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APPLICATION NUMBER:

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MEDICAL REVIEW(S)

CLINICAL REVIEW

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Reviewer Name(s)	Steven T. Dinsmore, D.O.
Review Completion Date	June 8, 2011
Established Name	Ezogabine
(Proposed) Trade Name	POTIGA
Therapeutic Class	Anticonvulsant
Applicant	Valeant Pharmaceuticals
Formulation(s)	Immediate release, film coated tablets
Dosing Regimen	Three times daily oral administration
Indication(s)	Adjunctive treatment of partial onset seizures
Intended Population(s)	18 years of age and older

Template Version: March 6, 2009

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1 Recommendations/Risk Benefit Assessment

1.1 Recommendation on Regulatory Action

Potiga is recommended for approval, based on the sponsor correction of non-clinical deficiencies communicated in a complete response (CR) letter dated November 30, 2010.

1.2 Risk Benefit Assessment

This response to CR, a Class 1 resubmission, addresses a non-clinical, chemistry, manufacturing and controls (CMC) deficiency which was the basis of NDA 22345 non-approval. This submission also contains safety update data to integrate into the risk benefit assessment. This data interval includes the time frame from the 120 day safety update of the original NDA submission (October 2, 2009) to the end of the "Final Safety Update" of this resubmission (September 30, 2010), henceforth to be abbreviated "FSU". **This one year interval contains safety data from 235 patient participants** in studies VRX-RET-E22-303 and VRX-RET-E22-304 which are the long term open label extension trials of placebo controlled trials VRX-RET-E22-301 and VRX-RET-E22-302. In addition there were three clinical pharmacology studies (RTG114137, RTG113214, RTG113215) completed in the interval **contributing data from 65 healthy subjects in multiple dose treatment sequences and 43 healthy subjects in single dose treatment sequences**. In two of these trials subjects had sustained ezogabine treatment for up to 5 weeks with incremental ezogabine dose escalations. Clinical pharmacology trial RTG113215 also contained a **nested but important study of gall bladder volume in 32 patients treated with ezogabine for approximately one month**. The key elements of the safety review are found in section 7, safety summary. There was no additional efficacy data in this submission thus no material is present in section 6 except to reference the reader to the initial clinical review.

The safety update presented in this submission does not alter the risk – benefit assessment assembled in the clinical review of the initial NDA submission although the review does find that safety concerns noted in the initial submission are reinforced. The Chemistry Review indicates that the outstanding safety issue of the initial submission, a high level of potentially mutagenic manufacturing impurity (b) (4) has been corrected. The correction of the high level of the mutagenic impurity " (b) (4) to levels of not more than (b) (4) places the approval package into and acceptable risk - benefit balance.

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1.3 Recommendations for Postmarket Risk Evaluation and Mitigation Strategies

See initial NDA 22345 Medical Review

1.4 Recommendations for Postmarket Requirements and Commitments

See initial NDA 22345 Medical Review

2 Introduction and Regulatory Background

2.1 Product Information

See initial NDA 22345 Medical Review

2.2 Tables of Currently Available Treatments for Proposed Indications

See initial NDA 22345 Medical Review

2.3 Availability of Proposed Active Ingredient in the United States

The active moiety (ezogabine) is a NCE (new chemical entity) and not currently marketed in any country.

2.4 Important Safety Issues with Consideration to Related Drugs

See initial NDA 22345 Medical Review

2.5 Summary of Presubmission Regulatory Activity Related to Submission

The initial submission for market approval of ezogabine was on October 30, 2009. A complete response letter (CR) was issued on November 16, 2011. No clinical deficiencies were identified, the NDA was not approvable based high acceptance limit proposed for the mutagenic impurity (b) (4) which was originally set at not more than (NMT) (b) (4). This deficiency was rectified in this submission by reducing the (b) (4) impurity levels to not more than (NMT) (b) (4), which is equivalent to (b) (4) ug/day based on a maximum daily dose of 1200 mg.

2.6 Other Relevant Background Information

none

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3 Ethics and Good Clinical Practices

3.1 Submission Quality and Integrity

The eCTD format was followed and fully functional. Some additions to the "All Phase II/III Combined Group" FSU were events that had an occurrence date earlier than the 120 day safety update of the initial submission. It was very difficult to compare the occurrence of new events in the FSU to events in the 120 day safety update of the original submission. Review would have been facilitated by the addition of a column in the FSU dataset which indicated new additions to the dataset. This would have allowed easy extraction of new adverse events for comparison to the array of events reported in the initial submission.

