	1483025	62/M	1200 mg	Baseline	404	-	398	-	Complete RBBB
				1	469	65	441	43	
				4	431	27	421	23	
				12	441	37	417	19	
				24	415	11	397	-1	
				36	451	47	431	33	
XP055	2065010	67/F	1800 mg	Baseline	378	-	361	-	Sinus tachycardia
				1	406	28	381	20	
				4	444	66	407	46	
				52/ET	395	17	394	33	

Continued

Table 124 (Continued) Summary of Subjects with QTc change from Baseline greater than or equal to 60 msec or post-Baseline QTc Value greater than or equal to 500 msec (Safety Population: RLS Long-Term Integration)

Study	Subject	Age/ Gender	Treatment	Week	QTcB (msec) & Change from Baseline		QTcF (msec) & Change from Baseline		Comment
					QTcB (msec)	Change from Baseline	QTcF (msec)	Change from Baseline	
XP055	1357006	64/M	1200 mg	Baseline	463	-	474	-	First degree AV block, abnormal left QRS axis deviation, and complete LBBB were noted for all visits
				1	470	7	473	-1	
				4	464	1	477	3	
				12	464	1	468	-6	
				24	507	44	491	17	
				36	458	-5	476	2	
				52/ET	481	18	497	23	
XP055	1337013	41/F	1800 mg	Baseline	408	-	406	-	No additional pertinent information
				1	419	11	398	-8	
				4	412	4	407	1	
				12	392	-16	381	-25	
				24	412	4	402	-4	
				36	444	36	437	31	
				52/ET	469	61	458	52	

Data Source: Listing 1.11

The 13 subjects presented in the table were part of the FSU. There is no clear trend in terms of association with dosage of drug. The concomitant abnormalities noted on the ECGs are also varied, including bundle branch blocks, first degree AV block and tachycardia. In summary, there does not appear to be a specific etiology for the QT abnormalities associated with the study drug.

Special Safety Studies/Clinical Trials

SAFETY TOPICS OF SPECIAL INTEREST- RLS

Sponsor Table 100 outlines safety topics of special interest associated with RLS. The table gives updated information for sudden onset of sleep (SOS) and suicidality. New presentations are shown for augmentation, although there is no new data. No new data is presented on early morning rebound (EMR), cognition, driving or impulse control disorders.

Table 100 Safety Topics of Special Interest for GEN in RLS

Special Interest Topic	Method	Data Evaluated in ISS	Data provided in FSU
Sudden Onset of Sleep	Search of AE preferred terms (PTs)	All Controlled Phase II and Phase III RLS studies plus Study XP021	Presentation of the SOS-Questionnaire results from the final CSR for XP055
	SOS Questionnaire (SOS-Q)	12-Week Placebo-Controlled RLS studies and Studies XP060 and XP055	
Impulse Control Symptoms including compulsive behaviors	Search of AE PTs and verbatim terms	12-Week Placebo-Controlled RLS studies	No new data for the study grouping
Suicidality	Search of AE PTs, verbatim terms and CRF free text fields with Columbia University rating of events (C-CASA) identified in the search and all On-Treatment SAEs as of 31 March 2008 NDA submission cut-off	All completed placebo-controlled multiple dose studies regardless of indication	Presentation of AE evaluation in XP055, as well as reporting process and findings from individual CSRs in completed GSK-sponsored studies for all indications
Augmentation	24-hour RLS diary-cumulative frequency plots as requested by FDA	12-Week Placebo-Controlled RLS studies Maintenance of Effect Study XP060 Long-Term Integration grouping	New displays provided for the Long-Term Integration grouping
Early morning rebound (EMR)	24-hour RLS diary- early morning interval symptoms	12-Week Placebo-Controlled RLS studies	No new data for the study grouping
Effects on driving	Simulated driving assessment	Study XP083	No new data, study was complete at time of ISS
Effects on cognition	Brief Assessment of Cognition	Studies XP053, XP081 and XP083	No new data, studies were complete at time of ISS
	Continuous Performance Test-IP	Study XP081	

SUDDEN ONSET OF SLEEP

During the open label extension study, XP055, 5 subjects reported possible sleep attacks on the SOS-Q. Three of these subjects reported a total of six possible sleep

attacks, according to the sponsor, at Week 0, Visit 1 of Study XP055. The other two subjects had confirmed events of sleep attacks. (Sponsor Table 101).

Table 101 Results of the SOS-Q by Visit (Safety Population: Study XP055)

Site No./ Subject No.	Visit ¹	Any sleep attacks?	How many?	What were you doing?
Naïve				
113/3008	7	Yes	3	Both passive and active activities
133/7005 ²	5	Yes	2	Passive activities

Data Source: CSR XP055, DSListing 16.1, DSListing 16.2, and DSListing 18

1. Visit 5: (End Of Week 24); Visit 7: (End of Week 52).

2. Also reported as an AE.

SUICIDALITY

In RLS Clinical Development Program

Prior to the FSU, one suicide in clinical pharmacology study, XP044, was noted. A 51 year old male healthy volunteer died from a self inflicted gunshot wound, 36 hours post study drug. (Please refer to DEATHS)

XP055

There were no AEs of suicide or suicide related AEs in the final study report for XP055.

Suicidality in Other Indications

RLS-associated sleep disturbance (RXP110908)

One subject (254), reported suicidal thoughts during the study. The subject, a 38 year old female, retrospectively reported during the washout period, that she had “dark thoughts” starting 13 days after treatment began and lasting 15 days. On further questioning she admitted to suicidal ideation without any behaviors or plan. The patient admitted to psychosocial stressors and there was a family history of OCD and alcoholism. The subject had already discontinued study drug by the time the AE was reported. She was referred to PCP or psychiatrist for mild depression.

Neuropathic pain (PXN110448)

One subject, a 40 year old white male was randomized to gabapentin enacarbil 3600mg/day. Five days after starting 3600mg gabapentin enacarbil (October 4, 2008), the subject reported an AE of mood disturbance. 51 days after starting study drug (November 19, 2008), the subject reported that he had thoughts of suicide, took his hand gun and went to the barn where his wife later found him. He was seen by his family doctor who started him on Cymbalta 30mg/day (December 3, 2008). The subject was withdrawn from the study after down titration (December 9, 2008).

Neuropathic pain (PXN110748)

One subject, a 44 year old female was randomized to gabapentin enacarbil 3600mg/day (December 17, 2008). 94 days after starting treatment with study drug, during taper phase the subject reported depression, anxiety and lack of energy. In addition, she admitted to a 'fleeting moment' of suicide. Ten days after the onset of symptoms, the subject reported resolution of suicidal ideation. Down titration and follow-up visits were completed with no further AE of suicidal ideation.

Migraine prophylaxis (MPX111381)

The subject, a 31 year old male, was randomized to gabapentin enacarbil 2400mg/day (November 3, 2009). During the down titration phase of the study (March 12, 2010) the subject died due to an accidental overdose (please refer to DEATHS). There was no history of suicidality during the study. According to the Police Department Incident Report, the County Medical Examiner's pathological diagnosis for the subject showed cause of death as "combined toxicity of multiple drugs". The manner of death was listed as "accident".

REVIEWER COMMENT: There have been two suicides and three cases of suicidal ideation, reported by the sponsor, in studies with gabapentin enacarbil (any indication). However, not all studies conducted with gabapentin enacarbil captured suicidal ideation using appropriate scales. While some studies for other indications prospectively evaluated suicidality, in the RLS clinical development program the sponsor retrospectively searched for adverse event reports of suicidality. Therefore it is difficult to make any conclusions about the risk of suicidality and gabapentin enacarbil. Since gabapentin enacarbil is classified as an anticonvulsant, it will have labeling for suicidality.

7.2.3 Special Animal and/or In Vitro Testing

Rat pancreatic acinar cell tumors were observed at high exposure of gabapentin in the gabapentin enacarbil carcinogenicity study. New studies performed to aid in the assessment of cancer risk to humans include:

- 7 day pilot toxicokinetic study and a definitive 14 day toxicokinetic study in Wistar rats
- Pilot study investigating cholecystinin (CCK) plasma levels in male Wistar rats after a single dose of gabapentin enacarbil.

- In vitro studies investigating the expression and localization of gabapentin transporter proteins in human, rat and mouse pancreatic tissue, accumulation of gabapentin in rat and human pancreas slices and blood-to-plasma ratios of gabapentin in mouse and rat blood.

(Please refer to Pharm-Tox Review for details)

7.6.1 Human Carcinogenicity

As part of the CR, the agency asked the sponsor to perform epidemiological studies to look at the possible risk of pancreatic cancer, as well as all cancers, in humans exposed to gabapentin. In summary, the sponsor performed two parallel case-control studies to address the two cancer signals (pancreatic and renal) as seen in an epidemiologic study conducted by Friedman et al (Cancer causes & control:CCC, 2009) using the Kaiser Permanente database. The two studies conducted by the sponsor used the GPRD database. The DEPI reviewer (JR Williams, 04/04/2011) stated that the studies were well-designed and conducted. The studies were based upon the assumption that epidemiologic investigations of gabapentin can be used to assess GE's safety profile. The two studies do not provide strong evidence of an association between gabapentin use and cancer, in particular pancreatic and renal cancers. However, the studies were limited due to short duration of exposure to gabapentin (Please refer to DEPI review for full details).

7.6.2 Human Reproduction and Pregnancy Data

As of June 18, 2010 cut off date there have been four pregnancies reported

- Study XP060 (RLS), Subject 207-4008. Healthy normal neonate. Examinations and assessments at 1 month were normal
- Study PXN 110748 (post-herpetic neuralgia). Healthy normal neonate at birth
- Study MPX111381 (migraine), subject 5165, estimated delivery August 17, 2010 and subject 10524 estimated delivery unknown

8 Postmarket Experience

N/A

23 Page(s) of Draft Labeling have been Withheld in Full as b4 (CCI/TS) immediately following this page

This is a representation of an electronic record that was signed electronically and this page is the manifestation of the electronic signature.

/s/

SUSANNE R GOLDSTEIN
04/06/2011

GERALD D PODSKALNY
04/06/2011

MEMORANDUM

DATE: March 23, 2011

FROM: Director
Division of Neurology Products/HFD-120

TO: File, NDA 22-399

SUBJECT: Recommendation for Action on NDA 22-399, for the use of Horizant (gabapentin enacarbil) Extended Release Tablets in the treatment of patients with moderate to severe Restless Legs Syndrome (RLS)

NDA 22-399, for the use of Horizant (gabapentin enacarbil) Extended Release Tablets in the treatment of patients with moderate to severe Restless Legs Syndrome (RLS), was submitted by GlaxoSmithKline on 1/9/09. Horizant is an extended release formulation of a pro-drug of gabapentin, a drug marketed (tradename Neurontin) for the treatment of patients with epilepsy, and for the treatment of patients with post-herpetic neuralgia.

The Agency issued a Complete Response (CR) letter to the sponsor on 2/17/10. Although the Agency had concluded that the sponsor had submitted substantial evidence of effectiveness for Horizant, and there were no clinical safety issues that would have precluded approval (a dose of 600 mg/day was found to have been as effective as higher doses, the latter of which were associated with an increased incidence of adverse reactions), there was a finding of pancreatic acinar cell carcinomas in the rat carcinogenicity study, which was the basis for the CR action. The plasma level of gabapentin at the no-effect level for tumors was considered to have been about 8 times the plasma level in humans at the 600 mg/day dose, a margin considered unacceptably low in this clinical setting (similar findings had been seen with gabapentin, but the potential risk was considered acceptable for a population of patients with refractory epilepsy).

In the CR letter, the Agency offered the sponsor several options to address this concern, including providing evidence of a mechanism of tumor formation that might be irrelevant in humans, providing epidemiologic evidence that demonstrated no important risk of pancreatic cancer in humans (gabapentin has been marketed for many years), or performing a clinical trial demonstrating that Horizant is superior to other approved treatments for RLS.

Subsequent to the issuance of the CR letter, we met with the sponsor to further discuss these matters.

The sponsor submitted a complete response to the Agency on 10/6/10. This submission contained the results of an epidemiologic study, further non-clinical data and arguments, additional clinical safety data, and draft labeling. In

addition, although the original application was submitted under 505(b)(1) of the FD&C Act, the resubmission was submitted under 505(b)(2), with Neurontin (gabapentin) as the referenced listed drug. This permits us to refer to the approved label for gabapentin, if necessary, in support of the NDA for Horizant.

The submission has been reviewed by Dr. Susanne Goldstein, medical officer, Dr. LuAnn McKinney, pharmacologist, Dr. Lois Freed, pharmacology team leader, Dr. James R. Williams, Office of Surveillance and Epidemiology, Dr. Zachary Oleszczuk, Division of Medication Error Prevention and Analysis, Robin Duer, Division of whatever, and Dr. Gerald Podskalny, medical team leader and Cross-discipline team leader (CDTL).

The clinical team recommends that the application be approved, primarily based on a re-analysis of the non-clinical data.

Effectiveness

There are no new effectiveness data.

Safety

At the time of the CR letter, the sponsor had submitted safety data on about 1600 patients with RLS who had received at least one dose of Horizant. In the complete response, the sponsor has provided data on no new, unique, RLS patients, although they have provided additional longer-term, open-label, follow-up for 58 patients who continued in Study 055.

However, they have provided summary data for an additional 1173 patients from controlled trials in other indications, including an RLS polysomnography study, four neuropathic pain studies, and a migraine prophylaxis study. An additional 673 patients have been exposed in Astellas-sponsored studies, for which we do not have adequate data.

In these studies, which examined doses from 1200 mg/day to 3600 mg/day, and which varied from 8-12 weeks in duration, there were 3 deaths (there were 3 deaths in the original NDA database). Two of the deaths occurred in the migraine-prophylaxis study (one case each of bronchopneumonia and multiple drug overdose) and one occurred in an Astellas RLS study (malignant lymphoma 171 days after starting Horizant).

Serious Adverse Events (SAEs)

A total of 29 Horizant-treated patients experienced at least one SAE in these studies. Dr. Goldstein's tables X-Y list these events. In a total of 13 patients the drug was withdrawn, with resolution of the event. In the other cases, the event resolved with continued treatment. In 4 patients, the event occurred after the

drug had been discontinued. No single event appeared to be clearly drug-related, although there were single cases of gastritis, edema (both at 3600 mg/day) and two cases of seizures (one at 1200 mg/day and one at 2400 mg/day; the latter considered related to treatment by the sponsor).

Discontinuations

In the new non-RLS studies, Dr. Goldstein has presented tabulations of those adverse events that led to discontinuations. Few patients discontinued for an adverse event at any dose, though there was an increase in the incidence with dose. In particular, few discontinued due to somnolence or dizziness. There were no important causes for discontinuations that we had not already been aware of.

Common adverse events

No new important adverse events were seen in the newly presented studies that had not been seen in previous studies.

Case control studies

At the request of the Agency, the sponsor performed two case-control studies based on data from the GPRD database in the UK, which were designed to evaluate whether or not gabapentin use is associated with pancreatic cancer.

The GPRD database contains computerized medical records for about 3.2 million patients in 487 general practices in the UK.

The two studies, 4774 and 4931, were nearly identical in design, except that Study 4774 did not exclude patients with a history of cancer (Study 4931 did exclude such patients), and Study 4774 evaluated only pancreatic and renal tumors; Study 4931 evaluated numerous tumor types.

The study periods began on 1/1/93, and ended on 12/31/08. Patients who were diagnosed with the relevant cancer (the index date was the date of the first diagnosis of cancer) were matched (on numerous demographic variables) with 10 controls. Only subjects with at least 2 years of follow-up in the database were included.

As Dr. Williams notes, exposure to gabapentin "...was defined as at least one prescription recorded in the patient's GPRD medical records.", and, according to Dr. Williams, exposure was classified in the following ways:

Ever vs never exposed

Number of prescriptions (tertiles vs never exposed)

Cumulative duration (tertiles vs never exposed)
Cumulative dose (tertiles vs never exposed)

Briefly, the following results for pancreatic cancer were seen.

A total of 3161 patients with pancreatic cancer were identified. A total of 82% of these cancers were adenocarcinomas; there was one case of acinar cell carcinoma. Twelve cases could not be matched to controls, so 3149 cases were matched to 30026 controls. The mean duration from entry into the cohort to the index date was about 9 years.

The sponsor performed two main analyses: analyses of the data with no lag between initiation of gabapentin and the index date, and analyses in which the period of case ascertainment began 2 years after the initiation of treatment.

The (adjusted) odds ratios (OR) for the no-lag and 2-year lag analyses that reached nominal significance are given below, taken from Dr. Williams's Table 5:

	No-lag OR	2-Year lag OR
Gabapentin		
(Ever vs Never Exposed)	1.8	1.33
P-value	<0.0001	0.22
Prescriptions		
Tertile 1 vs Never Exposed (1-2)	2.5	2.4
P-value	<0.0001	0.004
Duration		
Tertile 1 vs Never Exposed (0.01-1.55 months)	2.9	2.45
P-value	<0.0001	0.005
Cumulative Exposure		
Tertile 1 vs Never Exposed (0.01-33.6 gms)	2.65	1.95
P-value	<0.0001	0.05

The mean duration of exposure to gabapentin in patients with pancreatic cancer was about 6 months, and for controls was about 9.6 months. The median latency between first exposure to gabapentin and diagnosis was 573 days.

A similar pattern of significance was seen for renal cancer.

Non-clinical

As noted above, the reason for issuing a CR letter to the sponsor was the finding of pancreatic acinar cell carcinoma in the 2 year rat carcinogenicity study. That study examined doses of 500, 2000, and 5000 mg/kg, and the no-effect level was determined to be 500 mg/kg. The ratio of the plasma levels achieved in people at the proposed dose of 600 mg/day to that achieved in rats at the 500 mg/kg dose was about 8. This margin was considered too low to support approval of Horizant for patients with RLS. It is worth noting that, although the mid-dose of 2000 mg/kg was considered to be a dose associated with tumors, there was general agreement that the tumor finding was minimal at this dose. Specifically, only 1 carcinoma was seen at this dose (in the male rat), and a total of 5 tumors (adenoma plus carcinoma) were seen, compared to 4 (all adenomas) in the 500 mg/kg group and 2 (both adenomas) in the control group.

In response, the sponsor has submitted numerous arguments to support the view that the safety margin is considerably greater than 8. In particular, they assert that the safety margin at the 2000 mg/kg group is 38, and that, given that the no-effect dose in the ***gabapentin*** carcinogenicity study (1000 mg/kg, as described in the gabapentin label, a dose not studied in the Horizant carcinogenicity study), the safety margin should be calculated based on the exposure at that dose; when this is done, the margin is 25. They further assert that the safety margin is more appropriately based on comparative pancreatic tissue accumulation (rat:human) than plasma exposures; when this is done, the sponsor concludes that the relevant safety margin is >50.

In addition to these arguments based on the safety margin, the sponsor has submitted arguments to establish that rat pancreatic acinar cell tumors are not relevant to humans.

All of these arguments have been reviewed in detail by Dr. McKinney, and are presented in a detailed overview by Dr. Freed.

Briefly, with regard to the sponsor's arguments about the safety margin:

First, the sponsor notes that the exposure data on which the original margins were based was obtained with whole blood in the rat. The sponsor conducted new studies (7 and 14-day dietary studies with gabapentin; more on this below), and demonstrated that plasma level data yields consistently greater AUCs than whole blood data. A re-calculation of exposure data based on plasma levels increases the margin at the 500 mg/kg dose group to about 11 (as opposed to the original 8).

The sponsor also attempts to compare the rate of tumors seen in the 2000 mg/kg group to a new historical control background rate. In particular, the background

comparator data referred to in the original application consisted of data from Wistar and Wistar-Han rats. According to the sponsor, Wistar-Han rats have a lower spontaneous background rate of pancreatic cancer. Wistar rats were used in the carcinogenicity study. In the sponsor's view, if a background rate calculated based only on historical data for the Wistar rat were compared to the data in the 2000 mg/kg group, this dose would have been considered a no-effect dose for cancer. For numerous reasons, as described by Drs. McKinney and Freed, this comparison is inappropriate (age of the studies, lack of details of the study methodology, etc).

With regard to the species differences in accumulation of gabapentin in the pancreas, the sponsor makes several arguments.

First, they performed an in vitro study evaluating the uptake of gabapentin in rat and human pancreatic slices. They found significantly more uptake in rat than human pancreas slices. Literature reports also document increased uptake in rat (and mouse) pancreas compared to human pancreas. However, as Drs. McKinney and Freed note, multiple gaps in the information provided, as well as methodologic problems (e.g., different strain of rats used than that used in the carcinogenicity study, method of quantitation) render these studies less than definitive.

The sponsor also examined species differences in gabapentin transport proteins. They have demonstrated that there is considerably greater expression of the primary transporter protein in rat (and in mouse) than human. However, they have demonstrated that the location of these transporters is important: the transporter is primarily located in islet cells in the human, and in acinar cells in the rat. As the sponsor has noted elsewhere, human acinar cell cancer is very rare (we agree that this is true), but the data suggest that gabapentin may accumulate in islet cells in humans to the extent that it accumulates in acinar cells in rats.

As noted above, the sponsor performed two new studies, a 7 and 14-day gabapentin dietary PK study in Wistar rats (recall that the gabapentin carcinogenicity study was a dietary study done in Wistar rats). In the 14 day study, a dose of 1000 mg/kg (the dose considered in gabapentin labeling to be a no-effect dose, and a dose not studied in the gabapentin enacarbil carcinogenicity study) resulted in an AUC of about 1300 ng*hr/mL. As Dr. Freed points out, this level approximates the level seen at this dose in a TK study conducted by Parke-Davis (the sponsor of Neurontin), and published in 1995. Given that this dose was considered a no-effect dose for tumors, it is reasonable to consider using the exposure at this dose to calculate a margin compared to the human exposure at the 600 mg/day dose. When this is done, the margin is about 25.

The sponsor has also attempted to demonstrate that rat pancreatic acinar cell tumors are not relevant to humans for the following reasons:

- 1) the rat is “uniquely” sensitive to gabapentin-induced acinar cell cancer because of differential uptake and a high spontaneous background rate of these tumors in humans
- 2) the male rat is particularly sensitive to this tumor type
- 3) Gabapentin is non-genotoxic
- 4) In humans, ductal adenocarcinomas are the most common pancreatic cancer

Drs. Freed and McKinney find these arguments less than compelling.

In the first case, a single acinar cell cancer was seen in a female rat in the gabapentin enacarbil study, in which the background rate of this tumor type is rare. This suggests that gabapentin can induce this tumor-type in a setting in which the background rate is not high. Also, as noted, the drug does accumulate in human pancreas, but in a different cell type (islet cells), suggesting that, if accumulation is important to tumor formation, it could happen in humans, but in a different location within the pancreas (the sponsor also has not provided a compelling reason for why acinar cell tumors do not form in the mouse, which has considerable accumulation of the drug in acinar cells).

Although there is a higher background rate of acinar cell cancers in male compared to female rats, the literature suggests that in humans there is a higher rate of pancreatic cancer in males than females. The male rat predilection for pancreatic cancer, therefore, does not particularly support the view that the rat findings are not relevant to humans.

It is also worth noting that the mechanism of gabapentin-induced pancreatic cancer in rats remains unknown. The sponsor has not been able to demonstrate that treatment with gabapentin causes sustained increases in CCK, a mechanism that has been proposed for this tumor type in rat, and which presumably does not occur in humans.

The fact that gabapentin is not genotoxic (a conclusion with which we agree) does not support the conclusion that it cannot be carcinogenic in humans via an epigenetic mechanism.

Finally, it is true that pancreatic acinar cell tumors are rare in humans (as further confirmed by the results of the GPRD study described earlier). However, as described by Dr. Freed, accumulating evidence suggests that ductal carcinoma may result from a **transformation** of acinar cells to ductal cells. Clearly, the events underlying the formation of pancreatic cancer in humans is extremely complex, and only poorly understood. These observations make concluding that

pancreatic acinar cell cancer in the rat is not relevant to humans highly problematic.

Comments

As noted above, the Agency issued a CR letter to the sponsor at the end of the first review cycle based on a finding of pancreatic acinar cell cancer in rats seen in a 2 year carcinogenicity study. This was consistent with a similar finding seen in a 2 year carcinogenicity study performed with gabapentin years earlier. In the gabapentin enacarbil study, the low dose of 500 mg/kg was considered the no-effect level, resulting in an exposure margin of about 8 compared to the proposed human dose of 600 mg/day. The mid-dose in that study was 2000 mg/kg, and although it was a dose considered to have been associated with tumors (adenoma plus carcinoma), there was only one carcinoma at that dose, and it was generally considered that the effect seen at that dose was very weak.

The gabapentin carcinogenicity study studied 250, 1000, and 2000 mg/kg, and 1000 mg/kg was considered a no-effect dose, as described in the label. In an attempt to address the issue of the safety margin of 8 based on the no-effect level in the gabapentin enacarbil study, the sponsor administered a dose of 1000 mg/kg to the rat in a 14 day TK study, to determine the exposure at the no-effect dose in the gabapentin study. This TK study produced an AUC comparable to that seen at the 1000 mg/kg gabapentin dose as described in the literature. This AUC provides a safety margin of about 25 compared to the proposed human dose of 600 mg/day.

It is worth noting that Dr. Freed has attempted to re-examine the original gabapentin carcinogenicity study data, and has had difficulty re-constructing the historical record documenting the reasoning behind the Agency's conclusion that the mid-dose (MD=1000 mg/kg) in that study is a no-effect dose for carcinoma, as the label for that drug states. It appears that there were cancers at that dose (and even at the lowest dose), whereas there were none in the control group (though there were adenomas in the control group). Nonetheless, as she concludes, "Without a better understanding of what informed that decision, the MD is accepted as a "no-effect" dose for gabapentin."

The sponsor also provided arguments that the acinar cell cancers seen in the rat are not relevant to humans for various reasons described above. Although these arguments are interesting, none are definitive.

I believe that the sponsor's conclusion that the safety margin is about 25, based on their current approach, is reasonable. As described above, there was general agreement that the effect seen in the gabapentin enacarbil study at the mid-dose of 2000 mg/kg was a very minimal finding (about as minimal as a "positive" finding could be considered), suggesting that the "true" no-effect exposure to

gabapentin would be seen at a dose of gabapentin enacarbil between 500 mg/kg and 2000 mg/kg (the exposure at this high dose is about 38 times that seen at the human dose of 600 mg/day). The sponsor's finding that the exposure at the no-effect level (1000 mg/kg) in the gabapentin study yielded a safety margin of 25 is, therefore, compelling, in my view. I believe that there is general agreement within the review team that such a margin would justify approval of Horizant for patients with RLS.

Although the epidemiologic study the sponsor performed in the GPRD dataset yielded odds ratios of about 2 for pancreatic (and renal) cancer, results that were nominally statistically significant, these results do not, in any way, establish that gabapentin causes pancreatic cancer in people, for numerous reasons, as discussed by Dr. Williams.

In particular, the finding arises entirely from the first tertiles of all measures of exposure. The maximum duration of use of gabapentin in the first tertile was 1.55 months; the maximum cumulative dose of gabapentin in the first tertile was 33.6 gms; the maximum number of prescriptions in the first tertile was 2. The mean duration of exposure in patients treated with gabapentin who had pancreatic cancer was about 6 months. No significant findings were noted in the second and third tertiles of any measure of exposure. Gabapentin cannot credibly be considered to be causally related to these tumors, given the short-term exposures seen in patients with tumors.

Dr. Williams also describes the probable occurrence of a protopathic bias. That is, patients were treated with gabapentin for various indications that were likely related to the presence of cancer, before the cancer itself was diagnosed. Clearly, any conclusion reached about causal association with cancer on this sort of data would be spurious. According to Dr. Williams, 14% of patients with pancreatic cancer who were treated with gabapentin fell in this category.

In my view, then, the GPRD study does not provide evidence that gabapentin causes pancreatic cancer in people. It needs to be noted, however, that it was not capable of providing useful data on this question, because very few patients received gabapentin for a sufficient duration to adequately answer the question.

Given these results, and given the re-calculated safety margin from the rat data, I believe that the issue of carcinogenicity no longer precludes approval of Horizant for patients with moderate to severe RLS.

There is, however, one issue that needs to be discussed.

As noted in the reviews of the initial NDA submission, the sponsor performed a simulated driving test that demonstrated significant impairments in driving in the evening after dosing and in the morning after an evening dose, after about 2 weeks of dosing. These effects were comparable to the effects seen with the

active control, diphenhydramine (a description of the study taken verbatim from my previous memo is included as an attachment). The study was problematic, however, because the results seen at 1800 mg revealed very little effect on driving (my statement in my original review that the plasma levels of gabapentin were lower in the 1800 mg/day group than those in the 1200 mg/day group was, apparently, incorrect, according to Dr. Goldstein, who has re-examined the data from that study). In any event, the disparate findings in the two groups made definitive interpretation of that study difficult.

Nonetheless, taking the results of that study at face value, the possibility that the effects of a 600 mg/day dose may impair driving needs to be considered. Although the 600 mg dose was not included in the driving study, the incidence of somnolence in the controlled trials in the 600 mg group was quite similar to that in the 1200 mg group (approximately 20%), and the beneficial effects of the 600 mg dose were very similar to those seen at the 120 mg dose, suggesting that these doses are similar in many ways. This, then, raises the possibility that the effects on driving will be the same.

Although I do not believe that this should preclude approval at this time, I do think that labeling should include a strong, prominent warning about the potential effects of Horizant on driving, and should instruct prescribers that patients should not drive, at any time while taking Horizant, until they are confident that they are not somnolent, dizzy, and that the drug cannot affect their ability to drive. Of course, I recognize that patients may not be able to know that they are not impaired with any certainty, but the decision about driving should be made in close consultation with their health care professional. In this regard, it is worth noting that the data suggest (though do not definitively establish) that somnolence begins to wane after the first 2-3 weeks after treatment initiation (of course, we do not know that the impairment in driving is related to somnolence; indeed, the findings in the driving test were seen after 2 weeks of treatment).

We will impose several Post-Marketing Requirements (PMRs), almost all identified at the end of the first review cycle. These are:

- 1) a controlled trial examining doses of 300, 450, and 600 mg
- 2) an adequate driving study at these lower doses if they are effective
- 3) an adequate thorough QT study
- 4) an in vitro study examining the potential for the drug to inhibit CYP2C8 and 2B6
- 5) an in vitro alcohol dose dumping study
- 6) the development of a 300 mg dosage form (for patients with severe renal impairment)
- 7) a study to evaluate the potential interaction between morphine and Horizant (current gabapentin labeling describes a 44% increase in gabapentin levels when it was given with morphine)

In addition, because of our great concern for the possibility that 600 mg causes impaired driving, I believe it is critical to assess this possibility as soon as possible. For this reason, we will impose a PMR for a driving study of the 600 mg dose to be performed as soon as possible.

For these reasons, then, I recommend that the NDA be approved.

Russell Katz, M.D.

Attachment

Study 83

This study was designed to assess the effects of Horizant on driving ability.

In this study, healthy subjects were randomized to receive either placebo, Horizant 1200 mg, Horizant 1800 mg, or diphenhydramine 50 mg (active control).

In this study, there were 2 Baseline assessments. On Day -1, subjects were assessed with a baseline driving (simulator) test in the evening, as well as a cognitive battery. On Day 1, subjects were assessed with a baseline simulator test in the morning, as well as a cognitive battery in the morning.

On Day 1, subjects received their first dose of study medication at 5 PM. Subjects randomized to Horizant 1200 mg, 1800 mg, or placebo continued to receive this treatment for the next 13 days at 5 PM (a total of 14 days of study treatment). Subjects in these 3 groups then received a dose of study drug on Days 15 and 16 in the morning (10-11 AM). Subjects randomized to receive diphenhydramine 50 mg received placebo for Days 1-14 at 5 PM, then AM doses of placebo on Days 15 and 16, and then a single dose of diphenhydramine 50 mg at 5 PM on Day 16.

Driving testing and the cognitive battery were assessed on the evening of Day 14, (7-9 PM; 2-4 hours after the PM dosing) and in the morning of Day 15 (7-9 AM), and in the evening (7-9 PM; 2 hours after the PM dosing on that day) of Day 16.

The specific times of dosing and testing were designed to assess: 1) the effects of driving in the evening several hours after dosing at the recommended time, when it might be imagined that patients would, for example, be driving home from work (this was tested by comparing the baseline at Day -1 to the testing on the evening of Day 14); 2) the effects of driving the next morning after dosing the previous night at the recommended time (assessed by comparing the baseline at Day 1 with the testing on Day 15 in the AM). The PM testing on Day 16 was designed to assess the effects of the active control, diphenhydramine, several hours after it was administered, and this test was also compared to the baseline evening testing (Day -1), as well as to test the effects of Horizant at its approximate Tmax (recall that subjects were dosed in the AM on Days 15 and 16, and the PM testing was timed to be at the approximate Tmax of Horizant). See the figure in Dr. Yan's review, page 21, which outlines the design of this study.

A total of 130 subjects were randomized, and 33, 28, 33, and 28 subjects were included in the analysis for the placebo, 1200 mg, 1800 mg, and placebo/diphenhydramine groups, respectively.

The following chart displays the results of the driving simulator testing on the primary outcome, Lane Position Variability (LPV):

	Mean LPV on Days 14 and 15			
	Horiz 1800	Horiz 1200	Placebo	Pbo/DPH
Day 14 Change from Baseline (Day 1 to day 14; PM driving)	-0.01	0.17	-.06	-0.08
Day 15 Change from Baseline (Day -1 to Day 15; AM driving)	0.02	0.13	-0.01	-0.10
Day 16 Change from Baseline (Day -1 to Day 16; PM driving)	0.15	0.15	-0.11	0.16

As Dr. Yan points out, most patients had minimal changes in LPV, but between 10-20% of patients had large changes. A total of 20 subjects, none on placebo, had LPV changes of at least 0.3 on Day 16 (6, 7, and 6 subjects each in the 1200, 1800, and DPH groups, respectively). See Dr. Yan's Table 14, page 25 of her review for more details of this metric.

In addition to measuring LPV, the simulator study also assessed the number of crashes in each group.

As noted by Dr. Yan, patients in the 1200 mg group had more crashes at baseline (both Days -1 and 1) than in the other groups. The following table presents crash data by study day and treatment group:

Number (%) of Subjects with Crashes

Day	Horizant 1800	Horizant 1200	Placebo	Pbo/DPH
-1	3 (9)	6 (21)	3 (9)	2 (7)
1	3 (9)	4 (14)	1 (3)	3 (11)
14	1 (3)	6 (21)	4 (12)	1 (4)
15	1 (3)	10 (36)	1 (3)	0
16	6 (18)	8 (29)	0	3 (11)

It is important to note that the numbers in each cell do not necessarily represent the same individuals (that is, for example, the 6 subjects who had crashes in the 1200 mg group on Day -1 and the 6 on Day 14 in that group were not necessarily the same people).

Another way to assess these data is to examine the number of subjects who had multiple crashes. Dr. Yan has done this on page 27 of her review, Table 16. This table clearly shows a trend to a drug-related increase in the number of crashes in the drug-treated groups, especially in the Horizant 1200 mg dose group. Below I present only the placebo and Horizant 1200 mg data:

Day	Horizant 1200	Placebo
-1		
1 crash	4	2
2 crashes	1	0
3 crashes	1	1

1		
1 crash	2	0
2 crashes	0	1
3 crashes	2	0

14		
1 crash	1	2
2 crashes	2	2
>3 crashes	3	0

15		
1 crash	4	1
>1 crash	6	0

16		
1 crash	5	0
>1 crash	3	0

This is a representation of an electronic record that was signed electronically and this page is the manifestation of the electronic signature.

/s/

RUSSELL G KATZ
04/04/2011

CLINICAL FILING CHECKLIST FOR NDA/BLA or Supplement

NDA/BLA Number:022399

Applicant: Xenoport/GSK

Stamp Date: 01/09/2009

Drug Name: Horizant

NDA/BLA Type: NDA

Indication: RLS

On initial overview of the NDA/BLA application for filing:

	Content Parameter	Yes	No	NA	Comment
FORMAT/ORGANIZATION/LEGIBILITY					
1.	Identify the general format that has been used for this application, e.g. electronic CTD.	x			eCTD
2.	On its face, is the clinical section organized in a manner to allow substantive review to begin?	x			
3.	Is the clinical section indexed (using a table of contents) and paginated in a manner to allow substantive review to begin?	x			
4.	For an electronic submission, is it possible to navigate the application in order to allow a substantive review to begin (e.g., are the bookmarks adequate)?	x			
5.	Are all documents submitted in English or are English translations provided when necessary?	x			English
6.	Is the clinical section legible so that substantive review can begin?	x			
LABELING					
7.	Has the applicant submitted the design of the development package and draft labeling in electronic format consistent with current regulation, divisional, and Center policies?	x			
SUMMARIES					
8.	Has the applicant submitted all the required discipline summaries (i.e., Module 2 summaries)?	x			
9.	Has the applicant submitted the integrated summary of safety (ISS)?	x			
10.	Has the applicant submitted the integrated summary of efficacy (ISE)?	x			
11.	Has the applicant submitted a benefit-risk analysis for the product?	x			Issue with driving
12.	Indicate if the Application is a 505(b)(1) or a 505(b)(2). If Application is a 505(b)(2) and if appropriate, what is the reference drug?	x			505(b)1
DOSE					
13.	If needed, has the applicant made an appropriate attempt to determine the correct dosage and schedule for this product (i.e., appropriately designed dose-ranging studies)? Study Number: XP081 Study Title:A Randomized, Double-blind,Placebo Controlled Dose Response Study to Assess Efficacy, Safety and Pharmacokinetics of XP13512 in patients with Restless Leg Syndrome Sample Size: 217 randomized (159 completed) Arms:XP13512 600mg, 1200mg, 1800mg, 2400mg, PBO Location in submission:5.3.5.1	x			FDA had advised the sponsor to check lower doses as well.
EFFICACY					
14.	Do there appear to be the requisite number of adequate and well-controlled studies in the application? Pivotal Study #1XP052 A Double-Blind Placebo-Controlled Study to	x			XP052: 222 patients with RLS were randomized to either PBO or 1200mg XP13512 given as once daily dose, for 12 weeks.

File name: 5_Clinical Filing Checklist for NDA_BLA or Supplement 010908

CLINICAL FILING CHECKLIST FOR NDA/BLA or Supplement

	Content Parameter	Yes	No	NA	Comment
	<p style="text-align: center;">Assess Efficacy and Safety of Patients with Restless Leg Syndrome Indication:RLS</p> <p style="text-align: center;">Pivotal Study #2 XP053 A Randomized, Doble-Blind, Placebo-Controlled Study to Assess Efficacy and Safety of XP13512 in Patients with Restless Leg Syndrome Indication:RLS</p>				<p>Investigators at 22 centers in the Us participated.</p> <p>XP053: 325 patients with RLS were randomly assigned to XP13512 600mg ,1200mg or PBO. Investigators at 28 centers in the US participated.</p>
15.	Do all pivotal efficacy studies appear to be adequate and well-controlled within current divisional policies (or to the extent agreed to previously with the applicant by the Division) for approvability of this product based on proposed draft labeling?	x			
16.	Do the endpoints in the pivotal studies conform to previous Agency commitments/agreements? Indicate if there were not previous Agency agreements regarding primary/secondary endpoints.	x			<p>Original studies had one primary endpoint, XP021 and XP045. Endpoint was proportion of responders improved CGI-I for XP13512 compared to PBO btw baseline and week 2. After FDA recommendations, co primary endpoints were used in XP052 and XP053; proportion of responders on CGI-I for XP13512 compared to PBO btw baseline and wk 12 and difference in IRLS score for CP13512 compared to PBO btw baseline and wk. 12.</p>
17.	Has the application submitted a rationale for assuming the applicability of foreign data to U.S. population/practice of medicine in the submission?			x	Pivotal trials performed in US
SAFETY					
18.	Has the applicant presented the safety data in a manner consistent with Center guidelines and/or in a manner previously requested by the Division?	x			
19.	Has the applicant submitted adequate information to assess the arrythmogenic potential of the product (e.g., QT interval studies, if needed)?	x			<p>XP078 A Randomized, Double-Blind Placebo and Active Controlled, Four Period Corosover Study to Evaluate the Effect of XP13512 on Cardiac Repolarization by Thorough Analysis of QTc Effect in Healthy Adult Subjects. Study completed 11/07. Consult to QTc team for review. The sponsor confirms that ECGs are in electronic warehouse.</p>
20.	Has the applicant presented a safety assessment based on all current worldwide knowledge regarding this product?	x			

CLINICAL FILING CHECKLIST FOR NDA/BLA or Supplement

	Content Parameter	Yes	No	NA	Comment
21.	For chronically administered drugs, have an adequate number of patients (based on ICH guidelines for exposure ¹) been exposed at the dose (or dose range) believed to be efficacious?	x			1566 patients with RLS exposed. 812 pts 0-12 weeks, 496 pts 13wks-6mos, 120 pts up to a year. Not listed by dose exposure. Additional 48 pts exposed (total 1614) with other disease (PHN,DPN).
22.	For drugs not chronically administered (intermittent or short course), have the requisite number of patients been exposed as requested by the Division?			x	
23.	Has the applicant submitted the coding dictionary ² used for mapping investigator verbatim terms to preferred terms?	x			
24.	Has the applicant adequately evaluated the safety issues that are known to occur with the drugs in the class to which the new drug belongs?	x			Cognitive side effects, particularly somnolence and dizziness are issues. XP083 assess simulated driving performance, cognition as well as efficacy in RLS pts. Dosed with XP13512 at 1200mg, 1800mg, PBO or diphenhydramine50mg. Statistically significant difference in driving from PBO, but similar to diphenhydramine.
25.	Have narrative summaries been submitted for all deaths and adverse dropouts (and serious adverse events if requested by the Division)?	x			No deaths occurred in pivotal trials. Two deaths in total. XP060 (Maintenance of efficacy for responders. Single blind.) Pt. died of accidental asphyxiation. Second patient committed suicide after one dose of 1200mg in clin pharm study. Pt also positive for alcohol. One pt. had convulsion during withdrawal phase of study; found to have epileptic focus on EEG.
OTHER STUDIES					
26.	Has the applicant submitted all special studies/data requested by the Division during pre-submission discussions?	x			
27.	For Rx-to-OTC switch and direct-to-OTC applications, are the necessary consumer behavioral studies included (e.g., label comprehension, self selection and/or actual use)?			x	
PEDIATRIC USE					
28.	Has the applicant submitted the pediatric assessment, or provided documentation for a waiver and/or deferral?	x			Asking for waiver for less than 18 years of age. "Although there is some evidence of existence of

¹ For chronically administered drugs, the ICH guidelines recommend 1500 patients overall, 300-600 patients for six months, and 100 patients for one year. These exposures MUST occur at the dose or dose range believed to be efficacious.

² The "coding dictionary" consists of a list of all investigator verbatim terms and the preferred terms to which they were mapped. It is most helpful if this comes in as a SAS transport file so that it can be sorted as needed; however, if it is submitted as a PDF document, it should be submitted in both directions (verbatim -> preferred and preferred -> verbatim).

CLINICAL FILING CHECKLIST FOR NDA/BLA or Supplement

	Content Parameter	Yes	No	NA	Comment
					RLS in pediatrics, the prevalence is believed to be very low. Importantly, the diagnosis and pathology of pediatric RLS is complicated by extensive co-morbidities that are found in pediatrics with RLS such as ADHD. RLS symptoms are generally milder and often intermittent in children and adolescents, therefore non-pharmacological therapy is recommended."
ABUSE LIABILITY					
29.	If relevant, has the applicant submitted information to assess the abuse liability of the product?	x			Based on previous studies with gabapentin
FOREIGN STUDIES					
30.	Has the applicant submitted a rationale for assuming the applicability of foreign data in the submission to the U.S. population?	x			
DATASETS					
31.	Has the applicant submitted datasets in a format to allow reasonable review of the patient data?	x			
32.	Has the applicant submitted datasets in the format agreed to previously by the Division?	x			
33.	Are all datasets for pivotal efficacy studies available and complete for all indications requested?	x			
34.	Are all datasets to support the critical safety analyses available and complete?	x			
35.	For the major derived or composite endpoints, are all of the raw data needed to derive these endpoints included?	x			
CASE REPORT FORMS					
36.	Has the applicant submitted all required Case Report Forms in a legible format (deaths, serious adverse events, and adverse dropouts)?	x			
37.	Has the applicant submitted all additional Case Report Forms (beyond deaths, serious adverse events, and adverse drop-outs) as previously requested by the Division?	x			
FINANCIAL DISCLOSURE					
38.	Has the applicant submitted the required Financial Disclosure information?	x			
GOOD CLINICAL PRACTICE					
39.	Is there a statement of Good Clinical Practice; that all clinical studies were conducted under the supervision of an IRB and with adequate informed consent procedures?	x			

IS THE CLINICAL SECTION OF THE APPLICATION FILEABLE? __yes_____

If the Application is not fileable from the clinical perspective, state the reasons and provide comments to be sent to the Applicant.

CLINICAL FILING CHECKLIST FOR NDA/BLA or Supplement

Please identify and list any potential review issues to be forwarded to the Applicant for the 74-day letter.

Reviewing Medical Officer Date

Clinical Team Leader Date

Application Type/Number	Submission Type/Number	Submitter Name	Product Name
NDA-22399	ORIG-1	GLAXO GROUP LTD DBA GLAXOSMITHKLIN E	Horizant

This is a representation of an electronic record that was signed electronically and this page is the manifestation of the electronic signature.

/s/

SUSANNE R GOLDSTEIN
07/21/2010

GERALD D PODSKALNY
07/27/2010

Office Director Decisional Memo

Date	17 February 2010
From	Ellis F. Unger, M.D. Deputy Director, Office of Drug Evaluation-I
Subject	Office Director Decisional Memo
NDA/BLA #	22-399
Supplement #	0000
Applicant Name	GlaxoSmithKline
Date of Submission	9/16/08; resubmission 1/9/09
PDUFA Goal Date	11/9/09, extended by major amendment (solicited REMS proposal) to 2/9/10
Proprietary Name / Established (USAN) Name	Horizant gabapentin enacarbil
Dosage Forms / Strength	600-mg tablets
Proposed Indication(s)	Restless Leg Syndrome
Action:	Complete Response

Material Reviewed/Consulted	Names of discipline reviewers
Action Package, including:	
Project Manager	Beverly A Conner
Cross-Discipline Team Leader	Gerald D. Podskalny
Medical Officer	Susanne R. Goldstein
Biostatistical Review	Sharon Yan
Pharmacology Toxicology Review	Terry S. Peters/Lois Freed
Chemistry Manufacturing Controls	Chhagan G. Tele, Christine M. V. Moore
Clinical Pharmacology Review	Ju Ping Lai, Atul Bhattaram
Carcinogenicity/Statistical	Karl K. Lin
Division of Scientific Investigations	Antoine N. El Hage
Office of Surveillance and Epidemiology, Division of Medication Error Prevention and Analysis	Zachary Oleszczuk
QT Interdisciplinary Team	
Office of Pharmaceutical Science	Raanan Bloom

I concur with the recommendation of Dr. Russell Katz, Director, Division of Neurology Products, on a Complete Response action for Horizant (gabapentin enacarbil), NDA 22-399. The review team is in agreement with the planned action, and the conclusions and concerns will be transmitted to the applicant in a Complete Response Letter.

Background: Restless Legs Syndrome (RLS) is a relatively common and frequently underdiagnosed sensorimotor disorder with an estimated prevalence between 5 and 10%. Its prevalence increases with age and is higher among women than men. A family history of RLS is particularly common, especially in patients whose symptoms appear before age 40. The cardinal feature of RLS is a distressing, overwhelming urge to move the legs (akathisia), which often coexists with a deep discomfort within the legs. Symptoms typically begin or worsen during periods of rest or inactivity, e.g., lying or sitting, and worsen in the evening or night. Symptoms are partially or completely relieved by movement, such as walking or stretching.

There are two approved drugs for the treatment of moderate to severe RLS – ropinirole (Requip®) and pramipexole dihydrochloride (Mirapex®) – both dopaminergic agents. Gabapentin, an antiepileptic agent approved for the treatment of seizures and post-herpetic neuralgia, is used off-label for RLS, and its use is included in current RLS treatment guidelines (at doses of 300 to 2700 mg per day). Generic versions of gabapentin are available in the U.S. Benzodiazepines and opiates are used off-label for RLS as well.

Chemistry Manufacturing Controls: Gabapentin enacarbil is a pro-drug of the marketed drug gabapentin. The applicant provided adequate information regarding structure elucidation and confirmation, method of manufacture, in-process controls, test methods, container closure system, and stability testing of the drug substance. The drug product is also considered satisfactory, and the Chemistry review team opined that Horizant (gabapentin enacarbil) ER Tablets can be approved from their point of view.

Pharmacology/Toxicology: The pharmacology/toxicology findings underlie the review team's recommendation to take a Complete Response action. The findings have been extensively discussed by members of the review team, and are summarized below.

Gabapentin enacarbil is a pro-drug of gabapentin, and virtually all of it is converted to gabapentin by first-pass hydrolysis. Gabapentin's carcinogenicity data are, therefore, germane to this NDA. At the time gabapentin was approved for treatment of seizures, it was known to cause a statistically significant increase in the incidence of pancreatic acinar cell carcinoma in male rats. The no-effect dose was 1000 mg/kg, a dose that would produce a peak plasma concentration 6.5 times higher than would be produced in humans receiving a daily gabapentin dose of 3600 mg. Gabapentin was approved despite this concern, in part because of the serious nature of the disease (epilepsy). Moreover, particular factors provided reassurance regarding the non-clinical findings: carcinomas were observed in only one sex, they were not locally invasive, and they neither metastasized nor shortened survival. The drug was approved with a warning in the label, and the warning included a statement to the effect that the clinical significance of the findings was unknown.

With respect to the data included in the gabapentin enacarbil NDA, the drug was not found to be genotoxic in a standard battery of genetic toxicology assays, and mouse carcinogenicity studies were negative. The 2-year carcinogenicity study in rats, however, demonstrated dose-related pancreatic acinar cell carcinomas, as well as dose-related adenomas and hyperplasia, as summarized below:

Dose (mg/kg/d)	Males				Females			
	0	500	2000	5000	0	500	2000	5000
Hyperplasia	14/60	10/60	14/60	20/60	1/60	1/60	4/60	14/60
Adenoma	2/60	4/60	4/60	8/60	0/60	0/60	0/60	3/60
Carcinoma	0/60	0/60	1/60	1/60	0/60	0/60	0/60	1/60

Carcinoma were observed in both sexes and were locally invasive. (In contrast, as noted above, gabapentin's tumors were observed exclusively in males and were not locally invasive.) Of note, male rats in the 2000 and 5000 mg/kg/d groups developed chronic progressive nephropathy and were killed 7 and 14 weeks prior to the planned conclusion of the 104-week study. The review team has made the point that additional cancers might have been detected had the rats been maintained for the planned duration of the study.

The no effect doses for carcinoma were 500 and 2000 mg/kg/d in male and female rats, respectively, corresponding to exposures of approximately 8 times and 28 times the exposure in humans at a daily dose of 600 mg. Moreover, in a model where frank carcinoma has been observed, acinar cell hyperplasia and adenoma can be viewed as pre-cancerous lesions; there were trends for dose-related increases in these lesions in both sexes. Although the numbers are small, there appear to be excess adenomas in male rats at the lowest dose tested (500 mg/kg/d), such that the no-effect dose has not been established.

The non-clinical findings from the gabapentin enacarbil application substantiate the findings from the prior gabapentin NDA: there is now unequivocal evidence that gabapentin (and its pro-drug, gabapentin enacarbil) cause dose-related pancreatic acinar cell carcinoma in rats. One of the difficulties in extrapolating this risk to humans is the rarity of this particular tumor type: the vast majority of human pancreatic cancers are ductal in origin; acinar tumors are rare.

Because gabapentin is a marketed product (approved December, 1993), there is the opportunity to assess the numbers of spontaneous reports of pancreatic cancer during the post-marketing period. Dr. Katz has pointed out that exposure (as area under the curve) to 700 mg gabapentin enacarbil is similar to that of 1200 mg gabapentin – a standard dose for epilepsy. Duration of treatment would have to be considered as well: typical durations of treatment for epilepsy and post-herpetic neuralgia would need to be estimated; the duration of treatment for RLS could be many years. In any case, the post-marketing data for gabapentin in epilepsy patients seem at least somewhat relevant to gabapentin enacarbil.

Using a variety of search “strings,” Dr. Podskalny found 4 reports of pancreatic cancer in Neurontin-treated patients in the AERS database. The calculated EB05 score was 0.33. i.e., the number of reports was fewer than expected (an EB05 = 1 would be the expected number of reports; an EB05 of ≥ 2 would merit concern). Although the reliability of spontaneous adverse event reporting is inherently limited, an EB05 of < 1 provides at least a limited measure of reassurance.

Clinical Pharmacology: Unlike gabapentin, which is absorbed exclusively in the small intestine by a saturable amino acid transporter, gabapentin enacarbil is efficiently absorbed by high capacity transport mechanisms found throughout the intestinal tract. The pro-drug is rapidly and virtually entirely converted to gabapentin, leaving only negligible amounts (<2%)

of circulating parent drug. The pharmacokinetics of gabapentin are linear when the pro-drug (gabapentin enacarbil) is given over a range of doses up to 6 g.

Evidence of Effectiveness: The evidence of effectiveness has been addressed by Drs. Goldstein, Yan, Podskalny, and Katz. The applicant submitted data from three randomized controlled trials to establish gabapentin enacarbil's evidence of effectiveness for the treatment of moderate to severe RLS. The key trials included two standard, parallel-group randomized, controlled trials, one (Trial 52) compared gabapentin enacarbil 1200 mg daily to placebo, and the other (Trial 53), a 3-armed study, compared two doses of gabapentin enacarbil (600 and 1200 mg daily) to placebo. There was also a randomized withdrawal trial (Trial 60) to assess gabapentin enacarbil's long term effectiveness in responders, and an exploratory 5-armed trial (Trial 81) comparing 4 doses of gabapentin enacarbil (600 to 2400 mg/day) to placebo.

Trials 52 (n=222) and 53 (n=325) were multicenter, randomized, double blind, placebo-controlled, 12-week trials in subjects with moderate to severe RLS. In Trial 52, subjects were randomized to receive daily doses of gabapentin enacarbil 1200 mg or placebo. Trial 53 was an identically-designed study comparing gabapentin enacarbil 1200 mg/day to placebo, except that a lower-dose arm (600 mg) was added in an early protocol amendment in response to the Division's recommendations. Each arm was to enroll 105 subjects. The study drug was to be taken daily at 5 PM in both studies.

The trials had identical co-primary endpoints of: 1) International Restless Legs Scale (IRLS) score, a patient-rated 10-item score (summed score 0 [asymptomatic] to 40 [worst]) - change from baseline to end-of-treatment; and 2) proportion of responders based on the Clinical Global Impression of Improvement (CGI-I) scale, a 7-category scale that requires the investigator to assess how much the patient's illness has improved or worsened relative to baseline. Categories include: very much improved, much improved, minimally improved, no change, minimally worse, much worse, or very much worse. Subject who were rated as "very much improved" or "much improved" were categorized as "responders."

There was no adjustment for multiplicity: between-group comparisons were tested at the 0.05 significance level for both measures and both had to reach statistical significance in order for the trial to be considered positive. Of note, these metrics were also used in the registrational trials for ropinirole and pramipexole.

Trial 52 Results: A total of 222 subjects were randomized (114 gabapentin enacarbil; 108 placebo). Approximately 86% of subjects completed the trial in both groups, and essentially all were included in the modified ITT analysis. The mean change in the IRLS score from baseline to Week 12 was -13.2 in the gabapentin enacarbil group and -8.8 in the placebo group (p=0.0003). The proportions of responders on the investigator-rated CGI-I Scale at Week 12 were 76.1% in the gabapentin enacarbil group compared with 38.9% in the placebo group (p<0.0001).

Trial 53 Results: A total of 325 subjects were randomized (113 gabapentin enacarbil 1200 mg, 115 gabapentin enacarbil 600 mg, 97 placebo). Completion rates for the gabapentin enacarbil 1200 mg, 600 mg, and placebo groups were 87%, 90%, and 79%, respectively. A total of 111 subjects in the 1200 mg group, 114 in the 600 mg group, and 96 in the placebo group were included in the primary analysis.

The mean change from baseline to Week 12 for the IRLS score was -13.0 in the gabapentin enacarbil 1200 mg group, -13.8 in the gabapentin enacarbil 600 mg group, and -9.8 in the placebo group (1200 mg vs. placebo: $p < 0.002$; 600 mg vs. placebo: $p < 0.0001$). The proportions of responders on the CGI-I Scale at Week 12 were 77.5% for the gabapentin enacarbil 1200 mg group, 72.8% for the gabapentin enacarbil 600 mg group, and 44.8% in the placebo group (1200 mg vs. placebo: $p < 0.0001$; 600 mg vs. placebo: $p < 0.0001$).

Trial 60 was a randomized withdrawal trial, designed to demonstrate long-term effectiveness of gabapentin enacarbil. All subjects were to receive gabapentin enacarbil 1200 mg daily for 24 weeks (single-blind). After completion of the single-blind treatment, “responders” were randomized to receive either gabapentin enacarbil 1200 mg/d or placebo for 12 weeks in double-blind fashion.

The definition of a “responder” included the following:

- completed the entire 24-week single-blind treatment period
- total IRLS score decreased by ≥ 6 points relative to baseline, and ≤ 15
- categorized as “much improved” or “very much improved” on the CGI-I
- stable on 1200 mg gabapentin enacarbil for ≥ 1 month

The 1° outcome was the proportion of patients who met criteria for a relapse during the 12-week double-blind phase. Relapse criteria were defined as: 1) an increase in IRLS score of ≥ 6 points compared to Week 24, resulting in an IRLS score of ≥ 15 , and a rating of “very much worse” or “much worse” on the CGI-I. These criteria had to have been met on ≥ 2 consecutive visits ≥ 1 week apart, or 2) withdrawal due to lack of efficacy.

Of 327 subjects originally enrolled in the trial, 194 (59%) met responder criteria during the 24-week single-blind phase and were randomized to continue gabapentin enacarbil ($n=96$) or switch to placebo ($n=98$). The proportions of subjects who met criteria for relapse were 9.4% in the gabapentin enacarbil group and 22.7% in the placebo group ($p < 0.02$), providing support for the long-term effectiveness for the 1200 mg daily dose.

Trial 81 was an exploratory, multicenter, randomized, double-blind, multiple fixed-dose study wherein patients with RLS were randomized to receive placebo, or gabapentin enacarbil 600, 1200, 1800, or 2400 mg daily for 12 weeks. The protocol did not specify 1° or 2° outcomes, but the review team analyzed the endpoints designated as 1° in trials 52 and 53.

A total of 217 patients were randomized; results are shown below:

Change from Baseline in mean IRLS Score:

	<u>n</u>	<u>Baseline</u>	<u>End of Study</u>	<u>P-value</u>
Placebo	(n=40)	22.45	-9.28	
Gabapentin enacarbil 600	(n=47)	23.87	-13.81	0.04
Gabapentin enacarbil 1200	(n=43)	23.91	-13.81	0.04
Gabapentin enacarbil 1800	(n=37)	23.62	-13.95	0.026
Gabapentin enacarbil 2400	(n=44)	23.34	-12.86	0.09

Proportion of Responders:

	<u>Proportion of Responders</u>	<u>P-value</u>
Placebo	45%	
Gabapentin enacarbil 600	64%	0.08
Gabapentin enacarbil 1200	65%	0.07
Gabapentin enacarbil 1800	73%	0.01
Gabapentin enacarbil 2400	82%	0.0005

The study was neither designed nor powered to show differences in treatment effects between doses, but the results do provide some support of efficacy. Interestingly, there is no apparent trend to support the concept that doses higher than 600 mg/d lead to greater efficacy.

Efficacy Summary

All on the review team agree that the trials demonstrate satisfactory evidence of efficacy for the 1200 mg/day and 600 mg/day doses of gabapentin enacarbil. The trials were appropriate in design, reasonable in duration, utilized standard endpoint measures (measures that were used to establish efficacy for the two drugs currently approved for RLS), and enrolled subjects that seem relevant to the “real world.” The statistical analyses were performed as prospectively planned, and the results were reasonably persuasive. The results of both of the randomized, double-blind, placebo-controlled trials (52 and 53) were similar: in the gabapentin enacarbil groups, mean improvement on the IRLS score was approximately 4 points greater (absolute) than placebo. In both studies, there was a striking treatment effect in the responder analysis: approximately 40% of subjects in the placebo group were categorized as responders, compared to 75% in the gabapentin enacarbil groups. There were no apparent irregularities in trial conduct that would call the study results into question.

The review team opined that the 1200 mg/day dose failed to confer any advantage over the 600 mg/day dose; only the lower dose should be considered for approval. I agree with this recommendation.

Clinical Safety:

There were 3 deaths in the development program: a completed suicide in a 51 year-old male 36 hours after receiving a single 1200 mg dose of gabapentin enacarbil in a clinical pharmacology study; a 48 year-old male whose body was found at the bottom of an overpass (a possible suicide) 26 days after completing a course of gabapentin enacarbil; and a 63 year-old female who died after aspirating a piece of meat. Given that suicide is a known concern with AEDs, the deaths in the two male subjects are concerning; however, causality is unlikely in both cases: the 51 year-old male received only 1 dose of gabapentin enacarbil, and the 48 year-old male had been off of the drug for 26 days at the time of the event.

Sedation (and somnolence) is a major untoward effect of gabapentin enacarbil. Gabapentin is known to cause somnolence, and somnolence was clearly detected in the development program at a frequency of approximately 20% on drug and 5% on placebo. It accounted for half of the subjects who withdrew from clinical trials because of an adverse event.

Driving ability was assessed in Trial 83 using a computer-based driving simulation system. Healthy volunteers were randomized 1:1:1:1 to receive, at 5 PM, placebo, gabapentin enacarbil 1200 mg, gabapentin enacarbil 1800 mg, or diphenhydramine 50 mg (an active control used to gauge assay sensitivity). Of note, the 600 mg dose was not assessed in the trial. The assessed endpoints were variation in lane position and virtual “crashes.”

After a 5 PM dose, 1200 mg gabapentin enacarbil impaired driving ability, during both the following morning and evening (when patients may be driving to and from work, respectively). The impairment tended to be worse than that caused by diphenhydramine, the positive control. The results are somewhat questionable, however, because driving was more impaired in the 1200 mg group than in the 1800 mg group, and gabapentin plasma concentrations were higher in the 1200 mg group than in the 1800 mg group, suggesting a critical problem(s) with the trial. The anomalies in results in the 1200 and 1800 mg groups notwithstanding, two critical issues were not addressed by the trial. First, the 600 mg dose was not tested; therefore, it is not known to what extent, if any, the “approvable” dose would impair driving. Second, the time course of somnolence was not characterized, specifically, no assessment was made until more than 12 hours post-dose. It is not known to what extent the drug affects cognitive performance in the earlier hours, from 5 PM to bedtime. This would be important to determine.

Summary and Conclusions

The applicant has established efficacy using standard clinical trial methodology, and the results seem to be solid. The individual efficacy trials (52 and 53) demonstrated statistically significant treatment effects on both of their co-primary endpoints – a fairly conservative criterion for success. Considering efficacy in its most positive light, Trials 52 and 53 showed that the percentages of subjects judged as “very much improved” or “much improved” by their investigators were approximately 40% in the placebo group, versus approximately 75% in the gabapentin enacarbil groups. As noted above, differences in changes in IRLS scores were also statistically significant in both trials.

The clinical safety profile is reasonably well-characterized, although there are important gaps in knowledge regarding somnolence. Driving ability was not assessed for the 600 mg daily dose, and the time course of cognitive impairment was not characterized for any dose. The other principal risks are suicidality – associated with taking anti-epileptic drugs – and dizziness. Impaired cognition and suicidality are important risks that can be mitigated through REMS – REMS designed specifically to heighten awareness. Patients should avoid driving and operation of heavy machinery when gabapentin enacarbil's pharmacodynamic effects are present. Patients should also be able to recognize depression and seek medical attention for such symptoms.

The risk of cancer, however, based on the pancreatic acinar carcinomas, adenomas, and hyperplasia observed in the 2-year rat carcinogenicity studies, makes the risk-benefit analysis unfavorable for the RLS indication. In part this is because RLS, although very bothersome and distressing, is merely a symptom complex without serious consequences. Moreover, two drugs are already approved for RLS, and they are not known to be carcinogenic or tumor-promoting.

It would be difficult to support approval of gabapentin enacarbil for RLS unless one or more of the following conditions are met. All represent possible paths forward for the applicant:

1. The applicant is able to show that the rat data are not relevant to humans
2. The applicant is able to demonstrate efficacy for lower doses of gabapentin enacarbil – increasing the safety margin between human and rat exposure
3. The applicant is able to provide strong reassurance regarding the risk of cancer, based on gabapentin's post-marketing data
4. The applicant is able to show that gabapentin enacarbil imparts some advantage over existing therapies for RLS, presumably by studying patients who are non-responders or poor responders to the approved drug(s). Such a study(ies) could lead to an approval for second-line use.

Based on all of the above, I concur with the planned CR action.

Application Type/Number	Submission Type/Number	Submitter Name	Product Name
NDA-22399	ORIG-1	GLAXO GROUP LTD DBA GLAXOSMITHKLIN E	SOLZIRA

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/s/

ELLIS F UNGER
02/17/2010

CLINICAL REVIEW

Application Type	NDA
Submission Number	022399
Submission Code	(0000)
Letter Date	January 9,2009
Stamp Date	January 9, 2009
PDUFA Goal Date	November 9, 2009
Extension	February 9, 2010
Reviewer Name	Susanne R. Goldstein, MD
Review Completion Date	February 9, 2010
Established Name	gabapentin enacarbil
(Proposed) Trade Name	Horizant
Therapeutic Class	Antiepileptic
Applicant	GlaxoSmithKline
Priority Designation	S
Formulation	tablet extended release 600mg
Dosing Regimen	once daily
Indication	Restless Leg Syndrome
Intended Population	Adult

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1 Recommendations/Risk Benefit Assessment

The sponsor (GSK) is seeking approval for gabapentin enacarbil for moderate to severe Restless Leg Syndrome (RLS). In pre-clinical studies with gabapentin enacarbil there is an increased incidence of pancreatic hyperplasia and pancreatic acinar tumors. Similarly, with Neurontin, there is an increased incidence of pancreatic hyperplasia and pancreatic acinar tumors in male rats. However, pancreatic carcinoma was seen at a lower dose in male rats, and was also seen in female rats at the higher dose group with gabapentin enacarbil. The margin of exposure in humans compared to male rats is 8 fold with gabapentin enacarbil. The underlying mechanism of drug induced pancreatic hyperplasia and acinar tumor in gabapentin and gabapentin enacarbil is unknown. Of note, pancreatic hyperplasia and pancreatic acinar tumors have not been seen in primate studies. Data mining in AERS database revealed three cases of pancreatic carcinoma in patients taking Neurontin.

Secondly, the Sponsor is seeking approval of gabapentin enacarbil, for moderate to severe RLS,

 (b) (4)
The side effect profile (sedation, dizziness) at 600mg is consistent with its parent compound, gabapentin. In a study of Post herpetic Neuralgia with gabapentin (Neurontin), 28% of subjects had dizziness and 21.4% had somnolence as compared with placebo (7.5% and 5.3% respectively). Comparatively, treatment emergent adverse events in the safety population for gabapentin enacarbil at 600mg a day, were 13% for dizziness and 20% for somnolence.

Although RLS is not necessarily a benign disease, that is it may be disabling in severe and/or refractory cases, it is not fatal. The risk benefit ratio taking into consideration particularly the possibility of pancreatic carcinoma is in favor of a complete response. If the Sponsor is able to provide sufficient evidence that the potential for drug induced pancreatic carcinoma does not apply to humans, then approval of gabapentin enacarbil at 600mg/day for moderate to severe RLS would be recommended.

Recommendation on Regulatory Action

As indicated above, a complete response for gabapentin enacarbil 600mg a day for moderate to severe RLS is recommended by the reviewer on the basis of carcinogenicity studies in rats. The table below provided by Pharm Tox Reviewer, shows the incidence of pancreatic acinar carcinoma in 2 year rat study.

Combined Pancreatic Lesions in Rats Treated with XP13512 for Up to 104 Weeks

<u>Dose</u> <u>(mg/kg/d)</u>	Males				Females			
	<u>0</u>	<u>500</u>	<u>2000</u>	<u>5000</u>	<u>0</u>	<u>500</u>	<u>2000</u>	<u>5000</u>
Hyperplasia, acinar; min-mild	11	8	11	17	1	0	3	10
Mod-severe	3	2	3	3	0	1	1	4
Acinar adenoma	2	4	4	8	0	0	0	3
Acinar carcinoma	0	0	1	1	0	0	0	1

Review of the clinical data reveals evidence of efficacy of gabapentin enacarbil in moderate to severe RLS in the adult population. The basis for this efficacy are two pivotal trials of 12 weeks duration using co primary endpoints, change from baseline to week 12/early termination of 1) IRLSS scale, internationally accepted and validated, 2) Clinical Global Impression by the Investigator (CGI-I).

Study	XP052		XP053		
Treatment	Placebo	1200	Placebo	1200	600
N	108	112	96	114	111
Change in IRLSS:baseline to week 12	-8.8	-13.2	-9.8	-13	13.8
P-value		0.0003		0.0017	<0.0001
Proportion of responders on CGI-I at week 12	38.9%	76.1%	44.8%	77.5%	72.8%
Estimated odds ratio		5.1		4.29	3.32
p-value		<0.0001		<0.0001	<0.0001

(Data courtesy of primary statistical review)

In the pivotal efficacy trials, 600mg gabapentin enacarbil is similarly efficacious to 1200mg gabapentin enacarbil. If approved, the dose for gabapentin for the treatment of moderate to severe RLS should be 600mg a day.

Risk Benefit Assessment

The risk of gabapentin enacarbil for treatment of idiopathic moderate-severe RLS outweighs the benefit. The cancer risk as evidenced by an increase in pancreatic acinar cell tumors in rats, is concerning. The margin of exposure in humans compared to male rats is 8 fold. Until the mechanism of carcinogenicity is understood, gabapentin should not be approved for the treatment of a non fatal disorder such as RLS. There are approved medications (Requip and Mirapex) for moderate to severe RLS.

In addition, at the dosage sought by the sponsor (1200mg a day), for moderate to severe RLS the risk benefit assessment is not acceptable for issues related to sedation, somnolence and dizziness. However, (b) (4)

[REDACTED]

Safety data were obtained from placebo controlled efficacy trials in moderate to severe RLS.

Recommendations for Postmarketing Risk Management Activities

Gabapentin enacarbil is a pro-drug of gabapentin (Neurontin). All drugs belonging to the anticonvulsant class are subject to REMS for anti-epileptic drugs (AED), for suicide attempt and possible suicide. In this application, there was one suicide in a healthy volunteer, one drug overdose in a subject on study drug and one accidental death in a subject soon after discontinuation of study drug. A Medication Guide (see REMS letter for details), will need to be distributed to patients who are prescribed and dispensed gabapentin enacarbil.

Recommendations for other Post Marketing Study Commitments

In the original application, (b) (4) the division recommended performing studies down to age 8. The division's recommendation is based upon ongoing pediatric studies with other agents (Mirapex and Requip) for RLS indication. In addition, there is an NIH funded study providing guidelines as well as research and clinical criteria for diagnosing RLS in children (Restless Leg Syndrome: Prevalence and Impact in Children and Adolescents The Peds REST Study, August 2007).

Subsequently, the sponsor submitted a pediatric proposal plan. A teleconference on August 31, 2009, was held with the sponsor to discuss this plan. The division recommended a double-blind, placebo controlled parallel group trial in ages 13 to 17 years of age with a partial waiver for

ages \leq 12. The division agreed with the waiver due to the fact that the prevalence of idiopathic RLS in children is extremely low. In addition, the symptoms in children below age 13 are usually mild and intermittent, thus not warranting drug treatment.

During the PeRC meeting on September 16, 2009, the committee recommended an incomplete/inadequate response to the sponsor. This recommendation was based upon the fact that the sponsor did not meet regulatory criteria for a pediatric plan; specifically, the sponsor's pediatric plan lacked specific dates for starting, completing and sending in summary reports on pediatric studies. The sponsor has subsequently submitted a complete pediatric plan which is currently under review.

REMS will need to be developed for the risk of suicidality with gabapentin enacarbil, a pro-drug of gabapentin. A memo is being issued to the applicant and the sponsor will need to submit full REMS prior to marketing.

A Medication Guide will need to accompany the REMS. The Medication Guide will include information to patients with RLS about the potential for somnolence, effects on ability to drive a car, potential effects on developing fetus, increased risk for suicidality, and the potential association of withdrawal seizures if gabapentin enacarbil is discontinued abruptly.

Post Marketing Commitments

Post Marketing Requirements

1. Study the effects of gabapentin enacarbil 600mg at Tmax (4-5 hours after dosing) as well as delayed timing (12 hours), on driving. These two time points are chosen to most closely mimic real world scenario:
 - a. Patient takes drug at 5pm and drives the next morning,
 - b. Patient takes the drug as late as midnight and drives the next morning.
2. Alcohol dose dumping study using the final dissolution method and evaluate different concentrations of alcohol up to 40% (0, 5, 10, 20, and 40%).
3. In vitro study to evaluate the potential of gabapentin enacarbil and gabapentin to be an inhibitor of CYP2C8 and 2B6.
4. Repeat QTc study.
5. Exploration for mechanism of carcinogenicity prior to commencing studies in Pediatric population.

Post Marketing Commitments

1. Study the efficacy and safety of doses lower than 600mg (300mg, 450mg) in adult population of patients with moderate to severe RLS. In other words, the sponsor needs to explore the dose response-curve below 600mg a day.

