

**CENTER FOR DRUG EVALUATION AND
RESEARCH**

APPLICATION NUMBER:

022399Orig1s000

OTHER REVIEW(S)

3. If the study/clinical trial is a **PMR**, check the applicable regulation.

If not a PMR, skip to 4.

- **Which regulation?**

- Accelerated Approval (subpart H/E)
- Animal Efficacy Rule
- Pediatric Research Equity Act
- FDAAA required safety study/clinical trial

- **If the PMR is a FDAAA safety study/clinical trial, does it: (check all that apply)**

- Assess a known serious risk related to the use of the drug?
- Assess signals of serious risk related to the use of the drug?
- Identify an unexpected serious risk when available data indicate the potential for a serious risk?

- **If the PMR is a FDAAA safety study/clinical trial, will it be conducted as:**

- Analysis of spontaneous postmarketing adverse events?
Do not select the above study/clinical trial type if: such an analysis will not be sufficient to assess or identify a serious risk
- Analysis using pharmacovigilance system?
Do not select the above study/clinical trial type if: the new pharmacovigilance system that the FDA is required to establish under section 505(k)(3) has not yet been established and is thus not sufficient to assess this known serious risk, or has been established but is nevertheless not sufficient to assess or identify a serious risk
- Study: all other investigations, such as investigations in humans that are not clinical trials as defined below (e.g., observational epidemiologic studies), animal studies, and laboratory experiments?
Do not select the above study type if: a study will not be sufficient to identify or assess a serious risk
- Clinical trial: any prospective investigation in which the sponsor or investigator determines the method of assigning investigational product or other interventions to one or more human subjects?

4. What type of study or clinical trial is required or agreed upon (describe and check type below)? If the study or trial will be performed in a subpopulation, list here.

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

Required

- Observational pharmacoepidemiologic study
- Registry studies

Continuation of Question 4

- Primary safety study or clinical trial
 - Pharmacogenetic or pharmacogenomic study or clinical trial if required to further assess safety
 - Thorough Q-T clinical trial
 - Nonclinical (animal) safety study (e.g., carcinogenicity, reproductive toxicology)
 - Nonclinical study (laboratory resistance, receptor affinity, quality study related to safety)
 - Pharmacokinetic studies or clinical trials
 - Drug interaction or bioavailability studies or clinical trials
 - Dosing trials
 - Additional data or analysis required for a previously submitted or expected study/clinical trial (provide explanation)
-
- Meta-analysis or pooled analysis of previous studies/clinical trials
 - Immunogenicity as a marker of safety
 - Other (provide explanation)
-

Agreed upon:

- Quality study without a safety endpoint (e.g., manufacturing, stability)
 - Pharmacoepidemiologic study not related to safe drug use (e.g., natural history of disease, background rates of adverse events)
 - Clinical trials primarily designed to further define efficacy (e.g., in another condition, different disease severity, or subgroup) that are NOT required under Subpart H/E
 - Dose-response study or clinical trial performed for effectiveness
 - Nonclinical study, not safety-related (specify)
-
- Other
-

5. Is the PMR/PMC clear, feasible, and appropriate?

- Does the study/clinical trial meet criteria for PMRs or PMCs?
- Are the objectives clear from the description of the PMR/PMC?
- Has the applicant adequately justified the choice of schedule milestone dates?
- Has the applicant had sufficient time to review the PMRs/PMCs, ask questions, determine feasibility, and contribute to the development process?

PMR/PMC Development Coordinator:

This PMR/PMC has been reviewed for clarity and consistency, and is necessary to further refine the safety, efficacy, or optimal use of a drug, or to ensure consistency and reliability of drug quality.

(signature line for BLAs)

3. If the study/clinical trial is a **PMR**, check the applicable regulation.

If not a PMR, skip to 4.

- **Which regulation?**

- Accelerated Approval (subpart H/E)
- Animal Efficacy Rule
- Pediatric Research Equity Act
- FDAAA required safety study/clinical trial

- **If the PMR is a FDAAA safety study/clinical trial, does it: (check all that apply)**

- Assess a known serious risk related to the use of the drug?
- Assess signals of serious risk related to the use of the drug?
- Identify an unexpected serious risk when available data indicate the potential for a serious risk?

- **If the PMR is a FDAAA safety study/clinical trial, will it be conducted as:**

- Analysis of spontaneous postmarketing adverse events?
Do not select the above study/clinical trial type if: such an analysis will not be sufficient to assess or identify a serious risk
- Analysis using pharmacovigilance system?
Do not select the above study/clinical trial type if: the new pharmacovigilance system that the FDA is required to establish under section 505(k)(3) has not yet been established and is thus not sufficient to assess this known serious risk, or has been established but is nevertheless not sufficient to assess or identify a serious risk
- Study: all other investigations, such as investigations in humans that are not clinical trials as defined below (e.g., observational epidemiologic studies), animal studies, and laboratory experiments?
Do not select the above study type if: a study will not be sufficient to identify or assess a serious risk
- Clinical trial: any prospective investigation in which the sponsor or investigator determines the method of assigning investigational product or other interventions to one or more human subjects?

4. What type of study or clinical trial is required or agreed upon (describe and check type below)? If the study or trial will be performed in a subpopulation, list here.

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

Required

- Observational pharmacoepidemiologic study
- Registry studies

Continuation of Question 4

- Primary safety study or clinical trial
 - Pharmacogenetic or pharmacogenomic study or clinical trial if required to further assess safety
 - Thorough Q-T clinical trial
 - Nonclinical (animal) safety study (e.g., carcinogenicity, reproductive toxicology)
 - Nonclinical study (laboratory resistance, receptor affinity, quality study related to safety)
 - Pharmacokinetic studies or clinical trials
 - Drug interaction or bioavailability studies or clinical trials
 - Dosing trials
 - Additional data or analysis required for a previously submitted or expected study/clinical trial (provide explanation)
-
- Meta-analysis or pooled analysis of previous studies/clinical trials
 - Immunogenicity as a marker of safety
 - Other (provide explanation)
-

Agreed upon:

- Quality study without a safety endpoint (e.g., manufacturing, stability)
 - Pharmacoepidemiologic study not related to safe drug use (e.g., natural history of disease, background rates of adverse events)
 - Clinical trials primarily designed to further define efficacy (e.g., in another condition, different disease severity, or subgroup) that are NOT required under Subpart H/E
 - Dose-response study or clinical trial performed for effectiveness
 - Nonclinical study, not safety-related (specify)
-
- Other
-

5. Is the PMR/PMC clear, feasible, and appropriate?

- Does the study/clinical trial meet criteria for PMRs or PMCs?
- Are the objectives clear from the description of the PMR/PMC?
- Has the applicant adequately justified the choice of schedule milestone dates?
- Has the applicant had sufficient time to review the PMRs/PMCs, ask questions, determine feasibility, and contribute to the development process?

PMR/PMC Development Coordinator:

This PMR/PMC has been reviewed for clarity and consistency, and is necessary to further refine the safety, efficacy, or optimal use of a drug, or to ensure consistency and reliability of drug quality.

(signature line for BLAs)

**PMR/PMC Development Template for Gabapentin Enacarbil
PMC #11**

This template should be completed by the PMR/PMC Development Coordinator and included for ***each*** PMR/PMC in the Action Package.

PMR/PMC Description: Develop a 300 mg tablet for patients with renal impairment

PMR/PMC Schedule Milestones: Final protocol Submission Date: 04/2011
Study/Clinical trial Completion Date: 06/2011
Final Report Submission Date: 06/2011
Other: _____ MM/DD/YYYY

1. During application review, explain why this issue is appropriate for a PMR/PMC instead of a pre-approval requirement. Check type below and describe.

- Unmet need
- Life-threatening condition
- Long-term data needed
- Only feasible to conduct post-approval
- Prior clinical experience indicates safety
- Small subpopulation affected
- Theoretical concern
- Other

Development of a dosage form that would allow for a 300 mg dose for use in patients with severe renal impairment or on hemodialysis. This is appropriate for a post-marketing study as the labeling will indicate that "HORIZANT is not recommended for use in patients with a CrCl <30 mL/min or on hemodialysis because the dose cannot be reduced below 600 mg".

2. Describe the particular review issue and the goal of the study/clinical trial. If the study/clinical trial is a FDAAA PMR, describe the risk. If the FDAAA PMR is created post-approval, describe the "new safety information."

There is not currently an available dose or dosage form that could be used in patients with severe renal impairment or on dialysis. The goal of this study is to develop a 300 mg tablet that potentially could be used in those patients.

3. If the study/clinical trial is a **PMR**, check the applicable regulation.

If not a PMR, skip to 4.

- **Which regulation?**

- Accelerated Approval (subpart H/E)
 Animal Efficacy Rule
 Pediatric Research Equity Act
 FDAAA required safety study/clinical trial

- **If the PMR is a FDAAA safety study/clinical trial, does it: (check all that apply)**

- Assess a known serious risk related to the use of the drug?
 Assess signals of serious risk related to the use of the drug?
 Identify an unexpected serious risk when available data indicate the potential for a serious risk?

- **If the PMR is a FDAAA safety study/clinical trial, will it be conducted as:**

- Analysis of spontaneous postmarketing adverse events?
Do not select the above study/clinical trial type if: such an analysis will not be sufficient to assess or identify a serious risk
- Analysis using pharmacovigilance system?
Do not select the above study/clinical trial type if: the new pharmacovigilance system that the FDA is required to establish under section 505(k)(3) has not yet been established and is thus not sufficient to assess this known serious risk, or has been established but is nevertheless not sufficient to assess or identify a serious risk
- Study: all other investigations, such as investigations in humans that are not clinical trials as defined below (e.g., observational epidemiologic studies), animal studies, and laboratory experiments?
Do not select the above study type if: a study will not be sufficient to identify or assess a serious risk
- Clinical trial: any prospective investigation in which the sponsor or investigator determines the method of assigning investigational product or other interventions to one or more human subjects?

4. What type of study or clinical trial is required or agreed upon (describe and check type below)? If the study or trial will be performed in a subpopulation, list here.

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 .

Required

- Observational pharmacoepidemiologic study
 Registry studies

Continuation of Question 4

- Primary safety study or clinical trial
 - Pharmacogenetic or pharmacogenomic study or clinical trial if required to further assess safety
 - Thorough Q-T clinical trial
 - Nonclinical (animal) safety study (e.g., carcinogenicity, reproductive toxicology)
 - Nonclinical study (laboratory resistance, receptor affinity, quality study related to safety)
 - Pharmacokinetic studies or clinical trials
 - Drug interaction or bioavailability studies or clinical trials
 - Dosing trials
 - Additional data or analysis required for a previously submitted or expected study/clinical trial (provide explanation)
-
- Meta-analysis or pooled analysis of previous studies/clinical trials
 - Immunogenicity as a marker of safety
 - Other (provide explanation)
-

Agreed upon:

- Quality study without a safety endpoint (e.g., manufacturing, stability)
 - Pharmacoepidemiologic study not related to safe drug use (e.g., natural history of disease, background rates of adverse events)
 - Clinical trials primarily designed to further define efficacy (e.g., in another condition, different disease severity, or subgroup) that are NOT required under Subpart H/E
 - Dose-response study or clinical trial performed for effectiveness
 - Nonclinical study, not safety-related (specify)
-
- Other
-

5. Is the PMR/PMC clear, feasible, and appropriate?

- Does the study/clinical trial meet criteria for PMRs or PMCs?
- Are the objectives clear from the description of the PMR/PMC?
- Has the applicant adequately justified the choice of schedule milestone dates?
- Has the applicant had sufficient time to review the PMRs/PMCs, ask questions, determine feasibility, and contribute to the development process?

PMR/PMC Development Coordinator:

This PMR/PMC has been reviewed for clarity and consistency, and is necessary to further refine the safety, efficacy, or optimal use of a drug, or to ensure consistency and reliability of drug quality.

(signature line for BLAs)

**PMR/PMC Development Template for Gabapentin Enacarbil
PMR #10**

This template should be completed by the PMR/PMC Development Coordinator and included for each PMR/PMC in the Action Package.

PMR/PMC Description: A drug interaction clinical trial to evaluate pharmacokinetic and the pharmacodynamic interaction between gabapentin enacarbil and morphine

PMR/PMC Schedule Milestones: Final protocol Submission Date: 07/2011
Study/Clinical trial Completion Date: 12/2011
Final Report Submission Date: 04/2012
Other: MM/DD/YYYY

1. During application review, explain why this issue is appropriate for a PMR/PMC instead of a pre-approval requirement. Check type below and describe.

- Unmet need
- Life-threatening condition
- Long-term data needed
- Only feasible to conduct post-approval
- Prior clinical experience indicates safety
- Small subpopulation affected
- Theoretical concern
- Other

The language regarding drug-drug interaction between gabapentin and morphine is listed in the approved "Neurontin" Package Insert.

- Patients who require concomitant treatment with morphine may experience increases in gabapentin concentrations. Patients should be carefully observed for signs of CNS depression, such as somnolence, and the dose of Neurontin or morphine should be reduced appropriately.

Gabapentin enacarbil (Horizant) is a pro-drug of gabapentin. Although there is a different exposure profile between gabapentin enacarbil and gabapentin, it is reasonable to expect a similar drug-drug interaction. It is expected that this interaction with Neurontin results from reduced GI motility due to morphine. Horizant is already much better absorbed through out the GI tract compared to gabapentin which is only absorbed in a limited part of the small intestine. Therefore, the impact on plasma concentration of gabapentin from Horizant would be expected to be much less than observed with Neurontin if Horizant is given after oral morphine. Somnolence will be described in the approved Horizant label. Therefore, this can be a postmarketing trial.

2. Describe the particular review issue and the goal of the study/clinical trial. If the study/clinical trial is a FDAAA PMR, describe the risk. If the FDAAA PMR is created post-approval, describe the “new safety information.”

Gabapentin enacarbil is a pro-drug of gabapentin (Neurontin), which was approved by the Agency in 1993. The following paragraphs are found in the approved “Neurontin” Package Insert regarding the drug-drug interaction between gabapentin and morphine.

- Patients who require concomitant treatment with morphine may experience increases in gabapentin concentrations. Patients should be carefully observed for signs of CNS depression, such as somnolence, and the dose of Neurontin or morphine should be reduced appropriately.

- A literature article reported that when a 60-mg controlled-release morphine capsule was administered 2 hours prior to a 600-mg Neurontin capsule (N=12), mean gabapentin AUC increased by 44% compared to gabapentin administered without morphine (see PRECAUTIONS). Morphine pharmacokinetic parameter values were not affected by administration of Neurontin 2 hours after morphine. The magnitude of interaction at other doses is not known.

There has been no DDI study conducted between gabapentin enacarbil and morphine. As there is a potential risk of altered pharmacokinetics, and a potential risk of increased adverse events, such as somnolence, when these 2 drugs are used in combination, such a DDI clinical trial is necessary. The trial will evaluate pharmacokinetic interaction and the pharmacodynamic interaction between gabapentin enacarbil and morphine.

3. If the study/clinical trial is a **PMR**, check the applicable regulation.

If not a PMR, skip to 4.

- **Which regulation?**

- Accelerated Approval (subpart H/E)
 Animal Efficacy Rule
 Pediatric Research Equity Act
 FDAAA required safety study/clinical trial

- **If the PMR is a FDAAA safety study/clinical trial, does it: (check all that apply)**

- Assess a known serious risk related to the use of the drug?
 Assess signals of serious risk related to the use of the drug?
 Identify an unexpected serious risk when available data indicate the potential for a serious risk?

- **If the PMR is a FDAAA safety study/clinical trial, will it be conducted as:**

- Analysis of spontaneous postmarketing adverse events?
Do not select the above study/clinical trial type if: such an analysis will not be sufficient to assess or identify a serious risk
- Analysis using pharmacovigilance system?
Do not select the above study/clinical trial type if: the new pharmacovigilance system that the FDA is required to establish under section 505(k)(3) has not yet been established and is thus not sufficient to assess this known serious risk, or has been established but is nevertheless not sufficient to assess or identify a serious risk

- Study:** all other investigations, such as investigations in humans that are not clinical trials as defined below (e.g., observational epidemiologic studies), animal studies, and laboratory experiments?

Do not select the above study type if: a study will not be sufficient to identify or assess a serious risk

- Clinical trial:** any prospective investigation in which the sponsor or investigator determines the method of assigning investigational product or other interventions to one or more human subjects?

4. What type of study or clinical trial is required or agreed upon (describe and check type below)? If the study or trial will be performed in a subpopulation, list here.

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

Required

- Observational pharmacoepidemiologic study
 Registry studies

Continuation of Question 4

- Primary safety study or clinical trial
 Pharmacogenetic or pharmacogenomic study or clinical trial if required to further assess safety
 Thorough Q-T clinical trial
 Nonclinical (animal) safety study (e.g., carcinogenicity, reproductive toxicology)
 Nonclinical study (laboratory resistance, receptor affinity, quality study related to safety)
 Pharmacokinetic studies or clinical trials
 Drug interaction or bioavailability studies or clinical trials
 Dosing trials
 Additional data or analysis required for a previously submitted or expected study/clinical trial (provide explanation)

-
- Meta-analysis or pooled analysis of previous studies/clinical trials
 Immunogenicity as a marker of safety
 Other (provide explanation)

BE study

Agreed upon:

- Quality study without a safety endpoint (e.g., manufacturing, stability)
 Pharmacoepidemiologic study not related to safe drug use (e.g., natural history of disease, background rates of adverse events)
 Clinical trials primarily designed to further define efficacy (e.g., in another condition, different disease severity, or subgroup) that are NOT required under Subpart H/E
 Dose-response study or clinical trial performed for effectiveness
 Nonclinical study, not safety-related (specify)
-

5. Is the PMR/PMC clear, feasible, and appropriate?

- Does the study/clinical trial meet criteria for PMRs or PMCs?
 - Are the objectives clear from the description of the PMR/PMC?
 - Has the applicant adequately justified the choice of schedule milestone dates?
 - Has the applicant had sufficient time to review the PMRs/PMCs, ask questions, determine feasibility, and contribute to the development process?
-

PMR/PMC Development Coordinator:

This PMR/PMC has been reviewed for clarity and consistency, and is necessary to further refine the safety, efficacy, or optimal use of a drug, or to ensure consistency and reliability of drug quality.

(signature line for BLAs)

3. If the study/clinical trial is a **PMR**, check the applicable regulation.

If not a PMR, skip to 4.

- **Which regulation?**

- Accelerated Approval (subpart H/E)
 Animal Efficacy Rule
 Pediatric Research Equity Act
 FDAAA required safety study/clinical trial

- **If the PMR is a FDAAA safety study/clinical trial, does it: (check all that apply)**

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 Assess signals of serious risk related to the use of the drug?
 Identify an unexpected serious risk when available data indicate the potential for a serious risk?

- **If the PMR is a FDAAA safety study/clinical trial, will it be conducted as:**

- Analysis of spontaneous postmarketing adverse events?
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- Study: all other investigations, such as investigations in humans that are not clinical trials as defined below (e.g., observational epidemiologic studies), animal studies, and laboratory experiments?
Do not select the above study type if: a study will not be sufficient to identify or assess a serious risk
- Clinical trial: any prospective investigation in which the sponsor or investigator determines the method of assigning investigational product or other interventions to one or more human subjects?

4. What type of study or clinical trial is required or agreed upon (describe and check type below)? If the study or trial will be performed in a subpopulation, list here.

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

Required

- Observational pharmacoepidemiologic study
 Registry studies

Continuation of Question 4

- Primary safety study or clinical trial
 - Pharmacogenetic or pharmacogenomic study or clinical trial if required to further assess safety
 - Thorough Q-T clinical trial
 - Nonclinical (animal) safety study (e.g., carcinogenicity, reproductive toxicology)
 - Nonclinical study (laboratory resistance, receptor affinity, quality study related to safety)
 - Pharmacokinetic studies or clinical trials
 - Drug interaction or bioavailability studies or clinical trials
 - Dosing trials
 - Additional data or analysis required for a previously submitted or expected study/clinical trial (provide explanation)
-
- Meta-analysis or pooled analysis of previous studies/clinical trials
 - Immunogenicity as a marker of safety
 - Other (provide explanation)
-

Agreed upon:

- Quality study without a safety endpoint (e.g., manufacturing, stability)
 - Pharmacoepidemiologic study not related to safe drug use (e.g., natural history of disease, background rates of adverse events)
 - Clinical trials primarily designed to further define efficacy (e.g., in another condition, different disease severity, or subgroup) that are NOT required under Subpart H/E
 - Dose-response study or clinical trial performed for effectiveness
 - Nonclinical study, not safety-related (specify)
-
- Other
-

5. Is the PMR/PMC clear, feasible, and appropriate?

- Does the study/clinical trial meet criteria for PMRs or PMCs?
- Are the objectives clear from the description of the PMR/PMC?
- Has the applicant adequately justified the choice of schedule milestone dates?
- Has the applicant had sufficient time to review the PMRs/PMCs, ask questions, determine feasibility, and contribute to the development process?

PMR/PMC Development Coordinator:

This PMR/PMC has been reviewed for clarity and consistency, and is necessary to further refine the safety, efficacy, or optimal use of a drug, or to ensure consistency and reliability of drug quality.

(signature line for BLAs)

PMR/PMC Development Template for Gabapentin Enacarbil
PMR # 6

This template should be completed by the PMR/PMC Development Coordinator and included for ***each*** PMR/PMC in the Action Package.

PMR/PMC Description: 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%).

PMR/PMC Schedule Milestones:	Final protocol Submission Date:	<u>04/2011</u>
	Study/Clinical trial Completion Date:	<u>04/2011</u>
	Final Report Submission Date:	<u>06/2011</u>
	Other:	<u>MM/DD/YYYY</u>

1. During application review, explain why this issue is appropriate for a PMR/PMC instead of a pre-approval requirement. Check type below and describe.

- Unmet need
- Life-threatening condition
- Long-term data needed
- Only feasible to conduct post-approval
- Prior clinical experience indicates safety
- Small subpopulation affected
- Theoretical concern
- Other

There is a theoretical concern regarding dose-dumping following administration of modified release products with alcohol. There was a 30% increase in dissolution with 40% alcohol, and although we require testing with lower concentrations and in the final dissolution method, it is unlikely that the dissolution would be greater at lower concentrations.

2. Describe the particular review issue and the goal of the study/clinical trial. If the study/clinical trial is a FDAAA PMR, describe the risk. If the FDAAA PMR is created post-approval, describe the “new safety information.”

There is a theoretical risk of dose-dumping when modified release products are taken with alcohol. An in vitro alcohol interaction study was conducted for gabapentin enacarbil using 40% alcohol for 24 hours. The sponsor stated that a slight increase in the rate of release of gabapentin enacarbil in the presence of alcohol compared to buffer alone was observed. The sponsor therefore concluded that this result demonstrates that the formulation is resistant to dose dumping under these conditions. However, dissolution increased 20 to 30% within the first 2 hours with the presence of 40% alcohol. Although 40% alcohol is considered the worst scenario, the dissolution profile at lower percentage of alcohol is not known. Furthermore, the dissolution media and method used in this study is not the final dissolution method selected by the sponsor (as suggested in the draft guidance). These two methods are not comparable. Therefore, the sponsor should repeat this study using their final dissolution method and evaluate different concentrations of alcohol up to 40%.

3. If the study/clinical trial is a **PMR**, check the applicable regulation.

If not a PMR, skip to 4.

– **Which regulation?**

- Accelerated Approval (subpart H/E)
 Animal Efficacy Rule
 Pediatric Research Equity Act
 FDAAA required safety study/clinical trial

– **If the PMR is a FDAAA safety study/clinical trial, does it: (check all that apply)**

- Assess a known serious risk related to the use of the drug?
 Assess signals of serious risk related to the use of the drug?
 Identify an unexpected serious risk when available data indicate the potential for a serious risk?

– **If the PMR is a FDAAA safety study/clinical trial, will it be conducted as:**

- Analysis of spontaneous postmarketing adverse events?
Do not select the above study/clinical trial type if: such an analysis will not be sufficient to assess or identify a serious risk
- Analysis using pharmacovigilance system?
Do not select the above study/clinical trial type if: the new pharmacovigilance system that the FDA is required to establish under section 505(k)(3) has not yet been established and is thus not sufficient to assess this known serious risk, or has been established but is nevertheless not sufficient to assess or identify a serious risk
- Study: all other investigations, such as investigations in humans that are not clinical trials as defined below (e.g., observational epidemiologic studies), animal studies, and laboratory experiments?
Do not select the above study type if: a study will not be sufficient to identify or assess a serious risk
- Clinical trial: any prospective investigation in which the sponsor or investigator determines the method of assigning investigational product or other interventions to one or more human subjects?

4. What type of study or clinical trial is required or agreed upon (describe and check type below)? If the study or trial will be performed in a subpopulation, list here.

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%).

Required

- Observational pharmacoepidemiologic study
 Registry studies

Continuation of Question 4

- Primary safety study or clinical trial
 Pharmacogenetic or pharmacogenomic study or clinical trial if required to further assess safety
 Thorough Q-T clinical trial
 Nonclinical (animal) safety study (e.g., carcinogenicity, reproductive toxicology)
 Nonclinical study (laboratory resistance, receptor affinity, quality study related to safety)
 Pharmacokinetic studies or clinical trials
 Drug interaction or bioavailability studies or clinical trials
 Dosing trials
 Additional data or analysis required for a previously submitted or expected study/clinical trial (provide explanation)
-
- Meta-analysis or pooled analysis of previous studies/clinical trials
 Immunogenicity as a marker of safety
 Other (provide explanation)
-

Agreed upon:

- Quality study without a safety endpoint (e.g., manufacturing, stability)
 Pharmacoepidemiologic study not related to safe drug use (e.g., natural history of disease, background rates of adverse events)
 Clinical trials primarily designed to further define efficacy (e.g., in another condition, different disease severity, or subgroup) that are NOT required under Subpart H/E
 Dose-response study or clinical trial performed for effectiveness
 Nonclinical study, not safety-related (specify)
-
- Other
-

5. Is the PMR/PMC clear, feasible, and appropriate?

- Does the study/clinical trial meet criteria for PMRs or PMCs?
 Are the objectives clear from the description of the PMR/PMC?
 Has the applicant adequately justified the choice of schedule milestone dates?
 Has the applicant had sufficient time to review the PMRs/PMCs, ask questions, determine feasibility, and contribute to the development process?

PMR/PMC Development Coordinator:

This PMR/PMC has been reviewed for clarity and consistency, and is necessary to further refine the safety, efficacy, or optimal use of a drug, or to ensure consistency and reliability of drug quality.

(signature line for BLAs)

**PMR/PMC Development Template for Gabapentin Encarbil
PMR#7**

This template should be completed by the PMR/PMC Development Coordinator and included for each PMR/PMC in the Action Package.

PMR/PMC Description: A simulated driving trial in healthy adult subjects treated with 600 mg gabapentin encarbil that includes active comparator and placebo arms.

PMR/PMC Schedule Milestones: Final protocol Submission Date: 05/2011
Study/Clinical trial Completion Date: 10/2011
Final Report Submission Date: 02/2012
Other: _____ MM/DD/YYYY

1. During application review, explain why this issue is appropriate for a PMR/PMC instead of a pre-approval requirement. Check type below and describe.

- Unmet need
- Life-threatening condition
- Long-term data needed
- Only feasible to conduct post-approval
- Prior clinical experience indicates safety
- Small subpopulation affected
- Theoretical concern
- Other

The parent compound gabapentin (Neurontin™) is approved at higher doses (resulting in higher exposures) compared to the 600 mg dose of gabapentin encarbil. These higher dose of Neurontin are approved by the agency and considered safe. Gabapentin encarbil is safe and effective at the recommended dose of 600 mg that will be approved. The label contains a warning regarding somnolence at this dose and a warning regarding impaired driving at higher doses, stating that the effects at the 600-mg dose of HORIZANT on driving behavior has not been studied but may be similar to those seen at the 1,200-mg dose. Because this is addressed in labeling, the trial can be done post-marketing.

2. Describe the particular review issue and the goal of the study/clinical trial. If the study/clinical trial is a FDAAA PMR, describe the risk. If the FDAAA PMR is created post-approval, describe the “new safety information.”

The 600 mg/day dose of gabapentin encarbil appeared to have the same treatment effect as 1200mg/day dose. Doses higher than 1200mg/day were not associated with a greater treatment benefit. The 1200mg/day dose of gabapentin encarbil was studied in a simulated driving study and it was associated with a decline in simulated driving performance (lane position variability). The 600 mg/day dose of gabapentin encarbil was not included in the simulated driving study. The goal of this PMR is to determine if a dose of 600 mg/day dose of gabapentin encarbil impairs driving performance in healthy adults.

3. If the study/clinical trial is a **PMR**, check the applicable regulation.

If not a PMR, skip to 4.

- **Which regulation?**

- Accelerated Approval (subpart H/E)
- Animal Efficacy Rule
- Pediatric Research Equity Act
- FDAAA required safety study/clinical trial

- **If the PMR is a FDAAA safety study/clinical trial, does it: (check all that apply)**

- Assess a known serious risk related to the use of the drug?
- Assess signals of serious risk related to the use of the drug?
- Identify an unexpected serious risk when available data indicate the potential for a serious risk?

- **If the PMR is a FDAAA safety study/clinical trial, will it be conducted as:**

- Analysis of spontaneous postmarketing adverse events?
Do not select the above study/clinical trial type if: such an analysis will not be sufficient to assess or identify a serious risk
- Analysis using pharmacovigilance system?
Do not select the above study/clinical trial type if: the new pharmacovigilance system that the FDA is required to establish under section 505(k)(3) has not yet been established and is thus not sufficient to assess this known serious risk, or has been established but is nevertheless not sufficient to assess or identify a serious risk
- Study: all other investigations, such as investigations in humans that are not clinical trials as defined below (e.g., observational epidemiologic studies), animal studies, and laboratory experiments?
Do not select the above study type if: a study will not be sufficient to identify or assess a serious risk
- Clinical trial: any prospective investigation in which the sponsor or investigator determines the method of assigning investigational product or other interventions to one or more human subjects?

4. What type of study or clinical trial is required or agreed upon (describe and check type below)? If the study or trial will be performed in a subpopulation, list here.

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

Required

- Observational pharmacoepidemiologic study
- Registry studies

Continuation of Question 4

- Primary safety study or clinical trial
 - Pharmacogenetic or pharmacogenomic study or clinical trial if required to further assess safety
 - Thorough Q-T clinical trial
 - Nonclinical (animal) safety study (e.g., carcinogenicity, reproductive toxicology)
 - Nonclinical study (laboratory resistance, receptor affinity, quality study related to safety)
 - Pharmacokinetic studies or clinical trials
 - Drug interaction or bioavailability studies or clinical trials
 - Dosing trials
 - Additional data or analysis required for a previously submitted or expected study/clinical trial (provide explanation)
-
- Meta-analysis or pooled analysis of previous studies/clinical trials
 - Immunogenicity as a marker of safety
 - Other (provide explanation)
-

Agreed upon:

- Quality study without a safety endpoint (e.g., manufacturing, stability)
 - Pharmacoepidemiologic study not related to safe drug use (e.g., natural history of disease, background rates of adverse events)
 - Clinical trials primarily designed to further define efficacy (e.g., in another condition, different disease severity, or subgroup) that are NOT required under Subpart H/E
 - Dose-response study or clinical trial performed for effectiveness
 - Nonclinical study, not safety-related (specify)
-
- Other
-

5. Is the PMR/PMC clear, feasible, and appropriate?

- Does the study/clinical trial meet criteria for PMRs or PMCs?
 - Are the objectives clear from the description of the PMR/PMC?
 - Has the applicant adequately justified the choice of schedule milestone dates?
 - Has the applicant had sufficient time to review the PMRs/PMCs, ask questions, determine feasibility, and contribute to the development process?
-

PMR/PMC Development Coordinator:

This PMR/PMC has been reviewed for clarity and consistency, and is necessary to further refine the safety, efficacy, or optimal use of a drug, or to ensure consistency and reliability of drug quality.

(signature line for BLAs)

**PMR/PMC Development Template for Gabapentin Enacarbil
PMR #8**

This template should be completed by the PMR/PMC Development Coordinator and included for ***each*** PMR/PMC in the Action Package.

PMR/PMC Description: A simulated driving trial in healthy adult subjects treated with an appropriate dose of gabapentin enacarbil determined in PMC#12 that includes active comparator and placebo arms.

PMR/PMC Schedule Milestones: Final protocol Submission Date: 10/2014
Study/Clinical trial Completion Date: 05/2015
Final Report Submission Date: 09/2015
Other: MM/DD/YYYY

1. During application review, explain why this issue is appropriate for a PMR/PMC instead of a pre-approval requirement. Check type below and describe.

- Unmet need
- Life-threatening condition
- Long-term data needed
- Only feasible to conduct post-approval
- Prior clinical experience indicates safety
- Small subpopulation affected
- Theoretical concern
- Other

Because of the potential for somnolence and impaired driving, it is desirable to evaluate lower doses than the doses that will be approved. The recommended dose of 600 mg/day has been determined to be safe and effective, although the label will have warnings regarding somnolence and impaired driving. The trial can therefore be performed postmarketing.

2. Describe the particular review issue and the goal of the study/clinical trial. If the study/clinical trial is a FDAAA PMR, describe the risk. If the FDAAA PMR is created post-approval, describe the “new safety information.”

The 600 mg/day dose of gabapentin enacarbil appeared to have the same treatment effect as 1200mg/day dose. Doses higher than 1200mg/day were not associated with a greater treatment benefit. Because the treatment effect reached a plateau at 600 mg/day the lowest dose studied in a well controlled clinical trial the Agency recommended the sponsor conduct an additional dose response study to examine the efficacy of dose(s) < 600 mg/day in patients with moderate to severe RLS . The 1200mg/day dose of gabapentin enacarbil was studied in a simulated driving study and it was associated with a decline in simulated driving performance (lane position variability). The 600 mg/day dose of gabapentin enacarbil was not included in the simulated driving study. The sponsor is required (PMR) to conduct a simulated driving study evaluating the effect of the 600mg/day dose and lower doses on simulated driving in patients with moderate to severe symptoms of RLS. The goal of this PMC is to determine if doses below 600 mg/day dose of gabapentin enacarbil are likely to be associated with fewer or less severe adverse effects on driving.

3. If the study/clinical trial is a **PMR**, check the applicable regulation.

If not a PMR, skip to 4.

– **Which regulation?**

- Accelerated Approval (subpart H/E)
 Animal Efficacy Rule
 Pediatric Research Equity Act
 FDAAA required safety study/clinical trial

– **If the PMR is a FDAAA safety study/clinical trial, does it: (check all that apply)**

- Assess a known serious risk related to the use of the drug?
 Assess signals of serious risk related to the use of the drug?
 Identify an unexpected serious risk when available data indicate the potential for a serious risk?

– **If the PMR is a FDAAA safety study/clinical trial, will it be conducted as:**

- Analysis of spontaneous postmarketing adverse events?
Do not select the above study/clinical trial type if: such an analysis will not be sufficient to assess or identify a serious risk
- Analysis using pharmacovigilance system?
Do not select the above study/clinical trial type if: the new pharmacovigilance system that the FDA is required to establish under section 505(k)(3) has not yet been established and is thus not sufficient to assess this known serious risk, or has been established but is nevertheless not sufficient to assess or identify a serious risk
- Study: all other investigations, such as investigations in humans that are not clinical trials as defined below (e.g., observational epidemiologic studies), animal studies, and laboratory experiments?
Do not select the above study type if: a study will not be sufficient to identify or assess a serious risk
- Clinical trial: any prospective investigation in which the sponsor or investigator determines the method of assigning investigational product or other interventions to one or more human subjects?

4. What type of study or clinical trial is required or agreed upon (describe and check type below)? If the study or trial will be performed in a subpopulation, list here.

A simulated driving trial in healthy adult subjects treated with an appropriate dose of gabapentin enacarbil determined in PMC #12 that includes active comparator and placebo arms.

Required

Observational pharmacoepidemiologic study

Registry studies

Continuation of Question 4

Primary safety study or clinical trial

Pharmacogenetic or pharmacogenomic study or clinical trial if required to further assess safety

Thorough Q-T clinical trial

Nonclinical (animal) safety study (e.g., carcinogenicity, reproductive toxicology)

Nonclinical study (laboratory resistance, receptor affinity, quality study related to safety)

Pharmacokinetic studies or clinical trials

Drug interaction or bioavailability studies or clinical trials

Dosing trials

Additional data or analysis required for a previously submitted or expected study/clinical trial (provide explanation)

Meta-analysis or pooled analysis of previous studies/clinical trials

Immunogenicity as a marker of safety

Other (provide explanation)

Agreed upon:

Quality study without a safety endpoint (e.g., manufacturing, stability)

Pharmacoepidemiologic study not related to safe drug use (e.g., natural history of disease, background rates of adverse events)

Clinical trials primarily designed to further define efficacy (e.g., in another condition, different disease severity, or subgroup) that are NOT required under Subpart H/E

Dose-response study or clinical trial performed for effectiveness

Nonclinical study, not safety-related (specify)

Other

5. Is the PMR/PMC clear, feasible, and appropriate?

Does the study/clinical trial meet criteria for PMRs or PMCs?

Are the objectives clear from the description of the PMR/PMC?

Has the applicant adequately justified the choice of schedule milestone dates?

Has the applicant had sufficient time to review the PMRs/PMCs, ask questions, determine feasibility, and contribute to the development process?

PMR/PMC Development Coordinator:

This PMR/PMC has been reviewed for clarity and consistency, and is necessary to further refine the safety, efficacy, or optimal use of a drug, or to ensure consistency and reliability of drug quality.

(signature line for BLAs)

3. If the study/clinical trial is a **PMR**, check the applicable regulation.

If not a PMR, skip to 4.

- **Which regulation?**

- Accelerated Approval (subpart H/E)
- Animal Efficacy Rule
- Pediatric Research Equity Act
- FDAAA required safety study/clinical trial

- **If the PMR is a FDAAA safety study/clinical trial, does it: (check all that apply)**

- Assess a known serious risk related to the use of the drug?
- Assess signals of serious risk related to the use of the drug?
- Identify an unexpected serious risk when available data indicate the potential for a serious risk?

- **If the PMR is a FDAAA safety study/clinical trial, will it be conducted as:**

- Analysis of spontaneous postmarketing adverse events?
Do not select the above study/clinical trial type if: such an analysis will not be sufficient to assess or identify a serious risk
- Analysis using pharmacovigilance system?
Do not select the above study/clinical trial type if: the new pharmacovigilance system that the FDA is required to establish under section 505(k)(3) has not yet been established and is thus not sufficient to assess this known serious risk, or has been established but is nevertheless not sufficient to assess or identify a serious risk
- Study: all other investigations, such as investigations in humans that are not clinical trials as defined below (e.g., observational epidemiologic studies), animal studies, and laboratory experiments?
Do not select the above study type if: a study will not be sufficient to identify or assess a serious risk
- Clinical trial: any prospective investigation in which the sponsor or investigator determines the method of assigning investigational product or other interventions to one or more human subjects?

4. What type of study or clinical trial is required or agreed upon (describe and check type below)? If the study or trial will be performed in a subpopulation, list here.

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.

Required

- Observational pharmacoepidemiologic study
- Registry studies

Continuation of Question 4

- Primary safety study or clinical trial
 - Pharmacogenetic or pharmacogenomic study or clinical trial if required to further assess safety
 - Thorough Q-T clinical trial
 - Nonclinical (animal) safety study (e.g., carcinogenicity, reproductive toxicology)
 - Nonclinical study (laboratory resistance, receptor affinity, quality study related to safety)
 - Pharmacokinetic studies or clinical trials
 - Drug interaction or bioavailability studies or clinical trials
 - Dosing trials
 - Additional data or analysis required for a previously submitted or expected study/clinical trial (provide explanation)
-
- Meta-analysis or pooled analysis of previous studies/clinical trials
 - Immunogenicity as a marker of safety
 - Other (provide explanation)
-

Agreed upon:

- Quality study without a safety endpoint (e.g., manufacturing, stability)
 - Pharmacoepidemiologic study not related to safe drug use (e.g., natural history of disease, background rates of adverse events)
 - Clinical trials primarily designed to further define efficacy (e.g., in another condition, different disease severity, or subgroup) that are NOT required under Subpart H/E
 - Dose-response study or clinical trial performed for effectiveness
 - Nonclinical study, not safety-related (specify)
-
- Other
-

5. Is the PMR/PMC clear, feasible, and appropriate?

- Does the study/clinical trial meet criteria for PMRs or PMCs?
- Are the objectives clear from the description of the PMR/PMC?
- Has the applicant adequately justified the choice of schedule milestone dates?
- Has the applicant had sufficient time to review the PMRs/PMCs, ask questions, determine feasibility, and contribute to the development process?

PMR/PMC Development Coordinator:

This PMR/PMC has been reviewed for clarity and consistency, and is necessary to further refine the safety, efficacy, or optimal use of a drug, or to ensure consistency and reliability of drug quality.

(signature line for BLAs)

3. If the study/clinical trial is a **PMR**, check the applicable regulation.

If not a PMR, skip to 4.

- **Which regulation?**

- Accelerated Approval (subpart H/E)
- Animal Efficacy Rule
- Pediatric Research Equity Act
- FDAAA required safety study/clinical trial

- **If the PMR is a FDAAA safety study/clinical trial, does it: (check all that apply)**

- Assess a known serious risk related to the use of the drug?
- Assess signals of serious risk related to the use of the drug?
- Identify an unexpected serious risk when available data indicate the potential for a serious risk?

- **If the PMR is a FDAAA safety study/clinical trial, will it be conducted as:**

- Analysis of spontaneous postmarketing adverse events?
Do not select the above study/clinical trial type if: such an analysis will not be sufficient to assess or identify a serious risk
- Analysis using pharmacovigilance system?
Do not select the above study/clinical trial type if: the new pharmacovigilance system that the FDA is required to establish under section 505(k)(3) has not yet been established and is thus not sufficient to assess this known serious risk, or has been established but is nevertheless not sufficient to assess or identify a serious risk
- Study: all other investigations, such as investigations in humans that are not clinical trials as defined below (e.g., observational epidemiologic studies), animal studies, and laboratory experiments?
Do not select the above study type if: a study will not be sufficient to identify or assess a serious risk
- Clinical trial: any prospective investigation in which the sponsor or investigator determines the method of assigning investigational product or other interventions to one or more human subjects?

4. What type of study or clinical trial is required or agreed upon (describe and check type below)? If the study or trial will be performed in a subpopulation, list here.

Conduct a long-term safety study 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 trial described in PMR #2.