3.2 Compliance with Good Clinical Practices

Material for this section relevant to the pivotal controlled trials is provided in the initial NDA 22345 medical review, page 22.

3.3 Financial Disclosures

Financial disclosure for studies 303 and 304 has been covered by the financial disclosure for investigators participating in studies 301 and 302 in the initial NDA 2234 submission.

Financial disclosures are not provided for the clinical pharmacology studies providing safety data to this submission. These studies do not provide efficacy data to the approval application.

4 Significant Efficacy/Safety Issues Related to Other Review Disciplines

4.1 Chemistry Manufacturing and Controls

<u>Background</u>

Following the initial NDA 22345 submission a CR letter was issued indicating the NDA was not approvable due to the high specification limit proposed for the mutagenic impurity (b) (4) A limit of not more than (b) (4) was proposed by the sponsor.

In the initial NDA 22345 submission (b) (4) was reproducibly positive using the Ames test but negative when tested in vivo in a combined rat micronucleus and Comet assay. The

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CMC review team did not agree that the negative micronucleus and Comet assay provided an adequate basis for dismissing the mutagenic potential demonstrated in the Ames assay. The CMC reviewer pointed out that the in vivo assay evaluate different genotoxicity endpoints that do not always correlate, in addition there was inadequate data to determine whether a negative Comet assay has adequate negative predictive value to provide reassurance when an Ames test has been positive.

Response to Deficiency

The applicant has addressed the deficiency concerning the acceptance limit for (b) (4) by slightly modifying the drug substance manufacturing process. This change has reduced the (b) (4) impurity levels to not more than (NMT) (b) (4), which is equivalent to (b) (4) ug/day based on a maximum daily dose of 1200 mg.

The CMC review reports: "Specifically, lowering of the (b) (4)) impurity has been achieved by the (b) (4) . Furthermore, the applicant has demonstrated that the physical and chemical characteristics, including polymorphic form, particle size distribution and stability of the drug substance are unaffected by the minor modification to the manufacturing process. In addition, the analytical method for determination of (b) (4) content by HPLC mass spectrometry (LCMS) has been validated for specificity, linearity, repeatability, precision and accuracy, and is capable of quantifying at the new acceptance level of NMT (b) (4)

4.2 Clinical Microbiology

N/A

4.3 Preclinical Pharmacology/Toxicology

There is no additional Non-clinical study material submitted

4.4 Clinical Pharmacology

Completed review not submitted for integration into the review at the time of this writing 6-3-2011

4.4.1 Mechanism of Action

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4.4.2 Pharmacodynamics

4.4.3 Pharmacokinetics

5 Sources of Clinical Data

5.1 Tables of Studies/Clinical Trials

Studies covered in this review are the components requested in the FDA November 30, 2010 Complete Response letter. This includes updated safety data from the ongoing extension studies of the pivotal controlled trials. These are studies VRX-RET-E22-303 and VRX-RET-E22-304. In addition the final reports for three Phase 1 studies are included, these are studies RTG114137, RTG113214, and study RTG113215. An overview is seen in table 1.

Table 1 Overview of Clinical Studies Reviewed in this Submission

Protocol No.	No. Study Centers - Location(s)	**Study Objectives**	Study Design	Diagnosis; Key Inclusion Criteria	Treatment Details (Drug; Dose; Form; Route; Frequency; Duration)	No. of Subjects by Group Entered/ Completed	Primary Endpoint(S)
VRX-RET-E22-303 (ext to 301)	41 sites in 5 countries: 5 Argentina 4 Brazil 4 Canada 4 Mexico 24 US	Safety and tolerability of long-term treatment with RTG administered as adjunctive treatment in adult outpatients with epilepsy, who completed Study 301.	Uncontrolled , open-label extension to 301	Patient had successfully completed the 12-week maintenance and 4-week transition phases of Study 301	RTG 50mg, 100mg, 300 mg capsules 600 to 1200 mg/day, administered orally TID	RTG (various doses): 181/102 continuing in OLE	AEs, vital signs, ECGs, clinical laboratory tests The percentage change in the 28 day seizure frequency from the baseline phase (301) to open-label treatment.
VRX-RET-E22-304 (ext to 302)	57 sites in 13 countries 4 Australia 3 Belgium 3 France 6 Germany 2 Hungary 6 Israel 7 Poland 5 Russia 7 S Africa 5 Spain 5 UK 5 Ukraine 1 US	Safety and tolerability of long-term treatment with RTG administered as adjunctive treatment in adult outpatients with epilepsy, who completed Study 302	Uncontrolled ,open-label extension to 302	Patient had successfully completed the 12-week maintenance and 4-week transition phases of Study 302.	RTG 50mg, 100mg, 300 mg tablets 600 to 1200 mg/day, administered orally TID	RTG (various doses): *375/ 211 continuing in OLE	AEs, vital signs, ECGs, clinical Laboratory tests The percentage change in the 28 day seizure frequency from the baseline phase (302) to open-label treatment.
RTG114137	1 site in US	Primary objective is to assess the impact of the urine sample handling procedures on laboratory safety	Randomized , open-label, repeat dose	Healthy subjects, age 40 to 65 years	Multiple doses, starting at 300 mg/day (100 mg TID) and up-titrated to 450, 600, 750	33 subjects received EZO	urinalysis: proteinuria