2. Develop a 300mg tablet for patients with renal impairment.

In addition, the reviewer recommends assessing onset of sedation after dosing as part of the PMR driving study. It is important to understand the exact onset of sedation and somnolence in order to best assess the risks of the drug on activities during waking hours. The sponsor presented onset of AEs, specifically somnolence, sedation and dizziness, in days. The onset of efficacy does appear approximately 2-4 hours after dosing, as seen from 24 hour RLS diary data. However, it is not clear from the data presented in the current application how soon after dosing the adverse events occur (in minutes, hours). The goal is to better understand the temporal relation between onset of RLS symptom relief and adverse events.

2 Introduction and Regulatory Background

Restless Leg Syndrome (RLS) is a chronic, at times progressive disorder. The exact etiology is unknown but appears to involve dopaminergic pathways. Currently approved treatments for RLS include dopamine agonists, pramipexole and ropinirole. Commonly used off label drugs include Neurontin, benzodiazepines and opioids/analgesics.

Discomfort in the lower extremities while at rest, relieved by activity, is pathognomonic for RLS. However in more severe cases RLS symptoms may occur during daytime as well as evening hours and may include upper extremities as well as lower extremities. The increase in severity and earlier onset of RLS symptoms are defined as augmentation. Augmentation, worsening of symptoms, may be either from disease progression or as a result of drug treatment itself. It has been theorized that augmentation involves dopaminergic pathways.

Carbidopa/levodopa treatment for RLS leads to augmentation in approximately 70-80% of patients with RLS, whereas, treatment with dopamine agonists has been associated with augmentation in approximately 30% of RLS patients.

A major cause of disability from this syndrome is difficulty sleeping (insomnia secondary to symptoms); hence sleep deprivation. Current treatments are effective, but often have side effects including daytime sleepiness, sudden onset of sleep and impulse control disorders (ICD).

Gabapentin (Neurontin) has been used for RLS. Although the exact mechanism of action of gabapentin in the treatment of RLS is unknown, it has been theorized that an interaction of neuropathic pain, lumbosacral disease and RLS exists. Gabapentin does not appear to work via dopaminergic pathways and, therefore, may be less likely to be associated with augmentation and/or ICD.

There have been small clinical trials using gabapentin (Neurontin) in patients with RLS (Garcia-Borreguero, Neurology 2002), with some success. Gabapentin enacarbil is a pro-drug of gabapentin. The advantages of gabapentin enacarbil are enhanced absorption by enterocytes at the intestinal lumen with more predictable (linear) pharmacokinetics and pharmacodynamics.

A summary of the regulatory background is presented in Section 2.5.

Product Information

Gabapentin enacarbil is an extended release pro-drug of gabapentin. It comes in 600mg extended release tablets.

Gabapentin enacarbil has been approved by (????) for the trade name HORIZANT.

It is considered a new molecular entity (NME), because of structural changes to the gabapentin molecule. These changes allow increased absorption. It belongs to the class, anticonvulsant drugs.

The sponsor's proposed indication is moderate to severe Restless Leg Syndrome as defined by the IRLSS rating scale a score of ≥ 15 .

Table of Currently Available Treatments for Proposed Indications

<i>Drugs approved for the proposed indication:</i>			
Generic/ Chemical Name	Brand Name	Sponsor(s)	Dosage form
pramipexole dihydrochloride	Mirapex	Boehringer-Ingelheim	.375mg,0.75mg 3 mg, 4.5 mg
(b) (4)			
ropinirole	REQUIP XL	Glaxo/Smith/Kline	Extended -Release Tablets
ropinirole	REQUIP CR	Glaxo/Smith/Kline	Oral Controlled Release tablets
ropinirole	REQUIP HCL	Glaxo/Smith/Kline	tablets
<i>Drugs approved but not available for proposed indication:</i>			
Generic/ Chemical Name	Brand Name	Sponsor(s)	Dosage form
(b) (4)			

Availability of Proposed Active Ingredient in the United States

XP13512 is a pro-drug of gabapentin, Neurontin. Neurontin was first approved in the United States in December 1993 as an add-on medication for partial seizures. In May 2004, it was approved for post-herpetic neuralgia. There has been extensive experience in prescribing and monitoring gabapentin for the past 16 years.

Important Safety Issues with Consideration to Related Drugs

The main safety issues of gabapentin, the active ingredient in XP13512, are sedation, dizziness and cognitive effects. In terms of sedation, one of the main areas of concern is driving. This is particularly problematic in patients with RLS who already have impaired sleep and suffer from daytime sleepiness. This has not been specifically studied in gabapentin, but has been studied in XP13512 at 1200mg and 1800mg a day, but not at 600mg.

Secondly, gabapentin, and hence gabapentin enacarbil, belong to the class of anticonvulsant drugs. There is a well studied association between antiepileptic drugs and suicidality (Statistical Review and Evaluation: Antiepileptic Drugs and Suicidality, US Dept. of HHS, FDA, 2009).

The odds ratio (95% CI) for suicidality with gabapentin was 1.57 (0.12, 47.66). Clinical trials with gabapentin were included in the review, regardless of indication and duration, with at least 30 patients in total.

Thirdly, in rat studies (see Pharm Tox Review for details), there is an increase incidence of pancreatic hyperplasia and pancreatic acinar tumors. This has not been observed in primate studies.

Summary of Presubmission Regulatory Activity Related to Submission

Gabapentin enacarbil was initially reviewed under **IND 71352** which was filed in December 2004. This initial submission contained a 2 week protocol examining XP13512 at doses of 600mg and 1200mg a day, in 60 patients with RLS. In April 2005, a second Phase II protocol was submitted. This was a dose finding study (600mg v. 1200mg v. placebo). Initially the sponsor had one primary endpoint, change in IRLSS scale from baseline to end of study (Week 12). The division recommended using co primary endpoints, change in IRLSS and change in CGI between baseline and end of study. In addition, the division recommended longer duration study (3-6 months). Finally, the division did not agree with

(b) (4)

(b) (4)

In September 2005, the Xenoport/GSK, submitted a **Special Protocol Assessment** for one of the pivotal trials XP052. The division agreed with the two arm (1200mg vs. placebo) trial. The sponsor was also planning a pivotal trial including a third arm (600mg). The division recommended further safety evaluation for augmentation and rebound; these are known complications of RLS as well as the treatment of RLS. In addition, cognitive testing during phase III development was recommended. Finally, the division reiterated the ICH guideline for 100 patients on drug for a minimum of 1 year and 300-600 patients on drug for a minimum of 6 months.

End of Phase 2 meeting took place on December 6, 2005. Issues discussed at this meeting included, but were not limited to:

1. The possibility of pancreatic acinar tumors as seen with gabapentin, in rats. The sponsor had posed the following question during this meeting: "Assuming that there is a finding of pancreatic acinar cell tumors in rats from X13512 exposure, does the Agency agree that, like gabapentin, this specific finding is not an issue for approval of XP13512. The division's answer was "The significance placed on animal tumor findings will depend on the strength of the signal compared to that seen with

- gabapentin taking into account the new indication and the efficacy demonstrated clinically”
2. Evaluation of in vitro induction potential of XP13512 was recommended, particularly since this has not been studied in gabapentin.
 3. The division recommended that the sponsor evaluate the effect of various meal types on the exposure to gabapentin enacarbil, since the sponsor is planning on patients taking XP13512 with food.
 4. The division recommended changing XP060 study to a 24 week randomized withdrawal study (the sponsor agreed).
 5. The division felt a formal QTc study was necessary. The study and all data collected would need to meet the requirements of ICH Guidance for Industry E14 Clinical Evaluation of QT/QTc Interval Prolongation and Pro-arrhythmic Potential for Non-Antiarrhythmic Drugs. The study was performed; however, the Division of Cardiovascular and Renal Products, in consultation, did not feel that the study met ICH Guidance criteria. The control group using moxifloxacin did not show an effect and thus the study did not reveal assay sensitivity. Therefore, the study was seen as inadequate.
 6. The division recommended assessing the effect of the XP13512 (gabapentin enacarbil) on the ability to drive. Simulated driving in healthy volunteers was examined in study XP088. Study XP083 was performed on subjects with RLS. Two doses, 1200mg and 1800mg, were studied versus placebo and an active control, diphenhydramine was included. In a teleconference with the sponsor on 2/27/2006, the division recommended that the sponsor assess simulated driving on other measures as well. These measures included cognitive side effects, which were studied using the Brief Assessment of Cognition (BAC).

Pre-NDA meeting took place on 12/14/2007. The division recommended that population PK analyses and concentration-response relationship analyses datasets should follow Guidance for Industry: Providing Regulatory Submissions in Electronic Format. Also, any concentrations and/or subjects that have been excluded from the analysis should be flagged. The division agreed that the sponsor was not required to perform a PK study in hepatically impaired subjects. In addition, the division agreed that no specific drug interaction studies with cytochrome P450 substrates or inhibitors are necessary for filing and review of the data.

The original NDA was submitted on September 15, 2008. However, the submission was withdrawn due to statistical issues with data sets, specifically; data sets in study XP060, submitted with original application. The application was resubmitted January 1, 2009, with reformatted datasets.

Other Relevant Background Information

The original application was submitted on September 15, 2008, but withdrawn due to problems with the datasets. It was resubmitted on January 9, 2009, with reformatted data sets.

3 Ethics and Good Clinical Practices

Submission Quality and Integrity

The sponsor’s submission was in eCTD format. The initial submission was withdrawn due to inadequate datasets. The sponsor resubmitted the application, which is the focus of this review. All sections/modules were appropriately completed. Financial disclosures were included in module 1.3.4, Debarment Certification were included in module 1.3.3. All clinical trials were conducted in accordance with “good clinical practices” GCP, all applicable regulatory requirements, and the guiding principles of the Declaration of Helsinki. (m5.2 tabular listing of each study, protocol section 1.2).

There was some data reformatting that was requested during the process of the review. Specifically, data on protocol deviations and violations were not fully presented with the original resubmission. Initially, only protocol deviations based on inclusion and exclusion criteria were included for pivotal trials XP052 and XP053 as well as maintenance of efficacy XP060. (Appendix H).

After several requests for more detailed information as outlined by the review team, the sponsor sent in over 1000 protocol deviations/violations (May 29, 2009). Below is the reviewer’s analysis from supplemental data provided by the sponsor, of protocol deviations/violations for trials XP052 and XP053.

Prohibited medications for all pivotal trials combined (Source: Reviewer)

FDACAT	N Rows	Placebo	Mean duration (days)	1200mg	Mean duration (days)	600mg	Mean duration (days)
Anesthetics - general	3	1	1	2	1	0	
Anticonvulsants	2	1	68	1	84	0	
Benzodiazepines	9	5	25	2	1	2	1
Dopamine antagonists	3	3	51.33	0		0	
Opioids	47	19	3.16	14	4.29	14	2.64
Other prohibited medication	15	5	51.4	6	59.5	4	17.5
Sedating antihistamines	63	28	2.5	18	7.83	17	2.53

- The reviewer’s table confirms the sponsor’s findings of greater number of violations in using concomitant medications, in placebo group versus drug group.

- The reviewer's table shows that there were a more violations with drug compliance in the 1200mg drug cohort
- Use of sedating antihistamines was greater in the placebo group than 1200mg or 600mg cohort
- Use of opioids and other prohibited medications was similar among cohorts in number of subjects and duration of use.

REVIEWER'S COMMENT: When combining all protocol violations for the pivotal trials, there does not appear to be a significant difference in drug compliance with the exception of an increase use of sedating antihistamines among the placebo group. The numbers are fairly small and therefore are unlikely to affect the efficacy analyses.

Compliance with Good Clinical Practices

The DSI consult focused on 4 domestic sites as well as the CRO (b) (4) of the initial sponsor of XP13512, Xenoport as well as current sponsor GSK. Two of the 4 clinical investigator sites had some regulatory violation; recording of vital signs and physical exam findings, on case report reforms, were not countersigned or initialed by the principle investigator. In addition, adverse events of sedation were not reported in CRF. However, it was felt that these few events were '....unlikely to impact data integrity.'

The primary efficacy endpoints captured were as specified per protocol. Informed consents were in order at all sites inspected.

Financial Disclosures

Financial Disclosures

On 14 December 2007, a Pre-NDA meeting was held between XenoPort, GSK and the Division of Neurology Products, this was the agency's first knowledge of involvement of GSK's involvement with the development of XP13512 (gabapentin enacarbil). On April 8, 2008 (Serial No. 0146), sponsorship of IND 71,352 was transferred to GSK as XenoPort's joint development partner of GSK1838262 ER Tablets for primary RLS. XenoPort, Inc. filed the initial IND application and was the sponsor of the studies during study conduct; however, GlaxoSmithKline is the NDA applicant for this submission.

Financial Disclosures for Clinical Trials Included in The Application

Xenoport Study Number	GSK Study Number	Protocol Title	Overall Study Start Date	Overall Study Completion Date
XP021	RXP111457	A Randomized, Double-Blind, Placebo-Controlled, Crossover Study to Assess the Safety and Efficacy of XP13512 in Patients with Restless Legs Syndrome	09 JUN 2004	01 DEC 2004
XP045	RXP111409	A Randomized, Double-Blind, Placebo-Controlled Study to Assess the Safety and Efficacy of Once Daily XP13512 in Patients with Restless Legs Syndrome	31 JAN 2005	08 JUN 2005
XP052	RXP110963	A Randomized, Double-Blind, Placebo-Controlled Study to Assess the Efficacy and Safety of XP13512 in Patients with Restless Legs Syndrome	13 MAR 2006	22 FEB 2007
XP053	RXP111460	A Randomized, Double-Blind, Placebo-Controlled Study to Assess the Efficacy and Safety of XP13512 in Patients with Restless Legs Syndrome	21 AUG 2006	20 DEC 2007
XP060	RXP111461	A Long Term Study of XP13512 Versus Placebo Treatment Assessing Maintenance of Efficacy and Safety in Patients with Restless Legs Syndrome	18 APR 2006	14 NOV 2007

Xenoport Study Number	GSK Study Number	Protocol Title	Overall Study Start Date	Overall Study Completion Date
XP081	RXP111462	A Randomized, Double-Blind, Placebo-Controlled, Dose-Response Study to Assess the Efficacy, Safety, and Pharmacokinetics of XP13512 in Patients with Restless Legs Syndrome	16 JAN 2007	10 JAN 2008
XP078	RXP111421	A Randomized, Double-Blind, Placebo- and Active-Controlled, Four-Period Crossover Study To Evaluate the Effect of XP13512 on Cardiac Repolarization by Thorough Analysis of QTc Effect in Healthy Adult Subjects	20 JUL 2007	03 NOV 2007
XP083	RXP111463	A Randomized, Double-Blind, Active- and Placebo-Controlled Parallel Group Study Assessing the Effect of XP13512 on Simulated Driving in Patients with Restless Legs Syndrome	09 APR 2007	09 NOV 2007

Xenoport Financial Disclosures (FD)

There were no investigators reported by Xenport as having a disclosable financial relationship with the company during the time of clinical trial participation. Xenport was unable to obtain FDs for about 6-18 subinvestigators in each of the pivotal efficacy trials. The missing FDs often involved multiple study personnel from the same site. There was only 1 study (XP060) where a single P.I. that did not submit a financial disclosure.

GlaxoSmithKline Financial Disclosures (FD)

There is one disclosure per study in this category for Studies (b) (6) as described below, as a result of exceeding the \$25,000 threshold for payments from GlaxoSmithKline:

(b) (6) This investigator received \$36,375.00 in retainer fees for consulting services from GSK. He recruited (b) (6) randomized into (b) (6) (total n (b) (6)). It is unlikely (b) (6) or personnel at his site had the potential of biasing the outcome or conclusions for study (b) (6).

(b) (6) This investigator received \$300,000.00 from GSK in the form of research funding. He recruited (b) (6) randomized into study (b) (6) (total n (b) (6)). No analysis was conducted by the sponsor to explore the effect of this site on the results of the study but it is unlikely that (b) (6) or site personnel (b) (6) bias the outcome or conclusions for study (b) (6).

(b) (6) This investigator received \$63,375.00 and \$26,000.00 in honoraria. He recruited (b) (6) of all subjects randomized into (b) (6), with (b) (6) to placebo and (b) (6) to the (b) (6) group. None of these subjects met the primary endpoint definition of relapse; therefore, the site did not have the potential of biasing the outcome or conclusions. He also recruited (b) (6) of all subjects randomized into (b) (6), which had (b) (6) randomized treatment groups (b) (6) with the number of subjects distributed across all treatment groups ((b) (6) respectively). The sponsor did not conduct a formal analysis to explore the effect of this site on the results of the study. Patients were distributed approximately equally across all treatment groups and GSK concluded this site did not have the potential to bias the outcome or conclusions of the study.

Many of the responses for GSK's financial disclosures were missing data from the investigators and site personnel. GSK was made the request for FDs in some cases 4 years after the trials concluded, therefore it is plausible in many cases the study personnel could not be located. GSK also reported that the

Financial disclosures by all trials and investigators are provided in eCTD module 1.3.4. The disclosures meet ICH guidance for Financial Disclosures

Disbarment Certification

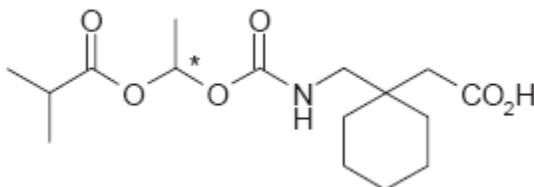
The applicant certified that none of the names of the clinical trials personnel appeared on the FDA's disbarment list. A review of the study site investigators listed for studies XP052, 053, and 081 (pivotal efficacy trials) did not find any names of investigators that appeared on the agency's disbarment list.

4 Significant Efficacy/Safety Issues Related to Other Review Disciplines

Chemistry Manufacturing and Controls:

Gabapentin enacarbil is a new molecular entity (NME). It is absorbed in the gut and nearly 100% hydrolyzed to form gabapentin. It is actively absorbed from the intestinal lumen and is rapidly converted to gabapentin by non-specific esterases, mainly in enterocytes (to a lesser extent in the liver). The exact mechanism of action for treatment of RLS is unknown.

Chemical name of XP13512 is 1-([isobutanoyloxyethoxy) carbonyl]-aminomethyl} - 1-cyclohexane acetic acid. The chemical name of gabapentin (Neurontin) is 1-(aminomethyl) cyclohexaneacetic acid.



During the midcycle meeting, CMC raised concerns about integrity of drug product; (b) (6) had been noted in the tablet. Further information from the sponsor was requested. In the final review by CMC, further dissolution studies were recommended as post-marketing commitments.

Clinical Microbiology

NA

Preclinical Pharmacology/Toxicology

Non clinical safety issues relevant to clinical use included:

1. **Pancreatic hyperplasia, adenoma and carcinoma all increase in rats treated with ≥ 2000 mg/kg/d.** The exposure multiple at the non-carcinogenic dose is approximately 4.3 times the human clinical exposure. In comparison, Neurontin elicited the same tumors in rats at higher exposures. The carcinogenic studies have been conducted in rats, and have not been replicated in primates. The mechanism for pancreatic hyperplasia and adenoma is unknown. (Please refer to Pharm-Tox Review for further details).
2. XP13512 is primarily excreted in urine of animals and humans. Its administration exacerbated age-related chronic progressive nephropathy in animal studies.
3. Embryo-fetal toxicity was found in rat pups and rabbit kits

REVIEWER COMMENT:

RLS is a relatively benign disease and therefore the unacceptable risk is lower than that of refractory seizures (indication for Neurontin). A lifetime exposure to gabapentin enacarbil without a clear delineation of carcinogenic mechanism does not seem warranted.

Although the QT study was seen as inadequate, gabapentin enacarbil does not appear to have significant effect on the QT interval. (Refer to Section 7 - Summary of Safety)

Clinical Pharmacology

There were 16 Phase I studies, conducted under IND 71,532 filed with DNP [REDACTED] (b) (4). [REDACTED] The initial two studies (XP006 and XP018) were conducted using an immediate release (IR) formulation of XP13512. Subsequently an extended release (ER) formulation was developed and compared to the IR formulation in study XP019.

The Phase II and Phase III development program consisted of four Phase III studies (XP052, XP053, XP055 and XP060) and four supporting Phase II studies (XP021, XP045, XP081 and XP083). All Phase II and III studies were conducted in the United States.

A population PK/PD analysis of efficacy and safety endpoints for RLS was also conducted (XP084), using integrated data from Phase I, Phase II and Phase III studies for pharmacokinetic analysis. Single doses of up to 6000mg ER and up to 2800mg IR XP13512 have been administered to healthy adult subjects. In multiple dose studies, XP13512 has been administered in doses up to 4200mg daily for IR formulation and up to 3600mg daily dose in ER formulation.

4.1.1 Mechanism of Action

Gabapentin enacarbil (XP13512) is a pro-drug of gabapentin (Neurontin). Following absorption in the intestinal tract, gabapentin enacarbil is converted to gabapentin by non-specific carboxylesterases in enterocytes and to a lesser extent in the liver. It is structurally related to the neurotransmitter gamma aminobutyric acid (GABA) but does not modify GABA A or GABA B radioligand binding. In vitro radioligand binding studies reveal gabapentin binding sites in areas of rat brain, including neocortex and hippocampus. A high affinity binding protein in animal brain tissue has been identified as an auxiliary subunit of voltage-activated calcium channels. The mechanism of action in Restless Leg Syndrome (RLS) is unknown.

4.1.2 Pharmacodynamics

In terms of intrinsic factors, there does not appear to be a racial effect of the drug either pharmacodynamically or upon pharmacokinetics. The majority of subjects in the trials were Caucasian. However, there have been several trials in the Japanese population.

In one trial, XP084, there was a slight gender effect; clearance in females was slightly lower than males (15%). There are no significant cardiovascular effects (orthostatic hypotension, QT prolongation). As noted throughout the review, the thorough QT study was felt to be inadequate by the QT consult service and will need to be repeated as part of the Post Marketing Requirements.

In the geriatric population, there may be reduced renal clearance and therefore gabapentin enacarbil dose should be adjusted as outlined in the renal clearance section of clinical pharmacology review (Also noted in labeling).

In terms of extrinsic factors, gabapentin enacarbil is not a substrate, inhibitor or inducer of CYP enzymes. Gabapentin enacarbil is not a substrate and/or inhibitor of p-glycoprotein transport processes. Drug-drug interactions are reviewed under a separate section of this review.

4.1.3 Pharmacokinetics

In Table 4, PK data is presented including C_{max}, T_{max} and AUC for XP13512 at doses of 600mg, 1200mg, 1800mg, and 2400mg. This data is derived from the dose response study, XP081.

(Source: Sponsor)

Table 4 Mean Pharmacokinetic Parameters for Gabapentin in Plasma At Steady State After Multiple Oral Doses of XP13512 in Fed RLS Patients in Study XP081 (Week 12)

XP13512 Dose (mg)	Dose (mg-eq. GP)	N	C _{ss,max} (µg/mL)	T _{max} (hr)	C _{ss,min} (µg/mL)	T _{1/2} (hr)	AUC _{ss,24} (µg ^h /mL)
600	312.5	32	4.14	6.96	0.600	6.27	51.4
1200	625	30	7.15	8.72	1.32	6.63	95.7
1800	937.5	30	12.0	8.00	1.60	5.89	146
2400	1250	31	13.3	8.13	2.41	6.09	173 ¹

GP = gabapentin; C_{ss,max} = maximum concentration at steady state ; T_{max} = time to C_{ss,max}; C_{ss,min} = minimum concentration at steady state; T_{1/2} = half-life; AUC_{ss,24} = area under the concentration-time curve at steady state.

1. n = 30

Following oral administration of XP13512 ER tablets, the drug was rapidly absorbed and converted to gabapentin. XP13512 has a linear pharmacokinetic profile. The only significant metabolic pathway is ester hydrolysis; gabapentin enacarbil, nor gabapentin, are substrates, inhibitors, or inducers for CYP1A2, 2C9, 2C19, 2D6, 2E1, and 3A4. The C_{max} and AUC of gabapentin after administration of gabapentin enacarbil appear to be dose proportional within single doses of 300 mg up to maximum of 6000 mg, in humans.

Pharmacokinetic Assessment.

Plasma gabapentin concentrations were measured at the end of the Baseline period (Visit 2) and at Visits 3, 4, and 8. In addition, PK profiles were measured at Visits 6 and 10 at the following time points: 0(pre-dose), 0.5,1,2,3,4,5,6,8,10,12,16,20, and 24 hours post dose.

There is a linear relationship between the dose of XP13512 and C_{max} and AUC₂₄ as shown in Sponsor Tables 17 and 18.

Table 17 Mean Pharmacokinetic Parameters for Gabapentin in Plasma at Steady State After Multiple Oral Doses of XP13512 in Fed RLS Subjects During Week 4 (Safety Population: Study XP081)

XP13512 Dose (mg)	Dose (mg-eq. GP)	N	C _{ss,max} (µg/mL)	T _{max} (hr)	C _{ss,min} (µg/mL)	T _{1/2} (hr)	AUC _{ss,24} (µg ^h /mL)
600	312.5	39	3.86	8.76	0.690	5.82 ^a	49.3 ^a
1200	625	33	7.14	8.57	1.37	6.67	96.1
1800	937.5	33	11.4	7.61	1.63	5.82	141
2400	1250	36	14.0	8.01	2.34	6.05 ^b	176 ^b

Data Source: Attachment 3, Table 2.1

a. N=38

b. N=35

Table 18 Mean Pharmacokinetic Parameters for Gabapentin in Plasma at Steady State After Multiple Oral Doses of XP13512 in Fed RLS Subjects During Week 12 (Safety Population: Study XP081)

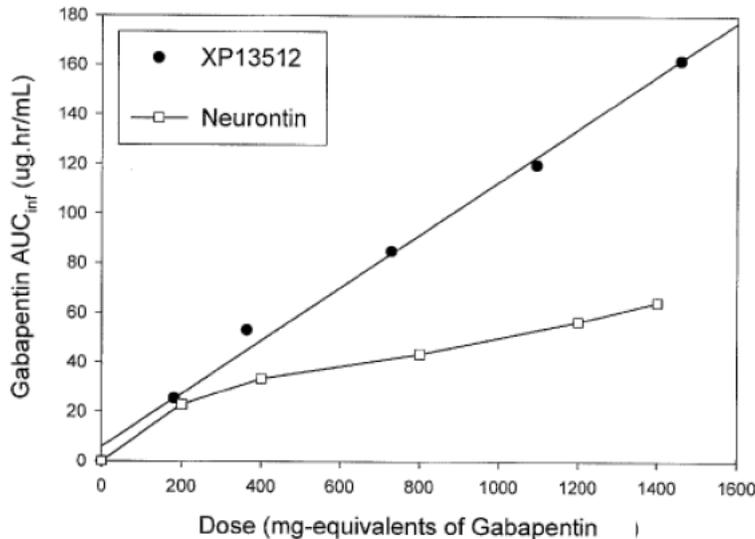
XP13512 Dose (mg)	Dose (mg-eq. GP)	N	C _{ss,max} (µg/mL)	T _{max} (hr)	C _{ss,min} (µg/mL)	T _{1/2} (hr)	AUC _{ss,24} (µg ^h /mL)
600	312.5	32	4.14	6.96	0.600	6.27	51.4
1200	625	30	7.15	8.72	1.32	6.63	95.7
1800	937.5	30	12.0	8.00	1.60	5.89	146
2400	1250	31	13.3	8.13	2.41	6.09 ^a	173 ^a

Data Source: Attachment 3, Table 2.2

a. N=30

The figure below shows the linear pharmacokinetics of gabapentin enacarbil versus Neurontin. At approximately 1200mg, Neurontin reaches saturation absorption.

The relationship of doses (mg-equivalents of gabapentin/kg) versus gabapentin exposure (AUC) after administration of XP13512 and Neurontin is shown below:



The sponsor recommends taking the drug with food. There is a significant effect of food on the bioavailability of gabapentin enacarbil. Food increases the bioavailability of gabapentin released from XP13512 by up to 50% change. In other words, if gabapentin enacarbil is taken on an empty stomach, without food, the half life is prolonged.

Parameter	XP13512 SR 300 mg		XP13512 SR 600 mg		XP13512 SR 1200 mg	
	Fasted (n=12)	Fed (n=12)	Fasted (n=12)	Fed (n=12)	Fasted (n=11)	Fed (n=12)
Dose (mg equivalent of gabapentin)	156		313		625	
C _{max} (µg/mL)	1.69 (±0.51)	2.26 (±0.55)	3.41 (±0.97)	4.41 (±1.26)	6.26 (±2.88)	7.59 (±1.65)
T _{max} (hr)	4.85 (±1.41)	9.83 (±2.76)	5.03 (±2.11)	7.27 (±1.68)	4.74 (±1.95)	7.92 (±2.19)
T _{1/2} (hr)	5.92 (±0.77)	5.96 (±1.05)	5.86 (±1.00)	5.37 (±0.94)	6.18 (±0.86)	5.49 (±0.87)
AUC _(0-inf) (µg•hr/mL)	18.0 (±6.26)	27.4 (±6.29)	37.8 (±9.83)	54.1 (±11.8)	69.7 (±24.0)	92.4 (±13.0)

(Courtesy Clinical Pharmacology Review)

The sponsor labeling recommends dosing [REDACTED]^{(b) (4)} If gabapentin enacarbil is taken as late [REDACTED]^{(b) (4)} without food, there could be significant adverse effects, such as morning sedation and somnolence. The adverse events, particularly sedation, could potentially interfere with work and driving.

RELATIVE BIOAVAILABILITY COMPARED TO NEURONTIN

The relative bioavailability of gabapentin enacarbil ER has not been studied. However, the research formulation, gabapentin enacarbil IR (350mg to 2800mg) was compared to Neurontin (200 to 1400mg), in healthy volunteers. The C_{max} of a dose of gabapentin enacarbil IR 700mg is similar to that of 1200mg of Neurontin. Of note, the bioavailability of gabapentin from Neurontin decreases from 65% at 200mg to 27% at 1400mg, consistent with saturated absorption. In contrast, the bioavailability of gabapentin from gabapentin enacarbil is nearly 70% over the 350 to 2800mg dose range of the IR formulation.

Report Date: June 25, 2004

Report Number: PK-2004-001
 Status: Final

2.0 SUMMARY TABLES

Table 2.1. Mean Pharmacokinetic Parameters for Gabapentin in Blood After Single Oral Doses of XP13512 in Study XP006

Group	Dose (mg)	Dose (mg-equiv. gabapentin)	N	C _{max} (µg/mL)	T _{max} (hr)	T _{1/2} (hr)	AUC _(0-inf) (µg*hr/mL)	F (%)
1	350	182	8	3.61	2.13	4.38	25.4	82.9*
2	700	365	8	6.55	2.06	5.38	53.0	85.4
3	1400	729	8	11.3	2.63	4.84	85.0	68.5
4	2100	1094	8	15.7	2.19	5.10	120	72.3
5	2800	1458	8	18.1	2.56	5.47	162	79.7

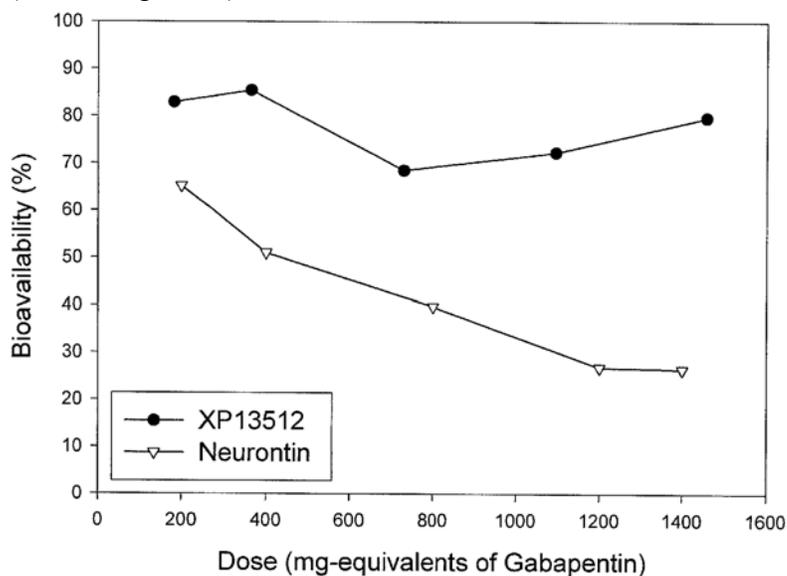
*One subject excluded due to an apparent error in urine volume measurement.

Table 2.2. Mean Pharmacokinetic Parameters for Gabapentin in Blood After Single Oral Doses of Neurontin® in Study XP006

Group	Dose (mg)	Dose (mg-equiv. gabapentin)	N	C _{max} (µg/mL)	T _{max} (hr)	T _{1/2} (hr)	AUC _(0-inf) (µg*hr/mL)	F (%)
1	200	200	10	2.61	2.85	5.40	22.8	65.2
2	400	400	10	3.41	3.06	6.69	33.4	51.0
3	800	800	10	4.78	2.80	7.34	43.4	39.7
4	1200	1200	10	6.13	3.30	9.26	56.6	26.9
5	1400	1400	10	5.76	3.20	8.27	64.5	26.5

The relative bioavailability of gabapentin from Neurontin versus gabapentin enacarbil in the fasted state is shown in the figure below.

(Source: Sponsor)



INTRINSIC FACTORS

Intrinsic factors including gender, race and age were examined.

Gender had a slight effect in one study (XP084) with 15% higher exposure in females.

Race, the majority of subjects (94%) were Caucasian with no other race having greater the 4% representation in the subject population. Therefore, the effect of race could not be determined.

Age; in and of itself did not have an effect, but the association of decreased renal function with age may lead to a reduced rate of clearance and thus higher exposure.

XP13512 is cleared by the kidneys. The sponsor has proposed [REDACTED] (b) (4) Clinical Pharmacology has recommended 300mg ER daily for patients with creatinine clearance of 15-29 mL/min.

In Table 5, clearance of gabapentin is shown based of rate of creatinine clearance. There is a clear reduction in renal clearance with increasing renal impairment.

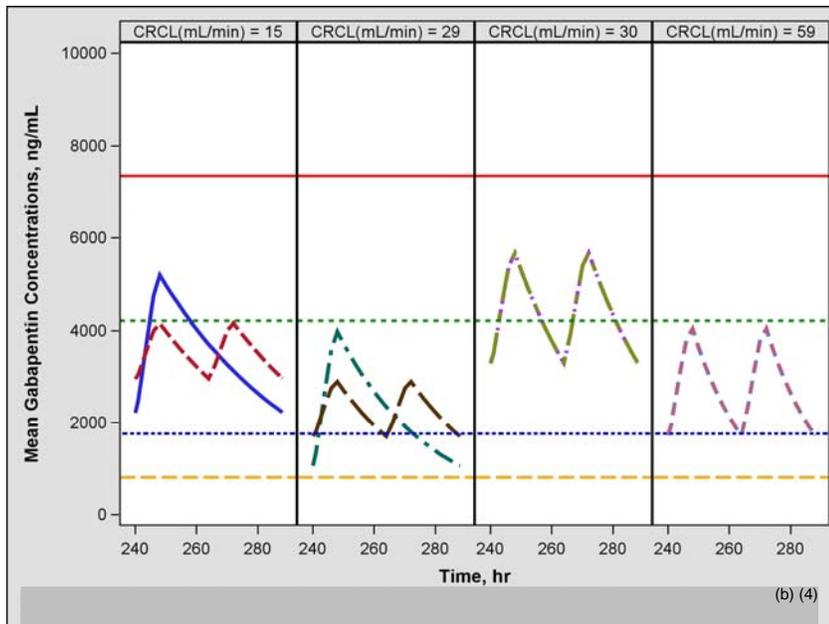
(Source: Sponsor)

Table 5 Gabapentin CL/F for Varying Degrees of Renal Function Predicted by the Population PK Model

Creatinine Clearance (mL/min)	Mean Predicted CL/F (Male and Female)
15	1.70
30	2.72
60	4.34
120	6.94

Note: An overall mean CL/F value was calculated based on men and women subjects with typical body weight values of 86.4 and 72.3 kg, respectively.

However, if renally impaired patients were dosed [REDACTED] (b) (4), versus 300mg a day, the plasma levels would drop below clinically therapeutic levels between dosing. This is shown in the diagram below (courtesy Clinical Pharmacology Review).



In order to maintain a steady plasma level of XP13512 it is recommended that patients with creatinine clearance below 30mL/min take 300mg gabapentin enacarbil a day.

FDA recommendations (courtesy Clinical Pharmacology)

Renal Function Creatinine Clearance (mL/min)	Titration Dose Regimen	Target Dose Regimen
≥60	600 mg per day for 3 days	600 mg per day starting day 4
30-59	300 mg per day for 3 days	600 mg per day starting day 4
15-29	no titration	300 mg per day

EXTRINSIC FACTORS

Extrinsic factors including drug-drug interactions, and effect of gabapentin enacarbil on pharmacokinetics of other drugs was studied. DDI studies were conducted with Naproxen (substrate of MCT1, found in small and large intestine) and cimetidine (an inhibitor of OCT2 present in kidney).

Naproxen and gabapentin enacarbil did not alter the PK of gabapentin enacarbil or gabapentin at steady state.

Cimetidine and gabapentin enacarbil showed slight increase in AUC of gabapentin enacarbil (24%) but no change in Cmax at steady state.

Clinical pharmacology also commented on alcohol interaction with XP13512 and the alcohol dose dumping studies. Dissolution increased from 20-30% within the first two hours in the presence of 40% alcohol. “Although 40% alcohol is considered the worst [case] scenario, the dissolution profile at lower percentage of alcohol is not known.” (courtesy Clin Pharm review).

Clinical Pharmacology has requested two Post Marketing Requirements:

1. In vitro study for evaluation of the potential of XP13512 and gabapentin to be an inhibitor of CYP2C8 and 2B6 should be conducted.
2. The sponsor should repeat the alcohol dose dumping study using their final dissolution method and evaluate different concentrations of alcohol up to 40%.

REVIEWER COMMENT:

Development of the 300mg dose of gabapentin enacarbil is important for renally impaired patients. In addition, the lower end of the dose response curve in adults has not been fully explored. The division recommends studying doses lower than 600mg in order to establish the minimally effective dosing.

The time of dosing gabapentin enacarbil as well as taking food with the dose is an important safety issue. In the driving study, XP083, there was significant sedation at Tmax with increased incidence of crashes and worsening in lane position variability. The effect of gabapentin enacarbil was similar to diphenhydramine.

Therefore, it is important to be precise with time and circumstances (fed state) associated with dosing of gabapentin enacarbil. The sponsor recommends taking gabapentin at 5pm with food, (b) (4). The reviewer recommends taking gabapentin enacarbil with food at 5pm (b) (4).

5 Sources of Clinical Data

All documents and datasets reviewed for this NDA submission are in the electronic form, and may found in the CDER Electronic Document Room, except for End of Study Report for open label trial XP055. This was received by the Agency in paper form on December 22, 2009.

The sponsor has performed 26 studies human subjects during the development for XP13512.

9 single dose studies in healthy volunteers at doses ranging from 600mg to 6000mg/day

3 multiple dose studies in healthy volunteers at doses ranging from 600mg to 3600mg/day

3 safety and tolerability studies performed in healthy volunteers

A QT study (XP078) was performed

1 study performed in end stage renal disease patients using single doses.

2 studies were performed for other indications (Post-Herpetic Neuralgia).

9 clinical studies for the indication of moderate to severe idiopathic Restless Legs Syndrome (RLS) were completed at the time of submission of this NDA, with the exception of XP055, a long-term open label study. A total of 1614 subjects with RLS were exposed to gabapentin enacarbil.

Clinical trials that support this NDA application are outlined in section 5, who are the focus of this review. One of the pivotal trials, XP052 was the subject of a Special Protocol Assessment. The trial proceeded without specific agreement on endpoints.

CLINICAL STUDIES SUPPORTIVE OF NDA APPLICATION FOR TREATMENT OF MODERATE TO SEVERE IDIOPATHIC RLS

(Source: Sponsor)

Tables of Clinical Studies

Study Number	Phase	Design and Control	Primary Objectives	Duration	Regimens	Number of Subjects
XP021	II	DB, randomized, PBO controlled, 2 period crossover	Efficacy and Safety	14 days for each period	XP13512 1800mg/PBO PBO/XP13512 1800mg	34
XP045	II	DB, randomized, PBO-controlled, parallel group	Efficacy and Safety	14 days	PBO/XP13512 1800mg	29
					XP13512 1200mg	32
					PBO	33
XP081	II	DB, randomized, PBO-controlled, parallel group	Efficacy and safety, dose/exposure response	12 weeks	XP13512 600mg	47
					XP13512 1200mg	43
					XP13512 1800mg	37
					XP13512 2400mg	44
					PBO	40
XP083	II	DB, randomized, PBO-controlled	Simulated driving performance, cognition, efficacy and Safety	14 days (for efficacy)	XP13512 1200mg	28
					XP13512 1800mg	33
					PBO	33
					PBO+diphenhydramine 50mg (once on Day 16)	28
XP052	III	DB, randomized, PBO controlled, parallel group	Efficacy and Safety	12 weeks	XP13512 1200mg	112
					PBO	108
XP053	III	DB, randomized, PBO controlled, parallel group	Efficacy and Safety	12 weeks	XP13512 1200mg (primary comparison)	111
					XP13512 600mg	114
					PBO	96
XP060	III	24 wk single blind phase with responders entering 12 wk, DB, randomized, PBO controlled, parallel group phase	Maintenance of Efficacy and safety	36 weeks	Single-blind:XP13512 1200mg	311
					Double-blind:XP13512 1200mg	97
					Double-blind PBO	96
XP055	III	Long-Term Safety	Safety	52 weeks	XP13512 1200mg	583

Adapted from Xenoport Module 2.5

Review Strategy

The key trials in clinical development of gabapentin enacarbil are summarized below.

PHASE II Clinical Trials

Two Week Clinical Trials

Trial **XP021** is a double-blind placebo-controlled crossover trial of placebo versus 1800mg XP13512.

Trial **XP045** is a double blind, placebo controlled parallel group trial of placebo versus 1200mg and 1800mg XP13512.

REVIEWER COMMENT: Both trials showed efficacy for study drug, gabapentin enacarbil, at the end of one week and two weeks on the single primary endpoint, change in IRLS between baseline and end of study (week 2). However, these trials will not be covered in detail in the efficacy section because of the short duration and lack of co-primary endpoints. In order to see clinically meaningful results from a trial of RLS, it should be at least 3-6 months duration. RLS is a chronic disease that may take several weeks to respond to optimal treatment. In addition, the division has recommended co primary endpoints be used in RLS trials.

Trial **XP083** is a 2 week study assessing effect of XP13512 on driving. The primary endpoint was change in lane position variability between baseline and day 16. This study will be covered in detail in the Safety Section of the Review.

Twelve Week Clinical Trials

Trial **XP081** is a dose exposure/response PK study. It is a 12 week double blind placebo controlled study with co primary endpoints of change in IRLS and change in proportion of responders on CGI between baseline and end of study. It will provide supportive efficacy for 600mg gabapentin enacarbil.

PHASE III Clinical Trials

Twelve Week Trials

Trials **XP052** and **XP053** are double blind, placebo controlled trials and are considered pivotal trials for efficacy. The co-primary endpoints are change in IRLS score from baseline to Week 12, end of study (EOS) and proportion of responders, patients who rated their symptoms of RLS as good and very good on CGI-I at EOS. The two trials are identical except for number of treatment arms.

Trial XP052 has two arms, placebo and 1200mg gabapentin enacarbil.

Trial XP053 has three arms, placebo, 1200mg gabapentin enacarbil and 600mg gabapentin enacarbil. Trial XP053 will be reviewed in detail in this section.

Maintenance of Efficacy

XP060 was a randomized withdrawal study, consisting of two phases. A single blind 24 week phase of 1200mg XP13512 followed by 12 week double blind phase. Subjects who met predesignated responder criteria for response during the 24 week single blind portion of the study were enrolled in the 12 week double blind portion of the study. The primary objective of XP060 was to assess maintenance of efficacy by measuring the proportion of subjects who relapsed during the 12 week double blind phase of the trial.

Open Label Extension Trial – 52 weeks

Trial **XP055** is a 52 week open label extension study of XP13512. At the time of the NDA submission, this study was still ongoing. A 120 day update (interim analysis) was submitted to the NDA with cut off date of July 31, 2008. An End of Study Report was submitted in paper format December 22, 2009.

Section 5.3 This section will outline the individual studies supporting the application that were least 12 weeks in duration including:

- PIVOTAL TRIALS FOR EFFICACY : XP052 and XP053
- TRIALS SUPPORTIVE EFFICACY : XP081
- MAINTENANCE OF EFFICACY: XP060
- LONG TERM OPEN LABEL: XP055

Section 6 will cover efficacy of key individual trials as well as integrated efficacy analyses as pertinent.

Section 7 will cover integrated safety analysis as well as individual clinical trial safety analysis as pertinent.

5.3 Discussion of Individual Studies

PIVOTAL TRIALS: XP053 and XP052

Protocol XP053 (RXP111460): A Randomized, Double-Blind, Placebo-Controlled Study to Assess the Efficacy and Safety of XP13512 (GSK1838262) in Patients with Restless Legs Syndrome, is a phase III study of efficacy and safety.

Phase III, Efficacy and Safety

Indication, Treatment of moderate to severe RLS (IRLS score >15)

Study Design

XP053 was a 12 week trial conducted at 28 centers in the United States, of which 27 sites enrolled subjects. It was a placebo controlled, double blind randomized trial. The original protocol was dated October 17th, 2005 with the first subject enrolled August 21, 2006. The protocol was amended three times prior to enrollment.

Subjects were scheduled for baseline visit; this visit occurred at least two weeks after discontinuation of previous RLS drug therapy. After a 7-day Screening/Baseline assessment period, subjects were assigned, to either drug (XP13512) at 600mg or 1200mg or placebo (PBO) in a 1:1:1 fashion. A blocked randomization schedule that was stratified by study site was used.

During, days 1 to 3, all subjects took one tablet of study drug (600 mg) or matching PBO at 5pm with food. On Days 4 to 84, subjects took 2 tablets of study drug or matching PBO at 5pm with food. On Days 85-91, subjects tapered to one tablet of study drug or matching PBO. Alternatively, on Day 85, subjects who successfully completed the entire 12-week double blind treatment period were eligible to participate in open-label Extension Study XP055. The subjects who entered the open label study, did not taper study drug.

Of note, if subject experienced sided effects, the dose of study medication could be maintained until side effects abated, decreased to prior dose level (if applicable), or withheld for a few days and then re-instituted.

Study XP052 differed from Study XP053 only in that subjects were randomized to either 1200mg gabapentin enacarbil or placebo; i.e., there was not 600mg group. The study was initiated sooner (March 6, 2006), and included 22 U.S. centers.

Entry Criteria

Key Inclusion/Exclusion Criteria.

All inclusion and exclusion criteria had to be met in order to be enrolled in the trial.

Inclusion criteria included:

1. Men or women greater than or equal to 18 years of age, diagnosed with restless leg syndrome based on IRLSSG Diagnostic criteria.
2. Subjects must have history of RLS symptoms for at least 15 nights in the month prior to starting study or current treatment.
3. The RLS symptoms must be documented for at least 4 of 7 consecutive evenings during Baseline study period.
4. RLS severity score of 15 or greater on IRLS Rating Scale at Visit 1 and 2
5. Current treatment with dopamine agonists and/or gabapentin must be discontinued at least two weeks prior to Baseline

6. Discontinuation of other treatments for RLS (e.g. opioids, benzodiazepines) at least 2 weeks prior to Baseline
7. Females of child bearing potential must agree to clinically acceptable birth control
8. Body Mass Index at or below 34
9. Estimated creatinine clearance of ≥ 60 mL/min

Exclusion criteria included:

1. sleep disorder that may affect assessment of RLS
2. Subjects may not have a history of augmentation or end of dose rebound with previous dopamine-agonist treatment.
3. Other neurologic disease or movement disorder
4. Other medical conditions (poorly controlled diabetes mellitus, iron deficiency anemia) or drug therapy (sedative/hypnotics) that could affect RLS treatment efficacy assessments.
5. At the investigators clinical discretion, clinically significant abnormal screening ECG or laboratories
6. Serum ferritin level below 20ng/mL
7. moderate or severe depression by DSM-IV
8. history of substance abuse or dependence within 12 months prior to enrollment
9. prior enrollment in another study with XP13512.

REVIEWER COMMENT:

1. The sponsor excluded subjects who did not respond to standard RLS treatment (dopamine agonists), had augmentation (RLS symptoms experienced earlier in the day associated with some RLS treatments) or early morning rebound (EMR), because they were not seeking a claim for treatment of refractory RLS, reducing augmentation or EMR
2. The IRLS rating scale has been validated and used in clinical trials. In addition, it is an accepted measure by experts treating RLS patients. XP053 study includes moderate to severe disease. IRLS score of 11-20 is considered moderate RLS, whereas, a 21-30 is considered severe RLS (Kohnen et al, Mov Dis 22;supp 118,2007). Therefore, a score of >15 is an acceptable cut off for a clinical trial of moderate to severe RLS subjects. The IRLSS scale has been used in other studies of RLS to support approval of dopaminergic drugs (REQUIP).
3. The inclusion of body mass index (BMI) criteria is important in trying to exclude subjects with obstructive sleep apnea (OSA). A high BMI and/or obesity are associated with sleep apnea. Sleep rating scale results for RLS symptoms may be obscured by subjects with sleep apnea.

4. Low normal to low serum ferritin levels have been associated with RLS in the presence or absence of anemia. Patients RLS and low to low normal ferritin levels are considered to have a secondary form of RLS and their symptoms may be more difficult to manage. Treatments designed to increase the low serum ferritin levels may be required in some of these patients.

DOSE SELECTION

The target dose selected for both pivotal trials (XP052, XP053), was 1200mg. The rationale for this decision was based the results from two earlier placebo controlled efficacy trials (XP021, XP045). In XP021 the dose was titrated over 5 days from 600mg, 1200mg or 1800mg once a day. The treatment period lasted 14 days with a one week washout. In XP045, the 600mg and 1200mg were compared to placebo. Both the 600mg and 1200mg treated groups were superior to placebo, with the 1200 mg demonstrating a larger treatment effect compared to 600mg (sponsor Table 3). In trial XP045, the results for the primary endpoint for 1200mg was a change of -16.1 (improvement) in the IRLS score at the end of week 2, whereas it was a change of -9.1 (improvement) in the 600mg group.

REVIEWER COMMENT: The drug treatment effect for RLS may take more than two weeks, hence the reason for recommending 12 week trials. The Sponsor's designed two week clinical trials early in the clinical development program. The two week trials showed superior efficacy of 1200mg to 600mg, leading the sponsor to use the 1200mg dose for Phase III clinical studies.

EFFICACY ENDPOINTS

Co-Primary Endpoints

1. change from Baseline to the end of treatment (week 12) in IRLS Rating Scale score
2. proportion of subjects at the end of treatment (week 12) who were "much improved" or "very much improved" on the CGI-I.

The co-primary endpoints were each to be tested at the $p < 0.05$ significance level. Only if both tests were statistically significant would the study be considered to have provided positive evidence of efficacy.

REVIEWER COMMENT: Initially, the sponsor designed the pivotal trials to have one primary endpoint (change in IRLS between baseline and end of treatment). However, after discussion, the division responded on May 3, 2005, that there should be co-primary endpoints to help insure that the change measured on the IRLS scale is clinically meaningful in patients. The change in IRLS score was felt to be acceptable, by the division as one of the endpoints, and a second global scale, such as CGI-I, would be an acceptable second primary endpoint. As

stated previously, the consensus from the Restless Leg Community (specifically recommendations in **Clinical Trials in Restless Legs Syndrome-Recommendations of the European RLS study Group**) felt the IRLS with CGI was most sensitive and specific at detecting efficacy of a drug.

At the meeting, the sponsor noted that they were planning studies of 8 weeks' duration, but the division responded that the minimal accepted duration of a trial is 12 weeks.

KEY SECONDARY EFFICACY ENDPOINTS:

1. change in IRLS score between Baseline and end of 1 week of treatment
2. change in proportion of much improved and very much improved at end of 1 week of treatment on CGI-I for XP13512 600mg versus placebo.
3. response to treatment from Patient-rated CGI of Improvement at the end of treatment

REVIEWER COMMENT: In the early studies, XP021 and XP045, efficacy in the 1200mg treatment group was observed as early as one week. [REDACTED] (b) (4)
[REDACTED] the division recommended including only primary efficacy endpoints in labeling. Although early onset of symptom relief is desirable, RLS is a chronic disease and by its nature may take several weeks to achieve clinically meaningful symptom relief.

The 24-hour RLS Record was included to help assess augmentation and early morning rebound (EMR). However, one may also use this scale to assess onset of drug effect for symptoms relief as well as duration of symptom relief. (Appendix A)

STATISTICAL ANALYSIS PLAN

Assessment of efficacy, as stated in statistical analysis plan (January 22, 2008-final), was measured as primary analysis in XP13512 1200mg treatment group on change in IRLS total score from baseline to the end of treatment (for completers week 12) and proportion of responders for the CGI-I defined as patients who were rated by the investigator as "much improved" or "very much improved" subjects on CGI-I at week 12. XP13512 600mg was set as a secondary comparison.

Both groups were analyzed using the Modified Intention To Treat (MITT) population with last observation carried forward (LOCF) method of imputation for missing data. The MITT was defined as all patients in the Safety Population who also satisfy all of the following conditions:

- completed the IRLS rating scale at baseline
- completed at least one on-treatment IRLS rating scale score during the treatment period

Sites were pooled together by region to form 6 larger consolidated sites; this was done prior to analyses. The main statistical analysis was a pair-wise comparison of the co-primary endpoints endpoints using an analysis of covariance (ANCOVA), which included the Baseline value as a covariate and pooled site, treatment, and treatment-by-pooled-site interaction term as exploratory factors. The data for the CGI-I were converted to responder versus non-responder status (1,0) and analyzed using logistic regression with treatment and pooled site as explanatory factors.

All secondary endpoint analyses were also conducted on the MITT population. The analysis methods for the secondary efficacy endpoints were chosen based on the type of data. The sponsor also listed several sensitivity analyses of the efficacy data. There was no planned hierarchy or procedure for adjusting the p-value for multiple comparisons.

RESULTS:

POPULATION:

A total of 645 subjects were screened of which 325 were randomized. An explanation for screen failures was not able to be located in the application. Virtually all randomized subjects were included in the safety and MITT populations.

DEMOGRAPHICS

Sponsor Table 59 presents the demographic characteristics of the MITT/Safety Population.

Table 59 Summary of Demographic Characteristics (MITT/Safety Population: Double-Blind, Placebo-Controlled Parallel Group Studies XP045, XP052, XP053, XP081 and XP083)

	Study XP045 Phase IIb 2-week			Study XP052 Phase III 12-week		Study XP053 Phase III 12-week			Study XP081 Dose Ranging 12-week					Study XP083 Driving Performance/Cognition 2-week			
	PBO	XP 600	XP 1200	PBO	XP 1200	PBO	XP 600	XP 1200	PBO	XP 600	XP 1200	XP 1800	XP 2400	PBO	XP 1200	XP 1800	PBO/ DPH
N (MITT/Safety Pop ¹)	33	29	33	108	112	96	114	111	40	47	43	37	44	33	28	33	28
Age (years)																	
n	33	29	33	108	112	96	114	111	40	47	43	37	44	33	28	33	28
Mean	49.4	51.9	50.2	50.2	52.0	49.1	48.3	49.5	47.2	47.9	50.2	51.1	46.5	49.3	46.6	49.6	41.7
SD	10.97	11.22	11.54	12.79	12.86	12.19	12.88	12.67	11.28	12.40	11.56	12.95	13.56	11.40	10.58	10.26	11.36
Min, Max	26, 69	23, 68	23, 70	19, 81	18, 79	21, 77	21, 74	21, 75	24, 77	20, 68	18, 73	20, 72	21, 75	25, 70	22, 63	27, 65	25, 62
Sex, %																	
n	33	29	33	108	112	96	114	111	40	47	43	37	44	33	28	33	28
Female	52	69	67	60	59	59	58	59	73	64	51	70	64	58	64	52	64
Male	48	31	33	40	41	41	42	41	28	36	49	30	36	42	36	48	36
Race, %																	
n	33	29	33	108	112	96	114	111	40	47	43	37	44	33	28	33	28
White/Caucasian	94	100	100	98	96	95	91	96	95	100	98	92	93	100	100	97	100
Black/African-American	3	0	0	2	3	1	4	1	3	0	2	5	4	0	0	0	0
American Indian/Alaska Native	3	0	0	1	1	0	3	0	3	0	0	0	2	0	0	0	0
Asian	0	0	0	0	1	2	0	1	0	0	0	3	2	0	0	0	0
Native Hawaiian/Pacific Islander	0	0	0	0	0	1	0	0	0	0	0	0	0	0	0	0	0
Mixed Race	0	0	0	1	0	1	<1	0	0	0	0	0	0	0	0	0	0
Other	0	0	0	0	0	0	2	2	0	0	0	0	0	0	0	3	0

Continued

Age: The mean age as well as the age range is similar among treatment groups.

Gender: There are approximately 60% females and 40% males in each treatment group, which is consistent with published estimates of gender differences in the published epidemiological studies in patients with RLS.

Race: There is greater than 90% Caucasians in each treatment group that is typical of the RLS patient population.

RLS SYMPTOM HISTORY

In the Sponsor's Table 60, they present a comparison of the duration of RLS symptoms and the average number of days per week subjects experienced RLS symptoms, which appeared to be similar for each treatment group. The 600mg and 1200mg groups have a slightly higher percentage of treatment naïve subjects compared to the placebo group. The disproportionate number of treatment naïve subjects in active treatment groups is unlikely to have significant impact on efficacy or safety.

Table 60 Summary of RLS History (MITT/Safety Population: Double-Blind, Placebo-Controlled Parallel Group Studies XP045, XP052, XP053, XP081 and XP083)

	Study XP045 Phase IIb 2-week			Study XP052 Phase III 12-week		Study XP053 Phase III 12-week			Study XP081 Dose Ranging 12-week					Study XP083 Driving Performance/Cognition 2-week			
	PBO	XP 600	XP 1200	PBO	XP 1200	PBO	XP 600	XP 1200	PBO	XP 600	XP 1200	XP 1800	XP 2400	PBO	XP 1200	XP 1800	PBO/ DPH
N (MITT/Safety Pop ¹)	33	29	33	108	112	96	114	111	40	47	43	37	44	33	28	33	28
IRLS Rating Scale total score at baseline																	
n	33	29	32	108	112	96	114	111	40	47	43	37	44	60 ²	28	32	ND
Mean	22.4	21.2	22.4	22.6	23.1	23.8	23.1	23.2	22.5	23.9	23.9	23.6	23.3	24.1	24.4	22.4	ND
SD	4.58	3.67	4.41	4.91	4.86	4.58	4.93	5.32	5.32	5.33	5.49	4.25	5.70	4.37	5.49	4.19	ND
Min, Max	15, 33	15, 32	16, 34	15, 37	15, 36	15, 32	10, 35	12, 40	15, 33	15, 37	15, 39	16, 32	15, 37	15, 34	17, 38	16, 34	ND
Duration of RLS symptoms (years)																	
n	33	29	33	108	111	96	114	111	40	47	43	37	44	33	28	33	28
Mean	16.8	12.8	18.0	14.5	13.7	14.4	13.6	14.1	11.0	13.4	16.7	12.2	13.3	15.4	11.5	8.5	12.5
SD	12.21	11.49	15.05	12.91	14.70	12.85	13.08	12.36	13.46	12.31	16.47	11.60	13.78	13.82	10.94	9.14	12.06
Min, Max	0.8, 40.3	0.3, 43.2	0.4, 47.8	0.6, 59.3	0.4, 65.9	0.3, 46.9	0.4, 58.9	0.3, 47.1	0.1, 44.0	0.1, 50.4	0.1, 63.8	0.1, 52.0	0.1, 47.8	0.1, 50.2	0.1, 44.0	0.1, 30.9	0.1, 45.0
Number of days RLS symptoms expressed on the 7-Day Subject RLS Record prior to baseline																	
n	33	29	33	108	112	96	113	111	40	46	43	37	44	33	28	33	28
Mean	5.6	5.8	5.7	6.1	5.9	6.3	6.2	6.3	6.0	5.7	5.9	6.1	6.1	5.8	5.8	5.7	6.0
SD	1.22	1.21	1.26	1.01	1.08	0.99	0.90	1.03	1.05	1.14	1.19	1.03	1.05	1.24	1.11	1.01	1.07
Min, Max	3, 7	3, 7	3, 7	4, 7	4, 7	3, 7	4, 7	2, 7	4, 7	4, 7	3, 7	4, 7	4, 7	4, 7	4, 7	4, 7	4, 7
Previously treated for RLS? %																	
n	ND	ND	ND	108	112	94	112	110	40	47	43	37	44	33	28	33	28
No	ND	ND	ND	65	71	61	67	65	65	72	72	54	61	67	61	55	68
Yes	ND	ND	ND	35	29	39	33	35	35	28	28	46	39	33	39	45	32

Data Source: CSR XP045, Table 3 and Table 4.1.1; CSR XP052, DS Table 3, DS Table 4.1 and Post-hoc DS Table 24; CSR XP053, DS Table 6.6 and DS Table 7.1.1.3; CSR XP081, DS Table 6.4 and DS Table 7.1; CSR XP083, DS Table 6.6 and DS Table 7.1.

DPH = diphenhydramine; ND = not determined; PBO = placebo; XP = XP13512 (dose in mg).

- For XP052, XP053 and XP081, data for the MITT Population are summarized. For XP045, data for the Safety Population are summarized, except for IRLS Rating Scale total score, which is summarized for the ITT Population.
- For Study XP083, the IRLS Rating Scale total score is summarized for the placebo + placebo/diphenhydramine groups (N=61).

Duration of RLS symptoms: The mean duration of RLS symptoms as well as the range of the duration of their symptoms in years is similar among treatment groups.

Number of days RLS symptoms expressed on 7-Day Subject Record: The mean and median number of days per week subjects were symptomatic prior to the Baseline visit was similar among treatment groups.

RLS treatment history: There were slightly more treatment naïve subjects in the 600mg and 1200mg treatment group (67.3% and 64.5% respectively) compared to placebo (60.6%)

REVIEWER COMMENT: None of the differences in Baseline disease characteristics are likely to cause an imbalance between the treatment groups in response to drug treatment.

SUBJECT DISPOSITION:

TRIAL XP053

Of the 279 subjects who completed this study, 90.3% (252) subjects entered the continuation study XP055.

The overall number of patients who withdrew from the trial prematurely was greater in the XP13512 groups compared to placebo. Eight patients withdrew consent in the placebo group and 7 from the XP13512 treated groups without further explanation by the sponsor. Patients who withdrew due to adverse events in study XP053 were evenly distributed among the treatment groups (6 withdrawals due to adverse event in the placebo group, 7 in the 600mg group and 8 in the 1200mg group). (Sponsor Table 15). No subjects withdrew because of treatment failure in either XP13512 treatment group compared to 3 in the placebo group.

Table 15 Overall Exposure and Disposition in Study XP053

Population	Number (%) of Subjects			
	Placebo	XP13512 600 mg	XP13512 1200 mg	Total
Randomized	97 (100)	115 (100)	113 (100)	325 (100)
MITT	96 (99.0)	114 (99.1)	111 (98.2)	321 (98.8)
Subject Disposition (Randomized Subjects)				
N	97	115	113	325
Completed	77 (79)	104 (90)	98 (87)	279 (86)
Withdrawn	20 (21)	11 (10)	15 (13)	46 (14)
Reason for Withdrawal (Randomized Subjects)				
Ineligibility	0	0	2 (2)	2 (<1)
Adverse event	6 (6)	7 (6)	8 (7)	21 (6)
Treatment failure	3 (3)	0	0	3 (<1)
Patient withdrew consent	8 (8)	3 (3)	4 (4)	15 (5)
Investigator judgment	0	0	0	0
Protocol non-compliance	1 (1)	0	1 (<1)	2 (<1)
Lost to follow-up	1 (1)	1 (<1)	0	2 (<1)
Termination of study or withdrawal of subject by sponsor	1 (1)	0	0	1 (<1)

Data Source: CSR XP053, DS Table 6.1.

TRIAL XP052

A total of 222 subjects were randomized, 114 subjects to XP13512 1200mg and 108 subjects to placebo

Overall, a slightly greater number of patients withdrew from the placebo group compared to the XP13512 group. Twice the percentage of patient withdrew for adverse events in the 1200mg XP13512 group compared to placebo (7.9% versus 2.8% respectively). Six patients withdrew from the placebo group because of treatment failure compared to none in the XP13512 group. Four subjects withdrew consent from the XP13512 group compared to 3 in the placebo group without further explanation from the sponsor.

Table 6 Overall Exposure and Disposition in Study XP052

Population	Number (%) of Subjects		
	Placebo	XP13512 1200 mg	Total
Randomized	108 (100)	114 (100)	222 (100)
MITT	108 (100)	112 (98.2)	220 (99.1)
Subject Disposition (Randomized Subjects)			
N	108	114	222
Completed	92 (85)	100 (88)	192 (86)
Withdrawn	16 (15)	14 (12)	30 (14)
Reason for Withdrawal (Randomized Subjects)			
Ineligibility	2 (2)	0	2 (<1)
Adverse event	3 (3)	9 (8)	12 (5)
Treatment failure	6 (6)	0	6 (3)
Patient withdrew consent	3 (3)	4 (4)	7 (3)
Investigator judgment	1 (<1)	0	1 (<1)
Protocol non-compliance	1 (<1)	0	1 (<1)
Lost to follow-up	0	0	0
Termination of study or withdrawal of subject by sponsor	0	1 (<1)	1 (<1)

Data Source: CSR XP052, DS Table 1.1.

SAFETY ASSESSMENTS

The safety population was comprised of all subjects who were randomized into the study and who received at least one dose of study drug. The plan of analysis was population treated. In addition all subjects in the safety population who met criteria for Modified Intent-to-Treat (completed IRLS Rating Scale at Baseline and completed at least one on treatment IRLS Rating Scale score) were analyzed as randomized.

Safety assessments included:

- Laboratory values
- Vital signs, including orthostatic blood pressure
- ECG (Verify Timing of ECG)
- Brief Assessment of Cognition (BAC)
- Epworth Sleepiness Scale (ESS)
- Sudden Onset of Sleep (SOS)

REVIEWER COMMENT: Medications in this class, anticonvulsants, as well as medication currently approved for RLS (REQUIP and Mirapex) have known side effects of sedation, sleep attacks, daytime sleepiness. The division had recommended adding the ESS to assess daytime sleepiness. In addition, the division had recommended adding a cognitive scale to assess possible cognitive side effects of gabapentin enacarbil. The sponsor chose the BAC.

The schedule of assessments for trial XP053 (and XP052) is shown in sponsor table 1 below.

Table 1 Time and Events Schedule

Period →	Baseline		Treatment												Taper	Follow-Up
Study Week →	-1	1	2	3	4	5	6	7	8	9	10	11	12/ET	13	14-17	
Study Day →	-7 (-1) ^a	1 2-7 ^a	8 9-14 ^a	15 16-21 ^a	22 23-28 ^a	29 30-35 ^a	36-42 ^a	43 44-49 ^a	50-56 ^a	57 58-63 ^a	64-70 ^a	71 72-78 ^a	80-84 ^a	85	85-91	92-119
Visit Number →	1	2	3	4	5	6	7	8	9	10	11	12	13	14	15	16
Visit Window (Days)		+1	+1	±1	±1	±1	±2	±2	±2	±2	±2	±2	±2	±2	±2	±3
Obtain Informed Consent	X															
Inclusion and Exclusion Criteria	X	X														
Demography, Medical, RLS, Drug History	X															
Physical Exam, Neurologic Exam	X															X
Vital Signs Including Orthostatic BP/PP	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
Electrocardiogram (ECG)	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
Clinical Lab Testing Blood/Urine	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
Serum Pregnancy Test-Females	X															X
Gabapentin Level/Dosing Record		X		X		X		X		X		X		X		X
IRLS Rating Scale	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
Post-Sleep Questionnaire (PSQ)		X				X				X				X		X
Collect 24-Hour RLS Record		X		X										X		X
MOS Sleep Scale		X				X				X				X		X
RLS QoL and POMS		X				X				X				X		X
Sudden Onset of Sleep (SOS) Questionnaire		X				X				X				X		X
Esworth Sleepiness Scale (ESS)		X				X				X				X		X
Brief Assessment of Cognition (BAC)		X												X		X
Mood Assessment						X				X				X		X
Collect 7-Day RLS Symptom Record		X														

Continued

Table 1 Time and Events Schedule (Continued)

Period →	Baseline		Treatment												Taper	Follow-Up
Study Week →	-1	1	2	3	4	5	6	7	8	9	10	11	12/ET	13	14-17	
Study Day →	-7 (-1) ^a	1 2-7 ^a	8 9-14 ^a	15 16-21 ^a	22 23-28 ^a	29 30-35 ^a	36-42 ^a	43 44-49 ^a	50-56 ^a	57 58-63 ^a	64-70 ^a	71 72-78 ^a	80-84 ^a	85	85-91	92-119
Visit Number →	1	2	3	4	5	6	7	8	9	10	11	12	13	14	15	16
7-Day PghSD Sleep/Pain Diary (Starts the week prior to the visit)		X		X		X		X		X		X		X		X
Record Adverse Events		X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
Record Concomitant Medications	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
Randomization (IVRS)		X														
Study Drug Dispensed		X		X		X		X		X		X		X		X ^b
Study Drug Accountability			X	X	X	X	X	X	X	X	X	X	X	X	X	X
Investigator & Patient CGI			X	X		X				X				X		X
Exit Study, Start Extension Study															X	
Study Drug Taper																X ^b
End of Study Follow-Up Call																X

Data Source: Attachment 1 (Protocol Study XP053)

a. Subjects were called prior to each visit as a reminder to start any required diaries or records and to bring these records, study drug, and log pads to the visit. Also, on Days 50 and 80 subjects were reminded to start 7-Day PghSD Sleep/RLS Pain Diary. Additional calls may have been required for electronic diary compliance.

b. Re-dispensed 7 study drug tablets.

BP/PP=Blood pressure and pulse; CGI=Clinical Global Impression; ET=Early termination; IRLS=International Restless Legs Syndrome; IVRS=Interactive voice recognition system; MOS=Medical Outcomes Study; PghSD=Pittsburgh Sleep Diary; POMS=Profile of Mood State; QoL=Quality of Life.

ADDITIONAL SAFETY ASSESSMENTS APPROPRIATE TO INDICATION AND DRUG CLASSIFICATION

Augmentation and Early Morning Rebound were assessed by 24 hour RLS. This has been an accepted form of data gathering to capture patient results over time.

Suicidality was retrospectively analyzed by searching Adverse Events for specific terms associated with suicidality. The data was then sent to (b) (4) for analysis of association with drug treatment.

REVIEWER COMMENT: A prospective data gathering tool, such as the Columbia Suicidality Scale would be a better measure of ‘real time’ suicidality.

AUGMENTATION

Augmentation is defined as worsening of RLS symptoms in time of onset (earlier in the day) and/or intensity. This is commonly seen with dopaminergic agents (add reference).

EARLY MORNING REBOUND (EMR):

EMR is defined as earlier onset, in the morning, of RLS symptoms.

Both Augmentation and EMR wear assessed using the RLS 24 hour sleep Record. (See Section 7 for Review of Safety Results).

SUICIDALITY:

Gabapentin enacarbil belongs to the class ANTICONVULSANT, ANTIPILEPTIC DRUGS. This class of drugs has a risk of suicidality. The method used by the sponsor to monitor for suicidality is covered in section 7 of the Review.

CLINICAL TRIALS SUPPORTING EFFICACY

PROTOCOL XP081 (RXP111462): A Randomized, Double-Blind, Placebo-Controlled, Dose-Response Study to Assess the Efficacy, Safety, and Pharmacokinetics of XP13512(GSK1838262) in Patients with Restless Leg Syndrome.

Phase II study Efficacy and Safety, Dose/Exposure Response Study

Indication Moderate to Severe RLS

ENTRY CRITERIA

Key Inclusion Criteria/Exclusion Criteria used for trial XP053 were used for trial XP081.

STUDY DESIGN:

Study XP081 is a 12-week multicenter, randomized, double-blind, placebo controlled, parallel group study comparing 4 doses of XP13512 (600mg, 1200mg, 1800mg, and 2400mg)with placebo. The study was conducted at 21 centers in the United States.

DOSE SELECTION

Similarly to Studies XP052 and XP053, doses for study XP081 were selected based upon results of earlier trials XP021 and XP045. (Sponsor Table 5) The 1800mg dose in study XP021 and the 1200mg dose in study XP045 were superior to placebo, whereas the 600mg dose in study XP045 was only marginally better than placebo.

Sponsor Table 1 shows the target dose titration scheme.

Table 1 Target Dosing Scheme

Target Dose/ Treatment Group	Double-Blind Treatment Phase ^a				Double-Blind Taper Phase ^b		
	Titration Period				Days 85-86	Days 87-88	Days 89-91
	Days 1-3	Days 4-6	Days 7-9	Days 10-84			
600 mg	✓	✓	✓	✓	600 mg	600 mg	600 mg
1200 mg	600 mg	✓	✓	✓	600 mg	600 mg	600 mg
1800 mg	600 mg	1200 mg	✓	✓	1200 mg	1200 mg	600 mg
2400 mg	600 mg	1200 mg	1800 mg	✓	1800 mg	1200 mg	600 mg

Note: Subjects were instructed to take study drug once-daily at 5 PM with food.
 a. The 84-day Double-Blind Treatment Phase included a 9-day titration period.
 b. XP13512 dose levels during the taper phase are shown by treatment group.
 ✓ = Target dose achieved.

The dosing and titration schedule used in study 081 increased the dose by one 600 mg tablet every 3 days until patients reached their target dose. This was similar to the schedule used in studies 052 and 053 except in study 081 the maximum target dose was 1800 mg/day instead of 1200 mg/day.