Required

- Observational pharmacoepidemiologic study
- Registry studies

Continuation of Question 4

- Primary safety study or clinical trial
 - Pharmacogenetic or pharmacogenomic study or clinical trial if required to further assess safety
 - Thorough Q-T clinical trial
 - Nonclinical (animal) safety study (e.g., carcinogenicity, reproductive toxicology)
 - Nonclinical study (laboratory resistance, receptor affinity, quality study related to safety)
 - Pharmacokinetic studies or clinical trials
 - Drug interaction or bioavailability studies or clinical trials
 - Dosing trials
 - Additional data or analysis required for a previously submitted or expected study/clinical trial (provide explanation)
-
- Meta-analysis or pooled analysis of previous studies/clinical trials
 - Immunogenicity as a marker of safety
 - Other (provide explanation)
-

Agreed upon:

- Quality study without a safety endpoint (e.g., manufacturing, stability)
 - Pharmacoepidemiologic study not related to safe drug use (e.g., natural history of disease, background rates of adverse events)
 - Clinical trials primarily designed to further define efficacy (e.g., in another condition, different disease severity, or subgroup) that are NOT required under Subpart H/E
 - Dose-response study or clinical trial performed for effectiveness
 - Nonclinical study, not safety-related (specify)
-
- Other
-

5. Is the PMR/PMC clear, feasible, and appropriate?

- Does the study/clinical trial meet criteria for PMRs or PMCs?
- Are the objectives clear from the description of the PMR/PMC?
- Has the applicant adequately justified the choice of schedule milestone dates?
- Has the applicant had sufficient time to review the PMRs/PMCs, ask questions, determine feasibility, and contribute to the development process?

PMR/PMC Development Coordinator:

This PMR/PMC has been reviewed for clarity and consistency, and is necessary to further refine the safety, efficacy, or optimal use of a drug, or to ensure consistency and reliability of drug quality.

(signature line for BLAs)

3. If the study/clinical trial is a **PMR**, check the applicable regulation.

If not a PMR, skip to 4.

- **Which regulation?**

- Accelerated Approval (subpart H/E)
- Animal Efficacy Rule
- Pediatric Research Equity Act
- FDAAA required safety study/clinical trial

- **If the PMR is a FDAAA safety study/clinical trial, does it: (check all that apply)**

- Assess a known serious risk related to the use of the drug?
- Assess signals of serious risk related to the use of the drug?
- Identify an unexpected serious risk when available data indicate the potential for a serious risk?

- **If the PMR is a FDAAA safety study/clinical trial, will it be conducted as:**

- Analysis of spontaneous postmarketing adverse events?
Do not select the above study/clinical trial type if: such an analysis will not be sufficient to assess or identify a serious risk
- Analysis using pharmacovigilance system?
Do not select the above study/clinical trial type if: the new pharmacovigilance system that the FDA is required to establish under section 505(k)(3) has not yet been established and is thus not sufficient to assess this known serious risk, or has been established but is nevertheless not sufficient to assess or identify a serious risk
- Study: all other investigations, such as investigations in humans that are not clinical trials as defined below (e.g., observational epidemiologic studies), animal studies, and laboratory experiments?
Do not select the above study type if: a study will not be sufficient to identify or assess a serious risk
- Clinical trial: any prospective investigation in which the sponsor or investigator determines the method of assigning investigational product or other interventions to one or more human subjects?

4. What type of study or clinical trial is required or agreed upon (describe and check type below)? If the study or trial will be performed in a subpopulation, list here.

Conduct a driving study in adolescent patients of legal driving age who have Restless Legs Syndrome, using diphenhydramine as active control.

Required

- Observational pharmacoepidemiologic study
- Registry studies

Continuation of Question 4

- Primary safety study or clinical trial
 - Pharmacogenetic or pharmacogenomic study or clinical trial if required to further assess safety
 - Thorough Q-T clinical trial
 - Nonclinical (animal) safety study (e.g., carcinogenicity, reproductive toxicology)
 - Nonclinical study (laboratory resistance, receptor affinity, quality study related to safety)
 - Pharmacokinetic studies or clinical trials
 - Drug interaction or bioavailability studies or clinical trials
 - Dosing trials
 - Additional data or analysis required for a previously submitted or expected study/clinical trial (provide explanation)
-
- Meta-analysis or pooled analysis of previous studies/clinical trials
 - Immunogenicity as a marker of safety
 - Other (provide explanation)
-

Agreed upon:

- Quality study without a safety endpoint (e.g., manufacturing, stability)
 - Pharmacoepidemiologic study not related to safe drug use (e.g., natural history of disease, background rates of adverse events)
 - Clinical trials primarily designed to further define efficacy (e.g., in another condition, different disease severity, or subgroup) that are NOT required under Subpart H/E
 - Dose-response study or clinical trial performed for effectiveness
 - Nonclinical study, not safety-related (specify)
-
- Other
-

5. Is the PMR/PMC clear, feasible, and appropriate?

- Does the study/clinical trial meet criteria for PMRs or PMCs?
 - Are the objectives clear from the description of the PMR/PMC?
 - Has the applicant adequately justified the choice of schedule milestone dates?
 - Has the applicant had sufficient time to review the PMRs/PMCs, ask questions, determine feasibility, and contribute to the development process?
-

PMR/PMC Development Coordinator:

This PMR/PMC has been reviewed for clarity and consistency, and is necessary to further refine the safety, efficacy, or optimal use of a drug, or to ensure consistency and reliability of drug quality.

(signature line for BLAs)

**PMR/PMC Development Template for Gabapentin Enacarbil
PMC #12**

This template should be completed by the PMR/PMC Development Coordinator and included for each PMR/PMC in the Action Package.

PMR/PMC Description: 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.

PMR/PMC Schedule Milestones: Final protocol Submission Date: 03/2012
Study/Clinical trial Completion Date: 07/2014
Final Report Submission Date: 02/2015
Other: MM/DD/YYYY

1. During application review, explain why this issue is appropriate for a PMR/PMC instead of a pre-approval requirement. Check type below and describe.

- Unmet need
- Life-threatening condition
- Long-term data needed
- Only feasible to conduct post-approval
- Prior clinical experience indicates safety
- Small subpopulation affected
- Theoretical concern
- Other

Because of the potential for somnolence and impaired driving, it is desirable to evaluate lower doses than the doses that will be approved. The recommended dose of 600 mg/day has been determined to be safe and effective, although the label will have warnings regarding somnolence and impaired driving. The trial can therefore be performed postmarketing.

2. Describe the particular review issue and the goal of the study/clinical trial. If the study/clinical trial is a FDAAA PMR, describe the risk. If the FDAAA PMR is created post-approval, describe the “new safety information.”

The sponsor's pre-approval clinical trials evaluated the potential efficacy of gabapentin enacarbil at a doses of 600 mg, 1200 mg, 1800 mg and 2400 mg given once daily. The data did not demonstrate additional effect on the primary clinical outcome measures at doses above 600 mg/day. Approval was requested for the 1200 mg dose but the dose response data indicated that the maximally effective dose was achieved at 600 mg/day. The goal of this study is to evaluate efficacy and safety of doses less than 600 mg/day (compared to 600 mg/day).

3. If the study/clinical trial is a **PMR**, check the applicable regulation.

If not a PMR, skip to 4.

- **Which regulation?**

- Accelerated Approval (subpart H/E)
- Animal Efficacy Rule
- Pediatric Research Equity Act
- FDAAA required safety study/clinical trial

- **If the PMR is a FDAAA safety study/clinical trial, does it: (check all that apply)**

- Assess a known serious risk related to the use of the drug?
- Assess signals of serious risk related to the use of the drug?
- Identify an unexpected serious risk when available data indicate the potential for a serious risk?

- **If the PMR is a FDAAA safety study/clinical trial, will it be conducted as:**

- Analysis of spontaneous postmarketing adverse events?
Do not select the above study/clinical trial type if: such an analysis will not be sufficient to assess or identify a serious risk
- Analysis using pharmacovigilance system?
Do not select the above study/clinical trial type if: the new pharmacovigilance system that the FDA is required to establish under section 505(k)(3) has not yet been established and is thus not sufficient to assess this known serious risk, or has been established but is nevertheless not sufficient to assess or identify a serious risk
- Study: all other investigations, such as investigations in humans that are not clinical trials as defined below (e.g., observational epidemiologic studies), animal studies, and laboratory experiments?
Do not select the above study type if: a study will not be sufficient to identify or assess a serious risk
- Clinical trial: any prospective investigation in which the sponsor or investigator determines the method of assigning investigational product or other interventions to one or more human subjects?

4. What type of study or clinical trial is required or agreed upon (describe and check type below)? If the study or trial will be performed in a subpopulation, list here.

Conduct 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.

Required

- Observational pharmacoepidemiologic study
- Registry studies

Continuation of Question 4

- Primary safety study or clinical trial
 - Pharmacogenetic or pharmacogenomic study or clinical trial if required to further assess safety
 - Thorough Q-T clinical trial
 - Nonclinical (animal) safety study (e.g., carcinogenicity, reproductive toxicology)
 - Nonclinical study (laboratory resistance, receptor affinity, quality study related to safety)
 - Pharmacokinetic studies or clinical trials
 - Drug interaction or bioavailability studies or clinical trials
 - Dosing trials
 - Additional data or analysis required for a previously submitted or expected study/clinical trial (provide explanation)
-
- Meta-analysis or pooled analysis of previous studies/clinical trials
 - Immunogenicity as a marker of safety
 - Other (provide explanation)
-

Agreed upon:

- Quality study without a safety endpoint (e.g., manufacturing, stability)
 - Pharmacoepidemiologic study not related to safe drug use (e.g., natural history of disease, background rates of adverse events)
 - Clinical trials primarily designed to further define efficacy (e.g., in another condition, different disease severity, or subgroup) that are NOT required under Subpart H/E
 - Dose-response study or clinical trial performed for effectiveness
 - Nonclinical study, not safety-related (specify)
-
- Other
-

5. Is the PMR/PMC clear, feasible, and appropriate?

- Does the study/clinical trial meet criteria for PMRs or PMCs?
- Are the objectives clear from the description of the PMR/PMC?
- Has the applicant adequately justified the choice of schedule milestone dates?
- Has the applicant had sufficient time to review the PMRs/PMCs, ask questions, determine feasibility, and contribute to the development process?

PMR/PMC Development Coordinator:

This PMR/PMC has been reviewed for clarity and consistency, and is necessary to further refine the safety, efficacy, or optimal use of a drug, or to ensure consistency and reliability of drug quality.

(signature line for BLAs)

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

/s/

SALLY U YASUDA
04/06/2011
PMR/PMC development templates



**Department of Health and Human Services
Public Health Service
Food and Drug Administration
Center for Drug Evaluation and Research
Office of Surveillance and Epidemiology**

Date: 04/04/2011

To: Rusty Katz, M.D.
Division Director
Division of Neurology Products

Gerald Podskalny, M.D.
Clinical Team Leader
Division of Neurology Products

Through: Solomon Iyasu, M.D., MPH
Division Director
Division of Epidemiology

Simone Pinheiro, ScD, MSc
Team Leader
Division of Epidemiology

From: James. R. Williams, PhD
Epidemiologist
Division of Epidemiology

Subject: Epidemiology Study Review – Association between
Gabapentin Exposure & Pancreatic and Renal Cancer

Drug Name(s): Gabapentin enacarbil

Submission Number: 0045

Application Type/Number: NDA 22-399

Applicant/sponsor: GlaxoSmithKline

OSE RCM #: 2010-2151

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EXECUTIVE SUMMARY

The Division of Epidemiology (DEPI) was consulted by the Division of Neurology Products (DNP) to review two parallel case-control studies submitted by GlaxoSmithKline in support of NDA 22-399 resubmission, gabapentin enacarbil. Gabapentin enacarbil, a gabapentin prodrug developed for the symptomatic treatment of primary restless leg syndrome, originally received a complete response letter in part due to two cancer signals (pancreatic and renal cancer). Both studies, conducted in the same database, were well-designed and conducted. Based on the assumption that epidemiologic investigations of gabapentin can be used to assess gabapentin enacarbil's safety profile, the reviewed studies do not provide strong evidence of an association between gabapentin use and cancer, in particular pancreatic and renal cancers. However, due to the short duration of gabapentin exposure seen in GPRD, these studies cannot comment on the potential carcinogenicity associated with chronic gabapentin enacarbil use.

The evidence in support of an association between incident cancer and gabapentin exposure is weak. First, statistically significant associations were seen in the first (lowest) tertile of exposure for pancreatic, renal, and penile cancers, but no associations were observed at higher exposures levels; precluding a dose-dependent relationship. Second, the likelihood that brief exposure to gabapentin is carcinogenic is questionable. The duration of use first (lowest) tertile spanned from 0 to 1.55 months and the number of prescriptions first tertile spanned from 1 to 2 prescriptions. As such, all associations were attenuated in two-year lagged analyses. Third, the short duration between first exposure to gabapentin and incidence of pancreatic cancer also calls into question gabapentin's carcinogenicity, especially given the long asymptomatic period associated with pancreatic cancer. The median latency between first gabapentin exposure and incidence was 416 days for renal cancer and 573 days for pancreatic cancer. Finally, the statistically significant associations observed are likely an artifact of a protopathic bias and potentially a surveillance bias. A post-hoc review of gabapentin use in pancreatic and renal cancer cases in study weuskop4774 suggested a potential protopathic bias. The post-hoc review revealed that 14% of pancreatic and 31% of renal cancer cases were prescribed gabapentin for the treatment of paraneoplastic syndromes, or had a READ code indicating clinical suspicion of cancer prior to first gabapentin exposure that was presumably confirmed after subsequent diagnostic testing. Also, the potential for a surveillance bias must also be acknowledged. It is possible that patients who receive gabapentin prescriptions may more frequently report symptoms that trigger diagnostic tests which identify pancreatic cancer more often than patients who do not receive gabapentin.

If gabapentin enacarbil is approved, DEPI does not recommend further evaluation of gabapentin enacarbil's carcinogenicity by means of an observational study post-marketing requirement. Additional retrospective case-control and cohort studies would likely not add substantially different information to the risk-benefit discussion. A prospective registry study would be hard to interpret given pancreatic cancer's long asymptomatic period. In order to attribute any cancer association to gabapentin, registry participants would need to undergo imaging studies and potential biopsies at baseline to identify any prevalent pancreatic and renal cancer cases. Recruitment for such an intensive study would likely be difficult and is likely unwarranted given the currently available carcinogenicity data. Additional epidemiologic studies can be discussed if new gabapentin enacarbil carcinogenicity data are generated in the future.

1 BACKGROUND/HISTORY

The Division of Neurology Products (DNP) has requested the Division of Epidemiology (DEPI) to review two case-control studies conducted by GlaxoSmithKline (GSK) in the General Practice Research Database (GPRD) to examine the association between gabapentin exposure and the

incidence of pancreatic cancer, renal cancer, and other cancer outcomes. GSK conducted this study to support the resubmission of New Drug Application (NDA) 22-399, gabapentin encarbil. Gabapentin encarbil is a gabapentin prodrug developed for the symptomatic treatment of primary restless leg syndrome (RLS). In the course of the original NDA review, two cancer signals were identified. A signal for pancreatic acinar cell carcinoma was identified from animal-based pharmacology and toxicology data. Another signal for kidney/renal pelvic cancer related to gabapentin exposure was identified from a case-control study in Kaiser Permanente (Friedman et al., 2009). DNP issued a complete response letter to the Sponsor stating that potential cancer signals outweighed the potential benefit to RLS patients. At a subsequent end of review conference meeting on May 18, 2010, the Sponsor was provided guidance from the FDA on the design of an epidemiologic study which might provide additional data regarding gabapentin encarbil's carcinogenicity in humans, based on the assumption that epidemiologic data about gabapentin can be imputed to gabapentin encarbil. In preparation for this conference, DEPI reviewed a GPRD study protocol and supplementary data from the Kaiser Permanente case-control study. In reviewing, the supplementary data, a number of weak associations between gabapentin and other cancer sites were identified. DEPI recommended the Sponsor also investigate the association between gabapentin and these additional cancer sites in their epidemiologic study.

NDA 22-399 was resubmitted on October 10, 2010 and contained results from two case-control studies conducted in GPRD. One study corresponded to the original protocol submitted by GSK and the other study incorporated the recommendations provided by DEPI. DEPI requested additional information from GSK to clarify the results on December 4, 2010, and received responses on December 21, 2010. The goal of the review is to assess the validity of the aforementioned studies and summarize the data they provide regarding potential carcinogenic effects of gabapentin.

2 REVIEW METHODS AND MATERIALS

This review focused on the following study reports and information request response from NDA 22-399.

- GSK study report weuskop4774, submitted October 10, 2010
- GSK study report weusrtp4931, submitted December 4, 2010
- GSK information request response, submitted December 21, 2010

In addition, this review makes reference to comments provided to DNP in preparation for the NDA 22-399 end of review conference meeting held on May 18, 2010 (Williams JR, RCM 2010-764), and a gabapentin drug utilization review conducted by DEPI which analyzed the duration of and indications for gabapentin use in U.S. between 1993-2010 (Chang SH, RCM 2010-2470).

3 RESULTS OF REVIEW

3.1 OBJECTIVES

3.1.1 Objective

The primary objective of the GPRD studies weuskop4774 and weusrtp4931 was to assess the association between gabapentin exposure and incidence of cancer. Study weuskop4774 focused on the incidence of pancreatic and renal cancer in all patients exposed to gabapentin. Study weusrtp4931 was a parallel study which was limited to patients without a prior history of cancer before their first gabapentin exposure. In addition to pancreatic and renal cancer, study weuskop4931 included the following cancer outcomes: A) all cancer, B) stomach, C) anus, anal

canal, and anorectum, D) lung and bronchus, E) bones and joints, F) breast, G) penis, H) urinary bladder, and I) other nervous system.

3.1.2 OSE Comments on Objectives

The study objectives corresponded to DEPI previous recommendations and are acceptable. A signal for pancreatic acinar cell carcinoma was identified from animal-based pharmacology and toxicology data during the original NDA review. Another signal for kidney/renal pelvic cancer related to gabapentin exposure was identified from a case-control study using data from Kaiser Permanente Northern California (Friedman et al., 2009). These were the two primary cancer outcomes of concern. However, inspection of supplementary data from the Kaiser Permanente study submitted by the Sponsor identified a number of additional weak cancer signals associated with gabapentin exposure (Williams JR, RCM-2010-764). The FDA requested the Sponsor also investigate these weak signals.

3.2 STUDY DESIGN

3.2.1 Study Design

A nested case-control design was utilized for both studies. A comparison of the major design characteristics for each study, as described by the Sponsor, is provided in Table 1, and will be discussed in greater detail in subsequent sections. Overall, there are two major differences between studies weuskop4774 and weusrtp4931. First, subjects with a past history of cancer before first gabapentin exposure were excluded from the study cohort in weusrtp4931. Second, the scope of the cancer outcomes was expanded in weuskop4931. Otherwise, the two studies used very similar, if not identical, methodology.

Cases were risk set matched with up to 10 controls by sex, age at cohort entry (within two years), calendar year of cohort entry (within one year), and general practice site. The index date for cases was the date of the first diagnosis of the respective cancer. The index date for controls was set as the date at which the follow-up time from cohort entry was the same as the case. The index date was chosen so as to give the control equal follow-up time to that of the case for ascertainment of gabapentin use. Controls were required to be free of the respective cancer in the database up to the control's index date in study weuskop4774. Controls were required to be free of any cancer in the database up to the control's index date in study weusrtp4931.

A control could serve only once as a control on any specific outcome date, but could serve as a control for a case occurring on another outcome date. A future case could serve as a control up to one day prior to first diagnosis of the respective cancer. Cases and controls were required to have at least two years of follow-up in the GPRD before their index date.

3.2.2 OSE Comments on Proposed/Actual Design

Study weuskop4774 corresponds to the original study protocol submitted to the FDA by the Sponsor. DEPI previously found study weuskop4774's overall design to be acceptable but advised the Sponsor to exclude patients with a history of cancer prior to gabapentin exposure so as to limit protopathic bias. Protopathic bias occurs when a pharmaceutical agent is prescribed for an early manifestation of a disease that has yet to be formally recorded in the medical record. The sponsor incorporated DEPI's recommendations into study weusrtp4931. The proposed study design was appropriate for this safety issue. DEPI finds the design of both studies to be acceptable. One can view study weusrtp4931 to be the primary analysis and study weuskop4774 to be a sensitivity analysis.

Table 1. Comparison of Studies WEUSKOP4744 AND WEUSRTP4931

Protocol Section	WEUSKOP4774 (Pancreatic and Renal Cancer)	WEUSRTP4931 (Current Study)	Rationale
Study Cohort	No exclusions related to history of cancer prior to cohort entry.	Subjects are excluded from the GPRD cohort if they have a cancer diagnosis or a history of cancer prior to the cohort entry date.	Control for protopathic bias. Limit misclassification of primary cancer diagnosis codes that may be metastatic.
Case Selection	No exclusions related to diagnosis of other cancers prior to index date.	Cases must have no history of any other cancer prior to the index date (either codes for all-cancer diagnosis, or codes for personal past medical history of cancer).	Control for protopathic bias. Limit misclassification of primary cancer diagnosis codes that may be metastatic.
Control Selection	Controls are required to be free of <u>the specific</u> cancer outcome in the database up to the control's index date.	Controls are required to be free of <u>any</u> cancer in the database up to the control's index date.	To match exclusionary criteria for cases in the current study.
Exposure	Tertiles based on pooled pancreatic and renal controls	Tertiles based on all-cancer controls	Comparability of exposure measures among all cancers.
Confounders – Back Pain	Non-neuropathic back pain not included as a covariate.	Back pain included as a covariate.	To control for confounding by indication and protopathic bias.
Confounders – BMI	Estimated based on each subject's recorded height (one year or longer prior to index date) and weight (<u>between one and three years prior to the index date</u> , closest to 1 year prior to index date).	Estimated based on each subject's recorded height (one year or longer prior to index date) and weight (<u>closest to cohort entry date</u> , up to one year prior to index date).	Reduce missing values.

3.3 INFORMED CONSENT

3.3.1 Actual Informed Consent (if any)

Both study protocols were approved by the Independent Scientific Advisory Committee of the GPRD. The GPRD database contains fully anonymized patient records.

3.3.2 OSE Comments Actual Informed Consent (if any)

DEPI finds the ethical conduct in both studies to be acceptable.

3.4 DATA SOURCE(S)

3.4.1 Data Source(s)

GPRD was the data source used in both studies. GPRD is managed by the United Kingdom (U.K.) Medicines and Healthcare products Regulatory Agency (MHRA), AND comprises the entire computerized medical records of a sample of general practitioners (GPs) in the U.K. Each member of the population is registered with a GP who provides care and acts a gatekeeper for specialist referrals and hospital attendances. The data are collected from over 487 contributing practices throughout the U.K. As of 2008, it counts 3.19 million active patients (5.54 million in total). The GPRD population closely matches the age and gender distribution of the U.K population as a whole.

According to the Sponsor, this dataset was primarily chosen for its size, availability of longitudinal prescription data, long term follow-up (mean 7 years), representation of the elderly, and availability of data on risk factors such as smoking and BMI that are often not available in U.S. managed care or claims databases. In addition, the Sponsor reports that GPRD has also been used in previous nested case-control studies that evaluated the risk of pancreatic cancer with use of non-steroidal anti-inflammatory drugs and statins (Kaye, 2004; Langman, 2000), and of renal cell carcinoma with acetaminophen (Kaye, 2001).

3.4.2 OSE Comments on Actual Data Sources

The use of GPRD is acceptable. Disparate drug utilization patterns or inadequate sample size are often two limitations that prevent generalization of GPRD results to U.S. patients. Neither limitation applies to this analysis as will be discussed in subsequent sections.

3.5 STUDY TIME PERIOD

3.5.1 Study Time Period

The study period began on January 1, 1993 and ended on December 31, 2008. Entry into the study cohort began January 1, 1993 for all patients who were registered in GPRD on or before that time, and at the time of registration if later than January 1, 1993. Both studies conducted analyses with no lag period as well as analyses that allowed for a lag between exposure and incidence of cancer. For the no lag period analyses, the exposure and outcome ascertainment period spanned the entire study period. In addition, both studies included analyses which incorporated a two-year lag period between first gabapentin exposure and incidence of cancer. In lagged analyses, the exposure ascertainment period spanned the entire study period, but the outcome ascertainment period began two years after a subject's first gabapentin exposure and ended on December 31, 2008. As such the outcome ascertainment period did not begin for any subject before January 5, 1995 in the lagged analyses. In both studies, follow-up ended at time of cancer diagnosis, death, end of study period, or if the subject left GPRD. The Sponsor only included subjects with at least two years of follow-up time in the GPRD prior to the index date. For cases, the index date was the date of the first diagnosis of the respective cancer. For controls, the index date was set as the date at which the follow-up time from cohort entry was the same as the case. Any case or control which did not have two years of follow-up time between cohort entry and index date were excluded from the study.

3.5.2 OSE Comments on Actual Study Time Period

DEPI finds the study period to be acceptable. Gabapentin was approved in the U.K. in May 1993, so the study period encompasses a 15 year time which includes gabapentin's introduction into the U.K. market. Incorporation of a two-year lag period helps to minimize, but may not eliminate, protopathic bias. In addition, the lag period accounts for the latency period between cancer onset and cancer diagnosis in which gabapentin may not be a carcinogenetic exposure, unless it promotes tumor growth.

3.6 POPULATION

3.6.1 Population

As previously mentioned, both studies utilized the GPRD database which contains data from over 487 contributing practices throughout the U.K. As of 2008, it counts 3.19 million active patients (5.54 million in total). The GPRD population closely matches the age and gender distribution of the U.K. population as a whole.

3.6.2 OSE Comments on Proposed/Actual Population

DEPI believes the results of this study are applicable to a U.S. population. As previously mentioned, disparate drug utilization patterns or inadequate sample size are often two limitations that prevent generalization of GPRD results to U.S. patients. As will be subsequently discussed, neither limitation applies to this analysis.

3.7 EXPOSURE

3.7.1 Exposure

Gabapentin exposure was defined as at least one prescription recorded in the patient's GPRD medical records. Data on prescriptions for gabapentin were extracted for each case and control from entry into the study cohort up to the index date. Gabapentin exposure was parameterized as follows:

1. Ever versus never exposed
2. Number of prescriptions (tertiles versus never exposed)
3. Cumulative duration of exposure (tertiles versus never exposed)
4. Cumulative dose (tertiles versus never exposed)

These exposure parameterizations were also examined with a two year lag period from the index date.

3.7.2 OSE Comments on Proposed/Actual Exposure

The exposures parameterizations were consistent with DEPI's recommendation and are acceptable.

3.8 DISEASE OUTCOME OF INTEREST

3.8.1 Disease Outcome of Interest

The index date for the case was the earliest date of a cancer diagnosis in GPRD between 1995 and 2008. Analyses were restricted to subjects with at least two years of follow up time in GPRD prior to the index date. Outcomes were defined by READ/OXMIS codes. Clinical definitions for each outcome are described below:

- Pancreatic cancer
 - Exocrine pancreatic cancer, endocrine pancreatic cancer, and carcinoma in situ
- Renal cancer
 - Renal cell carcinoma and renal pelvis cancers
 - Excluded: Wilm's tumor (nephroblastoma) and tumors metastatic to kidney. According to the Sponsor, this study did not include as cases ~800 individuals with a mixed READ/OXMIS diagnosis of "Renal adenoma and carcinoma", which the Sponsor deemed not sufficiently specific for renal malignancy.
- All-cancer sites
- Stomach
 - Adenocarcinoma, carcinoma in situ, and gastric lymphoma

- Anus, anal canal, and anorectum
 - Carcinoma and carcinoma in situ
- Lung and bronchus:
 - Lung, bronchial and tracheal cancers, mesothelioma, and carcinoma in situ
- Bones and joints
 - Osteosarcoma, chondrosarcoma, Ewing sarcoma, adamantinoma of long bones, and giant cell sarcoma of bone
- Breast (females)
 - Carcinoma and carcinoma in situ
- Penis (males)
 - Carcinoma and carcinoma in situ
- Urinary bladder
 - Bladder and transitional cell carcinoma
- Other nervous system
 - Malignant meningiomas, spinal glioblastoma, and malignant tumors of cranial and peripheral nerves

Listings of the specific READ/OXMIS codes used for each outcome were provided by the Sponsor in an appendix to the study reports. The READ/OXMIS codes for the all-cancer sites outcome were derived from an external review by William T. Hamilton, MD, FRCP, FRCGP, Chair of the Early Diagnosis Subgroup within the U.K. National Cancer Research Institute, Primary Care Section. The all-cancer outcome included non-melanoma skin cancers and metastatic disease. The Sponsor also referenced previous GPRD validation studies for the specific cancer outcomes. (Harret E et al, 2010; Jick H et al, 1997; Meier CR et al, 2000) The exclusion of renal cancer cases solely identified by READ/OXMIS code for a mixed “Renal adenoma and carcinoma” is reasonable since this code is not specific to malignant adenocarcinomas, and as such would have introduced a misclassification bias.

3.8.2 OSE Comments on Proposed/Actual Disease Outcome of Interest

The Sponsor included all cancer sites which were potential signals in the Kaiser Permanente study in addition to obtaining an outside review of all cancer sites as recommended by DEPI’s recommendations (Friedman et al, 2001; Williams JR, RCM 2010-754). A high-level review of the appendix with the outcome coding did not reveal irregularities. The Sponsor’s list of outcomes and their associated definitions are acceptable to DEPI.

3.9 COVARIATES

3.9.1 Covariates

The Sponsor controlled for the following potential confounders in study weuskop4774:

- Age at cohort entry (part of matching criteria)
- Sex (part of matching criteria)

- Smoking status: current (within 1 year of index date), ever, never, missing (mutually exclusive)
- Body mass index: missing, <18.50 (underweight), 18.50-24.99 (normal weight), 25-29.99 (overweight), ≥30 kg/m² (obese)
- Chronic pancreatitis: yes/no (2 years prior to index date)
- History of hypertension: yes/no (any time up to the index date)
- History of diuretic use: yes/no (any time up the index date)
- History of epilepsy: yes/no (any time up to the index date)
- History of a neuropathic pain condition: yes/no (at any time up to the index date)
- History of diabetes: yes/no
 - Pancreatic cancer - adjustment was for history of diabetes two years prior to index date (yes/no)
 - Sponsor stated diabetes is a potential confounder since painful diabetic neuropathy is an indication for gabapentin, and diabetes is a risk factor for pancreatic cancer. However, diabetes may also be an early symptom of neoplastic destruction of endocrine pancreatic tissue – a manifestation of pancreatic cancer rather than a risk factor.
 - Renal cancer - yes/no (adjustment was for diabetes up to the index date)

In study weusrtp4931, the Sponsor included all covariates from study weuskop4774. In all analyses, the Sponsor also included a history of back pain (dorsalgia, cervicgia, strain, sprain) at any time up to the index date. In addition, the Sponsor included the following covariates for specific cancer outcomes in study weusrtp4931:

- All-cancer
 - Alcohol consumption
- Stomach cancer
 - Upper gastrointestinal disorders (gastroesophageal reflux, peptic ulcer, gastritis), acid-suppressing drugs (proton-pump inhibitors, H₂-receptor antagonists) up to 6 months before index date, and alcohol consumption
- Anus, anal canal, and anorectum cancer
 - HIV and HPV (anogenital warts, condylomas)
- Lung and bronchus cancer
 - Chronic obstructive pulmonary disease and alcohol consumption
- Bones and joint cancer
 - No additional covariates
- Breast cancer
 - Previous hysterectomy, current (within 6 months of index date) or previous hormone replacement therapy (systemic estrogen, including patches but excluding creams, either alone or in combination with a progestin), benign breast

disease (fibrocystic disease, intraductal papilloma, or fibroadenoma), and alcohol consumption

- Penile cancer
 - HIV, HPV (genital warts, condylomas), and phimosis/balanitis
- Urinary and bladder cancer
 - No additional covariates
- Other nervous system
 - No additional covariates

3.9.2 OSE Comments on Actual Covariates

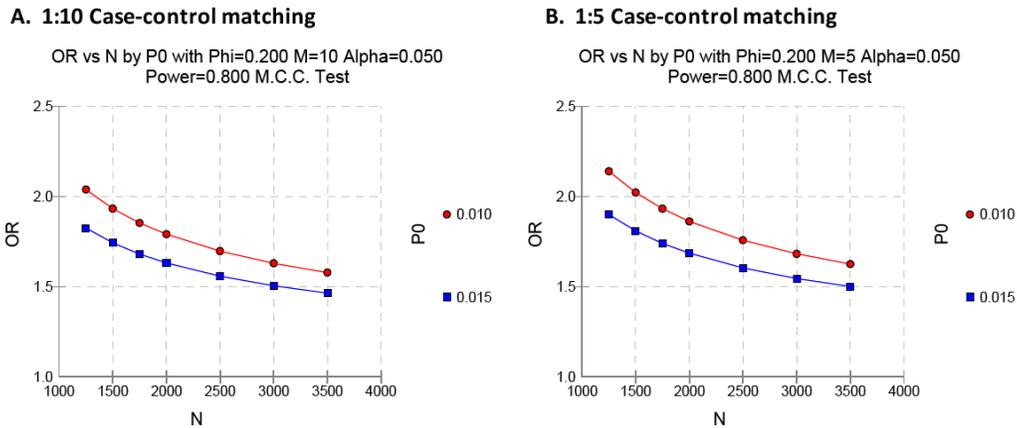
The covariates specified are acceptable and correspond to DEPI's recommendations. While conditions such as epilepsy, diabetic neuropathy, and back pain are not risk factors for cancer, they are conditions for which gabapentin is prescribed. Unmeasured confounding is a concern in any study, however the only major risk factor that is absent from the analyses is family history of cancer, which is not available in GPRD. Residual confounding related to missing covariate data is another concern. In both studies, smoking status was coded as missing in approximately 10% of patients in each cohort. BMI was coded as missing in approximately 60% of each cohort in study weuskop4774; whereas BMI was coded as missing in approximately 60% of each cohort in study weusrtp4931. The reason for such a discrepancy is highlighted in Table 1. BMI was calculated based on a patient's last recorded weight in an interval between one to three years before the index date in study weuskop4774, but was calculated with the weight recorded closest to the date one year prior to the index date in study weusrtp4931. The Sponsor stated the variable definition was changed to minimize the rate of missing data. Regardless, the potential for residual confounding must be acknowledged.

3.10 SAMPLE SIZE

3.10.1 Sample Size

The Sponsor provided power calculations for both studies. The Sponsor's initial feasibility assessment for study weuskop4774 identified approximately 3,300 incident pancreatic cancer cases and 68,599 distinct gabapentin users (a 1.1% gabapentin exposure rate) in GPRD from 1995-2008. Figure 1 provided by the Sponsor shows the power curves for a case-control study with either 1:10 or 1:5 case-control matching and gabapentin exposure rates of 1.0% or 1.5%. With 1:10 case-control matching, the Sponsor stated that a study could detect an odds ratio (OR)=1.70 with 2,500 cases and 1.0% gabapentin exposure or an OR=1.46 with 3,500 cases and 1.5% gabapentin exposure. Under 1:5 case:control matching, the respective range of detectable ORs is 1.76 to 1.50 (Figure 1).

Figure 1. Study WEUSKOP4774: Pancreatic Cancer Power Curves



Minimum detectable OR (=RR in a nested case-control study, y-axis) for 1,250-3,500 cancer cases (x-axis), each matched to 10 controls (A) or 5 controls (B), under rates of gabapentin exposure of 1.0% (red) and 1.5% (blue). (NCSS/PASS Software [J Hintze, 2006, Kaysville, UT]) Matched-Case-Control Study).

Table 2 provided by the Sponsor lists the minimum detectable odds ratios for study weusrtp4931 for different exposure parameterizations and assumptions of the outcome incidence rate.

Table 2. Study WEUSRTP4931: Minimum Detectable Odds Ratios

Cancer	UK incidence (per 100,000 person-years) ¹	Estimated GPRD Cases	Minimum OR ever/never	Minimum OR > 7 mo use	Minimum OR > 1 y use	Minimum OR > 2y use	Minimum OR > 5y use
Proportion Exposed			0.50%	0.20%	0.10%	0.06%	0.03%
All-cancer sites	375.4	125,000	1.13	1.20	1.29	1.38	1.55
Lung and bronchus	47.4	15,000	1.38	1.62	1.92	2.25	2.91
Breast	63.8	10,000	1.47	1.78	2.17	2.60	3.48
Bladder	11.8	4,000	1.79	2.34	3.06	3.88	5.70
Kidney	10.1	3,000	1.93	2.60	3.48	4.51	6.84
Pancreas	9.1	3,000	1.93	2.60	3.48	4.51	6.84
Stomach	8.9	3,000	1.93	2.60	3.48	4.51	6.84
Anus, anal canal, and anorectum	1.2	400	4.30	7.45	12.46	19.44	40.08
Penis	1.5 (men)	250	5.63	10.49	18.78	31.25	74.77
Bones and joints	0.8	250	5.63	10.49	18.78	31.25	74.77
Other nervous system	0.3	100	10.65	23.53	50.88	-	-

1. [Cancer Research UK, 2010]

3.10.2 OSE Comments on Actual Sample Size

The assumptions used for the power calculations are reasonable and the calculations appear to be valid. Both GPRD studies are powered to detect an OR of at least two for all specified cancer

outcomes, except for anus, anal canal, and anorectum, penile, bones and joints, and other nervous system cancers. The larger minimum detectable odds ratio for these outcomes is also acceptable as DEPI previously communicated to the Sponsor that ruling out large effect sizes for these rare outcomes would be informative. As such, DEPI finds these studies to be adequately powered to fulfill the study objectives. However, these studies cannot rule out associations smaller than those listed in Table 2. Therefore, these studies cannot be interpreted to exclude any association between gabapentin and cancer outcomes.

3.11 ANALYSIS PLAN

3.11.1 Analysis Plan

The Sponsor calculated crude and multivariable adjusted ORs to measure the association between gabapentin exposure and incident cancer outcomes using conditional logistic regression. For each cancer outcome, parallel two-year lag and no lag analyses were performed for each exposure parameterization (ever versus never, number of prescriptions, duration of exposure, and cumulative exposure). The covariates included in each multivariable model are listed in section 3.9.1. Pancreatic and renal cancers were the primary outcome for these studies, but they were not explicitly designated as co-primary endpoints.

3.11.2 OSE Comments on Analysis Plan

The analysis plan was adequately described. No specific exposure parameterization was pre-specified as the primary analysis. Also, there was no pre-specified α adjustment for multiple comparisons. Neither pre-specification of a primary exposure parameterization nor adjustment for multiple comparisons were among DEPI's recommendation provided to the Sponsor. The possibility of a type I error (false positive) must be taken into account when incorporating evidence from these studies into this NDA's risk/benefit discussion.

3.12 STUDY RESULTS

3.12.1 Study Results

3.12.1.1 Study WEUSKOP4774

All analyses conducted in study weuskop4774 allowed patients with a previous history of cancer to be included in the cohorts. The main findings for each outcome will be highlighted below.

3.12.1.1.1 Pancreatic Cancer

Between 1995 and 2008, 3,161 patients with a pancreatic cancer diagnoses were identified in GPRD. Exocrine pancreatic cancer accounted for 99.8% of cases, and overall 81.8% were pancreatic adenocarcinomas. There was only one case of acinar cell carcinoma. GPRD cohort's incidence rate for pancreatic cancer was 10.4 per 100,000 person-years which was lower than the reported crude incidence rate in the UK of 12.7 per 100,000 person-years (NCRI, 2008).

The 3,149 pancreatic cancer cases were risk set matched to 30,026 controls by sex, age at cohort entry (within two years), cohort entry date (within one year), and general practice. Twelve pancreatic cancer cases were not matched to any controls, and were excluded from the analyses. Cases and controls were similar in terms of age at index date, gender, duration of follow-up from cohort entry to index date, and duration of follow-up from GPRD registration to index date. Overall, mean duration of follow-up from cohort entry to index date was 9.0-9.1 (SD 3.9) years.

Cases were more likely to be current smokers, and to have a history of diabetes and chronic pancreatitis relative to controls (Table 3).

Table 3. Study WEUSKOP4774: Characteristics of GPRD Diagnosed Pancreatic Cancer Cases and Matched Controls

Characteristic	Level	Cases (N) N=3,149	Cases (%)	Controls (N) ⁴ N=30,026	Controls (%)
Age at Index Date (y)	Mean (SD)	71.9 (11.51)		71.5 (11.47)	
	< 40 y	18	0.6	199	0.7
	40-49 y	86	2.7	897	3.0
	50-59 y	367	11.7	3,616	12.0
	60-69 y	748	23.8	7,234	24.1
	70-79 y	1,033	32.8	10,092	33.6
	80+ y	897	28.5	7,988	26.6
Gender	Female	1,603	50.9	15,316	51.0
	Male	1,546	49.1	14,710	49.0
Duration of follow-up from registration to index date (y)	Mean (SD)	21.2 (15.38)		21.9 (15.33)	
	2-3 y	173	5.5	1,460	4.9
	4-5 y	185	5.9	1,509	5.0
	6-7 y	237	7.5	2,007	6.7
	>= 8 y	2,554	81.1	25,050	83.4
Duration of follow-up from cohort entry to index date (y) ³	Mean (SD)	9.0 (3.90)		9.1 (3.90)	
	2-3 y	446	14.2	4,121	13.7
	4-5 y	396	12.6	3,656	12.2
	6-7 y	447	14.2	4,213	14.0
	>= 8 y	1,860	59.1	18,036	60.1
BMI (kg/m ²) ¹	Mean (SD)	26.8 (4.97)		27.0 (4.94)	
	BMI: < 18.5	25	0.8	203	0.7
	BMI: 18.5 to 24.99	459	14.6	3,678	12.2
	BMI: 25 to 29.99	457	14.5	4,250	14.2
	BMI: 30 or greater	291	9.2	2,476	8.2
	BMI: Missing	1,917	60.9	19,419	64.7

Table 3. Study WEUSKOP4774: Characteristics of GPRD Diagnosed Pancreatic Cancer Cases and Matched Controls (continued)

Characteristic	Level	Cases (N) N=3,149	Cases (%)	Controls (N) ⁴ N=30,026	Controls (%)
Smoking Status	Current	731	23.2	4,857	16.2
	Ex	768	24.4	6,626	22.1
	Never	1,385	44.0	15,249	50.8
	Unknown	265	8.4	3,294	11.0
Comorbidities	Diabetes ²	363	11.5	2,137	7.1
	Epilepsy	53	1.7	458	1.5
	Neuropathic Pain	737	23.4	6,616	22.0
	Chronic Pancreatitis ²	13	0.4	17	0.1

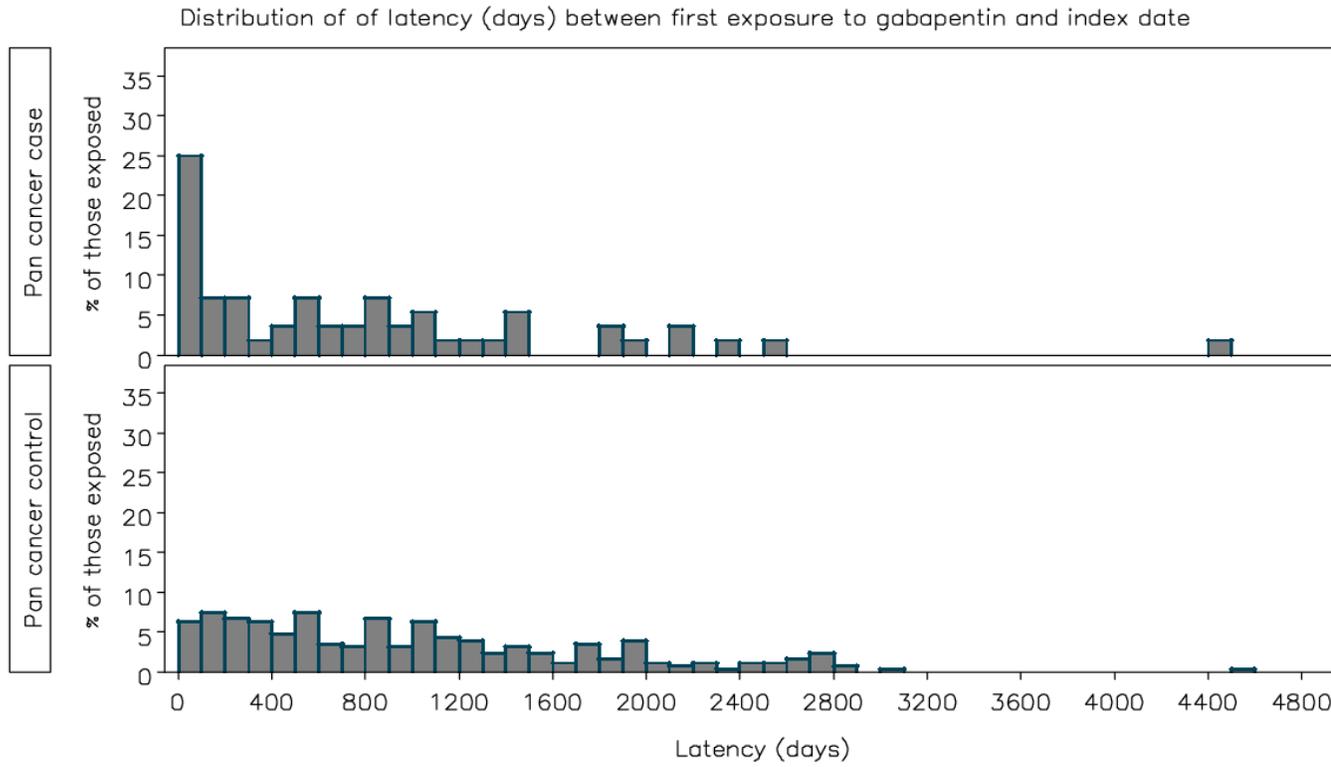
1. 1-3 years prior to index date.
2. 2 years prior to index date.
3. Entry into the study cohort began Jan 1, 1993 for all those who were registered in GPRD before that time, and at the time of registration if later than Jan 1, 1993.
4. NOTE: 2,868 (91.1%) of the 3,149 matched cases were 1:10 matched; 181 (5.7%) were 1:4 to 1:9 matched; 100 (3.2%) were 1:1 to 1:3 matched. N=12 of all pancreatic cancer cases were unable to be matched.