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Protocol No.	No. Study Centers - Location(s)	**Study Objectives**	Study Design	Diagnosis; Key Inclusion Criteria	Treatment Details (Drug; Dose; Form; Route; Frequency; Duration)	No. of Subjects by Group Entered/ Completed	Primary Endpoint(S)
		results			and 900 mg/day (150, 200, 250 and 300 mg TID).		
RTG113215	1 site in US	Part A: Relative BA of MR formulations compared with IR formulation; effect of high fat meal on MR formulations Part B: QD vs BID dosing of an MR formulation and dose proportionality	Randomized, Open label; Part A: 6 Periods Part B: 1 period	Healthy subjects	Part A: single dose RTG IR: 400mg RTG MR1: 480mg RTG MR2: 480mg RTG MR3: 480mg RTG MR4: 480mg RTG MR5: 480mg Part B: RTG MR: 160mg, 320mg, 480mg and 640mg BID RTG MR: 320, 960mg, 1280 QD	Part A: Group 1: 20/16 Group 2: 14/10 Group 3: 11/9 Part B: BID dosing: 16/13 QD dosing: 16/12	PK sampling There is a secondary investigation of gall bladder volume in this study.
RTG113214	1 site in US	of RTG administered as an aqueous suspension to the colon compared to the BA of RTG administered as an oral aqueous suspension to the stomach	Open-label, 5 period crossover	Healthy subjects	5 dosing periods, 5-7 day washout between periods: RTG oral 100mg RTG suspension in colon: 100mg RTG suspension in colon: 400mg RTG micronized suspension in colon: 400mg RTG suspension with surfactant in colon: 400mg	RTG: 8/8	PK of RTG

Reference ID: 2957637

Protocol No.	No. Study Centers - Location(s)	**Study Objectives**	Study Design	Diagnosis; Key Inclusion Criteria	Treatment Details (Drug; Dose; Form; Route; Frequency; Duration)	No. of Subjects by Group Entered/ Completed	Primary Endpoint(S)
Compassionate Use D-23129-3227 VALEANT	21 sites in 12 countries 12 in EU (Croatia, CZ Rep, Finland, France, Germany, Italy, Spain) 2 Australia 1 Israel 2 New Zealand 2 UK 1 US	Long term safety and benefit	Uncontrolled, open-label compassionate use	Partial epilepsy patients	RTG 50mg, 100mg, 300 mg tablets	RTG (various doses) 50/9 continuing	Long term safety and benefit data

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5.2 Review Strategy

Studies 303 & 304

1. Determine the number of patients remaining in each study
2. Determine the additional patient exposure in each study
3. Examine Key safety measures, Death, SAE, and Withdrawal.
4. Examine the new datasets in each of these studies for events of special interest in this submission- (7.3.5) Draw conclusions if there is a change in signal:
    a. increased frequency or severity
    b. greater or lesser predictability, urinary : urinary retention, Nephrolithiasis
    c. greater or lesser predictability, hallucinations / psychotic symptoms.
5. Re-examine the new dataset for additional items of interest for change in signal intensity:
    a. hypokalemia
    b. orthostatic hypotension
    c. syncope
    d. atrial fibrillation
    e. hepatic dysfunction
    f. blood dyscrasias

Clinical Pharmacology Studies RTG114137, RTG113214, RTG113215.