EFFICACY ASSESSMENT

There was no assignment of primary or secondary efficacy endpoints. Key efficacy endpoints included:

- Change from Baseline in IRLS Rating Scale total score at end of Week 1, Week 4 and Week 12 (end of treatment)
- Proportion of subjects responding to treatment where a response is a report of “very much improved” or “much improved” on the investigator-rated CGI-I. Response was assessed at Week 1, Week 4 and Week 12 (end of treatment).
- Change from Baseline in duration of RLS symptoms over 24 hours based upon the 24-hour RLS Record at the end of treatment.

RESULTS

DEMOGRAPHICS

The baseline characteristics for age, race and ethnicity were similar in treatment groups and placebo. There was a female preponderance in all groups except 1200mg cohort where it was nearly evenly distributed between males and females.

Sponsor Table 12 presents demographics for Study XP081-Safety population

Table 12 Summary of Demographic Characteristics (Safety Population: Study XP081)

	Placebo N=41	XP13512 600 mg N=48	XP13512 1200 mg N=45	XP13512 1800 mg N=38	XP13512 2400 mg N=45	Total N=217
Age (years)						
N	41	48	45	38	45	217
Mean (SD)	47.1 (11.16)	47.3 (12.78)	49.8 (11.51)	50.2 (13.79)	45.9 (13.93)	48.0 (12.67)
Range	24.0-77.0	20.0-68.0	18.0-73.0	19.0-72.0	21.0-75.0	18.0-77.0
Gender, n (%)						
N	41	48	45	38	45	217
Female	29 (70.7)	31 (64.6)	23 (51.1)	27 (71.1)	29 (64.4)	139 (64.1)
Male	12 (29.3)	17 (35.4)	22 (48.9)	11 (28.9)	16 (35.6)	78 (35.9)
Race^a, n (%)						
n	41	48	45	38	46	218
White or Caucasian	39 (95.1)	48 (100.0)	44 (97.8)	35 (92.1)	42 (91.3)	208 (95.4)
Black or African-American	1 (2.4)	0	1 (2.2)	2 (5.3)	2 (4.3)	6 (2.8)
American Indian or Alaska Native	1 (2.4)	0	0	0	1 (2.2)	2 (0.9)
Asian	0	0	0	1 (2.6)	1 (2.2)	2 (0.9)
Ethnicity, n (%)						
n	41	48	45	38	45	217
Hispanic/Latino	2 (4.9)	4 (8.3)	2 (4.4)	3 (7.9)	0	11 (5.1)
Not Hispanic/ Latino	39 (95.1)	44 (91.7)	43 (95.6)	35 (92.1)	45 (100.0)	206 (94.9)

Data Source: DStable 6.4

a. Subjects can be categorized to more than one race.

Age: The mean age of patients were similar in the placebo, 600mg and 1200mg groups but the 1200 mg group was slightly older by 2.5 years compared to the placebo and 600 mg groups. The 2400 mg group was younger (by approximately 4 years) compared to the 1200 mg and 1800 mg treatment groups. These differences are unlikely to impact the safety or efficacy results. The 1800 mg and 2400 mg dosages are not being considered for approval in this NDA.

Gender: Similar in all groups with female predominance, **except 1200mg cohort**. Males and females were evenly distributed. The female predominance is consistent with the history of RLS.

Race: Greater than 90% of all subjects in each cohort were Caucasian.

SUMMARY OF RLS HISTORY AT BASELINE:

Table 13 Summary of RLS History (MITT Population: Study XP081)

	Placebo N=41	XP13512 600 mg N=48	XP13512 1200 mg N=45	XP13512 1800 mg N=38	XP13512 2400 mg N=45	Total N=217
Baseline IRLS Rating Scale Total Score						
n	40	47	43	37	44	-
Mean (SD)	22.5 (5.32)	23.9 (5.33)	23.9 (5.49)	23.6 (4.25)	23.3 (5.70)	-
Median (Range)	22.5 (15.0-33.0)	24.0 (15.0-37.0)	23.0 (15.0-39.0)	24.0 (16.0-32.0)	23.0 (15.0-37.0)	-
Duration of RLS symptoms (years)						
N	40	47	43	37	44	211
Mean (SD)	11.0 (13.46)	13.4 (12.31)	16.7 (16.47)	12.2 (11.60)	13.3 (13.78)	13.4 (13.66)
Median (Range)	4.8 (0.1-44.0)	9.9 (0.1-50.4)	10.7 (0.1-63.8)	6.9 (0.1-52.0)	7.2 (0.1-47.8)	7.9 (0.1-63.8)
Number of days RLS symptoms expressed on the 7-Day Subject RLS Record prior to Baseline						
N	40	46	43	37	44	210
Mean (SD)	6.0 (1.05)	5.7 (1.14)	5.9 (1.19)	6.1 (1.03)	6.1 (1.05)	6.0 (1.10)
Median (Range)	6 (4.0-7.0)	6 (4.0-7.0)	6 (3.0-7.0)	6 (4.0-7.0)	7 (4.0-7.0)	6 (3.0-7.0)
RLS Treatment History						
N	40	47	43	37	44	211
No previous treatment	26 (65.0)	34 (72.3)	31 (72.1)	20 (54.1)	27 (61.4)	138 (65.4)
Yes, treatment terminated prior to the month before starting study drug ^a	8 (20.0)	5 (10.6)	2 (4.7)	3 (8.1)	9 (20.5)	27 (12.8)
Yes, treatment within the month of the start of study drug or within the previous month ^a	6 (15.0)	8 (17.0)	10 (23.3)	14 (37.8)	8 (18.2)	46 (21.8)

Data Source: DSTable 6.4 and DSTable 7.1

a. The term "month" refers to a calendar month, as opposed to a 30-day period.

Summary of RLS History is outlined in Sponsor Table 13. The baseline IRLS scores are similar for all groups as is duration of RLS symptoms, and number of days RLS symptoms expressed on 7 day RLS record.

DURATION OF RLS SYMPTOMS: The duration of RLS symptoms is similar in the four treatment groups and placebo, except for 1200mg XP13512 where the mean number of years was 17.

NUMBER OF DAYS RLS SYMPTOMS EXPRESSED ON 7 DAY RECORD:
 Similar at Baseline among all groups.

RLS TREATMENT HISTORY: The 1800mg XP13512 cohort had the least number of treatment naïve subjects; that is a greater number of subjects had been previously treated in the 1800mg cohort. Subjects who have been treated previously for RLS, may be more likely to experience augmentation or rebound. However, these subjects, according to entry criteria, should have been excluded. Therefore, the disproportionate number of treatment naïve subjects in the 1800mg cohort should not affect the outcome of the study.

SUBJECT DISPOSITION STUDY XP081

Table 9 Summary of Subject Disposition (All Subjects: Study XP081)

	Number (%) of Subjects					Total N=217
	Placebo N=41	XP13512 600 mg N=48	XP13512 1200 mg N=45	XP13512 1800 mg N=38	XP13512 2400 mg N=45	
Completion Status						
Completed	31 (75.6)	34 (70.8)	31 (68.9)	30 (78.9)	33 (73.3)	159 (73.3)
Prematurely Withdrawn	10 (24.4)	14 (29.2)	14 (31.1)	8 (21.1)	12 (26.7)	58 (26.7)
Primary Reason for Withdrawal						
Adverse Event	1 (2.4)	4 (8.3)	6 (13.3)	3 (7.9)	5 (11.1)	19 (8.8)
Subject Withdrew Consent	6 (14.6)	5 (10.4)	4 (8.9)	1 (2.6)	0	16 (7.4)
Lost to Follow-up	0	2 (4.2)	3 (6.7)	2 (5.3)	3 (6.7)	10 (4.6)
Protocol Non-Compliance (after randomization)	1 (2.4)	2 (4.2)	1 (2.2)	0	2 (4.4)	6 (2.8)
Termination of Study or Withdrawal of Subject by Sponsor ^a	1 (2.4)	0	0	1 (2.6)	1 (2.2)	3 (1.4)
Treatment Failure	1 (2.4)	1 (2.1)	0	0	0	2 (0.9)
Ineligibility (did not meet entry criteria)	0	0	0	0	1 (2.2)	1 (0.5) ^b
Investigator Judgment ^c	0	0	0	1 (2.6)	0	1 (0.5)

Data Source: DSTable 6.1

Note: Disposition is calculated based on the number of randomized subjects.

- These subjects withdrew at the Sponsor's requests. Subject 146/5024 in the XP13512 1800 mg group had PK sample collection difficulty. Subject 234/5007 in the XP13512 2400 mg group indicated her plan to consume alcohol, and Subject 233/5022 in the placebo group had been off study drug for 8 days prior to her final visit.
- Subject 192/5002 in the XP13512 2400 mg group did not meet Exclusion Criterion 4 (Subjects who had clinically significant or unstable medical conditions [e.g., history of cancer (except adequately treated basal cell carcinoma), cardiovascular disease, hepatic or renal disease, immunocompromised, or psychiatric illness), as the subject had a history of moderate bipolar disorder that was not reported at the time of Screening. When she came in for Visit 9, she reported new medications, and it was then discovered by the study site that she had bipolar disorder.
- Subject 144/5002 in the XP13512 1800 mg group experienced an AE of atrial fibrillation that was considered not study drug related and was withdrawn from the study because of the medical condition.

Approximately 1/3 (n=58) of the patients withdrew prematurely, 48 of those patients were assigned to XP13512. The primary reason patients withdrew from the placebo group was treatment failure 6/10. The primary reason patients withdrew from XP13512 treatment was adverse events. Ten patients withdrew consent in the XP13512 treated groups combined.

REVIEWER COMMENT: The increased rate of withdrawals in study XP081 compared to pivotal studies, XP052 and XP053, appears in part related to increase adverse events. Higher doses are included in study XP081 compared to the pivotal trials, and adverse events appear to be dose related.

TIME AND SCHEDULE OF ASSESSMENTS

Sponsor Table 2 shows the Time and Events Schedule for the study XP081.

Table 2 Time and Events Schedule

Period →	Screening ^a (If Washout is Not Required)	Screening ^a (If Washout is Required)		Double-Blind Treatment										Study Completion	Follow-Up	
		1A	1B	2	N/A	3	4	5	6	7	8	9	10		11	N/A
Visit Number →	1	1A	1B	2	N/A	3	4	5	6	7	8	9	10	11	N/A	
Study Week →	Week -3 to -1	Week -3	Week -1	Week 0	Week 1	Wk 2	Wk 3	Wk 4	Wk 6	Wk 8	Wk 10	Wk 12/ET	Wk 13	Wk 17		
Study Day →	-21 to -7	-21	-7	1	3	8	15	22	29	43	57	71	85	92	119	
Visit Window (Days) →				+2	N/A	+2	±2	±2	±2	±3	±3	±3	±3	±2	N/A	
Obtain Informed Consent	X	X														
Inclusion and Exclusion Criteria	X	X	X	X												
Demography, Medical, RLS, Drug History	X	X	X													
Physical Exam, Neurologic Exam	X		X										X			
Vital Signs Including Orthostatic BP/Pulse	X		X	X ^d		X	X	X	X	X	X	X	X			
Electrocardiogram (ECG)	X		X	X ^e		X			X		X		X			
Clinical Lab Testing Blood/Urine	X		X	X		X	X		X		X		X			
Serum Pregnancy Test-Females	X		X										X			
PK Samples for Gabapentin Level ^f				X		X	X		X ^b		X		X ^b			
IRLS Rating Scale	X		X	X		X	X	X	X	X	X	X	X			
Modified IRLS Scale (Telephone Call)					X											
Post-Sleep Questionnaire (PSQ)				X					X		X		X			
Collect 24-Hour RLS Record				X		X							X			
Profile of Mood State (POMS)				X					X		X		X			
Sudden Onset of Sleep (SOS) Questionnaire				X					X		X		X			
Epworth Sleepiness Scale (ESS)				X					X		X		X			
Continuous Performance Test (CPT)				X					X				X ^c			
Brief Assessment of Cognition (BAC)				X					X				X ^c			
CGI (Investigator & Patient)						X	X		X		X		X			

Continued

Table 2 Time and Events Schedule (Continued)

Period →	Screening ^a (If Washout is Not Required)	Screening ^a (If Washout is Required)		Double-Blind Treatment										Study Completion	Follow-Up	
		1A	1B	2	N/A	3	4	5	6	7	8	9	10		11	N/A
Visit Number →	1	1A	1B	2	N/A	3	4	5	6	7	8	9	10	11	N/A	
Study Week →	Week -3 to -1	Week -3	Week -1	Week 0	Week 1	Wk 2	Wk 3	Wk 4	Wk 6	Wk 8	Wk 10	Wk 12/ET	Wk 13	Wk 17		
Study Day →	-21 to -7	-21	-7	1	3	8	15	22	29	43	57	71	85	92	119	
Visit Window (Days) →				+2	N/A	+2	±2	±2	±2	±3	±3	±3	±3	±2	N/A	
Mood Assessment									X		X		X			
Collect 7-Day RLS Symptom Record				X					X		X		X			
RLS Pain Score				X		X		X	X	X	X	X	X			
Record Adverse Events	X	X	X	X	X	X	X	X	X	X	X	X	X	X		
Record Concomitant Medications	X	X	X	X	X	X	X	X	X	X	X	X	X	X		
Randomization (IVRS)				X												
Study Drug Dispensed				X		X		X	X	X	X	X	X (Taper)			
Study Drug Accountability						X	X	X	X	X	X	X	X	X		
Exit Study													X			
End of Study Follow-Up Call														X		

Data Source: Attachment 1 (Protocol XP081)

- Subjects requiring the 14-day washout completed 2 Screening visits (1A & 1B). Subjects that did not require the 14-day washout completed all Screening procedures at Visit 1 and returned in 7 days for Visit 2.
 - PK samples were collected with the clinical lab tests. PK profiles were collected at Visits 6 and 10: 0 (pre-dose), 0.5, 1, 2, 3, 4, 5, 6, 8, 10, 12, 16, 20, and 24 hours post dose.
 - Adverse events were assessed beginning with the signing of the Informed Consent Form and continued through the Follow-up Visit.
 - Blood pressure and pulse for orthostasis were taken 3 times in succession (for averaging this Baseline assessment).
 - Three ECGs were recorded, one immediately after the other at Visit 2.
 - BAC and CPT were done 2 times during Visit 10: (1) in the evening prior to going to sleep and (2) the next afternoon prior to the last PK blood draw.
- BP=Blood pressure; CGI=Clinical Global Impression; ET=Early termination; IRLS=International Restless Legs Syndrome; N/A=Not applicable; Wk=Week.

MAINTENANCE OF EFFICACY

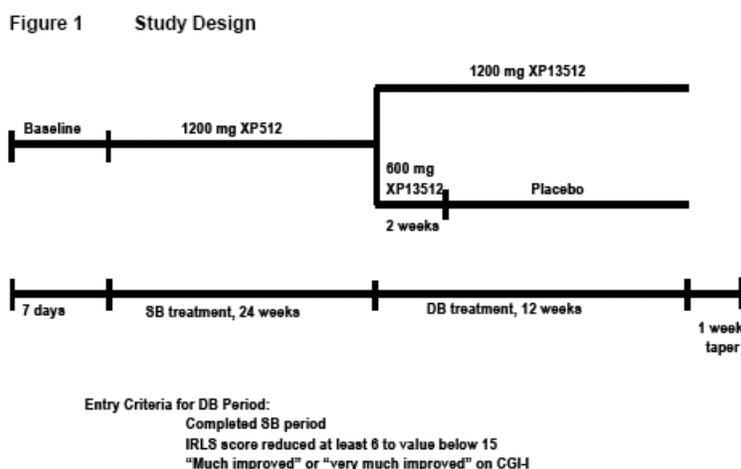
PROTOCOL XP060 (RXP111461): A Long-Term Study of XP13512 (GSK1838262) Versus Placebo Treatment Assessing Maintenance and Efficacy in Patients with Restless Leg Syndrome

PHASE III

Indication: Moderate to severe Restless Leg Syndrome

The study was initiated on April 18, 2006 and completed on November 14, 2007. XP060 was a multicenter study conducted at 27 centers (26 centers enrolled) in the United States.

Study Design Study XP060



The goal of this study was to show maintenance of efficacy. All subjects had a 7-day Screening/Baseline assessment period before enrolling into the single blind open label treatment period. All subjects took one tablet 600mg SR XP13512 on Days 1 to 3, and then two tablets 600mg SR XP13512 on Days 4 to Week 24. Subjects who completed the initial single blind period and met responder criteria were then randomized to receive either XP13512 1200mg or placebo during the 12-week double blind placebo controlled treatment period.

Responder Criteria were as follows:

1. Total IRLS Rating Scale score decreased by 6 or more points relative to baseline score
2. Total IRLS score decrease to less than 15
3. Had an assessment of "much improved" or "very much improved" on investigator rated CGI-I.

4. Were stable on 1200mg XP13512 dose for at least the month prior to entry into Double Blind treatment period
5. Successfully completed the entire 24-week single blind treatment period.

Subjects enrolled into the Double Blind treatment period were randomized 1:1 to receive 1200mg XP13512 or placebo. At the end of the 12 week double blind treatment period all subjects were tapered off study drug.

ENTRY CRITERIA

Entry criteria for **single blind** treatment period:

Key Inclusion/Exclusion Criteria.

All inclusion and exclusion criteria had to be met in order to be enrolled in the trial.

Inclusion criteria included:

1. Men or women greater than or equal to 18 years of age, diagnosed with restless leg syndrome based on IRLSSG Diagnostic criteria.
2. Subjects must have history of RLS symptoms for at least 15 nights in the month prior to starting study or current treatment.
3. The RLS symptoms must be documented for at least 4 of 7 consecutive evenings during Baseline study period.
4. RLS severity score of 15 or greater on IRLS Rating Scale at Visit 1 and 2
5. Current treatment with dopamine agonists and/or gabapentin must be discontinued at least two weeks prior to Baseline
6. Discontinuation of other treatments for RLS (e.g. opioids, benzodiazepines) at least 2 weeks prior to baseline
7. Females of child bearing potential must agree to clinically acceptable birth control
8. Body Mass Index at or below 34
9. Estimated creatinine clearance of ≥ 60 mL/min

Exclusion criteria included:

1. sleep disorder that may affect assessment of RLS
2. history of augmentation or end of dose rebound with previous dopamine-agonist treatment.
3. Other neurologic disease or movement disorder
4. Other medical conditions (poorly controlled diabetes mellitus, iron deficiency anemia) or drug therapy (sedative/hypnotics) that could affect RLS treatment efficacy assessments.

5. At the investigators clinical discretion, clinically significant abnormal screening ECG or laboratories
6. Serum ferritin level below 20ng/mL
7. Subjects with moderate or severe depression by DSM-IV
8. Subjects with history of substance abuse or dependence within 12 months prior to enrollment
9. Subjects previously enrolled in another study with XP13512.

Entry criteria for double blind treatment period as described for **Responder Criteria**, above.

EFFICACY ASSESSMENT

Primary Efficacy Endpoint

- Proportion of RLS subjects who relapsed , defined as worsening of RLS symptoms or withdrawal due to lack of efficacy during the 12-week double blind treatment period.

Key Secondary Efficacy Endpoints -Double Blind period

- Time to relapse in RLS symptoms or withdrawal due to lack of efficacy during the 12-week DB treatment period
- Response to treatment using investigator-rated CGI-I where response is defined as “much improved” or “very much improved” at the end of DB treatment period.
- Time to onset of first RLS symptom using the 24 hour RLS Record.

DEMOGRAPHICS

Sponsor Table 10 outlines the demographics for the single blind treatment period as well as the double blind treatment period.

**Table 10 Summary of Demographic Characteristics
 (ITT Populations: Study XP060)**

	SB-ITT Population	DB- ITT Population		
	N=311	Placebo N=97	XP13512 N=96	Total N=193
Age (years)				
Mean (SD)	50.3 (12.16)	52.2 (12.13)	50.7 (11.68)	51.5 (11.90)
Range	19 – 82	23 – 82	19 – 73	19 – 82
Sex, n (%)				
Female	179 (57.6)	52 (53.6)	62 (64.6)	114 (59.1)
Male	132 (42.4)	45 (46.4)	34 (35.4)	79 (40.9)
Race, n (%)				
White or Caucasian	292 (93.9)	91 (93.8)	93 (96.9)	184 (95.3)
Black or African-American	15 (4.8)	5 (5.2)	2 (2.1)	7 (3.6)
American Indian or Alaska Native	1 (0.3)	0	0	0
Other	3 (1.0)	1 (1.0)	1 (1.0)	2 (1.0)
Ethnicity, n (%)				
Hispanic/Latino	15 (4.8)	5 (5.2)	6 (6.3)	11 (5.7)
Not Hispanic/Latino	296 (95.2)	92 (94.8)	90 (93.8)	182 (94.3)

Data Source: DS Table 6.6

AGE, GENDER and RACE are similar between groups except for greater proportion of female subjects on active drug, XP13512, in double blind treatment period compared to placebo (64.6% versus 53.6% respectively).

RLS TREATMENT HISTORY

Sponsor Table 11 outlines the duration of RLS symptoms, number of days RLS symptoms expressed on 7 Day Record and RLS Treatment History for single blind and double blind treatment periods.

Table 11 Summary of RLS History (ITT Populations: Study XP060)

	SB-ITT Population	DB-ITT Population		
	N=311	Placebo N=97	XP13512 N=96	Total N=193
Duration of RLS symptoms (years)				
n	310	97	96	193
Mean (SD)	13.3 (13.67)	15.7 (15.33)	12.3 (12.74)	14.0 (14.17)
Median (Range)	7.5 (0.2 – 61.2)	10.4 (0.2 – 61.2)	7.1 (0.6 – 48.2)	8.7 (0.2 – 61.2)
Number of days RLS symptoms expressed on the 7-Day Subject RLS Record prior to Baseline				
n	302	93	91	184
Mean (SD)	6.1 (0.99)	6.1 (1.07)	6.2 (0.97)	6.1 (1.02)
Median (Range)	6 (4 – 7)	6 (4 – 7)	7 (4 – 7)	6 (4 – 7)
RLS Treatment History, n (%)				
n	310	97	95	192
No Previous Treatment	194 (62.6)	60 (61.9)	61 (64.2)	121 (63.0)
Yes, treatment terminated prior to the month before starting investigational drug ^a	38 (12.3)	14 (14.4)	7 (7.4)	21 (10.9)
Yes, treatment within the month of start of study drug or within the previous month ^a	78 (25.2)	23 (23.7)	27 (28.4)	50 (26.0)

Data Source: DS Table 6.6

a. The term "month" refers to a calendar month, as opposed to a 30-day period.

Duration of RLS symptoms, number of days RLS symptoms expressed on 7 Day Record and RLS Treatment History is similar between single blind and double blind treatment period. In addition, these characteristics are similar between placebo and drug in double blind treatment period.

SUBJECT DISPOSITION

During the SB treatment period, 133 subjects did not meet responder criteria and therefore were not randomized. Of the 133 subjects, 42 (31.6%) withdrew for an adverse event and another 27 withdrew consent for reasons not explained in greater detail. During the DB treatment period, none of the subjects in the XP13512 group withdrew for adverse events. 10 subjects in the DB period withdrew for "lack of efficacy", 6 in the placebo group and 4 in the XP13512 group. There was also one death due to asphyxiation in the DB period. Sponsor Table 9.

Table 9 Summary of Subject Disposition (All Subjects: Study XP060)

	Number (%) of Subjects			
	Placebo ^a N=98	XP13512 ^a N=96	Not Randomized ^b N=133	Total ^c N=327
SB Treatment Period-Completion Status				
Completed	98 (100.0)	96 (100.0)	27 (20.3)	221 (67.6)
Responders	98 (100.0)	96 (100.0)	0	194 (59.3)
Non-Responders	0	0	27 (20.3)	27 (8.3)
Prematurely Withdrawn	-	-	-	106 (32.4)
Primary Reason for Withdrawal^d	-	-	-	-
AE	-	-	42 (31.6)	42 (12.8)
Subject Withdrew Consent	-	-	27 (20.3)	27 (8.3)
Protocol Non-Compliance	-	-	8 (6.0)	8 (2.4)
Lost to Follow-up	-	-	12 (9.0)	12 (3.7)
Lack of Efficacy	-	-	13 (9.8)	13 (4.0)
Other	-	-	3 (2.3)	3 (0.9)
Death	-	-	1 (0.8)	1 (0.3)
DB Treatment Period-Completion Status^e				
Entered DB Treatment Period	98	96	-	194
Completed^f	84 (85.7)	84 (87.5)	-	168 (86.6)
Prematurely Withdrawn	14 (14.3)	12 (12.5)	-	26 (13.4)
Primary Reason for Withdrawal^g	-	-	-	-
AE ^f	3 (3.1)	0	-	3 (1.5)
Subject Withdrew Consent	2 (2.0)	4 (4.2)	-	6 (3.1)
Protocol Non-Compliance	1 (1.0)	2 (2.1)	-	3 (1.5)
Lost to Follow-up	1 (1.0)	2 (2.1)	-	3 (1.5)
Lack of Efficacy	6 (6.1)	4 (4.2)	-	10 (5.2)
Other	1 (1.0)	0	-	1 (0.5)

Data Source: DS Table 6.1

- The percent is with respect to the number of subjects randomized to each treatment group.
- The percent is with respect to the number of subjects not randomized (N=133).
- The percent is with respect to the number of subjects enrolled (N=327).
- The listed reasons for early termination are non-responder criteria-related and have non-zero counts for at least 1 treatment group.
- Includes 1 subject randomized to the 1200 mg XP13512 group who terminated during the taper period at the end of the DB period.
- Three subjects randomized to placebo withdrew due to an AE during the DB treatment period; however, 1 of these subjects withdrew due to an AE with onset during the SB treatment period (AE was not treatment-emergent during the DB period).
- The percent is with respect to the number of subjects randomized to placebo (N=98), XP13512 (N=96), or the total (N=194) number of subjects in the DB treatment period.

The subject disposition by site is summarized in DS Table 6.3 and the subject disposition by pooled site is summarized in DS Table 6.2.

SAFETY ASSESSMENTS

The same safety endpoints were used in study XP060 as were used in the pivotal trials (XP052 and XP053).

TIME AND SCHEDULE OF ASSESSMENTS

Time and Events Schedule

Table 1 Time and Events Schedule

Period →	Screen	Treatment																			Taper	Follow Up
Visit Number →	1	2	3	4	5	6	7	8	9	10	11	12	13	14	15	16	17	18	19	20		
Study Week →	-1	0	1	4	6	8	10	12	14	16	18	20	22	24	26	28	30	32	34	36/ET	37	41
Visit Window (Days)		+1	+1	±1	±1	±1	±2	±2	±2	±2	±2	±2	±2	±2	±2	±2	±2	±2	±2	±2		±3
RLS Diagnostic Criteria, Consent	X																					
Inclusion and Exclusion Criteria	X	X																				
Demography, Medical, RLS and Drug History	X																					
Physical Exam, Neurologic Exam	X							X						X								X
Vital Signs	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
Electrocardiogram (ECG)	X	X ^a	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
Clinical Lab Testing Blood/Urine	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
Pregnancy Test	X																					X
Gabapentin Level		X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
RLS Scale	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
Post-Sleep Questionnaire (PSQ)		X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
Medical Outcomes Scale (MOS) Sleep Scale		X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
RLS Quality of Life (QoL) Questionnaire		X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
Epworth Sleepiness Scale (ESS)		X						X						X								X
Sudden Onset of Sleep Questionnaire (SOS)		X						X						X								X
Study Coordinator Call 2 Days Before Visit ^b		X		X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
Collect 7-Day RLS Symptom Record		X																				
Collect 24-Hour RLS Record		X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
Record Adverse Events		X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
Record Concomitant Medications	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
IVRS Call		X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
Study Drug Dispensed		X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X ^c
Study Drug Accountability			X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X

Table 1 Time and Events Schedule (Continued)

Period →	Screen	Treatment																			Taper	Follow Up
Visit Number →	1	2	3	4	5	6	7	8	9	10	11	12	13	14	15	16	17	18	19	20		
Study Week →	-1	0	1	4	6	8	10	12	14	16	18	20	22	24	26	28	30	32	34	36/ET	37	41
Visit Window (Days)		+1	+1	±1	±1	±1	±2	±2	±2	±2	±2	±2	±2	±2	±2	±2	±2	±2	±2	±2		±3
Investigator & Patient Clinical Global Impression of Improvement or Change (CGI-I or CGI-C)				X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	
Exit Study														X ^c								X
Study Drug Taper														X ^c								X ^c
End of Study Follow Up Call														X ^c								X

- The Study Coordinator contacted the subject 2 days before visit to remind them of their visit and to complete the 24-Hour RLS Record (Appendix F), which covered the 24-hour time period starting at 8 AM the day before their visit and ending at 8 AM the day of their visit. The Study Coordinator also reminded the subject to bring their diary and all drug supplies and empty bottles to each visit.
 - Seven study drug tablets were re-dispensed.
 - Subjects who met the responder criteria continued in the study through Week 41 or ET. Subjects who did not meet the RLS responder criteria at the end of the SB treatment period tapered for 7 days and exited from the study. Follow-up call to subject occurred 4 weeks after last dose.
 - Three ECGs were recorded 1 immediately after the other at Visit 2 (Week 0).
- ET= Early termination, RLS= Restless Legs Syndrome, ECG= Electrocardiogram, PSQ= Post-Sleep Questionnaire, MOS= Medical Outcomes Scale, QoL= Quality of Life, ESS= Epworth Sleepiness Scale, SOS= Sudden Onset of Sleep Questionnaire, IVRS= Interactive Voice Response System, CGI-I= Clinical Global Impression-Improvement, CGI-C= Clinical Global Impression-Change; SB= Single-blind.

OPEN-LABEL EXTENSION

PROTOCOL XP055(RXP111490) An Open-Label, 52-Week Extension Study assessing XP13512 Safety and Efficacy in Patients with Restless Leg Syndrome

PHASE III

Time table of submission and data cut-off dates

- The study was initiated on June 5, 2006.
- The initial report for all enrolled subjects had a cut off date of December 7, 2007.
- An Interim Report was filed to the NDA application with a cut off date of July 31, 2008.
- A paper submission of the final study report was received by the Agency on December 22, 2009.

The study was conducted at 67 centers in the United States.

STUDY DESIGN:

This is a multicenter study which includes investigators who enrolled subjects in the 12 week placebo-controlled Studies XP052, XP053, and XP081, as well as the 2 week simulated driving Study XP083. Study XP055 was an open label study.

DOSE:

- Subjects entering the study took one 600mg XP13512 Sustained Release (SR) a day for 3 days.
- The dose was increased to maintenance dose 1200mg a day as tolerated
- The dose was able to be increased to a maintenance dose of 1800mg if needed.
- If the dose is not tolerated the dose may be reduced to the next lowest dose level.

EFFICACY ASSESSMENT

Key Efficacy endpoints:

- IRLS Rating Scale score at the end of treatment
- IRLS Rating Scale score at each study visit
- Patient-rated CGI-I at the end of treatment
- Investigator-rated CGI-I at the end of treatment
- Time to onset of RLS symptoms from the 24 hour RLS Record at the 6 and 12 month follow-up visits

RESULTS:

DEMOGRAPHICS

Table 5 Summary of Demographic Characteristics (Safety Population: Study XP055)

	Total N=572
Age (years)	
Mean (SD)	50.2 (11.90)
Range	19.0-79.0
Sex, n (%)	
Female	336 (58.7)
Male	236 (41.3)
Race, n (%)	
White or Caucasian	551 (96.3)
Black or African-American	7 (1.2)
American Indian or Alaskan Native	6 (1.0)
Asian	4 (0.7)
Native Hawaiian or Other Pacific Islander	1 (0.2)
Other	3 (0.5)
Ethnicity, n (%)	
Hispanic/Latino	36 (6.3)
Not Hispanic/Latino	536 (93.7)

Data Source: DSTable 6.2

A majority (range: 54.8% to 77.5%) of subjects from each of the parent studies entered to

REVIEWER COMMENT: The age, gender and racial distribution are similar to pivotal efficacy trials.

TREATMENT DOSE OF SUBJECTS PRIOR TO ENROLLMENT IN STUDY XP055

DOSING PRIOR TO ENTERING XP055

Table 6 Summary of Dosing in Parent Studies (Safety Population: Study XP055)

	Number (%) of Subjects
	XP13512 N=572
Prior Randomized Dose^a	
Placebo/DPH 50 mg	18 (3.1)
Placebo	179 (31.3)
600 mg	107 (18.7)
1200 mg	199 (34.8)
1800 mg	42 (7.3)
2400 mg	27 (4.7)
Prior Last Dose^b	
Naive ^c	197 (34.4)
0 mg ^d	69 (12.1)
600 mg	146 (25.5)
1200 mg	160 (28.0)

Data Source: DSTable 6.2

- A subject's prior randomized dose is the subject's randomized dose (treatment group) of XP13512 in the parent study. This may not have been the actual dose taken by the subject in the parent study based on dose adjustments.
- A subject's prior last dose is the subject's last dose prior to entering XP055.
- If a subject was randomized to placebo or placebo/DPH in the parent study, he/she was designated as "naive."
- The prior last dose for XP13512-treated subjects was designated as "0 mg" if subjects experienced a gap in treatment.

REVIEWER COMMENT: The majority of subjects randomized to study XP055 were previously randomized to 1200mg cohort in parent studies (34.8%). However, when looking at prior last dose (prior to enrollment) in trial XP055, there are nearly equally percentages of subjects who were taking 600mg and 1200mg. That is, although subjects may have been assigned to 1200mg cohort in parent study, a number of them decreased their maintenance dose to 600mg. This suggests that 600mg may be better tolerated.

Sponsor Table 12 shows the proportion of subjects who experienced dose changes, specifically those subjects who reached maintenance dose of 1200mg before adjusting dose. This table excludes subjects who did not reach a maintenance dose of 600mg.

Table 12 Proportion of Subjects on XP13512 Experiencing Dose Changes (Safety Population: Study XP055)

	Number (%) of Subjects	
	XP13512 N=572	
Number of Dose Changes Overall^a		
N	572	
0	31 (5.4) ^b	
1	236 (41.3)	
2	188 (32.9)	
3	53 (9.3)	
>3	64 (11.2)	
Dose Changes Starting from 1200 mg^c		
N	539	
Maintained 1200 mg	236 (43.8)	
Increased to 1800 mg and Maintained	135 (25.0)	
Decreased to 600 mg and Maintained	51 (9.5)	
Fluctuated ^d	117 (21.7)	

Data Source: DSTable 8.2 and DSTable 9.1

- a. Includes up-titration counted from Day 1 onward. Does not include study-end taper.
- b. Excludes Subject 202/2003 with a maximum dose of 600 mg who had more than one dose change between 0 and 600 mg.
- c. Excludes those subjects who never took the maintenance dose of 1200 mg and includes subjects who reached the maintenance dose of 1200 mg with one dose change and with more than one dose change (Subjects 108/3011, 120/7019, 217/3002, and 230/7004).
- d. Fluctuated means more than one dose change after reaching the maintenance dose of 1200 mg.

REVIEWER COMMENT: The sponsor presents dose adjustment from maintenance dose of 1200mg. However, this does not accurately represent the proportion of subjects who were not able to attain a maintenance dose of 1200mg, i.e. the number that were maintained on 600mg/day.

SUBJECT DISPOSITION BY PARENT STUDY

Table 2 Summary of Subject Disposition (All Subjects: Study XP055)

	Number (%) of Subjects from Each Parent Study				
	XP052 N=152	XP053 N=233	XP081 N=120	XP083 N=76	Total N=581
Safety Population ^a	151 (99.3)	230 (98.7)	115 (95.8)	76 (100.0)	572 (98.5)
Completion Status					
Completed	86 (56.6)	1 (0.4)	0	0	87 (15.0)
Ongoing	19 (12.5)	178 (76.4)	89 (74.2)	59 (77.6)	345 (59.4)
Prematurely Withdrawn	46 (30.3)	51 (21.9)	26 (21.7)	17 (22.4)	140 (24.1)
Primary Reason for Withdrawal					
Adverse Event ^b	21 (13.8)	26 (11.2)	5 (4.2)	5 (6.6)	57 (9.8)
Subject Withdrew Consent	12 (7.9)	14 (6.0)	9 (7.5)	5 (6.6)	40 (6.9)
Lost to Follow-up	8 (5.3)	10 (4.3)	8 (6.7)	4 (5.3)	30 (5.2)
Treatment Failure	1 (0.7)	0	3 (2.5)	2 (2.6)	6 (1.0)
Protocol Noncompliance	2 (1.3)	0	1 (0.8)	1 (1.3)	4 (0.7)
Investigator Judgment	1 (0.7)	1 (0.4)	0	0	2 (0.3)
Termination of Study or Withdrawal of Subject by Sponsor ^c	1 (0.7)	0	0	0	1 (0.2)

Data Source: DSTable 6.1

- a. Safety Population: all subjects who were enrolled in the study and took at least 1 dose (or any portion of a dose) of study medication.
- b. Includes both treatment-emergent and non-treatment-emergent AEs.
- c. Subject 191/2005 withdrew at the sponsor's request because the subject was moving out of state and could no longer complete the remaining XP055 study visits and other study-related procedures.

6 Review of Efficacy

Efficacy Summary

Gabapentin enacarbil, a pro-drug of gabapentin, has been studied for Restless Leg Syndrome (RLS) as well as neuropathic pain, post herpetic neuralgia and migraine. However, this review focuses only on moderate to severe, idiopathic RLS, the proposed indication for the drug in this application. There have been several trials in the US as well as outside of US (mainly Japan through Astellas Pharmaceuticals).

Study #	phase	objectives	duration	gabapentin dose (mg)	n
Principal efficacy studies: double-blind, randomized, placebo-controlled, parallel group					
52	3	efficacy & safety	12 weeks	1200	112
				placebo	106
53	3	maintenacne of efficacy & safety	12 weeks	1200	111
				600	114
				placebo	96
Randomized treatment withdrawal					
60	3	efficacy & safety	36 weeks	1200	311
				1200	97
				placebo	96
Supportive, double-blind, randomized, placebo-controlled, parallel group					
45	2	efficacy & safety	14 days	600	29
				1200	32
				placebo	33
81	2	efficacy & safety; dose response	12 weeks	600	47
				1200	43
				1800	37
				2400	44
				placebo	40
63	2	driving performance, cognition; efficacy & safety	14 days	1200	28
				1800	33
				placebo	33
				placebo + diphenhydramine	28
Supportive, double-blind, randomized, placebo-controlled, crossover					
21	2	efficacy & safety	14 days	1800 → placebo	34
				placebo → 1800	

In this section of the review, the efficacy results of the two pivotal trials (XP052 and XP053), the supportive, dose response trial, XP081, the maintenance of efficacy trial XP060 will be discussed. Efficacy results from the open label extension trial, XP055, will be briefly presented as well.

Please refer to section 5.3 of the Review for detail summary of individual trial design.

6.1.1 Analysis of Primary Endpoint(s)

The pivotal trials had co-primary endpoints:

1. change from baseline to the end of the treatment (Week 12) in IRLS Rating Scale Score
2. proportion of subjects at the end of treatment (Week 12) who were “much improved” or “very much improved” on the investigator rated CGI

XP053

In the table below the primary endpoint of change in IRLS score between baseline and end of study was significantly different from placebo for 1200mg cohort ($p < 0.0015$) as well as 600mg cohort ($p < 0.0001$).

Summary Statistics for the Change in IRLS Rating Scale Total Score from Baseline to Week 12 (XP13512 1200mg, 600mg vs. PBO) using LOCF (MITT Population: Study XP053)

	Placebo N=96	XP13512 1200mg N=111	Mean Treatment Difference 1200mg vs.PBO	Adjusted Analysis LS Mean Difference 1200mg vs. PBO	XP13512 600mg N=114	Mean Treatment Difference 600mg vs. PBO	Adjusted Analysis LS Mean Difference 600mg vs. PBO
	Mean (SD)	Mean (SD)			Mean (SD)		
Baseline	23.8 (4.58)	23.2 (5.32)			23.1 (4.93)		
Week 12	14.0 (7.87)	10.2 (8.03)			9.3 (7.77)		
Change from baseline to end of Wk 12	-9.8 (7.69)	-13.0 (9.12)	-3.1 (-5.4, -0.8)	-3.5 (-5.6, -1.3) p<0.0015	-13.8 (8.09)	-4.0 (-6.1, -1.8)	-4.3 (-6.4, -2.3) p<0.0001

Summary Statistics for Change in IRLS Rating Scale Total Score from Baseline by Visit

The change in IRLS score from baseline, compared to placebo is presented for each dose cohort for each visit for study XP053. (Courtesy Statistical Review)

Table 6 Change from Baseline in IRLS Total Score – XP053 (Source: Reviewer’s Analysis)

	Change from IRLS Total Score – XP053									
	Base-Line	Visit3 Week1	Visit4 Week2	Visit5 Week3	Visit6 Week4	Visit7 Week6	Visit8 Week8	Visit9 Wk10	Visit10 Wk12	Visit10 LOCF
Placebo										
N	96	88	91	87	84	83	81	74	74	96
Mean	23.81	-6.51	-7.80	-7.17	-8.62	-8.99	-8.09	-9.19	-10.97	-9.84
SD	(4.58)	(5.53)	(6.38)	(7.07)	(5.80)	(7.16)	(6.75)	(7.68)	(7.72)	(7.69)
600 mg										
N	114	110	110	105	104	102	102	103	101	114
Mean	23.11	-10.13	-11.13	-10.80	-11.44	-12.92	-12.64	-13.83	-14.17	-13.82
SD	(4.93)	(7.67)	(7.63)	(8.23)	(7.86)	(7.65)	(8.32)	(8.07)	(8.11)	(8.09)
p-value		<.0001	.0002	.0002	.0018	.0001	<.0001	<.0001	.0015	<.0001
1200 mg										
N	111	105	102	103	101	97	95	97	93	111
Mean	23.18	-9.25	-11.76	-12.36	-13.00	-12.69	-12.87	-13.02	-14.24	-12.95
SD	(5.32)	(8.03)	(8.78)	(8.99)	(9.22)	(9.85)	(8.50)	(9.49)	(8.74)	(9.12)
p-value		.0019	<.0001	<.0001	<.0001	.0012	<.0001	.0019	.0048	.0017

REVIEWER COMMENT: In an earlier trial, XP045 the results show a significant improvement in IRLS score compared to Baseline at week 2, in the 1200mg cohort. The sponsor based their decision to select the 1200mg dose of XP13512 as the recommended dose for the treatment of RLS on the results of the 045 trial. However, in trial 053 the treatment effect at 600mg is similar to 1200mg at week 1 through Week 12 (end of study). The results indicate there is no reason to suspect that the 1200 mg dose provided an add benefit compared to the 600 mg dose.

Summary Statistics for CGI-I Responders at Week 12

Similarly significant results were obtained for change in proportion of responders on CGI from baseline to end of study, for the comparison between 1200mg and placebo (p<0.0001) and 600mg and placebo (p<0.0001).

CGI-I Scale Responders at Week 12 (XP13512 1200mg, 600mg vs. PBO) using LOCF (MITT Population: Study XP053)

	Placebo N=96	XP13512 1200mg N=111	XP13512 600mg N=114
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N	96	111	114
Total Responders N(%)	43 (44.8)	86 (77.5)	83 (72.8)
Odds Ratio (CI)		4.287 (2.388, 7.861)	3.322 (1.841,5.992)
P value		< 0.0001	< 0.0001

Summary Statistics for Responders in CGI-I by visit

The proportion of responders on CGI compared to placebo, is presented by study visit for both the 600mg and 1200mg cohorts. With the exception of week 4, both XP13512 cohorts are significantly improved throughout the study (at the end of week 4 only, 600mg cohort does not meet statistical significance). (Courtesy Statistical Review)

Table 7 Responder Rate at Each Visit - XP053 (Source: Reviewer’s Analysis)

	CGI – XP053					
	Visit 3 Week 1	Visit 4 Week 2	Visit 6 Week 4	Visit 8 Week 8	Visit 10 Week 12	Visit10 LOCF
Placebo						
N	89	95	95	96	96	96
# (%) Responders	26 (29.21%)	36 (37.78%)	43 (45.26%)	41 (42.71%)	43 (44.79%)	43 (44.79%)
XP13512 600 mg						
N	108	112	113	114	114	114
# (%) Responders	54 (50%)	74 (66.07%)	71 (62.83%)	78 (68.42%)	83 (72.81%)	83 (72.81%)
p-value	.0030	<.0001	.0133	.0003	<.0001	<.0001
XP13512 1200 mg						
N	106	110	111	111	111	111
# (%) Responders	59 (55.66%)	74 (67.27%)	78 (70.27%)	77 (69.37%)	86 (77.48%)	86 (77.48%)
p-value	.0002	<.0001	.0004	.0001	<.0001	<.0001

Clinical Trial XP052

Summary Statistics for the Change in IRLS Rating Scale Total Score from Baseline to Week 12 (XP13512 1200mg vs. PBO) using LOCF (MITT Population: Study XP052)

Sponsor Table 13 shows the summary statistics for change in IRLS score from Baseline to Week 12 for placebo and 1200mg XP13512.

Table 13 Summary Statistics for the Change in IRLS Rating Scale Total Score from Baseline at Week 12 using LOCF (MITT Population: Study XP052)

	Placebo N=108	XP13512 1200 mg N=112	Mean Difference (XP13512- Placebo)	95% CI
	Mean (SD)	Mean (SD)		
Baseline	22.6 (4.91)	23.1 (4.86)		
Week 12	13.8 (7.47)	9.8 (8.70)		
Change from Baseline to End of Week 12	-8.8 (8.63)	-13.2 (9.21)	-4.5	-6.9, -2.1

Data Source: DSTable 4.1

As noted in previous trials as well as pivotal trial XP053, there is a significant improvement in IRLS Rating score from baseline to week 12 compared to placebo. Sponsor table 14.

Table 14 Adjusted Analysis of Change from Baseline in IRLS Rating Scale Total Score at Week 12 using LOCF (MITT Population: Study XP052)

Population	LS-Mean Difference (XP13512- Placebo)	95% CI for Treatment Difference	P-Value
Change from Baseline to End of Week 12	-4.0	-6.2, -1.9	0.0003

Data Source: DSTable 4.1

Least Square-Mean (LS-mean); CI (95% confidence interval) and P-value (p-value for the treatment difference) come from an analysis of covariance, adjusted for pooled site and Baseline score.

Summary Statistics for Change in IRLS Rating Scale Total Score from Baseline by Visit

Change in IRLS score from Baseline visit to visit is presented in Table 2. As seen in study XP053, there is an improvement in IRLS score as early as week1, which is maintained throughout the study. (Courtesy Statistical Review)

Table 2 Change from Baseline in IRLS Total Score - XP052 (Source: Reviewer's Analysis)

	Change from IRLS Total Score									
	Base-Line	Visit3 Week1	Visit4 Week2	Visit5 Week3	Visit6 Week4	Visit7 Week6	Visit8 Week8	Visit9 Wk10	Visit10 Wk12	Visit10 LOCF
Placebo										
N	108	104	103	102	99	97	93	92	90	108
Mean	22.57	-4.61	-6.53	-7.15	-7.49	-8.00	-8.59	-9.33	-9.39	-8.75
SD	(4.91)	(7.30)	(6.64)	(7.19)	(7.97)	(7.38)	(7.62)	(8.50)	(8.10)	(8.63)
XP13512										
N	112	107	107	104	101	102	102	96	98	112
Mean	23.07	-11.19	-11.86	-12.25	-13.87	-12.91	-13.67	-14.75	-13.76	-13.23
SD	(4.86)	(7.84)	(8.14)	(8.59)	(7.94)	(8.78)	(7.49)	(8.50)	(8.67)	(9.21)
p-value		<.0001	<.0001	<.0001	<.0001	<.0001	<.0001	<.0001	.0001	.0003

Summary Statistics for CGI-I Responders at Week 12

Sponsor Table 15 shows the CGI-I scale responders at week 12 for placebo versus 1200mg XP13512 in trial XP052.

Table 15 CGI-I Scale Responders at Week 12 using LOCF (MITT Population: Study XP052)

	Number (%) of Subjects		Odds ratio	95% CI	p-value
	Placebo N=108	XP13512 1200 mg N=112			
n	108	109			
Very much improved	20 (18.5)	55 (50.5)			
Much improved	22 (20.4)	28 (25.7)			
Minimally improved	21 (19.4)	10 (9.2)			
No change	39 (36.1)	15 (13.8)			
Minimally worse	6 (5.6)	0			
Much worse	0	1 (<1)			
Very much worse	0	0			
Total Responders	42 (38.9%)	83(76.1%)	5.1	2.8, 9.2	<0.0001

Data Source: DSTable 5.1 and DSTable 5.2
 Note: Odds ratio (odds of improvement, relative to placebo); 95% confidence interval and p-value (p-value for the treatment difference) come from a logistic regression model with effects for treatment and for pooled site.

The proportion of responders on CGI-I at week 12 is statistically significant favoring XP13512 1200mg compared to placebo.

Summary Statistics for Responders in CGI-I by visit

A visit by visit analysis for proportion of responders on CGI-I was also collected. Similarly to study XP053, there was improvement in the 1200mg XP13512 cohort compared to placebo starting at week 1 and continuing throughout the study.

Study XP052 CGI-I Responders by Visit (Courtesy Statistical Review)

	CGI – XP052					
	Visit 3 Week 1	Visit 4 Week 2	Visit 6 Week 4	Visit 8 Week 8	Visit10 Week 12	Visit10 LOCF
Placebo						
N	105	103	99	93	90	108
# (%) Responders	26 (24.76%)	33 (32.04%)	43 (43.43%)	43 (46.24%)	39 (43.33%)	42 (38.89%)
XP13512 1200 mg						
N	107	106	100	102	95	109
# (%) Responders	62 (57.94%)	74 (69.81%)	78 (78.00%)	82 (80.39%)	75 (78.95%)	83 (76.15%)
p-value	<.0001	<.0001	<.0001	<.0001	<.0001	<.0001

6.1.2 Analysis of Secondary Endpoints(s)

Key Secondary Efficacy Endpoints

Maximum RLS Severity as recorded by 24-hour RLS Record.- XP053

A 24-hour RLS symptom record was kept by subjects during the study. The Record recorded time and severity of RLS symptoms every 30 minutes for 24-hour period beginning at 8AM the day before the subject returned to the clinic for Visit 2 (Baseline) and Week 12. The data was captured by the patient filling in the 24-hour RLS Record. Maximum RLS severity and time to onset of first RLS symptom was obtained from the 24-hour RLS Record.

Sponsor Table 44 shows the number (percentage) of subjects with no RLS symptoms by 4 hour epochs at Baseline and at End of Week 12 (end of study). The data are obtained from 24 hour RLS diaries and is recorded by the subject from 8am to 8am the following day. All subjects were instructed to take study medication at 5pm.

(Source: Sponsor)

Table 44 Subjects Reporting No RLS Symptoms by 4-Hour Period at Baseline and at the End of Week 12 (MITT Population: Study XP053)

Time Window	Number (%) of Subjects with No Reported RLS Symptoms		
	Placebo N=96	XP13512 600 mg N=114	XP13512 1200 mg N=111
Baseline			
n ^a	93	110	110
8 AM to 12 PM	50 (53.8)	65 (59.6)	62 (56.4)
12 PM to 4 PM	44 (47.3)	63 (57.3)	59 (53.6)
4 PM to 8 PM	39 (41.9)	44 (40.0)	57 (51.8)
6 PM to 10 PM	24 (25.8)	30 (27.3)	31 (28.2)
8 PM to 12 AM	16 (17.2)	12 (10.9)	11 (10.0)
12 AM to 4 AM	30 (32.3)	30 (27.3)	34 (30.9)
4 AM to 8 AM	42 (45.2)	47 (42.7)	53 (48.2)
End of Week 12			
n ^b	74	99	92
8 AM to 12 PM	52 (72.2)	85 (86.7)	74 (80.4)
12 PM to 4 PM	51 (70.8)	74 (75.5)	69 (75.0)
4 PM to 8 PM	45 (61.6)	68 (69.4)	61 (66.3)
6 PM to 10 PM	39 (52.7)	55 (55.6)	55 (59.8)
8 PM to 12 AM	27 (36.5)	49 (49.5)	48 (52.2)
12 AM to 4 AM	38 (51.4)	74 (74.7)	67 (72.8)
4 AM to 8 AM	56 (75.7)	79 (79.8)	72 (78.3)

Data Source: DStable 7.13.1

- a. The XP13512 600 mg group had 109 subjects at the 8 AM to 12 PM time period.
- b. The placebo group had 73 subjects at the 4 PM to 8 PM time period, and had 72 subjects at the 8 AM to 12 PM and 12 PM to 4 PM time periods. The XP13512 600 mg group had 98 subjects at the 8 AM to 12 PM, 12 PM to 4 PM, and 4 PM to 8 PM time periods.

Most subjects with RLS experience peak symptoms between late evening and early morning (8pm-12am epoch). The three groups, PBO, XP13512 600mg, 1200mg, were similar at baseline visit (17.2, 10.9%, and 10% respectively). However, at the End of Week 12, there was a larger percentage of subjects who were taking either 600mg or 1200mg of drug, that were symptom free between 8pm and 12 am (PBO 36.5%, 600mg 49.5%, and 1200mg 52.2%), although all three groups improved from baseline.

I analyzed the individual data sets for 24 Hour RLS Record, at Week 12, at 30 minute epochs between 5pm and 11pm. Similarly to the sponsor, I considered all subjects who were either sleeping or awake without RLS symptoms to be without RLS symptoms, and calculated the percentage of patients who were symptom free in each cohort (XP13512 600mg, XP13512 1200mg or placebo).

Reviewer’s Table Percentage of Patients Who are Symptom Free* 5PM-11PM By Dose Study 053

	TIM E						
	5pm	6pm	7pm	8pm	9pm	10pm	11pm
600mg	75%	74%	75%	68%	65%	56%	70%
1200mg	80%	77%	76%	64%	64%	65%	69%
PBO	70%	68%	67%	60%	56%	55%	60%

*Symptom Free included patients who reported they were asleep or awake and free from RLS symptoms

The data from this analysis reveal a trend that suggests a drug effect for complete RLS symptoms relief (either by report or subject being asleep). However, compared to the sponsor, the drug effect when examined by one hour intervals rather than 4 hour epochs, appears to be less pronounced.

Maximum RLS Severity as recorded by 24-hour RLS Record.- XP052

Sponsor Table 29 presents number (percent) of subjects with **NO** RLS symptoms for 1200mg XP13512 and placebo, by 4 hour epochs. Starting at 4PM until 8AM, the 1200mg group have a larger percentage of symptom free subjects than placebo. The difference is most notable in the 8PM to 12AM epoch (38.5% placebo are symptom free, versus 64.6% symptoms free in the 1200mg group).

Table 29 Subjects Reporting No RLS Symptoms by 4 Hour Period at Week 12 (MITT Population: Study XP052)

	Number (%) of Subjects	
	Placebo N= 108	XP13512 N= 112
Maximum severity= None		
8 AM to 12 PM	73 (76.8)	78 (78.8)
12 PM to 4 PM	72 (75.8)	78 (78.8)
4 PM to 8 PM	52 (54.7)	69 (69.7)
6 PM to 10 PM	40 (41.7)	67 (67.7)
8 PM to 12 AM	37 (38.5)	64 (64.6)
12 AM to 4 AM	64 (66.7)	74 (74.7)
4 AM to 8 AM	71 (74.0)	81 (81.8)

Data Source: DSTable 14.1

OTHER SECONDARY ENDPOINTS FOR STUDY XP052 and STUDY XP053

The following table (sponsor Table 58) shows the results from pivotal studies XP052 and XP053, primary efficacy and key secondary efficacy endpoints of XP13512 600mg and 1200mg individually as well as integrated summary of efficacy. Interestingly, 600mg is observed to have a similar treatment effect as the 1200mg for the primary endpoint, as well as secondary endpoints including primary efficacy measures at the end of week 1. (Note: there are two secondary endpoints, POMS and somnolence that do not achieve statistical significance in 600mg cohort versus 1200mg). As pointed out previously in this review, the sponsor chose 1200mg as the target dose for the RLS indication, based on early trials (XP021 and XP045). These trials were two weeks in duration and failed to achieve statistical improvement in the 600mg cohort at week 1. In the pivotal trials (XP052 and XP053), 600mg appears to be equally efficacious as 1200mg not only at week 12 (end of study, primary endpoint), but also at week 1.

Table 58 Statistical Significance of Comparisons of XP13512 1200 mg and 600 mg to Placebo for Key Efficacy Endpoints (MITT Population: Studies XP052 & XP053 Individually and Integrated)

	XP13512 vs Placebo Statistical Significance				
	P-value				
	XP052	XP053		XP052 & XP053	
	1200 mg	600 mg	1200 mg	600 mg	1200 mg
IRLS Rating Scale Total Score: Change From Baseline					
IRLS Rating Scale total score at Week 12 (co-primary endpoint)	0.0003*	<0.0001*	0.0015*	<0.001*	<0.001*
IRLS Rating Scale total score at Week 1	<0.0001*	<0.0001*	0.0017*	<0.001*	<0.001*
Investigator-Rated CGI-I					
Proportion of responders on investigator-rated CGI-I at Week 12 (co-primary endpoint)	<0.0001*	<0.0001*	<0.0001*	<0.001*	<0.001*
Proportion of responders on investigator-rated CGI-I at Week 1	<0.0001*	0.0030*	0.0002*	<0.001*	<0.001*
Patient-Rated CGI-I					
Proportion of responders on patient-rated CGI-I at Week 12	<0.0001*	<0.0001*	0.0017*	<0.001*	<0.001*
RLS Symptom Record: RLS Severity During 4-Hour Period (for Intervals Associated with Evening, Late Evening, and Nighttime Symptoms)					
4 PM to 7:59 PM	0.0534	0.3703	0.1900	0.307	0.019*
8 PM to 11:59 PM	0.0011*	0.0348*	0.0076*	0.058	<0.001*
Midnight to 3:59 PM	0.1878	0.0035*	0.0117*	0.028*	0.007*
Pain Assessment Question: Change From Baseline					
Pain severity at Week 12	<0.0001*	<0.0029*	0.0015*	<0.001*	<0.001*
MOS Sleep Scale: Change From Baseline					
Sleep adequacy domain at Week 12	<0.0001*	0.0003*	<0.0001*	<0.001*	<0.001*
Sleep quantity domain at Week 12	0.0084*	0.0209*	0.0001*	0.036*	<0.001*
Sleep disturbance domain at Week 12	<0.0001*	<0.0001*	<0.0001*	<0.001*	<0.001*
Daytime somnolence domain at Week 12	0.0018*	0.8926	0.0309*	0.712	<0.001*
PSQ					
Overall sleep quality at Week 12	<0.0001*	0.0230*	0.0023*	0.002*	<0.001*
Ability to function during daytime at Week 12	0.0002*	0.0366*	0.0152*	0.012*	<0.001*
Number of nights with RLS symptoms at Week 12	<0.0001*	0.0001*	0.0006*	<0.001*	<0.001*
Number of awakenings during night at Week 12	0.0429*	0.0009*	0.0004*	0.001*	<0.001*
Number of hours awake per night due to RLS symptoms at Week 12	0.0189*	0.0019*	0.0187*	<0.001*	<0.001*
POMS Brief Form: Change From Baseline					
Total mood disturbance score at Week 12	0.0014*	0.1795	0.0893	0.052	<0.001*
Johns Hopkins RLS QoL Questionnaire: Change From Baseline					
Overall life impact score at Week 12	<0.0001*	0.0025*	0.0009*	<0.001*	<0.001*

* Comparisons for XP13512 vs placebo were statistically significant at the 5% level.

Data Source: CSR XP052, DS Table 4.1, DS Table 5.1, DS Table 7.1, DS Table 8.1, DS Table 9, DS Table 11, DS Table 12, DS Table 13 and DS Table 14.1; CSR XP053, DS Table 7.1.1.1, DS Table 7.1.1.2, DS Table 7.2.1.1, DS Table 7.2.1.2, DS Table 7.6.1, DS Table 7.7.1, DS Table 7.8, DS Table 7.10, DS Table 7.11, DS Table 7.12 and DS Table 7.13.1; Table 3.12, Table 3.16, Table 3.19, Table 3.22, Table 3.25, Table 3.28, Table 3.30, Table 3.33, Table 3.35.

Summary and Conclusions

XP13512 is a gabapentin pro-drug being studied for moderate to severe RLS. There were two pivotal trials (XP052 and XP053) which were double blind, placebo controlled. The study

reviewed in this section, XP053, had three arms (600mg, 1200mg and PBO). However, the primary analysis was 1.1200mg with co primary endpoints of change in IRLS score between baseline and week 12, 2. Change in proportion of subjects rated as much improved or very improved on CGI-I.

Overall, XP13512 600mg and 1200mg were superior to placebo on both co primary endpoints at end of treatment (week12). The SAP agreed upon between the sponsor and division was $p < .05$ on each of the co-primary endpoints. Although the sponsor appears to have the primary endpoints set as change in IRLS **AND** proportion of change in CGI-I, the statistical analysis was carried out for each endpoint independently at $p < .05$. Even if one corrects for multiplicity, the sponsor 'wins' on both primary endpoints.

Both XP13512 600 mg and 1200mg were significantly improved at 1 week on co primary endpoints.

6.1.3 Subpopulations

The pivotal trials and supportive efficacy trials did not include any special populations or subpopulations.

There was a mild difference seen in one study (XP081) in terms of gender, with females having a higher exposure than males. There did not appear to be a significant effect of weight otherwise. Greater than 90% of the study population was Caucasian making it difficult to interpret any racial differences.

6.1.4 Analysis of Clinical Information Relevant to Dosing Recommendations

XP081

Protocol XP081 was conducted to measure gabapentin pharmacokinetics of gabapentin enacarbil, and to assess a possible dose/exposure response relationship for the treatment of patients with moderate to severe idiopathic RLS. Dosages studied are outline in Sponsor Table 1.

Table 1 Target Dosing Scheme

Target Dose/ Treatment Group	Double-Blind Treatment Phase ^a				Double-Blind Taper Phase ^b		
	Titration Period				Days 85-86	Days 87-88	Days 89-91
	Days 1-3	Days 4-6	Days 7-9	Days 10-84			
600 mg	✓	✓	✓	✓	600 mg	600 mg	600 mg
1200 mg	600 mg	✓	✓	✓	600 mg	600 mg	600 mg
1800 mg	600 mg	1200 mg	✓	✓	1200 mg	1200 mg	600 mg
2400 mg	600 mg	1200 mg	1800 mg	✓	1800 mg	1200 mg	600 mg

Note: Subjects were instructed to take study drug once-daily at 5 PM with food.
 a. The 84-day Double-Blind Treatment Phase included a 9-day titration period.
 b. XP13512 dose levels during the taper phase are shown by treatment group.
 ✓ = Target dose achieved.

Efficacy Analysis

There was no assignment of primary or secondary endpoints in this study. The study design is detailed in Section 5.3 of this Review.

REVIEWER COMMENT: The biostatistics reviewer commented that “analyses of efficacy variables were limited to the presentation of descriptive statistics by dose group.” The study was not powered for the co-primary endpoints outlined in the pivotal trials XP052 and XP053. Overall, the trial fails to demonstrate superiority compared to placebo ($p < 0.05$). The same is true for the individual dose groups when the analysis is adjusted for multiple comparisons. The unadjusted (for multiple comparisons) analysis 600mg and 1200mg cohorts demonstrate statistical superiority compared to placebo at an $\alpha = 0.039$ and can be accepted as a supportive efficacy finding for the 600 mg dose. Study XP081, although not powered for efficacy, reveals that higher doses (1200, 1800 and 2400mg) are no more effective than 600mg gabapentin enacarbil.

Summary Statistics for Change in IRLS Rating Scale Total Score from Baseline by Visit

Sponsor Table 21 shows that all active treatment groups are superior to placebo as rated by IRLS score, throughout the study.

Table 10 IRLS Total Scores - XP081 (Source: Reviewer's Analysis)

	Base line	Change from Baseline in IRLS Total Score								
		Visit3 Week1	Visit4 Week2	Visit5 Week3	Visit6 Week4	Visit7 Week6	Visit8 Week8	Visit9 Wk10	Visit10 Wk12	Visit10 LOCF
Placebo										
N	40	34	32	36	34	31	32	33	30	40
Mean	22.45	-5.62	-6.84	-8.06	-8.71	-7.52	-9.41	-9.09	-9.17	-9.28
SD	(5.32)	(7.30)	(8.85)	(8.28)	(7.76)	(9.65)	(9.79)	(9.63)	(8.37)	(8.13)
600 mg										
N	47	45	44	42	38	38	36	34	33	47
Mean	23.87	-8.91	-11.20	-10.81	-12.42	-11.87	-13.58	-13.00	-15.67	-13.81
SD	(5.33)	(7.69)	(8.29)	(9.48)	(9.00)	(9.32)	(9.85)	(8.70)	(8.00)	(9.48)
p-value										.0394
1200 mg										
N	43	41	39	39	39	32	31	32	27	43
Mean	23.91	-10.10	-11.45	-12.38	-13.13	-14.88	-13.06	-14.75	-16.22	-13.81
SD	(5.49)	(7.68)	(8.07)	(8.87)	(7.44)	(8.78)	(9.78)	(8.14)	(9.74)	(9.84)
p-value										.0445
1800 mg										
N	37	37	35	35	30	32	33	32	33	37
Mean	23.62	-10.59	-13.89	-14.23	-15.13	-16.59	-15.24	-14.91	-15.15	-13.95
SD	(4.25)	(8.42)	(8.05)	(8.28)	(8.67)	(7.82)	(7.89)	(8.85)	(8.13)	(8.70)
p-value										.0256
2400 mg										
N	44	42	43	39	37	34	34	35	31	44
Mean	23.34	-9.02	-12.84	-11.92	-13.38	-15.24	-14.41	-13.74	-15.35	-12.86
SD	(5.70)	(7.10)	(8.39)	(7.21)	(7.57)	(7.38)	(9.08)	(8.24)	(7.86)	(9.52)
p-value										.0895

Summary Statistics for Responders in CGI-I by visit

The table below presents number (percent) of responders on CGI-I. All four active treatment groups are improved compared to placebo. There is slightly greater percentage of responders at 1800mg and 2400mg (73% and 81.8% respectively) compared to 600mg and 1200mg (63.8% and 65.1%) and Week 12 (Visit 10)

FDA Statistical Reviewers Analysis of the CGI Responder Rate Study XP081

Table 11 Responder Rate - XP081 (Source: Reviewer's Analysis)

	CGI – XP081					
	Visit 3 Week 1	Visit 4 Week 2	Visit 6 Week 4	Visit 8 Week 8	Visit 10 Week 12	Visit10 LOCF
Placebo						
N	35	32	34	31	29	40
# (%) Responders	11 (31.43%)	10 (31.25%)	17 (50.00%)	15 (48.39%)	13 (44.83%)	18 (45.00%)
XP13512 600 mg						
N	46	43	37	36	33	47
# (%) Responders	23 (50.00%)	24 (55.81%)	23 (62.16%)	23 (63.89%)	24 (72.73%)	30 (63.83%)
Nominal p-value						.0801
XP13512 1200 mg						
N	40	39	39	31	26	43
# (%) Responders	23 (57.50%)	27 (69.23%)	27 (69.23%)	25 (80.65%)	20 (76.92%)	28 (65.12%)
Nominal p-value						.0671
XP13512 1800 mg						
N	36	35	30	33	31	37
# (%) Responders	23 (63.89%)	27 (77.14%)	20 (66.67%)	27 (81.82%)	25 (80.65%)	27 (72.97%)
Nominal p-value						.0134
XP13512 2400 mg						
N	42	43	36	34	31	44
# (%) Responders	21 (50.00%)	33 (76.74%)	28 (77.78%)	28 (82.35%)	28 (90.32%)	36 (81.82%)
Nominal p-value						.0005

REVIEWER COMMENT:

Although the numbers are small in this study and therefore not powered for efficacy, it is supportive of the fact that there is a minimal difference in efficacy between 600mg and 1200mg as rated by change in IRLS and change in proportion of responders on CGI-I between baseline and week 12. There is a slight increase in response on CGI-I favoring the 1800mg and 2400mg cohort. Numerically at week 12 the percentage of responders was much higher compared to placebo. There were a significant number of patients who did not complete the trial in both the placebo and XP13512 arms that may have contributed to the loss of power and declining percentage of responders using the visit 12 (visit 10 LOCF analyses).

Maximum RLS Severity as recorded by 24-hour RLS Record.-

Sponsor Table 33 shows the 24-hour RLS record by 4 hour epochs at week 12. The number and percent of subjects with **NO** RLS symptoms is presented for each treatment group.

Table 33 Subjects Reporting No RLS Symptoms by 4-Hour Periods by Treatment Group at Week 12 (Safety Population: Study XP081)

Maximum severity= None	Number (%) of Subjects				
	Placebo N=41	XP13512 600 mg N=48	XP13512 1200 mg N=45	XP13512 1800 mg N=38	XP13512 2400 mg N=45
N	30	33	31	30	35
8 AM to 12 PM	25 (83.3)	26 (78.8)	26 (83.9)	21 (70.0)	27 (77.1)
12 PM to 4 PM	22 (73.3)	28 (84.8)	25 (80.6)	25 (83.3)	28 (80.0)
4 PM to 8 PM	18 (60.0)	23 (69.7)	22 (71.0)	20 (66.7)	24 (68.8)
6 PM to 10 PM	16 (53.3)	24 (72.7)	16 (51.6)	19 (63.3)	20 (57.1)
8 PM to 12 AM	13 (43.3)	22 (66.7)	14 (45.2)	16 (53.3)	17 (48.6)
12 AM to 4 AM	15 (50.0)	25 (75.8)	21 (67.7)	23 (76.7)	24 (68.8)
4 AM to 8 AM	21 (70.0)	25 (75.8)	26 (83.9)	24 (80.0)	28 (80.0)

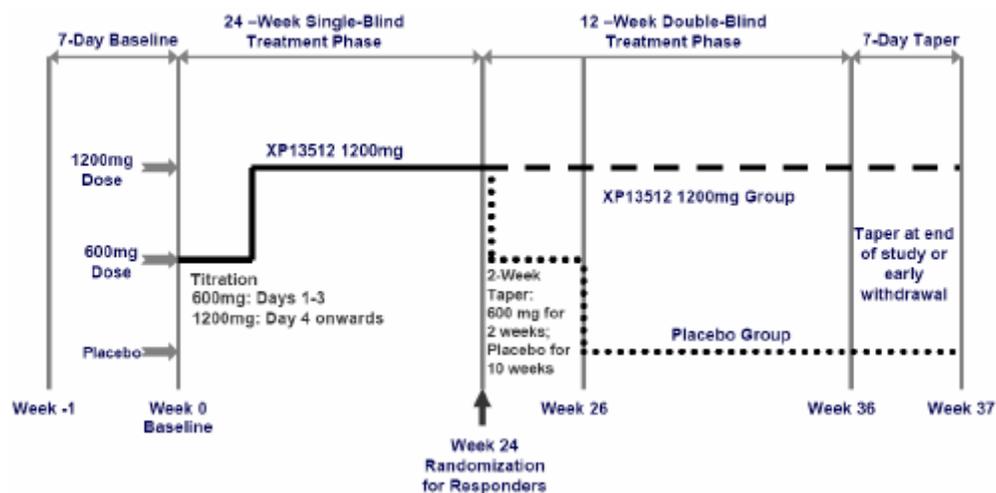
Data Source: DSTable 8.34

There does not appear to be a dose response, and again the study was not powered for efficacy. However, the 600mg cohort appears to have the largest number and percentage of subjects with NO RLS symptoms at peak hours between 8PM and 12AM.

6.1.5 Discussion of Persistence of Efficacy and/or Tolerance Effects

Trial XP060 was performed to study maintenance of efficacy of gabapentin enacarbil 1200mg taken once daily, in subjects with primary RLS.

Figure 3 Schematic Study Design for Study XP060



The primary efficacy measure for study XP060 was the proportion of subjects who relapsed during the 12-week double blind treatment period.

Relapse was defined as:

1. An increase in IRLS Rating Scale score of at least 6 points or a total IRLS rating scale score of 15 or more
2. An assessment of “much or very much worse” on the investigator CGI-I for two consecutive study visits compared to baseline (randomization).
3. Withdrawn due to lack of efficacy.

Efficacy Results

Table 26 Summary of Analysis of Proportion of Subjects who Relapsed During the Double-Blind Treatment Phase (DB-ITT Population: Study XP060)

	Placebo N=97	XP13512 1200 mg N=96
n	97	96
Subjects with Relapse ¹ , n (%)	22 (22.7)	9 (9.4)
Met IRLS Rating Scale and CGI-C Criteria ¹	18 (18.6)	5 (5.2)
Withdrawn due to Lack of Efficacy	4 (4.1)	4 (4.2)
Adjusted Odds Ratio	-	0.353
95% CI	-	0.2, 0.8
P-value	-	0.0158

Data Source: CSR XP060, DS Table 7.1 and DS Table 10.1.

1. Relapse was indicated by 2 consecutive visits at least one week (≥5 days) apart for confirmation that during Weeks 25-36 the subject reported an IRLS Rating Scale total score increase (i.e. worsening) of at least 6 points relative to the subject's score at randomization (Week 24), an IRLS Rating Scale total score of at least 15, and an assessment of 'much worse' or 'very much worse' on the CGI-C relative to randomization, or withdrawal due to lack of efficacy.

Method of analysis was logistic regression including terms for treatment group, Week 24 IRLS Rating Scale total score, and pooled study site. The model that included the treatment-by-pooled site interaction term did not converge.

REVIEWER COMMENT: There were a greater number (percentage) of subjects who relapsed on placebo compared to 1200mg XP13512 (22.7% versus 9.4% respectively.) There is an equal number (percent) of subjects withdrawn due to lack of efficacy between placebo and active treatment (4.1% versus 4.2%). This is notable for the low rate of withdrawal due to lack of efficacy in the placebo group suggestive of a larger than expected placebo effect.