Exposure patterns for cases and controls are shown in Table 4 as provided by the Sponsor. Most patients had limited exposure to gabapentin. For example, the first (lowest) tertile for the number of prescriptions ranged from one to two prescriptions. The distribution of latency between first exposure to gabapentin and the index date is shown in Figure 2. Of note, among the 56 pancreatic cancer cases exposed to gabapentin, 24 (25%) were first exposed within 100 days of the index date, and 32 (57%) were first exposed within two years of the index date (cancer diagnosis). In contrast, among the 253 control subjects exposed to gabapentin, 13 (5%) were first exposed within 100 days of the index date, and 110 (43%) were first exposed within two years of the index date. Overall, most gabapentin exposed pancreatic cancer cases were classified in the lowest exposure tertiles.

The association between pancreatic cancer and gabapentin exposure in the no lag and two-year lagged analyses is summarized in Table 5 provided by the Sponsor. In the crude analyses, gabapentin was associated with an increased risk of pancreatic cancer in the ever versus never exposure no lag analysis, but not in the two year lag analysis. In addition, gabapentin was associated with pancreatic cancer in comparisons of no exposure versus the first tertile of exposure for the number of prescriptions, duration of exposure, and cumulative dose parameterizations. No statistically significant associations were detected at higher levels of exposure, with point estimates considerably lower than those observed in the first tertile of exposure. The same pattern was observed after multivariate adjustment; however point estimates were reduced by approximately 10%.

The Sponsor conducted a post-hoc analysis of the demographic and clinical characteristics of the cases and controls stratified by gabapentin exposure. As shown in Figure 2, 55% of gabapentin-exposed pancreatic cancer cases had a history of neuropathic pain diagnosis compared to 73% of gabapentin-exposed controls. In addition, 5% of gabapentin-exposed cancer cases had a history of epilepsy, compared to 6% of controls. The Sponsor concluded that a greater proportion of gabapentin-exposed pancreatic cancer cases than controls lacked a diagnosis code for the approved indications for gabapentin. The Sponsor suggested that this pattern of use was also suggestive of a protopathic bias.

Figure 2. Study WEUSKOP4774: Distribution of Time from First Gabapentin Prescription (in Days) to Index Date in Gabapentin-Exposed Pancreatic Cancer Cases and Controls



Pan=pancreatic.

Table 4. Study WEUSKOP4774: Distribution of Gabapentin Exposure in Pancreatic Cancer Cases and Controls

Gabapentin Exposure		Cases (N) N=3,149	Cases (%)	Controls (N) N=30,026	Controls (%)
EXPOSURE WINDOW: Entry into GPRD to index date					
Gabapentin Exposure	Ever	56	1.8	253	0.8
	Never	3,093	98.2	29,773	99.2
Number of Prescriptions (n)	Mean (SD)	8.5 (16.74)		13.8 (24.44)	
	None	3,093	98.2	29,773	99.2
	Tertile 1 (1-2)	30	1.0	99	0.3
	Tertile 2 (3-8)	12	0.4	64	0.2
	Tertile 3 (9-218)	14	0.4	90	0.3
Duration of Use (months)	Mean (SD) ¹	6.1 (11.07)		9.6 (13.93)	
	None	3,093	98.2	29,773	99.2
	Tertile 1 (0.01 - 1.55 mo)	28	0.9	83	0.3
	Tertile 2 (1.56 - 6.44 mo)	14	0.4	79	0.3
	Tertile 3 (6.45 - 78.36 mo)	14	0.4	91	0.3
Cumulative Dose (g)	Mean (SD) ¹	305.1 (822.3)		395.3 (743.3)	
	None	3,093	98.2	29,773	99.2
	Tertile 1 (0.01 - 33.6 g)	28	0.9	88	0.3
	Tertile 2 (33.7 - 185.0 g)	14	0.4	74	0.2
	Tertile 3 (185.1 - 7500.2 g)	14	0.4	91	0.3
EXPOSURE WINDOW: Entry into GPRD to 2 years prior to index date					
Gabapentin Exposure	Ever	24	0.8	143	0.5
	Never	3,125	99.2	29,883	99.5
Number of Prescriptions (n)	Mean (SD) ¹	11.4 (19.98)		13.2 (22.62)	
	None	3,125	99.2	29,883	99.5
	Tertile 1 (1-2)	14	0.4	48	0.2
	Tertile 2 (3-10)	3	0.1	49	0.2
	Tertile 3 (11-191)	7	0.2	46	0.2
Duration of Use (months)	Mean (SD) ¹	8.0 (12.22)		9.2 (12.16)	
	None	3,125	99.2	29,883	99.5
	Tertile 1 (0.01 - 1.78 mo)	13	0.4	44	0.1
	Tertile 2 (1.79 - 7.20 mo)	4	0.1	47	0.2
	Tertile 3 (7.21 - 64.13 mo)	7	0.2	52	0.2
Cumulative Dose (g)	Mean (SD) ¹	413.2 (881.9)		373.7 (687.6)	
	None	3,125	99.2	29,883	99.5
	Tertile 1 (0.01 - 39.0 g)	11	0.3	46	0.2
	Tertile 2 (39.1 - 210.0 g)	7	0.2	47	0.2
	Tertile 3 (210.1 - 5623.8 g)	6	0.2	50	0.2

1. Among gabapentin users

Table 5. Study WEUSKOP4774: Risk of Pancreatic Cancer with Gabapentin Exposure

Exposure Model	Without 2 year lag		With 2 year lag	
	Unadjusted OR (95% CI) p-value	Adjusted OR (95% CI) p-value ¹	Unadjusted OR (95% CI) p-value	Adjusted OR (95% CI) p-value ¹
Gabapentin (Ever vs Never)	2.04 (1.51, 2.75) p < .0001	1.82 (1.34, 2.46) p = 0.0001	1.52 (0.98, 2.36) p = 0.0627	1.33 (0.85, 2.08) p = 0.2183
Gabapentin Prescriptions^{2,3}				
Tertile1 vs Never	2.82 (1.86, 4.28) p < .0001	2.53 (1.66, 3.85) p < .0001	2.75 (1.51, 5.03) p = 0.0010	2.44 (1.32, 4.49) p = 0.0042
Tertile2 vs Never	1.80 (0.97, 3.36) p = 0.0645	1.65 (0.87, 3.11) p = 0.1232	0.55 (0.17, 1.78) p = 0.3160	0.48 (0.15, 1.57) p = 0.2234
Tertile3 vs Never	1.35 (0.76, 2.42) p = 0.3071	1.17 (0.65, 2.11) p = 0.6062	1.31 (0.58, 2.97) p = 0.5205	1.11 (0.48, 2.57) p = 0.8042
Duration of exposure (mo)^{4,5}				
Tertile1 vs Never	3.15 (2.04, 4.86) p < .0001	2.88 (1.85, 4.46) p < .0001	2.75 (1.47, 5.13) p = 0.0015	2.45 (1.31, 4.62) p = 0.0053
Tertile2 vs Never	1.68 (0.94, 2.99) p = 0.0777	1.50 (0.83, 2.69) p = 0.1762	0.82 (0.29, 2.28) p = 0.6990	0.72 (0.26, 2.01) p = 0.5274
Tertile3 vs Never	1.34 (0.75, 2.39) p = 0.3245	1.15 (0.64, 2.07) p = 0.6388	1.11 (0.49, 2.51) p = 0.7960	0.94 (0.41, 2.15) p = 0.8772

Exposure Model	Without 2 year lag		With 2 year lag	
	Unadjusted OR (95% CI) p-value	Adjusted OR (95% CI) p-value ¹	Unadjusted OR (95% CI) p-value	Adjusted OR (95% CI) p-value ¹
Cumulative Exposure (g)^{6,7}				
Tertile1 vs Never	2.90 (1.88, 4.47) p < .0001	2.65 (1.71, 4.11) p < .0001	2.19 (1.12, 4.25) p = 0.0212	1.95 (0.99, 3.81) p = 0.0522
Tertile2 vs Never	1.87 (1.05, 3.32) p = 0.0337	1.64 (0.92, 2.95) p = 0.0947	1.42 (0.64, 3.16) p = 0.3928	1.21 (0.54, 2.72) p = 0.6502
Tertile3 vs Never	1.34 (0.75, 2.39) p = 0.3275	1.15 (0.64, 2.08) p = 0.6365	1.01 (0.42, 2.41) p = 0.9858	0.87 (0.36, 2.12) p = 0.7671

- Adjusted for smoking, BMI, diabetes, chronic pancreatitis, neuropathic pain, epilepsy
- The tertiles for number of prescriptions in the analysis without 2 year lag are: Tertile 1 (1-2). Tertile 2 (3-8). Tertile 3 (9-218).
- The tertiles for number of prescriptions in the analysis with 2 year lag are: Tertile 1 (1-2). Tertile 2 (3-10). Tertile 3 (11-191).
- The tertiles for cumulative duration in the analysis without 2 year lag are: Tertile 1 (0.01 - 1.55 mo). Tertile 2 (1.56 - 6.44 mo). Tertile 3 (6.45 - 78.36 mo).
- The tertiles for cumulative duration in the analysis with 2 year lag are: Tertile 1 (0.01 - 1.78 mo). Tertile 2 (1.79 - 7.20 mo). Tertile 3 (7.21 - 64.13 mo)
- The tertiles for cumulative dose in the analysis without 2 year lag are: Tertile 1 (0.01 - 33.6 g). Tertile 2 (33.7 - 185.0 g). Tertile 3 (185.1 - 7500.2 g).
- The tertiles for cumulative dose in the analysis with 2 year lag are: Tertile 1 (0.01 - 39.0 g) Tertile 2 (39.1 - 210.0 g). Tertile 3 (210.1 - 5623.8 g).

The Sponsor conducted an additional post-hoc analysis of gabapentin use patterns prior to pancreatic cancer diagnosis to examine potential latency and protopathic bias. The Sponsor identified 8/56 (14%) of gabapentin-exposed pancreatic cancer cases were likely first exposed to gabapentin after cancer onset (based on a non-specific cancer diagnosis or another malignancy) but before the index date (based on a specific record of pancreatic cancer). Among these patients, seven of the eight had pain or palliative care diagnoses concurrent with the gabapentin prescription. These cancer-related diagnoses occurred up to three years prior to the specific index pancreatic cancer diagnosis. Examples of potential protopathic bias in pancreatic cancer cases are shown in Figure 3.

Figure 3. Study WEUSKOP4774: Listing of Index Pancreatic Cancer Diagnosis, First Gabapentin Exposure, and Other Cancer Diagnoses.

ID	Index diagnosis	Index date	Related diagnosis	Date of related diagnosis	Possible gabapentin indication and date	Date of first gabapentin prescription	Latency between first prescription and index date (days)	Other cancer diagnoses	Date of other cancer diagnoses	Comment
2292051	Malignant neoplasm of pancreas	6/26/2008			Neuralgia unspecified (3/6/2006)	3/6/2006	843	TRANSURETHRAL RESECTION OF TUMOUR	5/9/1991	Possible past history of bladder cancer.
2373344	Malignant neoplasm of pancreas	9/17/2002	Carcinoma of other and unspecified sites	8/1/2001	Low back pain (4/11/2002)	4/11/2002	159	Malig neopoth/vill-defined sites digestive tract/peritoneum Cancer of ovary Carcinoma of other and unspecified sites Malignant neoplasm of other and unspecified site NOS Liver metastases [M]Carcinoma, metastatic, NOS	5/2/2001 7/22/2001 8/1/2001 2/5/2002 2/7/2002 3/14/2002	Gabapentin for back pain after nonspecific diagnosis of carcinoma. Past history of ovarian cancer.

3.12.1.1.2 Renal Cancer

1,988 specific renal cancer diagnoses were identified in GPRD between 1995-2008 (Table 6). 94.7% were renal cell carcinoma, and 4.8% were renal pelvis cancer. The GPRD incidence rate for renal cell carcinoma of 6.2 per 100,000 person-years is lower than the reported crude incidence rate in the UK of 10.6 per 100,000 person-years (NCRI, 2008). The Sponsor did not include as cases “approximately 800 individuals” with a mixed READ/OXMIS diagnosis of “Renal adenoma and carcinoma”. The Sponsor deemed this code not sufficiently specific for renal malignancy.

The 1,981 pancreatic cancer cases were risk set matched to 19,046 controls by sex, age at cohort entry (within two years), cohort entry date (within one year), and general practice. Seven

pancreatic cancer cases were not matched to any controls, and were excluded from the analyses. Cases and controls were similar in terms of age at index date, gender, duration of follow-up from cohort entry to index date, and duration of follow-up from GPRD registration to index date. Overall, mean duration of follow-up from cohort entry to index date was 9.4-9.5 (SD 4.1) years. Cases were more likely to be current smokers, and had a history of hypertension, diuretic use, and diabetes relative to controls (Table 7).

Exposure patterns for cases and controls are shown in Table 8, as provided by the Sponsor. As was seen in pancreatic cancer analysis, first exposure to gabapentin occurred closer to the index date for cases than for controls. The distribution of latency between first exposure to gabapentin and the index date in the renal cancer analysis is shown in Figure 3. Of note, among the 32 renal cancer cases exposed to gabapentin, 10 (31%) were first exposed within 100 days of the index date, and 19 (59%) were first exposed within two years of the index date (cancer diagnosis). In contrast, among the 166 control subjects exposed to gabapentin, 9 (5%) were first exposed within 100 days of the index date, and 90 (54%) were first exposed within two years of the index date.

As expected, the distribution of controls in each gabapentin exposure tertile was similar (i.e. 0.2-0.4% of controls were in each tertile of distribution in the unlagged exposure window; 0.1-0.2% in each tertile of the lagged exposure window). However, renal cancer cases tended to be weighted to the lower two exposure tertiles (i.e. 0.5-0.9% of cases were in the lower two tertiles, with 0.3-0.4% in each of the higher tertiles in the unlagged exposure window).

The odds of renal cancer with gabapentin exposure in the unlagged and two-year lagged analyses are summarized in Table 9, as provided by the Sponsor. In the crude analyses, gabapentin was associated with an increased risk of renal cancer in the no lag ever versus never exposure analysis, but not in the two year lag analysis. In addition, gabapentin was associated with renal cancer in no lag analyses of no exposure versus the first tertile of exposure for the number of prescriptions, duration of exposure, and cumulative dose parameterizations. No statistically significant associations were detected in two-year lagged analyses or at higher levels of exposure, with point estimates considerably lower than those observed in the first tertile of exposure. The same pattern was observed after multivariate adjustment; however there were no consistent effect on the magnitude of the point estimates.

The Sponsor conducted a post-hoc analysis of the demographic and clinical characteristics of the cases and controls stratified by gabapentin exposure. As shown in Figure 4, 53% of gabapentin-exposed renal cancer cases had a history of neuropathic pain diagnosis compared to 66% of gabapentin-exposed controls. In addition, 3% of gabapentin-exposed renal cancer cases had a history of epilepsy, compared to 5% of controls. The Sponsor concluded that a greater proportion of gabapentin-exposed cases than controls lacked a diagnosis code for the approved indications for gabapentin.

The Sponsor conducted an additional post-hoc analysis of gabapentin use patterns prior to renal cancer diagnosis to examine potential latency and protopathic bias. The Sponsor identified 12/32 (38%) of gabapentin-exposed renal cancer cases were likely first exposed to gabapentin after cancer onset (based on a non-specific cancer diagnosis or another malignancy) but before the index date (based on a specific record of pancreatic cancer). Among these patients, seven of the eight had pain or palliative care diagnoses concurrent with the gabapentin prescription. These cancer-related diagnoses occurred up to three years prior to the specific index renal cancer diagnosis. Examples of potential protopathic bias are provided in Figure 5.

Table 7. Study WEUSKOP4774: Characteristics of GPRD Diagnosed Renal Cancer Cases and Matched Controls

Characteristic	Level	Cases (N) N=1,981	Cases (%)	Controls (N) ³ N=19,046	Controls (%)
Age at Index Date (y)	Mean (SD)	67.1 (12.68)		66.7 (12.67)	
	< 40 y	43	2.2	446	2.3
	40-49 y	134	6.8	1,348	7.1
	50-59 y	355	17.9	3,418	17.9
	60-69 y	528	26.7	5,199	27.3
	70-79 y	594	30.0	5,604	29.4
Gender	80+ y	327	16.5	3,031	15.9
	Female	759	38.3	7,273	38.2
Duration of follow-up from registration to index date (y)	Male	1,222	61.7	11,773	61.8
	Mean (SD)	21.3 (15.44)		21.3 (14.91)	
	2-3 y	129	6.5	1,081	5.7
	4-5 y	117	5.9	1,135	6.0
	6-7 y	141	7.1	1,280	6.7
	>= 8 y	1,594	80.5	15,550	81.6
Duration of follow-up from cohort entry to index date (y) ²	Mean (SD)	9.4 (4.10)		9.5 (4.09)	
	2-3 y	286	14.4	2,653	13.9
	4-5 y	226	11.4	2,122	11.1
	6-7 y	246	12.4	2,338	12.3
	>= 8 y	1,223	61.7	11,933	62.7
	BMI (kg/m2) ¹	Mean (SD)	27.8 (5.29)		27.3 (4.92)
Smoking Status	BMI: < 18.5	18	0.9	110	0.6
	BMI: 18.5 to 24.99	237	12.0	2,236	11.7
	BMI: 25 to 29.99	326	16.5	2,938	15.4
	BMI: 30 or greater	250	12.6	1,773	9.3
	BMI: Missing	1,150	58.1	11,989	62.9
	Current	476	24.0	3,555	18.7
Comorbidities	Ex	524	26.5	4,589	24.1
	Never	867	43.8	9,121	47.9
	Unknown	114	5.8	1,781	9.4
Comorbidities	Hypertension	1,159	58.5	9,113	47.8
	Diuretic use	875	44.2	6,396	33.6
	Diabetes	240	12.1	1,598	8.4
	Epilepsy	33	1.7	303	1.6
	Neuropathic Pain	428	21.6	4,018	21.1

- 1-3 years prior to index date.
- Entry into the study cohort began Jan 1, 1993 for all those who were registered in GPRD before that time, and at the time of registration if later than Jan 1, 1993.
- NOTE: 1,821 (91.9%) of the 1,981 matched cases were 1:10 matched; 107 (5.4%) were 1:4 to 1:9 matched; 53 (2.7%) were 1:1 to 1:3 matched. N=7 of the GPRD renal cancer cases were unable to be matched.

Table 8. Study WEUSKOP4774: Distribution of Gabapentin Exposure in Renal Cancer Cases and Controls.

Gabapentin Exposure		Cases (N) N=1,981	Cases (%)	Controls (N) N=19,046	Controls (%)
EXPOSURE WINDOW: Entry into GPRD to index date					
Gabapentin Exposure	Ever	32	1.6	166	0.9
	Never	1,949	98.4	18,880	99.1
Number of Prescriptions (n)	Mean (SD) ¹	10.1 (19.30)		9.9 (13.48)	
	None	1,949	98.4	18,880	99.1
	Tertile 1 (1-2)	16	0.8	58	0.3
	Tertile 2 (3-8)	11	0.6	55	0.3
	Tertile 3 (9-218)	5	0.3	53	0.3
Duration of Use (months)	Mean (SD) ¹	7.6 (14.06)		7.8 (10.92)	
	None	1,949	98.4	18,880	99.1
	Tertile 1 (0.01 - 1.55 mo)	15	0.8	44	0.2
	Tertile 2 (1.56 - 6.44 mo)	10	0.5	67	0.4
	Tertile 3 (6.45 - 78.36 mo)	7	0.4	55	0.3
Cumulative Dose (g)	Mean (SD) ¹	407.6 (1338)		315.4 (525.2)	
	None	1,949	98.4	18,880	99.1
	Tertile 1 (0.01 - 33.6 g)	9	0.5	45	0.2
	Tertile 2 (33.7 - 185.0 g)	17	0.9	63	0.3
	Tertile 3 (185.1 - 7500.2 g)	6	0.3	58	0.3

Table 9. Study WEUSKOP4774: Risk of Renal Cancer with Gabapentin Exposure

Exposure Model	Without 2 year lag		With 2 year lag	
	Unadjusted OR (95% CI) p-value	Adjusted OR (95% CI) p-value ¹	Unadjusted OR (95% CI) p-value	Adjusted OR (95% CI) p-value ¹
Gabapentin (Ever vs Never)	1.79 (1.22, 2.63) p = 0.0031	1.68 (1.13, 2.49) p = 0.0095	1.65 (0.91, 2.99) p = 0.0970	1.63 (0.89, 2.97) p = 0.1123
Gabapentin Prescriptions ^{2,3}				
Tertile1 vs Never	2.53 (1.44, 4.44) p = 0.0012	2.34 (1.32, 4.14) p = 0.0034	2.18 (0.90, 5.32) p = 0.0856	2.14 (0.87, 5.28) p = 0.0996
Tertile2 vs Never	1.89 (0.98, 3.63) p = 0.0563	1.77 (0.92, 3.43) p = 0.0896	1.40 (0.49, 4.01) p = 0.5308	1.39 (0.48, 4.02) p = 0.5458
Tertile3 vs Never	0.87 (0.35, 2.19) p = 0.7744	0.83 (0.33, 2.11) p = 0.6999	1.32 (0.39, 4.47) p = 0.6528	1.30 (0.38, 4.47) p = 0.6722
Duration of exposure (mo) ^{4,5}				
Tertile1 vs Never	3.24 (1.79, 5.85) p = <.0001	2.90 (1.59, 5.28) p = 0.0005	2.54 (1.03, 6.25) p = 0.0420	2.40 (0.96, 5.98) p = 0.0603
Tertile2 vs Never	1.35 (0.69, 2.65) p = 0.3762	1.33 (0.68, 2.63) p = 0.4073	0.95 (0.29, 3.12) p = 0.9294	0.99 (0.30, 3.29) p = 0.9875
Tertile3 vs Never	1.19 (0.54, 2.63) p = 0.6600	1.10 (0.50, 2.45) p = 0.8110	1.70 (0.58, 4.96) p = 0.3336	1.63 (0.55, 4.84) p = 0.3782
Cumulative Exposure (g) ^{6,7}				
Tertile1 vs Never	1.89 (0.92, 3.88) p = 0.0841	1.75 (0.85, 3.63) p = 0.1313	2.03 (0.78, 5.34) p = 0.1488	2.05 (0.77, 5.46) p = 0.1495
Tertile2 vs Never	2.44 (1.42, 4.22) p = 0.0013	2.34 (1.35, 4.07) p = 0.0026	1.78 (0.68, 4.69) p = 0.2421	1.70 (0.64, 4.53) p = 0.2899
Tertile3 vs Never	0.99 (0.42, 2.29) p = 0.9723	0.91 (0.39, 2.13) p = 0.8206	1.15 (0.35, 3.82) p = 0.8135	1.15 (0.34, 3.86) p = 0.8173

1. Adjusted for smoking, BMI, hypertension, diuretic use, diabetes, neuropathic pain, and epilepsy.
2. The tertiles for number of prescriptions in the analysis without 2 year lag are: Tertile 1 (1-2). Tertile 2 (3-8). Tertile 3 (9-218).
3. The tertiles for number of prescriptions in the analysis with 2 year lag are: Tertile 1 (1-2). Tertile 2 (3-10). Tertile 3 (11-191).
4. The tertiles for cumulative duration in the analysis without 2 year lag are: Tertile 1 (0.01 - 1.55 mo). Tertile 2 (1.56 - 6.44 mo). Tertile 3 (6.45 - 78.36 mo).
5. The tertiles for cumulative duration in the analysis with 2 year lag are: Tertile 1 (0.01 - 1.78 mo). Tertile 2 (1.79 - 7.20 mo). Tertile 3 (7.21 - 64.13 mo).
6. The tertiles for cumulative dose in the analysis without 2 year lag are: Tertile 1 (0.01 - 33.6 g). Tertile 2 (33.7 - 185.0 g). Tertile 3 (185.1 - 7500.2 g).
7. The tertiles for cumulative dose in the analysis with 2 year lag are: Tertile 1 (0.01 - 39.0 g). Tertile 2 (39.1 - 210.0 g). Tertile 3 (210.1 - 5623.8 g).

Figure 4. Study WEUSKOP4774: Distribution of Time from First Gabapentin Prescription (in Days) To Index Date in Gabapentin-Exposed Renal Cancer Cases and Controls

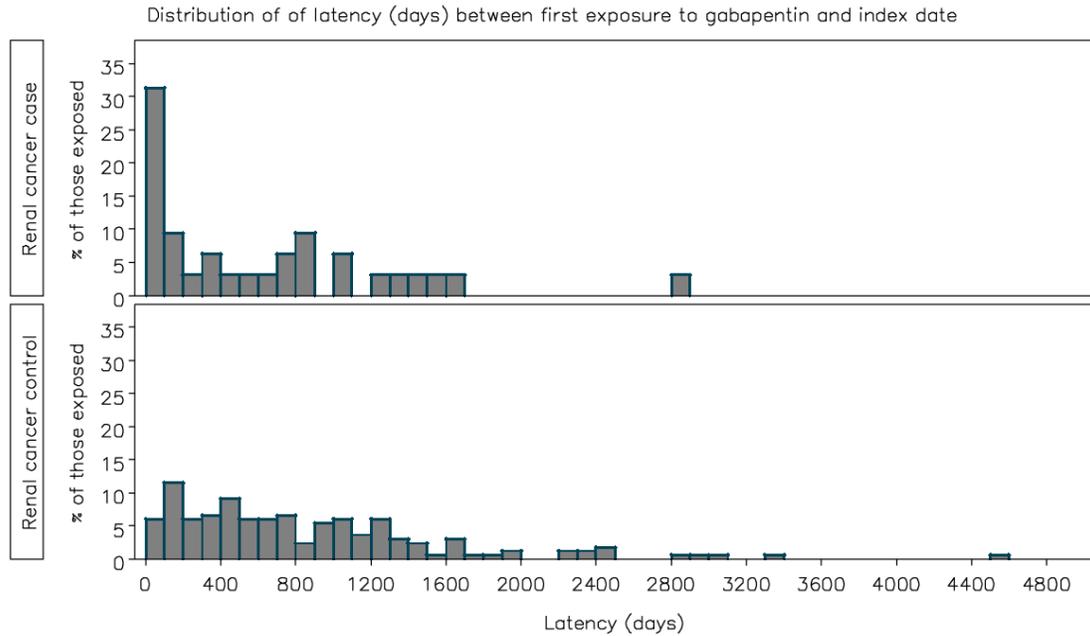


Figure 5. Study WEUSKOP4774: Listing of index renal cancer diagnosis, first gabapentin exposure, and other cancer diagnoses.

ID	Index diagnosis	Index date	Related diagnosis	Date of related diagnosis	Possible gabapentin indication and date	Date of first gabapentin prescription	Latency between first prescription and index date (days)	Other cancer diagnoses	Date of prior cancer diagnoses	Comment
1736777	Renal malignant neoplasm	11/21/2000	Carcinoma of other and unspecified sites	7/23/1999	Low back pain (10/25/2000) Leg pain (10/30/2000)	10/30/2000	22	Carcinoma of other and unspecified sites	7/23/1999	Gabapentin prescribed after non-specific carcinoma diagnosis, before record of renal cancer.
1955760	Malignant neoplasm of kidney parenchyma	9/21/2007			Neuralgia unspecified (11/17/2004)	11/17/2004	1038	Basal cell carcinoma [M]Basal cell neoplasms [M]Basal cell neoplasms Basal cell carcinoma [M]Basal cell neoplasms Basal cell carcinoma Basal cell carcinoma	1/1/1988 4/9/1999 12/14/2001 1/25/2002 2/14/2002 2/26/2002 3/8/2002	Past history of basal cell carcinoma.

3.12.1.2 Study WEUSRTP4931

Again study weusrtp4931 was conducted using the same methodology, but included additional cancer outcomes and excluded patients with a history of cancer before first gabapentin exposure. The main findings for each outcome will be highlighted below. A table summarizing the results of the multivariate models is provided in Appendix 1. As in study weuskop4774, most patients had a limited exposure to gabapentin. For example, as seen in the exposure pattern for patients included in the all-cancer outcome analysis, the patients in the first tertile of exposure had either 1-2 prescriptions, 0-1.38 months of use, or 0-30.g of cumulative exposure (Table 10).

Table 10. Study WEUSRTP4931: Distribution of Gabapentin Exposure in All-Cancer Outcome Cases and Controls.

EXPOSURE WINDOW: Entry into cohort to 2 years prior to index date		Cases (N)	Cases (%)	Controls (N)	Controls (%)
Gabapentin Exposure	Ever	804	0.4	6,507	0.4
	Never	178,334	99.6	1,704,443	99.6
Number of Prescriptions (n)	Mean (SD) ¹	9.9 (15.95)		9.5 (15.29)	
	None	178,334	99.6	1,704,443	99.6
	Tertile 1 (1 - 2)	319	0.2	2,739	0.2
	Tertile 2 (3 - 7)	216	0.1	1,645	0.1
	Tertile 3 (8 - 298)	269	0.2	2,123	0.1
Duration of Use (Months)	Mean (SD) ¹	7.5 (11.23)		7.2 (10.65)	
	None	178,334	99.6	1,704,443	99.6
	Tertile 1 (- 1.38 mo)	258	0.1	2,175	0.1
	Tertile 2 (1.39 - 5.56 mo)	269	0.2	2,163	0.1
	Tertile 3 (5.57 - 105.82 mo)	277	0.2	2,169	0.1
Long Duration of Use (years)	> 1 y	157	0.1	1,217	0.1
	> 2 y	64	0.0	463	0.0
	> 3 y	25	0.0	197	0.0
Cumulative Dose (g)	Mean (SD) ¹	338.1 (698.3)		319.0 (657.3)	
	None	178,334	99.6	1,704,443	99.6
	Tertile 1 (- 30.0 g)	269	0.2	2,222	0.1
	Tertile 2 (30.1 - 189.0 g)	268	0.1	2,118	0.1
	Tertile 3 (189.1 - 9600.0 g)	267	0.1	2,167	0.1

1. Among gabapentin users

3.12.1.2.1 Pancreatic Cancer

After excluding patients with a previous history of any cancer, the number of incident pancreatic cancer cases was reduced from 3,149 in weuskop4774 to 2,155 in weusrtp4931. Thus, approximately 1/3 of pancreatic cancer cases in weusrtp4931 had other cancers or non-specific cancer codes (e.g. “pancreatic adenomas and carcinomas” or “cancer”) prior to the index date (which was based on specific pancreatic cancer codes).

2,155 pancreatic cancer cases were matched to 20,382 controls. Mean duration of follow up from cohort entry was 8.9-9.0 years. 0.9% (n=20) of cancer cases were ever exposed to gabapentin, compared to 0.4% (n=86) of controls. Both ever exposure to gabapentin [adjusted OR 3.25 (95% CI 1.55, 6.83) relative to no exposure] and never versus the first tertile of exposure to gabapentin [adjusted OR 1.68 (95% CI 1.00, 2.82) relative to no exposure] was associated with an increased risk of pancreatic cancer. The highest tertiles of gabapentin exposure measures were not associated with risk of pancreatic cancer (point estimates of OR 1.00-1.36 relative to no exposure).

3.12.1.2.2 Renal Cancer

After excluding patients with a previous history of any cancer, the number of incident renal cancer cases was reduced from 1,981 in weuskop4774 to 1,272 in weusrtp4931. Thus, approximately 1/3 of renal cancer cases in weusrtp4931 had other cancers or non-specific cancer codes (e.g. “renal adenomas and carcinomas”) prior to the index date (which was based on specific renal cancer codes).

1,272 pancreatic cancer cases were matched to 12,167 controls. Mean duration of follow up from cohort entry was 9.3-9.4 years. 0.7% (n=9) of cancer cases were ever exposed to gabapentin, compared to 0.4% (n=86) of controls. No parameterization of gabapentin exposure was associated with incident renal cancer.

3.12.1.2.3 Other Cancer Outcomes

Appendix 1 contains a listing of the number of cases and matched controls for each cancer outcome. Except for anal cancer, there were no associations between any parameterization of gabapentin exposure and incidence of cancer. A single association was found for the first tertile of gabapentin exposure and anus, anal canal, and anorectum cancer [adjusted OR 21.47 (95% CI 1.78, 258.8)]. This analysis was based on 221 cases matched to 2067 controls.

3.12.2 OSE Comments on Study Results

Overall, the study results were clearly articulated and followed the pre-specified analyses plan previously submitted to the agency. The post-hoc analyses conducted by the Sponsor were appropriate to put the results into context and examine potential biases.

Selective associations between gabapentin exposure and pancreatic cancer were found in both studies, while only study weuskop4774 found selective associations between gabapentin and renal cancer. In addition, one association was found for anus, anal canal, and anorectum cancer in study weusrtp4931. No dose-dependent association was found for any of the cancer outcomes. A post-hoc examination of the pancreatic and renal cancer cases strongly suggests some degree of protopathic bias. Overall, selective associations with very short gabapentin exposures (less than two months), lack of a positive dose-response, and decreasing OR point estimates with longer exposures is not a pattern consistent with a carcinogen.

3.13 U.S. DRUG UTILIZATION

3.13.1 U.S. Drug Utilization (1993-2010)

In an effort to evaluate whether indications for use and duration of use for gabapentin products were similar in the U.S. and U.K., DEPI conducted an analysis of retail utilization patterns for gabapentin in the U.S. from December 1993 through November 2010 (Chang SH, RCM 2010-2470). A summary of the analysis is below.

Table 11 displays the selected diagnoses groups (ICD-9 codes) associated with the use of gabapentin for an aggregate time period from December 1993 (date of approval) through November 2010. Approximately (b) (4) of use was associated with pain-related ICD-9 codes, approximately (b) (4) of use was associated with psychiatric-related ICD-9 codes, approximately (b) (4) of use was associated with convulsion-related ICD-9 codes, and approximately (b) (4) of use was associated with epilepsy-related ICD-9 codes.

Table 12 displays the prescribed therapy days associated with the use of gabapentin stratified by selected diagnoses groups (ICD-9 codes) as reported by office-based physicians in the U.S. for an aggregate time period from December 1993 (date of approval) through November 2010. Among

patients with available duration of use data, duration of gabapentin use was less than 90 days for indications other than epilepsy and convulsions. Duration of use for convulsions was more evenly distributed, whereas most use for epilepsy was for greater than 90 days. However, between 12.6%-46.0% of patients across the indication categories were missing duration of use data.

Table 11. Diagnoses Associated with Use for Gabapentin as Reported by Office-Based Physicians in the U.S (December 1993-November 2010).

	DEC 2003 - NOV 2010	
	Uses (000)	Share %
Total Gabapentin Market	(b) (4)	100.0%
Grouped Indications[‡]		
<i>Pain</i>		(b) (4)
<i>Herpes Zoster</i>		
<i>All Others</i>		
<i>Psychiatric Disorders</i>		
<i>Convulsions</i>		
<i>Epilepsy</i>		
[‡] Pain = (b) (4); Herpes Zoster = (b) (4); Psychiatric disorders = (b) (4); Convulsions = (b) (4); Epilepsy = (b) (4)		
Source: SDI, Physicians Drug and Diagnosis Audit, 12/93-11/10, Extracted 1/11, File: PDDA 2010-2470 Gabapentin 4ddx 1-13-11.xls		

Table 12. Prescribed Therapy Days Associated with the Use of Gabapentin Stratified by Selected ICD-9 codes as Reported by Office-Based Physicians in the U S. (December 1993- November 2010)

Grouped Indications [†]	TOTAL		0-30 DAYS		31-60 DAYS		61-90 DAYS		91-120 DAYS		121-150 DAYS		151-180 DAYS		181+ DAYS		UNSPEC. DAYS	
	Uses (000)	Vertical Share	Uses (000)	Horiz. Share	Uses (000)	Horiz. Share	Uses (000)	Horiz. Share	Uses (000)	Horiz. Share	Uses (000)	Horiz. Share	Uses (000)	Horiz. Share	Uses (000)	Horiz. Share	Uses (000)	Horiz. Share
<i>Pain</i>	(b) (4)																	
<i>Herpes Zoster</i>																		
<i>All others</i>																		
<i>Psychiatric disorders</i>																		
<i>Convulsions</i>																		
<i>Epilepsy</i>																		

[†] Pain = (b) (4); Herpes Zoster = (b) (4); Psychiatric disorders = (b) (4); Convulsions = (b) (4); Epilepsy = (b) (4)

Source: SDI, Physicians Drug and Diagnosis Audit, 12/93-11/10, Extracted 1/11, File: PDDA 2010-2470 Gabapentin 4ddx 1-13-11.xls

3.13.2 OSE Comments Drug Use Compared to GPRD

Gabapentin exposure data from GPRD appears to be a reasonable proxy for U.S. gabapentin use. Pain was the most common indication for gabapentin use in the U.S. Most patients' gabapentin treatment episode lasted less than 90 days, whereas epilepsy patients tended to have treatment episodes longer than 90 days. U.S and U.K. utilization of gabapentin as measured by duration of use and indication for use appeared qualitatively similar; however, formal statistical tests were not conducted.

4 SUMMARY AND RECOMMENDATIONS

The Sponsor conducted two parallel nested-case control studies in GPRD to examine the associations between gabapentin exposure and a number of cancer outcomes. The first study specifically examined the association between gabapentin exposure and the incidence of pancreatic and renal cancers in all patients exposed to gabapentin between January 1, 1993 and December 31, 2008. The second study examined the association between gabapentin exposure and the incidence of pancreatic and renal cancers in addition to cancers at the following sites: A) all cancer, B) stomach, C) anus, anal canal, and anorectum, D) lung and bronchus, E) bones and joints, F) breast, G) penis, H) urinary bladder, and I) other nervous system. This study used the same study design, but excluded patients with any previous cancer diagnoses prior to their first gabapentin exposure. In both studies, cases were risk set matched with up to 10 controls for sex, age at cohort entry (within two years), calendar year of cohort entry (within one year), and general practice site. Crude and multivariate odd ratios were presented for a no lag and a two-year lagged analyses. Statistically significant associations between gabapentin exposure and pancreatic and renal cancer was seen in analyses of never versus ever use and in no use versus the first tertile of use. In addition, a statistically significant association was observed for anus, anal canal, and anorectum cancer in no use versus the first tertile of use.

At best, these studies provided weak evidence of an association between gabapentin exposure and incident cancer. First, the associations between gabapentin exposure and cancer risk were not dose-dependent. Statistically significant associations were only seen in the first tertile of exposure, instead of observing a positive correlation between increasing exposure levels and risk. However, these studies may be underpowered to detect associations at higher gabapentin exposure levels since, as previously stated, most patients had limited exposure to gabapentin. Second, the likelihood that brief exposure to gabapentin is carcinogenic is questionable. The duration of use of the first tertile spanned from 0 to 1.55 months and the number of prescriptions of the first tertile spanned from 1 to 2 prescriptions. As such, all associations were attenuated in two-year lagged analyses. Third, the short duration between first exposure to gabapentin and incidence of renal or pancreatic cancer also calls into question gabapentin's carcinogenicity, especially given the long asymptomatic period associated with pancreatic cancer. The median latency between first gabapentin exposure and incidence was 416 days for renal cancer and 573 days for pancreatic cancer, but the latency period was 100 days in 25% of pancreatic cancer cases and in 31% of renal cancer cases. Finally, the statistically significant associations observed are likely an artifact of a protopathic bias or potentially a surveillance bias. Post-hoc review of gabapentin use in pancreatic and renal cancer cases in study weuskop4774 revealed that 14% of pancreatic and 31% of renal cancer cases were prescribed gabapentin for the treatment of paraneoplastic syndromes, or had a READ code indicating clinical suspicion of cancer prior to first gabapentin exposure that was presumably confirmed after subsequent diagnostic testing. For these reasons, the Sponsor's primary contention that any statistically significant association is a result of protopathic bias seems plausible. Also, the potential for a surveillance bias must also be acknowledged. It is possible that patients who receive gabapentin prescriptions may more

frequently report symptoms that trigger diagnostic tests that identify pancreatic cancer more often than patients who do not receive gabapentin.

Overall, the studies were well conducted. The Sponsors used an appropriate study design which included clinically relevant covariates. Furthermore, outcome definitions were either based on previously validated definitions or were verified by an independent cancer expert at the UK National Cancer Research Institute. The major limitation of this study was the small number of patients who had chronic gabapentin exposure; a limitation of the available data rather than a study design flaw. For example, pancreatic cancers cases were exposed to gabapentin for an average of 6.1 months and controls for an average of 9.6 months before the index date. Overall, this is similar to gabapentin use patterns in the U.S. Although, these GPRD studies cannot address the risk of pancreatic or renal cancer in patients with chronic gabapentin use; it can address the risk of pancreatic or renal cancer in exposures which are typically seen in current clinical practice.