1. Determine the number of patients remaining in each study
2. Determine patient exposure in each study
3. Examine Key safety measures, Death, SAE, and Withdrawal.
4. Examine the datasets in each of these studies for events of special interest in these submission- (7.3.5) Draw conclusions if they contribute to an overall change in safety signal:
    a. increased frequency or severity
    b. greater or lesser predictability, urinary : urinary retention, Nephrolithiasis
    c. greater or lesser predictability, hallucinations / psychotic symptoms.
5. Examine the clinical pharmacology dataset for additional items of interest which may indicate a change in signal intensity for:
    a. hypokalemia
    b. orthostatic hypotension
    c. syncope
    d. atrial fibrillation
    e. hepatic dysfunction
    f. blood dyscrasias

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5.3 Discussion of Individual Studies/Clinical Trials

Safety Dataset Cut Off Dates

Table 2 Initial Submission Safety dataset cutoff dates

Initial NDA 22345 Submission	
ISS Integrated Data Cut-off:	120-Day Safety Data Cut-off:
30 June 2008	2 October 2009

Table 3 Resubmission, Final Safety Update (FSU) cut off date

NDA 22345 Complete Response Resubmission
Final Safety Data Cut-off:
30 September 2010

Open label extension trials of Phase 3 Controlled Trials

VRX-RET-E22-303: This was an open-label extension study of Study 301, a placebo-controlled, double-blind study in which patients were treated with retigabine 1200 mg/day, (400 mg TID) or placebo. In the current study, patients were treated with 600 mg/day to 1200 mg/day of retigabine as an adjunct therapy to their ongoing antiepileptic drugs (AEDs) with or without vagal nerve stimulation as established in Study 301.

VRX-RET-E22-304: This was an open-label extension study of the placebo-controlled, double-blind Study 302 in which patients received retigabine 900 mg/day as 300 mg three times a day (TID) or 600 mg/day as 200 mg three times a day (TID) or placebo. In the current study, patients were treated with 600 mg/day to 1200 mg/day of retigabine as an adjunct therapy to their ongoing antiepileptic drugs (AEDs) with or without vagal nerve stimulation as established in Study 302.

Completed Clinical Pharmacology Studies

The information to follow concerning the clinical pharmacology studies is focused primarily on the study structure and enrollment to provide the reader with a view of the nature of the safety data each study will yield. A discussion of the clinical pharmacology endpoints and statistical validity is not provided.