Statistical Reviewer’s Table Comparing IRLS and CGI-Investigator Scores for Patients at Baseline and Patients Meeting Criteria for Relapse

Table 9 IRLS Rating Scale and CGI-I during Double-Blind Period – XP060 (Source: Reviewer’s Analysis)

	All Subjects		Relapsed Subjects	
	Placebo N=97	XP13512 1200 mg N=96	Placebo N=22	XP13512 1200 mg N=9
IRLS				
Baseline	5.30 (6.00)	5.10 (6.00)	5.32 (5.00)	7.88 (8.00)
Last Visit	9.72 (9.00)	7.40 (6.50)	18.59 (17.50)	20.44 (21.00)
Change	4.42 (2.00)	2.29 (0.00)	13.27 (13.50)	12.56 (13.00)
CGI-C	4.32 (4.00)	3.92 (4.00)	6.14 (6.00)	6.11 (6.00)

REVIEWER COMMENT: The subjects on active treatment (120mgm XP13512) who relapsed had similar changes in IRLS Rating score as well change in CGI-C. However, the number of subjects who relapsed was small (9).

Maximum RLS Severity as recorded by 24-hour RLS Record.- XP060

Table 30 Subjects Reporting no RLS Symptoms by 4-hour Period at Randomization and Week 36 or Early Termination (DB-ITT Population: Study XP060)

Time Window	Number (%) of Subjects with No Reported RLS Symptoms			
	Placebo N=97		XP13512 N=96	
	Randomization (n=96)	Week 36 (n=87)	Randomization (n=95)	Week 36 (n=89)
8 AM to 12 PM	83 (86.5)	72 (82.8)	88 (92.6)	83 (93.3)
12 PM to 4 PM	85 (88.5)	71 (81.6)	85 (89.5)	78 (87.6)
4 PM to 8 PM	73 (76.0)	68 (78.2)	68 (71.6)	72 (80.9)
6 PM to 10 PM	66 (68.8)	53 (60.9)	61 (64.2)	62 (69.7)
8 PM to 12 AM	62 (64.6)	41 (47.1)	59 (62.1)	61 (68.5)
12 AM to 4 AM	82 (85.4)	66 (75.9)	79 (83.2)	77 (86.5)
4 AM to 8 AM	83 (86.5)	67 (77.0)	83 (87.4)	80 (89.9)

Data Source: DS Table 7.25

REVIEWER COMMENT: As seen in the pivotal trials, XP052 and XP053, as well as XP081, subjects on active treatment had a greater number of patients who were symptom free (Subjects reporting NO RLS symptoms), than placebo between 8pm and 12am. At Week 36 (end of treatment) there were 47.1 % of placebo subjects with NO RLS symptoms versus 68.5% in the 1200mg cohort, between 8pm and 12 am.

The sponsor includes an overlapping epoch in the analysis, 6pm to 10pm, in order to fully capture “peak RLS symptoms”. Including this epoch likely overestimates RLS symptom relief, since many RLS patients do not experience the onset of symptoms until later in the evening. The 8pm to 12am epoch better represents ‘real life’ RLS symptomatology.

6.1.6 Additional Efficacy Issues/Analyses

Sponsor Tables 70 and 71 show Integrated Dose Analysis for Trials XP052, XP053 and XP081.

Table 70 Change from Baseline in IRLS Rating Scale Total Score at Week 12 LOCF (MITT Population: Studies XP052, XP053 & XP081 Integrated)

	Placebo N=244	XP13512 600 mg N=161	XP13512 1200 mg N=266	XP13512 1800 mg N=37	XP13512 2400 mg N=44
IRLS Rating Scale Total Score: Change from Baseline to Week 12 LOCF					
N	244	161	266	37	44
Mean (SD) Change from Baseline to Week 12	-9.3 (8.17)	-13.8 (8.49)	-13.3 (9.25)	-14.2 (8.83)	-12.8 (9.52)
Adjusted Treatment Difference	-	-4.3	-3.9	-4.4	-3.2
95% CI	-	-6.0, -2.5	-5.3, -2.5	-7.5, -1.2	-6.2, -0.3
P-value	-	<0.001	<0.001	0.006	0.033

Data Source: Table 3.78 and Table 3.79.

The placebo and 1200 mg groups contained subjects from XP052, XP053 and XP081, the 600 mg group contained subjects from XP053 and XP081 only, and the 1800 mg and 2400 mg groups contained subjects from XP081 only. The analysis method was parametric ANCOVA adjusted for treatment, baseline score, pooled site and study.

Table 71 Proportion of Responders on Investigator-Rated CGI-I at Week 12 LOCF (MITT Population: Studies XP052, XP053 & XP081 Integrated)

	Placebo N=244	XP13512 600 mg N=161	XP13512 1200 mg N=266	XP13512 1800 mg N=37	XP13512 2400 mg N=44
Proportion of Responders on Investigator-Rated CGI-I at Week 12 LOCF					
n	244	161	263 ¹	37	44
Responders, n (%)	103 (42)	113 (70)	198 (75)	27 (73)	36 (82)
Odds Ratio	-	3.1	4.2	4.4	7.5
95% CI	-	2.0, 4.9	2.9, 6.1	1.9, 10.4	3.1, 18.1
P-value	-	<0.001	<0.001	<0.001	<0.001

Data Source: Table 3.80, Table 3.81.

The placebo and 1200 mg groups contained subjects from XP052, XP053 and XP081, the 600 mg group contained subjects from XP053 and XP081 only, and the 1800 mg and 2400 mg groups contained subjects from XP081 only. The analysis method was logistic regression adjusted for treatment, study, and pooled site.

1. Three subjects in the MITT Population (all from Study XP052) did not have an investigator-rated CGI-I assessment post-baseline.

In Study XP081, there is evidence of efficacy at 600mg as well. However, this was a dose response study and was not powered for efficacy. Refer to Section 6.1.7 for individual trial results for study XP081.

SUMMARY

REVIEWER COMMENT: The pivotal trials, XP052 and XP053 as well as supportive efficacy trial XP081, have shown statistically significant improvement in co primary endpoints at 1200mg/day. Pivotal trial 53 and supportive efficacy trial XP081 has shown statistically significant improvement in co primary endpoints at 600mg a day as well as secondary efficacy endpoints.

The Statistical Reviewer has also concluded similar efficacy with treatment at 600mg and 1200mg on primary and secondary endpoints. The Clinical Pharmacology Reviewer concluded that the dose response and exposure response data supported efficacy at 600mg a day of gabapentin enacarbil.

The overall findings by clinical review disciplines support the approval of 600mg/day of gabapentin enacarbil based on efficacy.

7.0 Safety Summary

Gabapentin enacarbil, has been developed for the treatment of moderate to severe restless leg syndrome (RLS). Currently available treatments for RLS include two non-ergot dopamine agonists, ropinirole and pramipexole. Although these agents are effective, there are associated side effects and safety issues. Both of these agents cause sedation, daytime sleepiness, nausea and in higher doses have been associated with sleep attacks. More recently, there have been cases in the literature of RLS patients experiencing impulse control disorders when treated with dopamine agonists.

Gabapentin has been used for RLS (Garcia-Borreguero, Neurology 2002) with benefit. However due to its short half life, its efficacy is limited. Therefore, a long acting version of the gabapentin, XP13512, is being developed. This class of drugs has a number of known associated side effects and safety issues.

7.1 Methods

Clinical Studies Used to Evaluate Safety

Twenty-four clinical and clinical pharmacology studies were included in the Integrated Summary of Safety analysis data set (ISS). These clinical trials include RLS clinical development program trials as well as one in clinical trial in post-herpetic neuralgia. These studies are summarized in Sponsor Table 2.

Table 2 Clinical Studies Providing Safety Information for XP13512 in RLS Integrated Summary of Safety

Xenoport Study Number	Status of study	Type of Study	Number of Randomized/ Assigned Subjects	Information Provided	GSK Study Report Document Number
Phase I/Clinical Pharmacology studies					
XP006	Complete	Single dose safety and PK IR formulation	50	All safety data	HM2008/00228/00
XP018	Complete	Multiple dose safety and PK IR formulation	38	All safety data	HM2008/00052/00
XP019	Complete	Single dose relative bioavailability (IR and ER)	24	All safety data	HM2008/00306/00
XP022	Complete	Single dose food effect	12	All safety data	HM2008/00054/00
XP044	Complete	Single dose relative bioavailability and food effect	36	All safety data	HM2008/00056/00
XP057	Complete	Single dose relative bioavailability	12	All safety data	GM2008/00182/00
XP065	Complete	Single dose ADME	6	All safety data	HM2008/00063/00
XP066	Complete	Renal impairment	15	All safety data	HM2008/00061/00
XP067	Complete	Naproxen drug interaction	12	All safety data	HM2007/00680/00
XP068	Complete	Cimetidine drug interaction	12	All safety data	HM2008/00059/00
XP069	Complete	Single dose safety and PK	32	All safety data	HM2007/00647/00
XP072	Complete	Single dose safety and PK, Japanese and Caucasian subjects	48	All safety data	HM2008/00253/00
XP073	Complete	Multiple dose safety and PK Japanese subjects	31	All safety data	HM2008/00308/00
XP078	Complete	Thorough QT	54	All safety data	HM2008/00066/00
XP086	Complete	Single dose in vitro in vivo correlation (IVIVC)	10	All safety data	HM2007/00707/00
XP087	Complete	Single dose food effect	12	All safety data	HM2007/00723/00
Phase II Clinical Studies – RLS Subjects					
XP021	Complete	2-Week Crossover	38	All safety data	RM2007/00919/00
XP045	Complete	2-Week Dose Finding	95	All safety data	RM2007/00805/00
XP081	Complete	12-week Dose-Response and PK	217	All safety data	RM2007/00913/00
XP083	Complete	2-Week Simulated Driving Performance	130	All safety data	RM2007/00914/00

Integrated Summary of Safety

Xenopt Study Number	Status of study	Type of Study	Number of Randomized/ Assigned Subjects	Information Provided	GSK Study Report Document Number
Phase III Clinical Studies – RLS Subjects					
XP052	Complete	Pivotal 12-week Efficacy and Safety	222	All safety data	RM2007/00410/00
XP053	Complete	Pivotal 12-week Efficacy and Safety	325	All safety data	RM2007/00923/00
XP060	Complete	36-Week Maintenance of Effect	327	All safety data	RM2007/00911/00
XP055	Ongoing	52-Week Open-label Extension	583	All safety data to 06 Dec 2008 SAEs, deaths, pregnancies, and withdrawal AEs to 31 March 2008	RM2007/00921/00 (Condensed Interim CSR)

Note: All studies used the ER formulation unless otherwise noted. Study XP065 used a capsule radio-labeled formulation. See Sections 1.1.4.2 and 1.1.4.3 for studies of XP13512 in other indications and/or non-GSK sponsored studies.

Pooling Data Across Studies to Estimate and Compare Incidence

The principal grouping for the ISS were the 12 Week Placebo Controlled RLS clinical trials (XP052, XP053, and XP081). The safety data was integrated for these three clinical trials because of similarity in design and duration.

There were three other groupings of safety data as follows:

1. **All Controlled Phase II and Phase III RLS** studies which were of similar design but varying durations. This provides the largest source of controlled safety data available. Note, however, that clinical trial XP021 was not included in this grouping because of the cross-over design of the trial.
2. **RLS long term integration** grouping included four parent clinical trials (XP052, XP053, XP082 and XP083). Subjects from these clinical trials continued into the extension clinical trial XP055. This grouping provides information for maximum continuous duration of exposure to XP13512.
3. **All RLS** grouping including clinical trials, XP021, XP045, XP052, XP053, XP055, XP066, XP081 and XP083. This grouping allowed supportive assessments of rare events.

REVIEWER COMMENT: The Sponsor did not consistently use one grouping for the presentation of safety data. Where possible, ALL RLS grouping will be used in this Review to present safety information. Otherwise, other safety groupings will be identified.

7.2 Adequacy of Safety Assessments

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

Sponsor Table 19 shows the overall Exposure to gabapentin enacarbil for all studies, any indication.

Table 19 Enumeration of Unique Subjects Exposed to Study Medication

Individual Phase II and Phase III Studies	Number of Subjects	
	Placebo	XP13512
XP052	108	113
XP053	96	226
XP081	41	176
XP083	34	65
XP060	98	326
XP045	33	62
XP021	36	36
XP055 (naïve subjects only)	0	197
Phase II and Phase III Study Groupings		
12-Week Placebo-Controlled RLS Studies	245	515
All Controlled Phase II and Phase III RLS Studies	312	642
Total All RLS Phase II and Phase III Studies	446	1201
Total Unique Exposures in Clinical Pharmacology Studies	39¹	365
Total Unique Exposures in RLS Clinical Development Program	485	1566
Other XP13512 Studies		
XP009 (PHN)	54	47
GSK-sponsored Study PXN110448 (DPN)	0	1
Astellas Study 8825-CL-0003 (CTR ID No. NCT00530530)	NA	NA
Astellas Study 8825-CL-0005	NA	NA
Astellas Study 8825-CL-0007 (CTR ID No. NCT00508430)	NA	NA
Total Unique Exposures to XP13512	539	1614

Data Source: Table 1.4 and individual clinical pharmacology CSRs

NA=not available

31 March 2008 Submission cut-off

1. Subjects may have received placebo only or placebo and another study drug

As of the original NDA submission, there have been a total of 1614 subjects exposed to gabapentin enacarbil, inclusive of all doses and all indications.

Safety Grouping for RLS Indication

Table 3 ISS Study Groupings for Phase II and Phase III Studies

Study Grouping	Studies
12-Week Placebo-Controlled RLS Studies (Integrated)	XP052, XP053, XP081
All Placebo-Controlled Phase II & Phase III RLS Studies (Integrated) ¹	12-Week Placebo-Controlled RLS Studies (XP052, XP053, XP081) plus: XP083 ² , XP045 ³
All RLS Studies ⁴ (Integrated and Individual)	XP052, XP053, XP081, XP083, XP060 ⁵ , XP021 ⁶ , XP045, XP055
RLS Long-Term Integration (Integrated)	12-Week Placebo-Controlled RLS Studies (XP052, XP053, XP081) plus: XP083 ² , XP055 ⁷

1. Includes only placebo-controlled parallel-group studies; Study XP060 is not included because it included a SB phase prior to the DB placebo-controlled phase and Study XP021 is not included because it employed a crossover design.
2. XP083 is a 16-day simulated driving performance and cognition study
3. XP045 is a 2-week dose-finding study
4. Studies are presented side-by-side, with the addition of an overall total column for XP13512.
5. XP060 is a 36-week maintenance of effect study. The study comprised of a 24-week single blind phase, with 'responders' being randomized to a 12-week double blind, placebo-controlled phase.
6. XP021 is a 2-week crossover study
7. XP055 is a 12-month extension study. The parent studies are the other 4 studies in the Long-Term integration grouping. Data collected for XP055 are included up to and including 06 December 2007

REVIEWER COMMENT: The most comprehensive grouping for safety data is ALL RLS Studies. Although, not all studies were of similar design and duration, this grouping captures all subjects with RLS exposed to gabapentin enacarbil at any dose and duration.

Sponsor Table 9 presents the composition, by study, drug and dose of ALL RLS grouping.

Table 9 Composition of All RLS Studies Grouping From Individual Studies (Safety Population: All RLS Studies)

Study	Number of Subjects						
	Placebo	Placebo/ diphenhydramine	XP13512 Dose (mg)				XP13512 All Doses
			600	1200	1800	2400	
XP052 ¹	108			113			113
XP053 ¹	96		115	111			226
XP081 ¹	41		48	45	38	45	176
XP083 ^{1,2}	34 ²	30 ²		31	34		65
XP060							
Single-Blind				326			326
Double-Blind	98			96			
XP021 ⁴							
Placebo-XP13512	17				15		15
XP13512-placebo	19				21		21
XP045	33		29	33			62
XP055 ⁵							[572] ⁶
Naive				197			197 ⁷
Non-naive							[375] ⁸
Total	446	30²	192	755	110	45	1201⁹

Data Source: Table 1.4

- Includes all subjects in the safety population, regardless of whether they subsequently entered extension Study XP055.
 - Subjects received placebo for XP13512 and placebo for diphenhydramine
 - Subjects received placebo for XP13512 and diphenhydramine (active). Diphenhydramine was given on a single day [Day 16].
 - Subjects are summarized by sequence. Two subjects in the placebo-XP13512 sequence did not receive XP13512 and 2 subjects in the XP13512-placebo sequence did not receive placebo.
 - Subjects are included in XP13512 Naive if they received placebo or diphenhydramine during the parent study. Subjects are included in XP13512 non-naive if they received any dose of XP13512 during the parent study.
 - Total number of subjects in Study XP055
 - Number of subjects who did not receive XP13512 in a parent study
 - Number of subjects who received XP13512 in a parent study and who are counted in the parent study rows.
 - Subjects are counted uniquely, regardless of whether they appear in more than one treatment column.
- Note: 2 subjects randomized to Placebo-XP13512 in Study XP021 did not crossover and receive XP13512 and 2 subjects randomized to XP13512-placebo did not crossover and receive placebo.

A total of 1201 subjects with RLS were exposed to gabapentin enacarbil inclusive of all doses.

EXTENT OF EXPOSURE

Duration of Unique Subject Exposures to XP13512 for ALL RLS and RLS Long-Term Integration Safety Groupings.

Table 2 Duration of Unique Subject Exposures to XP13512 for the All RLS and RLS Long-Term Integration Study Groupings (Safety Populations)

	All RLS		RLS Long-Term Integration	
	ISS Data Cut-off: 06 December 2007	120-Day Safety Data Cut-off: 31 July 2008	ISS Data Cut-off: 06 December 2007	120-Day Safety Data Cut-off: 31 July 2008
XP13512 All Doses: Duration of exposure in months (days)	XP13512 All Doses (N=1201)	XP13512 All Doses (N=1201)	XP13512 All Doses (N=777)	XP13512 All Doses (N=777)
<3 (<91 days)	389 (32)	378 (31)	214 (28)	203 (26)
≥3 (≥91 days)	812 (68)	823 (69)	563 (72)	574 (74)
≥6 (≥182 days)	495 (41)	602 (50)	329 (42)	436 (56)
≥9 (≥273 days)	192 (16)	398 (33)	192 (25)	398 (51)
≥12 (≥365 days)	120 (10)	313 (26)	120 (15)	313 (40)

Data Source: Table 4.5, Table 4.7; NDA 022399, 09 January 2009, Sequence Number 0004, m5.3.5.3 ISS, Table 1.13, Table 1.15

The maximum length of exposure is included for each subject (including on-treatment and taper).

Note: For subjects who entered Study XP055, their extent of exposure in the parent study and in the follow-up study is combined. Exposure may not be continuous.

All subjects were counted uniquely within each column; however, a subject may be represented in more than one exposure duration category e.g. a subject with 8 months exposure was counted in the 'at least 3 months' category and the 'at least 6 months' category (but not in the 'at least 9 months' or 'at least 12 months' categories).

REVIEWER COMMENT: In Sponsor Table 2 Exposure is presented for ALL RLS up through the 120 Day Cut Off . The total number of subjects exposed for 12 months or greater is 313, whereas all other tables presented for exposures with the application show a total of 144 exposures for 12 months or greater. This table (Sponsor Table 2) contains exposures which may NOT be continuous, and contains periods between tapering from parent study and enrolling in open label extension study, XP055.

The Sponsor was asked to submit extent of exposure by modal dose and study. On February 2, 2010, the Sponsor submitted Total days of Study Drug Exposure by Modal Dose.

Table 8.1.01, Total Days of Study Drug Exposure by Modal Dose

Protocol: RXP111490 FINAL (XP055)
 Population: Safety

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Table 8.101
 Total Days of Study Drug Exposure by Modal Dose

Duration of exposure in days (months) [1]	0mg (N=1) [2]	XP13512 600 mg (N=98)	XP13512 1200 mg (N=316)	XP13512 1800 mg (N=158)	Total XP13512 (N=573)
n	1	98	316	158	573
0-30 days (1 month)	1 (100%)	29 (30%)	38 (12%)	3 (2%)	71 (12%)
31-90 days (2-3 months)	0	8 (8%)	26 (8%)	8 (5%)	42 (7%)
91-180 days (4-6 months)	0	7 (7%)	18 (6%)	15 (9%)	40 (7%)
181-365 days (7-12 months)	0	41 (42%)	149 (47%)	86 (54%)	276 (48%)
>365 days (>12 months)	0	13 (13%)	85 (27%)	46 (29%)	144 (25%)

[1] Duration of exposure in days = date of last XP055 dose of study drug - date of first XP055 dose of study drug + 1.

[2] Note: Subject 2307004 has modal dose of 0mg because this subject was in the study for only eight days and missed treatment for four of these days. (Of the remaining days the subject took 600mg on one day and 1200mg on the other three days.)

Note: This summary includes data from XP055 study only and not the parent studies (XP052, XP053, XP081 and XP083). The safety population includes all subjects who enrolled into the study and who took at least one dose of study medication.

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There are a total of 144 subjects with RLS, who have been treated with gabapentin enacarbil for 12 months or greater. Thus, the sponsor meets ICH criteria for at least 100 subjects exposed for 12 months or greater.

REVIEWER COMMENT: The sponsor uses cumulative incidence of exposure, i.e. a subject who has taken drug for 6 months will be counted in 1month, 3 month and 6 month grouping.

EXTENT OF EXPOSURE BY DOSE

REVIEWER COMMENT: To date there is the sponsor has not provided the data to create an exposure table by dose in months. Tables have been submitted using patient days for each dose.

7.3 Major Safety Results

Deaths

There were **three** deaths that occurred during clinical development of gabapentin enacarbil.

1. XP044 Clinical Pharmacology Study/Subject 044222

A 51 year old male, healthy volunteer, admitted on March 27th 2005, to the clinical trial center to take part in the second treatment period. No adverse events were noted during the first treatment period. On March 28, 2005, during the second treatment period, the subject was dosed with 1200mg of XP13512 under fasted conditions at 7:50AM. The subject was discharged from the center 36 hours post study drug dose at 7:55PM on March 29, 2005. On [REDACTED] ^{(b) (6)}, the subject died from a “self inflicted gunshot wound of the head”. The incident had followed a domestic dispute. The subject’s toxicology screen was negative for opiates, cocaine, amphetamines, PCP, marijuana, methadone, propoxyphene, benzodiazepines, barbiturates, and tricyclic antidepressants. The subjects blood ethanol level was 0.17g/100mL at the time of autopsy (exact time unknown). The subject’s gabapentin level was less than 2mg/L.

The subject’s medical history included status post resection of lipoma on right shoulder (1985), spine compression fracture (1982), and status post tonsillectomy (1959). The subject had a history of adverse reaction to codeine (hallucinations). There was a family history of suicide and manic depression.

The subject’s social history was notable for alcohol consumption of 12 to 14 beers per week.

During the drug treatment study, the subject reported nasal congestion, sinus congestion, and somnolence. These symptoms had resolved by the time of study discharge.

2. XP060 Maintenance of Efficacy/Subject 186-4008

Subject was enrolled in protocol XP060, in the single blinded phase of the 36 week study. The subject received oral XP13512 QD from May 30, 2006 to November 8, 2006; 600mg QD for 3 days, then 1200mg QD for 159 days . Concurrent medical conditions include gastroesophageal reflux disease, hypertension, post menopausal, seasonal allergies, penicillin and sulfa allergies. Concomitant medications included hydrochlorothiazide, candesartan, cilexetil, pantoprazole, ibuprofen, hydrochlorothiazide/valsartan, citalopram, vitamin E, sertraline and hypercium. Of note, the subject had taken gabapentin from UK/UK/2005 until May 22, 2006.

On [REDACTED] (b) (6) days after start of XP13512, the subject aspirated on a piece of meat. Attempts were made to resuscitate the subject without success and the subject died on [REDACTED] (b) (6).

3. XP055 Open-Label Extension Study/Subject 181-3027

Subject 181-3027 was enrolled in XP055, An Open-Label Extension Study for the Treatment of Restless Legs Syndrome. The subject was a 48 year old male who had received XP13512 600mg QD from 03 May 2007 to 05 May 2007. The subject was then titrated to 1200mg XP13512 from 06 May 2007 until 03 April 2008. Of note the subject had previously been enrolled in study XP053 and received 600mg QD XP13512 from 08 February 2007 until 02 May 2007.

The subject's past history is notable for smoking 2 PPD for 8 years; he quit in 1981. Only concomitant medications noted were multivitamins.

On [REDACTED] (b) (6) days after the last dose of XP13512, the subject died due to an unknown cause.

The Death Certificate provided to the investigator stated that the subject fell from a highway overpass and died on [REDACTED] (b) (6). The cause of death was multiple blunt force injuries due to the fall. Acute alcohol intoxication was listed as a significant condition on the death certificate.

According to the subject's mother, final follow-up on report August 12, 2008 stated that the subject had been using alcohol and marijuana. According to the investigator, the subject's last dose of study medication was taken on April 30th, 2008, and the last dose of the taper medication was May 7, 2008. The subject was prescribed Neurontin starting on May 8th, 2008. However, it was unclear whether the subject took any of the Neurontin.

REVIEWER COMMENT: The first death appears to be unrelated to the study drug. Although gabapentin enacarbil belongs to a class of drugs with increased risk of suicidality, the subject took only one dose of study medication. In addition, the subject had a history of substance abuse which likely played a role in his suicide.

The second death appears to be accidental. However, the third death is unclear. The subject was within 30 days of taking study medication and it remains unclear whether he started Neurontin. The fall may have been accidental or may have been related to suicidal ideation. The current information available does not allow one to draw any definite conclusions.

Nonfatal Serious Adverse Events

Serious Adverse Events (SAEs) reported in Development Program Prior to 120 day Safety Update

Summary of Serious Nonfatal TEAEs Included in 120 Day Safety Update XP055

Table 23 Treatment-Emergent Serious Adverse Events Reported in Subjects (Safety Population: Study XP055)

Site/Subject Number	Age/Gender	SAE Preferred Term	Withdrawn?	Related?	Resolved?
Data cut-off up to and including 06 December 2007					
123/2021	57/F	Lumbar spinal stenosis	Yes	No	Yes (with sequelae)
128/2015	69/M	Cerebrovascular accident	No	No	Yes
129/2009	52/M	Angina unstable	No	No	Yes
133/2018	35/F	Cholecystitis acute	No	No	Yes
133/7012	44/F	Meningitis viral	No	No	Yes
142/5006	52/F	Road traffic accident	No	No	Yes (with sequelae)
150/3004	50/M	Non-cardiac chest pain	No	No	Yes
192/2026	58/F	Chest pain	No	No	Yes
200/3004	45/F	Pulmonary embolism	No	No	Yes
206/5010	67/F	Myocardial infarction	No	No	Yes
		Non-small cell lung cancer	Yes	No	Yes
903/3017	36/M	Colitis	No	No	Yes
Data from 07 December 2007 to cut-off of 31 July 2008					
104/7003	49/F	Intervertebral disc protrusion	Yes	No	Yes
128/5006	65/M	Back pain	No	No	Yes
		Drug withdrawal syndrome ^a	No	No	Yes
129/5014	56/F	Transient ischaemic attack	No	No	Yes
141/5010	37/F	Mental status changes	Yes	Yes	Yes
211/5007	49/M	Appendicitis	No	No	Yes
		Postoperative Infection ^b	No	No	No
228/7001	56/M	Lumbar vertebral fracture	No	No	Yes
		Back pain ^c	No	No	Yes
228/7008 ^d	53/F	Nerve compression	No	No	Yes (with sequelae)

Data Source: DSListing 2, DSListing 13, DSListing 14, and DSTable 8.10

- Withdrawal syndrome secondary to discontinuation of pain medication
- Narrative for Subject 211/5007 has the preferred term "Infection" (see Section 18.1.2).
- SAE of "Backpain" for Subject 228/7001 was updated to non-serious and is incorrectly reflected in the current DSListing 13 as an SAE. This will be corrected for the final report of this study.
- Subject 228/7008 also experienced an SAE of "exostosis" that is not included in DSListing 13, but is appropriately included in the narrative for this subject. This will be corrected for the final report of this study.

REVIEWER COMMENTS: The SAEs presented in the table do not present a clear pattern or safety signal.

CASE NARRATIVES FOR SAEs

Case narratives for the SAEs were reviewed with specific attention to suicidality, depression, and mood changes. Gabapentin enacarbil belongs to a class of drugs with an increased risk of suicidality..

In addition, one case was of special interest regarding seizures, is detailed below.

Subject 206-4019 - was at the time the event was reported a 50-year-old female with a history of hypertension, hypothyroidism and Turner's syndrome. The patient experienced a single

seizure during the taper phase of 1200 mg/day XP13512, however subsequent evaluation discovered focal abnormality on EEG. The patient had no further seizures and an initial CT scan of the head was unremarkable. The patient's seizure was not in the opinion of this reviewer related to the taper from XP13512.

SAEs Related to Liver Function

Case narratives for TEAEs related to Hepatic abnormalities were reviewed. None of the cases met criteria for Hy's Law. There were a few cases of elevated liver function studies in the Safety population. One of these is illustrated below.

Case 124/2013 Hepatic Enzyme Increased

36 year old female received XP13512 from April 4, 2006 until April 22, 2006. Past medical history included RLS, GERD, stress incontinence, herniated disc, degenerative disc disease, depression, anxiety and allergic rhinitis. Concomitant medications included cetirizine HCl, escitalopram oxalate, paracetamol, ibuprofen, ranitidine HCl and multivitamins. Laboratories including AST, ALT, alkaline phosphatase and total bilirubin were normal. Baseline GGTP was elevated at 139. Repeat labs drawn at start of treatment, April 4, 2006, revealed elevated AST of 63, ALT of 117, GGTP of 155 with normal alkaline phosphatase and bilirubin. After one week on study drug, AST was 60, ALT was 100, GGTP was 275 and alkaline phosphatase was 126, with normal total bilirubin (0.5). On April 19, 2006, AST was 95, ALT was 126, GGTP was 358, alkaline phosphatase was 159 and total bilirubin was 1.0 (normal). Subject was withdrawn from the study on April 22, 2006. The subject was referred to a gastroenterologist and repeat labs on June 26, 2006 revealed elevated GGTP at 156, and elevated ALT at 56, with normal AST, alkaline phosphatase, and total bilirubin.

REVIEWER COMMENT: Although there were several cases of elevated liver function tests, they did not cause severe liver injury and resolved spontaneously with discontinuation of the study drug. There does not appear to be a hepatic safety signal in human studies.

Adverse Events Leading to Withdrawal in Phase II and Phase III trials- Safety Population

Summary of Subject Disposition for ALL RLS safety population

Table 14 Summary of Subject Disposition (Safety Population: All RLS Studies)

	Number (%) of Subjects
	Total XP13512 (N=1201)
Completion Status	
Completed	479 (40) ³
Withdrawn	377 (31) ⁴
Ongoing	345 (29)
Primary Reason for Withdrawal⁴	
Ineligibility ¹	1 (<1)
Adverse Event	145 (12)
Treatment failure ²	51 (4)
Subject withdrew consent	93 (8)
Investigator judgement ¹	3 (<1)
Protocol non-compliance (after randomization)	21 (2)
Lost to follow-up	54 (4)
Death	1 (<1)

Data Source: Table 1.10

Note: Subjects can have only one reason for withdrawal. The disposition status within the parent study is presented for all subjects who received XP13512 within the parent study and did not continue into Study XP055. For subjects who continued into Study XP055, only the disposition status with regards to Study XP055 is presented.

Data is included for XP055 up to and including 06 December 2007.

- Reason not an option for Study XP060.
- Includes reason stated as 'Lack of efficacy' for Study XP060, this includes 27 subjects that completed the SB phase that were not randomized to the DB phase.
- One subject in Study XP060 who was withdrawn during taper because of a SAE (convulsion) is shown as completed.
- Note that only 2 of the 4 subjects from Study XP021 who withdrew are classified as withdrawals because the remaining 2 subjects were withdrawn after the subject had completed the XP13512 treatment phase.

Data cut-off: 06 December 2007

Appendix G contains detailed Table of 145 subjects who experienced AEs leading to Withdrawal

REVIEWER COMMENT: The most common adverse events leading to withdrawal were somnolence, sedation and dizziness. This is consistent with the safety results from efficacy trials.

Case Narratives

All case narratives were reviewed with special attention to AEs leading to Withdrawal with PT depression, mood swings, anxiety, cognitive disorders, mental status changes. One case narrative of special interest is detailed below. The remaining case narratives for AEs associated with cognitive and mood changes were mild and resolved with discontinuation of study medication.

Subject 14105010- was a 37-year-old at the time the SAE occurred. The subject was received 1200 mg/day of XP13512 for 165 days prior to experiencing the event. Her past medical history included hysterectomy, migraine, sacroiliitis, sinusitis, arthritis and dyshidrosis. The patient's neighbor who discovered the patient on the floor stated the subject possibly took an overdose of drug. She was found on the floor by the neighbor with "several empty medication bottles in her presence" and blood on her shirt. The investigator assessed the events as grade 3 or severe. Urine Drug Screen revealed Amitriptyline and Doxylamine were present. The patient was described as "incoherent and unable to walk, confused, disoriented and hallucinating after initially regaining consciousness, which lasted approximately 48 hours. The

site investigator "concluded that it is his opinion that the subject was previously taking medications that she did not report to his team" and the event was recoded from drug overdose to mental status change, which in the opinion of this reviewer was incorrect. The event should be considered a suicide attempt by ingestion.

REVIEWER COMMENT:

The sponsor listed this as an AE. In the Reviewer’s opinion, this should have been classified as an SAE under suicidality. This class of drugs is associated with increase incidence of suicidality.

Number of Patients Treated for RLS Who Withdrew From Placebo Controlled Trials By Dose

Table 31 TEAEs Leading to Withdrawal of at Least 1% of Subjects in Any Treatment Group (Safety Population: 12-Week Placebo-Controlled RLS Studies)

Preferred Term	Number (%) of Subjects					
	Placebo (N=245)	XP13512 600 mg (N=163)	XP13512 1200 mg (N=269)	XP13512 1800 mg (N=38)	XP13512 2400 mg (N=45)	XP13512 All Doses (N=515)
Any event	9 (4)	10 (6)	22 (8)	3 (8)	5 (11)	40 (8)
Dizziness	0	2 (1)	5 (2)	2 (5)	0	9 (2)
Somnolence	0	3 (2)	3 (1)	0	1 (2)	7 (1)
Sedation	0	1 (<1)	2 (<1)	0	1 (2)	4 (<1)
Nausea	0	0	2 (<1)	1 (3)	0	3 (<1)
Edema	0	0	0	0	1 (2)	1 (<1)
Back injury	0	0	0	0	1 (2)	1 (<1)
Neck injury	0	0	0	0	1 (2)	1 (<1)
Dyspnoea	0	0	0	0	1 (2)	1 (<1)
Vision blurred	0	0	0	0	1 (2)	1 (<1)

Data Source: ISS Table 2.31

Note: TEAEs with an onset date in the on-treatment and taper medication phases are included.

Sponsor Table 31 does not show a clear dose response for withdrawal due to dizziness, somnolence or sedation.

TREATMENT EMERGENT ADVERSE EVENTS

Sponsor’s Table of Nonserious TEAEs ≥ 2% XP13512 Compared to Placebo by dose

Protocol: RXPiSS XP13512 (GSK1838262)
 Population: Safety - 12-Week Controlled RLS Studies

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Table 2.7
 Summary of Treatment Emergent Adverse Events By Preferred Term
 in 12-Week Controlled RLS Studies

Preferred Term	Placebo (N=245)		XP13512 600mg (N=163)		XP13512 1200mg (N=269)		XP13512 1800mg (N=38)	
	Incidence	No. of events	Incidence	No. of events	Incidence	No. of events	Incidence	No. of events
Any event	182 (74%)	564	132 (81%)	418	226 (84%)	813	32 (84%)	101
Somnolence	12 (5%)	13	32 (20%)	37	61 (23%)	66	10 (26%)	11
Dizziness	11 (4%)	12	22 (13%)	29	59 (22%)	76	10 (26%)	15
Headache	28 (11%)	37	19 (12%)	22	41 (15%)	51	4 (11%)	4
Nasopharyngitis	17 (7%)	18	14 (9%)	15	21 (8%)	22	3 (8%)	5
Nausea	12 (5%)	13	9 (6%)	10	18 (7%)	21	3 (8%)	3
Fatigue	11 (4%)	12	9 (6%)	9	18 (7%)	20	1 (3%)	1
Dry mouth	5 (2%)	5	5 (3%)	5	12 (4%)	13	2 (5%)	2
Irritability	3 (1%)	3	6 (4%)	6	11 (4%)	11	2 (5%)	2
Diarrhoea	12 (5%)	14	6 (4%)	6	10 (4%)	10	2 (5%)	2
Insomnia	7 (3%)	7	9 (6%)	9	7 (3%)	7	2 (5%)	2
Sedation	3 (1%)	3	1 (<1%)	1	11 (4%)	15	3 (8%)	3
Upper respiratory tract infection	9 (4%)	10	10 (6%)	11	6 (2%)	6	1 (3%)	1
Feeling drunk	0	0	2 (1%)	2	7 (3%)	10	3 (8%)	5
Pain in extremity	7 (3%)	8	6 (4%)	6	8 (3%)	10	2 (5%)	2
Weight increased	5 (2%)	5	4 (2%)	4	9 (3%)	9	0	0
Constipation	8 (3%)	8	3 (2%)	3	10 (4%)	10	2 (5%)	2
Sinusitis	6 (2%)	6	5 (3%)	5	7 (3%)	8	0	0
Back pain	7 (3%)	7	6 (4%)	6	7 (3%)	8	0	0
Feeling abnormal	1 (<1%)	2	1 (<1%)	2	9 (3%)	9	3 (8%)	3
Muscle spasms	5 (2%)	6	6 (4%)	7	6 (2%)	7	0	0
Vertigo	0	0	2 (1%)	2	7 (3%)	7	2 (5%)	2
Arthralgia	5 (2%)	8	2 (1%)	3	8 (3%)	9	1 (3%)	1
Oedema peripheral	3 (1%)	3	1 (<1%)	1	7 (3%)	8	1 (3%)	1
Flatulence	2 (<1%)	3	5 (3%)	5	5 (2%)	5	0	0
Sinus congestion	8 (3%)	9	3 (2%)	3	7 (3%)	7	1 (3%)	1

Note: Adverse events with an onset date in the on-treatment and taper medication phases are included.
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REVIEWER COMMENT:

TEAE occurring during ALL 12-WEEK CONTROLLED RLS STUDIES reveals an increased incidence of sedation, somnolence and dizziness with increasing dose of gabapentin enacarbil. The type and pattern of adverse events is similar to the parent compound, Neurontin.

Peripheral edema has a greater incidence in drug groups, except gabapentin enacarbil 600mg, compared to placebo. Peripheral edema is also seen with related compound, Neurontin.

There is a greater incidence of irritability in drug treatment groups compared to placebo.

Overall, gabapentin enacarbil has a similar adverse event profile to its parent compound, Neurontin.

COMMON ADVERSE EVENTS

The Sponsor's Analysis of Somnolence and Sedation related TEAEs in The Combined 12 Week Controlled Trials

Table 47 Characteristics of Somnolence/ Sedation TEAEs Combined (Safety Population: 12-Week Placebo-Controlled RLS Studies)

Preferred Term	Number (%) of Subjects					
	Placebo (N=245)	XP13512 600mg (N=163)	XP13512 1200mg (N=269)	XP13512 1800mg (N=38)	XP13512 2400mg (N=45)	XP13512 All Doses (N=515)
Somnolence						
Number of subjects	12 (5)	32 (20)	61 (23)	10 (26)	23 (51)	126 (24)
Number of events	13	37	66	11	30	144
Sedation						
Number of subjects	3 (1)	1 (<1)	11 (4)	3 (8)	3 (7)	18 (3)
Number of events	3	1	15	3	4	23
Any event (somnolence and/or sedation)						
Number of subjects	15 (6)	33 (20)	72 (27)	12 (32)	26 (58)	143 (28)
Number of events	16	38	81	14	34	167
Treatment-related	15 (100)	31 (94)	68 (94)	12 (100)	26 (100)	137 (96)
Leading to dose reduction	1 (7)	1 (3)	16 (22)	1 (8)	7 (27)	25 (17)
Leading to interruption in study medication	0	0	1 (<1)	0	0	1 (<1)
Leading to withdrawal	0	4 (12)	5 (7)	0	2 (8)	11 (8)
Severe	0	3 (9)	3 (4)	0	1 (4)	7 (5)

Data Source: Table 2.84, Table 2.14

Note: TEAEs with an onset date in the on-treatment and taper medication phases are included.

REVIEWER COMMENT: The combined incidence of somnolence/sedation reveal a clear dose response; placebo 6% subjects, 600mg 20% of subjects, 1200mg 27% of subjects, 1800mg is 32% of subjects and 2400mg is 58% of subjects.

The greatest number of subjects with dose reduction, secondary to somnolence/sedation is in the 1200mg cohort.

DIZZINESS

Sponsor Table 48 shows the number of subjects as well as number of events of dizziness in ALL 12 WEEK CONTROLLED RLS STUDIES.

Table 48 Characteristics of Dizziness TEAEs (Safety Population: 12-Week Placebo-Controlled RLS Studies)

Preferred Term	Number (%) of Subjects					
	Placebo (N=245)	XP13512 600mg (N=163)	XP13512 1200mg (N=269)	XP13512 1800mg (N=38)	XP13512 2400mg (N=45)	XP13512 All Doses (N=515)
Any event						
Number of subjects	11 (4)	22 (13)	59 (22)	10 (26)	18 (40)	109 (21)
Number of events	12	29	76	15	23	143
Treatment-related	8 (73)	19 (86)	55 (93)	10 (100)	18 (100)	102 (94)
Leading to dose reduction	0	0	4 (7)	0	4 (22)	8 (7)
Leading to interruption in study medication	0	0	0	0	0	0
Leading to withdrawal	0	2 (9)	5 (8)	2 (20)	0	9 (8)
Severe	1 (9)	1 (5)	1 (2)	0	1 (6)	3 (3)

Data Source: Table 2.14

Note: TEAEs with an onset date in the on-treatment and taper medication phases are included.

REVIEWER COMMENT: Similarly to somnolence/sedation, there is a clear dose response to dizziness.

The greatest number of subject withdrawals secondary to dizziness occur in 1200mg and 2400mg cohort. There were no withdrawals due to dizziness in the 600mg cohort.

Reviewer's Analysis of Common Adverse Events

The table below, courtesy Dr. Podskalny, shows the Review Teams, independent assessment of AE by dose, and all doses of gabapentin enacarbil versus placebo. The table was created using AE.XPT dataset provided by the sponsor, recoding with preferred term. The preferred terms were selected by incidence.

(Source: Review Team)

Number of events grouped as indication impaired cognition/total number of AEs

Preferred Term	Placebo N=245 N AEs=564		XP13512 600mg N=163) N AEs=418	XP13512 1200mg N=269 N AEs=813	XP13512 1800mg N=38 N AEs=101	XP13512 2400mg N=45 N AEs=175	XP13512 All Doses N=515 N AEs=1507
Any event	182 (74)	132 (81)	226 (84)	32 (84)	44 (98)	434 (84)	

Somnolence	12 (5)	32 (20)	61 (23)	10 (26)	23 (51)	126 (24)
Dizziness	11 (4)	22 (13)	59 (22)	10 (26)	18 (40)	109 (21)
Fatigue	11 (4)	9 (6)	18 (7)	1 (3)	2 (4)	30 (6)
Sedation	3 (1)	1(<1)	11 (4)	3 (8)	3 (7)	18 (3)
Feeling drunk	0	2 (1)	7 (3)	3 (8)	4 (9)	16 (3)
Feeling abnormal	1(<1)	1(<1)	9 (3)	3 (8)	1 (2)	14 (3)
Vertigo	0	2 (1)	7 (3)	2 (5)	2 (4)	13 (3)
Disorientation	1(<1)	2 (1)	4 (1)	2 (5)	1 (2)	9 (2)
Vision blurred	0	1(<1)	4 (1)	0	4 (9)	9 (2)
Disturbance in attention	1(<1)	3 (2)	2(<1)	2 (5)	0	7 (1)
Total	40	75	182	36	58	351
% Total number of AEs	7.09	17.94	22.39	35.64	33.14	20.90

The reviewer coded up by preferred term (PT) to capture the sedating side effects of this class of drug. There is clearly a dose response relationship in adverse events.

(Source: Reviewer)

		XP13512	XP13512	XP13512	XP13512
Preferred Term	Placebo	600mg	1200mg	1800mg	2400mg
(MedDRA v11-0)	(N=246)	(N=163)	(N=272)	(N=38)	(N=45)
AT LEAST ONE EVENT	183 (74.4%)	132 (81.0%)	227 (83.5%)	32 (84.2%)	44 (97.8%)
Dizziness	11 (4.5%)	22 (13.5%)	59 (21.7%)	10 (26.3%)	18 (40.0%)
Somnolence	12 (4.9%)	32 (19.6%)	61 (22.4%)	10 (26.3%)	23 (51.1%)
Vision blurred	0 (0.0%)	1 (0.6%)	4 (1.5%)	0 (0.0%)	4 (8.9%)
Feeling drunk	0 (0.0%)	2 (1.2%)	7 (2.6%)	3 (7.9%)	4 (8.9%)
Non-cardiac chest pain	2 (0.8%)	1 (0.6%)	0 (0.0%)	0 (0.0%)	3 (6.7%)
Euphoric mood	0 (0.0%)	0 (0.0%)	0 (0.0%)	1 (2.6%)	1 (2.2%)
Restless legs syndrome	0 (0.0%)	0 (0.0%)	0 (0.0%)	1 (2.6%)	1 (2.2%)

REVIEWER COMMENT: Similarly to the Sponsor, the Reviewer found a dose response for the most common adverse events, dizziness and somnolence.

Adverse Events of Special Interest

SUICIDALITY

XP13512 is a pro-drug of gabapentin (Neurontin) and therefore belongs to the class of anti-epileptic drugs. FDA has evaluated 11 AEDs and suicidality (Statistical Review and Evaluation: Antiepileptic Drugs and Suicidality), including gabapentin. There is an increased risk of suicidality with all of the drugs studied including gabapentin. During clinical development, the division had recommended including a scale to rate suicidality, such as the Columbia Suicidality Scale. However the sponsor chose to retrospectively search the adverse event reports for suicidality.

Search Terms for Suicidality and Narrative Process

Search terms used in the process include the following: Any free text string, or events coded to PTs or verbatim term that include the text string “accident-“, “injur-“, “suic”, “overdos”, “accidental overdose”, “attempt”, “cut”, “gas”, “hang”, “hung”, “jump”, “mutilat-“, “self damag”, “self harm”, “self inflict”, “shoot”, “slash”, “poison”, “asphyxiation”, “suffocation”, “firearm”, “burn”, “drown”, “gun”, “immolat-“, “monoxide-“, “tox”, “lacerat”, “death”, “die” were identified as an AE of potential special interest.

Narratives were written for events that contain at least one of the above text strings, except for obvious false positives (e.g., ‘gastrointestinal’) determined by a sponsor medical reviewer or those outside of the exposure window (e.g., prior to randomized treatment). All narratives were blinded to treatment, dates and concomitant medications, given an alpha identifier from Dr. (b) (4) (followed by a GSK numeric identifier), and then delivered to (b) (4) for classification. A spreadsheet was returned from (b) (4) containing the narrative identifiers and corresponding classification ratings.

(b) (4) Classification of Events

Classification of the blinded narratives was conducted independently at (b) (4) using the C-CASA method [Posner, 2007]. The following ratings, which differ from the ratings provided in Posner, 2007, were applied [(b) (4) personal communication 23 April 2008]:

1. Completed suicide
2. Suicide attempt
3. Preparatory actions towards imminent suicidal behavior
4. Suicidal ideation
5. Self-injurious behavior, intent unknown
6. Not enough information, fatal
7. Nonsuicidal self-injurious behavior

- 8. Other
- 9. Not enough information, non-fatal

The sponsor stated in the application that none of the adverse events associated with suicidality were felt to be study drug related. As stated above, these adverse events were independently reviewed by (b) (4)

REVIEWER COMMENT: Retrospective review of TEAEs for suicidality is not the standard method of collecting this information. The division has recommended using scales, such as the Columbia Suicide Scale, prospectively. The sponsor's assessment is not informative and therefore, it is difficult to make any conclusions about the risk of suicidality and gabapentin enacarbil.

DAYTIME SLEEPINESS

Currently marketed drugs for idiopathic RLS have significant daytime sleepiness associated with them (REQUIP and Mirapex). In addition, gabapentin, gabapentin enacarbil being the pro-drug, also has associated sedation,

EPWORTH SLEEPINESS SCALE (ESS)

The ESS was used to assess daytime sleepiness in the pivotal trials. Sponsor Table 5.41 shows Summary of ANCOVA for 12-Week Controlled RLS Studies, for change from Baseline of Total ESS score.

Protocol: RXP1SS XP13512 (GSK1838262)
 Population: Safety - 12-Week Controlled RLS Studies

Table 5.41
 Summary of Analysis of Covariance of the Change from Baseline in the Total Score of the ESS

	Treatment	N	n	Adjusted Mean	S.E. of Adjusted mean	Difference XP13512 vs. Placebo [1]	95% CI for Treatment Difference	P-Value for treatment difference
Week 4	XP13512 600mg	163	138	-1.9	0.32	-0.51	(-1.32, 0.29)	0.211
	XP13512 1200mg	269	202	-2.3	0.25	-0.97	(-1.67, -0.27)	0.007
	XP13512 1800mg	38	32	-1.6	0.66	-0.23	(-1.67, 1.21)	0.752
	XP13512 2400mg	45	35	-1.0	0.64	0.40	(-0.99, 1.80)	0.570
	Placebo	245	172	-1.4	0.27			
	XP13512	515	407	-2.0	0.18	-0.71	(-1.34, -0.08)	0.026
	Placebo	245	172	-1.3	0.27			
Week 8	XP13512 600mg	163	138	-2.3	0.33	-0.38	(-1.20, 0.45)	0.371
	XP13512 1200mg	269	198	-3.0	0.26	-1.07	(-1.79, -0.35)	0.004
	XP13512 1800mg	38	32	-2.9	0.67	-0.95	(-2.42, 0.51)	0.200
	XP13512 2400mg	45	35	-3.0	0.65	-1.06	(-2.48, 0.36)	0.143
	Placebo	245	163	-1.9	0.28			
	XP13512	515	403	-2.8	0.19	-0.84	(-1.49, -0.20)	0.011
	Placebo	245	163	-2.0	0.28			
Week 12 / ET	XP13512 600mg	163	148	-2.7	0.34	-0.66	(-1.51, 0.18)	0.125
	XP13512 1200mg	269	218	-3.0	0.26	-0.92	(-1.66, -0.19)	0.014
	XP13512 1800mg	38	34	-2.0	0.70	0.09	(-1.42, 1.60)	0.909
	XP13512 2400mg	45	42	-1.9	0.64	0.15	(-1.25, 1.55)	0.834
	Placebo	245	188	-2.1	0.28			
	XP13512	515	442	-2.7	0.19	-0.72	(-1.38, -0.07)	0.031
	Placebo	245	188	-2.0	0.28			

[1] A negative treatment difference indicates a benefit of the dose of XP13512 relative to placebo
 Note: The total score of the ESS ranges from 0 to 24, where 0=least severe daytime sleepiness and 24=most severe daytime sleepiness
 Note: Analysis of covariance adjusted for study, pooled site, baseline ESS total score and treatment group
 Note: The p-value represents the results of the respective active dose of XP13512 vs. placebo
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REVIEWER COMMENT: Change from Baseline to Week 12 showed significant improvement (negative number) in 1200mg and placebo, with minimal change in the other treatment groups. Overall ESS did not appear to be affected by drug.

SUDDEN ONSET OF SLEEP (SOS)

For the currently approved medications for RLS (Mirapex, Requip), there is an increased incidence of sudden onset of sleep.

Sponsor Table 113 presents the sudden onset of sleep questionnaire results by dose.

Table 113 Sudden Onset of Sleep Questionnaire Results for Confirmed and Unable to Determine Events (Safety Population: 12-Week Placebo-Controlled RLS Studies)

	Placebo (N=245)	XP13512 600 mg (N=163)	XP13512 1200 mg (N=269)	XP13512 1800 mg (N=38)	XP13512 2400 mg (N=45)	XP13512 All Doses (N=515)
Baseline						
n	201	161	225	38	45	469
Any sleep attacks in past week, n (%)	2 (<1)	0	4 (2)	0	1 (2)	5 (1)
Number of sleep attacks in past week		0		0		
Mean (SD)	4.5 (2.12)		3.3 (0.50)		1.0 (NA)	2.8 (1.1)
Median	4.5		3.0		1.0	3.0
Any On Treatment Visit						
n	225	157	250	35	44	486
Any sleep attacks in past week, n (%)	5 (2)	0	1 (<1)	0	3(7)	4 (<1)
Number of sleep attacks in past week		0		0		
Mean (SD)	2.2 (1.10)		3.0 (NA)		2.3 (1.15)	2.5 (1.00)
Median	2.0		3.0		3.0	3.0

Data Source: Table 5.35

Gabapentin enacarbil 2400mg/day has the highest percentage of sleep attacks while on treatment. However, the placebo group has the greatest number of sleep attacks.

Sponsor tables 114 and 116 show sudden onset of sleep events by study.

Table 114 Listing of Subjects with Confirmed or Unable to Determine Events Reported on the SOS-Q (12 Week Placebo-Controlled RLS Studies)

Site No./ Subject	Treatment	Week	Number of sleep attack events reported in the past week	Any Event Confirmed	Activities engaged in at time of event
XP052					
124/2040	NA	Baseline	6	None	Both passive and active
	NA	ET ²	4	None	Both passive and active
129/2031	NA	Baseline	3	None	Passive
124/2030	NA	Baseline	3	None	Passive
124/2041	NA	Baseline	4	None	Both passive and active
133/2016	NA	Baseline	3	None	Passive
133/2018	Placebo	4	2	None	Passive
141/2009	Placebo	8	2	Yes	Both passive and active
129/2015 ¹	Placebo	12	2	None	Passive
142/2007 ¹	Placebo	12	1	None	Passive
XP053					
203/3001	NA	Baseline	3	None	Active
	XP 1200mg	4	1	Yes	Active
	XP 1200mg	8	3	Yes	Both passive and active
	XP 1200mg	12	1	Yes	Active
XP081					
206/5033	NA	Baseline	1	None	Passive
	XP 2400mg	ET ³	3	None	Passive
191/5002	XP 2400mg	4	1	Yes	Passive
	XP 2400mg	8	1	None	Active
206/5038	XP 2400mg	12	3	Yes	Passive

1. SOS-Q assessments were added after the start of study XP052 and thus some early assessment of the SOS-Q including the baseline visit were not completed.
 2. Early Termination Visit completed 6 days after the Baseline Visit.
 3. Early Termination Visit completed at Week 3.
- Data Source: CSR XP053 DS Listing 22.1 and DS Listing 22.2 ; XP081 CSR DS Listing 28.2, DS Listing 28.1, CSR XP052, Table 22; CSR XP052 Section 8.2.7; CSR XP053 Section 8.2.7; CSR XP081 Section 9.2.7.

Table 116 Listing of Subjects with Confirmed or Unable to Determine Events Reported on the SOS-Q in Study XP060 and Ongoing Study XP055

Study/ Site No./ Subject No	Treatment (XP 13512 or Placebo)	Week	Number of sleep attack events reported in the past week	Any Event Confirmed	Activities engaged in at time of event
XP060					
135/4010	NA	Baseline	2	None	Passive
175/4026	NA	Baseline	6	None	Both passive and active
190/4009	NA	Baseline	1	None	Passive
206/4030	NA	Baseline	1	None	Active
206/4033	NA	Baseline	7	None	Both passive and active
212/4025	NA	Baseline	2	None	Passive
139/4006 ²	XP 1200mg	8	1	None	Passive
145/4007 ²	XP 1200mg	8	3	None	Active
144/4006 ²	XP 1200mg	20	15	Yes	Both passive and active
175/4013 ²	XP 1200mg	20	3	Yes	Both passive and active
190/4004 ²	XP 1200mg	20	7	None	Passive
XP055					
191/2010 ¹	XP 1200mg	1	1	Yes	Active
133/7005 ²	XP 1200mg	24	2	Yes	Passive

Data Source: XP055 CSR DS Listing 10.2 and DS Listing 12, XP060 CSR DS Table 8.29.1, DS Table 8.29.2, DS Listing 25.2; CSR XP060 Section 8.2.6; Interim CSR XP055 Section 14.4.8.

1. Reported an AE but did not complete the SOS-Q form.
2. Did not complete an assessment of the SOS-Q prior to the start of treatment.

REVIEWER COMMENT: When viewing the result of the Sudden Onset of Sleep questionnaire by individual study, it appears that the number of sleep attack events is higher in drug treatment group compared to placebo, except for study XP052. Interestingly, all reports of sleep attacks occur in drug treatment groups at 1200mg or higher.

BRIEF ASSESSMENT OF COGNITION (BAC)

The sponsor included cognitive testing in placebo controlled trials. Drugs causing sedation, such as the dopamine agonists, may have an effect on cognition. There is also some suggestion that Neurontin (**look up reference**) has an effect on cognition. The sponsor used the BAC to assess cognition.

This battery includes:

- verbal memory recall,
- digit sequencing,
- token motor task,
- verbal fluency,
- symbol coding
- Tower of London.

The BAC was completed in 3 randomized, multicenter, parallel group, double-blind, placebo-controlled studies, XP053, XP081 and XP083.

Sponsor Table 200 shows the BAC Total Score, Change from Baseline by Visit in Combined Studies XP053, XP081 and XP083.

Table 200 BAC Total Score: Change from Baseline by Visit including Final Visit –LOCF (Safety Population: Combined Studies XP053, XP081 and XP083)

		Placebo ¹ N=201		XP13512 600 mg N=163		XP13512 1200 mg N=187		XP13512 1800 mg N=72		XP13512 2400 mg N=45		XP13512 All Doses N=467	
BAC Total Score		Observed Score	Change from Baseline	Observed Score	Change from Baseline	Observed Score	Change from Baseline	Observed Score	Change from Baseline	Observed Score	Change from Baseline	Observed Score	Change from Baseline
Baseline	n	201	-	163	-	185	-	72	-	44	-	464	-
	Mean	49.4	-	46.4	-	47.7	-	46.0	-	47.2	-	46.9	-
	SD	10.40	-	11.23	-	10.75	-	10.49	-	10.97	-	10.89	-
Week 2	n	61	61	-	-	28	28	33	33	-	-	61	61
	Mean	57.8	5.7	-	-	53.6	5.3	49.1	5.3	-	-	51.2	5.3
	SD	10.41	6.00	-	-	12.18	7.01	11.88	6.88	-	-	12.13	6.88
Week 4	n	34	34	40	40	36	36	33	33	37	36	146	145
	Mean	50.3	2.3	50.4	3.4	47.0	2.5	50.6	2.1	49.6	2.3	49.4	2.6
	SD	10.53	5.78	10.36	7.47	9.46	5.89	9.50	5.58	11.23	6.27	10.19	6.35
Week 12/ET ²	n	117	117	143	143	133	132	29	29	32	31	337	335
	Mean	51.8	4.7	50.6	3.0	50.2	2.8	51.9	3.5	54.0	6.1	50.9	3.2
	SD	10.32	7.19	10.17	6.92	10.41	6.39	12.57	7.50	12.91	7.45	10.78	6.85
Final Visit ³	n	182	182	149	149	166	165	66	66	37	36	418	416
	Mean	53.7	5.0	50.3	3.2	50.4	3.2	50.6	4.5	53.0	5.7	50.7	3.6
	SD	10.8	6.77	10.27	6.92	10.91	6.55	11.83	7.02	12.7	7.07	10.99	6.82

Data source: Table 5.42, Table 5.48, Table 5.44 and Table 5.50

1. Includes subjects randomized to placebo plus diphenhydramine treatment in Study XP083 (for visits prior to diphenhydramine administration only).
2. Week 12/ET includes all subjects who either completed the BAC at the Week 12 visit, or completed the BAC prior to Week 12 at an ET visit. The Week 12/ET visit does not include any imputation for missing values and is a report of observed cases.
3. The Final Visit includes the last post-baseline BAC assessment from within the integrated dataset, and includes the last observation carried forward technique for subjects who did not complete the BAC at the last planned visit included in the integrated dataset.

REVIEWER COMMENT: All dose groups, including PBO, showed improvement in BAC Total Scores compared to Baseline.

ANCOVA was performed for BAC Total score comparing active treatment to PBO. This is presented in Sponsor Table 201.

Table 201 BAC Total Score: Analysis of Covariance and Adjusted Mean Change from Baseline by Visit and at the Final Visit - LOCF (Safety Population: Combined Studies XP053, XP081 and XP083)

BAC Total Score		Individual Dose Comparisons					All Dose Comparison	
		Placebo ¹ N=201	XP13512 600 mg N=183	XP13512 1200 mg N=187	XP13512 1800 mg N=72	XP13512 2400 mg N=45	Placebo ¹ N=201	XP13512 All Doses N=487
Adjusted change from baseline ² - Week 2	Mean (SE)	6.5 (0.91)	-	5.5 (1.26)	5.0 (1.17)	-	6.5 (0.90)	5.2 (0.87)
Adjusted treatment difference ³ at Week 2 XP13512-Fbo ³	Mean 95% CI P-Value	-	-	-1.04 (-3.98, 1.91) 0.487	-1.54 (-4.47, 1.40) 0.302	-	-	-1.29 (-3.70, 1.12) 0.291
Adjusted change from baseline ² - Week 4	Mean (SE)	2.8 (1.03)	3.6 (0.96)	2.2 (1.04)	2.7 (1.07)	2.5 (1.01)	2.8 (1.03)	2.8 (0.56)
Adjusted treatment difference ³ at Week 4 XP13512-Fbo ³	Mean 95% CI P-Value	-	0.88 (-1.82, 3.58) 0.521	-0.51 (-3.30, 2.28) 0.717	-0.03 (-2.86, 2.80) 0.984	-0.22 (-2.98, 2.55) 0.876	-	0.06 (-2.13, 2.25) 0.957
Adjusted change from baseline ² - Week 12/ET	Mean (SE)	5.7 (0.62)	4.3 (0.57)	3.9 (0.59)	2.9 (1.24)	5.0 (1.20)	5.7 (0.61)	4.1 (0.37)
Adjusted treatment difference ³ at Week 12/ET XP13512-Fbo ³	Mean 95% CI P-Value	-	-1.41 (-2.96, 0.14) 0.074	-1.75 (-3.33, -0.18) 0.029	-2.84 (-5.65, -0.03) 0.047	-0.66 (-3.40, 2.08) 0.638	-	-1.59 (-2.93, -0.25) 0.020
Adjusted change from baseline ² - Final Visit	Mean (SE)	5.8 (0.49)	4.6 (0.60)	4.2 (0.53)	3.4 (0.82)	4.9 (1.15)	5.8 (0.49)	5.8 (0.49)
Adjusted treatment difference ³ at Final Visit XP13512-Fbo ³	Mean 95% CI P-Value	-	-1.22 (-2.68, 0.25) 0.103	-1.63 (-3.00, -0.26) 0.020	-2.35 (-4.24, -0.46) 0.015	-0.85 (-3.35, 1.65) 0.506	-	-1.58 (-2.73, -0.44) 0.007

Source Data: Table 5.46 and Table 5.52.

1. Includes subjects randomized to placebo plus diphenhydramine treatment in Study XP083 (for visits prior to diphenhydramine administration only).
2. A positive change from baseline indicates improved cognitive performance.
3. A negative treatment differences indicates more impaired cognitive performance of the respective dose of XP13512 treatment relative to placebo.

REVIEWER COMMENT: Significant differences in change of Baseline BAC Total Score are noted between 1200mg and 1800mg versus placebo (p=0.02 and p=0.015 respectively) versus 600mg and 2400mg (p=0.103 and p=0.506 respectively). Sponsor Table 5.52

Protocol: RXP13512 (GSK1838262) Page 1 of 1
 Population: Safety - Studies XP053, XP081 and XP083 combined
 Table 5.52
 Summary of Analysis of Covariance of the Change from Baseline in the BAC Total Score
 At Final Visit (LOCF)

Change from baseline to:	Treatment [2]	N	n	Adjusted mean	S.E.	Difference XP13512 vs. placebo [1]	95% CI for treatment difference	P-Value
Final Visit	XP13512 600mg	163	149	4.6	0.60	-1.22	(-2.68, 0.25)	0.103
	XP13512 1200mg	187	165	4.2	0.53	-1.63	(-3.00, -0.26)	0.020
	XP13512 1800mg	72	66	3.4	0.92	-2.35	(-4.24, -0.46)	0.015
	XP13512 2400mg	45	36	4.9	1.15	-0.85	(-3.35, 1.65)	0.506
	Placebo	201	192	5.8	0.49			
	XP13512 Placebo	467	416	4.2	0.35	-1.58	(-2.73, -0.44)	0.007
	Placebo	201	192	5.8	0.49			

[1] A negative treatment difference indicates reduced cognitive function with the dose of XP13512 relative to placebo
 [2] Includes subjects randomized to both placebo and diphenhydramine in study XP083
 Note: Analysis of covariance adjusted for study, pooled site, baseline BAC total score and treatment group
 Note: The p-value represents the results of the respective active dose of XP13512 vs. placebo
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AUGMENTATION AND EARLY MORNING REBOUND (EMR)

Augmentation and early morning rebound are known complications from the treatment of RLS with currently approved drugs. Augmentation is the worsening of RLS symptoms (earlier onset, worsening severity) with drug treatment. EMR refers to earlier onset of symptoms upon awakening. A 24 hour RLS diary was maintained. This data from this diary was used to assess augmentation and early morning rebound.

Augmentation and EMR – XP053

Sponsor Table 54, shows the percent of subjects with RLS symptoms by treatment group. It also shows the median time to first RLS symptom by 24-hour RLS records. All treatment groups (PBO, 600mg, 1200mg) had lower percentage of subjects with RLS symptoms (77%, 64.7% and 63% respectively) favoring drug treatment groups. The median onset to first RLS symptoms increased, therefore improved, in all groups as well, again slightly favoring drug treatment groups.

Table 54 Percent of Subjects with RLS Symptoms and Median Time of First RLS Symptom by 24-hour RLS Records (MITT Population: Study XP053)

	Percent of Subjects w/ RLS Symptoms ^a			Median Onset Time (hr) (CI)		
	Placebo N=96	XP13512 600 mg N=114	XP13512 1200 mg N=111	Placebo N=96	XP13512 600 mg N=114	XP13512 1200 mg N=111
Baseline	95.7	99.1	99.1	5.0 (2.0, 8.0)	5.8 (4.0, 9.5)	6.3 (2.0, 8.0)
Week 2	83.9	80.6	69.9	10.0 (6.5, 12.0)	12.0 (8.0, 13.5)	13.0 (12.0, 15.5)
Week 12	77.0	64.7	63.0	12.8 (9.5, 15.0)	13.5 (12.5, 16.5)	13.8 (11.5, 17.0)

Data Source: DSTable 7.13.2

a. Percentage calculated as 1 minus the symptom free rate times 100 at 24 hours.

Augmentation and EMR- XP052

Sponsor Table 40 outlines the Median Time of First RLS Symptoms by 24 hour RLS Record.

Table 40 Percent of Subjects with RLS Symptoms and Median Time of First RLS Symptom by 24-hr RLS Records

	Percent of Subjects w/ RLS symptoms		Median Onset Time (hr) (CI)		
	Placebo N=108	XP13512 N=112	Placebo N=108	XP13512 N=112	p value
	% ^a	% ^a			
Baseline	99	97	6.0 (2.5-9.5)	6.0 (2.5-9.5)	
Week 2	92	74	9.0 (5.0-12.0)	13.3 (10.5-14.5)	0.0006
Week 12	82	49	11.5 (10.5-13.0)	NA (>24 hrs)	<0.0001

a. Percentage calculated as 1 minus the symptom free rate times 100 at 23.5 hours.

Data Source: DSTable 14.2

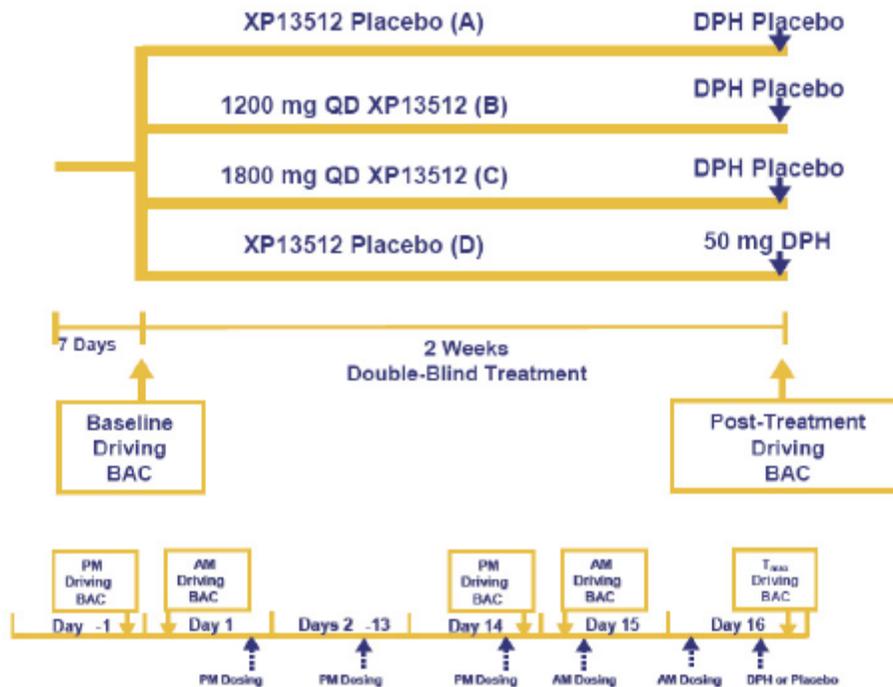
There was a statistically significant difference between placebo and XP13512 1200mg in median time of first RLS symptoms by 24 hour RLS records. At week 12, placebo group had median time of onset in hours of 11.5 as compared to Baseline of 6.0 hours. XP13512 had >24 hour median time of onset of first RLS symptoms compared to 6 hours at baseline.

There is improvement in median time to onset of RLS symptoms, i.e. no evidence of augmentation or EMR, in both groups. However, XP13512 group appeared to have continuous benefit, no RLS symptoms, by week 12 in 49% of the subjects.

SIMULATED DRIVING ASSESSMENT

STUDY XP083- Simulated Driving and Cognition

Figure 1 Overall Study Design



XP083 was a randomized, double-blind, active and placebo controlled study to assess simulated driving performance after treatment with gabapentin enacarbil for two weeks. Subjects were randomized in a 1:1:1:1 ration in a double blind placebo controlled trial.

The four treatment arms included:

- XP13512 Placebo + Diphenhydramine Placebo (PBO)
- XP13512 1200mg/day + Diphenhydramine Placebo
- XP13512 1800mg/day + Diphenhydramine Placebo
- XP13512 Placebo + 50mg Diphenhydramine

Sponsor Table 1 shows the Time and Events Schedule for Trial XP083

Table 1 Time and Events Schedule (Continued)

Period →	Screening	Baseline		Treatment Period				Taper Period	Follow-Up	Early-Term
Visit Number →	1		2 ^a			3 ^a		4		
Study Day →	-8	-3	-1	1	2-13	14	15	16	17-23	51
Visit Window (Days) →	-14		+1			+1		+1		±3
Approximate Drive Test Time →			5 PM ^a	7 AM ^a		7 PM ^a	7 AM ^a	5 PM		
Study Drug and Dosing Diary Dispensed				X						
Diphenhydramine Administration 2 Hours Pre-drive								X		
Study Drug Accountability						X	X	X		X
Record AEs			X	X	X ^d		X	X	X	
Record Concomitant Medications	X		X	X	X ^d		X	X	X	
Taper Study Drug Dispensed								X		
Study Coordinator Phone Call		X ^c			X ^d					
End of Study Follow-Up Call									X	

Data Source: Attachment 1 (Protocol Study XP083)

- a. Visits 2 and 3 were overnight stays with Simulated Driving Tests conducted between 5 PM and 8 PM (Visit 2[Day -1]) and 7 PM and 9 PM (Visit 3[Day 14]) and the following morning between 7 AM and 9 AM (Visit 2[Day 1] and Visit 3[Day 15]).
- b. Visit 1 or Visit 18 only: A 5-minute simulator practice test was conducted.
- c. Subject was called prior to visit as a reminder to start and complete any required diaries and to abstain from solid food from noon until 5 PM on the day of Visit 2.
- d. Day 9: Subject was called to inquire about their general health and to record any AEs and concomitant medications. Day 12: Subject was called prior to visit as a reminder to start and complete any required diaries and to abstain from solid food from noon to approximately 5 PM for Visit 3 (Day 14).

Note that there are two Baseline days (Day -1 and Day 1).

- Day -1 has Baseline driving at 5pm. This Baseline visit was used for comparison to assessments performed in the evening on Day 14 and Day 16 (evening).
- Day 1 has Baseline driving at 7am. This Baseline visit was used for comparison to assessments performed on Day 15 (morning).

In addition, diphenhydramine 50mg is only given on study Day 16 to XP13512 Placebo + 50mg Diphenhydramine group. All other study days, this group receives XP13512 placebo + diphenhydramine placebo.

ASSESSMENTS

Primary Assessment

To assess simulated driving on performance using change in Baseline-adjusted mean lane position variability (LPV) after XP13512 or placebo, measured by simulated driving performance at Tmax (Day 16 assessments).

REVIEWER COMMENT: The primary endpoint was the change from baseline (Day 1) in overall lane position variability (LPV) measured by simulated driving performance at the estimated time to maximum drug concentration (Tmax) on Day 16. Under normal prescribing conditions, the drug would be given at 5pm with Tmax occurring at approximately midnight. In order for the subject to be awake during driving time, the drug was given at 11am on Day 16 and driving was tested at Tmax, approximately 7 hours after dosing. Of note, diphenhydramine

was given two hours prior to simulated driving test. Day -1(evening) was used as baseline for change in LPV on Day 16.