Overall, the GPRD studies submitted by the Sponsor and an earlier study from Kaiser Permanente Northern California do not provide evidence of a causal association between gabapentin use and cancer, in particular pancreatic and renal cancers. The GPRD studies provided by the Sponsor suggest that any association between limited gabapentin exposure and cancer is likely explained by protopathic bias or potentially a surveillance bias. However, due to the aforementioned short duration of gabapentin use seen in current clinical practice, these studies cannot comment on the potential carcinogenicity associated with chronic gabapentin enacarbil use.

If gabapentin enacarbil is approved, DEPI does not recommend further evaluation of gabapentin enacarbil's carcinogenicity by means of an observational post-marketing requirement. Additional retrospective case-control and cohort studies would likely not add substantially different information to the risk-benefit discussion. A prospective registry study would be hard to interpret given pancreatic cancer's long asymptomatic period. In order to attribute any cancer association to gabapentin, registry participants would need to undergo imaging studies and potential biopsies at baseline to identify any prevalent pancreatic and renal cancer cases. Recruitment for such an intensive study would likely be difficult and is likely unwarranted given the currently available carcinogenicity data. Additional epidemiologic studies can be discussed if new gabapentin enacarbil carcinogenicity data is generated in the future.

5 REFERENCES

- Chang SH. Gabapentin Drug Use Analysis. Food and Drug Administration/Center for Drug Evaluation and Research/Office of Surveillance and Epidemiology. RCM# 2010-2470; 02/16/2011
- Friedman, G. D., Udaltsova, N., Chan, J., Quesenberry, C. P., Jr., & Habel, L. A. (2009). Screening pharmaceuticals for possible carcinogenic effects: initial positive results for drugs not previously screened. *Cancer causes & control : CCC*.
- Herrett E, Thomas SL, Schoonen WM, Smeeth L, Hall AJ. Validation and validity of diagnoses in the General Practice Research Database: a systematic review. *Br J Clin Pharmacol*. 2010;69:4-14.
- Jick H, Jick S, Derby LE, Vasilakis C, Myers MW, Meier CR. Calcium-channel blockers and risk of cancer. *The Lancet*. 1997;349:525-28.
- Kaye JA, Jick H. Statin use and cancer risk in the General Practice Research Database. *Br J Cancer*. 2004;90:635-377.

Kaye JA, Myers MW, Jick H. Acetaminophen and the risk of renal and bladder cancer in the General Practice Research Database. *Epidemiology*. 2001;12:690-694.

Langman MJS, Cheng KK, Gilman EA, Lancashire RJ. Effect of anti-inflammatory drugs on overall risk of common cancer: case-control study in general practice research database. *BMJ*. 2000;320:1642-1646.

Meier CR, Derby LE, Jick SS, Jick H. ACE-inhibitors, calcium channel blockers and breast cancer. *Arch Intern Med*. 2000;160:349-353.

National Cancer Research Institute (NCRI). Cancer Incidence and Mortality By Cancer Network, UK, 2005. National Cancer Intelligence Network, London; 2008.
http://library.ncin.org.uk/docs/081007-NCIN-UK_Incidence_Mortality_05-Report.pdf.

Williams JR. Gabapentin Enacarbil End of Review Conference – Response to Sponsor Questions. Food and Drug Administration/Center for Drug Evaluation and Research/Office of Surveillance and Epidemiology. RCM# 2010-764; 05/05/2010

APPENDIX

Appendix 1. Study WEUSRTP4931: Results Summary - Two-Year Lagged Analyses

Cancer	Cases, N Age, y (SD) GP exposed, N (%)	Controls, N Age, y (SD) GP exposed, N (%)	Adjusted OR (95% CI), p-value, for cancer relative to never exposure to gabapentin						
			Ever vs Never	Tertile 1 (0.01-1.38 mo) vs Never	Tertile 2 (1.39 - 5.56 mo) vs Never	Tertile 3 (>5.56 mo) vs Never	>1 y vs Never	>2 y vs Never	>3 y vs Never
All cancers	179,138 66.3 (15.12) 804 (0.4%)	1,710,950 65.8 (15.07) 6,507 (0.4%)	1.07 (0.99, 1.15) p = 0.0976	1.03 (0.90, 1.17) p = 0.7004	1.10 (0.96, 1.25) p = 0.1592	1.07 (0.95, 1.22) p = 0.2731	1.09 (0.92, 1.29) p = 0.3132	1.16 (0.89, 1.52) p = 0.2649	1.05 (0.69, 1.60) p = 0.8208
Breast	19,564 61.4 (14.04) 96 (0.5%)	188,924 61.4 (13.87) 725 (0.4%)	1.22 (0.99, 1.52) p = 0.0682	1.08 (0.73, 1.59) p = 0.7129	1.19 (0.82, 1.72) p = 0.3650	1.42 (0.99, 2.04) p = 0.0542	1.48 (0.92, 2.39) p = 0.1043	1.62 (0.79, 3.29) p = 0.1859	0.76 (0.18, 3.21) p = 0.7088
Lung and bronchus	10,855 70.8 (10.43) 55 (0.5%)	102,836 70.4 (10.38) 402 (0.4%)	0.94 (0.69, 1.27) p = 0.6710	1.05 (0.64, 1.73) p = 0.8357	0.93 (0.52, 1.66) p = 0.8075	0.84 (0.50, 1.39) p = 0.4950	0.79 (0.39, 1.58) p = 0.5070	1.13 (0.37, 3.43) p = 0.8276	1.87 (0.21, 16.86) p = 0.5770
Urinary Bladder	4,600 71.0 (11.59) 15 (0.3%)	43,559 70.6 (11.52) 144 (0.3%)	0.84 (0.49, 1.44) p = 0.5179	0.80 (0.32, 2.05) p = 0.6482	0.67 (0.24, 1.85) p = 0.4353	1.06 (0.44, 2.52) p = 0.8994			
Stomach	1,877 73.5 (11.19) 5 (0.3%)	17,853 73.0 (11.06) 70 (0.4%)	0.54 (0.21, 1.34) p = 0.1845	0.00 (0.00, 2E136) p = 0.9454	1.07 (0.24, 4.84) p = 0.9273	0.70 (0.21, 2.32) p = 0.5579			
Bone and joint	300 47.1 (24.96) 0 (0%)	2,935 46.8 (24.86) 10 (0.3%)	0.00 (0.00,) p = 0.9775	0.00 (0.00,) p = 0.9858	0.00 (0.00,) p = 0.9930	0.00 (0.00,) p = 0.9842			
Anus, anal canal, anorectum	212 65.1 (15.20) 4 (1.9%)	2,067 64.5 (14.86) 6 (0.3%)	3.39 (0.71, 16.17) p = 0.1251	21.47 (1.78, 258.8) p = 0.0158	1.00 (0.03, 32.21) p = 0.9990	0.93 (0.06, 13.87) p = 0.9608			
Penis	148 63.6 (14.26) 1 (0.7%)	1,396 62.9 (14.04) 2 (0.1%)	2.90 (0.24, 34.69) p = 0.3999	4.63 (0.28, 77.51) p = 0.2866	Inestimable (no exposed cases or controls)	0.00 (0.00,) p = 0.9975			

Appendix 1. Study WEUSRTP4931: Results Summary - Two-Year Lagged Analyses (continued)

Cancer	Cases, N Age, y (SD) GP exposed, N (%)	Controls, N Age, y (SD) GP exposed, N (%)	Adjusted OR (95% CI), p-value, for cancer relative to never exposure to gabapentin						
			Ever vs Never	Tertile 1 (0.01-1.38 mo) vs Never	Tertile 2 (1.39 - 5.56 mo) vs Never	Tertile 3 (>5.56 mo) vs Never	>1 y vs Never	>2 y vs Never	>3 y vs Never
Other Nervous System Cancers	38 58.5 (19.22) 0 (0%)	380 58.5 (19.08) 0 (0%)	Not estimable (no exposed cases or controls)	Not estimable (no exposed cases or controls)	Not estimable (no exposed cases or controls)	Not estimable (no exposed cases or controls)			
SUPPLEMENTARY ANALYSES									
Pancreas	2,155 71.6 (11.52) 20 (0.9%)	20,382 71.1 (11.47) 86 (0.4%)	1.68 (1.00, 2.82) p = 0.0494	3.25 (1.55, 6.83) p = 0.0019	0.61 (0.14, 2.62) p = 0.5103	1.32 (0.54, 3.21) p = 0.5391			
Renal and renal pelvis	1,272 65.8 (12.60) 9 (0.7%)	12,167 65.4 (12.59) 53 (0.4%)	1.33 (0.64, 2.75) p = 0.4405	1.73 (0.49, 6.15) p = 0.3951	1.10 (0.32, 3.75) p = 0.8743	1.29 (0.37, 4.58) p = 0.6899			

GP, gabapentin; mo, month; y, year; vs, versus; SD, standard deviation; CI, confidence interval.

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/s/

JAMES R WILLIAMS
04/04/2011

SOLOMON IYASU
04/04/2011

505(b)(2) ASSESSMENT

Application Information		
NDA # 022399	NDA Supplement #: S-	Efficacy Supplement Type SE-
Proprietary Name: Horizant Established/Proper Name: gabapentin encarbil Dosage Form: extended-release tablets Strengths: 600 mg		
Applicant: GSK		
Date of Receipt: original NDA 9-15-08; resubmission 10-06-10		
PDUFA Goal Date: April 6, 2011		Action Goal Date (if different):
Proposed Indication(s): the treatment of moderate-to-severe primary Restless Legs Syndrome (RLS)		

GENERAL INFORMATION

- 1) Is this application for a recombinant or biologically-derived product and/or protein or peptide product *OR* is the applicant relying on a recombinant or biologically-derived product and/or protein or peptide product to support approval of the proposed product?
- YES NO

If "YES" contact the (b)(2) review staff in the Immediate Office, Office of New Drugs.



**INFORMATION PROVIDED VIA RELIANCE
(LISTED DRUG OR LITERATURE)**

- 2) List the information essential to the approval of the proposed drug that is provided by reliance on our previous finding of safety and efficacy for a listed drug or by reliance on published literature. *(If not clearly identified by the applicant, this information can usually be derived from annotated labeling.)*

Source of information* (e.g., published literature, name of referenced product)	Information provided (e.g., pharmacokinetic data, or specific sections of labeling)
<p>published literature for Neurontin: Sigler RE, Gough AW, de la Iglesia FA. Pancreatic acinar cell neoplasia in male Wistar rats following 2 years of gabapentin exposure. Toxicology. 1995;98:73-82.</p> <p>Radulovic LL, Taylor CP and Walker RM. The preclinical pharmacology, pharmacokinetics and toxicology of gabapentin. Drugs of Today, 1995;31:597-611.</p> <p>Balkenohl M, Turck D, Kirste G, and Feuerstein TJ. Species-specific accumulation of gabapentin in rat pancreatic tissue compared with human and monkey tissue. Epilepsia, 1993;34:157.</p>	<p>Literature derived from the 2-year carcinogenicity study of gabapentin in Wistar rats, the 14-day toxicokinetic study of gabapentin in Wistar rats, and the in vitro tissue perfusion study of gabapentin in rat and human pancreas slices</p> <p>Sections of labeling that rely on this information include Warnings and Precautions and Nonclinical Toxicology</p>
Neurontin NDA 020235	<p>A 2-year carcinogenicity study of gabapentin in Wistar rats</p> <p>A 14-day toxicokinetic study of An in vitro tissue perfusion study of gabapentin in rat and human pancreas slices.</p>

*each source of information should be listed on separate rows

- 3) Reliance on information regarding another product (whether a previously approved product or from published literature) must be scientifically appropriate. An applicant needs to provide a scientific “bridge” to demonstrate the relationship of the referenced and proposed products. Describe how the applicant bridged the proposed product to the referenced product(s). (Example: BA/BE studies)

Oral bioavailability in terms of gabapentin was assessed for Neurontin® (gabapentin) Oral Capsules and gabapentin enacarbil extended-release tablets in the following studies:

- XP022; A Phase I, Randomized, Cross-Over, Fed/Fasted Single-Dose Study of the Safety, Tolerability, and Pharmacokinetics of Oral XP13512 in Healthy Adult Subjects

-  (b) (4)

- The pharmacokinetics of gabapentin enacarbil extended-release tablets and Neurontin[®] (gabapentin) Oral Capsules have been compared in patients with post-herpetic neuralgia in Study XP009

RELIANCE ON PUBLISHED LITERATURE

- 4) (a) Regardless of whether the applicant has explicitly stated a reliance on published literature to support their application, is reliance on published literature necessary to support the approval of the proposed drug product (i.e., the application *cannot* be approved without the published literature)?

YES NO

If "NO," proceed to question #5.

- (b) Does any of the published literature necessary to support approval identify a specific (e.g., brand name) *listed* drug product?

YES NO

If "NO", proceed to question #5.

If "YES", list the listed drug(s) identified by name and answer question #4(c).

- (c) Are the drug product(s) listed in (b) identified by the applicant as the listed drug(s)?

YES NO

Neurontin (gabapentin) Capsules

RELIANCE ON LISTED DRUG(S)

Reliance on published literature which identifies a specific approved (listed) drug constitutes reliance on that listed drug. Please answer questions #5-9 accordingly.

- 5) Regardless of whether the applicant has explicitly referenced the listed drug(s), does the application **rely** on the finding of safety and effectiveness for one or more listed drugs (approved drugs) to support the approval of the proposed drug product (i.e., the application cannot be approved without this reliance)?

YES NO

If "NO," proceed to question #10.

- 6) Name of listed drug(s) relied upon, and the NDA/ANDA #(s). Please indicate if the applicant explicitly identified the product as being relied upon (see note below):

Name of Drug	NDA/ANDA #	Did applicant specify reliance on the product? (Y/N)
Neurontin (gabapentin) Capsules	020235	Y

Applicants should specify reliance on the 356h, in the cover letter, and/or with their patent certification/statement. If you believe there is reliance on a listed product that has not been explicitly identified as such by the applicant, please contact the (b)(2) review staff in the Immediate Office, Office of New Drugs.

- 7) If this is a (b)(2) supplement to an original (b)(2) application, does the supplement rely upon the same listed drug(s) as the original (b)(2) application?

N/A YES NO

If this application is a (b)(2) supplement to an original (b)(1) application or not a supplemental application, answer "N/A".

If "NO", please contact the (b)(2) review staff in the Immediate Office, Office of New Drugs.

- 8) Were any of the listed drug(s) relied upon for this application:

- a) Approved in a 505(b)(2) application?

YES NO

If "YES", please list which drug(s).

Name of drug(s) approved in a 505(b)(2) application:

- b) Approved by the DESI process?

YES NO

If "YES", please list which drug(s).

Name of drug(s) approved via the DESI process:

- c) Described in a monograph?

YES NO

If "YES", please list which drug(s).

Name of drug(s) described in a monograph:

d) Discontinued from marketing?

YES NO

If "YES", please list which drug(s) and answer question d) i. below.

If "NO", proceed to question #9.

Name of drug(s) discontinued from marketing:

i) Were the products discontinued for reasons related to safety or effectiveness?

YES NO

(Information regarding whether a drug has been discontinued from marketing for reasons of safety or effectiveness may be available in the Orange Book. Refer to section 1.11 for an explanation, and section 6.1 for the list of discontinued drugs. If a determination of the reason for discontinuation has not been published in the Federal Register (and noted in the Orange Book), you will need to research the archive file and/or consult with the review team. Do not rely solely on any statements made by the sponsor.)

9) Describe the change from the listed drug(s) relied upon to support this (b)(2) application (for example, "This application provides for a new indication, otitis media" or "This application provides for a change in dosage form, from capsule to solution").

NDA 022399 provides for the use of Horizant to treat moderate to severe RLS. HORIZANT is an extended-release formulation of gabapentin enacarbil, a prodrug of gabapentin. HORIZANT provides approximately dose-proportional and extended exposure to gabapentin over the range 300 to 6,000 mg. HORIZANT and gabapentin are not interchangeable because the same daily dose of each results in different plasma concentrations of gabapentin.

The purpose of the following two questions is to determine if there is an approved drug product that is equivalent or very similar to the product proposed for approval that should be referenced as a listed drug in the pending application.

*The assessment of pharmaceutical equivalence for a recombinant or biologically-derived product and/or protein or peptide product is complex. If you answered **YES to question #1**, proceed to question #12; if you answered **NO to question #1**, proceed to question #10 below.*

10) (a) Is there a pharmaceutical equivalent(s) to the product proposed in the 505(b)(2) application that is already approved (via an NDA or ANDA)?

*(Pharmaceutical equivalents are drug products in identical dosage forms that: (1) contain identical amounts of the identical active drug ingredient, i.e., the same salt or ester of the same therapeutic moiety, or, in the case of modified release dosage forms that require a reservoir or overage or such forms as prefilled syringes where residual volume may vary, that deliver identical amounts of the active drug ingredient over the identical dosing period; (2) do not necessarily contain the same inactive ingredients; **and** (3) meet the identical compendial or other applicable standard of identity, strength, quality, and purity, including potency and, where applicable, content uniformity, disintegration times, and/or dissolution rates. (21 CFR 320.1(c)).*

Note that for proposed combinations of one or more previously approved drugs, a pharmaceutical equivalent must also be a combination of the same drugs.

YES NO

If "NO" to (a) proceed to question #11.
If "YES" to (a), answer (b) and (c) then proceed to question #12.

(b) Is the pharmaceutical equivalent approved for the same indication for which the 505(b)(2) application is seeking approval?

YES NO

(c) Is the listed drug(s) referenced by the application a pharmaceutical equivalent?

YES NO

If "YES" to (c) and there are no additional pharmaceutical equivalents listed, proceed to question #12.

If "NO" or if there are additional pharmaceutical equivalents that are not referenced by the application, list the NDA pharmaceutical equivalent(s); you do not have to individually list all of the products approved as ANDAs, but please note below if approved approved generics are listed in the Orange Book. Please also contact the (b)(2) review staff in the Immediate Office, Office of New Drugs.

Pharmaceutical equivalent(s):

11) (a) Is there a pharmaceutical alternative(s) already approved (via an NDA or ANDA)?

(Pharmaceutical alternatives are drug products that contain the identical therapeutic moiety, or its precursor, but not necessarily in the same amount or dosage form or as the same salt or ester. Each such drug product individually meets either the identical or its own respective compendial or other applicable standard of identity, strength, quality, and purity, including potency and, where applicable, content uniformity, disintegration times and/or dissolution rates. (21 CFR 320.1(d)) Different dosage forms and strengths within a product line by a single manufacturer are thus pharmaceutical alternatives, as are extended-release products when compared with immediate- or standard-release formulations of the same active ingredient.)

Note that for proposed combinations of one or more previously approved drugs, a pharmaceutical alternative must also be a combination of the same drugs.

YES NO

If "NO", proceed to question #12.

(b) Is the pharmaceutical alternative approved for the same indication for which the 505(b)(2) application is seeking approval?

YES NO

(c) Is the approved pharmaceutical alternative(s) referenced as the listed drug(s)?

YES NO

If "YES" and there are no additional pharmaceutical alternatives listed, proceed to question #12.

If "NO" or if there are additional pharmaceutical alternatives that are not referenced by the application, list the NDA pharmaceutical alternative(s); you do not have to individually list all

of the products approved as ANDAs, but please note below if approved generics are listed in the Orange Book. Please also contact the (b)(2) review staff in the Immediate Office, Office of New Drugs.

Pharmaceutical alternative(s):

NDA-021397 Neurontin (gabapentin) Hard Gelatin Capsules
NDA-020235 Neurontin (gabapentin) Capsules
NDA-020882 Neurontin (gabapentin) Tablets
NDA-021129 Neurontin (gabapentin) I Syrup
NDA-021424 Neurontin (gabapentin) Oral Solution
NDA-021216 Neurontin (gabapentin), Oral Liquid,
NDA-021423 Neurontin (gabapentin) Tablets
NDA-022544 Gralise (gabapentin) Extended-Release Tablets

There are generic products listed in the Orange Book for gabapentin capsules, tablets, and oral solution.

PATENT CERTIFICATION/STATEMENTS

12) List the patent numbers of all unexpired patents listed in the Orange Book for the listed drug(s) for which our finding of safety and effectiveness is relied upon to support approval of the (b)(2) product.

Listed drug/Patent number(s): U.S. Patent No. 6,054,482

No patents listed proceed to question #14

13) Did the applicant address (with an appropriate certification or statement) all of the unexpired patents listed in the Orange Book for the listed drug(s) relied upon to support approval of the (b)(2) product?

YES NO

If "NO", list which patents (and which listed drugs) were not addressed by the applicant.

Listed drug/Patent number(s):

14) Which of the following patent certifications does the application contain? (Check all that apply and identify the patents to which each type of certification was made, as appropriate.)

No patent certifications are required (e.g., because application is based solely on published literature that does not cite a specific innovator product)

21 CFR 314.50(i)(1)(i)(A)(1): The patent information has not been submitted to FDA. (Paragraph I certification)

21 CFR 314.50(i)(1)(i)(A)(2): The patent has expired. (Paragraph II certification)

Patent number(s):

- 21 CFR 314.50(i)(1)(i)(A)(3): The date on which the patent will expire. (Paragraph III certification)

Patent number(s):

Expiry date(s):

- 21 CFR 314.50(i)(1)(i)(A)(4): The patent is invalid, unenforceable, or will not be infringed by the manufacture, use, or sale of the drug product for which the application is submitted. (Paragraph IV certification). *If Paragraph IV certification was submitted, proceed to question #15.*

- 21 CFR 314.50(i)(3): Statement that applicant has a licensing agreement with the NDA holder/patent owner (must also submit certification under 21 CFR 314.50(i)(1)(i)(A)(4) above). *If the applicant has a licensing agreement with the NDA holder/patent owner, proceed to question #15.*

- 21 CFR 314.50(i)(1)(ii): No relevant patents.

- 21 CFR 314.50(i)(1)(iii): The patent on the listed drug is a method of use patent and the labeling for the drug product for which the applicant is seeking approval does not include any indications that are covered by the use patent as described in the corresponding use code in the Orange Book. Applicant must provide a statement that the method of use patent does not claim any of the proposed indications. (Section viii statement)

Patent number(s):

Method(s) of Use/Code(s):

- 15) Complete the following checklist **ONLY** for applications containing Paragraph IV certification and/or applications in which the applicant and patent holder have a licensing agreement:

(a) Patent number(s): *U.S. Patent No. 6,054,482*

(b) Did the applicant submit a signed certification stating that the NDA holder and patent owner(s) were notified that this b(2) application was filed [21 CFR 314.52(b)]?

YES NO

If "NO", please contact the applicant and request the signed certification.

(c) Did the applicant submit documentation showing that the NDA holder and patent owner(s) received the notification [21 CFR 314.52(e)]? This is generally provided in the form of a registered mail receipt.

YES NO

If "NO", please contact the applicant and request the documentation.

(d) What is/are the date(s) on the registered mail receipt(s) (i.e., the date(s) the NDA holder and patent owner(s) received notification):

Date(s): *10-18-10 and 10-21-10*

(e) Has the applicant been sued for patent infringement within 45-days of receipt of the notification listed above?

*Note that you may need to call the applicant (after 45 days of receipt of the notification) to verify this information **UNLESS** the applicant provided a written statement from the notified patent owner(s) that it consents to an immediate effective date of approval.*

YES NO Patent owner(s) consent(s) to an immediate effective date of approval

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/s/

SUSAN B DAUGHERTY
03/30/2011

**FOOD AND DRUG ADMINISTRATION
Center for Drug Evaluation and Research
Division of Drug Marketing, Advertising, and Communications**

Memorandum

****PRE-DECISIONAL AGENCY MEMO****

DATE: MARCH 25, 2011

To: Susan Daugherty
Senior Regulatory Health Project Manager
DNP

CC: Mary Dempsey
Project Management Officer
OSE, DRISK

Robin Duer
Senior Patient Labeling Reviewer
OSE, DRISK

From: Sharon Watson, PharmD
Regulatory Review Officer, DDMAC

Subject: Drug: Horizant (gabapentin enacarbil) Extended-Release Tablets

NDA: 022399

DDMAC has reviewed the 3/23/11 DRISK Med Guide Review for Horizant (gabapentin enacarbil) Extended-Release Tablets, and we offer the following comments. DDMAC's comments are provided directly on the clean version of this document, attached below.

Thank you for the opportunity to comment on this proposed Medication Guide.
If you have any questions or concerns regarding these comments, please contact me.

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

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/s/

SHARON M WATSON
03/25/2011

Internal Consult

Pre-decisional Agency Information

To: Susan Daugherty, Senior Regulatory Project Manager, Division of
Neurology Products (DNP)

From: Quynh-Van Tran, PharmD, BCPP
Regulatory Review Officer, Division of Drug Marketing, Advertising,
and Communications, (DDMAC)

Date: March 25, 2011

Re: DDMAC Comments on draft Prescribing Information (PI) for
HORIZANT (gabapentin enacarbil) Extended-Release Tablets

NDA 22-399

Thank you for the opportunity to review the proposed PI for HORIZANT (FDA dated version 3/22/2011). Please see attached PI with our comments incorporated therein.

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/s/

QUYNH-VAN TRAN
03/25/2011

**Department of Health and Human Services
Public Health Service
Food and Drug Administration
Center for Drug Evaluation and Research
Office of Surveillance and Epidemiology**

PATIENT LABELING REVIEW

Date: March 23, 2011

To: Russell Katz, M.D., Director
Division of Neurology Products (DNP)

Through: LaShawn Griffiths, RN, MSHS-PH, BSN
Acting Team Leader, Patient Labeling Reviewer,
Division of Risk Management (DRISK)

Melissa Hulett, MSBA, BSN, RN
Acting Team Leader, Patient Labeling Reviewer
Division of Risk Management

From: Robin Duer, MBA, BSN, RN
Senior Patient Labeling Reviewer
Division of Risk Management

Subject: DRISK Review of Patient Labeling (Medication Guide)

Drug Name: HORIZANT (gabapentin enacarbil) Extended Release
Tablets

Application
Type/Number: NDA 22-399

Applicant/sponsor: GlaxoSmithKline (GSK)

OSE RCM #: 2009-158

1 INTRODUCTION

This review is written in response to a request by the Division of Neurology Products (DNP) for the Division of Risk Management (DRISK) to review the Applicant's proposed Medication Guide (MG) and proposed Risk Evaluation and Mitigation Strategy (REMS) for HORIZANT (gabapentin enacarbil) Extended Release Tablets.

NDA 22-399 was originally submitted on January 9, 2009. On September 21, 2009 FDA issued a letter to GSK requesting safety labeling changes including a Medication Guide and REMS to inform patients of the increased risk for suicidal thoughts and behaviors. DRISK was consulted and provided a review of the Horizant (gabapentin enacarbil) MG and REMS on January 7, 2010. On September 21, 2010 FDA issued a Complete Response letter for this NDA. A Complete Response including revised professional and patient labeling and a revised REMS was submitted by GSK on October 6, 2010.

On Friday, February 25, 2011, FDA published a draft Guidance that addresses when a Medication Guide will be required as part of a REMS. Based on the risks of a drug and public health concerns, FDA has the authority to determine whether a Medication Guide should be required as part of a REMS or should be required as labeling but not part of a REMS.

On March 21, 2011 DNP and DRISK determined that the proposed REMS is not necessary for this drug product; therefore, we have removed the REMS documents/materials. The Medication Guide will continue to be part of the approved labeling in accordance with 21 CFR part 208.

Please send these comments to the Applicant and let us know if DNP would like a meeting to discuss this review or any of our changes prior to sending to the Applicant.

2 MATERIAL REVIEWED

- Draft HORIZANT (gabapentin enacarbil) Extended Release Tablets Prescribing Information (PI) submitted on October 6, 2010, revised by DNP throughout the review cycle and received by DRISK on March 22, 2011
- Draft HORIZANT (gabapentin enacarbil) Extended Release Tablets Medication Guide (MG) submitted on October 6, 2010 and received by DRISK on November 19, 2010
- DRISK patient labeling review (Medication Guide) for HORIZANT (gabapentin enacarbil) Extended Release Tablets dated January 7, 2010

3 REVIEW METHODS

To enhance patient comprehension, materials should be written at a 6th to 8th grade reading level, and have a reading ease score of at least 60%. A reading ease score of 60% corresponds to an 8th grade reading level. In our review of the MG the target reading level is at or below an 8th grade level.

Additionally, in 2008 the American Society of Consultant Pharmacists Foundation (ASCP) in collaboration with the American Foundation for the Blind (AFB) published Guidelines for Prescription Labeling and Consumer Medication Information for People with Vision Loss. The ASCP and AFB recommended using fonts such as Verdana, Arial or APFont to make medical information more accessible for patients with vision loss. We have reformatted the MG document using the Verdana font, size 11.

In our review of the Medication Guide, we have:

- simplified wording and clarified concepts where possible
- ensured that the MG is consistent with the PI
- removed unnecessary or redundant information
- ensured that the MG meets the Regulations as specified in 21 CFR 208.20
- ensured that the MG meets the criteria as specified in FDA's Guidance for Useful Written Consumer Medication Information (published July 2006)
- ensured that the MG is consistent with the approved comparator labeling where applicable

4 CONCLUSIONS

The proposed patient labeling is acceptable with our recommended changes.

5 RECOMMENDATIONS

Please send these comments to the Applicant and copy DRISK on the correspondence.

Our annotated versions of the MG are appended to this memo. Consult DRISK regarding any additional revisions made to the PI to determine if corresponding revisions need to be made to the annotated MG is appended to this memo. Any additional revisions to the PI should be reflected in the MG.

Please let us know if you have any questions.

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/s/

ROBIN E DUER
03/23/2011

LASHAWN M GRIFFITHS
03/23/2011

**Department of Health and Human Services
Public Health Service
Food and Drug Administration
Center for Drug Evaluation and Research
Office of Surveillance and Epidemiology**

Date: January 4, 2011
Application Type/Number: NDA 022399
To: Russell Katz, MD
Director, Division of Neurology Products (DNP)
Through: Carol Holquist, RPh, Director
Division of Medication Error Prevention and Analysis
From: Zachary Oleszczuk, Pharm.D., Team Leader
Division of Medication Error Prevention and Analysis
Subject: Label and Labeling Review
Drug Name(s): Horizant (Gabapentin Enacarbil) Extended-release Tablets
600 mg
Applicant/sponsor: GlaxoSmithKline
OSE RCM #: 2009-114-1

1. INTRODUCTION

This review evaluates the revised container labels and package insert labeling for NDA 022399. These revisions were made in response to comments from the Division of Medication Error Prevention and Analysis in OSE Review #2009-114 and 2009-158, dated October 26, 2009.

2. MATERIAL REVIEWED

The Applicant provided revised container label and package insert labeling on January 28, 2010, (see Appendix A). We also reviewed the recommendations from OSE Review #2009-114 and 2009-158, dated October 26, 2009, to ensure that all DMEPA recommendations have been incorporated into the revised labels and labeling.

3. RESULTS

The Applicant implemented DMEPA's recommendations from OSE Review #2009-114 and 2009-158, dated October 26, 2019. However, our evaluation of the container labels noted that the presentation of the statement "Tablets should not be cut, crushed, or chewed" is difficult to read because the statement appears in an orange color which provides for poor color contrast against the white background. Additionally, the warning statement can be revised state the tablets should be swallowed whole. Section 3.1 Comments to the Applicant contains our recommendations. We request this information be communicated to the Applicant prior to approval of the supplement.

Please copy the Division of Medication Error Prevention and Analysis on any communication to the Applicant with regard to this review. If you have further questions or need clarifications, please contact Laurie Kelley, Project Manager, at 301-796-5068.

3.1 COMMENTS TO THE APPLICANT

1. Revise the warning statement "Tablets should not be cut, crushed, or chewed" to include that the tablets should be swallowed whole. The revised warning statement should be similar to the one that appears in your package insert and states:

Tablets should be swallowed whole. Do not crush, crush or chew tablets.

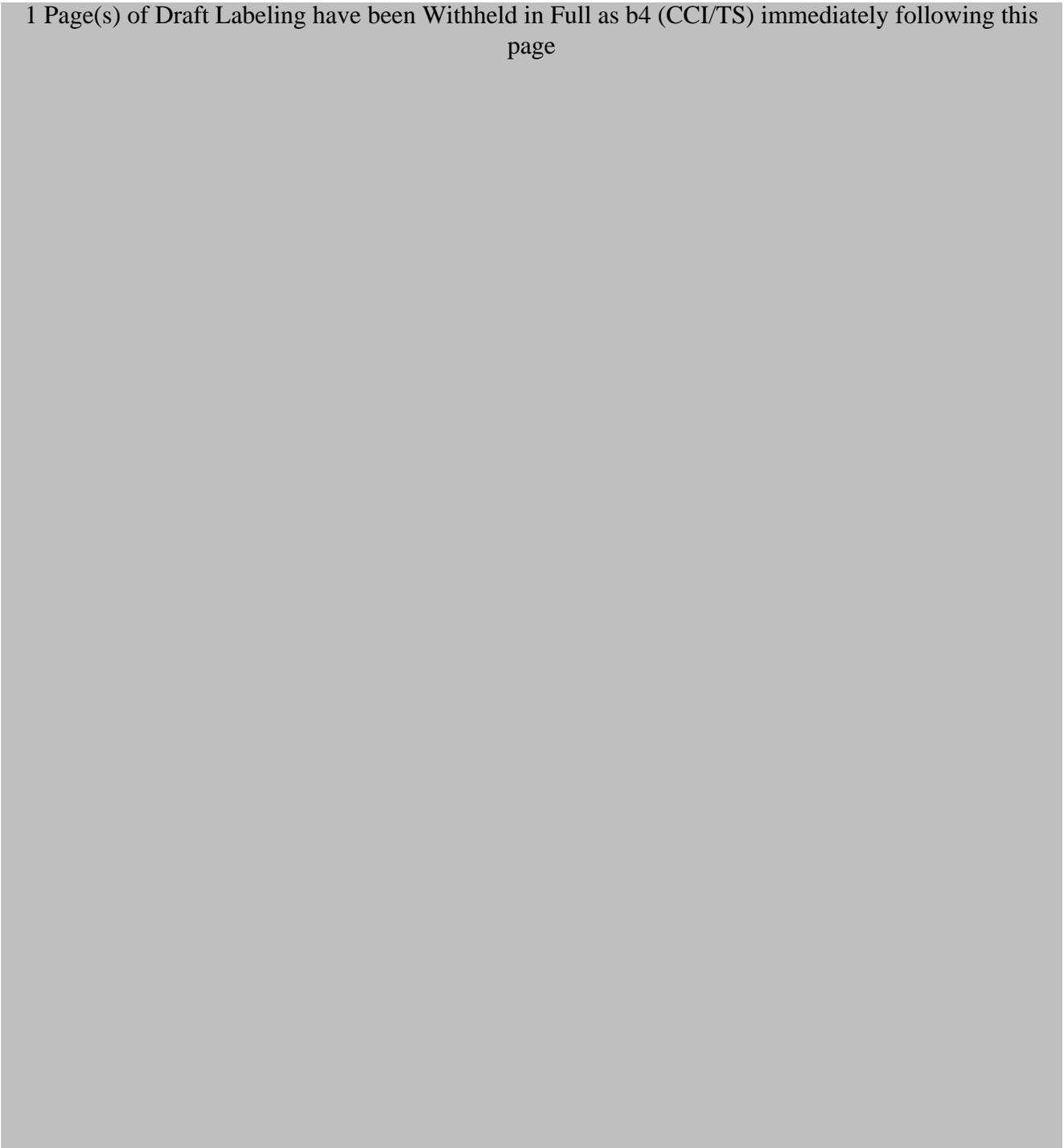
As currently presented the warning statement is a negative warning (e.g. do not do something; not for intravenous use). Negative warning statements are typically less effective than a positive warning (e.g. do something; for oral use only). The Institute for Safe Medication Practices (ISMP) has cited postmarketing cases of medication errors in which warning statements, for example the statement "Not for IV Use", have led to accidental misuse. In the case of Horizant patients or practitioners may overlook the word "not" and misinterpret the warning statement to mean the tablets can be cut, crushed, or chewed.

2. Revise the warning statement to increase the color contrast and improve the readability of the statement. We acknowledge that you increased the prominence of this warning statement by highlighting and relocating the statement to the principal display panel. However, the orange color font use for highlighting is difficult to read because it provides poor color contrast. Increased color contrast can be achieved by outlining the orange letters in black similar to the strength, selecting a color font other than orange for the warning, or some by some other means.
3. Revise the net quantity so it is not competing for prominence with the strength. This can be accomplished by debolding the net quantity, decreasing the size of the statement and removing the graphics that surround the net quantity. As currently presented the net quantity competes for prominence with the strength.

4. REFERENCES

OSE Review #2009-114 and 2009-158, Label and Labeling Review for Horizant (gabapentin) extended-release tablets; Oleszczuk, Z.: October 26, 2009.

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/s/

ZACHARY A OLESZCZUK
01/04/2011

CAROL A HOLQUIST
01/04/2011

Labeling meeting 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 (b) (4). Gabapentin enacarbil is (b) (4) 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 (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)

(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.

Cross Discipline Team Leader 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)

(b) (4)



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) (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>	<u>Males</u>				<u>Females</u>			
	<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:

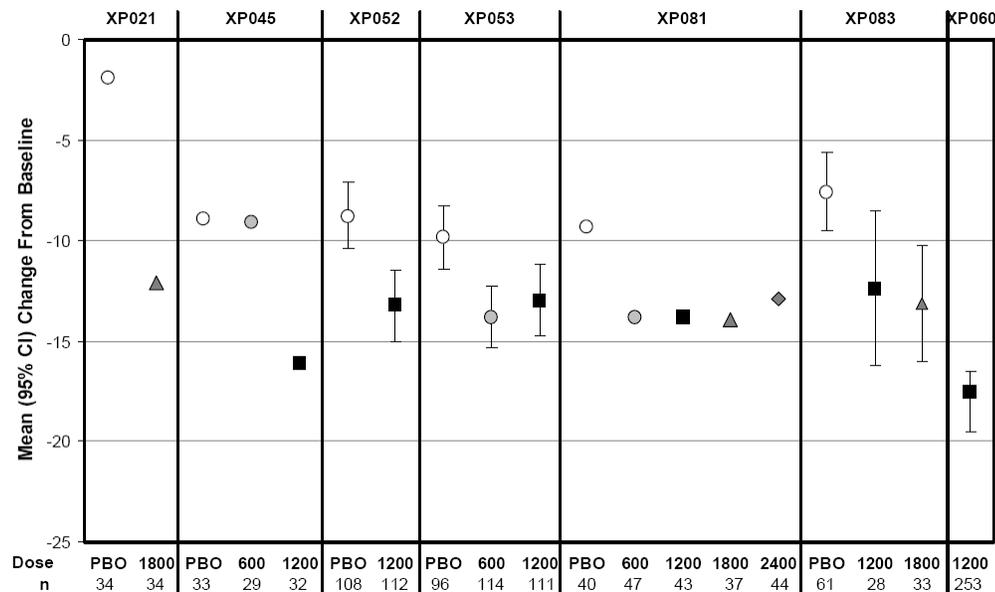
Gabapentin is not metabolized to any significant extent in humans, and the drug is cleared unchanged by renal elimination Following hydrolysis of XP13512 to gabapentin, the released gabapentin is excreted by renal elimination. Gabapentin is eliminated via an organic cation transporter (OCT2) present in the kidney. The t1/2 is approximately 5-7 hours for gabapentin.

Dose Dumping in Alcohol

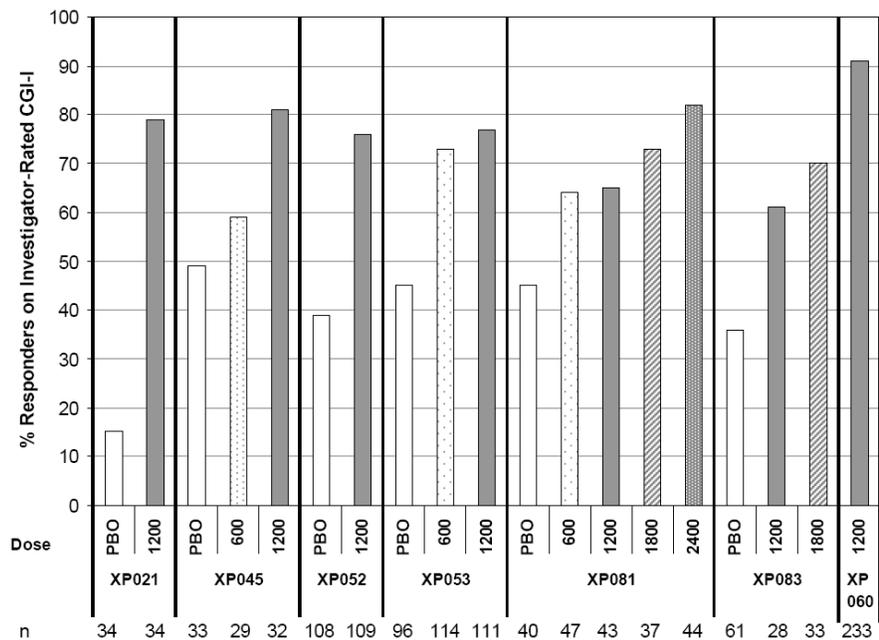
An alcohol interaction study was performed only using 40% alcohol compared to a buffer solution. The dissolution of XP13512 was increased by 20-30% within the first 2 hours. The sponsor’s method of testing for alcohol interaction was not consistent with the agency’s guidance and the dissolution at lower 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 t1/2 is approximately 5-7 hours for gabapentin in patients without renal impairment.