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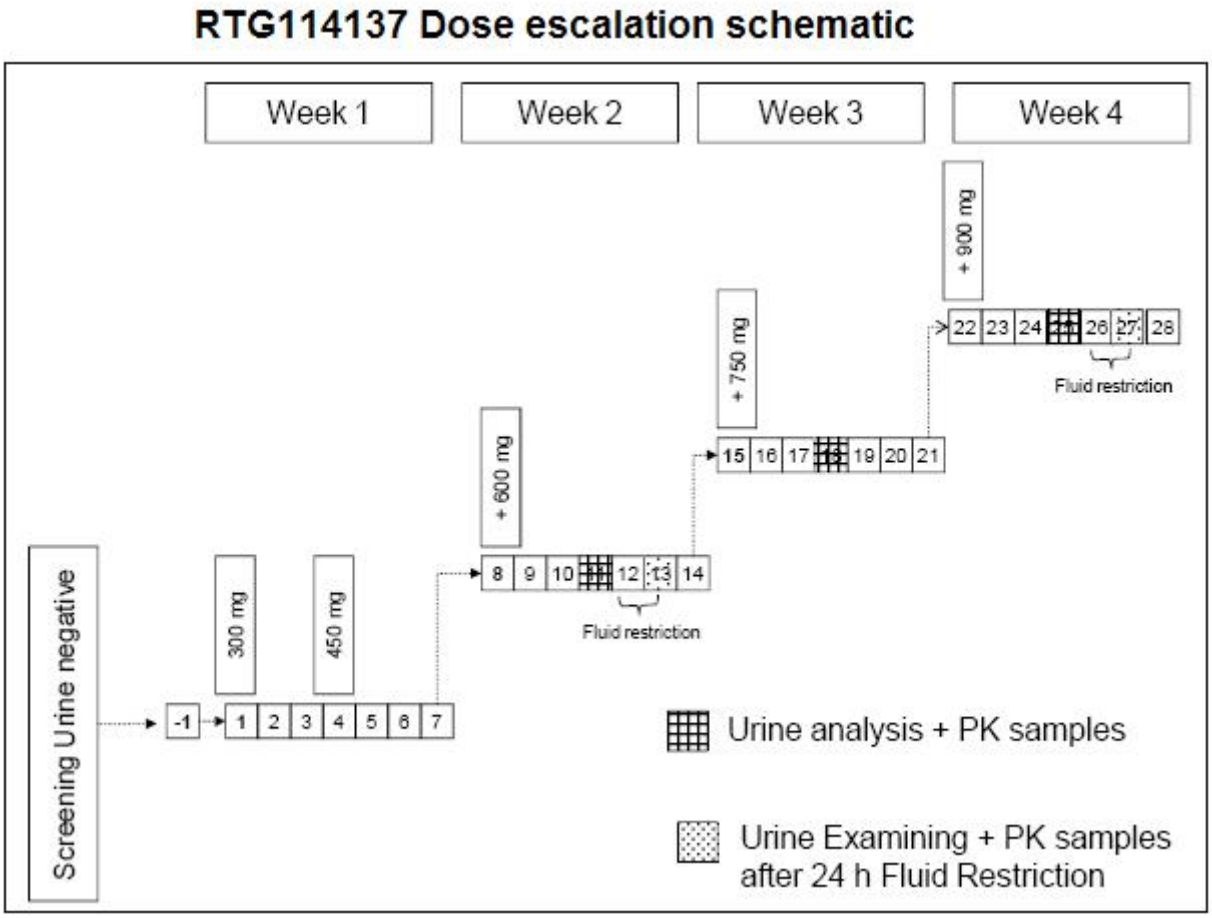
RTG114137: This was an open-label, randomised, repeat dose, up-titration study to assess the effect of urine sample handling procedures on urine safety results. The objective of the present study was to assess the impact of the urine sample handling procedures (interval between collection and analysis, role of preservatives) on laboratory safety results. Urine samples were obtained from healthy subjects receiving repeat doses of ezogabine/retigabine. Thirty three subjects were enrolled and 24 subjects completed this study. The dose escalation rate in week 2 and 3 of the study is 33% more rapid than the labeled escalation rate. This rate of titration and the duration of the study represent a sufficient exposure and rate of drug introduction that adverse effects similar to those seen in the pivotal trials are expected.

Figure 1 Study RTG114137 Dose escalation schematic



RTG113215: This was a two part study to assess the pharmacokinetic performance of three retigabine modified release (MR) formulations after single dose and to assess the pharmacokinetics and tolerability of titration with retigabine modified release at steady state following multiple doses of ezogabine.

Part A: in part A subjects were administered single doses of the prototype modified release formulation or ezogabine immediate release (IR). Each single dose is separated by a 5 to 7 day washout interval.

Subject enrollment for the subsets of part A is shown in the following table.

Study RTG113215: Summary of Subject Disposition and Demographic Characteristics in Part A			
Number of Subjects	**Group 1 (Fasted)**	**Group 2 (Fed)**	**Group 3 (Fed)**
Number of subjects planned, N:	20	12	12
Number of subjects randomized, N:	20	14	11

Subjects in group I received each of the 5 prototype MR formulations and an IR dose in a randomized 6 way crossover fashion, in the fasted state. See table 4.

Table 4 Study RTG113215: Part A Group I dose

Part A, Group 1 (fasted)	
400mg IR (A)	
480mg MR Formulation 1-	(b) (4)
480mg MR Formulation 2-	
480mg MR Formulation 3-	
480mg MR Formulation 4-	
480mg MR Formulation 5-	

Subjects in group 2 (part A) received 3 ezogabine prototype MR formulations and IR formulation in a randomized 4 way crossover, following a high fat meal. See table 5.

Table 5 Study RTG113215: Part A Group 2 dose

Part A, Group 2 (high fat meal)	
400mg IR (G)	
480mg	(b) (4)
480mg	
480m	

Subjects in Part A Group 3 were planned to receive 2 retigabine prototype MR formulations and IR formulation with a high fat meal in a randomised manner (3-way crossover), see table 6.

Table 6 Part A, Group 3

Part A, Group 3 (high fat meal)
400mg IR (K)
480mg MR Formulation 4-(L) (b) (4)
480mg MR Formulation 5-(M) (b) (4)

Part B: In part B of the study there are two groups. Group 1 subjects receive a single daily dose of the modified release formulations during the first 4 weeks of the study, then 3 day treatment with 200mg three times a day of the IR formulation. Group two subjects receive a twice a day dosing schedule of the modified release formulation followed by 3 days of the IR formulation, three times daily. Sixteen patients are randomized into each group. The treatment schedules of each group are shown in table 7.