Secondary Assessments:

Simulated Driving on Day 14 (evening assessment, no diphenhydramine group) and on Day 15 (morning assessment prior to drug dosing).

REVIEWER COMMENT: On Day 14, simulated driving was tested approximately two hours after treatment with gabapentin enacarbil and again the following morning (Day 15) approximately 14-16 hours post dose. Neither of these time points used an active comparator (diphenhydramine) only a comparison to placebo. The Day 15 assessment most accurately represents ‘real world’ situation; that is taking the drug at 5pm and driving the next morning.

Alertness – measured by Visual Analog Scale and Epworth Sleepiness Scale

Cognition- measured by Brief Cognitive Assessment.

LANE POSITION VARIABILITY

Lane position variability is a measurement of side to side movement within a pre defined width. Clinical trials have used this measurement to assess sedative side effects of drugs. In this study, the change from baseline, was used as the primary endpoint. A negative number correlates with less variability or an improvement in driving, whereas a positive number reflects an increase in variability or worsening of driving. As seen in the sponsor’s table 11, XP13512 600mg, XP13512 1200mg, and the active control diphenhydramine 50mg all cause an increase in lane position variability when simulated driving was tested at Tmax.

(Source: Sponsor)

Table 11 Lane Position Variability at Baseline (Day -1) and Day 16, and Change from Baseline (Day -1) to Day 16 in Overall (0 to 60 minutes) Lane Position Variability in Feet (MITT Population)

	Pbo	XP13512 1200 mg	XP13512 1800 mg	Pbo/DPH ^a	95% CI for Mean	ANOVA ^b 95% CI for LS Mean
	N=33	N=28	N=33	N=28		
	Mean (SD)	Mean (SD)	Mean (SD)	Mean (SD)		
Baseline (Day -1)	1.40 (0.32)	1.46 (0.32)	1.37 (0.20)	1.36 (0.25)		
Day 16	1.26 (0.31)	1.61 (0.48)	1.52 (0.37)	1.52 (0.50)		
Change from Baseline to Day 16						
Mean (SD)	-0.11 (0.17)	0.15 (0.38)	0.15 (0.27)	0.16 (0.40)		
LS Mean (SE)	-0.10 (0.06)	0.15 (0.06)	0.15 (0.06)	0.16 (0.06)		
XP13512 1200 mg – Pbo					0.10, 0.41	0.08, 0.42
XP13512 1800 mg – Pbo					0.14, 0.37	0.09, 0.41
Pbo/DPH - Pbo					0.10, 0.43	0.09, 0.42
XP13512 1200 mg – Pbo/DPH					-0.22, 0.20	
XP13512 1800 mg – Pbo/DPH					-0.18, 0.17	

Data Source: DSTable 8.4 and DSTable 9.4

- a. Pbo/DPH group received diphenhydramine on Day 16 only.
 b. Analysis was based on a repeated measures ANOVA model with fixed effects for treatment group, pooled site, visit, and treatment group by visit.

Subjects on active treatment performed worse than placebo but similarly to diphenhydramine.

Lane Position Variability change for Day 14 (evening) and Day 15 (morning) are outlined in Table 13 (Sponsor)

Table 13 Lane Position Variability on Day 14 and Day 15 – XP083 (Source: Table 12 of Sponsor’s Study Report)

	Pbo	XP13512 1200 mg	XP13512 1800 mg	Pbo/DPH ^a	95% CI for Mean	ANOVA ^b 95% CI for LS-Mean
	N=33	N=28	N=33	N=28		
	Mean (SD)	Mean (SD)	Mean (SD)	Mean (SD)		
Baseline (Day -1)	1.40 (0.32)	1.46 (0.32)	1.37 (0.20)	1.36 (0.25)		
Day 14	1.34 (0.38)	1.62 (0.62)	1.36 (0.38)	1.29 (0.26)		
Change from Baseline (Day -1) to Day 14						
Mean	-0.06 (0.17)	0.17 (0.43)	-0.01 (0.28)	-0.08 (0.15)		
LS Mean	-0.06 (0.05)	0.17 (0.05)	-0.01 (0.05)	-0.08 (0.05)		
XP13512 1200 mg – Pbo					0.06, 0.39	0.09, 0.37
XP13512 1800 mg – Pbo					-0.06, 0.17	-0.08, 0.19
Baseline (Day 1)	1.35 (0.28)	1.49 (0.36)	1.40 (0.29)	1.45 (0.35)		
Day 15	1.35 (0.31)	1.62 (0.45)	1.44 (0.46)	1.34 (0.28)		
Change from Baseline (Day 1) to Day 15						
Mean	-0.01 (0.14)	0.13 (0.40)	0.02 (0.32)	-0.10 (0.19)		
LS Mean	-0.01 (0.05)	0.13 (0.05)	0.02 (0.05)	-0.10 (0.05)		
XP13512 1200 mg – Pbo					-0.01, 0.29	-0.00, 0.28
XP13512 1800 mg – Pbo					-0.10, 0.15	-0.12, 0.16

Data Source: DSTable 8.4 and DSTable 9.4

- a. Pbo/DPH group received diphenhydramine on Day 16 only.
 b. Analysis was based on a repeated measures ANOVA model with fixed effects for treatment group, pooled site, visit, and treatment group by visit.

The 1200mg cohort performed worse than placebo as well as the 1800mg cohort on change in LPV from Baseline to Day 14 and Baseline to Day 15.

SIMULATED CRASHES

Table 14 summarizes the number of subjects with simulated crashes at Baseline and Day 14, Day 15 and Day 16.

(Source: Sponsor)

Table 14 Number of Subjects with Simulated Crashes at Baseline and Days 14, 15, and 16 (MITT Population)

		Pbo	XP13512 1200 mg	XP13512 1800 mg	Pbo/DPH ^a
		N=33	N=28	N=33	N=28
Number of Subjects with Crashes, n (%)					
	Day -1	3 (9.1)	6 (21.4)	3 (9.1)	2 (7.1)
	Day 1	1 (3.1)	4 (14.3)	3 (9.4)	3 (11.1)
	Day 14	4 (12.1)	6 (21.4)	1 (3.0)	1 (3.6)
	Day 15	1 (3.0)	10 (35.7)	1 (3.2)	0 (0)
	Day 16	0 (0)	8 (28.6)	6 (18.2)	3 (10.7)

Data Source: DSTable 8.7.1

a. Pbo/DPH group received diphenhydramine on Day 16 only.

The 1200mg cohort performed poorly at Baseline and worsened at Day 16, compared to placebo, diphenhydramine and 1800mg cohort. The 1800mg cohort performed similarly to placebo at Baseline and worse than placebo and diphenhydramine at Day 16.

REVIEWER COMMENT: The active treatment groups, 1200mg and 1800mg, both performed similarly to diphenhydramine at Day 16 suggestive of a drug effect. However, the 1200mg cohort consistently performed worse than the 1800mg cohort. The reasons for this are unclear; however, Clin Pharm Reviewers stated that the exposure at 1200mg was higher than 1800mg. (INSERT REF).

COGNITION

BAC was administered and results are summarized in Sponsor Table 22.

Table 22 BAC Composite Score at Baseline (Day -1 and Day 1) and Day 14, Day 15, and Day 16, and Change from Baseline (Day -1 or Day 1) to Day 14, Day 15, and Day 16 in BAC Composite Score (MITT Population)

		Pbo	XP13512 1200 mg	XP13512 1800 mg	Pbo/DPH ^a	Pairwise Treatment Differences Mean (95% CI)	
		N=33 ^a	N=28	N=33	N=28	XP13512 1200 mg - Pbo	XP13512 1800 mg - Pbo
Composite Score							
	Day -1	Mean (SD)	52.9 (9.88)	48.4 (9.73)	43.8 (10.28)	51.1 (11.24)	
	Day 1	Mean (SD)	53.4 (9.87)	49.9 (13.51)	47.9 (11.00)	53.9 (11.59)	
	Day 14	Mean (SD)	57.5 (10.04)	53.6 (12.18)	49.1 (11.88)	58.1 (11.00)	
	Day 15	Mean (SD)	58.2 (9.30)	53.3 (14.45)	48.1 (12.76)	58.7 (10.22)	
	Day 16	Mean (SD)	60.4 (10.98)	57.4 (15.32)	50.8 (12.47)	61.8 (11.36)	
	Change from Day -1 to Day 14	Mean (SD)	4.6 (5.64)	5.3 (7.01)	5.3 (6.88)	7.0 (6.25)	0.7 (-2.5, 3.9)
	Change from Day 1 to Day 15	Mean (SD)	4.8 (5.39)	3.4 (4.59)	0.2 (6.61)	4.8 (4.66)	-1.4 (-4.0, 1.2)
	Change from Day -1 to Day 16	Mean (SD)	7.2 (7.24)	9.1 (8.98)	7.1 (8.34)	10.7 (6.05)	1.9 (-2.3, 6.1)

Data source: DSTable 8.10

a. Day 16 data for the placebo group included only 32 subjects.

b. Pbo/DPH group received diphenhydramine on Day 16 only.

REVIEWER COMMENT: The BAC results do not reveal any significant drug effect; therefore, the changes in driving do not appear to be related to cognitive functioning.

ALERTNESS:

Results from the Visual Alertness Scale are presented in Sponsor Table 20. The VAS is administered to subjects by asking “How alert do you feel now?” The responses on the VAS range from ‘extremely sleepy’ to “extremely alert”. The score is determined by measuring (in millimeters), from the left hand end of the line to the point that the subject marked (range 0-100mm). The higher score correlates with increased alertness whereas the lower score indicates more sleepiness.

Table 20 Alertness VAS at Baseline (Day -1) and Day 16, and Change from Baseline (Day -1) to Day 16 in the Alertness VAS (MITT Population)

	Pbo	XP13512 1200 mg	XP13512 1800 mg	Pbo/DPH ^c	95% CI for Mean	ANOVA Results ^a	
	N=33 ^b	N=28	N=33	N=28		LS-Mean (SEM)	95% CI for LS Mean
Baseline (Day -1) Pre-Drive							
Mean (SD)	58.1 (23.95)	69.0 (24.38)	64.1 (20.34)	73.0 (18.68)			
Baseline (Day -1) Post-Drive							
Mean (SD)	41.5 (24.81)	56.4 (26.66)	47.5 (22.03)	52.4 (25.80)			
Day 16 Pre-Drive							
Mean (SD)	65.1 (17.46)	69.8 (25.76)	55.3 (24.90)	61.3 (22.20)			
Day 16 Post-Drive							
Mean (SD)	55.4 (19.07)	52.7 (29.02)	40.1 (28.46)	38.3 (25.16)			
Change from Baseline to Day 16 Pre-Drive							
Mean (SD)	6.3 (23.44)	0.8 (32.79)	-8.8 (27.61)	-11.8 (24.00)			
XP13512 1200 mg – Pbo					-20.0, 9.2	-6.2 (7.07)	-20.3, 7.8
XP13512 1800 mg – Pbo					-27.7, -2.3	-15.4 (6.76)	-28.8, -2.0
Pbo/DPH – Pbo					-30.3, -5.7	-18.3 (7.04)	-32.3, -4.4
XP13512 1200 mg – Pbo/DPH					-2.8, 28.0	12.1 (7.26)	-2.3, 26.5
XP13512 1800 mg – Pbo/DPH					-10.14, 16.3	2.9 (6.97)	-10.9, 16.7
Change from Baseline to Day 16 Post-Drive							
Mean (SD)	14.3 (22.23)	-3.6 (32.01)	-7.5 (26.17)	-14.0 (29.25)			
XP13512 1200 mg – Pbo					-32.2, -3.7	-16.8 (7.16)	-31.0, -2.6
XP13512 1800 mg – Pbo					-33.9, -9.6	-20.7 (6.85)	-34.2, -7.1
Pbo/DPH – Pbo					-41.8, -14.9	-27.4 (7.13)	-41.5, -13.3
XP13512 1200 mg – Pbo/DPH					-6.0, 26.8	10.6 (7.30)	-3.8, 25.1
XP13512 1800 mg – Pbo/DPH					-7.6, 20.8	6.7 (7.01)	-7.2, 20.6

Continued

When looking at sleepiness scales such as Alertness VAS (Visual Analog Scale) there appears to be a dose related decrease in alertness. There was a dose dependent worsening, increase in sleepiness, on this scale as seen in sponsor table 20. Placebo, change from baseline increased by 6.3mm, XP13512 1200mg decreased by 3.6mm, XP13512 1800mg decreased by 7.5mm and the active comparator diphenhydramine decreased by 14.0mm .

REVIEWER COMMENT: However, the VAS is not particularly sensitive and may be difficult to use properly. The Epworth Sleepiness Scale was also employed as a measurement of sleepiness. As stated previously, there was not a significant difference in sleepiness between drug and placebo when using this scale.

Consistently, throughout the study, the XP13512 1200mg group did worse than placebo as well as 1800mg and diphenhydramine. There were inconsistencies in PK studies at the 1200mg and 1800mg doses during this study which were difficult to explain. (Courtesy: Clinical Pharmacology Review).

The XP13512 1200mg group performed worse on several parameters as seen in above table, at baseline visits. There were no significant demographic differences between the groups otherwise (age, sex etc...). Although the baseline testing on XP13512 1200mg showed poorer performance, the overall measure is change in performance. This group had a greater change for the worse on all parameters versus placebo. In addition, this group performed more poorly than XP13512 1800mg group on several parameters, including change the primary endpoint, change in LPV between visit -1 and visit 16, as well as visual alertness scale (VAS) and crashes. Since the study drug is sedating, one may assume that the poor performance was due to sedation. However, being that the pharmacokinetics is linearly related, the XP13512 1800mg group should perform worse than the XP13512 1200mg group. In other words, the results appear to follow exposure response (see clinical pharm review), rather the dose response. One explanation may be that there was some type of error made in PK sampling, drug dose administration or record keeping. The effect of the study drug on driving may need to be further evaluated.

In discussion with statistics, the 1200mg cohort performed poorly mainly at baseline (Day-1) and end of study (Day 16). There did not appear to be one particular subject driving the data, i.e., and outlier. There were no differences by race or gender. The group performed poorly as a whole. In addition, there was a higher intra-subject variability in this group compared to the other cohorts.

Thorough QTc Study

STUDY XP078 – QT-QTc study

At the EOP 2 meeting, the division felt that a formal QT/QTc study was necessary. This study was performed, XP078, and is being analyzed. As of June 17, 2009, Interdisciplinary Review Team for QT Studies Consultation: Thorough QT Study Review, found XP078 to be inconclusive for the following reason; the moxifloxacin response failed to meet criteria for assay sensitivity. The expectations for assay sensitivity with moxifloxacin are increase in mean effect of QTc of greater than 5 ms .Without moxifloxacin assay sensitivity, the lack of QTc effect on gabapentin enacarbil cannot be reliably concluded.

7.3Supportive Safety Results

(Source: Sponsor)

Laboratory Findings

Laboratory values were presented by the sponsor in appropriate categories. Reference ranges were consistent with FDA standards except as noted.

HEMATOLOGY

Sponsor Table 132 summarizes Hematology Values Outside the Reference Range at Any Post-Baseline Assessment for Safety Population in 12-Week Controlled RLS Studies

Table 132 Hematology Values Outside the Reference Range at Any Post-Baseline Assessment (Safety Population: 12-Week Placebo-Controlled RLS Studies)

Parameter	Category	Number (%) of Subjects					
		Placebo (N=245)	XP13512 600 mg (N=163)	XP13512 1200 mg (N=269)	XP13512 1800 mg (N=38)	XP13512 2400 mg (N=45)	XP13512 All Doses (N=515)
Hemoglobin	High	19 (8)	13 (8)	18 (7)	1 (3)	1 (2)	33 (7)
	Low	7 (3)	1 (<1)	3 (1)	1 (3)	0	5 (<1)
Hematocrit	High	6 (2)	4 (2)	8 (3)	2 (5)	1 (2)	15 (3)
	Low	11 (5)	5 (3)	11 (4)	6 (16)	2 (5)	24 (5)
RBC	High	0	3 (2)	3 (1)	0	0	6 (1)
	Low	31 (13)	28 (17)	47 (18)	12 (32)	7 (16)	94 (19)
WBC	High	26 (11)	18 (11)	27 (10)	2 (5)	3 (7)	50 (10)
	Low	8 (3)	1 (<1)	3 (1)	2 (5)	1 (2)	7 (1)
Platelets	High	33 (14)	24 (15)	30 (11)	5 (14)	8 (18)	67 (13)
	Low	7 (3)	5 (3)	8 (3)	1 (3)	1 (2)	15 (3)

Data Source: Table 3.13

Note: number of subjects evaluated for each parameter are provided by treatment group in the data source table.

There does not appear to be a dose dependency for any of the hematologic abnormalities presented. There is no difference in drug treatment groups and placebo on any hematologic parameters with the exception of low RBC being greater in 1800mg gabapentin enacarbil cohort. (Check for outlier).

CLINICAL CHEMISTRY

Sponsor Table 133 summarizes clinical chemistry values outside the reference range at any post-baseline visit in 12 week placebo controlled Studies.

Table 133 Clinical Chemistry Values Outside the Reference Range at Any Post-Baseline Assessment (Safety Population: 12-Week Placebo-Controlled RLS Studies)

Parameter	Category	Number (%) of Subjects					
		Placebo (N=245)	XP13512 600 mg (N=163)	XP13512 1200 mg (N=269)	XP13512 1800 mg (N=38)	XP13512 2400 mg (N=45)	XP13512 All Doses (N=515)
Total bilirubin	High	7 (3)	5 (3)	9 (3)	1 (3)	2 (5)	17 (3)
	Low	0	0	0	0	0	0
AST (SGOT)	High	22 (9)	11 (7)	18 (7)	2 (5)	4 (9)	35 (7)
ALT (SGPT)	High	39 (16)	21 (13)	33 (12)	6 (16)	6 (14)	66 (13)
	Low	0	0	0	0	0	0
Alkaline phosphatase	High	8 (3)	6 (4)	15 (6)	0	0	21 (4)
	Low	0	1 (<1)	0	1 (3)	0	2 (<1)
Creatinine Phosphokinase	High	68 (28)	45 (28)	85 (32)	11 (30)	11 (25)	152 (30)
	Low	1 (<1)	4 (2)	2 (<1)	0	0	6 (1)
Blood urea nitrogen	High	19 (8)	9 (6)	21 (8)	3 (8)	0	33 (7)
	Low	0	1 (<1)	1 (<1)	0	0	2 (<1)
Sodium	High	1 (<1)	7 (4)	4 (2)	0	2 (5)	13 (3)
	Low	9 (4)	4 (2)	6 (2)	2 (5)	2 (5)	14 (3)
Potassium	High	11 (5)	10 (6)	11 (4)	3 (8)	2 (5)	26 (5)
	Low	16 (7)	8 (5)	13 (5)	3 (8)	3 (7)	27 (5)
Chloride	High	0	5 (3)	1 (<1)	1 (3)	1 (2)	8 (2)
	Low	16 (7)	7 (4)	14 (5)	4(11)	5(11)	30 (6)
Bicarbonate	High	9 (4)	0	10 (4)	0	1 (2)	11 (2)
	Low	59 (24)	55 (34)	72 (27)	22 (59)	14(32)	163 (32)
Uric acid	High	10 (4)	7 (4)	13 (5)	3 (8)	2 (5)	25 (5)
	Low	14 (6)	8 (5)	13 (5)	2 (5)	4 (9)	27 (5)
Protein (total)	High	3 (1)	1 (<1)	3 (1)	2 (5)	0	6 (1)
	Low	2 (<1)	0	0	1 (3)	0	1 (<1)
Albumin	High	1 (<1)	0	0	0	0	0
	Low	0	0	0	0	0	0
GGT	High	20 (8)	10 (6)	25 (9)	2 (5)	0	37 (7)
	Low	0	0	0	0	0	0
Glucose	High	21 (9)	10 (6)	19 (7)	4(11)	6(14)	39 (8)
	Low	34 (14)	17(11)	41(15)	5(14)	3 (7)	66(13)
Calcium	High	14 (6)	8 (5)	16 (6)	0	0	24 (5)
	Low	18 (7)	13 (8)	20 (8)	8 (22)	4 (9)	45 (9)
Phosphate	High	32 (13)	20 (12)	22 (8)	6 (16)	10 (23)	58 (11)
	Low	31 (13)	6 (4)	20 (8)	1 (3)	3 (7)	30 (6)
Cholesterol	High	154 (63)	92 (57)	170 (64)	21 (57)	26 (59)	309 (61)
	Low	0	0	0	0	0	0
Creatine phosphokinase	High	68 (28)	45 (28)	85 (32)	11 (30)	11 (25)	152 (30)
	Low	1 (<1)	4 (2)	2 (<1)	0	0	6 (1)

Data Source: Table 3.13

Note: number of subjects evaluated for each parameter are provided by treatment group in the data source table.

The Sponsor's table does not reveal a clear dose response for abnormal clinical chemistry values.

REVIEWER COMMENT: Based upon the Reviewer's analysis of the pooled safety data , 10 subjects on drug treatment, with potassium levels of 6.0 or greater, were found. The sponsor lists only one subject with hyperkalemia (value 6.7), without any associated narrative. There were no adverse events, discontinuations or EKG changes noted for these subjects.

Of note, 3 of the ten subjects (6 blood draws) were at one site (Center ID 000184). After reviewing the associated Appendix for each study, I noted that the sponsor had set lower and upper limits of potassium at (b) (4) mEq/L, whereas the FDA sets the limits at 3.0-6.0 mEq/L. There is not a clear explanation for the few cases of transient hyperkalemia.

Similarly, the Reviewer noted 16 subjects on drug treatment, with blood glucose levels less than 50 mg/dL. One study center (Center ID 000218) accounted for 4 of the subjects (6 blood draws). Again, no associated narrative, adverse events, discontinuations or deaths were associated with these findings. The sponsor had set the lower and upper limits of glucose levels as (b) (4) mg/dL, whereas the FDA sets the limits at 50-200.

Since there were no deaths or serious adverse events listed for these laboratory abnormalities, an alternative explanation is possible other than drug effect. These possibilities include errors in processing the samples (i.e. timing, hemolysis, packaging).

The sponsor has been queried on these cases; a response is pending.

Vital Signs

There was not a significant effect of the drug on blood pressure, respiratory rate or heart rate. Sponsor Table 140 summarizes the changes from baseline to most extreme high and low post-baseline values for subjects in 12-week placebo controlled RLS studies.

Table 140 Summary of Change from Baseline to Most Extreme High and Low Post-Baseline BP and Pulse Value (Supine and Standing) (Safety Population: 12-Week Placebo-Controlled RLS Studies)

Vital Signs Parameter	Change from Baseline	
	Placebo (N= 245)	XP13512 All Doses (N=515)
Vital Signs, n	203	469
Systolic BP, mmHg		
Supine Low		
Mean (SD)	-10.5 (9.68)	-10.1 (10.00)
Min, max	-41, 12	-46, 18
Standing Low		
Mean (SD)	-11.4 (10.52)	-12.0 (10.79)
Min, max	-56, 21	-61, 21
Supine High		
Mean (SD)	10.2 (10.76)	10.7 (9.85)
Range	-21, 47	-25, 48
Standing High		
Mean (SD)	9.8 (11.42)	10.5 (10.84)
Min, max	-35, 43	-30, 55
Diastolic BP, mmHg		
Supine Low		
Mean (SD)	-7.3 (7.20)	-7.8 (7.12)
Min, max	-23, 19	-27, 15
Standing Low		
Mean (SD)	-7.5 (6.66)	-9.1 (7.55)
Min, max	-29, 11	-34, 10
Supine High		
Mean (SD)	7.3 (7.94)	7.7 (7.58)
Min, max	-9, 32	-17, 41
Standing High		
Mean (SD)	7.0 (7.10)	7.3 (7.34)
Min, max	-13, 29	-13, 33
Pulse Rate, bpm		
Supine Low		
Mean (SD)	-4.6 (6.37)	-5.0 (7.06)
Min, max	-26, 11	-28, 19
Standing Low		
Mean (SD)	-6.7 (8.96)	-7.3 (9.07)
Range Min, max	-41, 24	-44, 19
Supine High		
Mean (SD)	11.3 (8.16)	11.9 (8.52)
Min, max	-12, 41	-9, 43
Standing High		
Mean (SD)	11.3 (9.51)	11.9 (10.16)
Min, max	-24, 44	-18, 47

Data Source: Table 4.3

Sponsor Table 141 summarized orthostatic blood pressure and pulse changes in 12-week placebo controlled RLS Studies.

Table 141 Summary of Orthostatic Change in Blood Pressure and Pulse (Safety Population: 12-Week Placebo-Controlled RLS Studies)

Vital Signs Parameter	Placebo (N=245)			XP13512 All Doses (N=515)		
	Baseline N=204	Week 12/ET N=228	Change ¹ N=198	Baseline N=474	Week 12/ET n=479	Change ¹ N=453
Orthostatic Measurement						
Systolic BP, mmHg						
Mean (SD)	0.8 (6.40)	0.1 (8.47)	-0.4 (9.57)	1.0 (6.16)	0.5 (8.47)	-0.6 (9.48)
Min, max	-22, 27	-36, 29	-31, 31	-23, 20	-45, 43	-44, 39
Diastolic BP, mmHg						
Mean (SD)	3.0 (4.83)	3.0 (6.71)	0.2 (7.10)	3.4 (4.86)	2.4 (6.00)	-1.1 (7.02)
Min, max	-12, 17	-18, 31	-19, 31	-9, 18	-23, 26	-33, 27
Pulse, bpm						
Mean (SD)	6.7 (6.43)	6.0 (8.23)	-0.6 (8.17)	6.7 (6.73)	5.0 (6.58)	-1.6 (7.75)
Min, max	-7, 33	-15, 47	-29, 30	-9, 39	-18, 31	-39, 26

Data Source: Table 4.11

Orthostatic change = standing minus supine

1. Week 12/ET change minus Day 1 (baseline) change. Where baseline was not available, screen value was used.

There were no specific vital sign abnormalities that were disproportionately represented in the XP13512 active treatment group.

Electrocardiograms (ECGs)

Sponsor Table 165 summarizes subjects with QT interval meeting outlier criteria for change from baseline at any post baseline assessment in subject in 12-week placebo controlled studies.

Table 165 Summary of Subjects with a QT Interval Meeting the Outlier Criteria for Change from Baseline at Any Post-Baseline Assessment (Safety Population: 12-Week Placebo-Controlled Studies)

ECG Parameter	Change from Baseline (msec)	Number (%) of Subjects					
		Placebo (N=245)	XP13512 600mg (N=163)	XP13512 1200mg (N=269)	XP13512 1800mg (N=38)	XP13512 2400mg (N=45)	XP13512 All Doses (N=515)
Uncorrected QT	n	243	159	266	37	44	506
	≥30	33 (14)	21 (13)	34 (13)	7 (19)	7 (16)	69 (14)
	≥60	4 (2)	0	2 (<1)	2 (5)	1 (2)	5 (<1)
QTcB	n	243	159	266	37	44	506
	≥30	42 (17)	21 (13)	39 (15)	8 (22)	4 (9)	72 (14)
	≥60	1 (<1)	0	2 (<1)	1 (3)	1 (2)	4 (<1)
QTcF	n	243	159	266	37	44	506
	≥30	14 (6)	6 (4)	26 (10)	4 (11)	5 (11)	41 (8)
	≥60	1 (<1)	0	2 (<1)	1 (3)	0	3 (<1)

Data Source: Table 4.21, Listing 4.4

Subjects with corrected QT intervals greater than 450msec were uncommon. The subjects were evenly distributed between drug and placebo; there did not appear to be a drug effect. There were no corrected QT intervals greater than 500msec

Special Safety Studies

XP083, Simulated Driving and Cognition Study. Please refer to section 7.3.5.

Immunogenicity

Not applicable.

Evaluation for Potential Adverse Events for Similar Drugs in Drug Class

Dose Dependency for Adverse Events

Study XP081 looked at dose response for XP13512 600mg, 1200mg, 1800mg and 2400mg. There appeared to be a dose response for adverse events, namely somnolence/sedation and dizziness.

Time Dependency for Adverse Events

As discussed in section 7.4.1 the most common adverse events, somnolence/sedation appear to resolve within 2 weeks, particularly at gabapentin enacarbil 600mg. Some earlier trials with different formulations of gabapentin enacarbil (IR) showed onset of sedation to be within 30 minutes. However, the shortest time interval recorded in the pivotal trials for onset of AE sedation/somnolence, was 0-3 days.

Drug-Demographic Interactions

There is no effect of gabapentin enacarbil on age other than accounting for changes in renal function. Race was not specifically studied, but the sponsor notes that the pharmacokinetics of XP13512 ER was similar between healthy Japanese and Caucasian subjects.

Age was looked at by dividing the study population into those above and below 65 years old.

(Source: Sponsor)

Protocol: RXP1SS XP13512 (GSK1030262) Page 1 of 1
 Population: Safety - 12-Week Controlled RLS Studies

Table 5.3
 Summary of Subject Disposition for Subjects Aged >= 65 Years in 12-Week Controlled RLS Studies

	Placebo (N=25)	XP13512 600mg (N=16)	XP13512 1200mg (N=37)	XP13512 1800mg (N=6)	XP13512 2400mg (N=3)	XP13512 All Doses (N=62)

Completion Status						
Completed	22 (88%)	16 (100%)	34 (92%)	4 (67%)	2 (67%)	56 (90%)
Withdrawn	3 (12%)	0	3 (8%)	2 (33%)	1 (33%)	6 (10%)
Reason* for withdrawal						
Ineligibility	1 (4%)	0	0	0	0	0
Adverse Event	1 (4%)	0	3 (8%)	1 (17%)	1 (33%)	5 (8%)
Treatment failure	1 (4%)	0	0	0	0	0
Patient withdrew consent	0	0	0	0	0	0
Investigator judgement	0	0	0	1 (17%)	0	1 (2%)
Protocol non-compliance (after randomization)	0	0	0	0	0	0
Lost to follow-up	0	0	0	0	0	0
Termination of study or withdrawal of patient by sponsor	0	0	0	0	0	0
Patient death	0	0	0	0	0	0

There were pharmacokinetic and clinical differences associated with sex. Population PK model should lower clearance in females (15%) and lower volume of distribution in females (25%).

Drug-Disease Interactions

Gabapentin enacarbil, XP13512, is nearly completely eliminated by the kidneys. Therefore subjects with renal insufficiency/failure need to be dosed accordingly. The pharmacokinetics of gabapentin enacarbil was examined in subjects with renal impairment. There is an approximately linear relationship between gabapentin clearance and creatinine clearance (CrCL). For every 2 fold increase in CrCL, there is an approximately 1.6 fold decrease in gabapentin CL/F.

Drug-Drug Interactions

DDI studies were performed for XP13512 with cimetidine (an OCT-2 substrate) and naproxen (a MCT-1 substrate). XP13512 ER 1200mg was co administered with naproxen 500mg bid. There was an 8% increase in Cmax and 13% increase in AUC.

Studies with co administration of XP13512 ER 1200mg and cimetidine 400mg qid were performed as well. There was a 24% increase in AUC of XP13512; however, Cmax was not affected.

Additional Safety Explorations

Human Carcinogenicity

In animal studies, 2 years study in rats, XP13512 was given at doses of 500, 2000 or 5000mg/kg/day. There was a significant increase in incidence of pancreatic acinar adenoma and carcinoma at the 2000 and 5000mg/kg/day doses. This dose is approximately represents plasma exposure 19-38 times human gabapentin exposure at recommended dose of 1200mg/day. In addition, gabapentin has been shown to accumulate in rat pancreas but not primate or human pancreas.

There are no reported cases of cancer in humans to date for gabapentin enacarbil.

Human Reproduction and Pregnancy Data

Studies of embryo fetal development, male/female fertility and pre/postnatal studies have been conducted in animals up to 5000mg/kg/day. No malformations were seen. Based upon AUCs of gabapentin, the NOAEL was 2 fold the clinical exposure of 1200mg/day.

There was one pregnancy during the single blind phase of study XP06. The subject was a 23 year old female who received 1200mg XP13512 from August 15, 2006 until October 25, 2006 when it was discontinued due to pregnancy. She had been on Yasmin and MVI as well. She gave birth to a normal female neonate on July 7, 2007. Last follow-up on August 31, 2007, stated that the infant had a normal one month follow-up examination (weight 9.5 pounds, length 22 inches). No congenital anomalies were noted.

Gabapentin (Neurontin) labeling places the drug in pregnancy Category C in precautions. Gabapentin was shown to be fetotoxic in rodents. There have been no adequate or well-controlled studies in pregnant women. Gabapentin is secreted into human milk following oral administration. A nursed infant could be exposed to a maximum dose of approximately 1mg/kg/day of gabapentin. The effect on the nursing infant is unknown. (Neurontin label, April 2009)

Pediatrics and Effect on Growth

No pediatric studies have been performed to date with gabapentin enacarbil. Gabapentin (Neurontin) has been studied in children down to the age of 3, for epilepsy. I have not found any specific statements on the effect of gabapentin on growth.

Overdose, Drug Abuse Potential, Withdrawal and Rebound

As reported in the SAE/death section, there were no overdoses or reports of abuse potential. There was one incident of withdrawal seizure after abrupt discontinuation of XP13512. This subject was found to have a seizure focus on EEG.

A lethal dose of gabapentin (Neurontin) was not identified in mice and rats receiving single oral doses as high as 8000 mg/kg. Acute oral overdoses of Neurontin up to 49 grams have been reported. Adverse reactions included diplopia, dysarthria, drowsiness, lethargy and diarrhea. All patients recovered with supportive care. (Neurontin label, April 2009).

Additional Submissions

Study XP055(RXP111490): An Open-Label, 52-Week Extension Study Assessing XP13512 Safety and Efficacy in Patients with Restless Legs Syndrome-**Interim Report No. 2**. The data cut-off date was July 31, 2008.

In addition, safety data for all SAEs, deaths and pregnancies as well as AEs leading to withdrawal were provided for time period between March 31, 2008 and January 16th, 2009. A few key tables are presented below. The majority of the Safety Update Data is incorporated into the safety section of this review.

SUMMARY:

The most serious safety issue for gabapentin enacarbil and drugs in its class, is the association of drug with pancreatic acinar tumors in the rat studies. Although this was rare and there have no reported cases in humans taking gabapentin enacarbil, pancreatic cancer is a serious and fatal disease. The Sponsor seeks an indication for moderate to severe idiopathic RLS, which is a chronic but nonfatal disease. In addition, there are currently marketed medications for the indication (REQUIP and Mirapex). The risk benefit assessment for gabapentin enacarbil for moderate to severe idiopathic RLS does not warrant approval at this time.

If the mechanism of carcinogenicity is identified and felt to be specific to rat pancreas and not human, approval of gabapentin enacarbil could be considered for RLS. The most common adverse events leading to withdrawal appear to be related to sedation and dizziness. The efficacy is clear at all doses studied from 600mg to 1200mg a day. However, the adverse event profile is clearly improved at the 600mg dose compared to the higher doses. The issue of sedation is important for RLS population for many reasons including a population which is usually sleep deprived at baseline and with excess daytime sleepiness. This poses a public health issue in terms of driving and operating heavy equipment. Repeat driving studies would need to be performed at the lower dose, 600mg and lower/ a day, before making a final assessment on risk benefit assessment.

8 Postmarketing Experience

The study drug is a new molecular entity and therefore, there is no post-marketing experience. However, it is a pro-drug of gabapentin which has extensive post-marketing experience. The sponsor included post-marketing experience with gabapentin in the application. The sponsor used the European Summary of Product Characteristics for gabapentin as a reference for the following data.

Gabapentin was first approved in the United States in 1993 as adjunctive therapy for partial seizures. Subsequently, in 2004, gabapentin was approved for post-herpetic neuralgia. The sponsor reviewed the AERS database (Q3/2007, public release version of AERS) using Multi-Item Gamma Poisson Shrinker (MGPS), "...an empirical Bayes data mining algorithm and GSK's preferred method for disproportionality analysis of post-marketing adverse event data in spontaneous reporting databases." This method was used to compute the "Empiric Bayes Geometric Mean (EBGM) for each observed drug-event combination in that database." In other words, EBGM is a ratio of observed reporting rate/ expected reporting rate. An EBGM value of 5 means that a drug-event combination has been reported at least 5 times as frequently as would be expected if the events were independent.

The sponsor used a threshold of EB05, where EB05, EB95 represent the 2-sided 90% confidence interval for each EBGM value.

Table 1 Event terms identified from the AERS database for further evaluation

System Organ Class	Preferred term	N	EB05
Ear and Labyrinth disorders	Hearing impaired	24	2.067
	Deafness	62	2.291
Injury, poisoning and procedural complications	Road traffic accident	89	2.538
	Gun shot wound	176	28.932
Investigations	Body height decreased	54	8.398
Nervous system disorders	Disturbance in attention	139	3.046
	Cognitive disorder	77	3.853
	Narcolepsy	8	2.213
	Hypersomnia	46	2.831
Psychiatric disorders	Agoraphobia	9	2.518
	Distractibility	6	2.098
	Dysphemia	23	4.372
	Paranoia	73	2.516
	Homicidal ideation	25	2.856
	Psychotic disorder	103	2.277
	Anorgasmia	21	2.327
	Conversion disorder	20	3.249

Impaired hearing, deafness, paranoia and psychosis are already in the labeling for gabapentin.

In terms of suicidality with gabapentin, the sponsor searched the AERS database with the following results. There appears to be an increased incidence of suicidality with Neurontin.

Table 2 Event terms identified from AERS potentially indicative of suicidality

System Organ Class	Preferred term	N	EB05
Injury, poisoning and procedural complications	Accidental overdose	64	1.443
	Alcohol poisoning	17	2.476
	Carbon monoxide poisoning	10	3.467
	Multiple drug overdose intentional	54	3.153
	Multiple drug overdose accidental	14	2.948
	Intentional overdose	189	2.76
	Overdose	355	2.333
	Multiple drug overdose	98	2.284
Psychiatric disorders	Suicidal behaviour	8	2.584
	Self injurious behaviour	23	5.152
	Completed suicide	619	5.82
	Intentional self-injury	66	6.7
	Suicidal ideation	489	6.731
	Suicide attempt	646	9.056
	Depression suicidal	3	0.574
	Self-injurious ideation	3	0.329

9 Appendices

Appendix A (Source: Sponsor)

CONFIDENTIAL

KM200070042700

Integrated Summary of Efficacy

6.2.5. 24-Hour RLS Symptom Record

		SITE NUMBER [] [] [] []	PATIENT NUMBER 3 [] [] [] []	PATIENT INITIALS FIRST MIDDLE LAST [] [] [] [] [] []	24-HOUR PATIENT RLS RECORD PATIENT RLS RECORD
START DATE [] [] [] [] [] [] [] [] [] [] <small>D D M M M Y Y Y Y</small>					<input type="checkbox"/> VISIT 2 <input type="checkbox"/> VISIT 4 <input type="checkbox"/> VISIT 10/ET
RLS SYMPTOMS 8:00 AM – 7:59 PM					
	ASLEEP	AWAKE			
TIME PERIOD	CHECK (✓) IF ASLEEP FOR ENTIRE TIME PERIOD	NOT PRESENT	PRESENT		
			MILD	MODERATE	SEVERE
8:00 AM – 8:29 AM	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>
8:30 AM – 8:59 AM	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>
9:00 AM – 9:29 AM	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>
9:30 AM – 9:59 AM	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>
10:00 AM – 10:29 AM	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>
10:30 AM – 10:59 AM	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>
11:00 AM – 11:29 AM	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>
11:30 AM – 11:59 AM	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>
NOON – 12:29 PM	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>
12:30 PM – 12:59 PM	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>
1:00 PM – 1:29 PM	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>
1:30 PM – 1:59 PM	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>
2:00 PM – 2:29 PM	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>
2:30 PM – 2:59 PM	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>
3:00 PM – 3:29 PM	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>
3:30 PM – 3:59 PM	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>
4:00 PM – 4:29 PM	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>
4:30 PM – 4:59 PM	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>
5:00 PM – 5:29 PM	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>
5:30 PM – 5:59 PM	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>
6:00 PM – 6:29 PM	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>
6:30 PM – 6:59 PM	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>
7:00 PM – 7:29 PM	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>
7:30 PM – 7:59 PM	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>
		PATIENT INITIALS FIRST MIDDLE LAST [] [] [] [] [] []			Page 1 of 2
<small>XP053 XenoPort, Inc.</small>		<small>WORKSHEET RLS24REC 24 HOUR PATIENT RLS RECORD</small>			

Appendix B (Source AAN Meeting 2009, Abstracts)

A Randomized, Double-Blind, Placebo-Controlled Study To Assess the Efficacy and Tolerability of Gabapentin Enacarbil in Subjects with Restless Legs Syndrome (RLS)

Daniel Lee, Greenville, NC, Ronald Ziman, Northridge, CA, A. Thomas Perkins, Raleigh, NC, J. Steven Poceta, La Jolla, CA, Arthur S. Walters, Nashville, TN, Ronald W. Barrett, Santa Clara, CA

OBJECTIVE: To assess the efficacy and tolerability of gabapentin enacarbil (GEN) 1200mg and 600mg compared with placebo in adults with moderate-to-severe primary Restless Legs Syndrome (RLS).

BACKGROUND: GEN is a non-dopaminergic treatment under investigation for RLS.

DESIGN/METHODS: In the 12-week, double-blind, placebo-controlled PIVOT RLS II study (XP053), subjects were randomized (1:1:1) to receive GEN 1200mg, 600mg, or placebo, once daily at 5pm with food. Co-primary endpoints: mean change from baseline in International Restless Legs Scale (IRLS) total score and proportion of responders (“much improved” or “very much improved”) on the investigator-rated Clinical Global Impression–Improvement (CGI-I) scale at Week 12 (LOCF) for GEN 1200mg versus placebo. Secondary comparison: GEN 600mg versus placebo on the same outcome measures. Tolerability evaluations included assessment of adverse events (AEs). **RESULTS:** The modified intent-to-treat population comprised 321 subjects (GEN 1200mg=111, 600mg=114, placebo=96). GEN 1200mg significantly improved mean IRLS total score versus placebo at Week 12 LOCF (–13.0 versus –9.8; adjusted mean treatment difference [AMTD] for change from baseline: –3.5; 95%CI: –5.6, –1.3; p=0.0015) and significantly more GEN subjects were CGI-I responders (77.5% versus 44.8%; adjusted odds ratio [AOR]: 4.3; 95%CI: 2.3, 7.9; p<0.0001). GEN 600mg significantly improved mean IRLS total score versus placebo (–13.8 versus –9.8; AMTD: –4.3; 95%CI: –6.4, –2.3; p<0.0001) and significantly more GEN subjects were CGI-I responders (72.8% versus 44.8%; AOR: 3.3; 95%CI: 1.8, 6.0; p<0.0001). The most commonly reported AEs for GEN 1200mg, 600mg, and placebo, respectively, were dizziness (24%, 10%, and 5%) and somnolence (18%, 22%, and 2%); most AEs were mild or moderate in intensity. AEs led to withdrawal in 7.2%, 6.1%, and 6.3% of subjects, respectively. **CONCLUSIONS/RELEVANCE:** GEN 1200mg once daily significantly improves RLS symptoms compared with placebo and is generally well tolerated. A significant treatment benefit is also seen with GEN 600mg once daily. Supported by: XenoPort, Inc., Santa Clara, CA, USA. Category - Sleep Disorders - Restless Leg Syndrome

Thursday, April 30, 2009 7:00 AM

Appendix C

Table 135 Summary of Subjects with Markedly Abnormal Hematology Values at Any Post-Baseline Assessment (Safety Population: 12-Week Placebo-Controlled RLS Studies)

Parameter	Category	Number (%) of Subjects with Any Post-Baseline Value Outside the Reference Range					
		Placebo (N=245)	XP13512 600 mg (N=163)	XP13512 1200 mg (N=269)	XP13512 1800 mg (N=38)	XP13512 2400 mg (N=45)	XP13512 All Doses (N=515)
Total bilirubin	High	3 (1)	2 (1)	2 (<1)	0	0	4 (<1)
AST (SGOT)	≥3xULN	2 (<1)	0	0	0	0	0
	≥5xULN	1 (<1)	0	0	0	0	0
	≥10xULN	0	0	0	0	0	0
ALT (SGPT)	≥3xULN	2 (<1)	0	1 (<1)	0	0	1 (<1)
	≥5xULN	1 (<1)	0	0	0	0	0
	≥10xULN	0	0	0	0	0	0
Alkaline phosphatase	High	0	0	0	0	0	0
Creatinine	High	0	0	0	0	0	0
BUN	High	0	0	0	0	0	0
Sodium	High	0	2 (1)	1 (<1)	0	0	3 (<1)
	Low	1 (<1)	0	0	0	0	0
Potassium	High	2 (<1)	2 (1)	0	1 (3)	0	3 (<1)
	Low	1 (<1)	0	1 (<1)	0	0	1 (<1)
Chloride	High	0	2 (1)	0	1 (3)	1 (2)	4 (<1)
	Low	4 (2)	1 (<1)	2 (<1)	1 (3)	0	4 (<1)
Bicarbonate	High	1 (<1)	0	0	0	0	0
	Low	7 (3)	5 (3)	4 (2)	3 (8)	2 (5)	14 (3)
Uric acid	High	0	0	0	0	0	0
Protein (total)	High	0	0	0	1 (3)	0	1 (<1)
	Low	0	0	0	0	0	0
Albumin	High	0	0	0	0	0	0
	Low	0	0	0	0	0	0
GGT	High	2 (<1)	0	4 (2)	0	0	4 (<1)
Glucose	High	0	2 (1)	4 (2)	0	2 (5)	8 (2)
	Low	1 (<1)	4 (2)	3 (1)	1 (3)	0	8 (2)
Calcium	High	0	0	2 (<1)	0	0	2 (<1)
	Low	2 (<1)	0	0	2 (5)	1 (2)	3 (<1)
Phosphate	High	2 (<1)	2 (1)	0	1 (3)	0	3 (<1)
	Low	1 (<1)	0	1 (<1)	0	0	1 (<1)
Cholesterol	High	35 (14)	15 (9)	46 (17)	6 (16)	4 (9)	71 (14)
	Low	0	0	0	0	0	0
CPK	High	28 (11)	14 (9)	30 (11)	3 (8)	4 (9)	51 (10)

Data Source: Table 3.22

BUN= Blood Urea Nitrogen

Note: number of subjects evaluated for each parameter are provided by treatment group in the data source table.

Appendix D

Table 132 Hematology Values Outside the Reference Range at Any Post-Baseline Assessment (Safety Population: 12-Week Placebo-Controlled RLS Studies)

Parameter	Category	Number (%) of Subjects					
		Placebo (N=245)	XP13512 600 mg (N=163)	XP13512 1200 mg (N=269)	XP13512 1800 mg (N=38)	XP13512 2400 mg (N=45)	XP13512 All Doses (N=515)
Hemoglobin	High	19 (8)	13 (8)	18 (7)	1 (3)	1 (2)	33 (7)
	Low	7 (3)	1 (<1)	3 (1)	1 (3)	0	5 (<1)
Hematocrit	High	6 (2)	4 (2)	8 (3)	2 (5)	1 (2)	15 (3)
	Low	11 (5)	5(3)	11(4)	6 (16)	2 (5)	24 (5)
RBC	High	0	3(2)	3(1)	0	0	6 (1)
	Low	31 (13)	28 (17)	47 (18)	12 (32)	7 (16)	94 (19)
WBC	High	26 (11)	18 (11)	27 (10)	2 (5)	3 (7)	50 (10)
	Low	8 (3)	1 (<1)	3 (1)	2 (5)	1 (2)	7 (1)
Platelets	High	33 (14)	24 (15)	30 (11)	5 (14)	8 (18)	67 (13)
	Low	7 (3)	5 (3)	8 (3)	1 (3)	1 (2)	15 (3)

Data Source: Table 3.13

Note: number of subjects evaluated for each parameter are provided by treatment group in the data source table.

Appendix E

Table 165 Summary of Subjects with a QT Interval Meeting the Outlier Criteria for Change from Baseline at Any Post-Baseline Assessment (Safety Population: 12-Week Placebo-Controlled Studies)

ECG Parameter	Change from Baseline (msec)	Number (%) of Subjects					
		Placebo (N=245)	XP13512 600mg (N=163)	XP13512 1200mg (N=269)	XP13512 1800mg (N=38)	XP13512 2400mg (N=45)	XP13512 All Doses (N=515)
Uncorrected QT	n	243	159	266	37	44	506
	≥30	33 (14)	21 (13)	34 (13)	7 (19)	7 (16)	69 (14)
	≥60	4 (2)	0	2 (<1)	2 (5)	1 (2)	5 (<1)
QTcB	n	243	159	266	37	44	506
	≥30	42 (17)	21 (13)	39 (15)	8 (22)	4 (9)	72 (14)
	≥60	1 (<1)	0	2 (<1)	1 (3)	1 (2)	4 (<1)
QTcF	n	243	159	266	37	44	506
	≥30	14 (6)	6 (4)	26 (10)	4 (11)	5 (11)	41 (8)
	≥60	1 (<1)	0	2 (<1)	1 (3)	0	3 (<1)

Data Source: Table 4.21, Listing 4.4

Appendix F

Table 164 Summary of Subjects with a QT Interval Meeting Observed Value Outlier Criteria (Safety Population: 12-Week Placebo-Controlled Studies)

ECG Parameter	Number (%) of Subjects					
	Placebo (N=245)	XP13512 600mg (N=163)	XP13512 1200mg (N=269)	XP13512 1800mg (N=38)	XP13512 2400mg (N=45)	XP13512 All Doses (N=515)
Uncorrected QT (msec)						
Baseline, n	243	159	268	38	44	509
Observed value ≥ 450	10 (4)	4 (3)	6 (2)	1 (3)	2 (5)	13 (3)
Observed value ≥ 500	0	0	1 (<1)	0	0	1 (<1)
Any On-treatment value, n	243	160	266	37	44	507
Observed value ≥ 450	12 (5)	6 (4)	12 (5)	2 (5)	3 (7)	23 (5)
Observed value ≥ 500	0	1 (<1)	2 (<1)	0	0	3 (<1)
QTcB (msec)						
Baseline, n	243	159	268	38	44	509
Observed value ≥ 450	9 (4)	1 (<1)	11 (4)	0	1 (2)	13 (3)
Observed value ≥ 500	0	0	0	0	0	0
Any On-treatment value, n	243	160	266	37	44	507
Observed value ≥ 450	19 (8)	8 (5)	21 (8)	6 (16)	3 (7)	38 (7)
Observed value ≥ 500	0	0	0	0	0	0
QTcF (msec)						
Baseline, n	243	159	268	38	44	509
Observed value ≥ 450	3 (1)	2 (1)	2 (<1)	0	0	4 (<1)
Observed value ≥ 500	0	0	0	0	0	0
Any On-treatment value, n	243	160	266	37	44	507
Observed value ≥ 450	8 (3)	4 (3)	3 (1)	2 (5)	1 (2)	10 (2)
Observed value ≥ 500	0	0	0	0	0	0

Data Source: Table 4.21, Listing 4.4

Appendix G

Subject	Age/ Gender	AE Leading to Withdrawal (Preferred Term)	Dose at Onset (mg)
Study XP021			
Placebo			
108/005	47/M	Anxiety	0
Study XP045			
XP13512			
103/111	44/M	Sedation	600
111/119	38/F	Feeling drunk	600
Study XP052			

XP13512			
103/2001	50/F	Somnolence	600
104/2004	58/M	Dizziness	1200
111/2017	57/M	Somnolence	600
124/2013	36/F	Hepatic enzyme increased	NOT TEAE
124/2015	52/F	Sedation	600
124/2016	49/F	Dyspepsia	1200
133/2004	41/F	Dizziness	600
133/2021	63/F	Deep vein thrombosis	1200
141/2002	64/F	Nausea, Vomiting, Dizziness	600
Placebo			
124/2005	59/F	Mood altered, Insomnia, Swelling face	0
191/2011	63/F	Chest discomfort	0
192/2002	69/F	Vomiting, Diarrhea	0
Study XP053			
XP13512			
107/3005	46/F	Depression	1200
146/3003	70/F	Hypotension	1200
148/3042	42/F	Vertigo	1200
149/3024	66/F	Depression	1200
150/3002	59/F	Nausea, Dizziness	600
150/3005	58/F	Fatigue, Somnolence	600
150/3026	47/F	Somnolence	600
175/3006	55/M	Platelet count increased	NOT TEAE
181/3013	56/M	Libido decreased	600
181/3033	51/F	Dizziness	600
194/3014	54/F	Sedation	600
197/3004	30/F	Joint sprain	1200
217/3021	23/F	Sedation	1200
217/3025	34/F	Somnolence	600
Placebo			
113/3005	55/F	Palpitations, Chest discomfort	0
148/3011	43/F	Mood swings	0
158/3010	48/F	Headache	0
181/3034	56/F	Pruritis	0
194/3001	34/M	Joint swelling	0
194/3016	62/M	Sleep apnoea syndrome	0
Study XP055			
AEs with Onset in Parent Study			
XP13512 in parent study			
103/2013	35/M	Libido decreased (XP052)	1200
181/3028	50/M	Somnolence (XP053)	600

195/3004	50/F	Weight increased (XP053)	NOT TEAE
218/3026	34/F	Fatigue (XP053)	600
AEs with Onset in Parent Study Plus AEs with Onset in XP055			
XP13512 in parent study			
137/2006	57/M	Restlessness (XP055)	1200
		Lethargy, Somnolence	600
		Feeling abnormal, Dizziness (XP052)	1200
149/3036	24/F	Anxiety (XP055) Irritability, Depression (XP053)	1200 600
Placebo in parent study			
158/3017	77/M	Somnolence (XP055) Dyspepsia (XP053)	600 0
AEs with Onset in XP055 (XP13512)			
102/2008	42/M	Vision blurred, Cognitive disorder	600
102/2009	48/F	Sedation	1200
104/7003	50/F	Intervertebral disc protrusion	1800
108/3002	66/F	Dizziness, Disorientation	600
108/3009	52/F	Somnolence	600
Study XP055			
AEs with Onset in XP055 (XP13512)			
111/2022	28/F	Somnolence	600
111/5021	33/M	Face oedema	600
120/5007	62/F	Oedema peripheral, Somnolence	1200
123/2006	39/M	Nausea	600
123/2007	57/M	Abdominal pain, Flatulence	600
123/2021	58/F	Lumbar spinal stenosis	1200 (2 days after last dose)
123/2035	65/F	Gastric ulcer	600
123/5002	45/F	Anxiety	600
124/2014	44/F	Dizziness, Somnolence	600
124/2022	56/M	Feeling abnormal, Somnolence	600
124/7002	47/M	Irritability	1800
124/7006	54/F	Vision blurred	1200
126/2011	31/F	Alanine aminotransferase increased, Aspartate aminotransferase increased, Blood creatine phosphokinase increased	1200
128/5003	48/F	Restless legs syndrome	1800
129/2015	56/F	Somnolence, Somnolence	600
129/2025	34/F	Vertigo, Disturbance in attention	600

129/2026	28/F	Feeling abnormal	600
129/2037	60/F	Sedation	600
141/5010	37/F	Mental status changes	1200
143/3009	44/M	Depression	1800
143/3013	65/F	Restless legs syndrome, Insomnia	1800
143/3015	52/M	Hangover	1200
148/3010	45/F	Amnesia	1800
148/3017	53/F	Weight increased	600
148/3023	68/M	Pain in extremity	1800
148/3033	66/F	Dizziness	600
151/7006	49/F	Dizziness, Syncope	1200
156/3001	47/F	Hepatic enzyme increased	1200
157/3008	36/F	Dizziness	1200
157/3009	46/F	Cardiac flutter	1200
158/3007	66/M	Lethargy, Loss of libido	1200, 1800
Study XP055			
AEs with Onset in XP055 (XP13512)			
160/2005	45/F	Abdominal pain upper, Dizziness, Headache, Somnolence	600
166/7003	25/F	Anxiety, Depression	1200
166/7007	35/M	Hepatic enzyme increased, Dyspnoea	1200
175/3005	39/F	Weight increased	1200
181/3026	60/F	Somnolence, Rash	600, 1200
182/7001	49/M	Liver function test abnormal	1800
187/3019	70/M	Dizziness	1800
187/3026	36/F	Rash generalised	600
191/2001	41/M	Depression, Disorientation	1200
191/2021	37/M	Abdominal pain upper	1800
191/2022	56/M	Rash	1200
200/3021	39/M	Mood swings Irritability, Anger	Unknown 1200
202/2005	54/F	Bladder neoplasm	600
206/5010	67/F	Non-small cell lung cancer	1800
217/3005	41/F	Nausea, Dizziness, Headache, Sedation	600
218/3049	28/F	Fatigue, Irritability, Depression, Acne	600
221/7011	34/M	Lip blister	1200
228/7008	53/F	Radiculopathy	1200
903/3012	44/F	Weight increased	1200
Study XP060			
XP13512 (Single-Blind)			

Phase)			
120/4004	57/F	Dissociation	1200
120/4016	65/F	Balance disorder	600
138/4007		Vision blurred, Dizziness, Disturbance in attention	1200
139/4014	52/F	Dizziness	600
144/4009	50/M	Insomnia, Vomiting, Diarrhoea, Headache	600
145/4004	55/F	Nausea, Fatigue	600
145/4014	44/M	Aggression	1200
145/4027	31/F	Blood creatine phosphokinase increased	Not treatment- emergent
146/4001	32/F	Somnolence	600
147/4007	66/F	Crying, Memory impairment	1200
Study XP060			
XP13512 (Single-Blind Phase)			
151/4026	29/M	Somnolence, Lethargy, Feeling abnormal	1200
161/4001	72/M	Vision blurred	1200
161/4006	52/M	Drug eruption	1200
166/4014	26/F	Endometriosis	1200
166/4017	48/M	Inguinal pain, Scrotal pain	1200
175/4006	48/M	Libido decreased	1200
175/4013	45/F	Hostility	1200
175/4021	64/M	Sleep walking	600
175/4026	50/F	Somnolence	600
182/4009	31/F	Cardiac disorder	Not treatment- emergent
182/4010	58/F	Constipation	1200
182/4020	23/F	Dizziness	1200
183/4025	42/F	Urinary tract infection	1200
183/4026	46/M	Premature ejaculation	1200
183/4034	51/F	Somnolence	1200
184/4004	42/M	Insomnia	1200
184/4005	52/F	Somnolence	1200
186/4008	63/F	Asphyxia (fatal outcome)	1200
186/4011	57/M	Expressive language disorder	1200
188/4008	69/F	Dizziness, Headache	600/1200
188/4011	48/F	Oedema peripheral	1200
188/4013	38/M	Fatigue	1200
189/4009	45/F	Face edema	1200
190/4002	52/M	Libido decreased	1200
190/4003	50/M	Sexual dysfunction	Unknown
190/4008	49/F	Headache	600

206/4033	47/F	Liver function test abnormal	NOT TEAE
208/4006	72/F	Coordination abnormal, Somnolence, Nausea	Unknown
208/4008	57/F	Foot fracture	1200
212/4004	42/F	Headache, Constipation	600/1200
212/4013	53/F	Renal impairment	1200
212/4022	54/F	Insomnia, feeling abnormal	600
Study XP060			
XP13512 (Single-Blind Phase)			
212/4026	60/M	Hot flush, Vertigo, Constipation,	600
		Hypoaesthesia, Diarrhoea, Cough, Dry eye,	
		Headache, Dry mouth, Poor quality sleep,	
		Feeling drunk, Disorientation, Feeling hot,	
		Fatigue	
XP13512 (AE Onset in Single-Blind Phase, Withdrawal in Double-Blind Phase)			
147/4005	48/F	Dizziness, Paraesthesia	1200
XP13512 (Double -Blind Phase)			
206/4019	50/F	Convulsion	600
Placebo (Double-Blind Phase)			
135/4004	56/F	Tarsal tunnel syndrome	0
186/4009	56/F	Anaphylactic reaction	0
Study XP081			
XP13512			
102/5009	49/F	Feeling abnormal	600
111/5015	75/M	Dyspnoea, Vision blurred	1800
120/5018	44/M	Ligament injury	Unknown
128/5001	36/F	Cholelithiasis	1200
129/5021	49/F	Weight increased	1200
142/5005	37/F	Neck injury, Back injury	2400
145/5016	22/F	Sedation	600
151/5001	57/M	Blood creatine phosphokinase increased	NOT TEAE
			1200
175/5004	46/F	Hypoaesthesia	600
191/5011	63/F	Nausea	1800
192/5001	72/F	Dizziness	600
205/5007	48/M	Somnolence	1800
206/5033	50/F	Oedema	600
211/5003	66/M	Dizziness	600

233/5014	61/F	Dizziness, Balance disorder, Musculoskeletal disorder	1800
234/5005	48/F	Dizziness	600, 1200
234/5012	48/F	Somnolence, Oedema peripheral	600
234/5015	64/F	Muscle spasms	
Study XP081			
Placebo			0
144/5004	43/M	Arteriosclerosis	
Study XP083			Never randomized
120/7013	55/F	Migraine, Headache, Nausea	
XP13512			600
120/7027	54/F	Vertigo, Neck pain, Tunnel vision, Musculoskeletal chest pain	600
220/7012	66/F	Balance disorder	

Appendix H

Table 2 Protocol deviation criteria based on inclusion criteria in Studies XP052, XP053 and XP060

Inclusion Criteria						
Criterion	Abbreviated label to use in displays (for Deviation Subcategory)	# in Study XP052	# in Study XP053	# in Study XP060	Deviation type	Clinical background information
Men or women at least 18 years of age	Men or women aged >=18	1	1	1	Major	Adult population studied
Patients with RLS, based on the International RLS Study Group Diagnostic Criteria	Patients with RLS	2	2	2	Major	Confirmation of RLS diagnosis – impact on primary outcome
History of RLS symptoms at least 15 nights in the prior month or, if on treatment, this frequency of symptoms before treatment was started	History of RLS symptoms	3	3	3	Major	Confirmation of RLS or Confirmation of target population minimum severity
Documented RLS symptoms for at least 4 of the 7 consecutive evenings/nights during the baseline study period	Documented evening/night RLS symptoms	4	4	4	Major	Confirmation of target disease population, minimum severity/frequency of disease symptoms
Total RLS severity score of 15 or greater on the IRLS rating scale at Visit 1 and at Visit 2	Total RLS severity score >= 15	5	5	5	Major	Confirmation of target disease population
Discontinuation of dopamine agonists and/or gabapentin at least 2 weeks prior to baseline	Discontinuation of dopamine agonists and/or gabapentin prior to baseline	6	6	6	Major	Possible effect on primary outcome if improper washout period
Discontinuation of other treatments for RLS (e.g., opioids, benzodiazepines) at least 2 weeks prior to baseline	Discontinuation of other treatments for RLS prior to baseline	7	7	7	Major	Possible effect on primary outcome if improper washout period
If female of child-bearing potential, the patient must agree to use clinically accepted birth control through completion of the study	If female of child-bearing potential, agree to use birth control	8	8	8	Major	Possible impact on subject safety
Body Mass Index of 34 or below	Body Mass Index <= 34	9	9	9	Minor	Not considered to have a major impact on efficacy or safety
Estimated creatinine clearance of at least 60 mL/min	Estimated creatinine clearance >= 60 mL/min	10	10	10	Major	Patients with CrCl below 60 mL/min are likely to experience increased exposure to medication and may present a safety risk
Signed IRB-approved consent form prior to any study procedures	Signed IRB-approved consent form prior to any study procedures	11	11	11	Major	Patient rights
Willing and able to follow the study procedures	Willing and able to follow the study procedures	12	12	12	Major	Patient compliance

Table 3 includes protocol deviations based on exclusion criteria in trials XP052, XP053 and XP060 Sponsor

Table 3 Protocol deviation criteria based on exclusion criteria in Studies XP052, XP053 and XP060

Exclusion Criteria						
Criterion	Abbreviated label to use in displays (for Deviation Subcategory)	# in Study XP052	# in Study XP053	# in Study XP060	Deviation type	Clinical background information
Significant RLS symptoms during the daytime, defined as symptoms of RLS between 10AM and 6PM for two or more days in the week prior to the baseline visit. NB This exclusion criterion was removed in protocol amendment #1 for both Study XP052 and XP060.	Significant daytime RLS symptoms	1	n/a	1	Minor	Considered minor as criteria was requested to be removed by FDA
A sleep disorder (e.g., sleep apnea) that may significantly affect the assessment of RLS.	Sleep disorder that may significantly affect the assessment of RLS.	2	1	2	Major*	Possible effect on primary outcome however each individual deviation was reviewed to determine clinical significance. Some sleep disorders may not affect RLS assessments or may have occurred in the past.
A history of RLS symptom augmentation or end-of-dose rebound with previous dopamine agonist treatment	History of RLS symptom augmentation or end-of-dose rebound	3	2	3	Minor	There is a two week washout prior to study start, and in addition, this active moiety is not believed to cause augmentation or EMR.
Neurologic disease or movement disorder (e.g., diabetic neuropathy, Parkinson's Disease, Multiple Sclerosis, dyskinesias, and dystonias)	Neurologic disease or movement disorder	4	3	4	Major	Possible effect on primary outcome as disorders may interfere with efficacy assessments
Other medical conditions [e.g., poorly controlled diabetes (i.e., HbA1c > 7.5% by history in last 6 months), iron deficiency anemia] or drug therapy (e.g., sedative-hypnotics) which could affect RLS treatment efficacy assessments	Other medical conditions which could affect RLS treatment efficacy assessments	5	4	5	Major*	Each deviation was individually reviewed to determine clinical significance (e.g. major or minor).
In the opinion of the Investigator, a clinically significant abnormal screening ECG or clinical laboratory test result	Clinically significant abnormal screening ECG or clinical laboratory test result	6	5	6	Minor	Active moiety has no known effect on ECG or clinical laboratory parameters
Serum ferritin level below 20 ng/mL	Serum ferritin level below 20 ng/mL	7	6	7	Major	Low ferritin may indicate secondary RLS
Patients currently suffering from moderate or severe depression using the DSM-IV-TR (Diagnostic and Statistical Manual of Mental Disorders and Treatment IV Text Revision)	Patients currently suffering from moderate or severe depression	8	7	8	Major	Potential to affect efficacy or safety

Appendix I

Protocol deviations/violations pivotal trial XP052 (Source: Reviewer)

PVTXT	N Rows	N(Placebo)	N(XP13512 1200mg)
>=1 alcoholic drink on any day	118	60	58
>=1 dose between midnight and 4pm	58	25	33
Anesthesia	2	1	1
Anti-epilepsy medications	2	1	1
Benzodiazepines	2	2	0
Body Mass Index <=34	1	1	0
Compliance <80% or >120%	20	5	15

Discontinuation of dopamine agonists and/or gabapentin prior to baseline	3	2	1
Dopamine agonists and antagonists	2	2	0
Ineligibility	2	2	0
Investigator judgment	1	1	0
Missing >3 consecutive days	55	24	31
Missing 2+ days within one week of final IRLS assessment	50	19	31
Opioids	17	11	6
Other	4	2	2
Other medical conditions which could affect RLS treatment efficacy assessments	2	0	2
Patients who have clinically significant or unstable medical conditions	16	8	8
Protocol non-compliance	1	1	0
Recent participation in drug or device study	2	2	0
Sedating antihistamines	20	15	5
Sedatives/hypnotics	2	0	2
Significant daytime RLS symptoms	2	0	2

In the table below, protocol violations/deviations for trial XP053 are presented. In contrast to trial XP052, there are more violations associated with the drug group, specifically 600mg dose. There are a greater number of violations involving alcohol and opiate use in the 600mg group as compared to 1200mg and placebo.

Protocol violations/deviations pivotal trial XP053 (Source: Reviewer)

PVTXT	N Rows	N(Placebo)	N (XP13512 1200mg)	N (XP13512 600mg)
>=1 alcoholic drink on any day	164	45	47	72
>=1 dose between midnight and 4pm	113	35	36	42
Anesthesia	2	0	1	1

Benzodiazepines	8	4	2	2
Body Mass Index <=34	2	0	2	0
Clinically significant abnormal screening ECG or clinical laboratory test result	4	0	3	1
Compliance <80% or >120%	20	8	5	7
Discontinuation of dopamine agonists and/or gabapentin prior to baseline	2	0	2	0
Discontinuation of other treatments for RLS prior to baseline	3	1	0	2
Documented evening/night RLS symptoms	2	1	1	0
Dopamine agonists and antagonists	3	2	1	0
Ineligibility	2	0	2	0
Missing >3 consecutive days	76	28	27	21
Missing 2+ days within one week of final IRLS assessment	76	28	27	21
Opioids	28	6	8	14
Other	13	4	5	4
Patients who have clinically significant or unstable medical conditions	16	4	6	6
Protocol non-compliance	2	1	1	0
Received incorrect study treatment due to dispensing error	1	0	1	0
Sedating antihistamines	32	10	9	13
Sedatives/hypnotics	2	0	0	2
Serum ferritin level below 20 ng/mL	2	0	2	0
Sleep disorder that may significantly affect the assessment of RLS	3	1	2	0
Termination of study or withdrawal by sponsor	1	1	0	0
Total RLS severity score >=15	3	1	1	1

10. Literature Review/References

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11. Labeling Recommendations

18 Page(s) of Draft Labeling have been Withheld in Full as b4 (CCI/TS) immediately following this page

Application Type/Number	Submission Type/Number	Submitter Name	Product Name
NDA-22399	ORIG-1	GLAXO GROUP LTD DBA GLAXOSMITHKLIN E	SOLZIRA

This is a representation of an electronic record that was signed electronically and this page is the manifestation of the electronic signature.

/s/

SUSANNE R GOLDSTEIN
02/12/2010

GERALD D PODSKALNY
02/12/2010

MEMORANDUM

DATE: February 8, 2010

FROM: Director
Division of Neurology Products/HFD-120

TO: File, NDA 22-399

SUBJECT: Recommendation for Action on NDA 22-399, for the use of Horizant (gabapentin enacarbil) Extended Release Tablets in the treatment of patients with moderate to severe Restless Legs Syndrome (RLS)

NDA 22-399, for the use of Horizant (gabapentin enacarbil) Extended Release Tablets in the treatment of patients with moderate to severe Restless Legs Syndrome (RLS), was submitted by GlaxoSmithKline on 1/9/09. Horizant is an extended release formulation of a pro-drug of gabapentin, a drug marketed (tradename Neurontin) for the treatment of patients with epilepsy and post-herpetic neuralgia.

Horizant is rapidly converted essentially entirely to gabapentin (with negligible amounts of parent compound circulating) which is excreted essentially unchanged in the urine. Although the absorption of gabapentin (when given as gabapentin) plateaus with increasing dose (that is, the bioavailability decreases with increasing doses), the pharmacokinetics of gabapentin are linear when given as gabapentin enacarbil over a range of doses up to 6 grams.

This application contains reports of three randomized controlled trials (Studies 52, 53, and 60) that purport to establish substantial evidence of effectiveness for Horizant in patients with moderate to severe RLS. In addition, the sponsor has submitted the results of another controlled trial (Study 81) designed to identify the doses to be studied in the definitive controlled trials. The application also contains the requisite Chemistry and Manufacturing Controls (CMC), pharmacology/toxicology, clinical pharmacology and other data. In addition, the sponsor has performed a formal thorough QT study, as well as a formal test of driving in subjects treated with Horizant.

The application has been reviewed by Dr. Susanne Goldstein, medical reviewer, Dr. Sharon Yan, statistician, Dr. Zachary Oleszczuk, Division of Medication Error Prevention and Analysis (DMEPA), Dr. Terry Peters, pharmacologist, Dr. Lois Freed, supervisory pharmacologist, Dr. Raanan Bloom, Office of Pharmaceutical Science, the Interdisciplinary Review Team for QT Studies, Dr. Karl Lin, statistics (carcinogenicity), Dr. Antoine El-Hage, Division of Scientific Investigations, Dr. Chhagan Tele, Office of New Drug Quality Assessment (ONDQA), Dr. Martha Heimann, ONDQA PAL, Drs. Ju-Ping Lai and Atul Bhattaram, Office of Clinical Pharmacology, and Dr. David Podskalny, neurology team leader. The clinical

team recommends that the application not be approved. I will briefly review the relevant data, and offer the division's recommendation for action on this application.

Effectiveness

As noted above, the sponsor has submitted three "definitive" controlled trials that they believe establish substantial evidence of effectiveness of Horizant in the treatment of patients with moderate to severe RLS.

Study 052

This was a randomized, parallel group, double blind multi-center study in which patients received either gabapentin enacarbil 1200 mg or placebo. The study drug was taken once a day, at 5 PM. Patients were treated in a 12 week double-blind period. The primary outcomes were:

- 1) Mean change from baseline to end of treatment in IRLS Score, and
- 2) Proportion of responders on the Investigator rated Clinical Global Impression of Improvement

The IRLS Scale is a 10 item scale rated by the patient. Each item is rated from 0 (best)-4 (worst), and the rating is to be applied to the previous week. The CGI-I is a 7 category scale rated by the investigator from "Very much improved" to "Very much worse". A responder was a patient who was rated as Very much improved or Much improved. Between-treatment comparisons on each measure were to be tested at an alpha of 0.05 in order for the study to be considered "positive".

A total of 222 patients were randomized (114 drug, 108 placebo). A total of 92 (85%) of placebo and 100 (88%) of Horizant patients completed the study, and 112 drug and 108 placebo patients were included in the analysis. The following table presents the results of the analyses of the two co-primary outcomes.

	Change from Baseline in Mean IRLS Score		
	Baseline	End of Study (LOCF)	P-value
Horizant	23.07	-13.23	0.0003
Placebo	22.57	-8.75	

As can be seen in Dr. Yan’s review (page 9, Table 2), statistically significant differences were seen at every visit (Weeks 1, 2, 3, 4, 6, 8, 10, and 12).

	Proportion of Responders		P-value
	Very Much (%)	Much (%)	
Horizant	55 (50.5)	28 (25.7)	<0.0001
Placebo	20 (18.5)	22 (20.4)	

As can also be seen in Dr. Yan’s review, page 10, Table 4, the comparisons reached statistical significance at all visits.