GSK’s Dosing Recommendation In Patients With Renal Impairment

Table 1. Dosage of SOLZIRA® Tablets Based on Creatinine Clearance		
Creatinine Clearance (mL/min)	Titration Dose Regimen	Target Dose Regimen (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)

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)

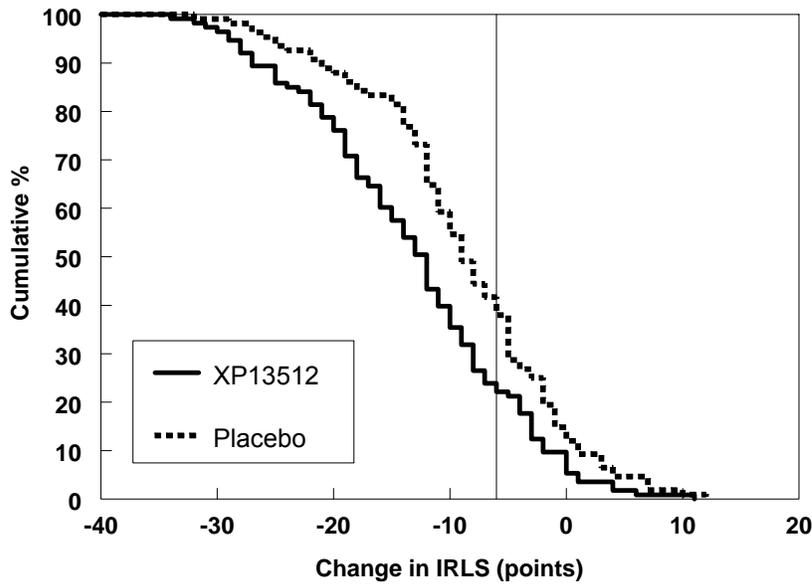
	Change from IRLS Total Score									
	Base-Line	Visit3 Week1	Visit4 Week2	Visit5 Week3	Visit6 Week4	Visit7 Week6	Visit8 Week8	Visit9 Wk10	Visit10 Wk12	Visit10 LOCF
Placebo										
N	108	104	103	102	99	97	93	92	90	108
Mean	22.57	-4.61	-6.53	-7.15	-7.49	-8.00	-8.59	-9.33	-9.39	-8.75
SD	(4.91)	(7.30)	(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)

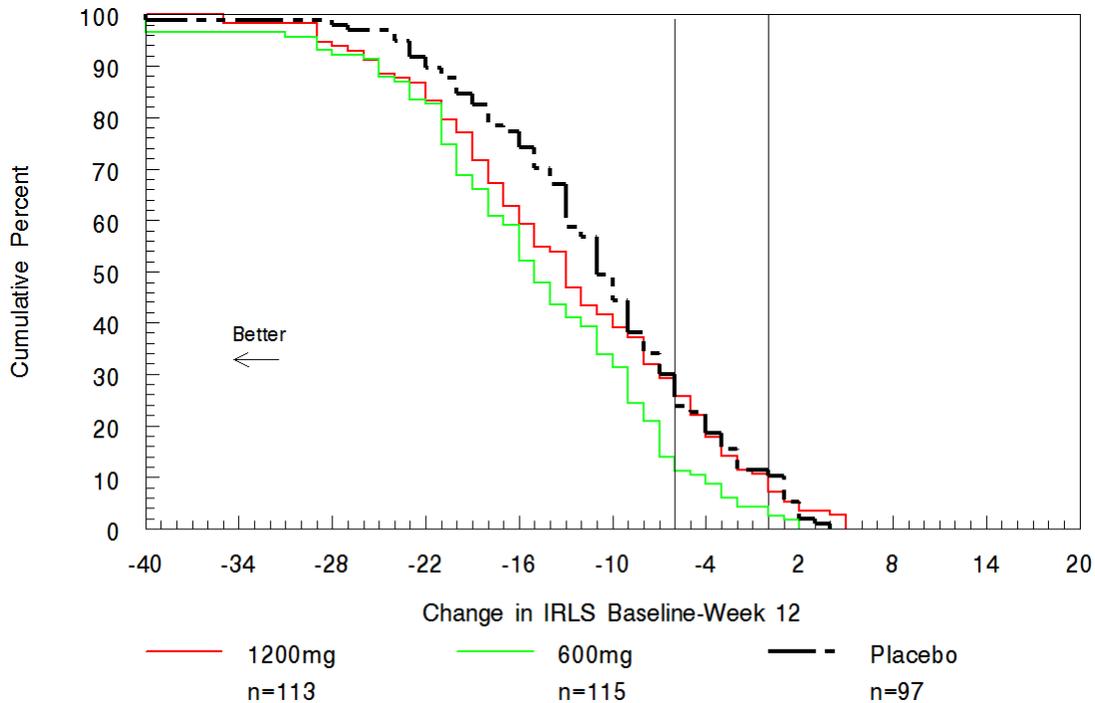
	Change from IRLS Total Score – XP053									
	Base-Line	Visit3 Week1	Visit4 Week2	Visit5 Week3	Visit6 Week4	Visit7 Week6	Visit8 Week8	Visit9 Wk10	Visit10 Wk12	Visit10 LOCF
Placebo										
N	96	88	91	87	84	83	81	74	74	96
Mean	23.81	-6.51	-7.80	-7.17	-8.62	-8.99	-8.09	-9.19	-10.97	-9.84
SD	(4.58)	(5.53)	(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.

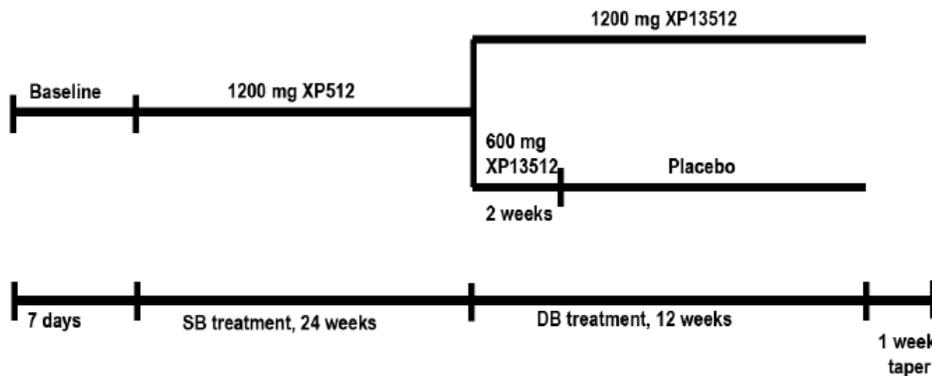
Open-Label Extension Safety Study XP055

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)

XenoPort, Inc.
Study XP052

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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)

XenoPort, Inc.
Study XP052

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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

XenoPort, Inc. Page 7 of 9
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.

- 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.
- 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.

- 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

- a. 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.
- b. Includes Subject 107/3017, who completed the study, but the reported TEAE of "Seasonal Allergy" was incorrectly recorded as a TEAE leading to withdrawal.
- c. 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.
- d. 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.
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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..

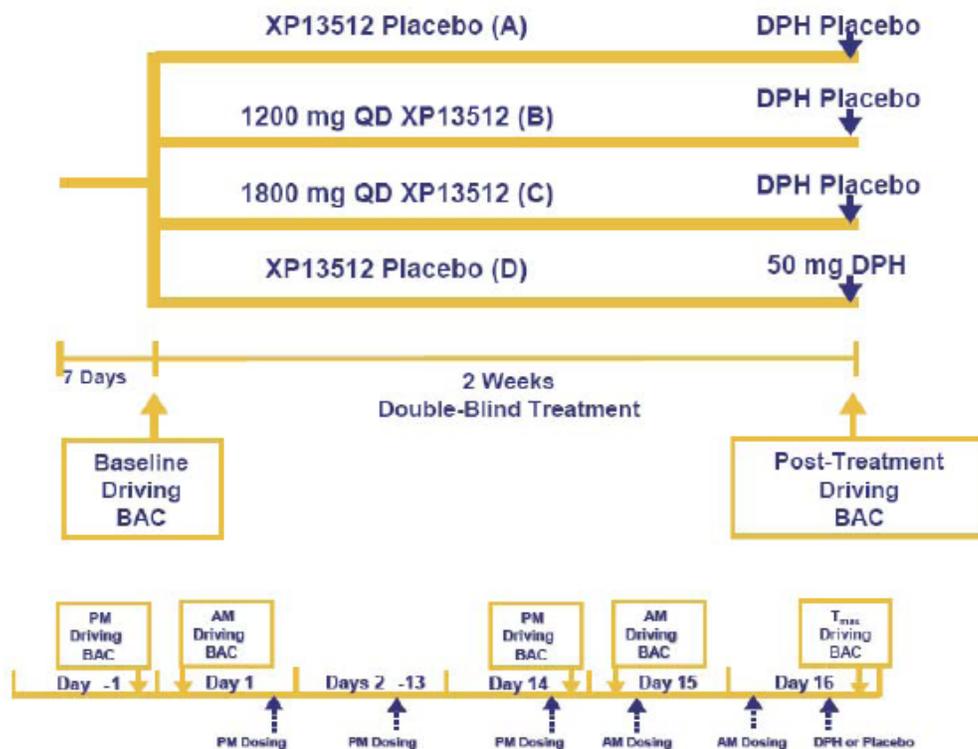
One XP13512-treated subject reported convulsion during the taper period following the DB phase of Study XP060 that was judged serious, possibly related to study medication and resulted in withdrawal from the study. This subject was subsequently found to have an abnormal EEG indicative of a possible underlying 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)

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)

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.

References

- Allen RP, Piechietti D, Hening WA, et al. Restless legs syndrome: diagnostic criteria, special considerations, and Epidemiology: A report from the restless legs syndrome diagnosis and epidemiology workshop at the National Institutes of Health. *Sleep Medicine*, 4; (2003): 101- 119
- Henning W. The clinical neurophysiology of the restless legs syndrome and periodic limb movements. Part I: diagnosis, assessment, and characterization *Clinical Neurophysiology*, 115; (20M): 1965-1974
- Manconi M, Fabbrini M, Bonanni E, Filippi M, Rocca M, Murri L, Ferini-Strambi L. High prevalence of restless legs syndrome in multiple sclerosis. *Eur J Neurol*. 2007 May;14(5):534-9.
- Hening W. Current Guidelines and Standards of Practice for Restless Legs Syndrome *Am J Med*; 2007: 120 (1A), 522-527
- Adler CH. Treatment of Restless Legs Syndrome. *Clin Neuropharmacol*, 1987;10:225-37
- Garcia-Borreguero D; Larrosa O; de la Llave Y, Verger K; X. Masramon X, Hernandez, G. Treatment of restless legs syndrome with gabapentin: A double-blind, cross-over study. *Neurology*, 2002;59:1573–1579
- Happe S, Klosch G, Bernd S, Zeitlhofer. Treatment of idiopathic restless legs syndrome with gabapentin. *Neurology* 2001;57:1717- 1719
- Happe S, Klosch G, Bernd S, Zeitlhofer. Gabapentin versus Ropinirole in the Treatment of Idiopathic Restless Legs Syndrome. *Neuropsychobiology* 2003;48:82-86
- Adler CH. Treatment of Restless Legs Syndrome with Gabapentin. *Clin Neuropharmacol*; 20.1: 148-151
- D. Garcia'-Borreguero, et al. Augmentation as a Treatment Complication of Restless Legs Syndrome: Concept and Management . *Movement Disorders*, Vol. 22, Suppl. 18, 2007, pp. S476–S484
- Baker WL, White MC, Coleman CI. Effect of Nonergot Dopamine Agonists on Symptoms of Restless Legs Syndrome. *Ann Fam Med*. 2008 May; 6(3): 253–262.
- Trenkwalder C, Hening WA, Montagna P. Treatment of Restless Legs Syndrome: An Evidence-Based Review and Implications for Clinical Practice *Movement Disorders* Vol. 23, No. 16, 2008, pp. 2267–2302
- Garcia-Borreguero D, Allen RP, Benes B. Augmentation as a Treatment Complication of Restless Legs Syndrome: Concept and Management *Movement Disorders* Vol. 22, Suppl. 18, 2007, pp. S476–S484
- Winkelman JW, Johnston L. Augmentation and tolerance with long-term pramipexole treatment of restless legs syndrome (RLS). *Sleep Medicine*, 5;2004:9-14.

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
02/07/2010



**Department of Health and Human Services
Public Health Service
Food and Drug Administration
Center for Drug Evaluation and Research
Office of Surveillance and Epidemiology**

Date: October 26, 2009

To: Russell Katz, MD
Director, Division of Neurology Products (DNP)

Through: Kellie Taylor, PharmD, MPH, Team Leader
Denise Toyer, PharmD, Deputy Director
Carol Holquist, RPh, Director
Division of Medication Error Prevention and Analysis (DMEPA)

From: Zachary Oleszczuk, PharmD, Safety Evaluator
Division of Medication Error Prevention and Analysis (DMEPA)

Subject: Label and Labeling Review

Drug Name(s): Horizant (Gabapentin Enacarbil) Extended-Release Tablets
600 mg

Application Type/Number: NDA 022399

Applicant: GlaxoSmithKline

OSE RCM #: 2009-114 and 2009-158

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1 BACKGROUND

1.1 Introduction

This review is written in response to a request from the Division Neurology Products (DNP) for a review of the container labels and package insert labeling for NDA 022399, to identify areas that could lead to medication errors.

Additionally the Applicant identified the possibility of intentional and unintentional substitution of Horizant and immediate release gabapentin products in a document entitled “Risk Management Plan” [the predecessor to the Risk Evaluation and Mitigation Strategy (REMS)] submitted on September 15, 2008. Although DMEPA agrees with the Applicant that intentional and unintentional substitution may occur, we believe that the risk of the substitution can be minimized with the label and labeling recommendations in Section 3.1. This product will be subject to a Medication Guide REMS, however this Medication Guide will contain information on suicidality related to the use of antiepileptic drugs and not the risk of intentional and unintentional substitution.

1.2 Product Information

Horizant (Gabapentin Enacarbil) is a prodrug that is structurally similar to the neurotransmitter gamma-aminobutyric acid (GABA) indicated for the treatment of moderate to severe primary Restless Leg Syndrome (RLS). Horizant is available as a 600 mg orally extended-release tablet. Horizant requires that a patient’s dose [REDACTED] (b) (4). The dose of Horizant is 600 mg orally once per day at 5 pm [REDACTED] (b) (4).

2 METHODS AND MATERIALS REVIEWED

The Division of Medication Error Prevention and Analysis used Failure Mode and Effects Analysis (FMEA)¹ in our evaluation of the Horizant container labels received on July 23, 2009 (see Appendix A) and insert labeling received April 7, 2009 (no image).

3 RECOMMENDATIONS

We would be willing to meet with the Division for further discussion, if needed. Please forward the comments provided in Section 3.2 to the Applicant and copy the Division of Medication Error Prevention and Analysis on any communication to the Applicant with regard to this review. If you have further questions or need clarifications, please contact Laurie Kelly, project manager, at 301-796-5068.

¹ Institute for Healthcare Improvement (IHI). Failure Modes and Effects Analysis. Boston. IHI:2004.

3.1 Comments to the Division

Add the statement “Horizant should not be interchanged with immediate release gabapentin products” to the highlights section. Section 12.3 contains a similar statement, however since this proposed product is not to be interchanged with immediate release gabapentin products, the differences of this product should be made prominent to help make healthcare providers aware of the differences and minimize the possibility of interchange.

3.2 Comments to the Applicant

3.2.1 Container Label

1. The words ‘EXTENDED RELEASE TABLETS’ are small and hard to read. Since this product is not to be interchanged with immediate release gabapentin products, the dosage form differences of this product should be prominent to help ensure healthcare providers are aware of the differences and minimize the possibility of interchange. Relocate the dosage form ‘extended release tablets’ to follow the established name and revise the text to be the same size, font, and weight of the rest of the established name gabapentin enacarbil.
2. The statement “Tablets should not be cut, crushed, or chewed” is not highlighted and is embedded in the surrounding text making it difficult to read. Since Horizant is an extended-release formulation and administering the product incorrectly could be a source for error, the prominence of this warning should be increased by relocating the statement to the principal display panel and revising the color of the font and/or highlighting the statement.
3. Remove the statement (b) (4) Horizant extended-release tablets can be dispensed in standard pharmacy vials, thus this statement is not necessary and should be removed from the container label.
4. Revise the statements “Do not use if printed safety seal under cap is broken or missing” and “Do not remove desiccant” to be unbolded and the same font and color of the rest of the text that is presented on the side of the label. While these messages are important, all prescription medications have a tamper resistant barrier and should not be used if that barrier is broken. Additionally, many products contain desiccants and the desiccants are to remain in the container. The statements “Do not use if printed safety seal under cap is broken or missing” and “Do not remove desiccant” could deliver the intended messages with out being bolded or in a different font color.

5. To comply with 21 CFR 208.24 (d), add a statement regarding the required distribution of a Medication Guide to the principal display panel of the container labels and carton labeling of all 4 package sizes (5, 30, 80, and 160 tablets). For example, we recommend:

“Dispense Enclosed Medication Guide To Each Patient”

or

“Dispense the accompanying Medication Guide to each patient”

3.2.2 Risk Evaluation Mitigation Strategy(REMS)

To comply with 21 CFR 208.24 (e) ensure that a sufficient number of Medication Guides are provided with containers of Horizant so that every patient can receive one Medication Guide with their prescription . For example, the 180 count bottle could be dispensed as six, 30 days supplies. Thus, the 180 count bottle should be supplied with a minimum of six Medication Guides .

2 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/

ZACHARY A OLESZCZUK
10/26/2009

KELLIE A TAYLOR
10/26/2009

DENISE P TOYER
10/28/2009

CAROL A HOLQUIST
10/28/2009



**Department of Health and Human Services
Public Health Service
Food and Drug Administration
Center for Drug Evaluation and Research
Office of Surveillance and Epidemiology**

Date: January 7, 2010

To: Russell Katz, M.D., Director
Division of Neurology Products (DNP)

Through: Claudia Karwoski, PharmD, Director
Division of Risk Management (DRISK)
LaShawn Griffiths, RN, MSHS-PH, BSN
Patient Labeling Reviewer, Acting Team Leader
Division of Risk Management (DRISK)

From: Robin Duer, RN, MBA, BSN
Patient Product Information Reviewer - MG
Jessica Diaz, RN, BSN
Patient Product Information Reviewer - REMS
Division of Risk Management

Subject: DRISK Review of Patient Labeling (Medication Guide)
and Proposed Risk Evaluation and Mitigation Strategy
(REMS)

Drug Name(s): HORIZANT (gabapentin enacarbil)

Application Type/Number: NDA 22-399

Applicant/sponsor: GlaxoSmithKline

OSE RCM #: 2009-158

1 INTRODUCTION

This memorandum is in response to a request by the Division of Neurology Products for the Division of Risk Management (DRISK) to review the Applicant's proposed Medication Guide (MG) and proposed Risk Evaluation and Mitigation Strategy (REMS) for HORIZANT (gabapentin enacarbil).

On September 21, 2009 FDA issued a letter to GSK requesting safety labeling changes including a Medication Guide and a Risk Evaluation Mitigation Strategy (REMS) to inform patients of the increased risk for suicidal thoughts and behavior.

Please send these comments to the Applicant and request a response within two weeks of receipt. Please let us know if you would like a meeting to discuss these comments before sending to the Applicant. The DRISK review of the methodology and survey instruments, once submitted by the Applicant to evaluate the REMS, will also be provided under separate cover.

2 MATERIAL REVIEWED

- Draft HORIZANT (gabapentin enacarbil) Extended Release Tablets Prescribing Information (PI) submitted on October 9, 2009 and revised by DNP throughout the review cycle
- Draft HORIZANT (gabapentin enacarbil) Extended Release Tablets Medication Guide (MG) submitted on October 9, 2009
- HORIZANT (gabapentin enacarbil) Risk Evaluation and Mitigation Strategy (REMS) Notification Letter dated September 21, 2009
- Proposed HORIZANT (gabapentin enacarbil) Risk Evaluation and Mitigation Strategy (REMS) and REMS Supporting Document, submitted on October 9, 2009

3 RESULTS OF REVIEW

In our review of the Medication Guide, we have:

- simplified wording and clarified concepts where possible
- ensured that the MGs are consistent with the PIs
- removed unnecessary or redundant information
- ensured that the MGs meet the Regulations as specified in 21 CFR 208.20
- ensured that the MGs meet the criteria as specified in FDA's Guidance for Useful Written Consumer Medication Information (published July 2006)

In our review of the proposed REMS, we have ensured it meets the statutory requirement under the Food and Drug Administration Amendments Act (FDAAA) of 2007.

4 CONCLUSIONS AND RECOMMENDATIONS

DRISK concurs with the MG and the elements of the REMS with revisions provided in this review.

Please note, the REMS timetable for submission of the assessments is required to be approved as part of the REMS, but not the Applicant's proposed information about the details of the REMS evaluation (methodology/instruments). The methodology and instruments **do not** need to be reviewed or approved prior to approval of the REMS.

We have the following comments and recommendations for the Applicant with regard to the proposed REMS.

Comments to DNP:

- a. Our annotated MG is appended to this memo. Appendix A is the marked up copy and Appendix B is the clean copy. Any additional revisions to the PI should be reflected in the MG.
- b. GSK does not believe they need to conduct certain assessments of Medication Guide distribution because at this time only the 30-count bottle is currently being marketed and this presentation is unit-of-use. While we agree that an assessment of the distribution and dispensing requirements need not be conducted for Medication Guides that are packaged in unit-of-use, the REMS applies as well to the 60 and 180 count containers. These presentations are not currently marketed but GSK plans to make them available at a later date; the 60 and 180 count presentations will not be unit-of-use. Therefore, to avoid having to modify what we want in the assessment when GSK introduces the 60 and 180 count presentations, we recommend the REMS approval letter include the following language regarding the REMS Assessment Plan:

The REMS assessment plan should include but is not limited to the following:

- a. An evaluation of patients' understanding of the serious risks of Horizant (gabapentin enacarbil) extended release tablets.
- b. If the product is distributed without the Medication Guide included in unit-of-use packaging, a report on periodic assessments of the distribution and dispensing of the Medication Guide in accordance with 21 CFR 208.24

- c. If the product is distributed without the Medication Guide included in unit-of-use packaging, a report on failures to adhere to distribution and dispensing requirements, and corrective actions taken to address noncompliance

Comments to Abbott Laboratories:

See the appended HORIZANT (gabapentin enacarbil) REMS proposal (Appendix C of this memo) for track changes corresponding to comments in this review.

a. GOAL

Revise your goal as follows:

The goal of this REMS is to inform patients about the serious risks associated with the use of Horizant (gabapentin enacarbil) extended-release tablets.

- b. The Medication Guide distribution plan for the 30-count bottle appears to be acceptable. We acknowledge your inclusion of 60 and 180 bottle counts in your REMS Supporting Document. You will need to ensure that sufficient Medication Guides are provided for those presentations once they become commercially available in accordance with 21 CFR 208.24 (b). We recommend that each packaging configuration contain enough Medication Guides so that one is provided for each “usual” or average dose. For example:

- A minimum of 4 Medication Guides would be provided with a bottle of 100 for a product where the usual or average dose is 1 capsule/tablet daily, thus a monthly supply is 30 tablets.
- A minimum of 1 Medication Guide would be provided with unit of use where it is expected that all tablets/capsules would be supplied to the patient.

We have some editorial comments in this section of the proposed REMS.

- c. Your proposed timetable for submission of assessments [REDACTED] (b) (4) [REDACTED] is acceptable.

We have some editorial comments in this section of the proposed REMS.

- d. We acknowledge your proposal to conduct a patient survey in the REMS Supporting Document to evaluate patients’ understanding about the serious risks of HORIZANT (gabapentin enacarbil). Your detailed plan should be submitted as part of the REMS supporting document. This information **does not** need to be submitted for FDA review prior to approval of your REMS, however it should be submitted at least 90 days before you plan to conduct the evaluation. The submission should be coded “REMS Correspondence.” Your submission should include:

- All methodology and instruments that will be used to evaluate the patients' understanding about the serious risks and safe use of HORIZANT (gabapentin enacarbil) should include, but not be limited to:
 - Sample size and confidence associated with that sample size
 - How the sample will be determined (selection criteria)
 - The expected number of patients to be surveyed
 - How the participants will be recruited
 - How and how often the surveys will be administered
 - Explain controls used to minimize bias
 - Explain controls used to compensate for the limitations associated with the methodology
 - The survey instruments (questionnaires and/or moderator's guide).
 - Any background information on testing survey questions and correlation to the messages in the Medication Guide.
- e. We agree that the "periodic assessments of distribution and dispensing of the Medication Guide" and "a report on the failures to adhere to distribution and dispensing requirements, and corrective actions to address noncompliance" are necessary when a product is distributed in unit-of-use that includes a Medication Guide with a quantity of product dispensed to a single patient and not divided. You will however, be required to assess these components when the 60-count and 180-count bottles are made available.

Please let us know if you have any questions.

17 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

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/s/

ROBIN E DUER
01/07/2010

CLAUDIA B KARWOSKI
01/07/2010
concur

MEMORANDUM

**DEPARTMENT OF HEALTH AND HUMAN SERVICES
PUBLIC HEALTH SERVICE
FOOD AND DRUG ADMINISTRATION
CENTER FOR DRUG EVALUATION AND RESEARCH**

CLINICAL INSPECTION SUMMARY

DATE: August 13, 2009

TO: Beverly Conner, Regulatory Health Project Manager
Suzan Goldstein, M.D., Medical Officer
Division of Neurology Drug Products

THROUGH: Tejashri purohit-Sheth, M.D.
Branch Chief
Good Clinical Practice Branch II
Division of Scientific Investigations

FROM: Antoine El-Hage, Ph.D.
Regulatory Pharmacologist
Good Clinical Practice Branch II
Division of Scientific Investigations

SUBJECT: Evaluation of Clinical Inspections

NDA: 22-399

APPLICANT: GlaxoSmithKline.

DRUG: Solazira (gabapentin enacarbil) Tablets

NME: Yes

THERAPEUTIC CLASSIFICATION: Standard Review

INDICATION: Adjunctive therapy in subjects with refractory partial seizures

CONSULTATION REQUEST DATE: February 24, 2009

DIVISION ACTION GOAL DATE: August 24, 2009

PDUFA DATE: November 9, 2009

I. BACKGROUND:

XP13512 is a prodrug of gabapentin designed to improve gabapentin pharmacokinetics and therapy. Patients with restless legs syndrome (RLS) suffer from a significant medical condition that requires treatment for their leg discomfort, urge to move, and sleep disturbance. Because XP13512 has been shown to significantly improve symptoms of RLS in phase 2 studies, additional studies were conducted to confirm the findings. The sponsor submitted data from two pivotal studies to support their application for marketing approval of orally administered doses of gabapentin (600 and 1600 mg) when compared to placebo in patients with restless leg syndrome. The review division requested inspection of Protocol XP052 entitled “A randomized, double-blind, placebo-controlled study to assess the efficacy and safety of XP13529 (GSK 18386262) in Patients with restless legs syndrome”; and Protocol XP053 under the same title as(XP052) but using only the 1200 mg once daily. The applicant submitted results from the above protocols in support of NDA 22-399.

The inspections targeted four domestic clinical investigators who enrolled a relatively large number of subjects. The goals of the inspections included validation of submitted data and compliance of study activities with FDA regulations. The records inspected included, but were not limited to, 100% informed consent forms, source documents, drug accountability records, protocol inclusion/exclusion criteria, randomization procedures, efficacy endpoints and documentation of adverse events.

Because the test article is a new molecular entity, the sponsor was also inspected. The inspection covered the two clinical investigators listed below under Protocol XP052.

II. RESULTS (by protocol/site):

Name of CI, or Sponsor site # and location	Protocol and # of subjects	Inspection Dates	Final Classification
Albert Razzetti, M.D. UCR Deland Inc. 860 Peachwood Drive Deland, FL 327206441	XP052 18 subjects	6/1-5/09	VAI
William Ellison, M.D. 552-A Memorial Dr. Greer, SC 29651	XP052 18 subjects	5/27-29/09	NAI
James Garrison, M.D 54 Fredricksburg Rd, Suite 400 San Antonio, TX 78229	XP053 29	4/28-5/1/09	NAI
Kurt w. Lesh, M.D. Lynn Institute 2500 North Circle Dr. Colorado Springs, CO 80909	XP053 27 subjects	5/25-6/2/09	VAI
GSK (Sponsor) Reasrech Triangle Park, NC 27709	XP052 47	6/9-11/09	NAI

Key to Classifications

NAI = No deviation from regulations

VAI = deviation(s) from regulations

OAI = Significant deviations for regulations. Data unreliable.

Pending = Preliminary classification based on information in 483 or preliminary communication from the field; EIR has not been received from the field and complete review of EIR is pending.

Protocol XP052

**1. Albert Razzetti, M.D.
Deland, FL32720**

At this site, a total of 29 subjects were screened, 11 subjects were reported as screen failures, and 18 subjects were randomized and 15 subjects completed the study. Three subjects were discontinued and the reason(s) were documented. Informed consent for all subjects was verified to be signed by subjects prior to enrollment.

The medical records/source documents for 18 subjects were reviewed in depth, including drug accountability, laboratory records, and IRB records, and source documents were compared to case report forms and data listings, including primary efficacy endpoints and adverse events.

At the end of the inspection, a Form FDA 483 was issued. Our investigation found inconsistencies in recording data and no record of the individual (initials) performing vital signs and physical assessments was noted. Corrections made by staff were not reviewed by the clinical investigator till later dates. Subject 2020 had breast cancer and was enrolled in the study contrary to protocol exclusion criteria; Subject 2022 received Crestor which was not reported on the case report form as concomitant medication, and Subject 2025 received prohibited medication acetaminophen/codeine for neck and shoulder pain, and missed 8 doses which were not reported in the case report form. With the exceptions noted above, no adverse findings were noted that would impact the subjects' safety or reflect negatively on the reliability of the data. In general, the study records reviewed were found to be in order and verifiable. There were no known limitations to this inspection.

Assessment of Data Integrity

Although regulatory violations were noted, the findings are unlikely to impact data integrity. The data appear acceptable in support of the pending application.

**2. William Ellison, M.D.
Greer, SC 29651**

At this site, a total of 43 subjects were screened; 25 subjects were reported as screen failures; 18 subjects were enrolled and 12 subjects completed the study. Six subjects were discontinued and the reason(s) were documented. Informed consent for all 18 subjects reviewed was verified to be signed by subjects prior to enrollment.

The medical records/source documents for 18 subjects were reviewed in depth including drug accountability, IRB records, laboratory results, and source documents were compared to case report forms and data listings, including primary efficacy endpoints and adverse events.

The medical records reviewed disclosed no adverse findings that would reflect negatively on the reliability of the data. In general, the study records reviewed were accurate in terms of data entries and reporting of adverse events. There were no known limitations to this inspection.

Assessment of Data Integrity

The data appear acceptable in support of the pending application.

Protocol XP053

**3. James Garrison, M.D.
San Antonio, TX 78229**

At this site, a total of 46 subjects were screened; 17 subjects were reported as screen failures; 29 subjects were enrolled and 24 subjects completed the study. Informed consent for all 10 subjects reviewed was verified to be signed by subjects prior to enrollment.

The medical records/source documents for 10 subjects were reviewed in depth including drug accountability, IRB records, laboratory results, and source documents were compared to case report forms and data listings, including primary efficacy endpoints and adverse events. Our investigation found that Subject 3026 experienced one episode of “poor diction” and Subject 3045 experienced “some drowsiness” associated with study medication.

The medical records reviewed disclosed no adverse findings that would reflect negatively on the reliability of the data. In general, the study records reviewed were accurate in terms of data entries and reporting of adverse events. There were no known limitations to this inspection.

Assessment of Data Integrity

The data appear acceptable in support of the pending application.

**4. Kurt W. Lesh, M.D.
Colorado Springs, CO 80909**

At this site, a total of 44 subjects were screened, 17 subjects were reported as screen failures, and 27 subjects were randomized and 24 subjects completed the study. Three subjects were discontinued and the reason(s) were documented. Informed consent for all subjects was verified to be signed by subjects prior to enrollment.

The medical records/source documents for 20 subjects were reviewed in depth, including drug accountability, laboratory records, and IRB records, and source documents were compared to case report forms and data listings, including primary efficacy endpoints and adverse events. Adverse events experienced by study subjects were not reported to the sponsor and IRB within the required time frames. Subjects 3008 and 3012 experienced episodes of excess tiredness and these events were not reported on the subject’s adverse events section of the case report form.

Our investigation found minor transcription errors in recording blood pressure for Subject 30044 at Visit 2 and not reporting concomitant medication (tetanus booster) for Subject 3005. With the exception note above, no adverse findings were noted that would impact the subjects' safety or reflect negatively on the reliability of the data. In general, the study records reviewed were found to be in order and verifiable. There were no known limitations to this inspection.

Assessment of Data Integrity

Although some regulatory violations were noted, these are unlikely to impact data integrity. The data appear acceptable in support of the pending application.

5. GlaxoSmithKline. Research Triangle Park, NC 27709

The inspection audited Protocol XP052 and focused on the following clinical investigators: Drs. Razzetti and Ellison during the course of this sponsor monitor inspection.

Initially, Xenoport held sole ownership of the study under IND 071352 for the XP052 study. GlaxoSmithKline (GSK) acquired sole ownership from Xenoport on April, 8 2008 and subsequently submitted the application to the FDA for marketing approval. While under Xenoport, the firm contracted (b) (4), a CRO to assist in monitoring activities and other responsibilities.

The inspection reviewed the following: Company history and officer responsibilities, training program, manufacturing/design operations, selection of clinical investigators, quality assurance, study monitoring procedures, data review and reports, protocol adherence, computerization, participating clinical investigators, and adverse events reporting.

The inspection found that the sponsor adhered to their SOPs regarding proper monitoring of their clinical investigators. The activities included, but not limited to, trial drug records, subject records, electronic database for entry of study data, protocol adherence, case report forms/source documents and adverse events reporting.

Assessment of Data Integrity

The sponsor monitoring procedures appears to have been conducted adequately and the data submitted by the sponsor may be used in support of the respective indication. In general, the data appear acceptable in support of the pending application.

III. 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 above clinical investigators and GSK revealed no significant problems that would adversely

impact data acceptability. The data generated and submitted by the sponsor from the above four inspected sites are acceptable in support of the pending application.

{See appended electronic signature page}

Antoine El-Hage, Ph.D.
Regulatory Pharmacologist
Good Clinical Practice Branch II
Division of Scientific Investigations

CONCURRENCE:

{See appended electronic signature page}

Tejashri Purohit-Sheth, M.D.
Branch Chief
Good Clinical Practice Branch II
Division of Scientific Investigations

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/s/

ANTOINE N EL HAGE
08/17/2009

TEJASHRI S PUROHIT-SHETH
08/17/2009

Executive CAC

Date of Meeting: August 4, 2009

Committee: David Jacobson-Kram, Ph.D., OND IO, Chair
Paul Brown, Ph.D., OND IO, Member
Todd Bourcier, Ph.D., DMEP, Alternate Member
Lois Freed, Ph.D., DNP Supervisor
Terry Peters, D.V.M., DNP Presenting Reviewer

Author of Draft: Terry Peters

The following information reflects a brief summary of the Committee discussion and its recommendations.

NDA #22-399

Drug Name: (b) (4)™ (proposed name)

Sponsor: GlaxoSmithKline

Background: (b) (4)™ is a novel prodrug of gabapentin intended for treatment of moderate to severe primary Restless Legs Syndrome.

The test article was not genotoxic in the in vitro Ames test, the in vivo micronucleus or the in vivo/in vitro UDS assay, but it was positive in the in vitro chromosomal aberration assay in human lymphocytes. The positive finding was attributed to in vitro release of acetaldehyde during the (b) (4).

The protocols for the lifetime carcinogenicity studies in mouse and rat were reviewed by the ECAC on 5/3/05 and the Committee concurred with the sponsor's proposed doses for both studies.

Rat Carcinogenicity Study

Wistar rats were treated for up to 104 weeks with 0, 500, 2000 or 5000 mg/kg/d of XP13512 in Tween 80 and methylcellulose by oral gavage. 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. There was an increased incidence of pancreatic acinar cell hyperplasia, adenomas, and adenomas + carcinomas in both sexes at 5000 mg/kg/d and in males at 2000 mg/kg/d. The study appears to have been appropriately conducted and the mid and high doses elicited toxicity as well as tumors. Thus XP13512 is considered a carcinogen in rats under the conditions of this 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	1	8	0	11	3	17	10
Mod-severe	3	0	2	1	3	1	3	4
Acinar adenoma	2	4	4	8	0	0	0	3
Acinar carcinoma	0	0	1	1	0	0	0	1

Mouse Carcinogenicity Study

B6C3F₁/Crl mice were treated with XP13512 in Tween 80 and methylcellulose by oral gavage at 0, 500, 2000 or 5000 mg/kg/d for up to 104 weeks. Decreased survival was found in mid (83% compared to controls) and high dose (83% compared to controls) males; however, a sufficient number of animals survived to scheduled termination to consider the study valid. Body weight was increased in the high dose males and females, compared to controls. No other significant adverse effects of treatment were found other than a minimal to mild exacerbation of age-related axonal/ myelin degeneration of the sciatic nerve found in mid dose females and both sexes at the high dose. No drug-related increases of any tumor type were found in this study.

Executive CAC Recommendations and Conclusions:

Rat:

- The Committee concluded that the study was adequate.
- The Committee found that the study was positive for carcinogenicity, noting increases in pancreatic acinar cell hyperplasia, adenomas, and adenomas + carcinomas in males at 2000 and 5000 mg/kg/d and in females at 5000 mg/kg/d.
- A survival adjusted statistical analysis of tumor incidences is pending.

Mouse:

- The Committee concluded that the study was adequate and negative for carcinogenicity.
- A survival adjusted statistical analysis of tumor incidences is pending.

David Jacobson-Kram, Ph.D.
Chair, Executive CAC

cc:\

/Division File, DNP
Freed/Team leader, DNP
Peters/Reviewer, DNP
Connor/CSO/PM, DNP
/ASeifried, OND IO

Linked Applications	Submission Type/Number	Sponsor Name	Drug Name / Subject
----- NDA 22399	----- ORIG 1	-----	----- SOLZIRA

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/s/

ADELE S SEIFRIED
08/05/2009

DAVID JACOBSON KRAM
08/05/2009

NDA REGULATORY FILING REVIEW
(Including Memo of Filing Meeting)

NDA # 22-399 Supplement # Efficacy Supplement Type SE-

Proprietary Name: SOLZIRA
Established Name: gabapentin enacarbil
Strengths: 600 mg

Applicant: SmithKline Beecham Corporation
Agent for Applicant: Elizabeth A. McConnell, Pharm.D.
Date of Application: January 8, 2009
Date of Receipt: January 9, 2009
Date clock started after UN: N/A
Date of Filing Meeting: February 20, 2009
Filing Date: February 20, 2009
Action Goal Date (optional): November 9, 2009

User Fee Goal Date: November 9, 2009

Indication(s) requested: Treatment of severe to moderate restless leg syndrome.

Type of Original NDA: (b)(1) (b)(2)
AND (if applicable)
Type of Supplement: (b)(1) (b)(2)

NOTE:

(1) If you have questions about whether the application is a 505(b)(1) or 505(b)(2) application, see Appendix A. A supplement can be either a (b)(1) or a (b)(2) regardless of whether the original NDA was a (b)(1) or a (b)(2). If the application or efficacy supplement is a (b)(2), complete Appendix B.

Review Classification: Standard P
Resubmission after withdrawal? Resubmission after refuse to file?
Chemical Classification: Type 1
NDA
Other (orphan, OTC, etc.)

Form 3397 (User Fee Cover Sheet) submitted: YES NO

User Fee Status: Paid Exempt (orphan, government)
Waived (e.g., small business, public health)

NOTE: If the NDA is a 505(b)(2) application, and the applicant did not pay a fee in reliance on the 505(b)(2) exemption (see box 7 on the User Fee Cover Sheet), confirm that a user fee is not required by contacting the User Fee staff in the Office of Regulatory Policy. The applicant is required to pay a user fee if: (1) the product described in the 505(b)(2) application is a new molecular entity or (2) the applicant claims a new indication for a use that has not been approved under section 505(b). Examples of a new indication for a use include a new indication, a new dosing regime, a new patient population, and an Rx-to-OTC switch. The best way to determine if the applicant is claiming a new indication for a use is to compare the applicant's proposed labeling to labeling that has already been approved for the product described in the application. Highlight the differences between the proposed and approved labeling. If you need assistance in determining if the applicant is claiming a new indication for a use, please contact the User Fee staff.

- Is there any 5-year or 3-year exclusivity on this active moiety in any approved (b)(1) or (b)(2) application? YES NO
If yes, explain:

Note: If the drug under review is a 505(b)(2), this issue will be addressed in detail in appendix B.

- Does another drug have orphan drug exclusivity for the same indication? YES NO
- If yes, is the drug considered to be the same drug according to the orphan drug definition of sameness [21 CFR 316.3(b)(13)]? YES NO

If yes, consult the Director, Division of Regulatory Policy II, Office of Regulatory Policy (HFD-007).

- Is the application affected by the Application Integrity Policy (AIP)? YES NO
If yes, explain:
- If yes, has OC/DMPQ been notified of the submission? YES NO
- Does the submission contain an accurate comprehensive index? YES NO
If no, explain:
- Was form 356h included with an authorized signature? YES NO
If foreign applicant, both the applicant and the U.S. agent must sign.
- Submission complete as required under 21 CFR 314.50? YES NO
If no, explain:
- Answer 1, 2, or 3 below (do not include electronic content of labeling as an partial electronic submission).

1. This application is a paper NDA NO
2. This application is an eNDA or combined paper + eNDA YES
This application is: All electronic Combined paper + eNDA
This application is in: NDA format CTD format
Combined NDA and CTD formats

Does the eNDA, follow the guidance?
(<http://www.fda.gov/cder/guidance/2353fml.pdf>) YES NO

If an eNDA, all forms and certifications must be in paper and require a signature.

If combined paper + eNDA, which parts of the application were submitted in electronic format? N/A

Additional comments: N/A

3. This application is an eCTD NDA. YES
If an eCTD NDA, all forms and certifications must either be in paper and signed or be electronically signed.

Additional comments: none

• Patent information submitted on form FDA 3542a? YES NO

• Exclusivity requested? YES, 5 yr Years NO

NOTE: An applicant can receive exclusivity without requesting it; therefore, requesting exclusivity is not required.

• Correctly worded Debarment Certification included with authorized signature? YES NO
If foreign applicant, both the applicant and the U.S. Agent must sign the certification.

NOTE: Debarment Certification should use wording in FD&C Act section 306(k)(1) i.e., "[Name of applicant] hereby certifies that it did not and will not use in any capacity the services of any person debarred under section 306 of the Federal Food, Drug, and Cosmetic Act in connection with this application." Applicant may not use wording such as "To the best of my knowledge . . ."

• Are the required pediatric assessment studies and/or deferral/partial waiver/full waiver of pediatric studies (or request for deferral/partial waiver/full waiver of pediatric studies) included? YES NO

• If the submission contains a request for deferral, partial waiver, or full waiver of studies, does the application contain the certification required under FD&C Act sections 505B(a)(3)(B) and (4)(A) and (B)? YES NO

• Is this submission a partial or complete response to a pediatric Written Request? YES NO

If yes, contact PMHT in the OND-IO

• Financial Disclosure forms included with authorized signature? YES NO
(Forms 3454 and/or 3455 must be included and must be signed by the APPLICANT, not an agent.)

NOTE: Financial disclosure is required for bioequivalence studies that are the basis for approval.

• Field Copy Certification (that it is a true copy of the CMC technical section) YES NO

• PDUFA and Action Goal dates correct in tracking system? YES NO
If not, have the document room staff correct them immediately. These are the dates EES uses for calculating inspection dates.

• Drug name and applicant name correct in COMIS? If not, have the Document Room make the corrections. Ask the Doc Rm to add the established name to COMIS for the supporting IND if it is not already entered. The established name has been entered.

• List referenced IND numbers: 71252

• Are the trade, established/proper, and applicant names correct in COMIS? YES NO
If no, have the Document Room make the corrections.

• End-of-Phase 2 Meeting(s)? yes December 6, 2005 NO
Date(s) _____
If yes, distribute minutes before filing meeting.

• Pre-NDA Meeting(s)? Yes December 14, 2007 NO
Date(s) _____

If yes, distribute minutes before filing meeting.

- Any SPA agreements? Date(s) 11/22/05, 4/19/06 NO
If yes, distribute letter and/or relevant minutes before filing meeting.