Table 7 RTG113215 Part B Dosing Regimen

Group 1: Once Daily Dosing Regimen				
Week	**Days**	**Dose**	**Tablet Strengths**	**TDD (mg)**
1	1-7	320mg QD	1x 320mg QD (N2)	320
2	8-14	640mg QD	1x 640mg QD (O2)	640
3	15-21	960mg QD	1x 320mg + 1x 640mg QD (P2)	960
4	22-25	1280mg QD	2 x 640mg QD (Q2)	1280
4	26-28	1280mg QD	4 x 320mg (R2)	1280
5	29-31	200mg TID	Retigabine IR 200mg TID (S2)	600
Group 2: Twice Daily Dosing Regimen				
Week	**Day**	**Dose**	**Tablet Strengths**	**TDD (mg)**
1	1-7	160mg BID	1x 160mg BID (T2)	320
2	8-14	320mg BID	1x 320mg BID (U2)	640
3	15-21	480mg BID	1x 480mg BID (V2)	960
4	22-25	640mg BID	1 x 640mg BID (W2)	1280
4	26-28	640mg BID	4 x 160mg BID (X2)	1280
5	29-31	200mg TID	Retigabine IR 200mg TID (Y2)	600

RTG113214: This is an open label, five way, partially randomized crossover study to evaluate the regional gastrointestinal absorption of retigabine in healthy volunteers. Eight subjects were randomized and completed the trial. Each subject was assigned to one of 4, five part treatment sequences (ABCDE, ABCED, CABDE or CABED). Treatment periods were separated by a minimum of 5 days. A follow up visit was conducted 7 - 10 days after the last dose of study drug in the last treatment period. Each treatment in the sequence consisted of a single dose of ezogabine delivered orally or via gastrointestinal release. Two of the doses were 100mg and three were 400mg each. The administration table is shown below (table 8).

Table 8 RTG113214 Dosing Regimen

Ezogabine Single Dose Treatments	
Treatment	Description
A	(Reference), Retigabine as a suspension administered *via* an oral syringe. Total dose: 100 mg of retigabine
B	Formulation 1, Retigabine as a suspension released in the colon. Total dose: 100 mg of retigabine
C	Formulation 2, Retigabine as a suspension released in the colon. Total dose: 400 mg of retigabine
D	Formulation 3, Retigabine (b) (4) drug substance as a suspension released in the colon. Total dose: 400 mg of retigabine
E	Formulation 4, Retigabine as a suspension with the surfactant sodium lauryl sulfate released in the colon. The surfactant is incorporated into the current lead modified release form. ((b) (4) Total dose: 400 mg of retigabine

6 Review of Efficacy

Efficacy Summary

There is no new efficacy data submitted to the NDA, see original submission Statistical and Medical review for NDA 22345

6.1 Indication

6.1.1 Methods

NA

6.1.2 Demographics

NA

6.1.3 Subject Disposition

NA

6.1.4 Analysis of Primary Endpoint(s)

NA

6.1.5 Analysis of Secondary Endpoints(s)

NA

6.1.6 Other Endpoints

Na

6.1.7 Subpopulations

NA

6.1.8 Analysis of Clinical Information Relevant to Dosing Recommendations

NA

6.1.9 Discussion of Persistence of Efficacy and/or Tolerance Effects

NA

6.1.10 Additional Efficacy Issues/Analyses

NA

7 Review of Safety

Safety Summary

There was one death reported during the FSU period and one approximately two months after the FSU reporting interval. The first death occurred in the compassionate use program due to a subdural hematoma. The second was a patient found dead by a roadside after leaving a hospital emergency room. This second case appears to be due to an interval of non-compliance. The deaths in the FSU interval do not appear to be related to ezogabine treatment.

There were 13 patients who reported a first serious adverse event in the “All Phase II/III Combined Group” of the FSU while there were three serious adverse events in the clinical pharmacology studies. Overall there was no notable spike in SAE frequency or indication of a previously unobserved signal of serious adverse events in this safety database. One notable case of psychotic symptoms occurred in a healthy volunteer in the urine handling study RTG114137, this case was reported in the safety review of the initial NDA submission and is noted here for completeness but does not contribute new insight into the ezogabine risk profile. A second SAE of note occurred in subject 15103 in the modified release formulation study has features that may be due to a complex partial seizure and subsequent post ictal state.