Study 53

This study was of essentially similar design as Study 52, except patients were randomized to one of three treatment groups: Horizant 600 mg, 1200 mg, or placebo.

A total of 325 patients were randomized (113 Horizant 1200 mg, 115 Horizant 600 mg, 97, placebo). A total of 87%, 90%, and 79% of 1200 mg, 600 mg, and placebo patients, respectively, completed the study. A total of 111 patients in the 1200 mg group, 114 patients in the 600 mg group, and 96 placebo patients were included in the primary analysis.

The following chart displays the results of the analyses of the primary outcomes:

	Change from Baseline in Mean IRLS Score		
	Baseline	End of Study (LOCF)	P-value
Horizant 1200	23.18	-12.95	0.0017
Horizant 600	23.11	-13.82	<0.0001
Placebo	23.81	-9.84	

As can be seen in Dr. Yan’s review (page 12, Table 6), statistically significant differences were seen at every visit (Weeks 1, 2, 3, 4, 6, 8, 10, and 12). In general, the treatment effects at all time points were similar in both active dose groups (there were slight numerical superiority in the treatment effects of the 1200 mg vs the 600 mg groups at Weeks 3 and 4).

Proportion of Responders

	Total	P-value
Horizant 1200	77%	<0.0001
Horizant 600	73%	<0.0001

Placebo

As can be seen in Dr. Yan's review, page 13, Table 7, statistically significant differences were seen between both dose groups and placebo at every time point. The proportion of responders in both dose groups were essentially similar. (There were slight numerical increases in the proportion of responders in the 1200 mg group compared to the 600 mg group at Weeks 4 and 12.)

In this study, patients were to record their RLS symptoms at half-hour intervals throughout the 24 hour day. The symptoms in these half-hour epochs were to be recorded as:

Asleep
Not Present
Mild
Moderate Severe

The sponsor then divided the day into 4 hour epochs, and analyzed the distribution of the symptom scores within these epochs. The following chart displays the results of these analyses (as % of patients) for the epochs surrounding dosing (when RLS symptoms are considered to be at their worst):

Time	Severity	Horiz 1200	Horiz 600	Placebo
4PM-8PM	Not Pres	66.3	69.4	61.6
	Mild	27.2	18.4	24.7
	Mod	5.4	9.2	9.6
	Severe	1.1	3.1	4.1
6 PM-10 PM	Not Pres	59.8*	55.6	52.7
	Mild	29.3	28.3	24.3
	Mod	9.8	15.2	14.9
	Severe	1.1	1.0	8.1
8 PM-12 AM	Not Pres	52.2*	49.5*	36.5
	Mild	29.3	28.3	29.7
	Mod	16.3	19.2	23.0
	Severe	2.2	3.0	10.8
12 AM-4 AM	Not Pres	72.8*	74.7*	51.4
	Mild	14.1	14.1	24.3
	Mod	10.9	8.1	20.3
	Severe	2.2	3.0	4.1

*- p<0.05 for dose vs placebo

The following chart (Sponsor’s Table 44) displays the proportion of patients with no RLS symptoms (rated as either Not Present or Asleep) for non-overlapping 4 hour epochs:

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XP053-RXP111460

Table 44 Subjects Reporting No RLS Symptoms by 4-Hour Period at Baseline and at the End of Week 12 (MITT Population: Study XP053)

Time Window	Number (%) of Subjects with No Reported RLS Symptoms		
	Placebo N=96	XP13512 600 mg N=114	XP13512 1200 mg N=111
Baseline			
n ^a	93	110	110
8 AM to 12 PM	50 (53.8)	65 (59.6)	62 (56.4)
12 PM to 4 PM	44 (47.3)	63 (57.3)	59 (53.6)
4 PM to 8 PM	39 (41.9)	44 (40.0)	57 (51.8)
6 PM to 10 PM	24 (25.8)	30 (27.3)	31 (28.2)
8 PM to 12 AM	16 (17.2)	12 (10.9)	11 (10.0)
12 AM to 4 AM	30 (32.3)	30 (27.3)	34 (30.9)
4 AM to 8 AM	42 (45.2)	47 (42.7)	53 (48.2)
End of Week 12			
n ^b	74	99	92
8 AM to 12 PM	52 (72.2)	85 (86.7)	74 (80.4)
12 PM to 4 PM	51 (70.8)	74 (75.5)	69 (75.0)
4 PM to 8 PM	45 (61.6)	68 (69.4)	61 (66.3)
6 PM to 10 PM	39 (52.7)	55 (55.6)	55 (59.8)
8 PM to 12 AM	27 (36.5)	49 (49.5)	48 (52.2)
12 AM to 4 AM	38 (51.4)	74 (74.7)	67 (72.8)
4 AM to 8 AM	56 (75.7)	79 (79.8)	72 (78.3)

Data Source: [DSTable 7.13.1](#)

- a. The XP13512 600 mg group had 109 subjects at the 8 AM to 12 PM time period.
- b. The placebo group had 73 subjects at the 4 PM to 8 PM time period, and had 72 subjects at the 8 AM to 12 PM and 12 PM to 4 PM time periods. The XP13512 600 mg group had 98 subjects at the 8 AM to 12 PM, 12 PM to 4 PM, and 4 PM to 8 PM time periods.

In addition, Dr. Goldstein has evaluated the percentage of patients in each treatment group whose RLS symptoms were rated as Not Present or Asleep at each hour from 5 PM to 11 PM:

	5 PM	6 PM	7 PM	8 PM	9 PM	10 PM	11 PM
Horizant 1200 mg	80%	77%	76%	64%	64%	65%	69%
Horizant 600 mg	75%	74%	75%	68%	65%	56%	70%
Placebo	70%	68%	67%	60%	56%	55%	60%

Study 60

This was a randomized withdrawal study, in which patients received Horizant 1200 mg daily in a single blind design for 24 weeks, after which they were

randomized into a 12 week double blind phase during which they received either 1200 mg or placebo. The primary outcome was the proportion of patients who met relapse criteria during the 12 week double blind phase. Relapse criteria were defined as:

- 1) an increase in IRLS score of at least 6 points compared to Week 24 score (just prior to randomization), resulting in an IRLS score of at least 15, AND a rating of “Very much worse” or “Much worse” on the Clinical Global Impression. These criteria had to have been met on at least 2 consecutive visits at least one week apart, OR
- 2) withdrawal due to lack of efficacy

A total of 194 patients met responder criteria during the 24 week single blind phase (of 327 patients enrolled in this phase). These 194 patients were randomized (96 drug, 98 placebo). The following chart displays the results of the primary analysis:

	Number (%) of patients who met Relapse criteria	P-value
Horizant	9 (9.4)	0.016
Placebo	22 (22.7)	

A total of 4 patients in each group withdrew due to lack of efficacy and did not meet criterion 1 above; they are included in this table.

In addition to the trials described above, the sponsor submitted the results of another fixed dose study designed to identify the doses to be studied in the definitive studies.

Study 81

This was a randomized, double blind, multi-center, multiple fixed dose study in which patients with RLS were randomized to receive placebo, Horizant 600 mg, 1200 mg, 1800 mg, or 2400 mg at PM for 12 weeks. The protocol did not specify primary or secondary outcomes, but the review team analyzed the outcomes designated as primary in the other studies: the difference from placebo in the mean change from baseline in the IRLS score and the proportion of patients who were rated as “Very much improved” or “Much improved” on the Clinical Global Impression of Change.

A total of 217 patients were randomized (41 placebo; 48, 600 mg; 45, 1200 mg; 38, 1800 mg; and 45, 2400 mg). The following chart displays the results of the analyses of these outcomes:

Change from Baseline in Mean IRLS Score

	Baseline	End of Study (LOCF)	P-value
Placebo N=40	22.45	-9.28	
Horizant 600 N=47	23.87	-13.81	0.04
Horizant 1200 N=43	23.91	-13.81	0.04
Horizant 1800 N=37	23.62	-13.95	0.026
Horizant 2400 N=44	23.34	-12.86	0.09

Proportion of Responders

	Total Prop	P-value
Placebo	45%	
Horizant 600	64%	0.08
Horizant 1200	65%	0.07
Horizant 1800	73%	0.01
Horizant 2400	82%	0.0005

Safety

A total of 1613 subjects/patients received at least one dose of gabapentin enacarbil, 1566 of whom had RLS. A total of 436 patients received treatment for at least 6 months, and 313 patients received treatment for at least one year; of these latter patients, the vast majority of the experience was at 1200 mg/day. A total of 326 patients received a dose of 600 mg a day, all in controlled trials. No patient who received the 600 mg dose received it for appreciably longer than 3 months.

Deaths

There were 3 deaths in the development program. They are described in detail by Drs. Goldstein and Podskalny. One was a 51 year old male volunteer who committed suicide (b) (6) hours after a single dose of 1200 mg. The second was a 48 year old man found under a highway overpass. He died (b) (6) days after his last dose of drug, after having been treated with 1200 mg for about 1 year. Alcohol intoxication was listed as a contributing factor in his death. The last death was a 63 year old woman who choked on a piece of meat, and who had been treated with 1200 mg for (b) (6) days at the time of her death.

Discontinuations

In controlled trials, a total of 42/515 (8%) of Horizant-treated patients discontinued due to an adverse event, compared to 4% of placebo patients, with 7, 9, 8, and 11% discontinuing in the 600, 1200, 1800, and 2400 mg dose groups, respectively. Only one event was responsible for causing discontinuation more frequently than 2%; that was dizziness, in the 1800 mg group (5%; n=2). The only adverse event responsible for withdrawal at a rate of 1% or higher was somnolence (overall 1%, no obvious dose response).

In long-term, open label exposure, there were 64/581(11%) of patients who discontinued due to adverse events. The most common adverse event leading to discontinuation was somnolence (1.6%), followed by dizziness (1.4%). No other adverse event was associated with an incidence of discontinuation greater than 0.5% (see Dr. Podskalny's Table 25, page 47 of his memo).

As Dr. Podskalny notes, there were a total of 96/581(16.5%) of patients in long-term, open-label treatment, discontinued due either to "subject withdrew consent" or "lost to follow-up". Further exploration of these patients should be undertaken.

Serious Adverse Events

Serious AEs were rare in the development program. In 12 week controlled trials (Studies 52, 53, and 81), there were a total of 3/515 (<1%) Horizant treated patients (1 case each of cellulitis and intervertebral disc protrusion in the 600 mg group and a rotator cuff syndrome in a 2400 mg patient) and 2/245 (<1%) placebo treated patients who experienced an SAE.

In Study 60, during the initial portion of the randomization phase, a 50 year old woman experienced a seizure. She was found subsequently to have a focal abnormality on an EEG. In the open-label portion of this same study, a 37 year old woman was found by a neighbor with several empty medication bottles

nearby and was incoherent, confused, disoriented, and hallucinating. A urine drug screen identified amitriptyline and doxylamine.

In a long-term open-label study (as of the cut-off date of 7/31/08 which provided data for almost all patients) 18 patients experienced SAEs, with no obvious pattern that suggested drug-relatedness (see Dr. Podskalny's review, Table 23, page 45 of his memo).

Common Adverse Events

The following chart displays the most frequently seen common adverse events in controlled trials:

Event	Placebo N=245	Horiz 600 N=163	Horiz 1200 N=269	Horiz 1800 N=38
Somnolence	5%	20%	23%	26%
Dizziness	4%	13%	22%	26%
Headache	11%	12%	15%	11%
Nasopharyngitis	7%	9%	8%	8%
Nausea	5%	6%	7%	8%
Fatigue	4%	6%	7%	3%
Dry Mouth	2%	3%	4%	5%
Irritability	1%	4%	4%	5%
Insomnia	3%	6%	3%	5%
Feeling drunk	0%	1%	3%	8%
Feeling abnormal	<1%	<1%	3%	8%
Peripheral edema	1%	<1%	3%	3%

The following charts display the common ADRs from the dose response studies (Studies 53, 81) separately:

Study 53

Event	Placebo N=96	Horiz 600 N=115	Horiz 1200 N=111
Somnolence	2%	22%	18%
Dizziness	5%	10%	24%
Headache	9%	15%	14%
Sedation	2%	<1%	5%

Study 81

Event	Placebo N=41	Horiz 600 N=48	Horiz 1200 N=45	Horiz 1800 N=38	H2400 N=45
Somnolence	5%	15%	24%	26%	51%
Dizziness	2%	21%	22%	26%	40%
Headache	17%	4%	20%	11%	13%
Sedation	2%	0	0	8%	7%

Adverse events of interest

Gabapentin is a moiety known to be associated with somnolence. In addition, other treatments used in the treatment of RLS have been known to be associated with the occurrence of other specific adverse reactions, including sudden onset of sleep, presumably in the absence of preceding somnolence (so-called sleep attacks); these events have, to date, been associated with dopaminergic therapies, and have occurred in settings in which these agents have been used, especially Parkinson's Disease. Another adverse event reportedly associated with dopaminergic therapy specifically in RLS is known as augmentation, which is the occurrence of RLS symptoms earlier in the day, and perhaps occurring in the arms as well as the legs. Whether this phenomenon is related to treatment or is just part of the natural history of the disease is unknown, although it is believed to be related to treatment.

Somnolence

As can be seen from the table of Common Adverse Events above, terms that may be related to somnolence appear to increase with increasing dose (somnolence, sedation, feeling drunk, fatigue, dizziness, feeling abnormal), with the largest dose-related effect seen for dizziness. Whether all of these events are, in fact, representative of an effect on somnolence is difficult to know. Further, and critically, we are particularly interested in whether or not Horizant causes significant somnolence rapidly after drug ingestion, because patients who take the drug at 5 PM may be likely to be driving in the hours immediately after dosing. Unfortunately, the data were not collected in a way that allows us to learn when during the day somnolence occurred. According to the sponsor, in the vast majority of patients, the onset of somnolence was during the first 1-2 weeks of the study.

Sleep attacks

The sponsor developed a specific questionnaire to assess whether patients experience sleep attacks during the previous week during the controlled trials (SOS-Q; see Dr. Podskalny's review for the details). As can be seen in his Table 113, there was no clear increase in the incidence of these events compared to placebo in these studies.

Augmentation

Inspection of the occurrence of RLS symptoms at half-hour intervals during the 24 hour dosing intervals during the course of the 12 week controlled trials did not identify augmentation as a drug-related event; to the contrary, symptoms seemed to decrease on drug throughout the day. Of course, augmentation is a phenomenon that is reported to occur (with dopaminergic therapies) with long-term exposure; such data was not collected in this application.

Suicide

All antiepileptic drugs (AEDs) carry a warning about increased suicidality, based on a meta-analysis of 199 controlled trials of 11 AEDs. The sponsor performed analyses similar to those performed in the meta-analysis on the data in this application. According to the sponsor's analysis, there were no cases of suicidality identified using this methodology.

Impulse Control Disorder (ICD)

Dopaminergic treatments are reported to cause ICD, including compulsive gambling, shopping, high-risk sexual behaviors and several others. The sponsor searched their ADR database for specific terms that might be considered to represent these events in their controlled trials, although these data were not systematically collected prospectively in any formal way: none were found.

Labs, vital signs

There were no systematic, significant changes in routine laboratory evaluations, including vital signs and EKG.

Thorough QT study

The sponsor performed a thorough QT study evaluating single doses of placebo, Horizant 1200 mg, 6000 mg, and moxifloxacin 400 mg.

The largest upper bounds of the 2 sided 90% CIs for the mean difference from placebo were 4.7 ms at 2 hours after the 6000 mg dose and 5.3 msec at 21

hours after the 1200 mg dose. However, the largest one-sided 90% lower CI for moxifloxacin was 3.8 msec, adjusted for multiple endpoints. In addition, the expected time course for moxifloxacin's effect on the Qt interval was not seen in this study. Because the expected effects of moxifloxacin were not seen (the study did not have assay sensitivity), the QT team has concluded that the study was inadequate.

Study 83

This study was designed to assess the effects of Horizant on driving ability.

In this study, healthy subjects were randomized to receive either placebo, Horizant 1200 mg, Horizant 1800 mg, or diphenhydramine 50 mg (active control).

In this study, there were 2 Baseline assessments. On Day -1, subjects were assessed with a baseline driving (simulator) test in the evening, as well as a cognitive battery. On Day 1, subjects were assessed with a baseline simulator test in the morning, as well as a cognitive battery in the morning.

On Day 1, subjects received their first dose of study medication at 5 PM. Subjects randomized to Horizant 1200 mg, 1800 mg, or placebo continued to receive this treatment for the next 13 days at 5 PM (a total of 14 days of study treatment). Subjects in these 3 groups then received a dose of study drug on Days 15 and 16 in the morning (10-11 AM). Subjects randomized to receive diphenhydramine 50 mg received placebo for Days 1-14 at 5 PM, then AM doses of placebo on Days 15 and 16, and then a single dose of diphenhydramine 50 mg at 5 PM on Day 16.

Driving testing and the cognitive battery were assessed on the evening of Day 14, (7-9 PM; 2-4 hours after the PM dosing) and in the morning of Day 15 (7-9 AM), and in the evening (7-9 PM; 2 hours after the PM dosing on that day) of Day 16.

The specific times of dosing and testing were designed to assess: 1) the effects of driving in the evening several hours after dosing at the recommended time, when it might be imagined that patients would, for example, be driving home from work (this was tested by comparing the baseline at Day -1 to the testing on the evening of Day 14); 2) the effects of driving the next morning after dosing the previous night at the recommended time (assessed by comparing the baseline at Day 1 with the testing on Day 15 in the AM). The PM testing on Day 16 was designed to assess the effects of the active control, diphenhydramine, several hours after it was administered, and this test was also compared to the baseline evening testing (Day -1), as well as to test the effects of Horizant at its approximate Tmax (recall that subjects were dosed in the AM on Days 15 and 16, and the PM testing was timed to be at the approximate Tmax of Horizant).

See the figure in Dr. Yan’s review, page 21, which outlines the design of this study.

A total of 130 subjects were randomized, and 33, 28, 33, and 28 subjects were included in the analysis for the placebo, 1200 mg, 1800 mg, and placebo/diphenhydramine groups, respectively.

The following chart displays the results of the driving simulator testing on the primary outcome, Lane Position Variability (LPV):

	Mean LPV on Days 14 and 15			
	Horiz 1800	Horiz 1200	Placebo	Pbo/DPH
Day 14 Change from Baseline (Day 1 to day 14; PM driving)	-0.01	0.17	-.06	-0.08
Day 15 Change from Baseline (Day -1 to Day 15; AM driving)	0.02	0.13	-0.01	-0.10
Day 16 Change from Baseline (Day -1 to Day 16; PM driving)	0.15	0.15	-0.11	0.16

As Dr. Yan points out, most patients had minimal changes in LPV, but between 10-20% of patients had large changes. A total of 20 subjects, none on placebo, had LPV changes of at least 0.3 on Day 16 (6, 7, and 6 subjects each in the 1200, 1800, and DPH groups, respectively). See Dr. Yan’s Table 14, page 25 of her review for more details of this metric.

In addition to measuring LPV, the simulator study also assessed the number of crashes in each group.

As noted by Dr. Yan, patients in the 1200 mg group had more crashes at baseline (both Days -1 and 1) than in the other groups. The following table presents crash data by study day and treatment group:

Number (%) of Subjects with Crashes

Day	Horizant 1800	Horizant 1200	Placebo	Pbo/DPH
-1	3 (9)	6 (21)	3 (9)	2 (7)
1	3 (9)	4 (14)	1 (3)	3 (11)
14	1 (3)	6 (21)	4 (12)	1 (4)
15	1 (3)	10 (36)	1 (3)	0
16	6 (18)	8 (29)	0	3 (11)

It is important to note that the numbers in each cell do not necessarily represent the same individuals (that is, for example, the 6 subjects who had crashes in the 1200 mg group on Day -1 and the 6 on Day 14 in that group were not necessarily the same people).

Another way to assess these data is to examine the number of subjects who had multiple crashes. Dr. Yan has done this on page 27 of her review, Table 16. This table clearly shows a trend to a drug-related increase in the number of

crashes in the drug-treated groups, especially in the Horizant 1200 mg dose group. Below I present only the placebo and Horizant 1200 mg data:

Day	Horizant 1200	Placebo
-1		
1 crash	4	2
2 crashes	1	0
3 crashes	1	1
1		
1 crash	2	0
2 crashes	0	1
3 crashes	2	0
14		
1 crash	1	2
2 crashes	2	2
>3 crashes	3	0
15		
1 crash	4	1
>1 crash	6	0
16		
1 crash	5	0
>1 crash	3	0

Pharmacology/Toxicology

Gabapentin is known to cause acinar cell carcinoma of the pancreas in male rats, based on studies performed by the sponsor of the Neurontin NDA.

Carcinogenicity studies were performed with gabapentin enacarbil, and these studies revealed the occurrence of pancreatic acinar cell hyperplasia, adenomas, and carcinomas in male and female rats according to the following table:

Dose (m/kg)	Males				Females			
	0	500	2000	5000	0	500	2000	5000
Hyperplasia	14/60	10/60	14/60	20/60	1/60	1/60	4/60	14/60
Adenoma	2/60	4/60	4/60	8/60	0/60	0/60	0/60	3/60
Carcinoma	0/60	0/60	1/60	1/60	0/60	0/60	0/60	1/60

The exposures at the NOAEL (for carcinoma) are about 8 times in the male and 28 times in the female the exposures in humans at what would be the recommended dose of 600 mg/day.

There are no CMC issues pending. The Office of Clinical Pharmacology recommends that the application be approved, but they request several Phase 4 studies (described below).

COMMENTS

The sponsor has submitted reports of four controlled trials, three parallel group 12 week studies and one longer term randomized withdrawal study, that, in their view, provide substantial evidence of effectiveness for gabapentin enacarbil as a treatment for patients with moderate to severe RLS. Further, the sponsor has submitted safety data that purport to establish the safety in use of gabapentin enacarbil for this population.

Regarding effectiveness, a few points need to be addressed.

I agree that the trials submitted provide evidence that gabapentin enacarbil is effective in this population. The trials were of appropriate design and duration, and utilized standard outcome measures in this condition. The results, according to protocol, were clearly positive. Certain issues, however, need to be discussed, especially the questions of dose and timing of measurement of effectiveness.

With regard to which dose or doses have been shown to be effective, it is clear that only two studies were even theoretically capable of evaluating dose response (Studies 53 and 81). Studies 52 and 60 studied only the 1200 mg dose and are incapable of addressing the question of dose response.

In Study 53, there were no important differences between the two doses on the IRLS score. An examination of the results of the IRLS scores over time reveals no systematic superiority of the 1200 mg dose compared to the 600 mg dose.

However, there was a numerical superiority of the 1200 mg dose compared to the 600 mg dose group on the Proportion of Responders on the LOCF analysis (77% vs 72%, respectively). Further, an examination of the time course of this measure reveals numerical superiority of the 1200 mg dose compared to the 600 mg dose at each time point, although all comparisons between these two groups and placebo are nominally statistically significant at each time point.

Study 81 did compare doses of 600, 1200, 1800, and 2400, although the study was not powered adequately to demonstrate statistical significance. Nonetheless, in this study, doses of 600, 1200, and 1800 mg did reach nominal

significance when compared to placebo on the IRLS scale. On this measure, there was no difference between any of the dose groups. However, on the Proportion of Responders outcome, there was a clear increase with dose (64%, 65%, 73%, and 82%, for the 600, 1200, 1800, and 2400 mg doses, respectively, with the latter two groups significantly superior to the placebo group, and no difference between the 600 and 1200 mg doses). Examination of the comparisons of these two outcomes at each visit during the study shows a general trend for numerically increased effectiveness of the 1800 mg dose group compared to the other dose groups at most time points, although it should be noted that there were a considerable number of discontinuations over the 12 weeks of treatment. Regarding the comparison of 600 and 1200 mg (the two doses under consideration for approval), there were a few scattered, but not systematic, numerical increases of the 1200 mg dose compared to the 600 mg dose over time for the IRLS score, but there were more Responders at every time point tested in the 1200 mg group compared to the 600 mg group (although the LOCF analysis of this latter endpoint revealed essentially identical rates, 64% vs 65%, respectively). Again, 13/46 (28%) and 14/40 (35%) of patients in the 600 and 1200 mg groups, respectively, discontinued treatment during this small study.

Another way to look for dose response is to examine the effects of the two doses on the time course of response.

Symptoms of RLS typically peak in the hours before sleep, but can occur earlier as well, and even throughout the day. The two approved treatments for RLS (immediate release Mirapex and Requip), are labeled to be taken at about 9 PM. Gabapentin enacarbil is an extended release product, with a T_{max} of between 5-7 hours, and is designed to be taken at 5 PM, presumably in order to produce a peak effect at the time of a patient's worst symptoms.

In an attempt to discern when an effect was seen with Horizant, the sponsor examined its effects on the severity of RLS symptoms at different times post-dosing. It is clear from the sponsor's analyses described above (examining overlapping 4 hour epochs post-dosing) that the treatment does have an effect (at least numerically, and in some cases statistically significantly compared to placebo) for the time periods 4-8PM, 6-10 PM, 8-12 AM, and 12-4 AM), but there is no clear dose response between 600 and 1200 mg doses. Dr. Goldstein has also performed an examination of the proportion of patients with no RLS symptoms each hour from 5-11PM. In this display, there are no consistent changes favoring the 1200 mg dose over the 600 mg dose.

In sum, in my view, there are few if any systematic changes favoring the 1200 mg dose over the 600 mg dose, except for some small increases in the proportion of patients meeting responder criteria in the 1200 mg dose compared to the 600 mg dose. These differences are small, although suggestive of a dose response. The loss of significant numbers of patients over the course of the

studies (especially in Study 81) makes the interpretation of these differences difficult, however. These data, taken together with the safety data (described below), argue, in my view, for recommending the 600 mg dose in labeling, should the drug be approved.

There are no obvious clinical safety concerns that would preclude approval, in my opinion. However, a few points need to be made.

Gabapentin is known to cause somnolence, and this was clearly detected in these trials at a rate of about 20% on drug and 5% on placebo for the pooled controlled trial data. In the trials in which the 600 and 1200 mg doses were studied together, the rates of somnolence were not consistently materially different from each other. There is, however, a clear increase in the incidence of dizziness at the 1200 mg dose compared to the 60 mg dose. In most patients, the onset of somnolence is shortly after the initiation of treatment; we have no well documented information about how long the somnolence persists. We have no information about the time of onset of somnolence post-dosing. This information would have been important, because given that the drug is to be dosed in the early evening, it would be important to know if somnolence occurs rapidly after dosing, because that is a time when patients are likely to be driving home from work or driving for other reasons. Although, as discussed above, there is evidence that the drug has an effect on the symptoms of RLS in the hours after dosing (numerical changes appear in the 4-8PM epoch), it would be useful to know how the time of onset of somnolence compares to the time of onset of effectiveness.

Regarding the important question of the effects of gabapentin enacarbil on driving, and the time course of these effects, the sponsor has performed a simulated driving study. In this study, there were clear negative effects of a 1200 mg dose (as measured by the primary outcome of variation in lane position as well as number of crashes), both in the morning after PM dosing (when patients may be driving to work), and in the evening after PM dosing (when patients may be driving home from work), as well as later in the day after AM dosing (when the drug should be having its peak effect). Indeed, the effects seemed to be worse than the effects of diphenhydramine, a known sedating drug. However, the study was problematic, in that the 1200 mg dose was clearly shown to be worse than the 1800 mg dose, and in this latter group, the plasma levels of gabapentin were lower than those seen with the 1200 mg dose. These latter findings suggest that the study was flawed in its conduct, making the results difficult to interpret. Also, and importantly, of course, the sponsor did not study the effects of the 600 mg dose.

Independent of any clinical concerns, the finding of acinar cell carcinoma in the rat is troubling.

As described above, gabapentin had previously been shown to cause acinar cell carcinoma of the pancreas in male rats. Carcinogenicity studies were performed with gabapentin enacarbil, and these studies revealed the occurrence of pancreatic acinar cell hyperplasia, adenomas, and carcinomas in male and female rats at 5000 mg/kg/day, and in the male at 2000 mg/kg day. The NOAEL was 500 mg/kg in the male, and 2000 mg/kg in the female for carcinoma.

The exposures at the NOAEL for carcinoma are about 8 and 28 times in males and females, respectively, the exposures in humans at what would be the recommended dose of 600 mg/day. Horizant is not genotoxic.

There presumably exist mechanisms of the formation of pancreatic cell carcinoma in the rat that are considered to be irrelevant for people, such that if a sponsor can demonstrate that these mechanisms are at work in a given case of drug-induced tumor, that finding would be considered to be of no concern for people. The current sponsor has not performed any studies to identify the mechanism of tumor formation. However, the sponsor for Neurontin did perform extensive studies, and failed to identify such a mechanism. We decided to approve Neurontin because of the severity of the condition under treatment (patients who were not adequately controlled on other AEDs).

The data in this case raise serious questions about the propriety of approving Horizant for the treatment of RLS.

Specifically, the findings in the study performed with gabapentin enacarbil clearly provide definitive replication of the findings seen with gabapentin, thereby documenting that gabapentin causes pancreatic acinar cell carcinoma without question. Further, and disturbingly, in this study, we now see a carcinoma in the high dose female (carcinoma was seen only in the high dose male previously), and we now see a carcinoma in the mid-dose male. Although the low dose male and the mid-dose female are now considered the NOAELs for carcinoma (and are the bases for the calculation of the margins stated above), in fact, we now see hyperplasia in the mid-dose females and adenomas in the low dose male. Adenomas are considered a precursor to carcinoma in this model, and, in the setting of frank carcinoma and adenoma, hyperplasia is reasonably considered to be pre-neoplastic. Given this, we could consider that there is no NOAEL in the male, and the low-dose to be the NOAEL in the female (were we to do this, of course, the “margins” would be considerably smaller than those quoted above).

However, even limiting our identification of the NOAEL based only on the occurrence of carcinoma, the margin of 8 in the male is quite low. Further, Dr. Freed has examined the data for the original gabapentin carcinogenicity studies and notes that, in that study, no tumors were noted to have been invasive. In the current study, however, the carcinomas have been described as locally invasive.

It is worth noting that gabapentin has been marketed for over 15 years, and we are unaware of any signal for carcinogenicity. In this regard, we can examine how the exposures to gabapentin when administered at therapeutic doses of gabapentin compare to those when a 600 mg dose of Horizant is given.

The AUC of gabapentin after a 700 mg dose of Horizant is about 53 mcg.hr/mL. This is comparable to the gabapentin AUC (about 56 mcg.hr/mL) after a gabapentin dose of 1200 mg/day, a standard anti-epilepsy dose. These data establish that the plasma levels of gabapentin achieved after a therapeutic dose of 600 mg of Horizant are consistent with the exposures achieved with already approved doses of gabapentin products.

Report Date: June 25, 2004

Report Number: PK-2004-001
Status: Final

2.0 SUMMARY TABLES

Table 2.1. Mean Pharmacokinetic Parameters for Gabapentin in Blood After Single Oral Doses of XP13512 in Study XP006

Group	Dose (mg)	Dose (mg-equiv. gabapentin)	N	C _{max} (µg/mL)	T _{max} (hr)	T _{1/2} (hr)	AUC _(0-inf) (µg*hr/mL)	F (%)
1	350	182	8	3.61	2.13	4.38	25.4	82.9*
2	700	365	8	6.55	2.06	5.38	53.0	85.4
3	1400	729	8	11.3	2.63	4.84	85.0	68.5
4	2100	1094	8	15.7	2.19	5.10	120	72.3
5	2800	1458	8	18.1	2.56	5.47	162	79.7

*One subject excluded due to an apparent error in urine volume measurement.

Table 2.2. Mean Pharmacokinetic Parameters for Gabapentin in Blood After Single Oral Doses of Neurontin® in Study XP006

Group	Dose (mg)	Dose (mg-equiv. gabapentin)	N	C _{max} (µg/mL)	T _{max} (hr)	T _{1/2} (hr)	AUC _(0-inf) (µg*hr/mL)	F (%)
1	200	200	10	2.61	2.85	5.40	22.8	65.2
2	400	400	10	3.41	3.06	6.69	33.4	51.0
3	800	800	10	4.78	2.80	7.34	43.4	39.7
4	1200	1200	10	6.13	3.30	9.26	56.6	26.9
5	1400	1400	10	5.76	3.20	8.27	64.5	26.5

We have examined the post-marketing adverse event reporting system (AERS) to identify cases of pancreatic cancer in patients taking gabapentin products. The Office of Surveillance and Epidemiology (OSE) has identified 4 cases. Dr.

Podskalny has described these cases. The details, as is typical in cases reported to AERS, are minimal. The duration of treatment was reported in 3 cases, and varied from 3-8 years of treatment. Datamining was also performed, and an EB05 score (a comparison of the percent of all reports of all events reported for gabapentin that were pancreatic cancer compared to a similar percent for all drugs in the system) of 0.33 was calculated (an EB05 of greater than 2 is considered a signal worth further exploration). We have not obtained usage data for gabapentin.

Despite the relatively extensive exposure to gabapentin for many years, though, the reports of 4 cases and an EB05 are not entirely reassuring, given the vagaries of post-marketing adverse event reporting, and the rarity of acinar cell carcinoma in humans. It is also worth noting that the sponsor makes no specific argument justifying the approval of this product for this population. Presumably, they rely on the fact of our approval of gabapentin for epilepsy as sufficient justification for approving this product for patients with RLS.

In summary, I conclude that the sponsor has provided substantial evidence of effectiveness for Horizant as a treatment for the symptoms of moderate to severe RLS, and that they have provided evidence of its safety in use. I agree with the review team that, should the application be approved, the recommended dose should be 600 mg given at 5 PM (the sponsor proposes (b) (4)

), because there is no meaningful increase in effectiveness at doses greater than 600 mg, but there is a suggestion of an increase in adverse events at this higher dose.

Although the sponsor has not evaluated the effects of a 600 mg dose on driving, it appeared that a dose of 1200 mg resulted in impairment both at night, in the several hours post dosing, but also the next morning. However, the study as conducted was problematic, in that the 1200 mg dose appeared to produce more impairment than the 1800 mg dose, and was worse than diphenhydramine. The reasons for this are unknown, but it is also true that patients randomized to the 1200 mg group were consistently worse at baseline than the patients in the other groups. Because these effects were difficult to evaluate, because the plasma levels at the to-be-recommended dose of 600 mg are substantially lower than those at the 1200 mg dose, and because the plasma levels of gabapentin at the 600 mg dose (Cmax and AUC) are similar to those achieved with therapeutic doses of gabapentin products, with which we have considerable experience, I do not believe that the results of the driving test preclude approval.

However, as discussed above, administration of gabapentin enacarbil produces pancreatic acinar cell carcinomas, adenomas, and hyperplasia in both male and female rats, a finding that is, for the reasons stated earlier, even more disturbing than the previous similar findings seen with gabapentin. Further, although I

believe one could argue for setting the NOAELs lower than those based on frank carcinomas, just basing the NOAELs on carcinomas gives a margin of 8 for the plasma levels of gabapentin in the male rat compared to the plasma levels of gabapentin in humans at a dose of 600 mg. In my view, absent a compelling argument to the contrary, this margin is too low to justify approval of the 600 mg dose for patients with RLS. I acknowledge, of course, that RLS can be a distressing condition, but I do not believe it is comparable to poorly controlled epilepsy in severity or clinical outcome, and there are other treatments approved for the treatment of RLS.

For these reasons, I recommend that the application not be approved at this time.

The sponsor may, of course, provide arguments/evidence that would support approval, and, of course, we remain open to such approaches.

For example, the sponsor might undertake an epidemiologic study that establishes that there is no increased risk of pancreatic carcinoma in patients taking gabapentin for extended durations (we believe that there is considerable exposure to gabapentin products), or, if there is an increased risk, this risk is acceptable in light of the benefits.

Alternatively, they may attempt to provide evidence that the mechanism of tumor formation is irrelevant for humans (however, again, based on previous data, our expectation that they can do so is low). Failing this, they might, for example, be able to demonstrate the effectiveness of doses substantially lower than 600 mg, so that the margins between gabapentin levels associated with cancer in male rats and the levels in humans at a therapeutic dose would be substantially greater than 8. However, exactly what would be an acceptable level should be a matter for further discussion (a level of about 30, as seen with the female rat, would likely be acceptable. I should note, however, that I am not convinced that the mid-dose female should be considered a NOAEL at this time). Other approaches may be for the sponsor to demonstrate that Horizant is superior to other approved treatments for RLS. In any event, I do not believe that, at this time, the sponsor has presented sufficient (or any) justification for marketing.

The review team has discussed with the sponsor several studies that should be performed in Phase 4; these studies are described:

- 1) The sponsor should be asked to perform a controlled trial examining doses lower than 600 mg. The fact that doses greater than 600 mg do not produce a meaningful additional benefit raises the question of whether or not 600 mg is itself an unnecessarily high dose. Therefore, the sponsor should study lower doses, for example, 300 and 450 mg.

2) The sponsor must also perform an adequate driving study at the appropriate lower doses.

3) The sponsor must also perform an adequate thorough QT study.

4) The Office of Clinical Pharmacology also has several recommendations for Phase 4 studies. They are:

- 1) An in vitro study to evaluate the potential for gabapentin enacarbil to inhibit CYP2C8 and 2B6
- 2) Conduct an in vitro dissolution study to evaluate dose dumping in the presence of alcohol using the final approved dissolution method
- 3) Develop a dosage form that will allow for a 300 mg dose (for patients with severe renal impairment)

5) Finally, the sponsor has submitted a plan for pediatric studies down to the age of 13. These studies should be required under PREA.

I believe that what studies should be performed remain an open question at this time.

Certainly, if the sponsor wishes to pursue marketing, it might be necessary to perform additional clinical studies as described above. Whether or not the sponsor should be required to perform pediatric studies is also a difficult question at this time (for example, if we become convinced that the tumors are irrelevant for humans, pediatric studies are likely to be required. If for some reason we are convinced that the drug should be marketed even if we cannot “erase” the tumor concern, pediatric studies may be inadvisable).

For the reasons stated above, I recommend that the sponsor be sent a Complete Response letter, describing our concerns, and possible routes to ultimate approval.

Russell Katz, M.D.

Application Type/Number	Submission Type/Number	Submitter Name	Product Name
NDA-22399	ORIG-1	GLAXO GROUP LTD DBA GLAXOSMITHKLIN E	SOLZIRA

This is a representation of an electronic record that was signed electronically and this page is the manifestation of the electronic signature.

/s/

RUSSELL G KATZ
02/15/2010

Cross-Discipline Team Leader Review

Date	February 7, 2010
From	Gerald D. Podskalny, D.O.
Subject	Cross-Discipline Team Leader Review
NDA/BLA # Supplement#	22,399 (0000)
Applicant	GlaxoSmithKline/Xenoport
Date of Submission	January 9, 2009
PDUFA Goal Date	February 9, 2010
Proprietary Name / Established (USAN) names	Horizant Gabapentin enacarbil
Dosage forms / Strength	600 mg tablets
Proposed Indication(s)	Treatment of moderate to severe symptoms of Restless Legs Syndrome
Recommended:	Complete Response

Cross Discipline Team Leader Review

1. Introduction

Restless Legs Syndrome (RLS) is a common nervous system disorder with an estimated prevalence between 5 and 10% in the general population, with 2 to 3% experiencing symptoms severe enough to warrant treatment based on epidemiological studies in the US [Allen, 2003;Hening, 2004b]. The diagnosis of RLS is based on four clinical criteria developed by the International Restless Legs Syndrome (IRLS) Study Group [Allen, 2003]:

- An urge to move the legs usually accompanied or caused by uncomfortable and unpleasant sensations in the legs. Sometimes the urge to move is present without the uncomfortable sensations and sometimes the arms or other body parts are involved in addition to the legs;
- The urge to move or unpleasant sensations begin or worsen during periods of rest or inactivity, such as lying or sitting;
- The urge to move or unpleasant sensations are partially or totally relieved by movement, such as walking or stretching, at least as long as the activity continues;
- The urge to move or unpleasant sensations are worse in the evening or night than during the day or only occur in the evening or night. (When symptoms are very severe, the worsening at night may not be noticeable, but must have been previously present.).

The net result of the symptoms of RLS is that patients with the disorder have difficulty falling asleep. Sleep can be disturbed further by periodic limb movements of sleep PLMS are estimated to affect more than 80% of all RLS patients.

1. Background

Sponsor's Requested Indication

"XP13512 is indicated for the treatment of moderate-to-severe primary Restless Legs Syndrome (RLS)."

Classification of RLS

RLS can be primary (idiopathic) or secondary to other conditions. Primary RLS is often associated with a family history of RLS. Secondary RLS has been associated with a variety of conditions and pathological disorders including iron deficiency, peripheral neuropathies, rheumatoid arthritis, Parkinson's disease, diabetes, and multiple sclerosis [Manconi, 2007]. Iron deficiency or anemia, uremia, and pregnancy are the most commonly recognized causes of secondary RLS [Hening, 2007]. Low serum ferritin and CNS intracellular iron have been reported in patients with RLS. Evidence for abnormality in central dopaminergic transmission is supported by autopsy and animal studies as well as the clinical response to dopaminergic medications. There have been several reports linking low serum ferritin with the presence of augmentation.

The mechanism of action of how gabapentin may improve the symptoms of RLS is unknown.

Approved Medications:

Ropinirole (REQUIP®) and pramipexole dihydrochloride (Mirapex®) are non-ergot dopamine agonists and are the only agents currently approved by the Food and Drug Administration (FDA) for the treatment of moderate-to-severe primary RLS. Gabapentin is prescribed for off label for the treatment of RLS and is included in RLS treatment guidelines [Silber, 2004].

Similar Medications

Gabapentin (Neurontin®) was approved by the FDA in 1993 US for the as adjunctive therapy in the treatment of partial seizures with and without secondary generalization. It was subsequently approved for the treatment of post-herpetic neuralgia. There are multiple generic gabapentin products available in the U.S. In this reviewer's opinion, there is likely substantial off label use of gabapentin used for the treatment of RLS.

There are several published reports on the effective use of gabapentin for the treatment of RLS, including 2 randomized, placebo-controlled, double-blind trials [Thorp, 2001; Garcia-Borreguero, 2002], 3 open-label trials [Adler, 1997; Happe, 2001; Happe, 2003]. The largest of these studies was a randomized, placebo-controlled, blinded crossover design in 24 subjects with RLS (22 with primary RLS and 2 with RLS secondary to iron deficiency) treated with gabapentin (two divided doses at noon and at 8PM) for 6 weeks [Garcia-Borreguero, 2002]. In the two double blind trials, the dose of gabapentin patients received a mean dose that ranged from 300 mg to 1300 mg (max dose 2400 mg/day). These double blind trials were too small (N=9, N= 24) to generalize the results to a larger

population with primary RLS but the results demonstrated gabapentin was able to relieve the symptoms of RLS in the study population. The safety experience in these small and other open label studies are insufficient to draw any conclusions regarding safety in patients with RLS. Based on the experience of gabapentin in patients treated for epilepsy gabapentin is expected to be safe in the dosages typically given to patients with RLS.

Safety Issues Related to RLS and XP13512

Suicidality

All anti-convulsants are required by the agency to inform patients and prescribers in labeling about an increased risk for suicidality associated with the class of anti-convulsants.

Augmentation

Augmentation is a change in the symptoms of RLS so that the symptoms start earlier in the day. Other definitions of augmentation include involvement of other body areas such as the arms. Augmentation is a complication of RLS that appears to be associated with persistent treatment of RLS with medications. It was described first in association with levodopa but is also associated with dopaminergic medications. Rebound is a symptom of RLS that occurs when medications for RLS are withdrawn or decreased abruptly. An increased risk for augmentation and rebound are unwanted complications for a perspective new treatment for RLS. The sponsor believes gabapentin enacarbil has a lower potential to cause compared to approved therapies.

Sedation

A very common (>20%) adverse effect associated with gabapentin is sedation. The concern regarding any long acting preparation of gabapentin is that it will produce sedation persisting into the morning after taking the medication, which may adversely impact cognitive performance and driving. A related concern is that gabapentin enacarbil is taken at 5 PM with food and it is expected to provide relief from the symptoms of RLS later in the evening beginning after 7 PM. Gabapentin enacarbil may cause sedation between 5 PM and 7 PM without providing significant relief from RLS or that patient's symptoms of RLS are not severe enough to require treatment between 5-7 PM. If this scenario is true then patients may be at risk for sedation after taking the medication at 5 PM while driving home without yet receiving the benefit of treating the symptoms of RLS.

2. CMC/Device

Drug Substance

The bulk drug substance is [REDACTED] (b) (4). Gabapentin enacarbil is [REDACTED] was reported.

Drug Product

Gabapentin enacarbil is produced as a 600 mg non-scored tablet as the only solid oral dose form. The commercial product will be identical to the investigational product with only minor changes made to the shape of the tablet and the addition to debossing the tablet.

Summary of Stability Data (from the CMC Review)

CMC reviewed 36 months stability data is provided for one supportive batch. The sponsor provided 24 months stability data for the three primary stability batches and 12 months long-term data for fourth primary stability batch using the proposed commercial process with the minor process improvements (stored at 5° C, 25° C/60% RH, and 30° C/65% RH and 6 months at 40° C/75% RH). The sponsor reported no significant change in description, content, drug-related impurities, and [REDACTED] (b) (4) was observed after storage at 5° C and 25° C/60% RH for 24 months and 30° C/65% RH for 12 months or 40° C/75% RH for 6 months. The stability data demonstrated the chemical and physical stability of the drug substance.

The CMR reviewed test results for the drug product, which remained within the shelf-life specifications after 12 months for commercial image and after 24 months for non-debossed tablets stored at 25° C/60% RH and 30° C/65% RH and after 6 months of storage at 40° C/75% RH. Photo-stability data are provided for one supportive stability batch of XP13512 ER Tablets. Photo stability was tested because the tablets developed a discoloration over time. The stability data for XP13512 ER tablets showed no significant change in assay, degradation products, and dissolution for any of the conditions tested. Results of accelerated and long-term stability studies demonstrated the chemical and physical stability of XP13512 ER tablets, therefore, no statistical analysis is provided.

A shelf-life of 36 months was proposed by the applicant to the product when stored under the following conditions: Store at 25° C (77° F); excursions permitted to 15 to 30° C (59 to 86° F). Discussions with the CMC review team members (Dr. Heimann) confirmed approval of the requested 36 month shelf life. Batch analysis data for three pilot scale commercial image batches of XP13512 ER Tablets (600 mg strength) are provided, which were manufactured according to the proposed commercial process at the commercial site and tested by the proposed commercial methods. The proposed commercial tablet formulation is qualitatively identical to the tablets used for Phase 3 clinical trials and will be manufactured at the same site.

CMC Reviewer Opinion Regarding Stability

Adequate-Results are provided for commercial tablets following storage for up to 12 months at 2-8° C, 25° C/60% RH, 30° C/65% RH, and 40° C/75% RH. Data demonstrated that the gabapentin enacarbil commercial drug product is stable.

CMC Evaluation of Excipients of XP13512 Gabapentin enacarbil ER) 600 mg tablets

Several excipients are present in the formulation of gabapentin enacarbil tablets are:

- dibasic calcium phosphate dehydrate,
- talc
- glyceryl behenate
- magnesium stearate
- sodium lauryl sulfate
- colloidal silicon dioxide

These excipients comply with USP/NF grade. **Adequate-The final formulation is acceptable as commercial formulation.**

Facilities Review and Inspection

1) (b) (4)

Responsibilities:

- Drug substance manufacturer
- Drug substance release tester
- Drug substance stability tester

Milestone Date: 16 Jan 2009

Conclusion: Acceptable

Based on: Profile

2) PATHEON PHARMACEUTICALS INC, CINCINNATI, OH USA

Responsibilities:

- Finished dose manufacturer
- Finished dose packager
- Finished dose release tester
- Finished dose stability tester

Milestone Date: 09.Sept. 2009

Decision: Acceptable

Based on: District Recommendation

3) GLAXOSMITHKLINE INC., ZEBULON, NC USA

Responsibilities:

- Finished dosage packager
- Finished dosage release tester
- Finished dosage stability tester

Milestone Date: 24.Sept. 2009

Decision: Acceptable

CMC Review Issue Regarding Dissolution

The CMC reviewer concluded the dissolution method proposed by the sponsor appeared to be over-discriminating and not clinically relevant: the method discriminates between two batches that have equal in vivo performance. CMC recommended the sponsor consider the development of a more clinically relevant dissolution method that is not over-discriminating.

The following dissolution specification are recommended for gabapentin enacarbil ER tablets:

Table 1 FDA Recommended Dissolution Specifications (Excerpted From The FDA CMC Review)

USP Apparatus	Spindle Rotation Speed	Media Volume	Temperature	Medium	Specifications
II	50 rpm	900 mL	37°C	10 nM potassium phosphate monobasic buffer at pH 7.4 with 1% SLS	4 hours: (b) (4) 8 hours: (b) (4) 12 hours: (b) (4) 24 hours: (b) (4)

A request was made to the sponsor to provide stability data from the three primary batches to support the dissolution specification using the agency’s recommended time intervals (see table 1).

The reviewer concluded that the mean dissolution profiles (Stage 1) for some lots under stability do not meet the proposed FDA dissolution specifications, but meet do the specification proposed by the sponsor.

A teleconference with the sponsor was held on October 21, 2009 to discuss the sponsor’s responses to comments sent on Oct 2, 2009 (refer also to Biopharm review entered on DARRTS on September 30, 2009 and to the Sponsor’s responses to comments received on Oct 8, 2008 regarding (b) (4)). The following agreements, which were also submitted in writing to the Agency on Oct 23, 2009, were reached during the teleconference:

The Agency accepted the following dissolution specifications for gabapentin enacarbil ER tablets after negotiation with the sponsor.

USP Apparatus	Spindle Rotation Speed	Media Volume	Temperature	Medium	Specifications
II	50 rpm	900 mL	37°C	10 nM potassium phosphate monobasic buffer at pH 7.4 with 1% SLS	4 hours: (b) (4) 8 hours: (b) (4) 12 hours: (b) (4) 24 hours: (b) (4)

CMC Comments to Sponsor [REDACTED] (b) (4)

[REDACTED]

[REDACTED]

[REDACTED]

[REDACTED]

[REDACTED]

[REDACTED]

[REDACTED]

[REDACTED]

[REDACTED]

Comparability Protocol Decision to be sent in the Action Letter

Environmental Assessment

Review of the Environmental Assessment (consult conclusion and recommendation, Raanan Bloom, 22-SEP-09) concluded that no significant adverse environmental impacts are expected from the approval of this NDA. A Finding of No Significant Impact (FONSI) is recommended.

CMC Overall Recommendation

From the CMC point of view, NDA 22-399 for Solzira (gabapentin enacarbil) ER Tablets is recommended **APPROVAL**.

FDA inspection of the proposed site is needed in addition to the proposed data package, which needs to be submitted in a CBE-30 supplement. CMC will send this decision and instruction for submitting this information in CBE-30, to the sponsor in the final action letter.

3. Nonclinical Pharmacology/Toxicology

Pharmacology Toxicology Review Summary (Excerpts from Dr. Peters's review)

General toxicology:

Repeated dose testing via the oral route was performed in several species: up to 26 weeks in albino rats at doses up to 5000 mg/kg/d, up to 39 weeks in cynomolgus monkeys at doses up to 2000 mg/kg/d. In rats, the doses were 0, 500, 2000 or 5000 mg/kg/d.

As in the previous, shorter term rat studies, increased age-related chronic progressive nephropathy with hyaline droplet formation was noted in all treated male groups. Reversal was incomplete at the end of the recovery period. Centrilobular hepatocellular hypertrophy was described in the high dose animals but was reversed by the end of the 1 month recovery period. No NOAEL for the histologic renal findings was found in this study but clinical chemistries and urinalyses were not affected. Cynomolgus monkeys were treated by oral gavage with 0, 250, 1000 or 2000 mg/kg/d of XP13512. No adverse effects of treatment were found in any of the parameters evaluated. The NOEL is determined to be 2000 mg/kg/d. Exposures to gabapentin at the highest dose were 3370 µg.h/mL at the end of the 9 month period while exposures to XP13512 were 54.3 µg.h/mL at the same time point demonstrating essentially complete hydrolysis of the test article to gabapentin. The associated Cmax values were 366 µg/mL and 13.7 µg/mL, respectively.

Genetic toxicology:

XP13512 was not genotoxic in multiple Ames assays, the micronucleus or the UDS assays. However, it was positive in the chromosomal aberration assay in human lymphocytes. The etiology of this finding was the release of acetaldehyde during the (b) (4) potential (b) (4) impurities were found to be genotoxic in the Ames assays but the levels in the final product are below the level of concern.

Maternal toxicity shown by adverse clinical signs, decreased body weights and premature parturition (rabbits only) was evident in all studies. Embryo-fetal toxicity was found in rat pups at 5000 mg/kg/d and rabbit kits at 2500 mg/kg/d.

Toxicity Observed in Rat Carcinogenicity Study

General Toxicology Findings

“The 2000 and 5000 mg/kg/d males were terminated early (Weeks 97 and 90, respectively) due to exacerbation of chronic progressive nephropathy. Females were not similarly affected”.

Carcinogenicity Signal

Combined Pancreatic Lesions in Rats Treated with XP13512 for Up to 104 Weeks (Pharmacology Toxicology Reviewer Table)

<u>Dose (mg/kg/d)</u>	Males				Females			
	<u>0</u>	<u>500</u>	<u>2000</u>	<u>5000</u>	<u>0</u>	<u>500</u>	<u>2000</u>	<u>5000</u>
Hyperplasia, acinar; min-mild	11	8	11	17	1	0	3	10
Mod-severe	3	2	3	3	0	1	1	4
Acinar adenoma	2	4	4	8	0	0	0	3
Acinar carcinoma	0	0	1	1	0	0	0	1

Pharmacology Reviewer Comments Regarding Carcinogenicity

Evaluation of tumor findings: An increased incidence of pancreatic acinar adenomas and adenocarcinomas were found at 5000 mg/kg/d in both sexes and a trend towards an increase was also noted in the 2000 mg/kg/d males. Although the 2000 mg/kg/d males had slightly increased severity of the hyperplasia, there was an increased incidence of adenomas and a carcinoma was found. The decreased survival and early termination in the 2000 and 5000 mg/kg/d males may be responsible for a lesser incidence of both non-neoplastic and neoplastic lesions.

In the rat carcinogenicity study, Wistar rats were treated for up to 104 weeks with 0, 500, 2000 or 5000 mg/kg/d of XP13512 by oral gavage. The most notable finding was “an increased incidence of pancreatic acinar cell hyperplasia, adenomas and carcinomas in both sexes at 5000 mg/kg/d and in males at 2000 mg/kg/d. The decreased survival and early termination in the 2000 and 5000 mg/kg/d males may be responsible for a lesser incidence of both non-neoplastic and neoplastic lesions. Thus XP13512 is considered a carcinogen in rats under the conditions of this study”.

Statistical Review of Animal Carcinogenicity Data

The statistician's review of the animal carcinogenicity statistical data was reported in 2 parts, the initial review and an addendum. The review concentrated on the 104 week carcinogenicity studies performed in mice and rats. The initial review reported results from a survival unadjusted analysis. The conclusions by the statistical reviewer were that the survival adjusted analysis may indicate that the tumor finding that were not statistically significant in the unadjusted analysis of the animal data. These data may become significant using a survival adjusted analysis (adjusting for early mortality in some of the dose groups) for pancreatic acinar carcinoma and potentially other carcinoma reported in the data. Findings in "Report 2" reported the results of a more detailed survival analysis of the carcinogenicity data for mice and rats. In Mice, there was a difference in survival overall with a reduced survival in the high dose males showing the greatest effect however, the survival curves for the medium and low dose groups were intertwined but still had a greater mortality compared to mice that received placebo. The reviewer reported there was "no particular evidence of differences in survival" (all $p \geq 0.2987$) in female mice.

In rats, the test for trend and no trend were statistically significant for acinar cell adenoma in both genders. In female rats, only the no trend test of combined adenoma and carcinoma in the high dose group compared to controls were statistically significant. In male rats, the results from a trend and no trend test using pooled analysis of acinar adenoma and carcinoma were statistically significant compared to controls. In addition, the test of trend was close to being statistically significant in female rats in the high dose group compared to controls for the finding of benign granular tumors of the uterus. In report 1, the reviewer expressed concern about granular cell tumors in female rats affecting the uterus and vagina. The statistical reviewer expressed a difference in opinion regarding the general statistical approach used to analyze and interpret animal data for carcinogenicity signals. Although these comments were highly detailed, they were clearly not specific or relevant to this application or gabapentin.

CDTL Comment

The findings reported by the statistical reviewer and the Pharmacology Toxicology review team are compatible. Both report an animal signal for pancreatic acinar cell adenoma and carcinoma in rats that raise concern. The finding of benign granular cell tumors nearly reaching statistically significant levels is also noted.

Neurontin Carcinogenicity Data From The Label

Gabapentin was given in the diet to mice at 200, 600, and 2000 mg/kg/day and to rats at 250, 1000, and 2000 mg/kg/day for 2 years. A statistically significant increase in the incidence of pancreatic acinar cell adenomas and carcinomas was found in male rats receiving the high dose; the no-effect dose for the occurrence of carcinomas was 1000 mg/kg/day.

CDTL Comment

Similar findings appear in the gabapentin product label regarding increased pancreatic carcinomas observed in rat carcinogenicity studies. The signal for pancreatic adenoma and carcinoma appears to be more common, at lower doses compared to the carcinogenicity findings in Neurontin. Since the approval of gabapentin for the treatment of epilepsy, a human signal indicating an increased risk for pancreatic carcinoma has not been reported (reviewer's PubMed and MeSH database search). The doses of gabapentin are typically higher for the treatment of epilepsy compared to the doses and exposures associated with labeled and off label use of gabapentin as well as the proposed doses of gabapentin enacarbil for the treatment of RLS. The life-time exposures for gabapentin are likely to be much longer since Neurontin is approved for the treatment of epilepsy for children age 2 potentially providing a life-long exposure to Neurontin at levels of exposure that are higher than those associated with XP13512 at 600 mg/day. Comparing exposure in humans at the propose dose of XP13512 at 600 mg/day, to the exposure in male rats at the lowest dose associated with pancreatic carcinoma, finds the projected margin of safety between the human exposure and the carcinoma signal in male rats is only 8 fold. Although, there is no universally recognized margin for safety for a carcinoma signal in animal studies, given the poor prognosis associated with human pancreatic carcinoma the safety margin seems small in relation to the potential risks. The product label for gabapentin enacarbil should include a warning describing the finding in animal studies similar to the information contained in the gabapentin label.

Reproductive Toxicology Finding in Pharmacology Toxicology Review (From the PT Review)

A complete battery of reproductive toxicity testing was conducted in rats and rabbits and no adverse effects were found on fertility, development of terata or developmental parameters. Maternal toxicity shown by adverse clinical signs, decreased body weights and premature parturition (rabbits only) was evident in all studies. Embryo-fetal toxicity was found in rat pups at 5000 mg/kg/d and rabbit kits at 2500 mg/kg/d.

Gabapentin is listed as Pregnancy Category C has been shown to be fetotoxic in rodents, causing delayed ossification of several bones in the skull, vertebrae, forelimbs, and hindlimbs. These effects occurred when pregnant mice received oral doses of 1000 or 3000 mg/kg/day during the period of organogenesis, or approximately 1 to 4 times the maximum dose of 3600 mg/day given to epileptic patients on a mg/m² basis. The no-effect level was 500 mg/kg/day or approximately ½ of the human dose on a mg/m² basis. When rats were dosed prior to and during mating, and throughout gestation, pups from all dose groups (500, 1000 and 2000 mg/kg/day) were affected. These doses are equivalent to less than approximately 1 to 5 times the maximum human dose on a mg/m² basis. There was an increased incidence of hydroureter and/or hydronephrosis in rats in a study

Similar fetal skeletal abnormalities and hydroureter or hydronephrosis were not reported in offspring exposed to doses of gabapentin enacarbil that were higher than fetotoxic dose of gabapentin. Pharmacology Toxicology conclusion is that "Embryo-fetal toxicity was found in rat pups at 5000 mg/kg/d and rabbit kits at 2500 mg/kg/d".

CDTL Comment

XP13512 (gabapentin enacarbil) should carry a similar category C rating regarding its use in pregnancy.

4. Clinical Pharmacology/Biopharmaceutics

XP13512 is a prodrug of gabapentin designed to be absorbed by the high capacity transport mechanisms found throughout the intestine. In preclinical and clinical studies, XP13512 was absorbed efficiently throughout the intestinal tract. The conversion of XP13512 to gabapentin occurs rapidly after absorption leaving < 2% of detectable prodrug in the plasma. This is in contrast to gabapentin which utilizes a low capacity amino acid transporter, found in the small intestine only. This amino acid transporter becomes saturated at effective gabapentin doses, limiting the absorption of gabapentin. Because gabapentin is only absorbed in restricted area of the small intestine, a sustained-release formulation for the original product is not available.

Absorption:

The corresponding mean bioavailability of gabapentin from XP13512 ER by urinary recovery ranged from 64.3% to 86.1%. Exposure to intact XP13512 in systemic blood after oral dosing of XP13512 was consistently low ($\leq 2\%$ of the corresponding gabapentin exposures based on AUC) at all dose levels examined. Steady state was achieved in 1 day after BID dosing of ER XP13512. Based on the PK, steady state with QD should be achieved within 2 days.

Distribution:

XP13512 was 78 to 87% bound to human serum albumin over the concentration range 5 to 100 μM (1.7 $\mu\text{g/mL}$ -32.9 $\mu\text{g/mL}$). Protein binding of gabapentin has previously been reported to be <3.0% in plasma of rats, monkeys, and humans. Based on the population PK model, for typical male and female subjects weighing 79 kg and 51 years of age, the apparent volume of distribution values were 86.3 and 65.6 L, respectively.

Metabolism:

Following absorption from the intestinal tract, XP13512 undergoes extensive first-pass hydrolysis by non-specific carboxylesterases to form gabapentin with no other significant metabolites of XP13512.

Neither XP13512 nor gabapentin are substrates, inducers or inhibitors of the major isoforms of human cytochrome P450, including CYP1A2, CYP2C9, CYP2C19, CYP2D6, CYP2E1, and CYP3A4 [Report PK-2003-002]. However, the potential of XP13512 and gabapentin to be substrate or inhibitor of CYP2C8 and 2B6 were not evaluated. The studies to evaluate the potential of XP13512 and gabapentin to be inhibitor of CYP2C8 and 2B6 have been accepted by the sponsor as postmarketing requirements

Elimination:

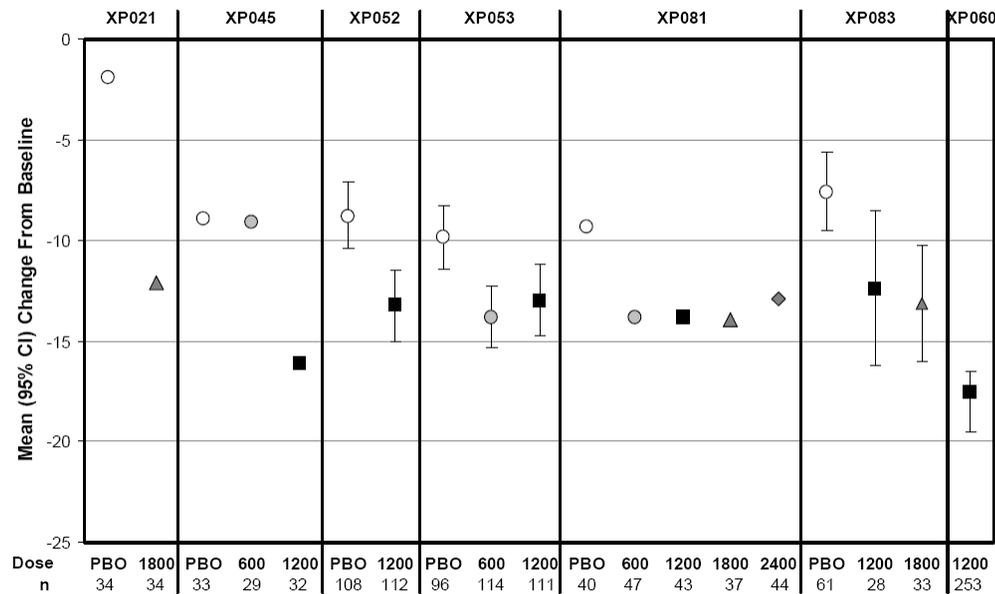
Gabapentin is not metabolized to any significant extent in humans, and the drug is cleared unchanged by renal elimination. Following hydrolysis of XP13512 to gabapentin, the released gabapentin is excreted by renal elimination. Gabapentin is eliminated via an organic cation transporter (OCT2) present in the kidney. The t1/2 is approximately 5-7 hours for gabapentin.

Dose Dumping in Alcohol

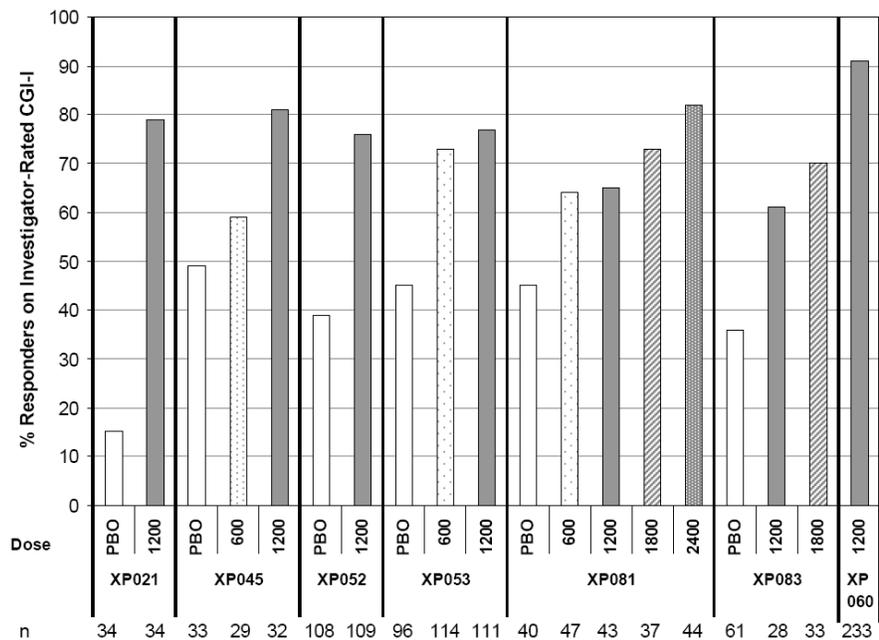
An alcohol interaction study was performed only using 40% alcohol compared to a buffer solution. The dissolution of XP13512 was increased by 20-30% within the first 2 hours. The sponsor’s method of testing for alcohol interaction was not consistent with the agency’s guidance and the dissolution at lower concentration of alcohol is not known. The clinical pharmacology reviewer recommended the sponsor repeat the alcohol interaction study in accordance with the agency’s guidance.

Clinical Pharmacology Assessment of Primary Efficacy Endpoints over Clinical Trials Program

**IRLS Scale Change From Baseline By Clinical Trial and Dose
(Clinical Pharmacology Reviewer Table)**



Change in CGI By Clinical Trial and Dose (Clinical Pharmacology Reviewer Table)



Clinical Pharmacology Dosing Recommendations

Clinical Pharmacology’s analysis of the exposure-response using the co-primary endpoints led to the recommend that the maintenance dose be 600 mg qd (and not 1200 mg). They do not recommend



Effects of Age:

Elimination of gabapentin is dependent on kidney and renal clearance which is known to decline with increasing age. The decline in elimination of gabapentin after administration of gabapentin enacarbil is explained by the age related decline in renal function. Clinical Pharmacology did not recommended a dose adjustment based on advancing age.

Effect of Gender

There was a small effect of gender an elimination of gabapentin observed in the Pop-PK study XP084. Males were observed to have a gabapentin clearance of 6.7 L/hr and the clearance in females was 5.7L/hr. The gender difference was considered non-significant after the clearance was corrected for the gender difference in body weight observed between males and females. There is no dose adjustment recommended based on gender.

Effect of Race:

In the whole clinical program, the majority of the subjects were Caucasian (94%) while no other single race was greater than 4%. The effect of race therefore could not be studied. Based on one study

(XP072), pharmacokinetics of gabapentin released from XP13512 were similar in Caucasian and Japanese subjects. No dosage adjustment is recommended based on race.

Effect of Hepatic Impairment:

A specific study in subjects with hepatic impairment has not been conducted because CYP enzymes do not significantly metabolize gabapentin released by hydrolysis of XP13512. It does not inhibit nor induce CYP enzymes. Although hydrolysis of XP13512 to gabapentin could potentially be affected by alterations in the level of carboxylesterase activity, but given the abundance and wide distribution of hCE-2 in the body it is unlikely that concomitant medications would affect conversion of XP13512 to gabapentin. Further, the conversion of XP13512 to gabapentin occurs mainly in enterocytes and not liver. No dose adjustment is recommended based on hepatic function.

Effects of Renal Impairment

Following hydrolysis of XP13512 to gabapentin, the released gabapentin is excreted by renal elimination via an organic cation transporter (OCT2). The elimination $t_{1/2}$ is approximately 5-7 hours for gabapentin in patients without renal impairment.

GSK's Dosing Recommendation In Patients With Renal Impairment

(b) (4)

The Clinical Pharmacology Reviewer indicated that the sponsor's proposed dosing regimen in patients with renal impairment is based on the relationship between gabapentin clearance and creatinine clearance (CrCL) derived from population pharmacokinetic analysis. The reviewer simulated the gabapentin concentration-time profile after administration of XP13512 tablets in patients with various degrees of renal function. The simulations were conducted using the dosing regimen as proposed by the sponsor compared with the FDA's dosing recommendations.

Clinical Pharmacology recommend that patients with creatinine clearance ≥ 60 mL/min (normal renal function), the (b) (4) should be changed to 600 mg since both doses were equally efficacious in Study XP053 and XP081. Also the incidence of adverse events were higher (numerical) in (b) (4) in comparison to 600 mg.

FDA-Clinical Pharmacology’s Dosing Recommendations For Patients With Renal Impairment

Creatinine Clearance (mL/min)	Titration Dose Regimen	Target Dose Regimen
≥60	600 mg per day for 3 days	600 mg per day starting day 4
30-59	300 mg per day for 3 days	600 mg per day starting day 4
15-29	no titration	300 mg per day
<15	Not recommended for use in patients with a CrCl <15 mL/min as it has not been adequately studied in this patient population and the dose cannot be reduced below 600 mg.	

Effect of Food On Bioavailability

The results of the sponsor’s food effects PK study showed that taking a single oral dose of XP13512 ER with a high fat meal increases gabapentin AUC by ~50% and Cmax by ~ 30% and delays Tmax from at 5 hours to 7 hours post-dose.

(b) (4) **5PM dose is missed as proposed by the sponsor?**

The sponsor recommends that gabapentin enacarbil should be taken with food at 5 PM placing the Tmax at approximately 12 AM when the symptoms of RLS are still at their peak and when peak dose adverse effects (such as sedation) may occur while the patient is asleep. The goal is that by the next morning the drug concentration should diminish reducing the effect for hangover effects. However, if the dose at 5 PM is missed (b) (4)

(b) (4) The Clinical Pharmacology reviewer does not agree with the sponsor’s alternative dosing regimen.

Drug-drug Interactions:

Effect of other drugs on gabapentin pharmacokinetics after XP13512 ER administration:

- **Naproxen:** It is believed that XP13512 absorption involves active transport via monocarboxylate transporter (MCT1), which is abundant in both small and large intestine. Naproxen is known to be a substrate of MCT1. Co-administration of naproxen didn’t alter PK of gabapentin and XP13512 at steady state.
- **Cimetidine:** It is believed that after XP13512 absorption and conversion to gabapentin, gabapentin renal excretion involves active secretion via organic cation transporter (OCT2), which is present in the kidney. Cimetidine is known to be a substrate (inhibitor) of OCT2. Co-administration of cimetidine didn’t alter Cmax of gabapentin at steady state as shown by 90 % confidence interval (CI) whereas AUCss was slightly increased by 24%. This slight increase is not considered clinical significant.

Clinical Pharmacology's Recommendation for Phase IV requirements

1. In vitro study for evaluation of the potential of XP13512 and gabapentin to be an inhibitor of CYP2C8 and 2B6 should be conducted.
2. The sponsor should repeat the alcohol dose dumping study using their final dissolution method and evaluate different concentrations of alcohol up to 40% (0, 5, 10, 20, and 40%).
3. Development of a 300 mg dose is recommended by the agency for patients with moderate to severe renal impairment. To obtain this dose, a new 300 mg strength needs to be developed. Alternatively, the 600 mg tablet can be scored to allow splitting of the tablet. Depending upon the formulation of the new strength, in vivo or in vitro data will be necessary to demonstrate bioequivalence. If the 600 mg tablet is scored, in vitro dissolution comparisons between half and whole tablet is necessary.

Results of The Agency Review of the Sponsor's Thorough QTc Study

The moxifloxacin response failed to meet the agency's criteria for assay sensitivity. Our expectations for assay sensitivity are (1) the $\Delta\Delta\text{QTc}$ -time profile follows the expected moxifloxacin concentration-time profile (peak around C_{max} and taper off over time) and (2) the mean effect on the QTc is greater than 5 ms as evidenced by the lower 90% confidence interval > 5 ms at least one time point. Therefore, lack of QTc effect of gabapentin enacarbil can not be reliably concluded. We found no problems with the PK of moxifloxacin or with the measurement of QT on ECGs so, we do not believe further analysis of existing data will be fruitful.

IRT Findings and Recommendations Regarding QTc Study

This study is inconclusive.

The QTc IRT recommend that the sponsor conducts a repeat Thorough QT study to fulfill the requirements outlined in ICH E14 guidelines.

CDTL Comments

I agree with the Clinical Pharmacology (CP) reviewer's analysis that the dose-response analysis supports the approval of the 600 mg/day dose as the recommended dose, which should be taken at 5 PM. The dose-response data does not demonstrate that (b) (4)

I also agree that a missed dose should not be taken

Although, the dedicated driving safety study (XP083) was designed to examine this question, the 600 mg/day dose of XP13512 was not studied in this trial. The results of the XP083 indicate that the 1200 mg/day does is associated with increased lane position variability (poor performance) and an increased number of simulated crashes compared to subjects who received placebo or diphenhydramine (positive control).