Project Management

- If Rx, was electronic Content of Labeling submitted in SPL format? YES NO
If no, request in 74-day letter.
- If Rx, for all new NDAs/efficacy supplements submitted on or after 6/30/06:
Was the PI submitted in PLR format? YES NO

If no, explain. Was a waiver or deferral requested before the application was received or in the submission? NO If before, what is the status of the request:

- If Rx, all labeling (PI, PPI, MedGuide, carton and immediate container labels) has been consulted to DDMAC? YES NO
- If Rx, trade name (and all labeling) consulted to OSE/DMETS? YES NO
- If Rx, MedGuide and/or PPI (plus PI) consulted to ODE/DSRCS? YES NO
- Risk Management Plan consulted to OSE/IO? YES NO
- If a drug with abuse potential, was an Abuse Liability Assessment, including a proposal for scheduling submitted? NA YES NO

If Rx-to-OTC Switch or OTC application:

- Proprietary name, all OTC labeling/packaging, and current approved PI consulted to OSE/DMETS? YES NO
- If the application was received by a clinical review division, has DNPCE been notified of the OTC switch application? Or, if received by DNPCE, has the clinical review division been notified? YES NO

Clinical

- If a controlled substance, has a consult been sent to the Controlled Substance Staff? YES NO

Chemistry

- Did applicant request categorical exclusion for environmental assessment? YES NO
If no, did applicant submit a complete environmental assessment? YES NO
If EA submitted, consulted to EA officer, OPS? YES NO
- Establishment Evaluation Request (EER) submitted to DMPQ? YES NO

- If a parenteral product, consulted to Microbiology Team? YES NO

ATTACHMENT

MEMO OF FILING MEETING

DATE: February 20, 2009

NDA #: 022-399

DRUG NAMES: The established name is gabapentin encarbil, and GSK is proposing that the new tradename be Solzira.

APPLICANT: GlaxoSmithKline

BACKGROUND: Solzira (gabapentin encarbil) is a new molecular entity for the treatment of moderate to severe primary Restless Legs Syndrome. The extended release tablets for gabapentin encarbil has in two doses, 1200 mg and 600 mg and the product is taken once daily at 5 PM. Gabapentin may cause somnolence, sedation, and dizziness, and impair the ability to drive or operate complex machinery.

On November 11, 2008, GlaxoSmithKline, sent an electronic message to alert the FDA they were formally withdrawing NDA 22-399 due to the statistical issues with Study XP060 datasets. On January 9, 2009, GlaxoSmithKline resubmitted the NDA for the treatment of moderate-to-severe primary Restless Legs Syndrome (RSL).

ATTENDEES: Dr. Russell Katz, Division of Neurology Products, Dr. Ellis Unger, M.D., Dr. Hao Zhu, Dr. Sally Yusada (Safety), Zackary Oleszczuk, ODS, Daniel Brounstein, Jackie Ware (Supervisor)

ASSIGNED REVIEWERS (including those not present at filing meeting) :

Discipline/Organization

Medical:

Statistical:

Pharmacology:

Chemistry:

Toxicity:

DSI:

Environmental Assessment):

Biopharmaceutical:

Per reviewers, are all parts in English or English translation?

If no, explain: N/A

Reviewers

Dr. Suzanne Goldstein

Dr. Sharon Yan

Dr. Kun Jin (Supervisor)

Veneeta Tandon, Team Leader

Dr. Hao Zhu

Dr. Terry Peters

Antoine EL Hage

Dr. Chhagan

Dr. Martha Heiman (supervisor)

Dr. Chhagan Tele

YES NO

CLINICAL

FILE

REFUSE TO FILE

- Clinical site audit(s) needed? YES NO
If no, explain:
- Advisory Committee Meeting needed? YES NO
- late October, 2009

- If the application is affected by the AIP, has the division made a recommendation regarding whether or not an exception to the AIP should be granted to permit review based on medical necessity or public health significance?
N/A YES NO

CLINICAL MICROBIOLOGY N/A FILE REFUSE TO FILE

STATISTICS N/A FILE REFUSE TO FILE

BIOPHARMACEUTICS FILE REFUSE TO FILE

- Biopharm. study site audits(s) needed? YES

PHARMACOLOGY/TOX N/A FILE REFUSE TO FILE

- GLP audit needed? YES NO

CHEMISTRY FILE REFUSE TO FILE

- Establishment(s) ready for inspection? YES NO
- Sterile product? YES NO
- If yes, was microbiology consulted for validation of sterilization?
YES NO

ELECTRONIC SUBMISSION:
Any comments: No Comments

**REGULATORY CONCLUSIONS/DEFICIENCIES:
(Refer to 21 CFR 314.101(d) for filing requirements.)**

- The application is unsuitable for filing. Explain why:
- The application, on its face, appears to be well-organized and indexed. The application appears to be suitable for filing.
 - No filing issues have been identified.
 - Filing issues to be communicated by Day 74. List (optional):

ACTION ITEMS:

1. Ensure that the review and chemical classification codes, as well as any other pertinent classification codes (e.g., orphan, OTC) are correctly entered into COMIS.
2. If RTF, notify everybody who already received a consult request of RTF action. Cancel the EER.

3. If filed and the application is under the AIP, prepare a letter either granting (for signature by Center Director) or denying (for signature by ODE Director) an exception for review.
4. If filed, complete the Pediatric Page at this time. (If paper version, enter into DFS.)
5. Convey document filing issues/no filing issues to applicant by Day 74.

Beverly Conner, Pharm.D.
Regulatory Project Manager

Appendix A to NDA Regulatory Filing Review

NOTE: The term "original application" or "original NDA" as used in this appendix denotes the NDA submitted. It does not refer to the reference drug product or "reference listed drug."

An original application is likely to be a 505(b)(2) application if:

- (1) it relies on published literature to meet any of the approval requirements, and the applicant does not have a written right of reference to the underlying data. If published literature is cited in the NDA but is not necessary for approval, the inclusion of such literature will not, in itself, make the application a 505(b)(2) application,
- (2) it relies for approval on the Agency's previous findings of safety and efficacy for a listed drug product and the applicant does not own or have right to reference the data supporting that approval, or
- (3) it relies on what is "generally known" or "scientifically accepted" about a class of products to support the safety or effectiveness of the particular drug for which the applicant is seeking approval. (Note, however, that this does not mean *any* reference to general information or knowledge (e.g., about disease etiology, support for particular endpoints, methods of analysis) causes the application to be a 505(b)(2) application.)

Types of products for which 505(b)(2) applications are likely to be submitted include: fixed-dose combination drug products (e.g., heart drug and diuretic (hydrochlorothiazide) combinations); OTC monograph deviations (see 21 CFR 330.11); new dosage forms; new indications; and, new salts.

An efficacy supplement can be either a (b)(1) or a (b)(2) regardless of whether the original NDA was a (b)(1) or a (b)(2).

An efficacy supplement is a 505(b)(1) supplement if the supplement contains all of the information needed to support the approval of the change proposed in the supplement. For example, if the supplemental application is for a new indication, the supplement is a 505(b)(1) if:

- (1) The applicant has conducted its own studies to support the new indication (or otherwise owns or has right of reference to the data/studies),
- (2) No additional information beyond what is included in the supplement or was embodied in the finding of safety and effectiveness for the original application or previously approved supplements is needed to support the change. For example, this would likely be the case with respect to safety considerations if the dose(s) was/were the same as (or lower than) the original application, and.
- (3) All other "criteria" are met (e.g., the applicant owns or has right of reference to the data relied upon for approval of the supplement, the application does not rely for approval on published literature based on data to which the applicant does not have a right of reference).

An efficacy supplement is a 505(b)(2) supplement if:

- (1) Approval of the change proposed in the supplemental application would require data beyond that needed to support our previous finding of safety and efficacy in the approval of the

original application (or earlier supplement), and the applicant has not conducted all of its own studies for approval of the change, or obtained a right to reference studies it does not own. For example, if the change were for a new indication AND a higher dose, we would likely require clinical efficacy data and preclinical safety data to approve the higher dose. If the applicant provided the effectiveness data, but had to rely on a different listed drug, or a new aspect of a previously cited listed drug, to support the safety of the new dose, the supplement would be a 505(b)(2),

- (2) The applicant relies for approval of the supplement on published literature that is based on data that the applicant does not own or have a right to reference. If published literature is cited in the supplement but is not necessary for approval, the inclusion of such literature will not, in itself, make the supplement a 505(b)(2) supplement, or
- (3) The applicant is relying upon any data they do not own or to which they do not have right of reference.

If you have questions about whether an application is a 505(b)(1) or 505(b)(2) application, consult with your ODE's Office of Regulatory Policy representative.

**Appendix B to NDA Regulatory Filing Review
Questions for 505(b)(2) Applications**

1. Does the application reference a listed drug (approved drug)? YES NO

If "No," skip to question 3.

2. Name of listed drug(s) referenced by the applicant (if any) and NDA/ANDA #(s):
3. Is this application for a drug that is an "old" antibiotic (as described in the draft guidance implementing the 1997 FDAMA provisions? (Certain antibiotics are not entitled to Hatch-Waxman patent listing and exclusivity benefits.) YES NO

If "Yes," skip to question 7.

4. Is this application for a recombinant or biologically-derived product? YES NO

If "Yes "contact your ODE's Office of Regulatory Policy representative.

5. The purpose of the questions below (questions 5 to 6) is to determine if there is an approved drug product that is equivalent or very similar to the product proposed for approval that should be referenced as a listed drug in the pending application.
- (a) Is there a pharmaceutical equivalent(s) to the product proposed in the 505(b)(2) application that is already approved? YES NO

(Pharmaceutical equivalents are drug products in identical dosage forms that: (1) contain identical amounts of the identical active drug ingredient, i.e., the same salt or ester of the same therapeutic moiety, or, in the case of modified release dosage forms that require a reservoir or overage or such forms as prefilled syringes where residual volume may vary, that deliver identical amounts of the active drug ingredient over the identical dosing period; (2) do not necessarily contain the same inactive ingredients; and (3) meet the identical compendial or other applicable standard of identity, strength, quality, and purity, including potency and, where applicable, content uniformity, disintegration times, and/or dissolution rates. (21 CFR 320.1(c))

If "No," to (a) skip to question 6. Otherwise, answer part (b and (c)).

- (b) Is the pharmaceutical equivalent approved for the same indication for which the 505(b)(2) application is seeking approval? YES NO

- (c) Is the approved pharmaceutical equivalent(s) cited as the listed drug(s)? YES NO

If "Yes," (c), list the pharmaceutical equivalent(s) and proceed to question 6.

If "No," to (c) list the pharmaceutical equivalent and contact your ODE's Office of Regulatory Policy representative.

Pharmaceutical equivalent(s):

6. (a) Is there a pharmaceutical alternative(s) already approved? YES NO

(Pharmaceutical alternatives are drug products that contain the identical therapeutic moiety, or its precursor, but not necessarily in the same amount or dosage form or as the same salt or ester. Each such drug product individually meets either the identical or its own respective compendial or other applicable standard of identity, strength, quality, and purity, including potency and, where applicable, content uniformity, disintegration times and/or dissolution rates. (21 CFR 320.1(d)) Different dosage forms and strengths within a product line by a single manufacturer are thus pharmaceutical alternatives, as are extended-release products when compared with immediate- or standard-release formulations of the same active ingredient.)

If “No,” to (a) skip to question 7. Otherwise, answer part (b and (c)).

- (b) Is the pharmaceutical alternative approved for the same indication for which the 505(b)(2) application is seeking approval? YES NO

- (c) Is the approved pharmaceutical alternative(s) cited as the listed drug(s)? YES NO

If “Yes,” to (c), proceed to question 7.

NOTE: *If there is more than one pharmaceutical alternative approved, consult your ODE’s Office of Regulatory Policy representative to determine if the appropriate pharmaceutical alternatives are referenced.*

If “No,” to (c), list the pharmaceutical alternative(s) and contact your ODE’s Office of Regulatory Policy representative. Proceed to question 7.

Pharmaceutical alternative(s):

7. (a) Does the application rely on published literature necessary to support the proposed approval of the drug product (i.e. is the published literature necessary for the approval)? YES NO

If “No,” skip to question 8. Otherwise, answer part (b).

(b) Does any of the published literature cited reference a specific (e.g. brand name) product? Note that if yes, the applicant will be required to submit patent certification for the product, see question 12.

8. Describe the change from the listed drug(s) provided for in this (b)(2) application (for example, “This application provides for a new indication, otitis media” or “This application provides for a change in dosage form, from capsules to solution”).

9. Is the application for a duplicate of a listed drug and eligible for approval under section 505(j) as an ANDA? (Normally, FDA may refuse-to-file such NDAs (see 21 CFR 314.101(d)(9)).) YES NO

10. Is the application for a duplicate of a listed drug whose only difference is that the extent to which the active ingredient(s) is absorbed or otherwise made available to the site of action less than that of the reference listed drug (RLD)? (See 314.54(b)(1)). If yes, the application may be refused for filing under 21 CFR 314.101(d)(9)). YES NO

11. Is the application for a duplicate of a listed drug whose only difference is YES NO

that the rate at which the product's active ingredient(s) is absorbed or made available to the site of action is unintentionally less than that of the RLD (see 21 CFR 314.54(b)(2))? If yes, the application may be refused for filing under 21 CFR 314.101(d)(9).

12. Are there certifications for each of the patents listed in the Orange Book for the listed drug(s) referenced by the applicant (see question #2)? (This is different from the patent declaration submitted on form FDA 3542 and 3542a.) YES NO

13. Which of the following patent certifications does the application contain? (Check all that apply and identify the patents to which each type of certification was made, as appropriate.)

- Not applicable (e.g., solely based on published literature. See question # 7)
- 21 CFR 314.50(i)(1)(i)(A)(1): The patent information has not been submitted to FDA. (Paragraph I certification)
Patent number(s):
- 21 CFR 314.50(i)(1)(i)(A)(2): The patent has expired. (Paragraph II certification)
Patent number(s):
- 21 CFR 314.50(i)(1)(i)(A)(3): The date on which the patent will expire. (Paragraph III certification)
Patent number(s):
- 21 CFR 314.50(i)(1)(i)(A)(4): The patent is invalid, unenforceable, or will not be infringed by the manufacture, use, or sale of the drug product for which the application is submitted. (Paragraph IV certification)
Patent number(s):

NOTE: IF FILED, and if the applicant made a "Paragraph IV" certification [21 CFR 314.50(i)(1)(i)(A)(4)], the applicant must **subsequently** submit a signed certification stating that the NDA holder and patent owner(s) were notified the NDA was filed [21 CFR 314.52(b)]. The applicant must also submit documentation showing that the NDA holder and patent owner(s) received the notification [21 CFR 314.52(e)]. OND will contact you to verify that this documentation was received.

- 21 CFR 314.50(i)(3): Statement that applicant has a licensing agreement with the patent owner (must also submit certification under 21 CFR 314.50(i)(1)(i)(A)(4) above).
Patent number(s):
- Written statement from patent owner that it consents to an immediate effective date upon approval of the application.
Patent number(s):
- 21 CFR 314.50(i)(1)(ii): No relevant patents.
- 21 CFR 314.50(i)(1)(iii): The patent on the listed drug is a method of use patent and the labeling for the drug product for which the applicant is seeking approval does not include any indications that are covered by the use patent as described in the corresponding use code in the Orange Book. Applicant must provide a statement that the method of use patent does not claim any of the proposed indications. (Section viii statement)
Patent number(s):

14. Did the applicant:

- Identify which parts of the application rely on the finding of safety and effectiveness for a listed drug or published literature describing a listed drug or both? For example, pharm/tox section of application relies on finding of preclinical safety for a listed drug.

YES NO

If “Yes,” what is the listed drug product(s) and which sections of the 505(b)(2) application rely on the finding of safety and effectiveness or on published literature about that listed drug

Was this listed drug product(s) referenced by the applicant? (see question # 2)

YES NO
- Submit a bioavailability/bioequivalence (BA/BE) study comparing the proposed product to the listed drug(s)?

N/A YES NO

15. (a) Is there unexpired exclusivity on this listed drug (for example, 5 year, 3 year, orphan or pediatric exclusivity)? Note: this information is available in the Orange Book.

YES NO

If “Yes,” please list:

Application No.	Product No.	Exclusivity Code	Exclusivity Expiration

NDA Resubmission

This resubmission includes two new datasets for the primary (including sensitivity analyses) and secondary efficacy endpoints in study XP060 to address FDA’s concern with the initial submission. These datasets will allow the statistical reviewer to obtain the endpoints in a straightforward manner (RELAPSE), and to facilitate reviewing the cause of relapse (RELAPVIS). This resubmission also includes a navigation guide in the case report tabulations package for the primary and secondary endpoints for each of the Phase 2 and Phase 3 studies and the Population PK-PD analysis to allow the statistical reviewer to easily obtain the primary and secondary endpoints for the studies.

Background

Gabapentin enacarbil is a novel transported prodrug of gabapentin designed to overcome the pharmacokinetic limitations of gabapentin. The compound was developed by XenoPort, Inc. under the compound number XP13512 and has been in-licensed by GSK under the GSK compound number GSK1838262. Gabapentin enacarbil was engineered *a priori* to be stable in gastrointestinal contents and to be actively absorbed after oral dosing by high-capacity nutrient transporters present throughout the intestinal tract. Following absorption, the prodrug is rapidly converted to gabapentin by non-specific carboxylesterases primarily in enterocytes and to a lesser extent in the liver. Treatment with gabapentin enacarbil in the clinic achieved efficient oral absorption and conversion to gabapentin, and provided dose proportional systemic gabapentin exposure over a wide dose range.

The enhanced absorption of gabapentin enacarbil in the large intestine has permitted the development of an extended release (ER) formulation. Gabapentin enacarbil ER tablets provide extended delivery of gabapentin to the systemic circulation, superior bioavailability compared to gabapentin, and the opportunity for once-daily dosing in the treatment of RLS.

Regulatory History

The development program for gabapentin enacarbil ER tablets in the treatment of moderate-to-severe primary RLS presented in this NDA was designed and conducted based on comprehensive communications with FDA. A comprehensive tabular listing of regulatory interactions is provided in [m1.6.3](#).

Proposed Proprietary Name

The Request for Review of Proposed Proprietary Name was submitted to IND 071352 on April 30, 2008 (Serial No. 0154) ([m1.14.1.4](#)). The proposed proprietary name is SOLZIRA™. GSK hereby requests the FDA's preliminary agreement with the proposed trade name, as well as, communication of the results of this preliminary assessment regarding the acceptability of the proposed proprietary name to GSK early in the NDA review to allow for preparation of manufacturing supplies.

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

/s/

Beverly A. Conner
5/8/2009 04:36:35 PM
CSO

Beverly A. Conner
6/17/2009 10:33:26 AM
CSO

**Interdisciplinary Review Team for QT Studies Consultation:
Thorough QT Study Review**

NDA	22-399
Brand Name	SOLZIRA®
Generic Name	Gabapentin Enacarbil (XP13512)
Sponsor	XenoPort, Inc., GlaxoSmithKline
Indication	Treatment of Moderate-to-severe Primary Restless Legs Syndrome (RLS)
Dosage Form	Extended-Release Tablets
Drug Class	Anticonvulsant
Therapeutic Dosing Regimen	1200 mg q.d.
Duration of Therapeutic Use	Acute
Maximum Tolerated Dose	6000 mg
Submission Number and Date	N 000 RS 8 Jan 2009
Review Division	DNP / HFD 120

1 SUMMARY

1.1 OVERALL SUMMARY OF FINDINGS

This study is inconclusive.

The moxifloxacin response failed to meet our criteria for assay sensitivity. Our expectations for assay sensitivity are (1) the $\Delta\Delta Q_{Tc}$ -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 Q_{Tc} is greater than 5 ms as evidenced by the lower 90% confidence interval > 5 ms at least one time point.

In this study, the largest lower bound of the two-sided 90% CI of $\Delta\Delta Q_{TcI}$ for moxifloxacin 400 mg around C_{max} (2 hours after dosing) was lower than 5 ms (4.2 ms) even before multiple endpoint adjustment, and the moxifloxacin profile over time is also not adequately demonstrated (Figure 5). A lack of PD profile for moxifloxacin can be further supported by the individual PK and PD plots in Figure 7. Therefore, lack of Q_{Tc} 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.

We recommend that the sponsor conducts a repeat TQT study to fulfill the requirements outlined in ICH E14 guidelines.

2 PROPOSED LABEL

No labeling statements can be made based on the data collected in this study.

3 BACKGROUND

3.1 PRODUCT INFORMATION

XP13512 (SOLZIRA) is a Transported ProdrugTM₁ of gabapentin. According to the sponsor, this product is designed to overcome the pharmacokinetic properties that potentially limit the effectiveness of gabapentin. It is under clinical development for the treatment of Restless Legs Syndrome (RLS) under NDA 22399. XP13512 ER tablets are

(b) (4)

3.2 MARKET APPROVAL STATUS

XP13512 is not approved for marketing in any country

3.3 PRECLINICAL INFORMATION

Source: Pharmacology Written Summary eCTD 2.6.2

“A study was conducted to measure the effect of XP13512 on hERG currents recorded from human embryonic kidney (HEK)-293 cells stably transfected with hERG-1 cDNA at concentrations of 10 and 100 M (3.3 and 33 µg/ml) [Report RD2007/01532/00, m4.2.1.3]. XP13512 was dissolved in 0.1% DMSO and terfenadine (60 nM) was used as a positive control. XP13512 did not affect hERG current at either concentration.

“The effects of XP13512 (2, 20 or 200 µg/ml; equivalent to 6.06, 60.6 or 606 µM) on resting membrane potential (RMP), action potential amplitude (APA), action potential maximum rate of rise (V_{max}) or action potential duration (APD) at 60% or 90% repolarization (APD₆₀ or APD₉₀, respectively) were investigated in isolated dog Purkinje fibers [Report RD2007/01531/00, m4.2.1.3]. XP13512 was dissolved in Purkinje fiber tyrode’s solution (PFT). Fibers were paced continuously at a basic cycle length (BCL) of 2 seconds (corresponding to a pulse frequency of 0.5 Hz) for <20 minutes of equilibration followed by 3 cycles of stimulus trains at decreasing BCL (2, 1 and 0.5 seconds). XP13512 had no effect on resting membrane potential, action potential amplitude, action potential maximum rate of rise or action potential duration (APD₆₀ and APD₉₀).

“A separate, dedicated non-rodent cardiovascular safety pharmacology study was not performed as recommended by the guidelines; however, this aspect was thoroughly and adequately evaluated within the context of the repeat dose toxicity studies in monkeys. No ECG effects (e.g., heart rate, PR, QRS, QT, RR and QTc intervals) were seen in monkeys in repeat dose toxicity studies of up to 39 weeks duration at doses up to 2000 mg/kg/day (Day 171 gabapentin C_{max} = 329 µg/ml).”

3.4 PREVIOUS CLINICAL EXPERIENCE

(Source: Summary of Clinical Safety-eCTD 2.7.4)

“Gabapentin (Neurontin®) is approved in the US for the treatment of post-herpetic neuralgia and as an adjunctive therapy in the treatment of partial seizure with and without secondary generalization [Neurontin® Package Insert, 2007]. Since approval, gabapentin has become one of the most commonly used medications in the US with over [REDACTED] (b) (4) prescriptions in 2007 alone [Verispan, 2007].

“As of the 06 December 2007 data cut-off, a total of 1566 unique subjects (365 subjects from the clinical pharmacology studies and 1201 subjects from Phase II and Phase III studies) were exposed to at least one dose of XP13512 in the RLS clinical development program.

“As of the March 31 2008 submission cut-off, there were 2 deaths among the 1566 unique subjects exposed to XP13512 in the RLS clinical development program. Both deaths were judged unrelated to study medication.

“The AE profile of XP13512 across all clinical studies was similar to that noted with gabapentin with dizziness and somnolence/sedation the most commonly reported TEAEs for XP13512.

“ECG data from the Phase II and Phase III studies showed no evidence of drug-related effects. There was no evidence of an effect of XP13512 on cardiac repolarization.

“There is no notable difference between XP13512 and placebo in ECG findings. There is no evidence of drug-related effects on the incidence of markedly abnormal values for any of the parameters evaluated.

Based on data from 12-Week Placebo-Controlled RLS Studies:

- Mean changes in ECG parameters were generally small with no trends within or across treatment groups. At Week 12, there did not appear to be any effect of study medication on changes from baseline in ECG values. There was no apparent relationship to XP13512 dose.
- Mean changes from baseline to most extreme low or high values for ECG parameters were comparable between the placebo and XP13512 All Doses group.
- No subject in either the placebo or XP13512 All Doses group had a QTcF or QTcB value ≥ 500 ms
- The incidence of subjects with a QTcF or QTcB change from baseline ≥ 60 ms was $<1\%$ in both the placebo and XP13512 All Doses group.

Data from the Long-Term Integration grouping suggest that long-term XP13512 therapy does not raise any clinically relevant safety concerns with regard to ECG findings. There were no notable changes in ECG parameters over time.”

Reviewer’s Comments: There are no reports of sudden cardiac death, syncope, seizure or significant ventricular arrhythmias. The sponsor conducted an analysis of post-marketing experience with gabapentin with respect to overdose and drug-abuse and found no potential safety issues in this regard based on AERS database and literature searches.

3.5 CLINICAL PHARMACOLOGY

Appendix 6.1 summarizes the key features of XP13512’s clinical pharmacology.

4 SPONSOR’S SUBMISSION

4.1 OVERVIEW

The QT-IRT reviewed the protocol prior to conducting this study under IND 71352. The sponsor submitted the study report XP078 for the study drug, including electronic datasets.

4.2 TQT STUDY

4.2.1 Title

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.

4.2.2 Protocol Number

XP078 (XenoPort Study)

4.2.3 Study Dates

July 20 – November 3, 2007

4.2.4 Objectives

The primary objective of this study was to demonstrate a lack of effect of XP13512 on cardiac repolarization (QTcIb interval duration) at the 6000-mg supratherapeutic dose compared with placebo in healthy volunteers.

4.2.5 Study Description

4.2.5.1 Design

This was a randomized, double-blind, placebo- and active-controlled, four-period crossover study to evaluate the effect of XP13512 on cardiac repolarization in healthy adult subjects. Subjects were enrolled and each was assigned to receive a four-period dose group sequence in a randomized order with a 7-day washout between treatments. Allocation to each of the four dose periods followed a William’s Latin Square design.

4.2.5.2 Controls

The Sponsor used both placebo and positive (moxifloxacin) controls.

4.2.5.3 Blinding

All treatment arms were administered blinded using a double dummy approach.

4.2.6 Treatment Regimen

4.2.6.1 Treatment Arms

Subjects were randomized to one of four different treatment sequences. Subjects each received four different treatments as follows:

- Treatment A: single dose of placebo.
- Treatment B: single dose of XP13512 1200 mg.
- Treatment C: single dose of XP13512 6000 mg.
- Treatment D: single dose of moxifloxacin 400 mg.

4.2.6.2 Sponsor's Justification for Doses

“XP13512 6000 mg dose, which was five-times the proposed clinical dose for the restless legs syndrome indication, could be adequately used as the supra-therapeutic dose for the thorough QTc study. This supra-therapeutic dose could potentially cover any exposure expected to occur as a result of the clinical administration of XP13512 to patients with restless legs syndrome. XP13512 and gabapentin are not substrates of cytochrome P450 enzymes, XP13512 is rapidly converted to gabapentin after absorption by high capacity esterases. Released gabapentin is excreted renally without further metabolism. Therefore, drug interactions are not expected to significantly affect gabapentin exposures after administration of XP13512. The increase in gabapentin exposures in renally impaired patients taking Neurontin has been shown to be proportional to creatinine clearance. It is anticipated that the XP13512 dose would be adjusted for renally impaired subjects, and therefore gabapentin exposures anticipated in subjects with impaired renal function would be adequately covered by the 6000 mg dose.”

Reviewer's Comment: The selected supra-therapeutic dose of 6000 mg is acceptable because it covers the highest observed clinical exposure scenario of 24% increase in gabapentin AUCs with co-administration of cimetidine as well as the expected increase in exposure in patients with renal impairments (Table 1). The potential for CYP-based increase in exposure is minimal since gabapentin is not a substrate of CYP enzymes.

Table 1: Predicted PK Parameters for Gabapentin at Steady-State following Multiple Administration of XP13512 in Subjects with Renal Impairment

CrCL (mL/min)	Day 1 AUC _{SS} (µg*h/mL)	Day1 C _{max,SS} (µg/mL)	Day 2 AUC _{SS} (µg*h/mL)	Day 2 C _{max,SS} (µg/mL)	Day 3 AUC _{SS} (µg*h/mL)	Day 3 C _{max,SS} (µg/mL)
30 ^a	115	6.28	115	6.29	116	6.30
59 ^a	73.3	4.55	73.3	4.55	73.3	4.55
15 ^b	110	5.75	74.0	3.98	110	5.77
29 ^b	77.3	4.47	41.0	2.52	77.4	4.47

a: 600 mg/day; b: 600 mg every other day

4.2.6.3 Instructions with Regard to Meals

All treatments were administered with food. No food was allowed after midnight on both study days (Day -1 and Day 1) of each treatment period. Water was allowed *ad libitum*. On dosing days (Day1) of each treatment period. A standard moderate-fat breakfast (30% calories from fat, total calories of 500 kcal) was served 30 minutes prior to the dosing time. Subjects had 25 minutes to complete the meal. A standard lunch was served at approximately 4 h post-dose. A standard dinner was served at approximately 10 h post-dose. An evening snack was served at approximately 13 h post-dose. Total daily caloric content of meals was approximately 2000 kcal and was not to exceed 2500 kcal.

Reviewer's Comment: The standardized food arrangement is reasonable since high fat/calorie meals are associated with higher gabapentin AUC_{0-inf} compared to low fat meals or fasted state. High fat/calorie meals also increase the T_{max} of gabapentin..

4.2.6.4 ECG and PK Assessments

Holter ECG was continuously monitored on day -1 and 1 and ECGs were extracted at pre-dose and 15 minutes prior to nominal times of 1, 2, 3, 4, 6, 7, 8, 9, 10, 12, 15, 18, 21, and 22.5 h post-dose at exactly the same times in Period 1-4. PK samples were collected pre-dose and 1, 2, 3, 4, 6, 7, 8, 9, 10, 12, 15, 18, 21, 22.5 h post-dose on day 1 only. Electrocardiogram extraction acquisition windows occurred prior to blood draws.

Reviewer's Comment: The timing for ECG extraction is acceptable. It covers the T_{max} of gabapentin (4.6 hr to 5.9 hr in fasted subjects, 5.7 to 9.8 hr in fed subjects).

4.2.6.5 Baseline

The sponsor used time-matched baseline QTc values on Day -1.

4.2.7 ECG Collection

Continuous Holter ECG monitoring was performed on Day –1 of each period for baseline readings, and on Day 1 of each period for post-dose readings at the time points specified above.

Each 12-lead ECG acquisition window was approximately 10 minutes in duration from which cardiac data analysis lab extracted 10 second ECGs. This window was preceded by 15 minutes of quiet supine rest. Three 10-second ECGs separated by approximately one minute were extracted for analysis at each extraction window.

All Holter ECG data were digitally transferred to a central ECG laboratory for analysis. The measurements were made in lead II (first priority if reliable), or V2, or V3 using a validated on-screen method, for manual over-read by a limited number of treatment- and subject-blinded Cardiologists. The same reader measured all ECGs from the same subject. The Holter data in a listing form (not including wave forms) was reviewed by an external cardiology consultant in a blinded manner prior to the database lock and unblinding.

12-lead ECGs will be collected during the study conduct for safety monitoring.

4.2.8 Sponsor's Results

4.2.8.1 Study Subjects

Fifty four healthy subjects (54 subjects: 31 males and 23 females), 18-50 years of age with a normal baseline ECG and BMI 20-31 kg/m² between were randomly assigned to one of four different treatment sequences in a Williams design and 48 subjects completed the study. Subjects included were between 18 to 50 years of age. Six subjects (6) discontinued: adverse events (2 subjects), withdrew consent (3 subjects), and protocol non-compliance (1 subject).

4.2.8.2 Statistical Analyses

4.2.8.2.1 Primary Analysis

The sponsor designated the QTcIb as the primary QT assessment. (QTcIb interval is defined as the QT interval corrected for the RR interval using the individual baseline adjustment: $QTcIb = QT + RR \text{ Coefficient} * (1000 - RR)$. The RR coefficient is obtained from the linear regression of QT on RR for all Day -1 assessments for a given subject in the given period.) The primary endpoint was maximum time-matched mean difference between the baseline subtracted QTcIb intervals for XP13512 6000 mg and placebo.

The model was a linear mixed model with the following terms: Treatment (placebo or XP13512 6000 mg), Period (indicator of treatment period of the crossover design), Hour (the ECG assessment hour), Period-by-Hour interaction, Treatment-by-Hour interaction, and Subjects. The factor “Subjects” is a random effect factor. The other factors are the fixed effect factors. The model also included the baseline QTcIb as a covariate. Baseline was defined as time-matched QTcIb values at Day -1.

Table 2 presents Linear Mixed Effects Model analysis results in QTcIb for XP13512 (1200 mg and 6000 mg) and moxifloxacin. The upper bound of the 95% one-sided confidence interval for the time-matched maximum mean difference between QTcIb for XP13512 and placebo was below 10 ms. The largest one-sided 95% upper confidence interval was 3.6 ms at 22.5 hour post-dose for the XP13512 6000-mg dose level. The similar result was also obtained for the XP13512 1200-mg dose level, with the largest upper bound being 3.0 ms at 2 hour pose-dose.

Table 2: Sponsor's Mixed Model $\Delta\Delta$ QTcIb Analysis

Table 8.7.14.1 (Continued)
 Holter ECG Extraction Linear Mixed-Effects Model: QTcIb (ms)
 (ECG Safety Population)

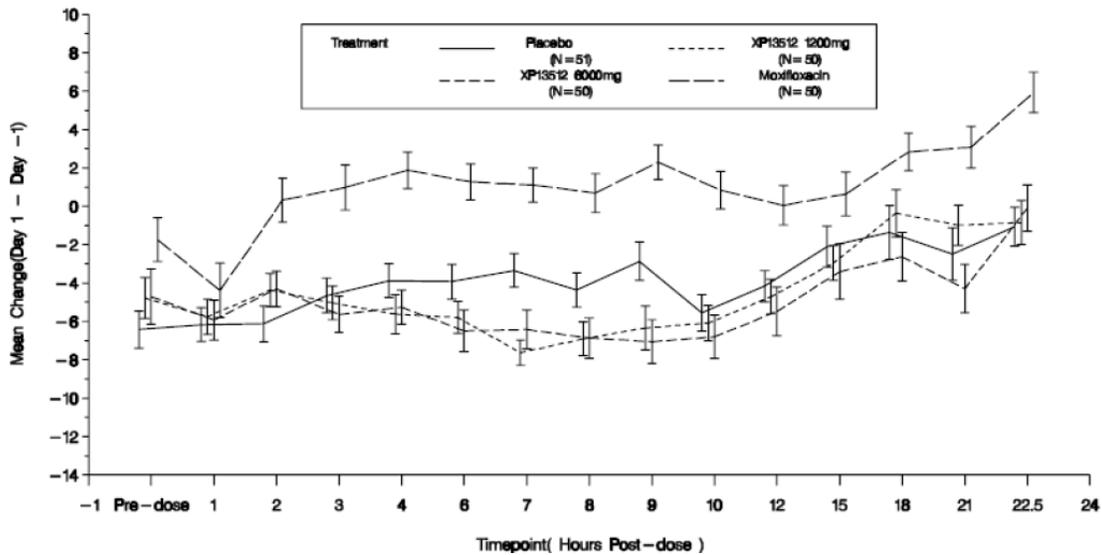
Day 1 Post-dose Timepoint	Placebo (N=51)	XP13512 1200mg (N=50)	XP13512 6000mg (N=50)	Moxifloxacin (N=50)
----- Change (Day 1 - Day -1): Point estimate (95%/90% One-Sided Confidence Bound) [1] -----				
		----- Upper Confidence Bound -----		----- Lower Confidence Bound -----
1 hour		-0.3 (1.9)	0.8 (3.1)	1.9 (-0.4/ 0.1)
2 hours		0.7 (3.0)	0.6 (2.8)	5.7 (3.5/ 4.0)
3 hours		-0.8 (1.5)	-1.3 (1.0)	5.7 (3.4/ 3.9)
4 hours		-1.7 (0.6)	-1.1 (1.2)	6.9 (4.7/ 5.2)
6 hours		-1.3 (1.0)	-2.0 (0.2)	6.1 (3.8/ 4.3)
7 hours		-4.0 (-1.8)	-2.8 (-0.5)	4.7 (2.4/ 2.9)
8 hours		-2.8 (-0.5)	-2.5 (-0.3)	5.5 (3.2/ 3.7)
9 hours		-4.4 (-2.1)	-4.5 (-2.2)	5.4 (3.1/ 3.6)
10 hours		-1.5 (0.7)	-2.4 (-0.1)	6.1 (3.8/ 4.3)
12 hours		-1.4 (0.9)	-1.4 (0.9)	4.3 (2.0/ 2.5)
15 hours		-1.3 (1.0)	-1.3 (1.0)	3.2 (0.9/ 1.5)
18 hours		-0.5 (1.9)	-1.7 (0.6)	4.0 (1.7/ 2.2)
21 hours		0.4 (2.7)	-1.6 (0.7)	5.9 (3.6/ 4.1)
22.5 hours		0.3 (2.6)	1.3 (3.6)	7.4 (5.1/ 5.6)

Note: From a linear mixed-effects model on change from Day 1 Pre-dose QTcIb interval values (dQTcIb), with Period, Treatment, Hour (categorical), Period-by-Hour interaction, and Treatment-by-Hour interaction as fixed effects, and Day -1 QTcIb as a covariate included in the model. Subject is included in the model as a random effect.
 [1] 95% and 90% one-sided confidence interval bounds are calculated from the model at each timepoint comparing each treatment group to placebo (treatment - placebo) using the change from Day 1 Pre-dose QTcIb interval values (dQTcIb). This difference in change scores is $\Delta\Delta$ QTcIb. The XP13512 treatment groups have the 95% upper confidence bound presented while the moxifloxacin treatment group has the 95% and 90% lower confidence bounds presented.

Source: listing 11 1-11.2 (xp078-report), page 101-102 of 1324

The following figure displays $\Delta\Delta$ QTcIb at each time point for XP13512 (1200 mg and 6000 mg) and moxifloxacin 400 mg.

Figure 1: Sponsor's $\Delta\Delta$ QTcIb Time Course



Source: Figure 5 (xp078-report), page 43 of 1324

4.2.8.2.2 Assay Sensitivity

The assay sensitivity for QTcIb measurement was assessed using moxifloxacin 400 mg as a positive control in the study. The largest one-sided 95% lower confidence interval was 5.1 ms at 22.5 hours post-dose for the mean difference between the moxifloxacin 400 mg and placebo. Table 2 presents the analysis results.

Reviewer's Comments: The Sponsor mentioned that their results were slightly lower than anticipated magnitude of QTcIb changes seen with moxifloxacin 400 mg. Our own analysis results showed that the largest two-sided 90% lower confidence bound near C_{max} of moxifloxacin was 4.2 ms before any multiple endpoint adjustment. The time-course of moxifloxacin was also not adequately demonstrated in this study (See Section 5.2.1.2).

4.2.8.2.3 Categorical Analysis

The results from the categorical analyses by the sponsor were presented in Table 3 and Table 4. Large QTcIb intervals were defined as >450, >480, and >500 ms, and large changes in QTcIb intervals were increases from baseline of >30 and >60 ms. The categorical descriptive analysis shows that no subject observed a QTcIb>500 ms or a change from baseline QTcIb>60 ms.

Table 3: Sponsor's Categorical Analysis of QTc

Table 17 Summary of QT/QTc intervals by treatment

Parameter	Category	Placebo (N = 51) n (%)	XP13512 1200 mg (N = 50) n (%)	XP13512 6000 mg (N = 50) n (%)	Moxifloxacin 400 mg (N = 50) n (%)
QT					
Day -1	<450 msec	50 (98.0)	50 (100.0)	49 (98.0)	49 (98.0)
	450-479 msec	1 (2.0)	0	1 (2.0)	2 (4.0)
	480-499 msec	0	0	0	0
	≥500 msec	0	0	0	0
Day 1	<450 msec	51 (100.0)	50 (100.0)	50 (100.0)	48 (96.0)
	450-479 msec	0	0	0	1 (2.0)
	480-499 msec	0	0	0	0
	≥500 msec	0	0	0	0
QTcIb					
Day -1	<450 msec	51 (100.0)	50 (100.0)	50 (100.0)	50 (100.0)
	450-479 msec	0	0	0	0
	480-499 msec	0	0	0	0
	≥500 msec	0	0	0	0
Day 1	<450 msec	51 (100.0)	50 (100.0)	50 (100.0)	50 (100.0)
	450-479 msec	0	0	0	0
	480-499 msec	0	0	0	0
	≥500 msec	0	0	0	0
QTcF					
Day -1	<450 msec	51 (100.0)	50 (100.0)	50 (100.0)	50 (100.0)
	450-479 msec	0	0	0	0
	480-499 msec	0	0	0	0
	≥500 msec	0	0	0	0
Day 1	<450 msec	51 (100.0)	50 (100.0)	50 (100.0)	50 (100.0)
	450-479 msec	0	0	0	0
	480-499 msec	0	0	0	0
	≥500 msec	0	0	0	0
QTcB					
Day -1	<450 msec	51 (100.0)	50 (100.0)	50 (100.0)	50 (100.0)
	450-479 msec	0	0	0	0
	480-499 msec	0	0	0	0
	≥500 msec	0	0	0	0
Day 1	<450 msec	51 (100.0)	50 (100.0)	50 (100.0)	49 (98.0)
	450-479 msec	0	0	0	1 (2.0)
	480-499 msec	0	0	0	0
	≥500 msec	0	0	0	0

Source Data: Attachment 4, [Table 8.7.10](#)

Source: Sponsor's xp078-report, Table 17, page 54 of 1324

Table 4: Sponsor's Categorical Analysis of Δ QTc

Table 18 Summary of QT/QTc interval changes from Day -1 to Day 1: change at any post-dose time

Parameter	Placebo (N = 51) n (%)	XP13512 1200 mg (N = 50) n (%)	XP13512 6000 mg (N = 50) n (%)	Moxifloxacin 400 mg (N = 50) n (%)
QT interval				
N	51	50	50	50
≤ 30 msec	50 (98.0)	47 (94.0)	49 (98.0)	46 (92.0)
31-60 msec	1 (2.0)	3 (6.0)	1 (2.0)	4 (8.0)
>60 msec	0	0	0	0
QTcIb interval				
N	51	50	50	50
≤ 30 msec	51 (100.0)	50 (100.0)	50 (100.0)	50 (100.0)
31-60 msec	0	0	0	0
>60 msec	0	0	0	0
QTcF interval				
N	51	50	50	50
≤ 30 msec	51 (100.0)	50 (100.0)	50 (100.0)	50 (100.0)
31-60 msec	0	0	0	0
>60 msec	0	0	0	0
QTcB interval				
N	51	50	50	50
≤ 30 msec	49 (96.1)	49 (98.0)	50 (100.0)	46 (92.0)
31-60 msec	2 (3.9)	1 (2.0)	0	4 (8.0)
>60 msec	0	0	0	0

Source Data: Attachment 4, [Table 8.7.11](#)

Source: Sponsor xp078-report, Table 18, page 53 of 1324

4.2.8.2.4 Additional Analyses

In addition to QTcIb, the sponsor also performed analyses based on other correction methods. The results were consistent with those using QTcIb.