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In the “All Phase II/III Combined Grouping”, 17 patients experienced adverse events leading to study withdrawal. In the clinical pharmacology studies there were 16 patients who experienced adverse events leading to study withdrawal in the FSU. Overall the profile of adverse events leading to withdrawal is similar to those in the initial NDA submission with predominance of CNS and psychiatric symptoms. The occurrence of psychotic symptoms in healthy subjects participating in the clinical pharmacology studies indicates that ezogabine may produce these adverse effects independently of a background central nervous system disorder or concomitant anticonvulsant medications.

The profile of common adverse events (non SAE) is similar to those seen in the safety dataset of the initial ezogabine medical review.

Submission specific safety concerns are examined in this reporting interval. These included urinary tract disorders (primarily voiding dysfunction), seizure worsening, cardiac rhythm abnormalities, ezogabine effects on the gall bladder, ezogabine effects on hepatic function, ezogabine and psychotic symptoms.

Voiding dysfunction: In the “All Phase II/III Combined Grouping” new reports of voiding dysfunction occurred in this reporting interval. At this point in the open label extension studies patients have been on ezogabine treatment for an extended period of time. The events of “urinary retention” occur in three patients after treatment for 761 days, 845 days and 889 days respectively. Those affected are two male and one female patient. One male patient is 20 years old and the female patient is 26 years old. Due to their young age these two patients are unlikely to have pre-existing cause for urinary retention. There were also three new events of “urinary hesitation” and one new event of urine flow decreased. The events of “urinary retention” in the two young patients (one female) support the concern that there is persistent risk of voiding dysfunction after ezogabine treatment for several years.

In the clinical pharmacology studies the most frequent Renal / Urinary events occur in the study which had the longest duration and highest maximum dose. The majority of Renal / Urinary events were in the category of voiding dysfunction. There were 7 events of urinary hesitation and one event of “micturition frequency decreased”. There were two events of dysuria. These events occurred in healthy volunteers and are consistent with prior observations in ezogabine treatment but also demonstrate the events of voiding dysfunction are not restricted to the epilepsy population.

Psychotic symptoms: Two patients in the open label extension studies had SAEs due to psychotic symptoms, in one patient there was a positive dechallenge. In the clinical pharmacology studies one healthy control subject had an SAE due to psychotic symptoms (covered fully in the initial NDA safety review) also with a positive dechallenge. In all of the clinical pharmacology studies 8 patients had adverse events of “hallucination”, “hallucination, auditory” or “hallucination, visual”.

Reference ID: 2957637

Seizure Worsening: In the FSU there is no seizure type subset that appears to emerge in an increased frequency. Epilepsy related events continue to occur in the long term open label studies. This is not unexpected in an epilepsy population; those events which occur are difficult to distinguish from the natural history of the underlying disease process. Overall frequency of these events does not appear to change in the FSU interval compared to the 120 day safety update interval. There is one case of possible absence seizure in a healthy volunteer (15103 discussed in section 7.3.2) after his 5th dose of ezogabine where the subject received single doses of ezogabine each separated by approximately 1 week. The first 4 doses were 480mg of a modified release form and the 5th dose was 400mg of ezogabine IR. This case triggers a concern for development of seizure like events following a high single dose in patients naive to ezogabine; however the true physiology of the event is unknown.

Neutropenia / Blood dyscrasia: The PCC values from the "All Phase II/III Combined Grouping" do not provide evidence for a new safety signal for blood dyscrasia. The observations of AEs due to infections and cytopenias in the FSU are similar in frequency and severity to those seen in the initial NDA safety review. The data from the clinical pharmacology studies demonstrate the capacity to depress neutrophils and WBC counts in healthy subjects as was seen in the epilepsy patient trials.

Cardiac Rhythm / Conduction abnormalities: During the FSU there were no observed occurrences of cardiac rhythm or conduction disorder of sufficient magnitude to indicate a new or worsening safety signal. The QT interval outliers are examined for both the "All Phase II/III Combined Group" and the clinical pharmacology studies, the results were similar to those presented in the original ISS and 120-Day Safety Update.

Ezogabine effect on the gall bladder: The reader is referred to the dedicated section on gall bladder effects (section 7.3.5) for the full discussion of this new information presented to the approval package. The reviewer concludes that ezogabine may have an influence on gall bladder contractility but there is currently insufficient evidence of clinical sequelae of impaired gall bladder contractility such as "cholecystitis", cholelithiasis, biliary colic, or upper abdominal pain to change labeling. Focused pharmacovigilance is appropriate and is currently planned by the sponsor.