The development of a 300 mg/day dose for patients with moderate renal impairment is appropriate based on the CP reviewer's model created from the sponsor's data. The exposure (C_{max} and AUC) is predicted to more closely mimic the exposure associated with the 600 mg/day dose in patients with normal renal function.

The alcohol dissolution (Dose Dumping) study and the Thorough QTc study were inadequate and therefore they should be repeated. The sponsor has already received feedback from the agency requesting they repeat these safety studies as Postmarketing Requirements (PMRs).

5 Clinical/Statistical- Efficacy

Studies XP052 (n=222) and XP053 (n=325) were pivotal, Phase III, 12-week, multicenter, randomized, double-blind, placebo-controlled, parallel-group studies in subjects with moderate-to-severe primary RLS. The co-primary efficacy endpoints were the change from baseline in IRLS Rating Scale total score and the proportion of subjects who were rated as responders ("much improved" or "very much improved") on the investigator-rated CGI-I. Study XP060 was a 12 week randomized withdrawal study that enrolled 194 subjects who met responder criteria after 24 weeks of treatment with 1200 mg/day of XP13512 in a single blind phase. Subjects were randomized to receive either 1200 mg/day for XP13512 or placebo for the next 12 weeks. Subjects who worsened to a pre-specified level were withdrawn from the study and treated with XP13512. XP060 was not intended to support efficacy for approval but rather to demonstrate the long-term effectiveness of the 1200 mg dose of XP13512.

A total of 222 subjects were randomized in 22 centers in Study XP052, and 325 subjects were randomized in 27 centers in Study XP053. Both studies were conducted in US. Study XP060 enrolled patients in 26 centers in the U.S.

Statistical Analysis Methods

Both of the pivotal phase III trials used the same co-primary endpoint structure with the same statistical analysis plan. The change from baseline in IRLS total score was analyzed by an analysis of covariance (ANCOVA) including effects for pooled site, treatment, and the baseline value as a covariate. The treatment-by-pooled-site interaction is to be evaluated at 0.10 significance level and to be removed if it was not significant. The response to treatment from the Investigator-rated CGI of Improvement at the end of treatment is to be analyzed using a logistic regression model that included treatment and pooled site as explanatory factors.

The primary efficacy analysis was conducted on the modified ITT (MITT) population, which includes all patients in the Safety Population who also satisfies all of the following conditions: (i) completed the IRLS rating scale at baseline; and (ii) completed at least one on-treatment IRLS rating scale score during the treatment period.

The FDA Statistical Review of Efficacy (Pivotal Trials)

In Study XP052, the mean change from baseline to Week 12 for the IRLS Rating Scale total score was -13.2 in the XP13512 1200 mg group and -8.8 in the placebo group. The difference was statistically significant (p=0.0003). The proportion of responders on the investigator-rated CGI-I Scale at Week 12 was 76.1% in the XP13512 1200 mg group compared with 38.9% in the placebo group, and the estimated odds of improvement for XP13512 1200 mg relative to placebo were 5.1 (p<0.0001). Study XP052 was submitted for Special Protocol Assessment.

Statistical Reviewer’s Table Study 052 Change in IRLS Total Score by Visit

Table 2 Change from Baseline in IRLS Total Score - XP052 (Source: Reviewer's Analysis)

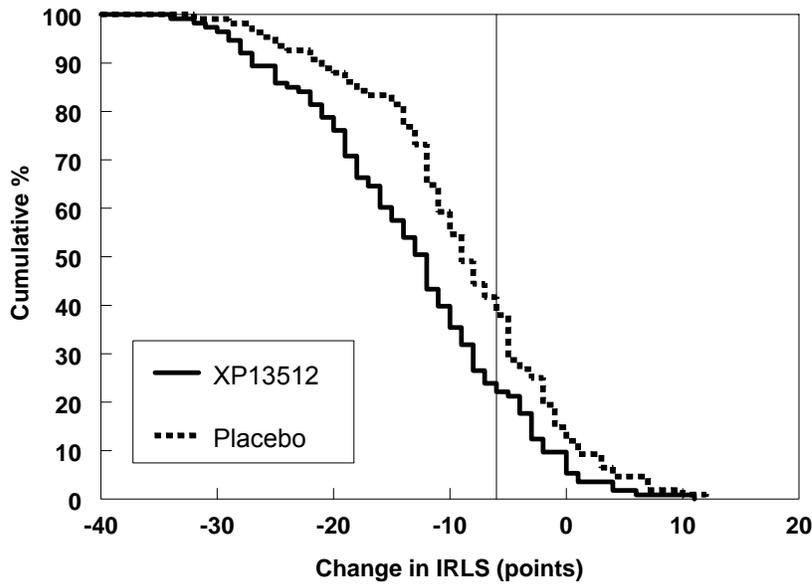
	Change from IRLS Total Score									
	Base-Line	Visit3 Week1	Visit4 Week2	Visit5 Week3	Visit6 Week4	Visit7 Week6	Visit8 Week8	Visit9 Wk10	Visit10 Wk12	Visit10 LOCF
Placebo										
N	108	104	103	102	99	97	93	92	90	108
Mean	22.57	-4.61	-6.53	-7.15	-7.49	-8.00	-8.59	-9.33	-9.39	-8.75
SD	(4.91)	(7.30)	(6.64)	(7.19)	(7.97)	(7.38)	(7.62)	(8.50)	(8.10)	(8.63)
XP13512										
N	112	107	107	104	101	102	102	96	98	112
Mean	23.07	-11.19	-11.86	-12.25	-13.87	-12.91	-13.67	-14.75	-13.76	-13.23
SD	(4.86)	(7.84)	(8.14)	(8.59)	(7.94)	(8.78)	(7.49)	(8.50)	(8.67)	(9.21)
p-value		<.0001	<.0001	<.0001	<.0001	<.0001	<.0001	<.0001	.0001	.0003

Statistical Reviewer’s Table 4 CGI Responder Rates at Each Visit – XP052 (Source: Reviewer’s Analysis)

	CGI – XP052					
	Visit 3 Week 1	Visit 4 Week 2	Visit 6 Week 4	Visit 8 Week 8	Visit10 Week 12	Visit10 LOCF
Placebo						
N	105	103	99	93	90	108
# (%) Responders	26 (24.76%)	33 (32.04%)	43 (43.43%)	43 (46.24%)	39 (43.33%)	42 (38.89%)
XP13512 1200 mg						
N	107	106	100	102	95	109
# (%) Responders	62 (57.94%)	74 (69.81%)	78 (78.00%)	82 (80.39%)	75 (78.95%)	83 (76.15%)
p-value	<.0001	<.0001	<.0001	<.0001	<.0001	<.0001

*No Baseline visit reported for since there could be no change at Baseline

Cumulative Distribution Study 052 Placebo versus 1200 mg XP13512 Change in IRLS



*A change of 6 (3-7 point range) points on the IRLS is considered by some as being a clinically meaningful change (Baker WL 2008).

CDTL Comment

The cumulative distribution of change in IRLS scores demonstrates a treatment effect is present over the entire distribution of scores.

Efficacy Analysis of Study 053

In Study XP053, the mean change from baseline to Week 12 for the IRLS Rating Scale total score was -13.0 in the XP13512 1200 mg group, -13.8 in the XP13512 600 mg group, and -9.8 in the placebo group (1200 mg vs. placebo: $p=0.0017$; 600 mg vs. placebo: $p<0.0001$). The proportion of responders on the investigator-rated CGI-I Scale at Week 12 LOCF was 77.5% in the XP13512 1200 mg group, 72.8% in the XP13512 600 mg group, compared with 44.8% in the placebo group. The odds of being a responder were 4.29 times that in the placebo group in the XP13512 1200 mg group ($p<.0001$) and 3.32 time that in the placebo group in the XP13512 600 mg group ($p < .0001$).

Change from baseline in Total IRLS Score Study 053 (Statistical reviewer’s table)

Table 6 Change from Baseline in IRLS Total Score – XP053 (Source: Reviewer’s Analysis)

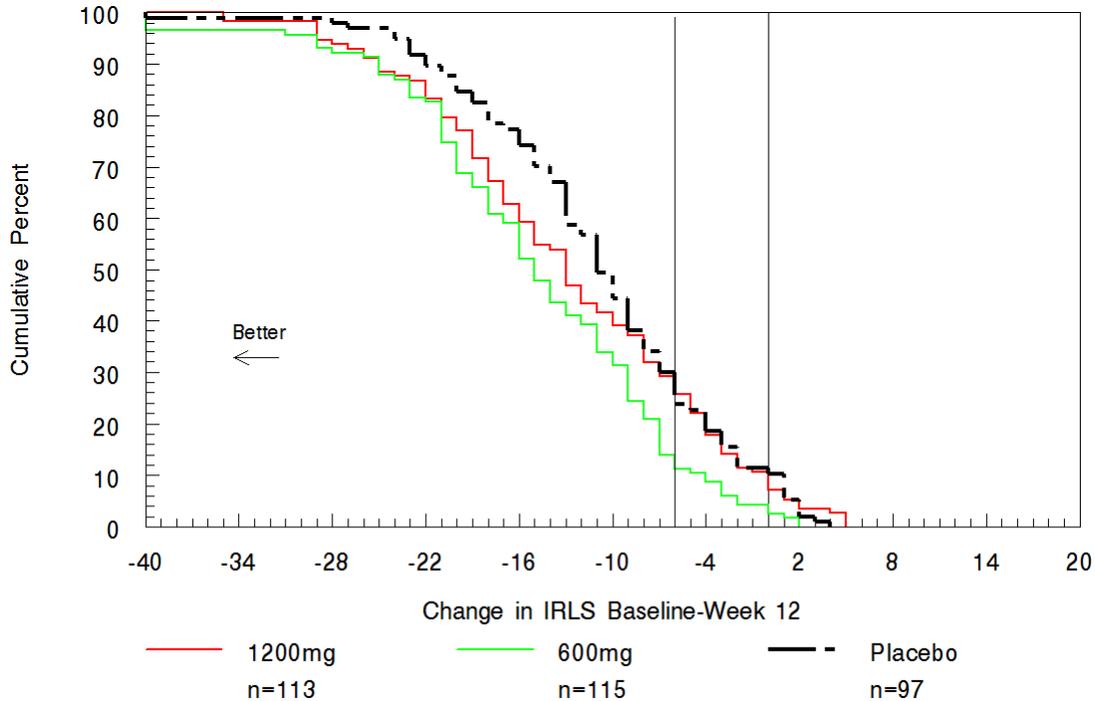
	Change from IRLS Total Score – XP053									
	Base-Line	Visit3 Week1	Visit4 Week2	Visit5 Week3	Visit6 Week4	Visit7 Week6	Visit8 Week8	Visit9 Wk10	Visit10 Wk12	Visit10 LOCF
Placebo										
N	96	88	91	87	84	83	81	74	74	96
Mean	23.81	-6.51	-7.80	-7.17	-8.62	-8.99	-8.09	-9.19	-10.97	-9.84
SD	(4.58)	(5.53)	(6.38)	(7.07)	(5.80)	(7.16)	(6.75)	(7.68)	(7.72)	(7.69)
600 mg										
N	114	110	110	105	104	102	102	103	101	114
Mean	23.11	-10.13	-11.13	-10.80	-11.44	-12.92	-12.64	-13.83	-14.17	-13.82
SD	(4.93)	(7.67)	(7.63)	(8.23)	(7.86)	(7.65)	(8.32)	(8.07)	(8.11)	(8.09)
p-value		<.0001	.0002	.0002	.0018	.0001	<.0001	<.0001	.0015	<.0001
1200 mg										
N	111	105	102	103	101	97	95	97	93	111
Mean	23.18	-9.25	-11.76	-12.36	-13.00	-12.69	-12.87	-13.02	-14.24	-12.95
SD	(5.32)	(8.03)	(8.78)	(8.99)	(9.22)	(9.85)	(8.50)	(9.49)	(8.74)	(9.12)
p-value		.0019	<.0001	<.0001	<.0001	.0012	<.0001	.0019	.0048	.0017

Rating of CGI By Visit Study 053 Statistical Reviewer’s Analysis

Table 7 Responder Rate at Each Visit - XP053 (Source: Statistical Reviewer’s Analysis)

	CGI – XP053					
	Visit 3 Week 1	Visit 4 Week 2	Visit 6 Week 4	Visit 8 Week 8	Visit 10 Week 12	Visit10 LOCF
Placebo						
N	89	95	95	96	96	96
# (%) Responders	26 (29.21%)	36 (37.78%)	43 (45.26%)	41 (42.71%)	43 (44.79%)	43 (44.79%)
XP13512 600 mg						
N	108	112	113	114	114	114
# (%) Responders	54 (50%)	74 (66.07%)	71 (62.83%)	78 (68.42%)	83 (72.81%)	83 (72.81%)
p-value	.0030	<.0001	.0133	.0003	<.0001	<.0001
XP13512 1200 mg						
N	106	110	111	111	111	111
# (%) Responders	59 (55.66%)	74 (67.27%)	78 (70.27%)	77 (69.37%)	86 (77.48%)	86 (77.48%)
p-value	.0002	<.0001	.0004	.0001	<.0001	<.0001

Cumulative Distribution Change in IRLS Study 053



CDTL Comment

The treatment effect of XP13512 is maintained over the whole range of scores for the 600 mg/day treated group. The 1200 mg/day treated group only appears to maintain a treatment effect that is superior to placebo above the 40th percentile and it appears to be inferior to the 600 mg/day dose at every point on the curve.

Secondary Endpoints in The Pivotal Efficacy Trials.

In study 052 the sponsor selected 16 secondary outcome variables and in study 053 there were 24 secondary outcome measures. The analysis plan for the secondary outcomes did not contain a plan to protect against increasing the type I error rate. Most of the secondary endpoints were patient rated and the majority were developed as sleep questionnaires and are not know to be useful in measuring change in RLS symptoms. Most of the other secondary outcomes were redundant to the IRLS scale. The patient rated CGI at week 12, is a potentially clinically important secondary endpoint, it demonstrate a statistically significant proportion of responders compared to placebo for both the 600 and 1200 mg in study 053. A similar finding on the patient rated CGI was observed in study 052 for the 1200 mg dose. The RLS maximum severity recorded for seven 4 hour time periods will be discussed later in this review.

Key Endpoints For Pivotal Trials 052 and 053 (Sponsor’s Table)

Table 58 Statistical Significance of Comparisons of XP13512 1200 mg and 600 mg to Placebo for Key Efficacy Endpoints (MITT Population: Studies XP052 & XP053 Individually and Integrated)

	XP13512 vs Placebo Statistical Significance				
	P-value				
	XP052 1200 mg	XP053		XP052 & XP053	
		600 mg	1200 mg	600 mg	1200 mg
IRLS Rating Scale Total Score: Change From Baseline					
IRLS Rating Scale total score at Week 12 (co-primary endpoint)	0.0003*	<0.0001*	0.0015*	<0.001*	<0.001*
IRLS Rating Scale total score at Week 1	<0.0001*	<0.0001*	0.0017*	<0.001*	<0.001*
Investigator-Rated CGI-I					
Proportion of responders on investigator-rated CGI-I at Week 12 (co-primary endpoint)	<0.0001*	<0.0001*	<0.0001*	<0.001*	<0.001*
Proportion of responders on investigator-rated CGI-I at Week 1	<0.0001*	0.0030*	0.0002*	<0.001*	<0.001*
Patient-Rated CGI-I					
Proportion of responders on patient-rated CGI-I at Week 12	<0.0001*	<0.0001*	0.0017*	<0.001*	<0.001*
RLS Symptom Record: RLS Severity During 4-Hour Period (for Intervals Associated with Evening, Late Evening, and Nighttime Symptoms)					
4 PM to 7:59 PM	0.0534	0.3703	0.1900	0.307	0.019*
8 PM to 11:59 PM	0.0011*	0.0348*	0.0076*	0.058	<0.001*
Midnight to 3:59 PM	0.1878	0.0035*	0.0117*	0.028*	0.007*
Pain Assessment Question: Change From Baseline					
Pain severity at Week 12	<0.0001*	<0.0029*	0.0015*	<0.001*	<0.001*
MOS Sleep Scale: Change From Baseline					
Sleep adequacy domain at Week 12	<0.0001*	0.0003*	<0.0001*	<0.001*	<0.001*
Sleep quantity domain at Week 12	0.0084*	0.0209*	0.0001*	0.036*	<0.001*
Sleep disturbance domain at Week 12	<0.0001*	<0.0001*	<0.0001*	<0.001*	<0.001*
Daytime somnolence domain at Week 12	0.0018*	0.8926	0.0309*	0.712	<0.001*
PSQ					
Overall sleep quality at Week 12	<0.0001*	0.0230*	0.0023*	0.002*	<0.001*
Ability to function during daytime at Week 12	0.0002*	0.0366*	0.0152*	0.012*	<0.001*
Number of nights with RLS symptoms at Week 12	<0.0001*	0.0001*	0.0006*	<0.001*	<0.001*
Number of awakenings during night at Week 12	0.0429*	0.0009*	0.0004*	0.001*	<0.001*
Number of hours awake per night due to RLS symptoms at Week 12	0.0189*	0.0019*	0.0187*	<0.001*	<0.001*
POMS Brief Form: Change From Baseline					
Total mood disturbance score at Week 12	0.0014*	0.1795	0.0893	0.052	<0.001*
Johns Hopkins RLS QoL Questionnaire: Change From Baseline					
Overall life impact score at Week 12	<0.0001*	0.0025*	0.0009*	<0.001*	<0.001*

* Comparisons for XP13512 vs placebo were statistically significant at the 5% level.

Study XP081

Study XP081 was designed as a multicenter, randomized, double-blind, placebo-controlled, parallel-group study, comparing 4 doses of XP13512 with placebo given once daily to subjects with symptoms of RLS. Subjects were randomized (1:1:1:1) to receive XP13512 600 mg, 1200 mg, 1800 mg, or 2400 mg or placebo once a day. Subjects were titrated for the first 9-day, then they continued on the target maintenance dose for the next for 12 weeks.

The goal of study 081 was to evaluate the dose-response and exposure-response relationships of the four dose levels of XP13512.

Randomization

Randomization was stratified by study site and Baseline IRLS total score category (<22 versus >22).

- 48 subjects to XP13512 600 mg,
- 45 subjects to XP13512 1200 mg,
- 38 subjects to XP13512 1800 mg,
- 45 subjects to XP13512 2400 mg,
- 41 subjects to placebo.

Efficacy Results

The agency's statistical reviewer found that the "difference among all treatment groups did not reach statistical significance ($p=.1581$) in the overall statistical testing using the same ANCOVA model that applied in the two pivotal studies (XP052 and XP053). When all XP13512 dose groups were compared to placebo group using Dunnett's adjustment for multiplicity, none of the dose group reached statistical significance of 0.05 as well, though the pair-wise comparison without multiplicity adjustment showed that all but XP13512 2400 mg dose groups were statistically significantly different from placebo group at significance level of 0.05. The sample size of each treatment group was about half of the sizes of the pivotal studies, which could be the reason of resulted insignificance of statistical testing".

The nominal p-values for XP 600 mg, 1200 mg, 1800 mg, were statistically superior to placebo compared to placebo group for the change in the IRLS total score compared to placebo, the size of the treatment effect compared to baseline was similar to the results of served in studies 052 and 053 similar to the levels found in the two pivotal studies.

FDA Statistical Reviewers Analysis Study XP081 Change from Baseline By Week in IRLS Scale Total Score

Table 10 IRLS Total Scores - XP081 (Source: Reviewer's Analysis)

	Base line	Change from Baseline in IRLS Total Score								
		Visit3 Week1	Visit4 Week2	Visit5 Week3	Visit6 Week4	Visit7 Week6	Visit8 Week8	Visit9 Wk10	Visit10 Wk12	Visit10 LOCF
Placebo										
N	40	34	32	36	34	31	32	33	30	40
Mean	22.45	-5.62	-6.84	-8.06	-8.71	-7.52	-9.41	-9.09	-9.17	-9.28
SD	(5.32)	(7.30)	(8.85)	(8.28)	(7.76)	(9.65)	(9.79)	(9.63)	(8.37)	(8.13)
600 mg										
N	47	45	44	42	38	38	36	34	33	47
Mean	23.87	-8.91	-11.20	-10.81	-12.42	-11.87	-13.58	-13.00	-15.67	-13.81
SD	(5.33)	(7.69)	(8.29)	(9.48)	(9.00)	(9.32)	(9.85)	(8.70)	(8.00)	(9.48)
p-value										.0394
1200 mg										
N	43	41	39	39	39	32	31	32	27	43
Mean	23.91	-10.10	-11.45	-12.38	-13.13	-14.88	-13.06	-14.75	-16.22	-13.81
SD	(5.49)	(7.68)	(8.07)	(8.87)	(7.44)	(8.78)	(9.78)	(8.14)	(9.74)	(9.84)
p-value										.0445
1800 mg										
N	37	37	35	35	30	32	33	32	33	37
Mean	23.62	-10.59	-13.89	-14.23	-15.13	-16.59	-15.24	-14.91	-15.15	-13.95
SD	(4.25)	(8.42)	(8.05)	(8.28)	(8.67)	(7.82)	(7.89)	(8.85)	(8.13)	(8.70)
p-value										.0256
2400 mg										
N	44	42	43	39	37	34	34	35	31	44
Mean	23.34	-9.02	-12.84	-11.92	-13.38	-15.24	-14.41	-13.74	-15.35	-12.86
SD	(5.70)	(7.10)	(8.39)	(7.21)	(7.57)	(7.38)	(9.08)	(8.24)	(7.86)	(9.52)
p-value										.0895

A summary of the proportions of responders (much improved or very much improved) in the investigator-rated CGI-I Scale at each visit (observed cases) and at Week 12 using LOCF is presented in Table 11. The proportion of responders (very much improved or much improved) on the CGI-I Scale at Week 12 using LOCF in the MITT Population was numerically greater in the XP13512 600 mg, 1200 mg, 1800 mg, and 2400 mg groups (63.8%, 65.1%, 73.0%, and 81.8%, respectively) compared with the placebo group (45.0%).

FDA Statistical Reviewers Analysis of the CGI Responder Rate Study XP081

Table 11 Responder Rate - XP081 (Source: Reviewer's Analysis)

	CGI – XP081					
	Visit 3 Week 1	Visit 4 Week 2	Visit 6 Week 4	Visit 8 Week 8	Visit 10 Week 12	Visit10 LOCF
Placebo						
N	35	32	34	31	29	40
# (%) Responders	11 (31.43%)	10 (31.25%)	17 (50.00%)	15 (48.39%)	13 (44.83%)	18 (45.00%)
XP13512 600 mg						
N	46	43	37	36	33	47
# (%) Responders	23 (50.00%)	24 (55.81%)	23 (62.16%)	23 (63.89%)	24 (72.73%)	30 (63.83%)
Nominal p-value						.0801
XP13512 1200 mg						
N	40	39	39	31	26	43
# (%) Responders	23 (57.50%)	27 (69.23%)	27 (69.23%)	25 (80.65%)	20 (76.92%)	28 (65.12%)
Nominal p-value						.0671
XP13512 1800 mg						
N	36	35	30	33	31	37
# (%) Responders	23 (63.89%)	27 (77.14%)	20 (66.67%)	27 (81.82%)	25 (80.65%)	27 (72.97%)
Nominal p-value						.0134
XP13512 2400 mg						
N	42	43	36	34	31	44
# (%) Responders	21 (50.00%)	33 (76.74%)	28 (77.78%)	28 (82.35%)	28 (90.32%)	36 (81.82%)
Nominal p-value						.0005

CDTL Comment

Although, the statistical reviewer did not find that the overall efficacy result for the change in IRLS score was statistically superior to placebo. The findings for the 600 mg treated group was statistically significant for both co-primary endpoints (although not corrected for multiple comparisons of dose arms), it is acceptable as supportive evidence (to the finding in study 053) for effectiveness for the 600 mg dose.

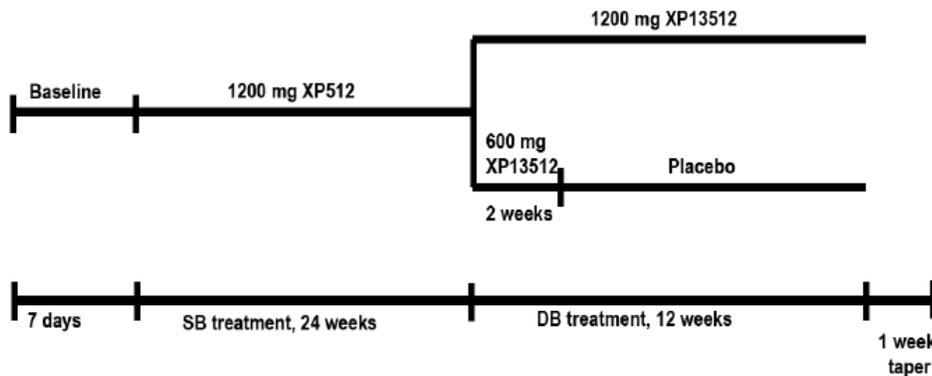
Open-Label Extension Safety Study XP055

Study XP055 was a multi-center, open-label, 52-week extension study of XP13512 given once daily to subjects with RLS who had completed Study XP052, XP053, XP081, or XP083 (parent studies). Subjects entering Study XP055 initially took a 600 mg tablet for 3 days. The dose was then up-titrated to the 1200 mg maintenance dose on Day 4. Dose adjustments (by one tablet=600 mg) were permitted at the discretion of the investigator (based on efficacy and tolerability) to a maximum of 1800 mg or a minimum of 600 mg per day. If the investigator concluded a subject did not tolerate a particular dose, the medication could be held for a few days or reduced to the next lowest dose level. Study XP055 is the source for all patients who were exposed to XP13512 for 1 year and study 055 in conjunction with study 060 accounts for all patient exposures of 6 months or more. Study XP055 was ongoing at the time of NDA filing and at the time the 120 day update was submitted to the agency. The final report of study was filed with the agency on 12/22/2009 as a paper only submission in the last 6 weeks of the review cycle. The results of the study up to the 120 day update (2nd interim analysis) will be discussed in detail in the safety section of this review.

Maintenance of Long-Term Effectiveness: Study 060

Study XP060 was a multicenter, randomized withdrawal study in subjects with moderate-to severe primary RLS. Eligible subjects were initially enrolled in a 24-week single blind treatment period during which they received XP13512. Subjects who completed the initial single blind treatment period and met the responder criteria were then randomized to receive either XP13512 or placebo during the 12-week double-blind treatment period. The primary study objective was to assess the maintenance of efficacy of XP13512 1200 mg in the long-term treatment of subjects with moderate-to-severe primary RLS. The primary efficacy variable was the proportion of RLS subjects who relapsed during the double-blind treatment period. A total of 194 subjects were randomized into 26 study sites in US. The randomized withdrawal design of study 060 may provide the best opportunity to observe for the effects of rebound and withdrawal.

Sponsor’s Schematic of the Trial Design for Study XP060



Responder Criteria During the 24-week Single Blind Phase

Patients eligible for enrollment into the responder criteria were as follows:

- total IRLS score decreased by 6 or more points relative to their Baseline score
- total IRLS score decreased to less than 15
- had an assessment of “much improved” or “very much improved” on the investigator rated Clinical Global Impression of Improvement (CGI-I)
- stable on 1200 mg XP13512 dose for at least the month prior
- successfully completed the entire 24-week SB treatment period

Randomization

A total of 180 subjects (90 subjects per arm) were planned to be randomized into DB period, and 194 subjects were actually randomized.

Study Population

There were no significant differences in demographic or disease related factors for patients randomized to placebo compared to XP13512 in the double blind phase of study XP060.

Efficacy Analysis

- The primary efficacy variable was the proportion of subjects who met pre-specified Relapse Criteria during the 12-week DB treatment period (the period from Randomization on Visit 14 [Week 24] through the end of treatment). Patients who “relapsed” must have been met at 2 consecutive visits at least 1 week apart during the 12 week, double blind (randomized withdrawal) phase of the study. The date of relapse was counted as the first date at which the above criteria were met. Subjects who met the definition of relapse were not required to withdraw from the study.

Relapse Criteria:

- an increase (i.e., worsening) in the total IRLS score by at least 6 or more points relative to the subject's score at Randomization on Visit 14 (Week 24)
- achieving an IRLS score of at least 15 and an assessment of "much worse" or "very much worse" on the investigator rated Clinical Global Impression of Change (CGI-C). In order for a subject to be defined as having achieved the endpoint of relapse
- withdrawal due to lack of efficacy during the DB treatment period. The primary analysis variable was to be analyzed by a logistic regression model, which included terms for treatment group, Visit 14 (Week 24) IRLS total score, and pooled study site

Efficacy Results

Proportion of Patients Who Met Criteria for Relapse in Study 060 (sponsor’s table)

Table 8 Proportion of Subjects who Experienced a Relapse During the Double-Blind Period – XP060 (Source: Table 15 of Sponsor’s Study Report)

	Number (%) of Subjects		Odds ratio ^a	95% CI	p-value
	Placebo N=97	XP13512 N=96			
Subjects who Relapsed	22 (22.7)	9 (9.4)	0.353	(0.2, 0.8)	0.0158

Data Source: DS Table 7.1

a. From a logistic regression model including terms for treatment group, Visit 14 (Week 24) IRLS assessment, and pooled study site.

Sponsor Table for Study XP060 Maintenance of Effect

Xenoport Study Number/ GSK Study Number	Treatment Arm	No. Enrolled/ Completed	Primary Efficacy Variable: Proportion of Subjects Relapsing during Double-Blind Treatment		Secondary Endpoints	Other Comments
			Percentage of Subjects Relapsing or Withdrawing due to Lack of Efficacy	Logistic Regression Analysis		
XP060 / RXP111461	Placebo DB-ITT	98 randomized/ 84 completed	22.7%	Odds ratio: 0.353 95% CI: 0.2, 0.8 p=0.0158	Statistically significant treatment differences in favor of XP13512, compared to placebo, were observed for the change from randomization to Week 36 in the IRLS Rating Scale total score, and the MOS sleep adequacy and sleep disturbance domains. Treatment differences for the MOS sleep quantity and daytime somnolence domains, RLS QoL overall life impact score, proportion of responders on the investigator-rated CGI-I and proportion of responders on the patient-rated CGI-I were not statistically significant.	Results of this study demonstrate that XP13512 1200 mg, had statistically significant efficacy compared with placebo in the maintenance of efficacy in long term treatment (up to 36 weeks) of subjects with primary RLS symptoms.
	XP13512 1200 mg DB-ITT	96 randomized/ 84 completed	9.4%			

Statistical Reviewer’s Table Comparing IRLS and CGI-Investigator Scores for Patients at Baseline and Patients Meeting Criteria for Relapse

Table 9 IRLS Rating Scale and CGI-I during Double-Blind Period – XP060 (Source: Reviewer’s Analysis)

	All Subjects		Relapsed Subjects	
	Placebo N=97	XP13512 1200 mg N=96	Placebo N=22	XP13512 1200 mg N=9
IRLS				
Baseline	5.30 (6.00)	5.10 (6.00)	5.32 (5.00)	7.88 (8.00)
Last Visit	9.72 (9.00)	7.40 (6.50)	18.59 (17.50)	20.44 (21.00)
Change	4.42 (2.00)	2.29 (0.00)	13.27 (13.50)	12.56 (13.00)
CGI-C	4.32 (4.00)	3.92 (4.00)	6.14 (6.00)	6.11 (6.00)

CDTL Comments

The number and percentage of patients meeting criteria for relapse was greater in the placebo treated group compared to XP13512 treated patients. There were no significant differences in the IRLS of CGI scores at baseline or among the patients to met relapse criteria. The study demonstrates that XP13513 is able to maintain efficacy and the effect of discontinuing the medication was meaningful for some patients.

Maximum RLS Severity

The maximum RLS severity record, created for use in RLS trials conducted by the then sponsor Xenoport, assessed whether the subject experienced RLS symptoms throughout a 24-hour period, in 4 hour epochs. The 24-hour record allowed subjects to indicate whether symptoms were “not present”, “mild”, “moderate”, or “severe” if the subject was awake, and also allowed the subject to note times when they were asleep and RLS symptoms could not be measured. Subjects were instructed to complete a maximum RLS severity record t Baseline (Week 0), and the end of Week 12 (or ET).

Effect by Hour of The Day

Baseline Maximum RLS Severity By 4 hour Epochs (Sponsor's table 14.1)

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Table 14.1
Maximum RLS Severity by 4-hour Period
from the 24-hour RLS Record by Visit
(MITT Population)

Visit Period Maximum Severity	Placebo (N = 108) n (%)	XP13512 1200 mg (N = 112) n (%)	p-value [1]
Baseline			
8 am - 12 pm			
None	60 (56.1)	63 (56.3)	0.7576
Mild	32 (29.9)	28 (25.0)	
Moderate	11 (10.3)	18 (16.1)	
Severe	4 (3.7)	3 (2.7)	
12 pm - 4 pm			
None	55 (50.9)	59 (52.7)	0.6608
Mild	30 (27.8)	32 (28.6)	
Moderate	19 (17.6)	18 (16.1)	
Severe	4 (3.7)	3 (2.7)	
4 pm - 8 pm			
None	39 (36.1)	54 (48.2)	0.0675
Mild	31 (28.7)	28 (25.0)	
Moderate	25 (23.1)	22 (19.6)	
Severe	13 (12.0)	8 (7.1)	
6 pm - 10 pm			
None	29 (26.9)	35 (31.3)	0.2063
Mild	34 (31.5)	34 (30.4)	
Moderate	23 (21.3)	32 (28.6)	
Severe	22 (20.4)	11 (9.8)	

Note: Missing data were imputed using LOCF methods within a visit but not across visits.
[1] p-value derived from a Cochran-Mantel-Haenszel test with interval scoring and stratification by pooled site.

Baseline Maximum RLS Severity By 4 hour Epochs Continued (Sponsor's table 14.1 continued)

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Table 14.1 (Continued)
Maximum RLS Severity by 4-hour Period
from the 24-hour RLS Record by Visit
(MITT Population)

Visit Period Maximum Severity	Placebo (N = 108) n (%)	XP13512 1200 mg (N = 112) n (%)	p-value [1]
Baseline (continued)			
8 pm - 12 am			
None	14 (13.0)	17 (15.2)	0.2508
Mild	43 (39.8)	23 (20.5)	
Moderate	31 (28.7)	52 (46.4)	
Severe	20 (18.5)	20 (17.9)	
12 am - 4 am			
None	36 (33.3)	30 (26.8)	0.2933
Mild	21 (19.4)	22 (19.6)	
Moderate	30 (27.8)	35 (31.3)	
Severe	21 (19.4)	25 (22.3)	
4 am - 8 am			
None	52 (48.1)	54 (48.2)	0.7460
Mild	24 (22.2)	29 (25.9)	
Moderate	22 (20.4)	19 (17.0)	
Severe	10 (9.3)	10 (8.9)	
End of Week 2			
8 am - 12 pm			
None	66 (65.3)	80 (76.9)	0.0606
Mild	25 (24.8)	20 (19.2)	
Moderate	10 (9.9)	3 (2.9)	
Severe	0 (0.0)	1 (1.0)	

Note: Missing data were imputed using LOCF methods within a visit but not across visits.
[1] p-value derived from a Cochran-Mantel-Haenszel test with interval scoring and stratification by pooled site.

Reviewer Comment

The table above lists the baseline RLS maximum severity in 4 hour epochs (epochs chosen by the sponsor) that demonstrate that RLS symptoms increase after dinner 7 PM and continue to worsen until 1-4 AM. The symptoms reach their peak severity between 10 PM and 1 AM. Before starting to decline after 1 AM to 4 AM. The baseline RLS symptom severity scores are consistent with the expected fluctuations of RLS symptoms throughout the day, consistent with the history of the disease. There were no significant difference in maximum symptom severity rating between the two groups at baseline.

IRS Symptom Severity End of Week 12 By Time of Day (GSK Table) 060 Study

Table 14.1 (Continued)
Maximum RLS Severity by 4-hour Period
from the 24-hour RLS Record by Visit
(MITT Population)

Visit Period Maximum Severity	Placebo (N = 108) n (%)	XP13512 1200 mg (N = 112) n (%)	p-value [1]
End of Week 12 (End of Treatment) (continued)			
4 pm - 8 pm			
None	52 (54.7)	69 (69.7)	0.0534
Mild	30 (31.6)	22 (22.2)	
Moderate	11 (11.6)	6 (6.1)	
Severe	2 (2.1)	2 (2.0)	
6 pm - 10 pm			
None	40 (41.7)	67 (67.7)	0.0024
Mild	36 (37.5)	22 (22.2)	
Moderate	16 (16.7)	6 (6.1)	
Severe	4 (4.2)	4 (4.0)	
8 pm - 12 am			
None	37 (38.5)	64 (64.6)	0.0011
Mild	33 (34.4)	22 (22.2)	
Moderate	23 (24.0)	10 (10.1)	
Severe	3 (3.1)	3 (3.0)	
12 am - 4 am			
None	64 (66.7)	74 (74.7)	0.1878
Mild	14 (14.6)	12 (12.1)	
Moderate	12 (12.5)	10 (10.1)	
Severe	6 (6.3)	3 (3.0)	

Note: Missing data were imputed using LOCF methods within a visit but not across visits.
[1] p-value derived from a Cochran-Mantel-Haenszel test with interval scoring and stratification by pooled site.

CDTL Comment:

The sponsor’s Table 14.1 (above) demonstrates several important points. The first is that RLS symptoms may not be severe enough to demonstrate a statistically significant difference before the 4-8 PM based on the lower severity rating seen in the placebo treated group during this epoch. The difference in RLS severity scores achieves clear statistical significance at 8 PM to 12 AM and there are more patients who are symptom free at 4-8 PM and at 6-10 PM in the XP13512 treated group compared to placebo. The dose of XP13512 was given at 5PM the there is statistically significant evidence of benefit in the 6 PM to 10 PM and borderline statistically significant effect at 4-8 PM epochs but what is not known is exactly when during the hours of 6-10 PM or 4-8 PM the benefit started. A similar analysis was performed on the RLS Symptom Severity Scale in study XP053 comparing the 600 mg/day and 1200 mg/day doses. The results (see table below) indicate a statistically significant benefit of both doses of XP13512 for the 8PM-12AM and 12AM-4AM epochs. In the 6PM-10 PM epoch the group treated with 600 mg/day of XP13512 failed to demonstrate a statistically significant reduction in RLS severity

scores compared to placebo (p=0.27) and the 1200 mg/day dose demonstrated only a marginally significant difference (p=0.053).

Study XP053 Maximum IRLS Symptom Severity Scale

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Study XP053

Table 7.13.1 (Continued)
Maximum RLS Severity by 4-Hour Period from the 24-hour RLS Record by Visit
(MITT Population)

Visit Period Maximum Severity	Placebo [1] (N=96) n (%)	XP13512 600mg (N=114) n (%)	XP13512 1200mg (N=111) n (%)	Pairwise Treatment Difference XP13512 600mg vs. Placebo	p-value[1] XP13512 1200mg vs. Placebo	All Treatment Difference
End of Week 12/ET						
8 am - 12 pm						
N	72	98	92	0.0109	0.2565	0.0421
None	52 (72.2)	85 (86.7)	74 (80.4)			
Mild	13 (18.1)	12 (12.2)	12 (13.0)			
Moderate	6 (8.3)	0	5 (5.4)			
Severe	1 (1.4)	1 (1.0)	1 (1.1)			
12 pm - 4 pm						
N	72	98	92	0.4162	0.9833	0.6119
None	51 (70.8)	74 (75.5)	69 (75.0)			
Mild	15 (20.8)	19 (19.4)	12 (13.0)			
Moderate	5 (6.9)	4 (4.1)	9 (9.8)			
Severe	1 (1.4)	1 (1.0)	2 (2.2)			
4 pm - 8 pm						
N	73	98	92	0.3703	0.1900	0.4475
None	45 (61.6)	68 (69.4)	61 (66.3)			
Mild	18 (24.7)	18 (18.4)	25 (27.2)			
Moderate	7 (9.6)	9 (9.2)	5 (5.4)			
Severe	3 (4.1)	3 (3.1)	1 (1.1)			

Note: Missing data were imputed using LOCF methods within a visit but not across visits.
[1] p-value derived from a Cochran-Mantel-Haenszel mean score test with equally spaced scores and stratification by pooled site.

Study XP053 Maximum IRLS Symptom Severity Scale (continued)

Table 7.13.1 (Continued)
Maximum RLS Severity by 4-Hour Period from the 24-hour RLS Record by Visit
(MITT Population)

Visit Period Maximum Severity	Placebo [1] (N=96) n (%)	XP13512 600mg (N=114) n (%)	XP13512 1200mg (N=111) n (%)	Pairwise Treatment Difference XP13512 600mg vs. Placebo	p-value[1] XP13512 1200mg vs. Placebo	All Treatment Difference
End of Week 12/ET (Continued)						
6 pm - 10 pm						
N	74	99	92	0.2701	0.0533	0.1413
None	39 (52.7)	55 (55.6)	55 (59.8)			
Mild	18 (24.3)	28 (28.3)	27 (29.3)			
Moderate	11 (14.9)	15 (15.2)	9 (9.8)			
Severe	6 (8.1)	1 (1.0)	1 (1.1)			
8 pm - 12 am						
N	74	99	92	0.0348	0.0076	0.0166
None	27 (36.5)	49 (49.5)	48 (52.2)			
Mild	22 (29.7)	28 (28.3)	27 (29.3)			
Moderate	17 (23.0)	19 (19.2)	15 (16.3)			
Severe	8 (10.8)	3 (3.0)	2 (2.2)			
12 am - 4 am						
N	74	99	92	0.0035	0.0117	0.0063
None	38 (51.4)	74 (74.7)	67 (72.8)			
Mild	18 (24.3)	14 (14.1)	13 (14.1)			
Moderate	15 (20.3)	8 (8.1)	10 (10.9)			
Severe	3 (4.1)	3 (3.0)	2 (2.2)			

Note: Missing data were imputed using LOCF methods within a visit but not across visits.
[1] p-value derived from a Cochran-Mantel-Haenszel mean score test with equally spaced scores and stratification by pooled site.

CDTL Comment

Study 053 demonstrated a similar statistically significant finding for efficacy at the 8PM-12MN epoch for both the 600 mg and 1200 mg groups compared to patients treated with placebo.

Summary Results of Efficacy for Pivotal Studies (sponsor tables)

Xenoport Study Number/ GSK Study Number	Treatment Arm	No. Enrolled/ Completed	Co-Primary Efficacy Variable: Change from Baseline in IRLS Rating Scale Total Score				Co-Primary Efficacy Variable: Proportion of CGI-I Responders		Other Comments
			Baseline Mean (SD)	Week 12 Mean (SD)	Change from Baseline to Week 12 Mean (SD)	ANCOVA for Adjusted Treatment Difference (XP13512 minus Placebo)	Percentage of Responders at Week 12	Logistic Regression Analysis	
XP052 / RXP110963	Placebo	108 randomized/ 92 completed	22.6 (4.91)	13.8 (7.47)	-8.8 (8.63)	-	38.9%	-	Results of this study demonstrate that XP13512 1200 mg had statistically significant efficacy compared with placebo in the treatment of primary RLS
	XP13512 1200 mg	114 randomized/ 100 completed	23.1 (4.86)	9.8 (8.70)	-13.2 (9.21)	LS mean: -4.0 95% CI: -6.2, -1.9 p=0.0003	76.1%	Odds ratio: 5.1 95% CI: 2.8, 9.2 p<0.0001	
XP053 / RXP111460	Placebo	97 randomized/ 77 completed	23.8 (4.58)	14.0 (7.87)	-9.8 (7.69)	-	44.8%	-	Results of this study demonstrate that XP13512 1200 mg and 600 mg had statistically significant efficacy compared with placebo in the treatment of primary RLS
	XP13512 600 mg	115 randomized/ 104 completed	23.1 (4.93)	9.3 (7.77)	-13.8 (8.09)	LS mean: -4.3 95% CI: -6.4, -2.3 p<0.0001	72.8%	p<0.0001	
	XP13512 1200 mg	113 randomized/ 98 completed	23.2 (5.32)	10.2 (8.03)	-13.0 (9.12)	LS mean: -3.5 95% CI: -5.6, -1.3 p=0.0015	77.5%	p<0.0001	

Xenoport Study Number/ GSK Study Number	Treatment Arm	No. Enrolled/ Completed	Efficacy Variable: Change from Baseline in IRLS Rating Scale Total Score			Efficacy Variable: Proportion of CGI-I Responders	Other Endpoints	Other Comments
			Baseline Mean (SD)	Week 12 Mean (SD)	Change from Baseline to Week 12 Mean (SD)			
XP081 / RXP111462	Placebo	41 randomized/ 31 completed	22.5 (5.32)	13.2 (8.55)	-9.3 (8.13)	45.0%	Improvements were also observed on sleep, mood, and RLS associated pain outcomes.	The results suggested that each of the 4 dose levels of XP13512 (600 mg, 1200 mg, 1800 mg, and 2400 mg) provided greater relief of symptoms in subjects with RLS compared with placebo.
	XP13512 600 mg	48 randomized/ 34 completed	23.9 (5.33)	10.1 (9.84)	-13.8 (9.48)	63.8%		
	XP13512 1200 mg	45 randomized/ 31 completed	23.9 (5.49)	10.1 (10.77)	-13.8 (9.84)	65.1%		
	XP13512 1800 mg	38 randomized/ 30 completed	23.6 (4.25)	9.7 (8.97)	-13.9 (8.70)	73.0%		
	XP13512 2400 mg	45 randomized/ 33 completed	23.3 (5.70)	10.5 (9.19)	-12.9 (9.52)	81.8%		

Efficacy Conclusion

Studies 052 and 053 demonstrate a statistically significant difference (improvement) for the co-primary endpoints at the 1200 mg/day (study 052 and 053) and for the 600 mg/day group in studies 053 and 081. Analysis of the primary and secondary endpoints does not find that there is meaningful difference between the treatment effect for the 600 mg dose versus the 1200 mg/day dose. The statistical reviewers arrived at a similar conclusion after conducting their own independent evaluation of the efficacy data. The clinical pharmacology reviewer also came to a similar conclusion after they analyzed the dose-response and exposure-response data. The consensus opinion is that efficacy is demonstrated with replication for the 1200 mg dose. There is clear efficacy demonstrated in the 053 and 081 studies for the 600 mg/day dose. There does not appear to be additional benefit associated with the 1200 mg dose, therefore only the 600 mg/day dose should be considered for approval from an efficacy perspective.

5. Safety

Safety Data Pooling Strategy

Table 3 ISS Study Groupings for Phase II and Phase III Studies

Study Grouping	Studies
12-Week Placebo-Controlled RLS Studies (Integrated)	XP052, XP053, XP081
All Placebo-Controlled Phase II & Phase III RLS Studies (Integrated) ¹	12-Week Placebo-Controlled RLS Studies (XP052, XP053, XP081) plus: XP083 ² , XP045 ³
All RLS Studies ⁴ (Integrated and Individual)	XP052, XP053, XP081, XP083, XP060 ⁵ , XP021 ⁶ , XP045, XP055
RLS Long-Term Integration (Integrated)	12-Week Placebo-Controlled RLS Studies (XP052, XP053, XP081) plus: XP083 ² , XP055 ⁷

1. Includes only placebo-controlled parallel-group studies; Study XP060 is not included because it included a SB phase prior to the DB placebo-controlled phase and Study XP021 is not included because it employed a cross-over design.
2. XP083 is a 16-day simulated driving performance and cognition study
3. XP045 is a 2-week dose-finding study
4. Studies are presented side-by-side, with the addition of an overall total column for XP13512.
5. XP060 is a 36-week maintenance of effect study. The study comprised of a 24-week single blind phase, with 'responders' being randomized to a 12-week double blind, placebo-controlled phase.
6. XP021 is a 2-week crossover study
7. XP055 is a 12-month extension study. The parent studies are the other 4 studies in the Long-Term integration grouping. Data collected for XP055 are included up to and including 06 December 2007.

The original sponsor (Xenoport) referred to the safety data pools as “Groupings” the Division and the sponsor agreed to the following groupings prior to submission:

1. Pivotal 12 Week Placebo Controlled RLS clinical trials (XP052, XP053, and XP081).
2. All Controlled Phase II and Phase III RLS studies which were of similar design but varying durations. This provides the largest source of controlled safety data available. Note, however, that clinical trial XP021 was not included in this grouping because of the cross-over design of the trial.
3. RLS long term integration grouping included four parent clinical trials (XP052, XP053, XP081 and XP083). Subjects from these clinical trials continued into the extension clinical trial XP055. This grouping provides information for maximum continuous duration of exposure to XP13512.
4. All RLS grouping including clinical trials, XP021, XP045, XP052, XP053, XP055, XP066, XP081 and XP083. This grouping allowed supportive assessments of rare events.

Patient Disposition

Table 7 Summary of Subject Disposition (Study XP052)

	Number (%) of Subjects		
	Placebo N=108	XP13512 N=114	Total N=222
Completion Status			
Completed	92 (85.2)	100 (87.7)	192 (86.5)
Prematurely Withdrawn	16 (14.8)	14 (12.3)	30 (13.5)
Primary Reason for Withdrawal			
Adverse event	3 (2.8)	9 (7.9)	12 (5.4)
Subject Withdrew Consent	3 (2.8)	4 (3.5)	7 (3.2)
Treatment Failure	6 (5.6)	0	6 (2.7)
Ineligibility (did not meet entry criteria)	2 (1.9)	0	2 (.9)
Termination of Study or Withdrawal of Subject by Sponsor ^a	0	1 (0.9)	1 (0.5)
Protocol Non-Compliance (after randomization)	1 (0.9)	0	1 (0.5)
Investigator Judgement ^b	1 (0.9)	0	1 (0.5)

Data Source: DSTable 1.1

Note: Disposition is calculated based on the number of randomized subjects.

- a. Subject 140/2010 withdrew at the sponsor's request because of the subjects work schedule (shift work) which made them ineligible for the study, and the subject had not taken a dose of drug.
- b. Subject 133/2005 was withdrawn at the request of the Investigator because the investigator judged the subject to be non-compliant with investigational product and was requesting to use a prohibited medication.

Table 7 Summary of Subject Disposition (All Randomized Subjects: Study XP053)

	Number (%) of Subjects			
	Placebo N=97	XP13512 600 mg N=115	XP13512 1200 mg N=113	Total N=325
Completion Status				
Completed	77 (79.4)	104 (90.4)	98 (86.7)	279 (85.8)
Prematurely Withdrawn	20 (20.6)	11 (9.6)	15 (13.3)	46 (14.2)
Primary Reason for Withdrawal				
Adverse Event	6 (6.2)	7 (6.1)	8 (7.1)	21 (6.5)
Subject Withdrew Consent	8 (8.2)	3 (2.6)	4 (3.5)	15 (4.6)
Treatment Failure	3 (3.1)	0	0	3 (0.9)
Ineligibility (did not meet entry criteria)	0	0	2 (1.8)	2 (0.6)
Protocol Non-Compliance (after randomization)	1 (1.0)	0	1 (0.9)	2 (0.6)
Lost to Follow-Up	1 (1.0)	1 (0.9)	0	2 (0.6)
Termination of Study or Withdrawal of Subject by Sponsor ^a	1 (1.0)	0	0	1 (0.3)

Data Source: DSTable 6.1

Note: Disposition is calculated based on the number of randomized subjects.

- a. Subject 197/3025 was withdrawn per the sponsor's request due to ineligibility (did not meet entrance criteria).

CDTL Comment

In study XP053 there was a dose relationship for the patients who withdrew from the XP3512 arms. Overall, more patients withdrew from the placebo group but only a few for treatment failure. The percentage of patients who withdrew because of an adverse event was the nearly the same for the placebo group and both of the XP13512 dose groups.

Final Disposition of Patients in Long-Term Study XP055 (Sponsor Table)

Table 8 Summary of Subject Disposition (Study XP055)

	Number (%) of Subjects ^a		
	Naïve N=199	Non-naïve N=382	Total N=581
Safety Population ^b	197 (99.0)	376 (98.4)	573 (98.6)
Completed	126 (63.3)	260 (68.1)	386 (66.4)
Prematurely Withdrawn ^{c, d}	71 (35.7)	116 (30.4)	187 (32.2)
Primary Reason for Withdrawal			
Adverse event ^{cd}	29 (14.6)	35 (9.2)	64 (11.0)
Subject withdrew consent	19 (9.5)	37 (9.7)	56 (9.6)
Lost to follow-up	15 (7.5)	25 (6.5)	40 (6.9)
Treatment failure	3 (1.5)	8 (2.1)	11 (1.9)
Protocol non-compliance	2 (1.0)	8 (2.1)	10 (1.7)
Investigator judgment	2 (1.0)	2 (0.5)	4 (0.7)
Termination of study or withdrawal of subject by sponsor	1 (0.5)	1 (0.3)	2 (0.3)

Data Source: DS Table 6.1

Note: The listed reasons for early termination were those with a non-zero count for at least 1 prior exposure category (naïve/non-naïve).

- a. Percentages were recorded as a function of N=581 subjects enrolled from parent studies XP052, XP053, XP081, and XP083.
- b. Safety Population: all subjects who were enrolled in the study and were reported to have taken at least 1 dose (or any portion of a dose) of study medication.
- c. Includes both treatment-emergent and non-treatment emergent AEs leading to withdrawal. Non-treatment emergent AEs leading to withdrawal are events that started prior to Study XP055 that did not worsen, and resulted in withdrawal during Study XP055.
- d. Five subjects discontinued due to an adverse event that began during the parent study. These adverse events are not regarded as treatment-emergent in XP055.

CDTL Comment

The sponsor submitted the final study report for Study XP055 in the last 6 week of the review cycle. The report for the 120 day update did not account for the disposition of patients the study 055 for reasons of “withdrew consent” or “lost to follow-up”. Thirty percent (n=187) withdrew from study XP055 prematurely leaving only 386 of 572 patients who completed the trial. A significant percentage of patients withdrew for these reasons and the sponsor did not provide an adequate explanation of why patients withdrew consent or were lost to follow-up leaving open the possibility that they withdrew for reasons related to study medication. It is likely the missing data in this case would be informative.

Exposure

Although, studies XP045, 083 and 021 are included in the All RLS grouping they are all 2 weeks or less in duration and the design of the trials (dose finding, driving and crossover) make the data unsuitable to use for assessing safety. Study XP060 is a randomized withdrawal trial of patients who are known responders to XP13512 and are known to tolerate the drug well. The 060 trial is only placebo controlled and double blind in the last 12 weeks (randomized withdrawal portion). Exposure that is 6 months or longer can only be achieved by counting the 12-week exposure in trials 052, 053, 081 and 083 as continuous (ignoring the 1 week taper period between the end of studies XP081 and 083 and entering study 055) with entry into the long term study XP055 (1 year duration). Patients that entered study XP055 after participation in study 052, 053 or 081 were stratified as non-naïve and patients that were enrolled without previous trial participation were considered naïve. The percentage of patients that originated from each of the controlled studies who entered study XP055 are as

follows: XP052 (151 [26.4%] subjects), XP053 (230 [40.2%] subjects), XP081 (115 [20.1%] subjects), and XP083 (76 [13.3%] subjects).

Exposure by Dose in Trials 12 Weeks or Less in Duration (600 mg and 1200 mg)

Table 24 Duration of Exposure for Subjects Randomized to Receive XP13512: 600 mg

Duration of exposure in months (days)	600 mg XP13512			
	XP053 (N=115)	XP081 (N=48)	XP045 (N=29)	Total
<3 (<91 days)	100 (87)	16 (33)	29 (100)	145
≥3 (≥91 days)	15 (13)	32 (67)	0	47
≥6 (≥182 days)	0	0	0	0
≥9 (≥273 days)	0	0	0	0
≥12 (≥365 days)	0	0	0	0

Data Source: Table 1.14

Table 25 Duration of Exposure for Subjects Randomized to Receive XP13512: 1200 mg

Duration of exposure in months (days)	1200 mg XP13512							Total
	XP052 (N=113)	XP053 (N=111)	XP081 (N=45)	XP083 (N=31)	XP045 (N=33)	XP060 SB (N=326)	XP060 DB (N=96)	
<3 (<91 days)	100 (88)	97 (87)	17 (38)	31 (100)	33 (100)	77 (24)	37 (39)	392
≥3 (≥91 days)	13 (12)	14 (13)	28 (62)	0	0	249 (76)	59 (61)	363
≥6 (≥182 days)	0	0	0	0	0	71 (22)	0	71
≥9 (≥273 days)	0	0	0	0	0	0	0	0
≥12 (≥365 days)	0	0	0	0	0	0	0	0

Data Source: Table 1.14

Safety Data Cutoff Dates for Long-Term Study XP055

The NDA Application used a cutoff date of December 6, 2007 also referred to Interim report 1. Interim Report No. 2 was prepared for inclusion in the 120-Day Safety Update for XP13512, which contains safety-related data obtained up to and including a cut-off date of July 31, 2008. The final report of study XP055 was received in the agency on December 22, 2009.

Exposure for All RLS Safety Grouping for All Doses XP13512 at The Cut-Off for NDA Application and The 120-Day Update (Sponsor Table)

Table 14 Duration of Unique Subject Exposures to XP13512 by Time Interval for the All RLS and RLS Long-Term Integration Groupings (Safety Populations)

	All RLS		RLS Long-Term Integration	
	NDA Data Cut-off: 06 December 2007	120-Day Safety Data Cut-off: 31 July 2008	NDA Data Cut-off: 06 December 2007	120-Day Safety Data Cut-off: 31 July 2008
XP13512 All Doses: Duration of exposure in months (days)	XP13512 All Doses (N=1201)	XP13512 All Doses (N=1201)	XP13512 All Doses (N=777)	XP13512 All Doses (N=777)
<3 (<91 days)	389 (32)	378 (31)	214 (28)	203 (26)
≥3 (≥91 days)	812 (68)	823 (69)	563 (72)	574 (74)
≥6 (≥182 days)	495 (41)	602 (50)	329 (42)	436 (56)
≥9 (≥273 days)	192 (16)	398 (33)	192 (25)	398 (51)
≥12 (≥365 days)	120 (10)	313 (26)	120 (15)	313 (40)

Data Source: Table 4.5, Table 4.7; NDA 022399, 09 January 2009, Sequence Number 0004, m5.3.5.3 ISS, Table 1.13, Table 1.15

The maximum length of exposure is included for each subject (including on-treatment and taper).

Note: For subjects who entered Study XP055, their extent of exposure in the parent study and in the follow-up study is combined. Exposure may not be continuous.

All subjects were counted uniquely within each column; however, a subject may be represented in more than one exposure duration category e.g. a subject with 8 months exposure was counted in the 'at least 3 months' category and the 'at least 6 months' category (but not in the 'at least 9 months' or 'at least 12 months' categories).

*Exposures of 3 months or more can not include the 300 mg/day dose

Exposure By Modal Dose for Long-Term Open-Label Study XP055 at the 120 Day Safety Update Cut-Off (Sponsor Table)

Table 11 Maximum Dose, Modal Dose, and Final Dose in Study XP055 (Safety Population: Study XP055)

	Number (%) of Subjects
	XP13512 N=572
Modal Dose	
0 mg ^a	1 (0.2)
600 mg	99 (17.3)
1200 mg	316 (55.2)
1800 mg	156 (27.3)
Maximum Dose	
600 mg	32 (5.6)
1200 mg	338 (59.1)
1800 mg	199 (34.8)
2400 mg ^b	3 (0.5)
Final Dose	
0 mg ^a	3 (0.5)
600 mg	103 (18.0)
1200 mg	302 (52.8)
1800 mg	164 (28.7)

Data Source: DSTable 8.2

- a. Any subject who had an interruption in dosing was considered to be on 0 mg.
- b. This dose was not specified per Protocol. Three subjects (102/5014, 129/2005, and 234/5002) titrated up to 2400 mg without investigator approval.

The interim data from the 120 day cut-off data indicate that the majority of subjects on long-term XP13512 therapy for the treatment of RLS were taking 1200 mg modal dose even when they were allowed to titrate the dose up or down, while fewer subjects were maintained on the 1800 mg dose (27.3%) and even fewer on the 600 mg dose (17.3%).

Duration of Exposure (in days) By Modal Dose Final Study Report Study Long-Term Open Label Study XP055 (Sponsor Table)

Protocol: RXP111490 FINAL (XP055)
 Population: Safety

Table 8.101
 Total Days of Study Drug Exposure by Modal Dose

Duration of exposure in days (months) [1]	0mg (N=1) [2]	XP13512 600 mg (N=98)	XP13512 1200 mg (N=316)	XP13512 1800 mg (N=158)	Total XP13512 (N=573)
n	1	98	316	158	573
0-30 days (1 month)	1 (100%)	29 (30%)	38 (12%)	3 (2%)	71 (12%)
31-90 days (2-3 months)	0	8 (8%)	26 (8%)	8 (5%)	42 (7%)
91-180 days (4-6 months)	0	7 (7%)	18 (6%)	15 (9%)	40 (7%)
181-365 days (7-12 months)	0	41 (42%)	149 (47%)	86 (54%)	276 (48%)
>365 days (>12 months)	0	13 (13%)	85 (27%)	46 (29%)	144 (25%)

[1] Duration of exposure in days = date of last XP055 dose of study drug - date of first XP055 dose of study drug + 1.
 [2] Note: Subject 2307004 has modal dose of 0mg because this subject was in the study for only eight days and missed treatment for four of these days. (Of the remaining days the subject took 600mg on one day and 1200mg on the other three days.)
 Note: This summary includes data from XP055 study only and not the parent studies (XP052, XP053, XP081 and XP083). The safety population includes all subjects who enrolled into the study and who took at least one dose of study medication.
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CDTL Comment

This table lists only continuous exposures not including taper periods only for patients enrolled in XP055. The sponsor discussed final 12-month exposure targets with the agency and the sponsor anticipated they would reach approximately 130 patients treated with 1200 mg/day or more for 12 months or more.

In the final study report, the sponsor did not present a table listing the number of patients exposed by modal dose and duration. The presentation of the data makes it difficult to know the exact number of patients exposed to 600 mg or more for 1 year or more. The final study report for XP055 was sent to the agency on December 22, 2009 and the sponsor did not update the ISS. The previous Tables listing larger numbers of patients exposed for 12 months or more include the exposure from patients who

started their exposure to XP13512 in 12-Week placebo controlled trials or Study XP060 (24-36 Week duration) prior to entering XP055.

Reviewer Comments:

The size of the safety database including patients reported in the 120 day safety update meet ICH guidelines for long-term exposure at both 6 and 12 months continuous exposure at 600 mg, 1200 mg, 1800 mg and 2400 mg/day. The duration of exposure was calculated as unique exposures at doses of ≥ 1200 mg/day. The subjects who received 600 mg/day only contributed to the number of patients exposed to XP13512 for 3 months or less in the placebo controlled trials and 33 in study XP055.

Deaths

There were 3 deaths in the development program, all of which occurred in XP13512 treat individuals.

Study XP044- A Single Dose Clinical Pharmacology Study

Subject 222-was a 51 year-old healthy male volunteer who died of a self-inflicted gunshot wound (b) (6) hours after receiving a single 1200 mg dose of XP13512. It is unlikely that study medication is causally related to this patient's suicide. The subjects had consumed ethanol prior to committing suicide but no other illicit substances were present on toxicology screen. He had no personal history of depression but there was a positive family history for bipolar disease. The patient committed suicide after a dispute with his fiancée.

Study XP055 Open-label Extension Study

Subject 1813027- was a 48-year-old man who was found by police dead at the bottom a highway overpass. The subject had taken his last dose of XP13512 (b) (6) and died (b) (6) days later. The subject's car was parked on an overpass above the site where his body was discovered. The Death Certificate provided to the investigator stated that the subject fell from a highway overpass and died on (b) (6). The cause of death was multiple blunt force injuries due to the fall. Acute alcohol intoxication was listed as a significant condition on the death certificate. A follow-up on report August 12, 2008 stated that the subject had been increasingly using alcohol and marijuana. According to the investigator, the subject's last dose of study medication was taken on (b) (6), and the last dose of the taper medication was (b) (6). The subject Neurontin was prescribed on May 8th, 2008 but the prescription was found unfilled.

Study XP060 Long-term Maintenance of Efficacy Study

Subject 186-4008A was a 63 year-old female subject who died (b) (6) days after starting 1200 mg/day of XP13512. The subject aspirated a piece of meat, which caused airway occlusion on (b) (6). Attempts were made to resuscitate the patient was unsuccessful and the subject died on the same day. This subject's death appears unrelated to XP13512.

CDTL Comment

The death for the 48-year-old man after a single dose of XP13512 is unlikely related to the study medication. However, the patient found deceased at the bottom of the highway overpass should be considered a case of possible suicide. In addition, there was another case of subject who ingestion multiple medications in a suicide attempt although the sponsor did not classify the case as such. These two suicide relate events raises concern that the potential increased risk for suicidality is similar to the increased risk associated with gabapentin, which would be expected. It also supports the inclusion of the class label language regarding the increased risk for suicidality and anticonvulsants medications in the gabapentin enacarbil label.

Serious Nonfatal Adverse Events

The there did not appear to be a dose response relationship between the overall number or type of SAE to the dose of XP13512.

There were two cases of serious non-fatal TEAEs of special interest were reported in study XP060 the sponsor's Long-term Maintenance of Efficacy Study, the narratives are presented below

Subject 206-4019 - was at the time the event was reported a 50-year-old female with a history of hypertension, hypothyroidism and Turner's syndrome. The patient experienced a single seizure during the taper phase of 1200 mg/day XP13512, however subsequent evaluation discovered focal abnormality on EEG. The patient had no further seizures and an initial CT scan of the head was unremarkable. The patient's seizure was not in the opinion of this reviewer related to the taper from XP13512.

Subject 14105010- was a 37-year-old at the time the SAE occurred. The subject was received 1200 mg/day of XP13512 for 165 days prior to experiencing the event. Her past medical history included hysterectomy, migraine, sacroilitis, sinusitis, arthritis and dyshidrosis. The patient's neighbor who discovered the patient on the floor stated the subject possibly took an overdose of drug. She was found on the floor by the neighbor with "several empty medication bottles in her presence" and blood on her shirt. The investigator assessed the events as grade 3 or severe. Urine Drug Screen revealed Amitriptyline and Doxylamine were present. The patient was described as "incoherent and unable to walk, confused, disoriented and hallucinating after initially regaining consciousness, which lasted approximately 48 hours. The site investigator "concluded that it is his opinion that the subject was previously taking medications that she did not report to his team" and the event was recoded from drug overdose to mental status change, which in the opinion of this reviewer was incorrect. The event should be considered a suicide attempt by ingestion.

Serious Non-fatal TEAEs in Placebo Controlled Trials

Incidence of All Serious TEAEs in 12 Week Placebo Controlled Clinical Trials (Sponsor Table)

Table 29 TESAEs (Safety Population: 12-Week Controlled RLS Studies)

Study	Number (%) of Subjects					
	Placebo	XP13512 600mg	XP13512 1200mg	XP13512 1800mg	XP13512 2400mg	XP13512 All Doses
XP052	1/108 (<1)	-	0/113	-	-	0/113
XP053	1/96 (1)	2/115 (2)	0/111	-	-	2/226 (<1)
XP081	0/41	0/48	0/45	0/38	1/45 (2)	1/176 (<1)
Total	2/245 (<1)	2/163 (1)	0/269	0/38	1/45 (2)	3/515 (<1)

Data Source: ISS Table 2.27, ISS Table 2.30

Note: TEAEs with an onset date in the on-treatment and taper medication phases are included.

Table of Serious TEAEs Reported in Development Program Prior to 120 Day Safety Update

Table 30 TESAEs Reported as of 06 December 2007 Data Cut-off (Safety Population: All RLS)

Study	Subject	Treatment ¹	Preferred Term	Related	Withdrawn	Outcome
Placebo						
XP052	1042009	placebo	Appendicitis	No	No	Recovered
XP053	1873002	placebo	Cholelithiasis	No	No	Recovered
XP060	1204023	placebo	Diverticulitis	No	No	Recovered
	1864009	placebo	Anaphylactic reaction	No	Yes	Recovered
XP13512						
XP053	1143025	600mg	Cellulitis	No	No	Recovered
	1873005	600mg	Intervertebral disc protrusion	No	No	Resolved/with sequelae
XP081	1115011	2400mg	Rotator cuff syndrome	No	No	Recovered
XP060	1354008	1200mg	Angina pectoris	No	No	Recovered
	1514021	1200mg	Chest pain	No	No	Recovered
	2064019	1200 mg	Convulsion (taper)	Yes	Yes	Recovered
XP055	2003004	naive 600 mg	Pulmonary embolism	No	No	Recovered
XP055	1337012	naive 1200 mg	Meningitis viral	No	No	Recovered
XP055	1332018	naive 1800 mg	Cholecystitis acute	No	No	Recovered
XP055	1503004	naive 1800 mg	Non-cardiac chest pain	No	No	Recovered
XP055	1282015	non-naive 600 mg	Cerebrovascular accident	No	No	Recovered
XP055	1232021	non-naive 1200 mg ²	Lumbar spinal stenosis	No	Yes	Resolved/with Sequelae
XP055	1292009	non-naive 1200 mg	Angina unstable	No	No	Recovered
XP055	9033017	non-naive 1200 mg	Colitis	No	No	Recovered
XP055	1922026	non-naive 1200 mg	Chest pain	No	No	Recovered
XP055	2065010	non-naive 1800 mg	Myocardial infarction	No	No	Recovered
			Non-small cell lung cancer	No	Yes	Recovered

m5.3.5.3, ISS Table 86

Data Source: Listing 2.4

1. Subject's dose during Study XP055 is reported (see individual subject narratives; m5.3.5.3, Narratives). Naive subjects received placebo in parent study. Non-naive subjects received XP13512 in parent study.

2. Reported 2 days after last dose.

Data cut-off: 06 December 2007

Summary of Serious Nonfatal TEAEs Included in The 120-Day Safety Update Study XP055

Table 23 Treatment-Emergent Serious Adverse Events Reported in Subjects (Safety Population: Study XP055)

Site/Subject Number	Age/Gender	SAE Preferred Term	Withdrawn?	Related?	Resolved?
Data cut-off up to and including 06 December 2007					
123/2021	57/F	Lumbar spinal stenosis	Yes	No	Yes (with sequelae)
128/2015	69/M	Cerebrovascular accident	No	No	Yes
129/2009	52/M	Angina unstable	No	No	Yes
133/2018	35/F	Cholecystitis acute	No	No	Yes
133/7012	44/F	Meningitis viral	No	No	Yes
142/5006	52/F	Road traffic accident	No	No	Yes (with sequelae)
150/3004	50/M	Non-cardiac chest pain	No	No	Yes
192/2026	58/F	Chest pain	No	No	Yes
200/3004	45/F	Pulmonary embolism	No	No	Yes
206/5010	67/F	Myocardial infarction	No	No	Yes
		Non-small cell lung cancer	Yes	No	Yes
903/3017	36/M	Colitis	No	No	Yes
Data from 07 December 2007 to cut-off of 31 July 2008					
104/7003	49/F	Intervertebral disc protrusion	Yes	No	Yes
128/5006	65/M	Back pain	No	No	Yes
		Drug withdrawal syndrome ^a	No	No	Yes
129/5014	56/F	Transient ischaemic attack	No	No	Yes
141/5010	37/F	Mental status changes	Yes	Yes	Yes
211/5007	49/M	Appendicitis	No	No	Yes
		Postoperative Infection ^b	No	No	No
228/7001	56/M	Lumbar vertebral fracture	No	No	Yes
		Back pain ^c	No	No	Yes
228/7008 ^d	53/F	Nerve compression	No	No	Yes (with sequelae)

Data Source: DSListing 2, DSListing 13, DSListing 14, and DSTable 8.10

- a. Withdrawal syndrome secondary to discontinuation of pain medication
- b. Narrative for Subject 211/5007 has the preferred term "Infection" (see Section 18.1.2).
- c. SAE of "Backpain" for Subject 228/7001 was updated to non-serious and is incorrectly reflected in the current DSListing 13 as an SAE. This will be corrected for the final report of this study.
- d. Subject 228/7008 also experienced an SAE of "exostosis" that is not included in DSListing 13, but is appropriately included in the narrative for this subject. This will be corrected for the final report of this study.

*Subject 142/5006 was a passenger in the automobile at the time of the accident.

Subjects with Adverse Events Related to Abnormal Liver Chemistry Reported by 3 or more Subjects (Safety Population: Study XP055) 120-Day Safety Update

Site/Subject Number Age/Gender	AE Related to Clinical Chemistry	Baseline Value	Visit ^a /AE Associated Abnormal Value ^a	Reference Range	Severity	Related?	Resolved?	Action Taken ^b
Liver function test abnormal								
145/5023 55/F	Liver function test abnormal	AST: 62 ALT: 75 GGT: 79	V2: 112 V2: 99 V2: 118	0-41 U/L 0-45 U/L 2-65 U/L	Mild	Possibly	No	None
182/7001 49/M	Liver function test abnormal	AST: 40 ALT: 76 GGT: 75	V5: 76 V5: 151 V5: 80	0-41 U/L 0-45 U/L 2-65 U/L	Moderate	No	No	Withdrawn
220/7010 48/F	Liver function test abnormal	ALT: 43 GGT: 100	V6: 63 V6: 157	0-45 U/L 2-65 U/L	Mild	No	No	None
228/7001 56/M	Liver function test abnormal	AST: 24 ALT: 40 GGT: 46 Bilirubin, Total: 0.4	V5: 94 V5: 133 V5: 330 V5: 1.6	0-41 U/L 0-45 U/L 2-65 U/L 0.1-1.2 mg/dL	Moderate	No	No	None

Isolated Elevations of ALT Reported by 3 or more Subjects Study XP055 (including 120-day safety update)

Alanine aminotransferase increased									
107/3017 29/M	ALT Increased	27	V7: 52	0-45 U/L	Mild	Possibly	No	None	
126/2011 31/F	ALT Increased	34	V2: 135	0-45 U/L	Moderate	No	Yes	Withdrawn	
181/3001 46/M*	ALT Increased	75	V1: 75	0-45 U/L	Moderate	Possibly	No	Withdrawn	
210/3008 62/F	ALT Increased	34	V5: 129	0-45 U/L	Moderate	No	Yes	None	

CDTL Comment

The frequency of serious but nonfatal TEAEs were not increased compared in patients treated with XP13512 compared to placebo treated patients. There is no apparent dose response relationship for SAEs among patients treated with XP13512 and the events are not consistent with any rare drug related events including Hy’s Law cases even among patients who withdraw for ALT or liver enzyme elevation..