4.2.8.3 Safety Analysis

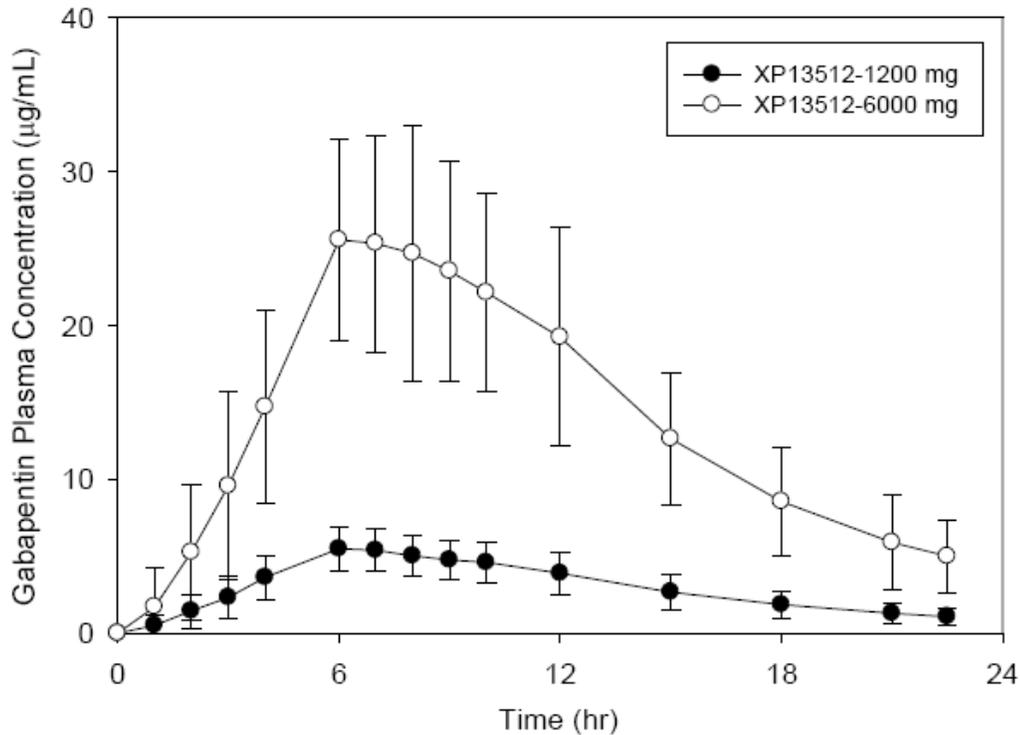
- There were no deaths or SAEs in this study
- Subject 309 received placebo in Period 1. She experienced syncope of severe intensity prior to dosing in Period 2. The syncope resolved after 30 minutes and was considered not related to study drug (ECGs from the 12 lead holter were read by the cardiologist as a 11.7-second sinus pause and sick sinus syndrome.
- Subject 327 experienced vasovagal syncope of severe intensity 7 days after receiving a single dose of XP13512 1200 mg in Treatment Period 1 (at Baseline Treatment Period 2). The vasovagal syncope resolved after 20 minutes and was judged not related to study drug. No treatment was required. ECG prior to the event was normal. Two and a half hours after the end of the AE, the subject underwent a 12-lead ECG, which was found to be normal. The subject was withdrawn from the study because of this AE.
- Subject 306 was withdrawn from the study in treatment period 2 due to the AE of constipation

4.2.8.4 Clinical Pharmacology

4.2.8.4.1 Pharmacokinetic Analysis

The PK results following a single dose of drug and moxifloxacin are summarized in Table 6 (gabapentin) and Table 7 (moxifloxacin) and demonstrated in Figure 2 (gabapentin) and Figure 3 (moxifloxacin). C_{max} and AUC values in the thorough QT study were 4.8-fold and 4.7-fold higher following administration of XP13512 6000 mg compared with XP13512 1200 mg, the intended clinical dose.

Figure 2: Mean (standard deviation) concentration of gabapentin in plasma of fed subjects following oral dosing of XP13512 at 1200- and 6000-mg doses (N=50 at both dose levels)



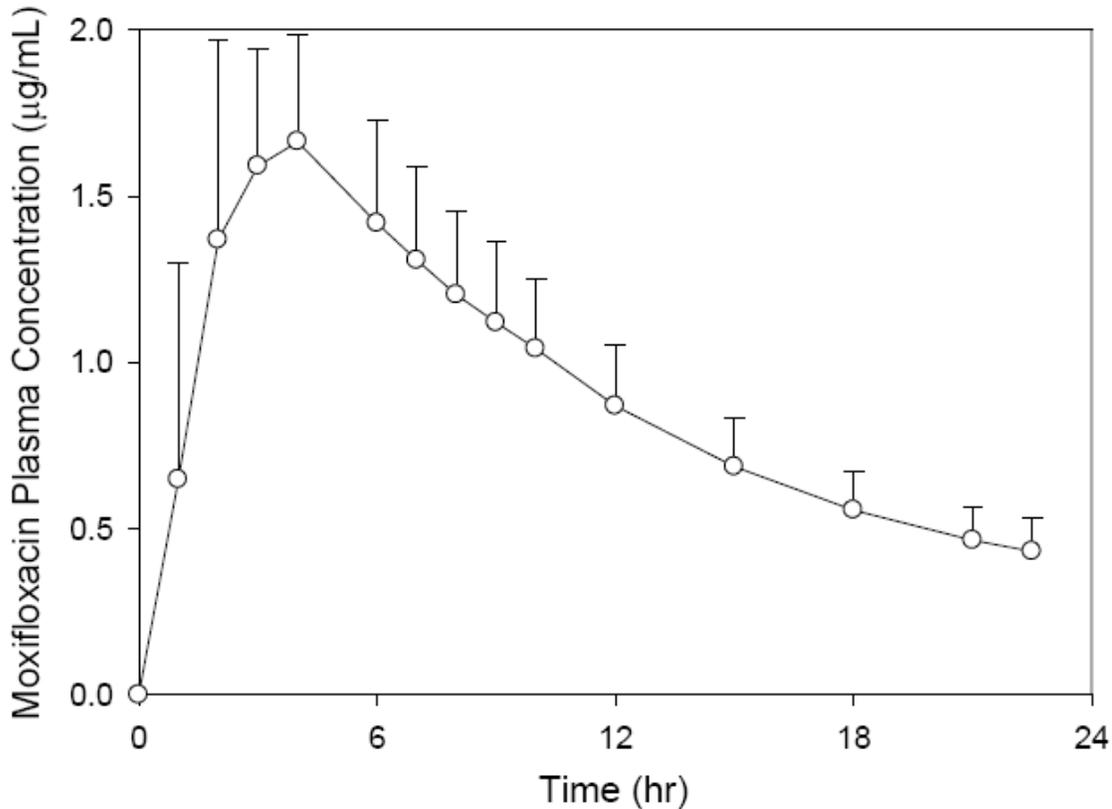
Source: Figure 7 from page 59 of the Sponsor's Report

Table 5: Mean (range) pharmacokinetic parameters for gabapentin in plasma after a single oral dose of XP13512 in fed healthy subjects

	XP13512 1200 mg (N = 50)	XP13512 6000 mg (N = 50)
Dose (mg-eq. GP)	625	3125
C_{max} (µg/mL)	6.21 (3.36–9.26)	30.1 (9.15–44.3)
T_{max} (h)	6.83 (4.00–15.0)	7.51 (3.00–12.0)
$T_{1/2}$ (h)	5.70 (3.66–8.12)	5.79 (3.60–13.3)
AUC_{inf} (µg*hr/mL)	76.1 (40.2–123)	358 (188–737)

Source: Table 20 from page 58 of the Sponsor's Report

Figure 3: Mean (standard deviation) concentrations of moxifloxacin in plasma of fed subjects following oral dosing of moxifloxacin 400 mg tablets (N=49)



Source: Figure 8 from page 60 of Sponsor's report

Table 6: Mean (range) pharmacokinetic parameters for moxifloxacin in plasma after a single oral dose of 400 mg moxifloxacin tablets in fed subjects.

	Moxifloxacin 400 mg (N = 49 ¹)
C _{max} (µg/mL)	1.79 (1.19-2.85)
T _{max} (h)	3.01 (1.00-4.05)
T _{1/2} (h)	10.7 (6.90-16.7)
AUC _{inf} (µg*h/mL)	27.5 (17.5-39.9)

Source: Table 21 from page 60 of Sponsor's report

4.2.8.4.2 Exposure-Response Analysis

The sponsor did not evaluate the dose/concentration-QTcI relationship.

5 REVIEWERS' ASSESSMENT

5.1 EVALUATION OF THE QT/RR CORRECTION METHOD

The observed QT-RR interval relationship is presented in Figure 4 together with the Bazett's (QTcB), Fridericia (QTcF), and individual correction (QTcI). This reviewer

used notation of QTcI instead of QTcIb as used by the sponsor for the individual correction method.

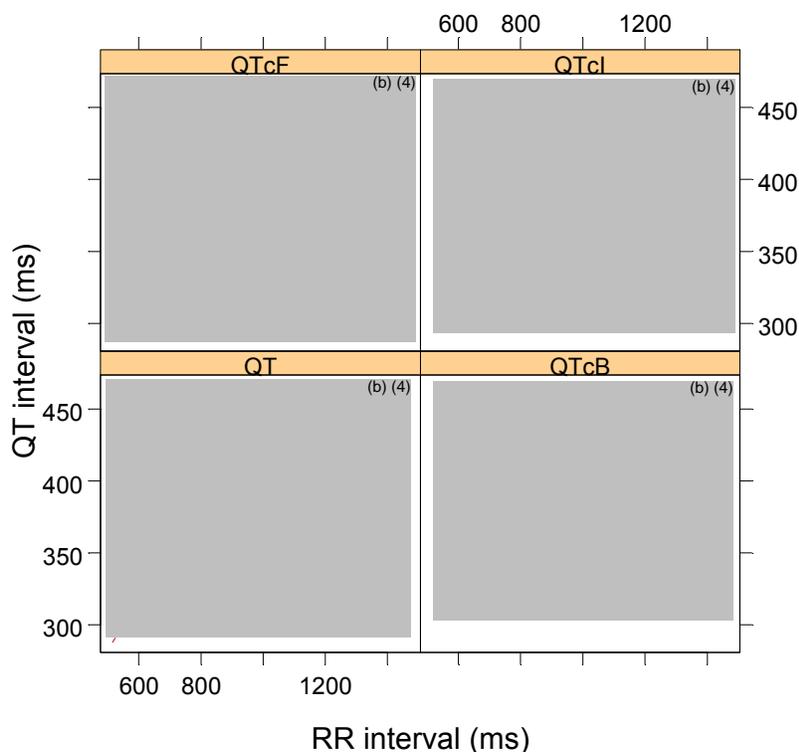
We also evaluated the linear relationships between different correction methods (QTcB, QTcF, QTcI) and RR. We used the average sum of squared slopes as the criterion. The smaller this value is, the better the correction. The results appear similar for both QTcF and QTcI (see Table 7 below). Therefore, this statistical reviewer used QTcI for the primary statistical analysis.

Table 7: Average of Sum of Squared Slopes for Different QT-RR Correction Methods

Method	Treatment Group									
	All [†]		Moxifloxacin		Placebo		XP13512 1200 mg		XP13512 6000 mg	
	n	MSSS	n	MSSS	n	MSSS	n	MSSS	n	MSSS
QTcB	54	0.0039	50	0.0045	51	0.0049	50	0.0040	50	0.0051
QTcF	54	0.0015	50	0.0021	51	0.0018	50	0.0020	50	0.0019
QTcI	54	0.0014	50	0.0024	51	0.0015	50	0.0021	50	0.0021

Note: All[†]: Combined all treatment groups. MSSS: Mean of Sum of Squared Slope

Figure 4: QT, QTcB, QTcF, and QTcI vs. RR (Each Subject's Data Points are Connected with a Line)



5.2 STATISTICAL ASSESSMENTS

The statistical reviewer used the following data set to carry out the independent analyses for statistical evaluation of the results: qtpk.xpt in http://erom.fda.gov/eRoom/CDER1/CDERnterdisciplinaryReviewTeamQTGroup/0_17e02

5.2.1 QTc Analysis

5.2.1.1 The Primary Analysis for the Study Drug

The statistical reviewer used a mixed model to analyze the Δ QTcI effect. The model includes TREATMENT as a fixed effect and SUBJECT as a random effect, and BASELINE as a covariate. The analysis results are listed in Table 8.

The largest upper bounds of the 2-sided 90% CI for the mean difference between XP13512 6000 mg and placebo, and between XP13512 1200 mg and placebo were 4.7 ms at 2 hours after dose and 5.3 ms at 21 hours after dose, respectively. (See Table 8)

Table 8: ANCOVA Analysis of $\Delta\Delta Q T c I$ for XP13512 1200 mg, XP13512 6000 mg, and Moxifloxacin 400 mg

		Treatment Group									
		Moxifloxacin				XP13512 1200 mg			XP13512 6000 mg		
	Placebo	$\Delta Q T c I$	$\Delta\Delta Q T c I$			$\Delta Q T c I$	$\Delta\Delta Q T c I$		$\Delta Q T c I$	$\Delta\Delta Q T c I$	
Time (hrs.)	LS* Mean	LS* Mean	Diff** LS Mean	90%CI**	Unadjusted 90% CI	LS* Mean	Diff** LS Mean	90% CI**	LS* Mean	Diff** LS Mean	90% CI**
1	-6.2	-4.4	1.8	(-1.5, 5.1)	(-0.6, 4.2)	-5.9	0.3	(-3.0, 3.6)	-5.9	0.3	(-3.1, 3.6)
2	-6.0	0.3	6.3	(3.4, 9.3)	(4.2, 8.5)	-4.5	1.5	(-1.5, 4.5)	-4.3	1.7	(-1.3, 4.7)
3	-4.7	1.0	5.7	(2.8, 8.6)	(3.6, 7.8)	-5.2	-0.5	(-3.4, 2.4)	-5.6	-0.9	(-3.9, 2.0)
4	-3.9	1.9	5.7	(2.9, 8.5)	(3.7, 7.8)	-5.7	-1.9	(-4.7, 0.9)	-5.3	-1.4	(-4.2, 1.3)
6	-4.0	1.4	5.3	(2.4, 8.3)	(3.2, 7.5)	-5.8	-1.8	(-4.7, 1.1)	-6.5	-2.5	(-5.5, 0.4)
7	-3.4	1.1	4.5	(1.7, 7.3)	(2.4, 6.5)	-7.6	-4.3	(-7.1, -1.5)	-6.4	-3.1	(-5.9, -0.3)
8	-4.4	0.8	5.1	(2.1, 8.2)	(2.9, 7.4)	-6.9	-2.6	(-5.6, 0.5)	-6.9	-2.5	(-5.6, 0.5)
9	-2.9	2.4	5.3	(2.1, 8.5)	(3.0, 7.6)	-6.5	-3.6	(-6.8, -0.4)	-7.0	-4.2	(-7.3, -1.0)
10	-5.5	0.9	6.4	(3.3, 9.6)	(4.1, 8.7)	-6.1	-0.6	(-3.8, 2.6)	-6.8	-1.3	(-4.4, 1.9)
12	-4.2	0.1	4.3	(1.2, 7.5)	(2.1, 6.6)	-4.8	-0.6	(-3.7, 2.6)	-5.4	-1.2	(-4.3, 1.9)
15	-2.5	0.8	3.3	(-0.1, 6.6)	(0.8, 5.7)	-3.1	-0.7	(-4.0, 2.7)	-3.4	-0.9	(-4.3, 2.5)
18	-1.5	3.0	4.5	(0.8, 8.2)	(1.8, 7.2)	-0.6	0.9	(-2.8, 4.6)	-2.6	-1.1	(-4.7, 2.6)
21	-2.6	3.2	5.9	(2.1, 9.6)	(3.1, 8.6)	-1.1	1.5	(-2.2, 5.3)	-4.2	-1.5	(-5.3, 2.3)
22.5	-1.1	6.0	7.2	(3.8, 10.5)	(4.7, 9.6)	-0.8	0.3	(-3.1, 3.7)	-0.1	1.1	(-2.4, 4.5)

++: Bonferroni method was applied for multiple endpoint adjustment for 4 time points.

*: Least Square Mean (ms). **:Least Square Mean Difference (ms)

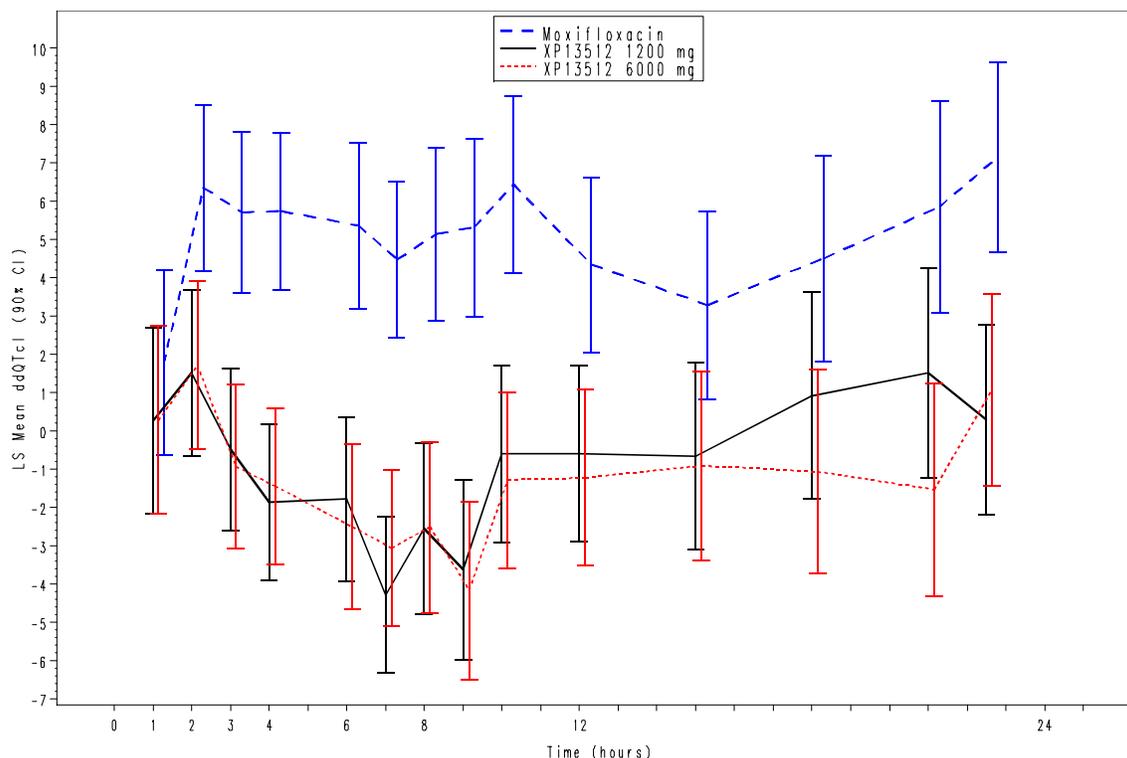
5.2.1.2 Assay Sensitivity Analysis

The statistical reviewer used the same statistical model to analyze moxifloxacin and placebo data. The results are presented in Table 8. The largest unadjusted 90% lower confidence interval is 4.7 ms at 22.5 hours after dose. Around C_{max} of moxifloxacin, the largest unadjusted 90% lower confidence interval is 4.2 ms at hour 2 post-dose. By considering Bonferroni multiple endpoint adjustment, the largest lower confidence interval is 3.8 ms. The time-course of moxifloxacin is not adequately demonstrated based on the following Figure 5.

5.2.1.3 Graph of $\Delta\Delta Q T c I$ Over Time

The following figure displays the time profile of $\Delta\Delta Q T c I$ for different treatment groups.

Figure 5: Mean and 90% CI $\Delta\Delta$ QTcI Time course



(Note: CIs are all unadjusted including moxifloxacin)

5.2.1.4 Categorical Analysis

Table 9 lists the number of subjects as well as the number of observations whose absolute QTcI values are ≤ 450 ms, between 450 ms and 480 ms. No subject's QTcI was above 480 ms. All subjects' Δ QTcI were below or equal to 30 ms.

Table 9: Categorical Analysis for QTcI

Treatment Group	Total N		Value \leq 450	
	# Subj.	# Obs.	# Subj.	# Obs.
Moxifloxacin	50	1486	50 (100%)	1486 (100%)
Placebo	51	1478	51 (100%)	1478 (100%)
XP13512 1200 mg	50	1485	50 (100%)	1485 (100%)
XP13512 6000 mg	50	1482	50 (100%)	1482 (100%)

5.2.2 PR Analysis

The same statistical analysis was performed based on PR interval. The point estimates and the 90% confidence intervals are presented in Table 10. The largest upper limits of 90% CI for the PR mean differences between XP13512 1200 mg and placebo and XP13512 6000 mg and placebo are 4.4 ms and 5.3 ms, respectively.

The outlier analysis results for PR are presented in Table 11. There were two subjects in XP13512 1200-mg group and one subject in XP13512 6000-mg group who experienced absolute PR interval ≥ 200 ms. The details for those subjects (PR ≥ 200 ms) was listed in Table 12.

Table 10: Analysis Results of Δ PR and $\Delta\Delta$ PR for XP13512 1200 mg and XP13512 6000 mg

Treatment Group							
		XP13512 1200 mg			XP13512 6000 mg		
	Placebo	Δ Pr	$\Delta\Delta$ Pr		Δ Pr	$\Delta\Delta$ Pr	
Time (hrs.)	LS* Mean	LS* Mean	Diff**	90% CI	LS* Mean	Diff**	90% CI
			LS Mean			LS Mean	
1	-1.7	-1.3	0.4	(-1.6, 2.4)	-1.8	-0.1	(-2.1, 2.0)
2	-2.1	-2.8	-0.7	(-2.7, 1.2)	-1.7	0.4	(-1.6, 2.4)
3	-1.4	-1.8	-0.4	(-2.3, 1.5)	-0.3	1.1	(-0.8, 3.0)
4	-1.9	-1.2	0.8	(-1.1, 2.7)	-0.0	1.9	(-0.0, 3.8)
6	-1.8	-0.7	1.1	(-0.7, 3.0)	1.4	3.3	(1.4, 5.1)
7	-1.6	-0.1	1.4	(-0.5, 3.3)	0.3	1.9	(-0.0, 3.8)
8	-1.6	-1.0	0.5	(-1.4, 2.5)	1.8	3.3	(1.4, 5.3)
9	-0.3	-1.3	-1.0	(-3.1, 1.1)	0.1	0.4	(-1.7, 2.5)
10	-1.4	-2.5	-1.1	(-3.6, 1.5)	0.4	1.8	(-0.7, 4.4)
12	-1.4	-0.7	0.8	(-1.3, 2.9)	-1.0	0.4	(-1.7, 2.5)
15	-1.6	0.2	1.8	(-0.3, 3.9)	-1.5	0.0	(-2.1, 2.1)
18	-1.7	0.0	1.8	(-0.8, 4.4)	-1.7	0.0	(-2.5, 2.6)
21	-1.7	-0.5	1.2	(-1.7, 4.0)	-0.2	1.5	(-1.4, 4.4)
22.5	-0.8	1.3	2.0	(-0.4, 4.4)	0.5	1.3	(-1.1, 3.7)

*: Least Square Mean (ms). **:Least Square Mean Difference (ms)

Table 11: Categorical Analysis for PR

Treatment Group	Total N		Value<200		Value \geq 200	
	# Subj.	# Obs.	# Subj.	# Obs.	# Subj.	# Obs.
Baseline	54	2782	52 (96.3%)	2758 (99.1%)	2 (3.7%)	24 (0.9%)
XP13512 1200	50	692	48 (96.0%)	688 (99.4%)	2 (4.0%)	4 (0.6%)
XP13512 6000	50	691	49 (98.0%)	688 (99.6%)	1 (2.0%)	3 (0.4%)

Table 12: Subjects with PR \geq 200 ms

XP 13512 1200 mg			
Subject ID	Time (hrs.)	Baseline PR	Post-dose PR
001309	12	191.7	200.0
001324	12	198.0	203.3
	18	209.0	208.3
	21	211.7	205.7
XP 13512 6000 mg			
001324	18	202.7	204.7
	21	204.3	206.3
	22.5	207.3	200.0

5.2.3 QRS Analysis

The same statistical analysis was performed based on QRS interval. The point estimates and the 90% confidence intervals are presented in Table 13. The largest upper limits of 90% CI for the QRS mean differences between XP13512 1200 mg and placebo and XP13512 6000 mg and placebo are 3.5 ms and 3.3 ms, respectively. No subjects had an absolute QRS interval greater than 100 ms in both XP13512 1200-mg group and XP13512 6000-mg group.

Table 13: Analysis Results of Δ QRS and $\Delta\Delta$ QRS for XP13512 1200 mg and XP13512 6000 mg

Treatment Group							
Time (hrs.)	XP13512 1200 mg				XP13512 6000 mg		
	Placebo	Δ QRS	$\Delta\Delta$ QRS		Δ QRS	$\Delta\Delta$ QRS	
	LS* Mean	LS* Mean	Diff**	90% CI	LS* Mean	Diff**	90% CI
1	-0.8	-0.8	0.0	(-1.3, 1.3)	-0.1	0.7	(-0.6, 2.0)
2	-0.9	-0.0	0.9	(-0.3, 2.1)	1.0	1.9	(0.7, 3.1)
3	-1.0	-0.3	0.8	(-0.5, 2.0)	-0.2	0.9	(-0.4, 2.1)
4	-1.7	0.6	2.3	(1.2, 3.5)	0.5	2.2	(1.1, 3.3)
6	-1.0	-0.2	0.8	(-0.6, 2.2)	0.0	1.0	(-0.3, 2.4)
7	-0.5	-0.6	-0.0	(-1.3, 1.3)	1.0	1.5	(0.3, 2.8)
8	-1.3	0.0	1.3	(-0.0, 2.7)	-0.8	0.5	(-0.9, 1.9)
9	-1.0	0.6	1.6	(0.2, 3.0)	0.3	1.3	(-0.1, 2.7)
10	-1.4	0.8	2.3	(1.0, 3.5)	-0.7	0.7	(-0.5, 2.0)
12	0.5	0.1	-0.3	(-1.8, 1.2)	-0.9	-1.4	(-2.9, 0.1)
15	0.3	0.6	0.3	(-1.0, 1.6)	0.0	-0.3	(-1.6, 1.0)
18	0.1	1.0	1.0	(-0.4, 2.3)	0.0	-0.0	(-1.4, 1.3)
21	-0.5	0.5	1.0	(-0.4, 2.4)	-0.6	-0.1	(-1.5, 1.3)
22.5	-0.5	-0.6	-0.1	(-1.4, 1.1)	0.5	1.0	(-0.2, 2.2)

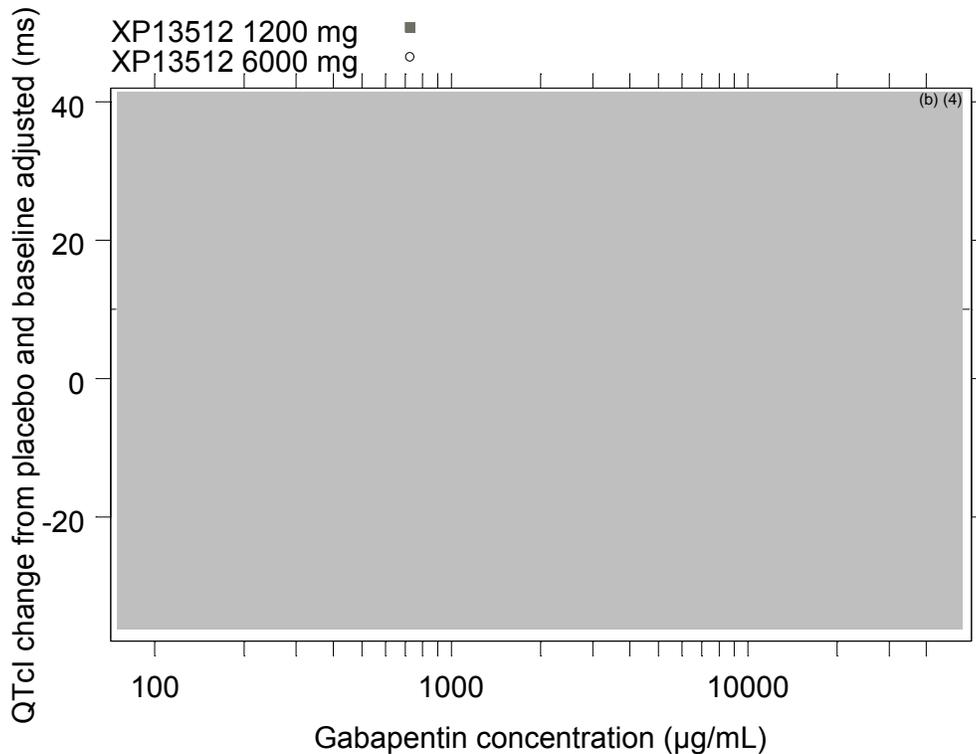
*: Least Square Mean (ms). **:Least Square Mean Difference (ms)

5.3 CLINICAL PHARMACOLOGY ASSESSMENTS

5.3.1 Gabapentin Concentration-QTcI Analysis

The relationship between $\Delta\Delta\text{QTcI}$ and Gabapentin concentrations is visualized in Figure 6. There is no evident exposure-response relationship.

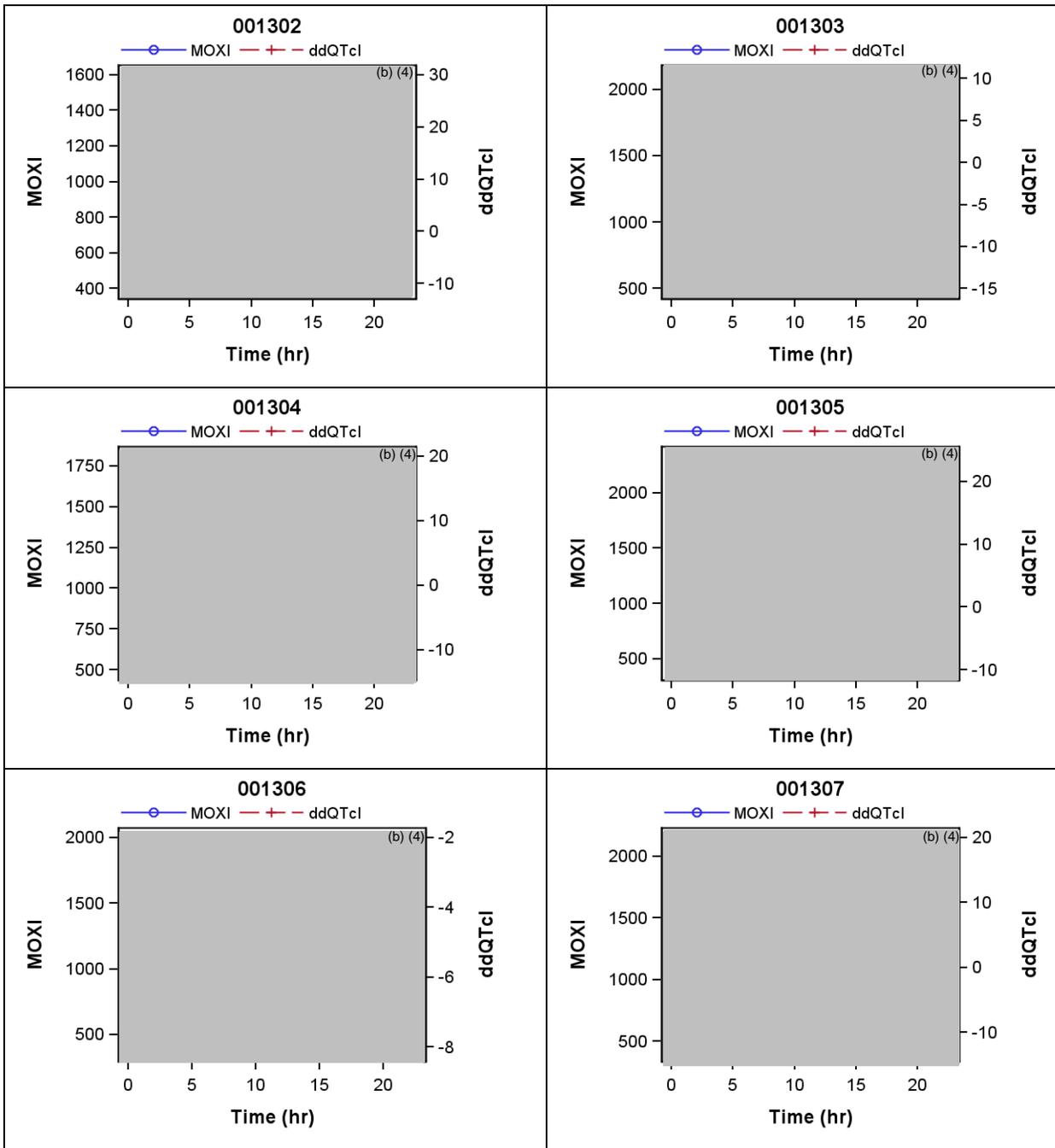
Figure 6: $\Delta\Delta\text{QTcI}$ vs. Gabapentin Concentration

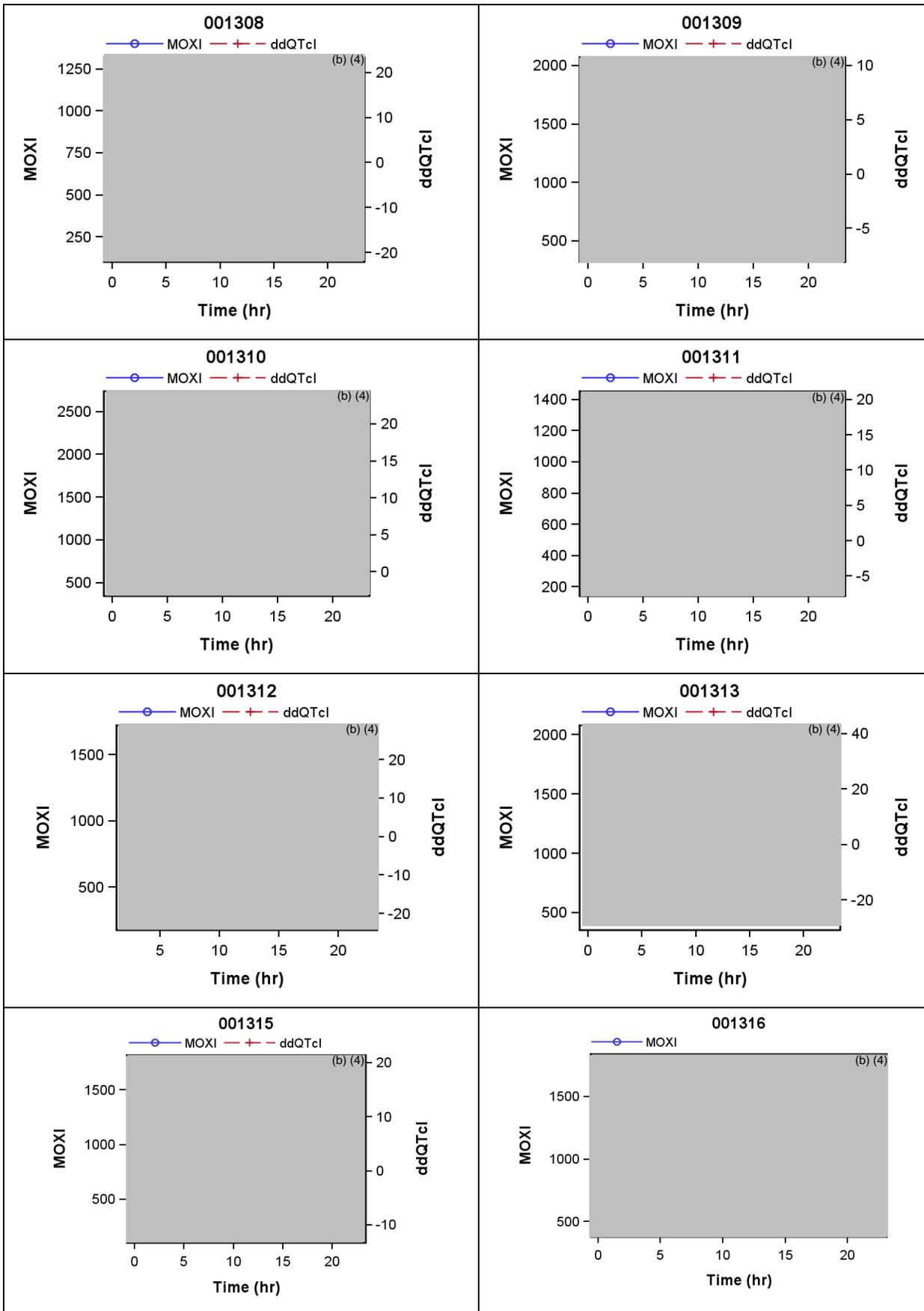


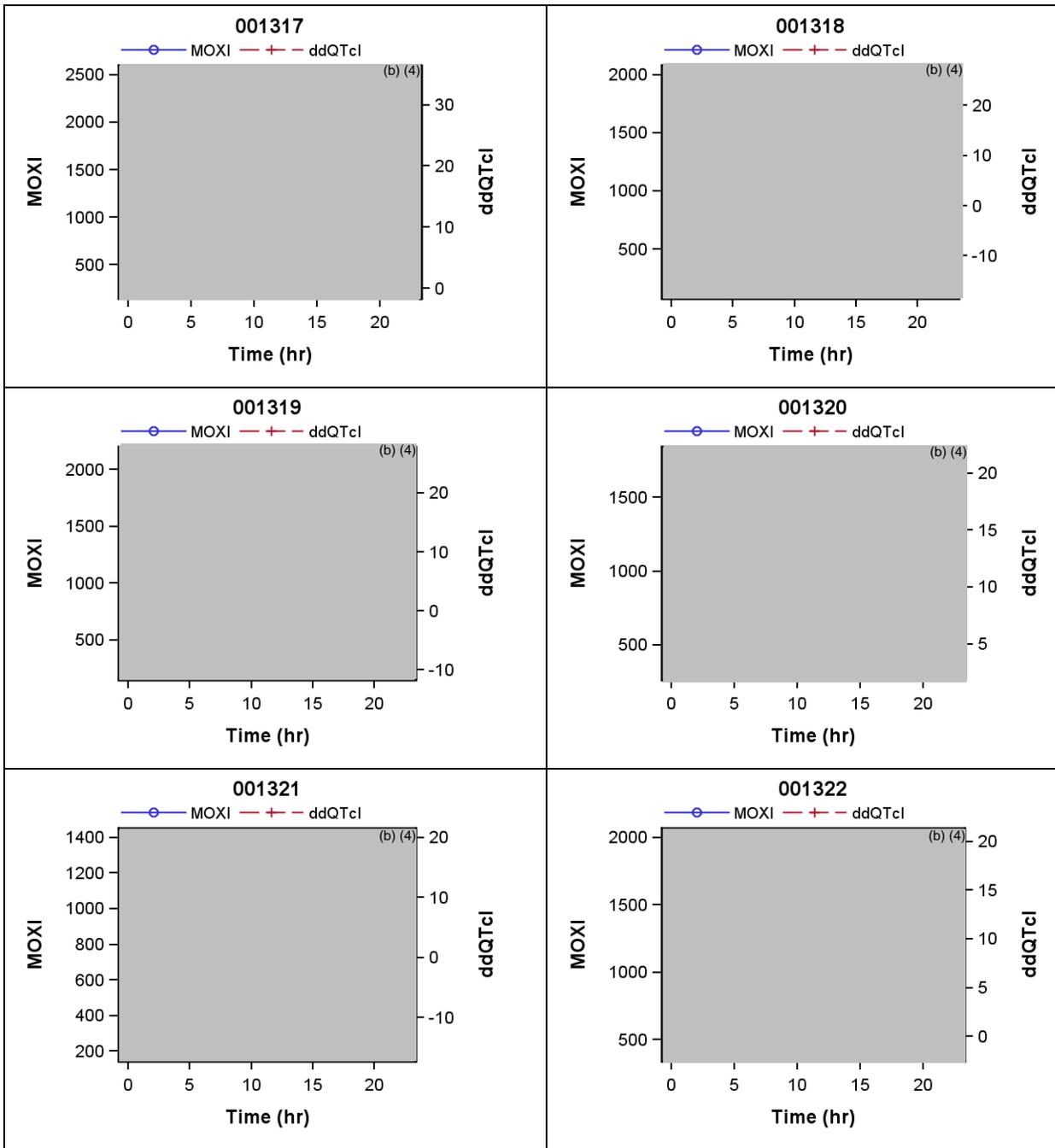
5.3.2 Individual Moxifloxacin PK and $\Delta\Delta\text{QTcI}$ Time Course Analysis

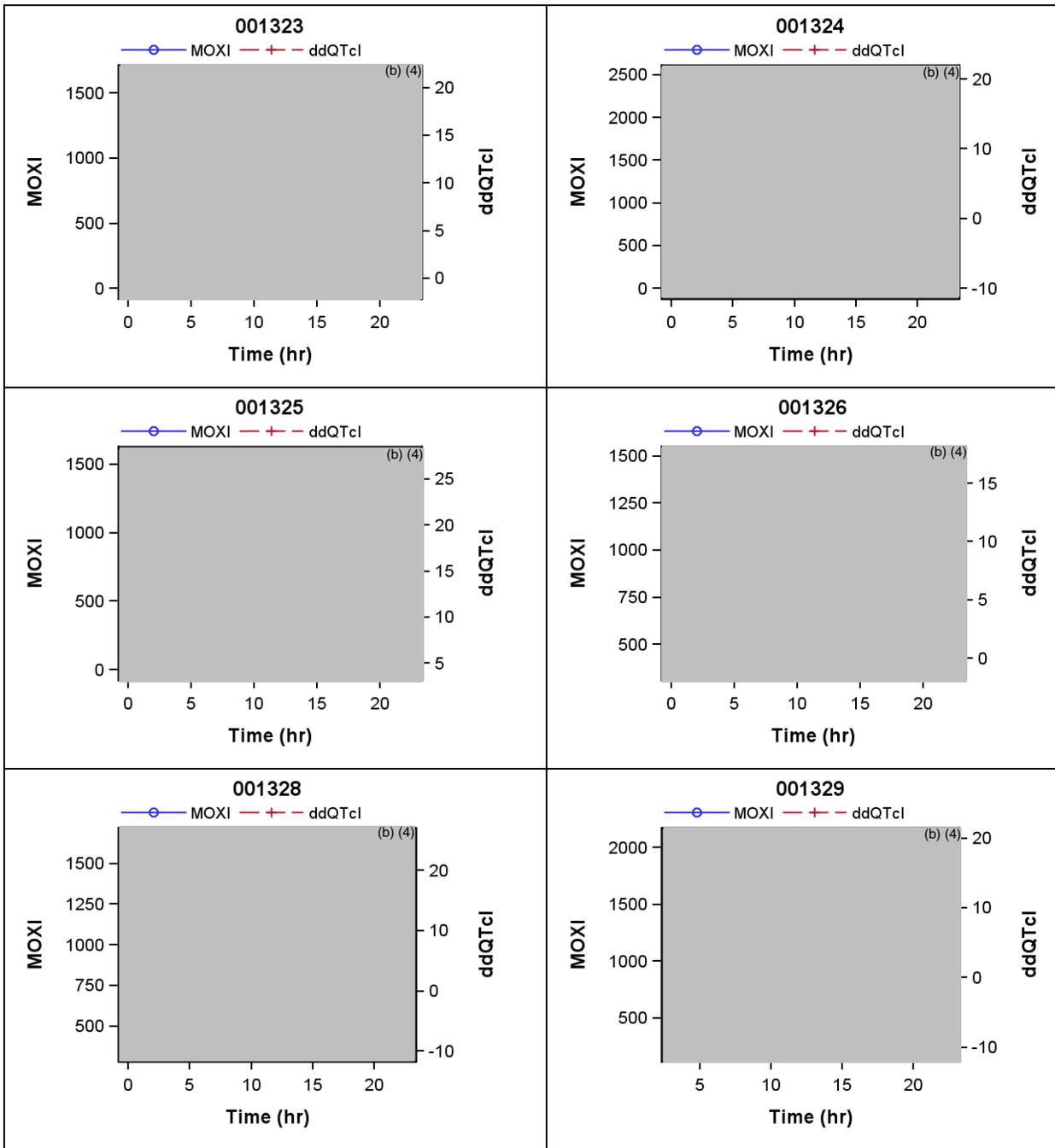
The time profile for moxifloxacin concentration ($\mu\text{g/mL}$) and $\Delta\Delta\text{QTcI}$ (ms) for each subject is plotted in Figure 7. The time profile for moxifloxacin concentration is reasonable; however, there is no time profile for $\Delta\Delta\text{QTcI}$. This finding is consistent with the mean time profile shown in Figure 5. The failure to demonstrate assay sensitivity does not appear to be related to pharmacokinetics.