Adverse Events Associated with Withdrawal

Number of Patients Treated for RLS Who Withdrew From Placebo Controlled Trials By Dose

Table 31 TEAEs Leading to Withdrawal of at Least 1% of Subjects in Any Treatment Group (Safety Population: 12-Week Placebo-Controlled RLS Studies)

Preferred Term	Number (%) of Subjects					
	Placebo (N=245)	XP13512 600 mg (N=163)	XP13512 1200 mg (N=269)	XP13512 1800 mg (N=38)	XP13512 2400 mg (N=45)	XP13512 All Doses (N=515)
Any event	9 (4)	10 (6)	22 (8)	3 (8)	5 (11)	40 (8)
Dizziness	0	2 (1)	5 (2)	2 (5)	0	9 (2)
Somnolence	0	3 (2)	3 (1)	0	1 (2)	7 (1)
Sedation	0	1 (<1)	2 (<1)	0	1 (2)	4 (<1)
Nausea	0	0	2 (<1)	1 (3)	0	3 (<1)
Edema	0	0	0	0	1 (2)	1 (<1)
Back injury	0	0	0	0	1 (2)	1 (<1)
Neck injury	0	0	0	0	1 (2)	1 (<1)
Dyspnoea	0	0	0	0	1 (2)	1 (<1)
Vision blurred	0	0	0	0	1 (2)	1 (<1)

Data Source: ISS Table 2.31

Note: TEAEs with an onset date in the on-treatment and taper medication phases are included.

TEAEs Associated with Withdrawal Study XP055 Before and After 120-Day Cutoff (July 31, 2008)

Table 25 Summary of Treatment-Emergent Adverse Events Leading to Withdrawal in at least 2 Subjects (Safety Population: Study XP055)

Preferred Term	Number (%) of Subjects	
	XP13512 N=572 n (%)	
	Data cut-off up to and including 06 December 2007	Data cut-off of 31 July 2008
All Withdrawal Adverse Events	52 (9.1)	62 (10.8) ^{abc}
Somnolence	9 (1.6)	9 (1.6)
Dizziness	8 (1.4)	8 (1.4)
Depression	3 (0.5)	3 (0.5)
Irritability	3 (0.5)	3 (0.5)
Rash	2 (0.3)	3 (0.5)
Sedation	3 (0.5)	3 (0.5)
Weight Increased	2 (0.3)	3 (0.5)
Abdominal Upper Pain	2 (0.3)	2 (0.3)
Anxiety	3 (0.5)	2 (0.3) ^d
Disorientation	2 (0.3)	2 (0.3)
Feeling Abnormal	2 (0.3)	2 (0.3)
Headache	2 (0.3)	2 (0.3)
Hepatic Enzyme Increased	-	2 (0.3)
Nausea	2 (0.3)	2 (0.3)
Restless Legs Syndrome	2 (0.3)	2 (0.3)
Vision Blurred	2 (0.3)	2 (0.3)

Data Source: DSTable 8.11

- Includes Subject 181/3001 who withdrew in Study XP055 with an incorrect onset date for an AE of elevated ALT that was found to have occurred in Study 053 and is thus not treatment emergent.
- Includes Subject 107/3017, who completed the study, but the reported TEAE of "Seasonal Allergy" was incorrectly recorded as a TEAE leading to withdrawal.
- Subject 192/5013 discontinued due to a TEAE of "Fluttering in Chest" that the investigator considered possibly drug related. The TEAE leading to withdrawal was not recorded in the dataset with cut-off date 31 July 2008.
- Subject 123/5002 was reported with a TEAE leading to withdrawal in Interim 1 that was subsequently revised as a protocol violation and no longer appears in the data source.

CDTL Comments

The number and percentage of subjects who withdrew from placebo controlled trials because of a treatment emergent adverse event (AE) was greater in the XP13512 treated groups compared to placebo. Dizziness, somnolence sedation were the most common AEs associated with withdrawal together they account for 50% of the subjects who withdrew for AEs. There is also a dose response relationship of for the overall number of AEs leading to withdrawal. These findings are similar to the AEs reported among patients who remained in the trial. The only 4 subjects in XP055 withdrew because of a serious adverse event, 2 for lumbar spine problems that led to hospitalization, one with mental status change and one case of non-small cell lung carcinoma.

Eight naïve subjects withdrew due to an AE that started on their first day of treatment with XP13512 and the sponsor counted their dose on the day prior to the AE onset as 0 mg.

Nonserious TEAEs

Headache and sedation related adverse events were the most frequent common TEAEs (Table below). There appeared to be a dispersion of the number of events reported as sedation/somnolence over several preferred terms. The overall the type of TEAEs and frequency of nonserious TEAEs are similar to the nonserious adverse events reported in the Neurontin product label.

Sponsor’s Table of Nonserious TEAEs ≥ 2% XP13512 Compared to Placebo

Protocol: RXPISS XP13512 (GSK1838262)

Population: Safety - 12-Week Controlled RLS Studies

Table 2.7
Summary of Treatment Emergent Adverse Events By Preferred Term
in 12-Week Controlled RLS Studies

Preferred Term	Placebo (N=245)		XP13512 600mg (N=163)		XP13512 1200mg (N=269)		XP13512 1800mg (N=38)	
	Incidence	No. of events	Incidence	No. of events	Incidence	No. of events	Incidence	No. of events
Any event	182 (74%)	564	132 (81%)	418	226 (84%)	813	32 (84%)	101
Somnolence	12 (5%)	13	32 (20%)	37	61 (23%)	66	10 (26%)	11
Dizziness	11 (4%)	12	22 (13%)	29	59 (22%)	76	10 (26%)	15
Headache	28 (11%)	37	19 (12%)	22	41 (15%)	51	4 (11%)	4
Nasopharyngitis	17 (7%)	18	14 (9%)	15	21 (8%)	22	3 (8%)	5
Nausea	12 (5%)	13	9 (6%)	10	18 (7%)	21	3 (8%)	3
Fatigue	11 (4%)	12	9 (6%)	9	18 (7%)	20	1 (3%)	1
Dry mouth	5 (2%)	5	5 (3%)	5	12 (4%)	13	2 (5%)	2
Irritability	3 (1%)	3	6 (4%)	6	11 (4%)	11	2 (5%)	2
Diarrhoea	12 (5%)	14	6 (4%)	6	10 (4%)	10	2 (5%)	2
Insomnia	7 (3%)	7	9 (6%)	9	7 (3%)	7	2 (5%)	2
Sedation	3 (1%)	3	1 (<1%)	1	11 (4%)	15	3 (8%)	3
Upper respiratory tract infection	9 (4%)	10	10 (6%)	11	6 (2%)	6	1 (3%)	1
Feeling drunk	0	0	2 (1%)	2	7 (3%)	10	3 (8%)	5
Pain in extremity	7 (3%)	8	6 (4%)	6	8 (3%)	10	2 (5%)	2
Weight increased	5 (2%)	5	4 (2%)	4	9 (3%)	9	0	0
Constipation	8 (3%)	8	3 (2%)	3	10 (4%)	10	2 (5%)	2
Sinusitis	6 (2%)	6	5 (3%)	5	7 (3%)	8	0	0
Back pain	7 (3%)	7	6 (4%)	6	7 (3%)	8	0	0
Feeling abnormal	1 (<1%)	2	1 (<1%)	2	9 (3%)	9	3 (8%)	3
Muscle spasms	5 (2%)	6	6 (4%)	7	6 (2%)	7	0	0
Vertigo	0	0	2 (1%)	2	7 (3%)	7	2 (5%)	2
Arthralgia	5 (2%)	8	2 (1%)	3	8 (3%)	9	1 (3%)	1
Oedema peripheral	3 (1%)	3	1 (<1%)	1	7 (3%)	8	1 (3%)	1
Flatulence	2 (<1%)	3	5 (3%)	5	5 (2%)	5	0	0
Sinus congestion	8 (3%)	9	3 (2%)	3	7 (3%)	7	1 (3%)	1

Note: Adverse events with an onset date in the on-treatment and taper medication phases are included.
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Somnolence Related Adverse Events

Somnolence and Dizziness are the two most frequently reported adverse events, similar to the adverse events reported in the Neurontin (gabapentin) product label. However, several other the preferred terms are likely to indicate somnolence or impaired cognition such as “feeling drunk, sedation, feeling abnormal and irritability”.

The Sponsor’s Analysis of Somnolence and Sedation related TEAEs in The Combined 12 Week Controlled Trials

Table 47 Characteristics of Somnolence/ Sedation TEAEs Combined (Safety Population: 12-Week Placebo-Controlled RLS Studies)

Preferred Term	Number (%) of Subjects					
	Placebo (N=245)	XP13512 600mg (N=163)	XP13512 1200mg (N=269)	XP13512 1800mg (N=38)	XP13512 2400mg (N=45)	XP13512 All Doses (N=515)
Somnolence						
Number of subjects	12 (5)	32 (20)	61 (23)	10 (26)	23 (51)	126 (24)
Number of events	13	37	66	11	30	144
Sedation						
Number of subjects	3 (1)	1 (<1)	11 (4)	3 (8)	3 (7)	18 (3)
Number of events	3	1	15	3	4	23
Any event (somnolence and/or sedation)						
Number of subjects	15 (6)	33 (20)	72 (27)	12 (32)	26 (58)	143 (28)
Number of events	16	38	81	14	34	167
Treatment-related	15 (100)	31 (94)	68 (94)	12 (100)	26 (100)	137 (96)
Leading to dose reduction	1 (7)	1 (3)	16 (22)	1 (8)	7 (27)	25 (17)
Leading to interruption in study medication	0	0	1 (<1)	0	0	1 (<1)
Leading to withdrawal	0	4 (12)	5 (7)	0	2 (8)	11 (8)
Severe	0	3 (9)	3 (4)	0	1 (4)	7 (5)

Data Source: Table 2.84, Table 2.14

Note: TEAEs with an onset date in the on-treatment and taper medication phases are included.

CDTL Comment

The sponsor combined the preferred terms of somnolence and sedation in the table 47 (above). The increase in somnolence related adverse events are more frequent in patients treated with XP13512 compared to placebo. In addition, there is a clear dose-response relationship in the number of patients reporting somnolence or sedation. Overall there is a 7% increase in sedation or somnolence reported in the 1200 mg/day group compared to the 600 mg/day. Somnolence or sedation appeared to have its onset with in the first two weeks for all studied doses of XP13512 (see table below) but there is no data that documents resolution of somnolence or sedation or the duration of these symptoms.

Time to First Onset of Somnolence or Sedation in 12-Week Controlled Trials of XP13512 (sponsor’s table)

Protocol: RXP1SS XP13512 (GSK1838262) Page 4 of 5
 Population: Safety - 12-Week Controlled RLS Studies
 Table 2.85
 Summary of Characteristics of Somnolence and Sedation Treatment Emergent Adverse Events Leading to Withdrawal in 12-Week Controlled RLS Studies

Preferred Term: Somnolence and Sedation

	Placebo (N=245)	XP13512 600mg (N=163)	XP13512 1200mg (N=269)	XP13512 1800mg (N=38)	XP13512 2400mg (N=45)	XP13512 All Doses (N=515)

Summary Statistics for Maximum Duration of Adverse Event (days)						
n	0	4	5	0	2	11
Mean		11.3	6.4		4.0	7.7
SD		3.40	8.76		1.41	6.56
Median		10.5	2.0		4.0	5.0
Min.		8	2		3	2
Max.		16	22		5	22
Time of first occurrence (days)						
Number	0	4 (100%)	5 (100%)	0	2 (100%)	11 (100%)
0-3	0	2 (50%)	4 (80%)	0	2 (100%)	8 (73%)
4-14	0	2 (50%)	1 (20%)	0	0	3 (27%)
15-28	0	0	0	0	0	0
29-42	0	0	0	0	0	0
43-56	0	0	0	0	0	0
57-70	0	0	0	0	0	0
71-84	0	0	0	0	0	0
>84	0	0	0	0	0	0
Missing	0	0	0	0	0	0

* Subjects may appear in more than one category for Event Characteristics, Outcome and Study Drug Action Taken.
 Note: Subjects only included where the adverse event being summarized was indicated as leading to withdrawal
 Note: Adverse events with an onset date in the on-treatment and taper medication phases are included.
 "Treatment-related" includes any event with a relationship to study drug of Possibly, Probably or unknown.
 kxm30728: /arenv/arprod/gsk1838262/rxp1ss/final/drivers/ae t070.sas 25JUL2008 15:51

Reanalysis of Sedation related TEAEs

Regrouping of sedation related Preferred Terms (PTs) together increased the number of reported events but did not significantly change the percentage of sedation related TEAEs (using total # of TEAEs or # of patients as the denominator) nor did it change the relationship of the dose of XP13512 to the increasing frequency of sedation related adverse events (see table below). Dizziness, somnolence, sedation feeling drunk or abnormal are the most frequent events with a relation to dose.

Table Regrouping of Sedation Related AEs

Preferred Term	Number (%) of AEs					
	Placebo N=245 N AEs=564	XP13512 600mg N=163 N AEs=418	XP13512 1200mg N=269 N AEs=813	XP13512 1800mg N=38 N AEs=101	XP13512 2400mg N=45 N AEs=175	XP13512 All Doses N=515 N AEs=1507
Any event	182 (74)	132 (81)	226 (84)	32 (84)	44 (98)	434 (84)
Somnolence	12 (5)	32 (20)	61 (23)	10 (26)	23 (51)	126 (24)
Dizziness	11 (4)	22 (13)	59 (22)	10 (26)	18 (40)	109 (21)
Fatigue	11 (4)	9 (6)	18 (7)	1 (3)	2 (4)	30 (6)
Sedation	3 (1)	1(<1)	11 (4)	3 (8)	3 (7)	18 (3)
Feeling drunk	0	2 (1)	7 (3)	3 (8)	4 (9)	16 (3)
Feeling	1(<1)	1(<1)	9 (3)	3 (8)	1 (2)	14 (3)

abnormal						
Vertigo	0	2 (1)	7 (3)	2 (5)	2 (4)	13 (3)
Disorientation	1(<1)	2 (1)	4 (1)	2 (5)	1 (2)	9 (2)
Vision blurred	0	1(<1)	4 (1)	0	4 (9)	9 (2)
Disturbance in attention	1(<1)	3 (2)	2(<1)	2 (5)	0	7 (1)
Total	40	75	182	36	58	351
% Total number of AEs	7.09	17.94	22.39	35.64	33.14	20.90

Study XP055 Final Study Report: Patients Requiring Dose Reduction (Sponsor Table)

Table 21 Number of Dose Reductions by Reduction Type and Reason for Reduction (Safety Population: Study XP055)

Group Reason for Reduction	Number (%) of Subjects		
	1200 to 600 mg N=114	1800 to 1200 mg N=52	2400 to 1800 mg N=3
Naive			
Number of Dose Reductions, n	56	15	1
Adverse Event	41 (73.2)	10 (66.7)	0
Per Protocol	3 (5.4)	0	0
Other	12 (21.4)	5 (33.3)	1 (100.0)
Non-Naive			
Number of Dose Reductions, n	72	48	2
Missed Doses	1 (1.4)	0	0
Adverse Event	45 (62.5)	19 (39.6)	0
Per Protocol	4 (5.6)	0	0
Other	22 (30.6)	29 (60.4)	2 (100.0)
Total			
Number of Dose Reductions, n	128	63	3
Missed Doses	1 (0.8)	0	0
Adverse Event	86 (67.2)	29 (46.0)	0
Per Protocol	7 (5.5)	0	0
Other	34 (26.6)	34 (54.0)	3 (100.0)

Data Source: DS Table 8.3 and DS Listing 8

CDTL Comment

The largest number of patients who required a dose reduction occurred in patients who went from 1200 mg to 600 mg. The majority of these patients required dose reduction for reasons related to adverse events.

Pregnancies

There was one pregnancy that occurred in the single blind treatment phase of Study XP060. The outcome was a healthy normal neonate and examinations and developmental assessments at 1 month were normal. There were no other pregnancies in any Phase II/III clinical or clinical pharmacology study (completed or ongoing) in the XP13512 clinical development program for RLS.

Adverse Events of Special Interest

Suicidality

During Phase II and Phase III studies in the XP13512 in RLS clinical development program, suicidality was monitored on an ongoing basis through review of AE listings, which were blinded to treatment.

Placebo Controlled Clinical Trials Included in The Sponsor’s Suicidality Assessment

Table 117 Description of Studies Included in the Assessment of Suicidality

Study	Phase/ Indication	Age Range (years)	Design	Duration of DB Period	Number of Subjects Evaluated		XP13512 Treatment Groups (mg/day)
					XP1351 2	Placebo	
XP018	I/Healthy subjects	19 to 49	Parallel	7 to 10 days	34	4	700 1400 2800 4200
XP073	I/Healthy subjects	20 to 53	Parallel	9 to 11 days	24	7	2400 3600
XP021	II/RLS	19.7 to 72.7	Crossover ¹	2 weeks	21	17	1800
XP045	II/RLS	22 to 70	Parallel	2 weeks	62	33	600 1200
XP052	III/RLS	18 to 81	Parallel	12 weeks	113	108	1200
XP053	III/RLS	21 to 77	Parallel	12 weeks	226	96	600 1200
XP060 DB Phase	III/RLS	19 to 82	SB followed by DB parallel	12 weeks	96 ²	98 ²	1200
XP081	II/RLS	18 to 77	Parallel	12 weeks	176	41	600 1200 1800 2400
XP083	II/RLS	21 to 70	Parallel	2 weeks	65	34	1200 1800
XP009	II/PHN	23 to 87.2	Parallel	2 weeks	47	54	2400
Total number of subjects evaluated					864	492	-

1. First period of randomization treatment only, including within 1 day of stopping.
2. Number of subjects randomized to the DB phase

The Sponsor’s Suicidality Assessment Method

Search Terms for Suicidality and Narrative Process

Search terms used in the process include the following: Any free text string, or events coded to PTs or verbatim term that include the text string “accident-“, “injur-“, “suic“, “overdos”, “accidental overdose”, “attempt”, “cut”, “gas”, “hang”, “hung”, “jump”, “mutilat-“, “self damag”, “self harm”, “self inflict”, “shoot”, “slash”, “poison”, “asphyxiation”, “suffocation”, “firearm”, “burn”, “drown”, “gun”, “immolat-“, “monoxide-“, “tox”, “lacerat”, “death”, “die” were identified as an AE of potential special interest.

Narratives were written for events that contain at least one of the above text strings, except for obvious false positives (e.g., ‘gastrointestinal’) determined by a sponsor medical reviewer or those

outside of the exposure window (e.g., prior to randomized treatment). All narratives were blinded to treatment, dates and concomitant medications, given an alpha identifier from Dr [REDACTED] (b) (4) (followed by a GSK numeric identifier), and then delivered to [REDACTED] (b) (4) for classification. A spreadsheet was returned from [REDACTED] (b) (4) containing the narrative identifiers and corresponding classification ratings.

(b) (4) **Classification of Events**

Classification of the blinded narratives was conducted independently at [REDACTED] (b) (4) using the C-CASA method [Posner, 2007]. The following ratings, which differ from the ratings provided in Posner, 2007, were applied [REDACTED] (b) (4):

1. Completed suicide
2. Suicide attempt
3. Preparatory actions towards imminent suicidal behavior
4. Suicidal ideation
5. Self-injurious behavior, intent unknown
6. Not enough information, fatal
7. Nonsuicidal self-injurious behavior
8. Other
9. Not enough information, non-fatal

CDTL Comment

Only studies XP052, 053, 060, 081 and 055 enrolled a sufficient number of patients, treated for a reasonable duration (12 weeks) are adequate to examine for a suicidality safety signal. It is likely that even 12 weeks of observation is inadequate to study suicidality in patients taking XP13512.

The assessment for suicidality was not prospective. Active monitoring for suicidality by administering the Columbia Suicidality Questionnaire to patients while they participated in their respective clinical trials would have been a better monitoring procedure. Active questioning is a better method for symptom ascertainment and would have allowed for intervention, if a suicidality signal was detected, thereby improving the safety of the trial. The sponsor should continue to treat suicidality as an event of special interest in the postmarketing period.

Sudden Onset of Sleep

The SOS-Q was developed by XenoPort to specifically probe for potential sleep attacks during the week prior to questionnaire completion. The number of attacks and activities (passive or active) during which these potential attacks occurred were recorded. The investigator further evaluated positive events of sleep attack reported by the subject prior to unblinding during placebo controlled studies (Studies XP052, XP053, XP081) and during the double blind phase of Study XP060.

The SOS Questionnaire defines Sleep Attack as “A sudden onset of sleep that is irresistible and overwhelming and comes without warning.”

The SOS consists of three questions:

1. In the past week, have you had any sleep attacks?
 - a. Yes
 - b. No
2. In the past week, how many sleep attacks did you have? _____
3. What were you doing when the sleep attack(s) occurred?
 - a. Passive activities (e.g., resting, reading, watching TV)
 - b. Active activities (e.g., eating, conversation, driving)
 - c. Both active and passive activities

Sudden Onset of Sleep Questionnaire Results (sponsor table)

Table 113 Sudden Onset of Sleep Questionnaire Results for Confirmed and Unable to Determine Events (Safety Population: 12-Week Placebo-Controlled RLS Studies)

	Placebo (N=245)	XP13512 600 mg (N=163)	XP13512 1200 mg (N=269)	XP13512 1800 mg (N=38)	XP13512 2400 mg (N=45)	XP13512 All Doses (N=515)
Baseline						
n	201	161	225	38	45	469
Any sleep attacks in past week, n (%)	2 (<1)	0	4 (2)	0	1 (2)	5 (1)
Number of sleep attacks in past week		0		0		
Mean (SD)	4.5 (2.12)		3.3 (0.50)		1.0 (NA)	2.8 (1.1)
Median	4.5		3.0		1.0	3.0
Any On Treatment Visit						
n	225	157	250	35	44	486
Any sleep attacks in past week, n (%)	5 (2)	0	1 (<1)	0	3(7)	4 (<1)
Number of sleep attacks in past week		0		0		
Mean (SD)	2.2 (1.10)		3.0 (NA)		2.3 (1.15)	2.5 (1.00)
Median	2.0		3.0		3.0	3.0

Data Source: Table 5.35

Study 053 Epiworth Sleepiness Scale Study 053 (sponsor table)

Table 53 Epworth Sleepiness Scale Score by Visit (Safety Population: Study XP053)

	Placebo N=96		Change from Baseline		XP13512 600 mg N=115		Change from Baseline		XP13512 1200 mg N=111		Change from Baseline	
	N	Mean (SD)	N	Mean (CI)	N	Mean (SD)	N	Mean (CI)	N	Mean (SD)	N	Mean (CI)
Day 1	96	9.6 (4.98)			113	9.7 (5.22)			110	9.0 (4.76)		
End of Week 4	84	7.8 (4.92)	84	-2.0 (-2.7, -1.3)	103	7.7 (4.83)	101	-2.2 (-3.1, -1.4)	100	6.8 (4.39)	99	-2.3 (-3.0, -1.5)
End of Week 8	78	7.6 (5.21)	78	-2.3 (-3.1, -1.5)	104	7.2 (4.73)	102	-2.6 (-3.5, -1.7)	98	5.9 (4.02)	97	-3.2 (-4.0, -2.4)
End of Week 12	89	7.3 (5.09)	89	-2.4 (-3.2, -1.5)	110	7.0 (4.54)	108	-2.9 (-3.8, -1.9)	109	6.2 (4.68)	108	-2.8 (-3.7, -2.0)

Data Source: DSTable 8.28

CDTL Comment

Sudden onset of sleep (SOS) is an adverse event associated with most often associated dopamine agonist treatment in patients with Parkinson’s disease. SOS that occurs while driving is one of the most worrisome times when SOS can happen. The Epiworth sleepiness scale (ESS) is a predictor of daytime sleepiness, however it is not clear that it captures SOS or that SOS is always associated with a

feeling of excess daytime sleepiness. There are no universally accepted and validated scales that reliably capture SOS. The sponsor's patient reported outcome (the SOS-Q) is not a validated or universally recognized measure for SOS. The results of the Epiworth Sleepiness Scale (ESS) suggest that daytime sleepiness in patients treated with XP13512 is only slightly higher than placebo and seems to improve with time.

Augmentation

Based on the 12-Week Placebo-Controlled RLS studies, a smaller proportion of subjects in the XP13512 treatment groups reported earlier onset of symptoms compared with baseline at all of the on-treatment visits relative to placebo. In general, there was no pattern of earlier symptom onset that would suggest augmentation associated with up to 64 weeks or more of treatment with XP13512 based on results from exploratory analyses in the Long-term Integration grouping and XP Maintenance of Effect Study 060.

CDTL Comment

The finding that augmentation is not associated with XP13512 treatment is not surprising given the relatively short follow-up period (12 weeks in placebo controlled trials). Augmentation is most often attributed to long-term levodopa treatment of RLS. In patients treated with levodopa, augmentation typically requires long-term treatment (Garcia-Borreguero, 2007). The association of augmentation with treatment of RLS with dopamine agonists has not been adequately evaluated (Trenkwalder, 2008). The sponsor should not be allowed to include claims in the label that XP13512 is associated with a lower incidence of augmentation until they perform a well designed trial to systematically evaluate augmentation.

Rebound

The design of Study XP060 which included a post randomization taper phase (double blind phase Weeks 26-28) provided the best opportunity to compare placebo and the 1200mg dose of XP13512 (n=194) for evidence of rebound in the taper period and the period following taper. The distribution of time to relapse events in Study XP060 does not suggest rebound (worsening) of RLS symptoms during taper or following discontinuation of study medication. There was no increase in IRLS scores among patients treated with XP13512 to or worse than their baseline scores during the taper and withdrawal for XP13512 during the randomized withdrawal portion (Double Blind) portion of the study.

Early Morning Rebound

The sponsor studied the change from baseline in number of 30-minute time periods in patients with moderate to severe, or severe RLS symptoms present from 8AM to 11:59AM, across the 12-Week Placebo-Controlled RLS studies.

At baseline, the number of 30-minute periods with moderate to severe RLS symptoms was similar across all treatment groups in each of the studies (range: 0.4 to 0.9). There were small decreases in the number of intervals with moderate or severe RLS symptoms at the end of Week 12 compared with

baseline in all XP13512 treated groups (range at Week 12: 0 to 0.6) as well as the placebo group (0.3 intervals). Similarly, the duration of severe symptoms reported in the 8AM to 11:59AM time interval was decreased or unchanged at Week 12 compared to baseline in all treatment groups.

CDTL Comment

The XP060 study presented an opportunity to evaluate for EMR in a well controlled clinical trials environment. Although, the time period studied may not have been early enough to capture EMR, which can occur from 12 midnight to 10 AM (Garcia-Borreguero, 2007).

Impulse Control Disorders (ICD)

The sponsor reported there were no AEs associated with impulse control symptoms including compulsive behaviors in the 12-Week Placebo Controlled Studies for subjects who received XP13512. The sponsor conducted a search of reported adverse events by preferred terms possibly related to ICD.

AE Search Terms

Preferred terms included: gambling, gambling pathological, high risk sexual behavior, libido increased, obsessive thoughts, obsessive-compulsive disorder, obsessive-compulsive personality disorder, sexual activity increased, obsessive rumination, libido disorder, feeling of despair, thinking abnormal, eating disorder, excessive eating, agitation, hypomania, mania, emotional disorder, emotional distress, euphoric mood, mood altered, mood swings, disturbance in social behavior, personality change, personality disorder, abnormal behavior, alcoholism, mental disorder, mental status changes, psychotic disorder, disturbance in sexual arousal, exhibitionism, male orgasmic disorder, economic problem, promiscuity, sexual abuse, drug abuser, hyperphagia, impulsive behavior, disinhibition, excessive masturbation, alcohol use, alcohol abuse, alcohol problem or Verbatim text search for strings containing “shop” or “eat” (added by sponsor).

Terms meeting at least one of the following criteria are included:

- Any term including “gambling” or “high risk sexual behavior” or “libido increased”, or “increased shopping” or “increased eating” **OR**
- Any term including “obsess” or “compuls” or “libido” **AND** verbatim term suggests gambling, shopping, eating or sexual behavior **OR**
- Any term specifying a host of personality or psychiatric disorders (e. g. mania) **AND** verbatim text suggests compulsion.

CDTL Comments

Review of the narratives and tabular data for the subjects identified by first broad and then filtered by narrow search criteria failed to identify a single case of ICD in the 12 week placebo controlled efficacy trials. ICD have been reported in patients with RLS treated with dopamine agonist medications. ICD is most frequently associated with the use of dopamine agonists in patients with

Parkinson's disease. The sponsor did not conduct a similar analysis of the long-term data at the time of the 120 day cut-off. The search of preferred terms is only minimally better to passive surveillance. Currently the agency usually recommends that clinical trials monitor for ICDs (where appropriate) by administering a questionnaire (mMIDI) that actively clinical trials participants about symptoms of ICD. This reviewer's opinion is that a claim that XP13512 is associated with a reduced rate of ICD compared to dopamine agonists should not be allowed in labeling unless an active comparator study is performed that systematically examines this question.

Cognitive Changes Associated with XP13512

The analysis of cognitive change was performed using data from the Brief Assessment of Cognition (BAC) score based on Week 12 data from Studies XP053 and XP081 and XP083.

For the significant effects seen for the BAC Total Score at Final Visit, the differences between the placebo and XP13512 were -1.63 for the 1200 mg group, -2.35 for the 1800 mg group, and -1.58 for XP13512 All Doses group. More improvement was seen for subjects in the placebo group compared with the XP13512 group, differences that were generally half the size of the improvements seen in the change from baseline (ranging from 3.4 to 5.8). Thus while there were statistically significant treatment differences between the XP13512 all doses group, 1200 mg and 1800 mg groups compared with placebo in the BAC Total Score at the Final Visit, they were very small and resulted from slightly larger improvements observed in the placebo group rather than from decreases in cognitive performance observed in the XP13512 groups. A similar effect was seen at Week 12 final visit for the 1200 mg, 1800 mg, and All Doses XP13512 dose groups compared to Placebo.

Overall, changes from baseline in the BAC Total Score at Weeks 2, 4, 12/ET and the Final Visit (LOCF) for subjects in both the placebo and XP13512 groups were all positive, showing improvements in cognitive performance at each visit relative to the baseline visit. The change values ranged from 2.1 to 6.1, less than one standard deviation, suggesting that the improvements in cognitive performance, while consistent were small.

Change from Baseline in Brief Assessment of Cognition Scores By Dose of XP13512 (sponsor table)

Table 201 BAC Total Score: Analysis of Covariance and Adjusted Mean Change from Baseline by Visit and at the Final Visit - LOCF (Safety Population: Combined Studies XP053, XP081 and XP083)

BAC Total Score		Individual Dose Comparisons					All Dose Comparison	
		Placebo ¹ N=201	XP13512 600 mg N=163	XP13512 1200 mg N=187	XP13512 1800 mg N=72	XP13512 2400 mg N=45	Placebo ¹ N=201	XP13512 All Doses N=467
Adjusted change from baseline ² - Week 2	Mean (SE)	6.5 (0.91)	-	5.5 (1.26)	5.0 (1.17)	-	6.5 (0.90)	5.2 (0.87)
Adjusted treatment difference ³ at Week 2 XP13512-Pbo ³	Mean 95% CI P-Value	-	-	-1.04 (-3.98, 1.91) 0.487	-1.54 (-4.47, 1.40) 0.302	-	-	-1.29 (-3.70, 1.12) 0.291
Adjusted change from baseline ² - Week 4	Mean (SE)	2.8 (1.03)	3.6 (0.96)	2.2 (1.04)	2.7 (1.07)	2.5 (1.01)	2.8 (1.03)	2.8 (0.56)
Adjusted treatment difference ³ at Week 4 XP13512-Pbo	Mean 95% CI P-Value	-	0.88 (-1.82, 3.58) 0.521	-0.51 (-3.30, 2.28) 0.717	-0.03 (-2.86, 2.80) 0.984	-0.22 (-2.98, 2.55) 0.876	-	0.06 (-2.13, 2.25) 0.957
Adjusted change from baseline ² - Week 12/ET	Mean (SE)	5.7 (0.62)	4.3 (0.57)	3.9 (0.59)	2.9 (1.24)	5.0 (1.20)	5.7 (0.61)	4.1 (0.37)
Adjusted treatment difference ³ at Week 12/ET XP13512-Pbo ³	Mean 95% CI P-Value	-	-1.41 (-2.96, 0.14) 0.074	-1.75 (-3.33, -0.18) 0.029	-2.84 (-5.65, -0.03) 0.047	-0.66 (-3.40, 2.08) 0.638	-	-1.59 (-2.93, -0.25) 0.020
Adjusted change from baseline ² - Final Visit	Mean (SE)	5.8 0.49	4.6 0.60	4.2 0.53	3.4 0.82	4.9 1.15	5.8 0.49	5.8 0.49
Adjusted treatment difference ³ at Final Visit XP13512-Pbo ³	Mean 95% CI P-Value	-	-1.22 (-2.68, 0.25) 0.103	-1.63 (-3.00, -0.26) 0.020	-2.35 (-4.24, -0.46) 0.015	-0.85 (-3.35, 1.65) 0.506	-	-1.58 (-2.73, -0.44) 0.007

Source Data: Table 5.46 and Table 5.52.

1. Includes subjects randomized to placebo plus diphenhydramine treatment in Study XP083 (for visits prior to diphenhydramine administration only).
2. A positive change from baseline indicates improved cognitive performance.
3. A negative treatment differences indicates more impaired cognitive performance of the respective dose of XP13512 treatment relative to placebo.

CDTL Comments

The change in cognitive function is a result of a lesser degree of improvement in BAC scores in the XP13512 treated patients compared to those who received placebo. This should be interpreted as a worsening of cognitive function for XP13512 treated patients since their ability to improve their scores with repeated administration (practice effect) was likely impaired compared to those that received placebo.

Withdrawal Effects and Rebound

In the Phase II and Phase III clinical development program for RLS, study medication was to be tapered over a one week period for subjects receiving doses of at least 1200 mg, unless considered inappropriate (e.g. patient was experiencing a treatment related AE) in the judgment of the investigator. Subjects in Phase II studies XP021 and XP045 did not taper medication, and subjects entering directly into open label Study XP055 from parent Studies XP052 and XP053 did not taper before ending trial participation or entering open label trials. The Maintenance of Effect Study XP060 included 3 taper periods and likely provided the best opportunity to observe patients for acute withdrawal or rebound effect from stopping XP13512..

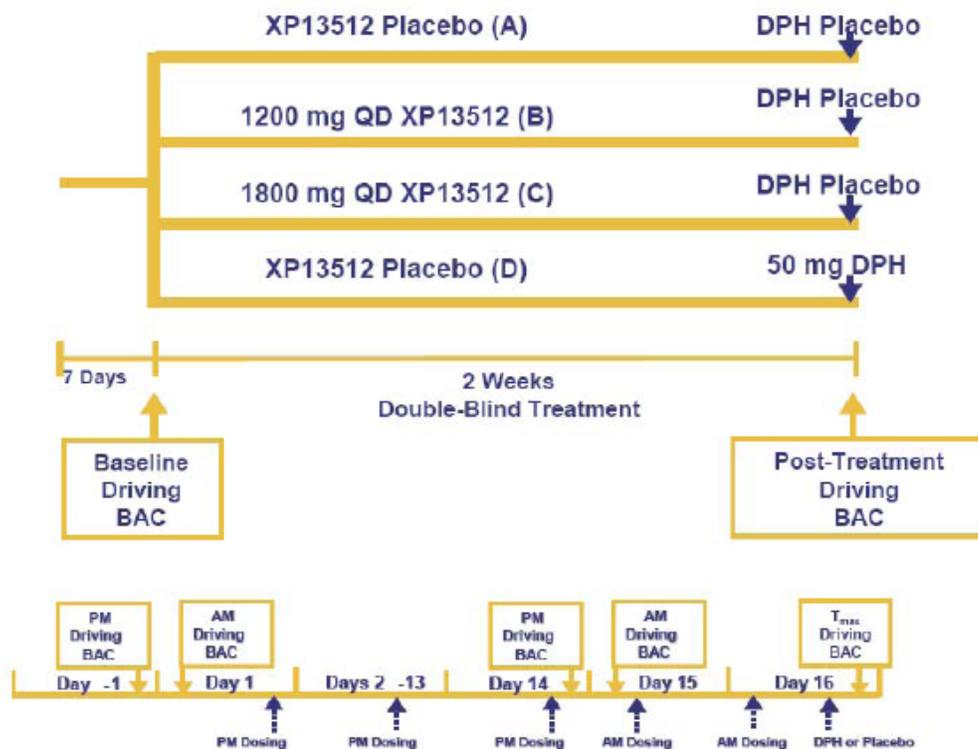
One XP13512-treated subject reported convulsion during the taper period following the DB phase of Study XP060 that was judged serious, possibly related to study medication and resulted in withdrawal from the study. This subject was subsequently found to have an abnormal EEG indicative of a possible underlying epileptic focus. No other TEAE were reported during the taper period was judged serious or resulted in withdrawal.

Overall, there was no evidence to indicate a rebound effect (worsening of RLS symptoms) following taper or discontinuation of XP13512 based on TEAEs and relapse events during taper phase.

Study Design of Study XP083 to Examine The Effect of XP13512 on Driving

This study is a randomized, double blind, placebo- and active-controlled, parallel group trial. The study evaluated the effect of XP13512 on simulated driving performance compared to placebo and diphenhydramine (active control).

Figure 1 Overall Study Design



Eligible RLS patients were randomly assigned to one of four treatment groups in a 1:1:1:1 ratio, including XP13512 1200 mg, XP13512 1800 mg, diphenhydramine 50 mg once, or matching placebo. After a 7-day Baseline assessment period, treatment was initiated, maintained, and discontinued as follows:

- On Days 1-3, patients received one tablet of study drug (XP13512 or matching placebo) at 5 PM with food

- On Days 4-7, patients received two tablets of the study drug (XP13512 or matching placebo) at 5 PM with food
- On Days 8-14, patients received three tablets of the study drug (XP13512 or matching placebo) at 5 PM with food
- On Day 15, patients received three tablets of the study drug (XP13512 or matching placebo) between 10 AM – 1 PM with food
- On Day 16, patients received three tablets of the study drug (XP13512 or matching placebo) between 10 AM – 1 PM (approximately 8 hours prior to the simulated driving test) with food. Also on Day 16 only, patients received 2 capsules of diphenhydramine (or matching placebo) 2 hours prior to the simulated driving test (e.g., 4 PM for a simulated driving test at 6 PM), which was followed by a snack one-hour post dose
- On Days 17-23, patients will enter the 7-Day Taper Period:
 - On Days 17-20, patients received 2 tablets of the study drug (XP13512 or matching placebo) at 5 PM with food
 - On Days 21-23, patients received one tablet of the study drug (XP13512 or matching placebo) at 5 PM with food. If a patient has dose-dependent side effects, the dose could be maintained until side effects abate, decreased to the prior dose level, or withheld for a few days and then re-instituted, as clinically indicated

Study XP083 Medication and Driving Schedule

Study Day	Time Study Medication Given	Time Driving Tested (clinical significant)
Baseline (Day -1 and Day 1)	N/A	5 PM (day-1) and 7 AM (day 1)
Day 14	5 PM (days 13-XP13512)	7 PM (2 hours post-dose driving)
Day 15	10 AM-1 PM (XP13512)	7 AM (next morning after dose)
Day 16	10 AM-1 PM -XP13512/placebo and diphenhydramine/placebo 2 hours before driving	5 PM peak dose XP13512 driving compared to active control (diphenhydramine) at peak dose

*Doses of XP13512 tested were 1200 mg and 1800 mg. The t_{1/2} of XP31512 is 5-7 hours

Driving Simulator

For the current study, STISIM *Drive*[™], a fixed-platform PC -based driving simulation system (Systems Technology, Inc., Hawthorne, California), was used. The simulator setup and placement of controls was similar to an actual car.

Primary Measure

- To assess simulated driving performance using the change in Baseline-adjusted mean lane position variability (LPV) after a XP13512 versus placebo dose, measured by simulated driving performance at T_{max} (day 16)

Driving, Alertness, and Cognition Measures

- To assess the change from Baseline to the end of treatment in simulated driving performance, measured by LPV, speed variation, brake reaction time, and crash frequency
- To assess alertness and cognition, measured by Epiworth Sleepiness Scale (ESS), Alertness Visual Analogue Scale (VAS), and brief assessment of cognition (BAC)

Results

At the Day 14 assessment, the adjusted mean changes from Baseline (Day -1) to Day 14 (PM) were -0.06 ft, -0.01 ft and -0.08 ft for the placebo, XP13512 1800 mg, and Placebo (Pbo)/Diphenhydramine (DPH) groups, respectively. The Pbo/DPH group received placebo on Day 14. The corresponding change was greater for the XP13512 1200 mg group (0.17 ft). The treatment difference between the XP13512 1200 mg group and placebo was 0.23 ft with 95% CI [0.09, 0.37].

At the Day 15 assessment, the adjusted mean change from Baseline (Day 1) to Day 15 (AM) was small for the placebo (-0.01 ft), XP13512 1800 mg (0.02 ft), and Pbo/DPH (who received placebo) (0.10 ft) groups. The corresponding change was numerically greater for the XP13512 1200 mg group (0.13 ft). The treatment difference was: 0.13 ft with 95% CI [-0.00, 0.28]) between the XP13512 1200 mg group and placebo group.

Change Lane Position Variability (LPV)

Table 12 Lane Position Variability at Baseline (Day -1 and Day 1), Day 14, and Day 15, and Change from Baseline (Day -1 or Day 1) to Day 14 and Day 15 in Overall (0 to 60 minutes) Lane Position Variability (MITT Population)

	Pbo	XP13512 1200 mg	XP13512 1800 mg	Pbo/DPH ^a	95% CI for Mean	ANOVA ^b
	N=33	N=28	N=33	N=28		
	Mean (SD)	Mean (SD)	Mean (SD)	Mean (SD)		95% CI for LS-Mean
Baseline (Day -1)	1.40 (0.32)	1.46 (0.32)	1.37 (0.20)	1.36 (0.25)		
Day 14	1.34 (0.38)	1.62 (0.62)	1.36 (0.38)	1.29 (0.26)		
Change from Baseline (Day -1) to Day 14						
Mean	-0.06 (0.17)	0.17 (0.43)	-0.01 (0.28)	-0.08 (0.15)		
LS Mean	-0.06 (0.05)	0.17 (0.05)	-0.01 (0.05)	-0.08 (0.05)		
XP13512 1200 mg – Pbo					0.06, 0.39	0.09, 0.37
XP13512 1800 mg – Pbo					-0.06, 0.17	-0.08, 0.19
Baseline (Day 1)	1.35 (0.28)	1.49 (0.36)	1.40 (0.29)	1.45 (0.35)		
Day 15	1.35 (0.31)	1.62 (0.45)	1.44 (0.46)	1.34 (0.28)		
Change from Baseline (Day 1) to Day 15						
Mean	-0.01 (0.14)	0.13 (0.40)	0.02 (0.32)	-0.10 (0.19)		
LS Mean	-0.01 (0.05)	0.13 (0.05)	0.02 (0.05)	-0.10 (0.05)		
XP13512 1200 mg – Pbo					-0.01, 0.29	-0.00, 0.28
XP13512 1800 mg – Pbo					-0.10, 0.15	-0.12, 0.16

Data Source: DSTable 8.4 and DSTable 9.4

- a. Pbo/DPH group received diphenhydramine on Day 16 only.
- b. Analysis was based on a repeated measures ANOVA model with fixed effects for treatment group, pooled site, visit, and treatment group by visit.

On day 14 (driving tested 2 hours post-dose) driving in the placebo group and in the diphenhydramine/placebo group (received placebo prior to testing on day 14) reported an improvement in mean LPV scores. The group treated with 1200 mg of XP13512 worsened (0.17) compared to the 1800 mg group who actually improved slightly indicated patients who received 1200 mg performed worse than those who received 1800 mg. The same worsening of the LPV scores for the 1200 mg group compared to the 1800 mg group was repeated on day 15 (morning after dose driving evaluation).

Table 11 Lane Position Variability at Baseline (Day -1) and Day 16, and Change from Baseline (Day -1) to Day 16 in Overall (0 to 60 minutes) Lane Position Variability in Feet (MITT Population)

	Pbo	XP13512 1200 mg	XP13512 1800 mg	Pbo/DPH ^a	95% CI for Mean	ANOVA ^b 95% CI for LS Mean
	N=33	N=28	N=33	N=28		
	Mean (SD)	Mean (SD)	Mean (SD)	Mean (SD)		
Baseline (Day -1)	1.40 (0.32)	1.46 (0.32)	1.37 (0.20)	1.36 (0.25)		
Day 16	1.26 (0.31)	1.61 (0.48)	1.52 (0.37)	1.52 (0.50)		
Change from Baseline to Day 16						
Mean (SD)	-0.11 (0.17)	0.15 (0.38)	0.15 (0.27)	0.16 (0.40)		
LS Mean (SE)	-0.10 (0.06)	0.15 (0.06)	0.15 (0.06)	0.16 (0.06)		
XP13512 1200 mg – Pbo					0.10, 0.41	0.08, 0.42
XP13512 1800 mg – Pbo					0.14, 0.37	0.09, 0.41
Pbo/DPH - Pbo					0.10, 0.43	0.09, 0.42
XP13512 1200 mg – Pbo/DPH					-0.22, 0.20	
XP13512 1800 mg – Pbo/DPH					-0.18, 0.17	

Data Source: DSTable 8.4 and DSTable 9.4

- a. Pbo/DPH group received diphenhydramine on Day 16 only.
- b. Analysis was based on a repeated measures ANOVA model with fixed effects for treatment group, pooled site, visit, and treatment group by visit.

On day 16, driving was tested at approximately the Tmax for XP13512 or if patients were assigned to the diphenhydramine or placebo group they were tested 2 hours after dosing. The placebo group experienced a mean improvement (-0.10) in LPV compared to the 1200 mg and 1800 mg groups that both worsened by 0.15 and the mean worsening reported in the diphenhydramine treated group was 0.16.

Number of Subjects with Simulated Crashes and Distribution of Simulated Crashes

At each of the Baseline (Day -1 or Day 1) assessments, a greater proportion of subjects in the XP13512 1200 mg group experienced simulated crashes compared with the placebo, XP13512 1800 mg, and Pbo/DPH groups (Day -1 [PM]: 6 (21.4%) vs. 3 (9.1%), 3 (9.1%), and 2 (7.1%), respectively; Day 1 [AM]: 4 (14.3%) vs. 1 (3.1%), 3 (9.4%), and 3 (11.1%), respectively).

At the Day 14 [PM] assessment, the number or proportion of subjects who had simulated crashes was greater for the XP13512 1200 mg group (6 [21.4%]) when compared with the other 3 groups: 4 (12.1%) for the placebo group, 1 (3.0%) for the XP13512 1800 mg group, and 1 (3.6%) for the

Pbo/DPH group (received placebo). Most subjects had 1 to 3 simulated crashes. Three subjects in the XP13512 1200 mg group each had 4, 5, and 13 crashes, respectively.

At the Day 15 [AM] assessment, a total of 10 subjects (35.7%) in the XP13512 1200 mg group experienced simulated crashes, an increase from 4 subjects (14.3%) at Baseline (Day 1). Seven of them had 1 to 2 simulated crashes, 2 subjects had 4 crashes, and 1 subject had 13 simulated crashes. The placebo and XP13512 1800 mg group each had 1 subject with 1 simulated crash. No subjects had simulated crashes in the Pbo/DPH group (received placebo).

At the Day 16 (estimated T_{max}) assessment, no subjects in the placebo group experienced simulated crashes, whereas all the active treatment groups had an increase from Baseline (Day -1) in the number of subjects with simulated crashes, with 8 (28.6%) in the XP13512 1200 mg group, 6 (18.2%) in the XP13512 1800 mg group, and 3 (10.7%) in the Pbo/DPH group. Most subjects had only 1 or 3 simulated crashes. One subject in the XP13512 1200 mg group and 1 subject in the Pbo/DPH group (received diphenhydramine) had 4 simulated crashes. One subject each in the XP13512 1200 mg and 1800 mg groups experienced 17 and 13 simulated crashes, respectively.

Table 14 Number of Subjects with Simulated Crashes at Baseline and Days 14, 15, and 16 (MITT Population)

	Pbo	XP13512 1200 mg	XP13512 1800 mg	Pbo/DPH ^a
	N=33	N=28	N=33	N=28
Number of Subjects with Crashes, n (%)				
Day -1	3 (9.1)	6 (21.4)	3 (9.1)	2 (7.1)
Day 1	1 (3.1)	4 (14.3)	3 (9.4)	3 (11.1)
Day 14	4 (12.1)	6 (21.4)	1 (3.0)	1 (3.6)
Day 15	1 (3.0)	10 (35.7)	1 (3.2)	0 (0)
Day 16	0 (0)	8 (28.6)	6 (18.2)	3 (10.7)

Data Source: DSTable 8.7.1

a. Pbo/DPH group received diphenhydramine on Day 16 only.

The number of crashes was higher on all testing days for the 1200 mg dose of XP13512 compared to placebo and the active control. Only at peak dose did the 1800 mg dose of XP13512 and active control groups perform worse than placebo.

CDTL Comment

The results from study XP083 for the 1200 and 1800 mg doses are inconsistent and do not indicate any dose ordering in the effect of XP13512 on driving. Study XP083 also did not evaluate the 600 mg/day dose. Single subjects who experienced a large number of simulated crashes on isolated testing days, which may skew the interpretation of the descriptive results, further confound the results. The results of study XP13512 appear to be of little value in predicting the effect of XP13512 on driving and did not include an evaluation of the 600 mg dose, which is likely to be the maximum recommended dose.

Evaluation of Gabapentin Post-Marketing Data for Reports of Carcinoma and Specifically Pancreatic Carcinoma.

Empirica Data-Mining of Carcinoma Related AERS Reports

A request was made of the FDA's Office of Surveillance and Epidemiology (OSE) to conduct a data-mining search of the AERS database for cases of carcinoma and pancreatic carcinoma because of the signal reported in the rat carcinogenicity study for both gabapentin and XP13512. The OSE reviewer used the following list of Preferred Terms to conduct the search.

Adenocarcinoma pancreas, Biopsy pancreas abnormal, Carcinoid tumour of the pancreas, Pancreatic carcinoma, Pancreatic carcinoma metastatic, Pancreatic carcinoma non-resectable, Pancreatic carcinoma recurrent, Pancreatic carcinoma resectable, Pancreatic carcinoma stage 0, Pancreatic carcinoma stage I, Pancreatic carcinoma stage II, Pancreatic carcinoma stage III, Pancreatic carcinoma stage IV, Pancreatic neuroendocrine tumour

The results showed 5 reports of pancreatic carcinoma, only. The EB05 score was only 0.330. Attached is the information from Empirica.

Case level information

Case 1 is a 48-year-old man (report filed by his attorney); the report mentioned the patient was taking Neurontin at an undisclosed dose and duration for chronic back pain. The attorney appears to be representing the patient for issues related to cisapride. The patient underwent cholecystectomy and had a diagnosis chronic pancreatitis and common bile duct stricture. An abdominal ultrasound was reportedly positive for a hypoechoic area "highly suspicious for occult pancreatic carcinoma" but the ultrasound finding remained unconfirmed.

Case 2 concerns a 66-year-old woman who was started on Neurontin 600 mg tid (5/2006) for pain associated with ovarian carcinoma in 2002. She received conventional treatment and in 8/2006, she was discovered to have metastasis to the lung and abdomen.

Case 3 follow up report sent in by a physician concerns a male patient (unknown age) reported to the FDA on 6/13/2002. The patient was treated for 3 years with Neurontin at an unknown dose and duration for symptoms of RLS and chronic insomnia. The patient was diagnosed with pancreatic carcinoma on an undisclosed date.

Case 4 was reported by a physician who was also the patient. The patient at the time of the report (5/7/2001) was a 75 year old male who reported a diagnosis of pancreatic carcinoma after taking Neurontin 400 mg tid for 3 years to treat symptoms of diabetic neuropathy.

Case 5 was reported by the wife of a 73-year-old male who received Neurontin 2700 mg/day (divided) for 8 years for a diagnosis of absence or partial seizure epilepsy as a result for a head injury. In May of 2004, the patient was diagnosed with a pancreatic mass with additional tumor in the liver on CT scan. The mass was biopsied but no information regarding the histopathology was provided in the report. The report indicated he had a diagnosis of "advanced pancreatic cancer" and he died (b) (6)

after diagnosis. The person providing the information in the report appeared to have some knowledge of medicine and the finding of pancreatic carcinoma in animal studies of Neurontin.

CDTL Comment

Three of the 5 cases appear to have reasonable information to call confirmed cases of patients who took Neurontin and later developed pancreatic carcinoma. Of course it not establish cause and effect and the comparison of the rate for pancreatic CA in the general population and its comparison to reporting rate for pancreatic CA associated with Neurontin is also unknown. The EB05 score is also low. These results are encouraging that the risk to humans taking gabapentin may be low but convincing evidence should be reinforced with additional data such case-control studies from large health care systems databases. Since the animal data in rats has been independently replicated in another companies development program, a better understanding of the animal signal would also be helpful. It remains unknown at this time but the signal in rats for pancreatic carcinoma could be species specific. A better understanding of the mechanism underlying the development of pancreatic carcinoma in the studies conducted in rats for both gabapentin and XP13512 could also prove helpful in evaluating the risk to humans.

CDTL Safety Conclusions

The most serious risk is the potential association of gabapentin (parent or derived from a prodrug) with an increased risk for carcinoma in particular pancreatic carcinoma. RLS is a disease that is not associated with an increased mortality or shortened life expectancy. The symptoms may be uncomfortable and in rare cases the symptoms may be disabling, most patients do not experience significant disease related morbidity or physical disability. Pancreatic carcinoma is difficult to detect in the early stages and the prognosis is usually very poor by the time the tumor is clinically apparent. The human correlate to the carcinoma signal detected in animals may not be equivalent and other forms of carcinoma besides pancreatic cancer may result. The potential for depriving patients with RLS of a uniquely effective treatment for their illness, is in this reviewer's opinion extremely unlikely. There are two approved treatments for the exact same indication that is being sought by the sponsor of this product. Both of the approved medications, while not free of adverse effects, neither is associated with a safety signal in animal studies suggesting a potential increased risk for pancreatic carcinoma.

Sedation (and somnolence) is the other major risk associated with this medication, accounting for 50% of the patients who withdrew from clinical trials because of an adverse event. Most concerning is the potential to cause reduced performance during activities that are cognitively demanding and require high levels of attention such as driving. The effect of the 600 mg dose on driving has not been studied in simulated driving.

There is also the issue of a potential increased risk for suicidality associated with taking anti-epileptic medications that applies to gabapentin even in patients treated for indications besides epilepsy. This will be addressed by adopting call labeling for anti-convulsant drugs regarding the increased risk for suicidality associated with this class of drugs.

The applicant has not presented information or an adequate explanation that addresses these safety concerns making it impossible to assess the potential risk for carcinoma and effects on driving/cognition in RLS patients for the 600 mg/day dose. Add to this, the potential for considerable use in indications where gabapentin is approved and also in situations where gabapentin is used off label. There is the potential for over dosing that may result from the assumption that the dose of gabapentin enacarbil ER is a 1 to 1 conversion from the standard gabapentin product, when in reality the exposure associated with gabapentin enacarbil is much higher on a per mg basis compared to the approved gabapentin product. The approved dose of gabapentin is between 1200 and 1800 mg/day divided. A misguided 1 to 1 switch to gabapentin enacarbil would result in exposures similar to taking 2400 to 3600 mg of the approved gabapentin product leading to sedation. At the high levels of exposure to gabapentin enacarbil, the 8 fold margin of safety between the exposure associated with 600 mg dose in humans and the exposure levels of exposure associated with pancreatic carcinoma in male rats would approach 1 fold.

Follow-up actions by DNP include opening a DARRTS trackable safety issue and requesting a formal consult to OSE to evaluate the reporting frequency of carcinoma, pancreatic carcinoma as well as benign and malignant tumors of the uterus and vagina associated with gabapentin.

6 Pediatrics

The PeRC granted a waiver for patients age 12 years and below. A deferral was granted for children ages 13-16 years until the gabapentin enacarbil is approved in adults. The sponsor submitted a pediatric plan, which has been reviewed by PeRC and judged to be acceptable. The following pediatric postmarketing requirements are under review by PeRC with a decision expected by 1/29/10.

Proposed Pediatric Postmarketing Requirements:

1. Children ages ≥ 13 years to 17 years with moderate to severe symptoms of primary Restless Legs Syndrome. PK/PD study, including development of age appropriate dose(s) designed to identification of the lowest maximally effective in this age group. At a minimum, the 300 mg/day, 450 mg/day, 600 mg/day and 1200 mg/day oral doses must be included in this PK/PD study.
2. An efficacy and safety evaluation study, designed as a double-blind, randomized, placebo controlled, parallel groups. Children ages ≥ 13 years to 17 years with moderate to severe symptoms of Primary Restless Legs Syndrome must be maintained and monitored on targeted doses of study medication for at least 12 weeks. The primary outcome measure must include the IRLSS Scale Score and a co-primary global rating, along with standard measures of safety (clinical-including signs and symptoms-and laboratory). Safety measures must also include monitoring of cognitive/neuropsychiatric (including behavioral) effects of gabapentin enacarbil. It must also monitor for the potential risk for increased suicidality.
3. Children ages ≥ 13 years to 17 years with moderate to severe symptoms of primary Restless Legs Syndrome. The study must provide a descriptive analysis of safety data in pediatric patients during long-term treatment (at least 12 months of continuous treatment) with gabapentin enacarbil at individualized doses. The number of patients exposed to gabapentin enacarbil must meet or exceed the

ICH recommendation of 100 patients for 12 months at any dose with the substantial majority of patients exposed to the highest dose for 12 months.

4. Driving study in ≥ 15 -17 year old population using diphenhydramine as active control. The dose(s) of gabapentin enacarbil should evaluate the full range of doses of gabapentin enacarbil that has been determined to be safe and effective for use in children ages ≥ 15 years to 17 years with moderate to severe symptoms of primary Restless Legs Syndrome.

7. Other Relevant Regulatory Issues

DSI Inspection Reports

DSI Inspection Sites

Name of CI, or Sponsor site # and location	Protocol and # of subjects	Inspection Dates	Final Classification
Albert Razzetti, M.D.	XP052	6/1-5/09	VAI
UCR Deland Inc. 860 Peachwood Drive Deland, FL 327206441	18 subjects		
William Ellison, M.D. 552-A Memorial Dr. Greer, SC 29651	XP052 18 subjects	5/27-29/09	NAI
James Garrison, M.D	XP053	4/28-5/1/09	NAI
54 Fredricksburg Rd, Suite 400 San Antonio, TX 78229	29		
Kurt w. Lesh, M.D.	XP053	5/25-6/2/09	VAI
Lynn Institute 2500 North Circle Dr. Colorado Springs, CO 80909	27 subjects		
GSK (Sponsor) Reasrech Triangle Park, NC 27709	XP052 47	6/9-11/09	NAI

DSI OVERALL ASSESSMENT OF FINDINGS AND GENERAL RECOMMENDATIONS

Four clinical investigators and the sponsor, GSK, were inspected in support of this application. There was sufficient documentation to assure that all audited subjects at the sites of Drs. Razzetti, Ellison, Garrison and Lesh did exist, fulfilled the eligibility criteria, and had their primary efficacy endpoint captured as specified in the protocol. Overall, the inspection of the individual study sites was adequate.

REMS Review

The proposed REMS was reviewed by DRISK and the comments were forwarded to the sponsor with a completed REMS document expected shortly. The REMS contains a medication Guide. The review of the medication guide is complete (DRISK) and it will be forwarded to the sponsor if and when gabapentin enacarbil is apprived. The REMS and Medication Guide will include the same comments regarding the potential increased risk for suicidality associated with anticonvulsant mediations.

Post Marketing Requirements and Commitments

The agency has been negotiating PMRs and PMCs with the sponsor only two issues remain unresolved. The Agency's latest counter proposals to PMR #1 and PMC #1 were forwarded to the sponsor. GSK will need to update the milestone dates proposed with the PMRs and PMCs. They will likely change significantly if the applicant submits a complete response to this action.

FDA Comments: Please see the FDA counter proposals to GSK' proposed revisions for PMC#1 and PMR #1. The remaining PMR are acceptable but the proposed milestone dates will need to be updated.

PMC #1

FDA Proposed: Randomized, placebo controlled, double blind, parallel groups clinical trial of several doses of gabapentin enacarbil below 600 mg/day. The study design should be adequately powered to be able to demonstrate a statistically and clinically significant benefit compared to placebo in patients with moderate to severe symptoms of RLS. The duration must be sufficient to demonstrate that benefit is maintained for a period of at least 12 weeks.

GSK Revised Proposed:

(b) (4)

FDA Revised Proposed: Randomized, placebo controlled, double blind, parallel groups clinical trial of gabapentin enacarbil at 300 mg/day, 450 mg/day and 600 mg/day. The study design should be adequately powered to be able to demonstrate a statistically and clinically significant benefit compared to placebo in patients with moderate to severe symptoms of RLS. The duration must be sufficient to demonstrate that benefit is maintained for a period of at least 12 weeks.

Estimated Submission of SPA: March 2010

Estimated Submission of Final Protocol: 8 weeks after receipt of SPA comments from FDA

Estimated Study Completion: Study initiated 3 months after FDA agreement on the final protocol; study duration 25 months

Estimated Submission of Final Report: 6 months from study completion

PMR #1

FDA Proposed: A simulated driving trial in patients with moderate to severe symptoms of RLS treated with the newly established minimum maximally effective dose of gabapentin enacarbil. The trial must contain an active comparator and placebo arms in addition to the new minimum maximally effective dose of gabapentin enacarbil. The trial must be designed to at least study the effect of gabapentin enacarbil at timepoints between dosing at 5PM to Cmax and a separate evaluation on the morning following dosing at 5PM, to simulate times when patients will be likely to drive after taking gabapentin enacarbil.

GSK Revised Proposed:

 (b) (4)

FDA Revised Proposed: A simulated driving trial in patients with moderate to severe symptoms of RLS treated with 300 mg 450 mg and 600 mg gabapentin enacarbil. The trial must contain an active comparator and placebo arms in addition to 300 mg, 450 mg and 600 mg of gabapentin enacarbil. The trial must be designed to at least evaluate the effect of gabapentin enacarbil at timepoints between dosing at 5 PM (*or an alternative time of administration*) to Cmax and a separate evaluation on the morning following dosing at 5PM, to simulate times when patients will be likely to drive after taking gabapentin enacarbil.

Estimated Submission of Final Protocol: March 2010

Estimated Study Completion: Study initiated 4 months after FDA agreement on the final protocol; study duration 13 months

Estimated Submission of Final Report: 6 months from study completion

PMR #2

FDA Proposed: A simulated driving trial in patients with moderate to severe symptoms of RLS treated with 600 mg gabapentin enacarbil. The trial must contain an active comparator and placebo arms in addition to 600 mg/day of gabapentin enacarbil. The trial must be designed to at least evaluate the effect of gabapentin enacarbil at timepoints between dosing at 5 PM (*or an alternative time of administration*) to Cmax and a separate evaluation on the

morning following dosing at 5PM, to simulate times when patients will be likely to drive after taking gabapentin enacarbil.

GSK Revised Proposed: [REDACTED] (b) (4)

PMR #3

FDA Proposed: Conduct an in vitro study to evaluate the potential of gabapentin enacarbil (XP13512) and gabapentin to be an inhibitor of CYP2C8 and 2B6.

GSK Response: GSK agree to conduct the proposed study.

Estimated Submission of Final Protocol: [REDACTED] (b) (4)

Estimated Study Completion: [REDACTED] (b) (4)

Estimated Submission of Final Report: [REDACTED] (b) (4)

PMR #4

FDA Proposed: Develop a dosage form that will allow for a 300 mg dose that could be taken once daily in patients with severe renal impairment including patients on hemodialysis.

GSK Response: [REDACTED] (b) (4)

[REDACTED] (b) (4)

PMR #5

FDA Proposed: Conduct an in vitro dissolution study to evaluate alcohol dose dumping using the final dissolution method, and evaluate different concentrations of alcohol up to 40% (0, 5, 10, 20, and 40%).

GSK Response: GSK agree to conduct the proposed in vitro dissolution study using the approved dissolution method.

Estimated Submission of Data: [REDACTED] (b) (4)

PMR #6

FDA Proposed: The sponsor must conduct an adequate randomized, double-blind, placebo- and moxifloxacin controlled study to evaluate the effect of XP13512 on cardiac repolarization in healthy adult subjects.

GSK Response: GSK agree to conduct the proposed study.

Estimated Submission of Final Protocol: (b) (4)
Estimated Study Completion: (b) (4)
Estimated Submission of Final Report: (b) (4)

Financial Disclosures

On 14 December 2007, a Pre-NDA meeting was held between XenoPort, GSK and the Division of Neurology Products, this was the agency’s first knowledge of involvement of GSK’s involvement with the development of XP13512 (gabapentin enacarbil). On April 8, 2008 (Serial No. 0146), sponsorship of IND 71,352 was transferred to GSK as XenoPort’s joint development partner of GSK1838262 ER Tablets for primary RLS. XenoPort, Inc. filed the initial IND application and was the sponsor of the studies during study conduct; however, GlaxoSmithKline is the NDA applicant for this submission.

Financial Disclosures for Clinical Trials Included in The Application

Xenoport Study Number	GSK Study Number	Protocol Title	Overall Study Start Date	Overall Study Completion Date
XP021	RXP111457	A Randomized, Double-Blind, Placebo-Controlled, Crossover Study to Assess the Safety and Efficacy of XP13512 in Patients with Restless Legs Syndrome	09 JUN 2004	01 DEC 2004
XP045	RXP111409	A Randomized, Double-Blind, Placebo-Controlled Study to Assess the Safety and Efficacy of Once Daily XP13512 in Patients with Restless Legs Syndrome	31 JAN 2005	08 JUN 2005
XP052	RXP110963	A Randomized, Double-Blind, Placebo-Controlled Study to Assess the Efficacy and Safety of XP13512 in Patients with Restless Legs Syndrome	13 MAR 2006	22 FEB 2007
XP053	RXP111460	A Randomized, Double-Blind, Placebo-Controlled Study to Assess the Efficacy and Safety of XP13512 in Patients with Restless Legs Syndrome	21 AUG 2006	20 DEC 2007
XP060	RXP111461	A Long Term Study of XP13512 Versus Placebo Treatment Assessing Maintenance of Efficacy and Safety in Patients with Restless Legs Syndrome	18 APR 2006	14 NOV 2007

Xenoport Study Number	GSK Study Number	Protocol Title	Overall Study Start Date	Overall Study Completion Date
XP081	RXP111462	A Randomized, Double-Blind, Placebo-Controlled, Dose-Response Study to Assess the Efficacy, Safety, and Pharmacokinetics of XP13512 in Patients with Restless Legs Syndrome	16 JAN 2007	10 JAN 2008
XP078	RXP111421	A Randomized, Double-Blind, Placebo- and Active-Controlled, Four-Period Crossover Study To Evaluate the Effect of XP13512 on Cardiac Repolarization by Thorough Analysis of QTc Effect in Healthy Adult Subjects	20 JUL 2007	03 NOV 2007
XP083	RXP111463	A Randomized, Double-Blind, Active- and Placebo-Controlled Parallel Group Study Assessing the Effect of XP13512 on Simulated Driving in Patients with Restless Legs Syndrome	09 APR 2007	09 NOV 2007

Xenoport Financial Disclosures (FD)

There were no investigators reported by Xenoport as having a disclosable financial relationship with the company during the time of clinical trial participation. Xenoport was unable to obtain FDs for about 6-18 subinvestigators in each of the pivotal efficacy trials. The missing FDs often involved multiple study personnel from the same site. There was only 1 study (XP060) where a single P.I. that did not submit a financial disclosure.

GlaxoSmithKline Financial Disclosures (FD)

There is one disclosure per study in this category for Studies (b) (6) as described below, as a result of exceeding the \$25,000 threshold for payments from GlaxoSmithKline:

Dr. (b) (6) This investigator received \$36,375.00 in retainer fees for consulting services from GSK. He recruited (b) (6) randomized into (b) (6) (total n=(b) (6)). It is unlikely Dr. (b) (6) or personnel at his site had the potential of biasing the outcome or conclusions for study (b) (6).

Dr. (b) (6) This investigator received \$300,000.00 from GSK in the form of research funding. He recruited (b) (6) randomized into study (b) (6) (total n=(b) (6)). No analysis was conducted by the sponsor to explore the effect of this site on the results of the study but it is unlikely that Dr. (b) (6) or site personnel could bias the outcome or conclusions for study (b) (6).

Dr. (b) (6) This investigator received \$63,375.00 and \$26,000.00 in honoraria. He recruited (b) (6) of all subjects randomized into (b) (6), with (b) (6) to placebo and (b) (6) to the (b) (6) group. None of these subjects met the primary endpoint definition of relapse; therefore, the site did not have the potential of biasing the outcome or conclusions. He also recruited (b) (6) of all subjects randomized into (b) (6), which had (b) (6).

The sponsor did not conduct a formal analysis to explore the effect of this site on the results of the study. Patients were distributed approximately equally across all treatment groups and GSK concluded this site did not have the potential to bias the outcome or conclusions of the study.

Many of the responses for GSK's financial disclosures were missing data from the investigators and site personnel. GSK was made the request for FDs in some cases 4 years after the trials concluded, therefore it is plausible in many cases the study personnel could not be located. GSK also reported that the filing timeline was short and they were not able to locate study personnel in time to file the application.

CDTL Comment

Overall, the FDs for Xenoport and GSK were acceptable. GSK requested FDs late in the course of development, therefore much of the FD data is incomplete. GSK reported disclosable financial relationships with 3 investigators. Xenoport chose the investigators and they conducted the trials at a time when GSK reported they were not a stakeholder in XP13512. GSK reported they were not a stakeholder in XP13512 until the pivotal efficacy trials were completed. It is unlikely that study site personnel with a significant financial relationship with GSK would have influenced the efficacy trials conducted by Xenoport. In addition, the number of patients enrolled by the investigators with disclosable relationships with GSK was too small to effect the efficacy conclusion of the respective trials.

Disbarment Certification

The applicant certified that none of the names of the clinical trials personnel appeared on the FDA's disbarment list. A review of the study site investigators listed for studies XP052, 053, and 081 (pivotal efficacy trials) did not find any names of investigators that appeared on the agency's disbarment list.

8. Labeling

Proprietary name **Horizant**

All of the following issues will need to be negotiated with the sponsor if and when this drug is approved on resubmission.

- Physician labeling
- Highlight major issues that were discussed, resolved, or not resolved at the time of completion of the CDTL review.
- Carton and immediate container labels
- Patient labeling/Medication guide

9. Recommendations/Risk Benefit Assessment

Recommended Regulatory Action

Complete Response –based on safety concerns.

Risk Benefit Assessment

Benefits

Gabapentin enacarbil has demonstrated effectiveness in two adequately controlled clinical trials. The sponsor requested approval of 1200 mg/day as the recommended dose, however there was no meaningful additional benefit associated with doses above 600 mg/day. If approved, the recommended dose of gabapentin enacarbil should be 600 mg/day.

Potential Risks

The signal for pancreatic carcinoma observed in rats during the carcinogenicity studies for gabapentin enacarbil occurred at lower doses, both genders and in more animals compared to rats in the gabapentin carcinogenicity studies, indicating a potentially increased risk to humans. The projected margin of exposure between humans taking 600 mg/day of gabapentin enacarbil and the exposures associated with pancreatic carcinoma in male rats is only 8 fold. There is no absolute margin of exposure that can be used to conclude safe levels of human exposure based on animal data but a margin of 8 fold raises concern from the Clinical and Pharmacology Toxicology review team members. RLS is also a non-life-threatening illness with approved medications available to treat the symptoms of the illness that do not have the same animal signal for pancreatic carcinoma. Pancreatic carcinoma is a rapidly progressing form of cancer with poor early detection and survival. If the association of gabapentin enacarbil and an increased risk for pancreatic carcinoma in humans is true, it would greatly affect the risk benefit ratio against approval. Before gabapentin enacarbil and perhaps before any gabapentin product is approved for the treatment of RLS, the potential risk for pancreatic carcinoma in humans caused by gabapentin must be more clearly defined.

Recommendation for Postmarketing Risk Management Activities

See section 6 of this review.

Recommendation for other Postmarketing Study Commitments

See section 6 of this review.

Recommended Comments to Applicant

- Update the ISS with the data from the final study report from study XP055. List all patient exposures in days not only patient-years.
- Please list all exposures by modal dose and duration for all flexible dose trails of XP13512

- Please include a detailed accounting of the reasons why patients discontinued trial participation for patients listed as “withdrew consent” or “lost to follow-up” for all pivotal efficacy trials, long-term safety studies and long-term maintenance of effect trials (study XP060).
- Please conduct a driving safety study on the maximally effective minimum dose of XP13512.

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Application Type/Number	Submission Type/Number	Submitter Name	Product Name
NDA-22399	ORIG-1	GLAXO GROUP LTD DBA GLAXOSMITHKLIN E	SOLZIRA

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/s/

GERALD D PODSKALNY
02/10/2010
Amended CDTL Review