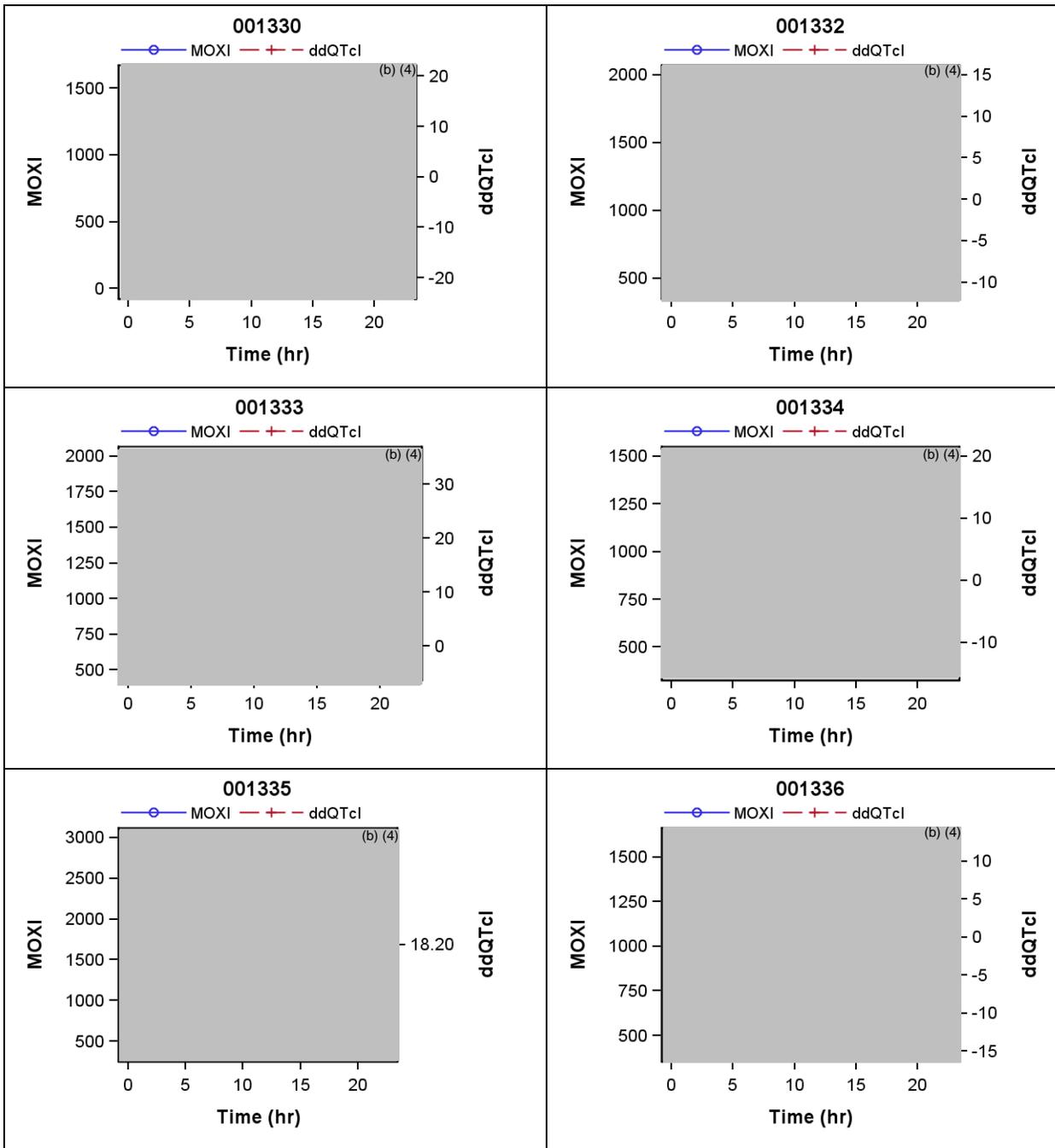
Figure 7: Individual moxifloxacin plasma concentration and $\Delta\Delta\text{QTcI}$ time curves

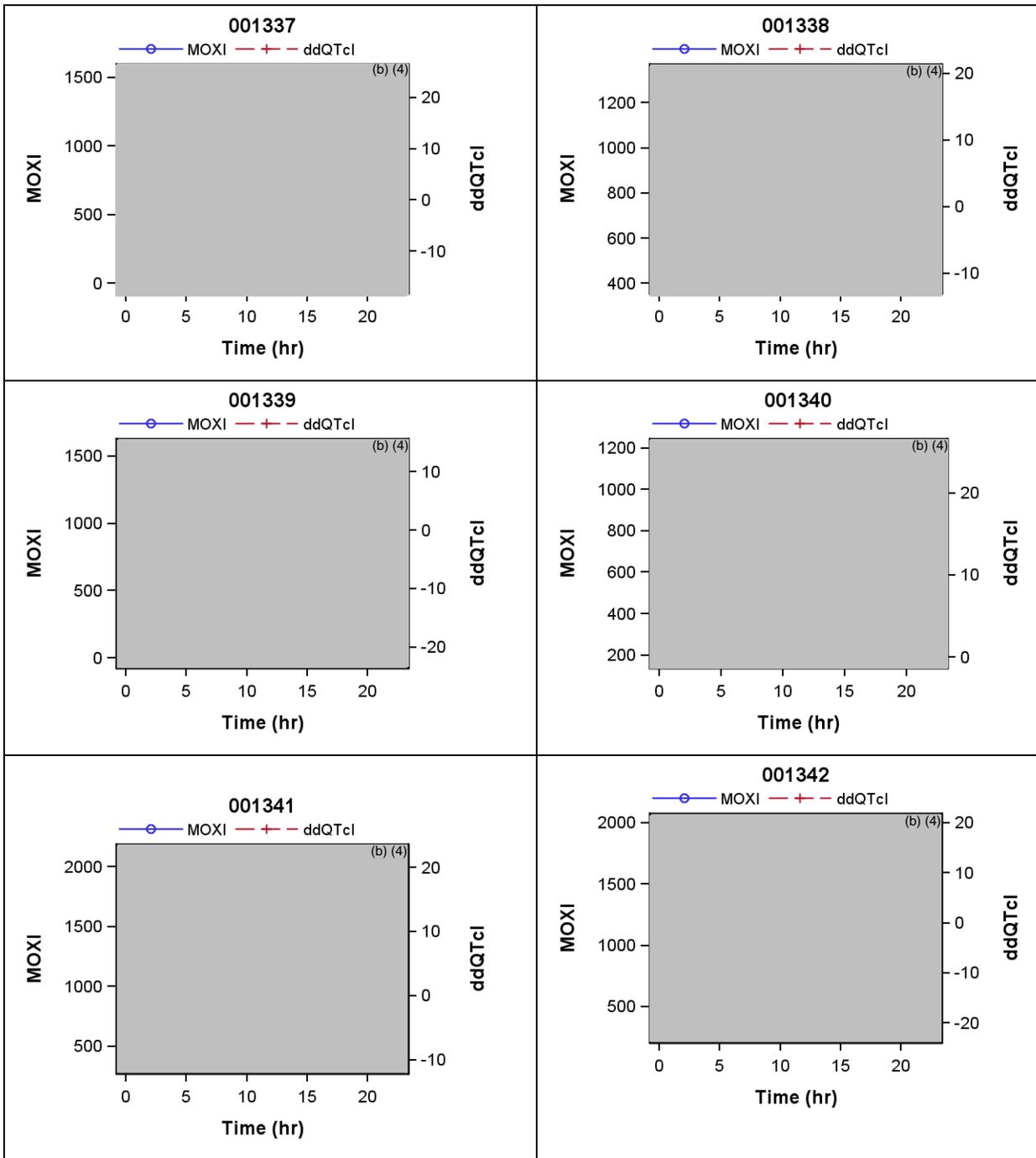


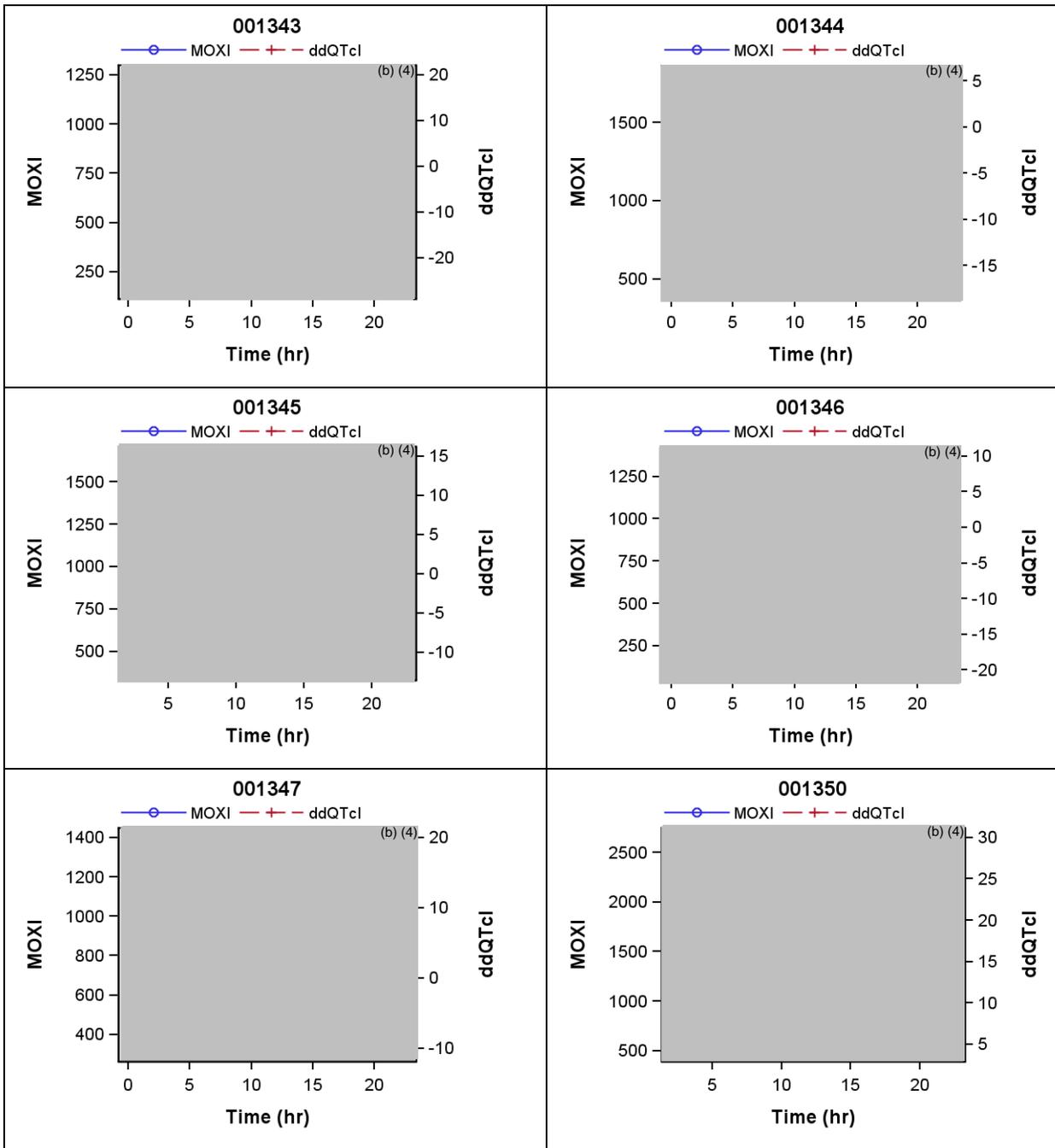


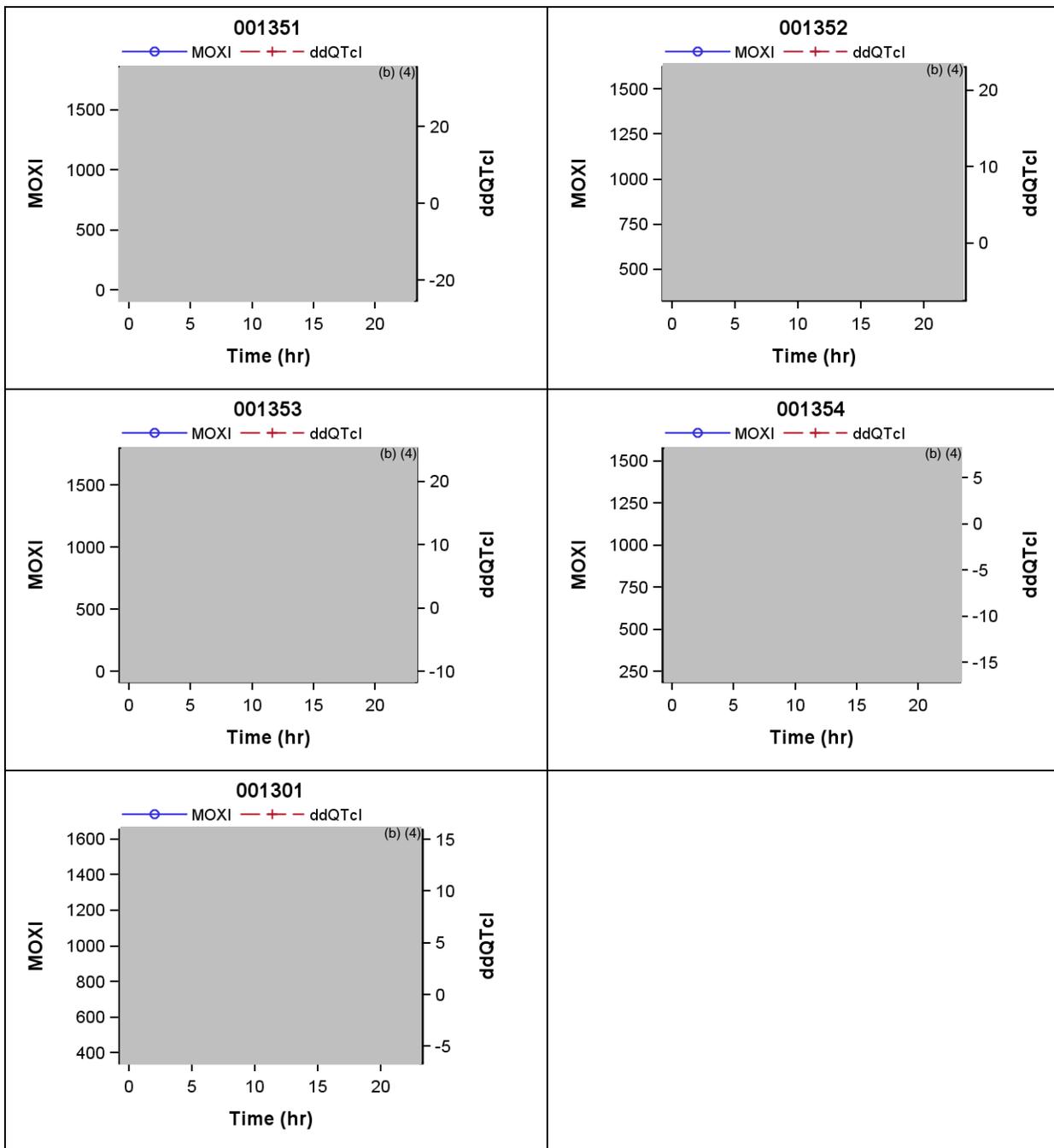












5.4 CLINICAL ASSESSMENTS

5.4.1 Safety assessments

None of the events identified to be of clinical importance per the ICH E 14 guidelines i.e. syncope, seizure, significant ventricular arrhythmias or sudden cardiac death occurred in this study.

5.4.2 ECG assessments

Waveforms from the ECG warehouse were reviewed. According to ECG warehouse statistics over 99% of the ECGs were annotated in the primary lead II, with less than 0.5% of ECGs reported to have significant QT bias, according to the automated algorithm. Overall ECG acquisition and interpretation in this study appears acceptable.

Some of the ECGs submitted to the warehouse from the other studies (XP053, 053, 055, 060, 069, 073, 081 and 083). QT analysis scores could not be computed for these studies by the ECG warehouse. Subsets of ECGs from these studies were reviewed at random. Acquisition and interpretation of ECGs from these studies appear adequate to detect large effects in the QT interval.

5.4.3 PR and QRS Interval

There were no clinically relevant effects on the PR and QRS intervals. The 3 Subjects with a post-dose PR of over 200 ms with XP 13512 also had a baseline PR over 190 ms

5.4.4 MGPS data mining analysis for gabapentin

We conducted an MGPS data mining analysis of the AERS database for AE's related to QT prolongation with gabapentin. Consistent with its indication for treatment of partial seizures the signal score (EBGM value) for seizures was greater than 2. The signal scores for all other AEs related to QT prolongation indicating incidence similar to background rate in the general population which is similar to the sponsors report.

Configuration: CBAERS BestRep (S) **Run :** Generic (S) **Run ID:** 548

Dimension: 2 **Selection Criteria:** Generic name(Gabapentin) + PT(...) **Where:** EBGm > 1.0

3 rows Sorted by Generic name, EBGm desc

Generic name	Level 1	PT	HLT	N	EBGM	EB05	EB95	PRR
Gabapentin	Other Antiepileptics	Convulsion	Seizures and seizure disorders NEC	956	4.27	4.05	4.50	4.52
Gabapentin	Other Antiepileptics	Sudden death	Death and sudden death	38	1.66	1.26	2.14	2.08
Gabapentin	Other Antiepileptics	Cardiac arrest	Ventricular arrhythmias and cardiac arrest	144	1.31	1.14	1.50	1.31

ID:	548
Type:	MGPS
Name:	Generic (S)
Description:	Generic; Suspect drugs only; Minimum count=1; Standard strata (Age, FDA Year, Gender); includes PRR and ROR; includes hierarchy information
Project:	CBAERS Standard Runs
Configuration:	CBAERS BestRep (S)
Configuration Description:	CBAERS data; best representative cases; suspect drugs only; with duplicate removal
As Of Date:	03/27/2009 00:00:00
Item Variables:	Generic name, PT
Stratification Variables:	Standard strata
Highest Dimension:	2
Minimum Count:	1
Calculate PRR:	Yes
Calculate ROR:	Yes
Base Counts on Cases:	Yes
Use "All Drugs" Comparator:	No
Apply Yates Correction:	Yes
Stratify PRR and ROR:	No
Fill in Hierarchy Values:	Yes
Exclude Single Itemtypes:	Yes
Fit Separate Distributions:	Yes
Save Intermediate Files:	No
Created By:	Empirica Signal Administrator
Created On:	04/03/2009 17:13:50 EDT
User:	Suchitra Balakrishnan
Source Database:	Source Data: CBAERS data from Extract provided by CBER as of 03/27/2009 00:00:00 loaded on 2009-04-01 08:27:50.0

Dimension: 2 **Selection Criteria:** Generic name(Gabapentin) + PT(Cardiac arrest, Convulsion, Electrocardiogram QT prolonged, Sudden cardiac death, Sudden death, Torsade de pointes, Ventricular arrhythmia, Ventricular fibrillation, Ventricular flutter, Ventricular tachyarrhythmia, Ventricular tachycardia) **Where:** EBGm > 1.0

```
SELECT * FROM OutputData_548 WHERE (DIM=2 AND EBGm>1.0 AND ((P1='D' AND ITEM1 IN ('Gabapentin') AND P2='E' AND ITEM2 IN ('Cardiac arrest','Convulsion','Electrocardiogram QT prolonged','Sudden cardiac death','Sudden death','Torsade de pointes','Ventricular arrhythmia','Ventricular fibrillation','Ventricular flutter','Ventricular tachyarrhythmia','Ventricular tachycardia')))) ORDER BY ITEM1,EBGM desc
```

These data do not, by themselves, demonstrate causal associations; they may serve as a signal for further investigation.

6 APPENDIX

6.1 HIGHLIGHTS OF CLINICAL PHARMACOLOGY

Therapeutic dose	The therapeutic dose of XP13512 Extended Release (ER) for the treatment of the signs and symptoms of moderate-to-severe primary Restless Legs Syndrome (RLS) is 1200 mg once daily with food at about 5 PM.	
Maximum tolerated dose	<p>The dose of 6000 mg XP13512 ER is the highest single dose studied in healthy volunteer subjects. This dose was generally well tolerated but was associated with a higher incidence of AEs as compared to 1200 mg in the same study, some of which were reported as severe.</p> <p>The maximum dose of XP13512 ER administered in a repeated-dose study to healthy volunteer subjects was 1800 mg BID, and was well tolerated.</p>	
Principal adverse events	In the 12-week placebo controlled RLS studies, the treatment-emergent AEs with the highest incidences in the XP13512 All Doses group (600, 1200, 1800 and 2400 mg doses combined QD) were somnolence (24%) and dizziness (21%).	
Maximum dose tested	Single Dose	6000 mg XP13512 ER
	Multiple Dose	<p>1800 mg BID XP13512 ER in healthy subjects for 6 days</p> <p>2400 mg QD XP13512 ER in RLS subjects for 12 weeks</p>
Exposures Achieved at Maximum Tested Dose	Single Dose	<p>Following a single dose of 6000 mg XP13512 ER tablets after a standard meal in healthy volunteers, C_{max} and AUC_{0-inf} for gabapentin are as follows:</p> <ul style="list-style-type: none"> • C_{max}: $30.1 \pm 7.01 \mu\text{g/mL}$ and $28.9 \pm 6.06 \mu\text{g/mL}$ • AUC_{0-inf}: $358 \pm 88.8 \mu\text{g}\cdot\text{h/mL}$ and $322 \pm 55.8 \mu\text{g}\cdot\text{h/mL}$ <p>Note: Data are mean \pm SD from 2 studies</p>
	Multiple Dose	<p>Following administration of 1800 mg XP13512 ER tablets BID with a standard meal to healthy subjects, $C_{max,ss}$ and $AUC_{0-12,ss}$ values for gabapentin in plasma were as follows:</p> <ul style="list-style-type: none"> • $C_{max,ss}$: $16.1 \pm 3.44 \mu\text{g/mL}$ • $AUC_{0-12,ss}$: $120 \pm 24.7 \mu\text{g}\cdot\text{h/mL}$ <p>Following administration of 2400 mg XP13512 ER tablets QD with a standard meal to RLS subjects, $C_{max,ss}$ and $AUC_{0-24,ss}$ values for gabapentin in plasma were as follows:</p> <ul style="list-style-type: none"> • $C_{max,ss}$: $14.0 \pm 4.23 \mu\text{g/mL}$

		<ul style="list-style-type: none"> AUC_{0-24,ss}: 176 ± 53.8 µg*h/mL <p>Note: Data are mean ± SD</p>
Range of linear PK	The pharmacokinetics of gabapentin were approximately linear in the dose range of 300 mg to 6000 mg XP13512 ER	
Accumulation at steady state	Accumulation of gabapentin following once daily administration of XP13512 ER tablets is minimal	
Metabolites	<ul style="list-style-type: none"> XP13512 undergoes extensive first-pass hydrolysis by non-specific carboxyl-esterases, primarily in intestine and to a lesser extent in the liver, to form gabapentin (the active species), carbon dioxide, acetaldehyde, and isobutyric acid. The released gabapentin from XP13512 ER is not significantly metabolized and is eliminated exclusively by renal excretion. ¹⁴C-gabapentin recovered in the urine accounted for 90% of a radioactive dose of XP13512 in a mass balance study 	
Absorption	Absolute Bioavailability	In the food effect study with 1200 mg of XP13512 ER, the mean bioavailability of gabapentin (determined by urinary recovery of gabapentin) was 42.0 ± 6.12%, 64.3 ± 13.2%, 64.9 ± 16.9%, and 76.1 ± 14.4% for fasted, low fat, moderate, and high fat/calorie meals, respectively.
	Tmax	<p>Following single administration of XP13512 ER tablets in the Phase I studies with healthy volunteer subjects, the Tmax of gabapentin in plasma ranged:</p> <ul style="list-style-type: none"> [4.6 hr to 5.9 hr] in fasted subjects [5.7 hr to 9.8 hr] in fed subjects <p>Note: Data are ranges of means of data from all Phase I single dose studies with XP13512 ER, excluding formulations with altered release characteristics.</p>
Distribution	Vd/F	Based on a population PK model, for typical male and female subjects weighing 79 kg and 51 years of age, the apparent volume of distribution values for gabapentin were 86.3 and 65.6 L, respectively
	% bound	<ul style="list-style-type: none"> XP13512 is 78 to 87% bound to human serum albumin over the concentration range 5 µM to 100 µM (1.7 µg/mL to 32.9 µg/mL) Protein binding of gabapentin has previously been reported to be <3.0% in plasma of rats, monkeys, and humans

Elimination	Route	Gabapentin released from XP13512 is mainly eliminated unchanged by the kidney
	Terminal t _{1/2}	<p>Following single administration of XP13512 ER tablets in Phase I studies, the t_{1/2} of gabapentin in plasma ranged:</p> <ul style="list-style-type: none"> • [5.9 hr to 6.3 hr] in fasted subjects • [5.1 hr to 6.0 hr] in fed subjects <p>Note: Data are ranges of means of data from all Phase I single dose studies with XP13512 ER, excluding formulations with altered release characteristics.</p>
	CL/F	<p>Following single administration of XP13512 ER tablets in Phase I studies, the apparent plasma clearance of gabapentin ranged:</p> <ul style="list-style-type: none"> • [8.78 L/hr to 12.1 L/hr] in fasted subjects • [5.96 L/hr to 9.31 L/hr] in fed subjects <p>Note: Data are ranges of means of data from all Phase I single dose studies with XP13512 ER, excluding formulations with altered release characteristics.</p>
Intrinsic Factors	Age	There is no additional effect of age on gabapentin CL/F, after accounting for changes in renal function
	Sex	<p>Based on a population PK model,</p> <ul style="list-style-type: none"> • CL/F is 15% lower in females than males when weight and creatinine clearance are taken as covariates. • V/F is 25% lower in females than males when weight and age are taken as covariates.
	Race	<ul style="list-style-type: none"> • The effect of race was not specifically studied • The pharmacokinetics of gabapentin released from XP13512 ER were similar between healthy Japanese and Caucasian subjects
	Renal Impairment	There is an approximately linear relationship between gabapentin clearance and creatinine clearance (CrCL): for every 2-fold decrease in CrCL, there is an approximately 1.6-fold decrease in gabapentin CL/F.
	Hepatic Impairment	Not relevant. XP13512 and gabapentin are not inhibitors, inducers or substrates of the major CYP450 enzymes

Elimination	Route	Gabapentin released from XP13512 is mainly eliminated unchanged by the kidney
	Terminal t _{1/2}	<p>Following single administration of XP13512 ER tablets in Phase I studies, the t_{1/2} of gabapentin in plasma ranged:</p> <ul style="list-style-type: none"> • [5.9 hr to 6.3 hr] in fasted subjects • [5.1 hr to 6.0 hr] in fed subjects <p>Note: Data are ranges of means of data from all Phase I single dose studies with XP13512 ER, excluding formulations with altered release characteristics.</p>
	CL/F	<p>Following single administration of XP13512 ER tablets in Phase I studies, the apparent plasma clearance of gabapentin ranged:</p> <ul style="list-style-type: none"> • [8.78 L/hr to 12.1 L/hr] in fasted subjects • [5.96 L/hr to 9.31 L/hr] in fed subjects <p>Note: Data are ranges of means of data from all Phase I single dose studies with XP13512 ER, excluding formulations with altered release characteristics.</p>
Intrinsic Factors	Age	There is no additional effect of age on gabapentin CL/F, after accounting for changes in renal function
	Sex	<p>Based on a population PK model,</p> <ul style="list-style-type: none"> • CL/F is 15% lower in females than males when weight and creatinine clearance are taken as covariates. • V/F is 25% lower in females than males when weight and age are taken as covariates.
	Race	<ul style="list-style-type: none"> • The effect of race was not specifically studied • The pharmacokinetics of gabapentin released from XP13512 ER were similar between healthy Japanese and Caucasian subjects
	Renal Impairment	There is an approximately linear relationship between gabapentin clearance and creatinine clearance (CrCL): for every 2-fold decrease in CrCL, there is an approximately 1.6-fold decrease in gabapentin CL/F.
	Hepatic Impairment	Not relevant. XP13512 and gabapentin are not inhibitors, inducers or substrates of the major CYP450 enzymes

Extrinsic Factors	Drug interactions	<ul style="list-style-type: none"> • Co-administration of 1200 mg XP13512 ER QD with the MCT-1 substrate, naproxen (500 mg BID), produced on average 8 and 13% increase in gabapentin $C_{max,ss}$ and AUC_{ss}, respectively as compared to XP13512 administered alone. However, these small changes are not considered clinically significant. • Naproxen $C_{max,ss}$ and AUC_{ss} were not affected by co-administration with XP13512. • Administration of 1200 mg XP13512 ER QD with 400 mg QID of the OCT2 substrate cimetidine (Tagamet[®]) produced on average 24% increase in gabapentin AUC_{ss}. However, its $C_{max,ss}$ was not affected. • The $C_{max,ss}$ and AUC_{ss} values of cimetidine were similar for cimetidine in combination with XP13512 relative to cimetidine alone.
	Food Effects	<ul style="list-style-type: none"> • When XP13512 ER was administered with food, gabapentin AUC_{0-inf} values were 58.8, 72.1, 77.2 and 82.1 $\mu\text{g}\cdot\text{h}/\text{mL}$ following fasted, low, medium and high fat/calorie meals, respectively (increased by 23, 31 and 40% following a low, medium and high fat/calorie meal, respectively as compared to the fasted state). • Gabapentin C_{max} values were 5.04, 7.34, 6.57 and 7.20 $\mu\text{g}/\text{mL}$ following fasted, low, medium and high fat/calorie meals, respectively (increased by 46, 30 and 43% following a low, medium and high fat/calorie meal, respectively, as compared to the fasted state). • The T_{max} values of gabapentin in plasma following fasted, low, moderate, and high fat/calorie meals were 5.3, 5.7, 7.0, and 7.3 hr, respectively.
Expected High Clinical Exposure Scenario		<ul style="list-style-type: none"> • Accumulation of gabapentin following daily administration of XP13512 ER tablets is minimal. • The mean and ranges of parameters for gabapentin following administration of XP13512 ER tablets in drug-drug interaction (DDI) studies with naproxen and cimetidine are reported in Table 1.

Table 1. Mean [range] of PK Parameters for Gabapentin at Steady-State on day 5 following Multiple Dosing with XP13512 in DDI Studies

Treatment	C _{max,ss} (µg/mL)	AUC _{0-24,ss} (µg*hr/mL)
XP13512 (1200 mg/day) ^a	6.17 [4.68-8.19]	63.3 [47.1-84.3]
XP13512 (1200 mg/day) with Naproxen (500 mg BID)	6.52 [5.11-8.34]	71.7 [57.2-85.5]
XP13512 (1200 mg/day) ^b	7.05 [4.43-9.01]	70.8 [51.7-85.3]
XP13512 (1200mg/day) with Cimetidine (400 mg QID)	7.44 [6.12-9.15]	87.6 [75.3-104]

a: XP13512-naproxen DDI study, b: XP13512-Cimetidine DDI study

- Following administration of a single dose of 600 mg XP13512 ER to subjects with renal impairment (mean CrCL 32.0 mL/min), the mean C_{max} and AUC_{0-inf} values were 5.92 µg/mL ranging [3.87 µg/mL to 7.92 µg/mL] and 195 µg*hr/mL ranging [123 µg*hr/mL to 350 µg*hr/mL].
- Table 2 shows gabapentin predicted exposure in subjects with renal impairment following a proposed dosing adjustment for the XP13512 label. Predictions were obtained with the parameters of a population PK model for gabapentin following XP13512.

Table 2. Predicted PK Parameters for Gabapentin at Steady-State following Multiple Administration of XP13512 in Subjects with Renal Impairment.

CrCL (mL/min)	Day 1 AUC _{ss} (µg*h/mL)	Day1 C _{max,ss} (µg/mL)	Day 2 AUC _{ss} (µg*h/mL)	Day 2 C _{max,ss} (µg/mL)	Day 3 AUC _{ss} (µg*h/mL)	Day 3 C _{max,ss} (µg/mL)
30 ^a	115	6.28	115	6.29	116	6.30
59 ^a	73.3	4.55	73.3	4.55	73.3	4.55
15 ^b	110	5.75	74.0	3.98	110	5.77
29 ^b	77.3	4.47	41.0	2.52	77.4	4.47

a: 600 mg/day; b: 600 mg every other day

- Following administration of a single dose of 6000 mg of XP13512 ER to 50 healthy volunteers, the mean and ranges of C_{max} and AUC_{0-inf} values were 30.1 µg/mL ranging [9.15 µg/mL to 44.3 µg/mL] and 358 µg*hr/mL ranging [188 µg*hr/mL to 737 µg*hr/mL], respectively.

	<p>Conclusions:</p> <ul style="list-style-type: none"> Exposure (C_{max} and AUC) to gabapentin following co-administration of XP13512 ER tablets at the therapeutic dose of 1200 mg/day with naproxen or cimetidine is below the range observed with the supra-therapeutic dose of 6000 mg. Exposure (C_{max} and AUC) to gabapentin following administration of XP13512 ER tablets in subjects with renal impairment following the proposed dosage adjustment is below the range observed with the supra-therapeutic dose of 6000 mg.
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Source: sponsor's ClinPharm Table

6.2 TABLE OF STUDY ASSESSMENTS

3.0 SCHEDULE OF EVENTS

Nominal Time→	Screening	Day	Day -1 and Day 1 ¹																			Day	Day
	Day -28 ²	-2	-1*	0	1	2	3	4	6	7	8	9	10	12	13	15	18	21	22.5	26	g ¹¹ or ET		
Informed Consent	X																						
Medical History ³	X	X																					
Prior Medication Record	X	X																					
Height and Weight	X																						
Physical Examination	X																					X	
Routine Laboratory Testing ⁴	X	X		X ¹³																	X	X	
HIV, HbsAg, Anti-HCV	X																						
Urine Drug/Alcohol Screen	X	X																					
Serum Pregnancy Test ⁵	X	X																				X	
Holter Monitoring										X ⁶													
Vital Signs/Orthostatic BP	X ¹	X ⁸	X ⁸	X ⁸	X ⁸	X ⁸	X ⁸	X ⁸	X ⁸	X ⁸	X ⁸	X ⁸	X ⁸	X ⁸	X ⁸	X ⁸	X ⁸	X ⁸	X ⁸	X ⁸	X ⁸	X ⁸	
Safety ECG (12 lead)	X	X	X ¹⁰							X ¹⁰				X ¹⁰							X	X	
Study Drug Administration				X ¹¹																			
Meal				X				X					X		X ¹³								
Water ¹⁴			X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	
PK Blood Sample ¹²			X		X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	
Adverse Event Monitoring & Concomitant Medications										X													
Admit and Confinement										X													

* Pre-Dose

- All Day -1 and Day 1 procedures will be identical for all periods.
- To be performed within 28 days prior to dosing day (Day 1) or 26 days prior to check-in day (Day -2), Period 1.
- Including demographics, concomitant medication.
- Chemistry, Hematology, Urinalysis.
- For females.
- Holter monitoring with a 12-lead recording device will be done for a minimum of 23.5 hours on Day -1 and Day 1. ECGs may be extracted from Holter monitoring data by a central cardiac data analysis lab at the following time points: pre-dose and 10 minutes prior to nominal times of 1, 2, 3, 4, 6, 7, 8, 9, 10, 12, 15, 18, 21, and 22.5 hours post-dose Day 1 and matching time points on Day -1. These ECGs will not be used in the safety analysis.
- Triplicate blood pressure and heart rate will be collected at screening in the supine position.
- Orthostatic blood pressure and heart rate will be collected in triplicate at 15-20 min apart.
- Orthostatic blood pressure and heart rate will be collected.
- Day 1 only.
- Exit visit occurs on Day 8 (±2) of period 4.
- PK blood samples will be obtained only on Day 1.
- Snack only
- Water (240 mL) will be consumed at specified hours and ad lib.

Source: protocol for XP078

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/s/

Joanne Zhang
5/5/2009 02:01:29 PM
BIOMETRICS

Misook Park
5/5/2009 02:23:18 PM
BIOEQUIVALENCE STATISTICIAN

Fang Li
5/6/2009 04:33:01 PM
BIOPHARMACEUTICS

Suchitra Balakrishnan
5/6/2009 04:47:58 PM
MEDICAL OFFICER

Christine Garnett
5/7/2009 02:17:30 PM
BIOPHARMACEUTICS

Norman Stockbridge
5/7/2009 05:49:54 PM
MEDICAL OFFICER

DSI CONSULT: Request for Clinical Inspections

Date: February 4, 2009

To: Constance Lewin, M.D., M.P.H, Branch Chief, GCP1
Joseph Salewski, Branch Chief (Acting), GCP2
Antoine EL Hage, Primary Reviewer
Division of Scientific Investigations, HFD-45
Office of Compliance/CDER

Through: Susanne R. Goldstein M.D. Division of Neurology Products
Center of Drug Evaluation I

From: Beverly Conner, *RPM, Regulatory Health Project Manager/DNP*

Subject: **Request for Clinical Site Inspections**

I. General Information

Application#: NDA-22-399

Applicant contact information: Debra Lake Tel: 919-483-4411; e-mail: debra.h.lake@gsk.com

Drug Proprietary Name: SOLZIRA (gabapentin enacarbil)

NME or Original BLA Yes:

Review Priority: Standard

GlaxoSmithKline mail Address:

Glaxo Group Limited d/b/a GlaxoSmithKline

Attention: Debra Lake, M.S.

Manager Regulatory Affairs

Five Moore Drive P.O. 13398

Research Triangle Park, NC 27709

Study Population includes < 17 years of age, No

Is this for Pediatric Exclusivity (Yes/No):

Proposed New Indication(s): Restless Leg Syndrome

PDUFA:

Action Goal Date: August 24, 2009

Inspection Summary Goal Date: August 1, 2009

DSI Consult

version: 5/08/2008

II. Protocol/Site Identification

Include the Protocol Title or Protocol Number for all protocols to be audited. Complete the following table.

Site # (Name,Address, Phone number, email, fax#)	Protocol ID	Number of Subjects	Indication
192 (Albert Razzetti, MD, University Clinical Research Deland, Inc, 860 Peachwood Drive, Deland, FL 32720)	XP052	18	Restless Leg Syndrome
124 William Ellison, MD, (Radiant Research-Greer, 552-A Memorial Drive, Extension, Greer, SC 29651)	XP052	18	Restless Leg Syndrome
148 James E. Garrison, III, MD (Innovative Clinical Trials, 5430 Fredericksburg Road, Suite 400, San Antonio, TX 78229)	XP053	29	Restless Leg Syndrome
149 Kurt W. Lesh, MD (Lynn Institute of the Rockies, 2500 North Circle Drive, Colorado Springs, CO 80909)	XP053	27	Restless Leg Syndrome

III. Site Selection/Rationale

Site selection for protocols XP052 and XP053 were selected after preliminary review of efficacy and safety data as well as enrollment numbers by site. The sponsor did not submit a listing of protocol deviations other than inclusion/exclusion problems.

Sites 192 and 124 for protocol XP052 were high enrollers. After discussion with statistician, it was noted that these two sites also had high withdrawal rate.

Sites 148 and 149 for protocol XP053 had missing data points.

Rationale for DSI Audits

Page 3-Request for Clinical Inspections

The sponsor stated in the NDA submission, that site #149 had results that 'were not consistent with the results from the other sites. The results from this site appeared to be errant, that they were contradictory to the study results overall, with placebo-treated subjects outperforming XP13512-treated subjects on" co primary endpoints. In addition, there had been a change in study coordinator during the clinical trial.

Domestic Inspections:

Reasons for inspections (please check all that apply):

- Enrollment of large numbers of study subjects
- High treatment responders (specify):
- Significant primary efficacy results pertinent to decision-making
- There is a serious issue to resolve, e.g., suspicion of fraud, scientific misconduct, significant human subject protection violations or adverse event profiles.
- Other (specify):

International Inspections:

Reasons for inspections (please check all that apply):

- There are insufficient domestic data
- Only foreign data are submitted to support an application
- Domestic and foreign data show conflicting results pertinent to decision-making
- There is a serious issue to resolve, e.g., suspicion of fraud, scientific misconduct, or significant human subject protection violations.
- Other (specify) (Examples include: Enrollment of large numbers of study subjects and site specific protocol violations. This would be the first approval of this new drug and most of the limited experience with this drug has been at foreign sites, it would be desirable to include one foreign site in the DSI inspections to verify the quality of conduct of the study).

Note: International inspection requests or requests for five or more inspections require sign-off by the OND Division Director and forwarding through the Director, DSI.

IV. Tables of Specific Data to be Verified (if applicable)

If you have specific data that needs to be verified, please provide a table for data verification, if applicable.

Should you require any additional information, please contact *Beverly Conner, PM at 301-796-1173* or *Susanne Goldstein, Medical Reviewer, at 301-796-5013.*

Concurrence: (as needed)

Dave Podskalny - Medical Team Leader
Susanne Goldstein - Medical Reviewer

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/s/

Beverly A. Conner
4/2/2009 12:53:51 PM
NONE

Susanne Goldstein
4/9/2009 11:03:11 AM