Ezogabine effect on the Liver: In the "All Phase II/III Combined Group" there is no evidence of a new safety signal for hepatic dysfunction seen upon examination of the PCC values for hepatic function parameters or by occurrence of hepatic function adverse events in the FSU interval. In the clinical pharmacology studies there is no evidence of a new safety signal for clinical chemistry values or hepatic dysfunction seen upon examination of the PCC values or adverse events. In those cases where transaminase elevation was seen, none of the hepatic function abnormalities breached the Hy's law threshold and transaminase values trended rapidly back to normal after medication discontinuation (except subject 15617 where the abnormality is first noted in follow up).

Reference ID: 2957637

During the initial safety review of NDA22345 there was focus among clinical chemistry abnormalities on hyperkalemia and among vital signs data on hypotension. These safety items were given additional attention in this review. There was a single elevated potassium value in an ezogabine treated patient in RTG113215 part B, an elevation of similar magnitude was observed in one subject at screening (pre-treatment). Among values for blood pressure there is approximately equal distribution and magnitude of low and high blood pressure measurements in standing position in both diastolic and systolic phases. There is no data to lend further support of a signal for hyperkalemia or orthostatic hypotension in ezogabine treatment.

7.1 Methods

7.1.1 Studies/Clinical Trials Used to Evaluate Safety

Table 9 Studies/Clinical Trials Used to Evaluate Safety

Study	All Phase II/III Combined Analysis Set (13 studies)	Presented Separately
RTG114137		X
RTG113124		X
RTG113215		X
3065 A1-200/201	X	
3065 A1-202	X	
3065 A1-205	X	
3065 A1-208	X	
3065 A1-209	X	
3065 A1-212	X	
3065 A1-214	X	
3065 A1-216	X	
3227-CU		X
D-23129-8017	X	
VRX-RET-E22-301	X	
VRX-RET-E22-302	X	
VRX-RET-E22-303	X	
VRX-RET-E22-304	X	

Also see section 5.1 for a table of descriptions of the studies in highlighted rows which provide safety data for this submission.

Reference ID: 2957637

Table 10 Clinical Pharmacology Study dose range and Patient exposure

Clinical Pharmacology Study dose range and Patient exposure				
Study	**Type of study**	**Min – max dose**	**Duration of exposure to each dose**	**Number of patients**
RTG114137	OL, dose escalation. Urine handling on urine safety parameters	300mg to 900mg	3 week titration, total study duration 4 weeks	Healthy 33/24
RTG113215	PK performance of MR formulations	A 400 - 480	A Single dose x 5 , each separated by 5 -7 day washout	A Healthy male Group 1: 20/16 Group 2: 14/10 Group 3: 11/9
		B 320- 1280 Escalate by 320mg /wk	B 4 weeks, , max dose 4th wk.	B Healthy male & female BID dosing: 16/13 QD dosing: 16/12
RTG113214	OL, x over, GI absorbtion	100mg / 400mg	Single dose, 48 hr obs, return in 5 days for next dose in sequence, five doses in complete sequence (example CABDE)	8 Healthy

7.1.2 Categorization of Adverse Events

No change from categorization of the initial NDA medical review.

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

Safety data from open label extension studies 303 and 304 was pooled with the previously reported data from the open label extension studies as well as the controlled clinical trial data from studies 205, 301 and 302. Ongoing open label extension trials 303 and 304 contributed safety data for a total of 313 patients exposed to ezogabine during the interval from the initial submission 120 day safety cut off date (10/2/09) to the FSU safety cut off date (9/30/10).

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7.2 Adequacy of Safety Assessments

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

Exposures at appropriate dose and duration were met in the initial NDA submission.

7.2.2 Explorations for Dose Response

No dedicated dose response studies were presented in this submission

7.2.3 Special Animal and/or In Vitro Testing

N/A

7.2.4 Routine Clinical Testing

Routine clinical testing for studies 303 and 304 was accepted in the initial NDA submission. Clinical testing for the clinical pharmacology studies presented in this submission was adequate.

7.2.5 Metabolic, Clearance, and Interaction Workup

See initial NDA 22345 medical review, page 94

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

None available

7.3 Major Safety Results

All Phase II/III Group (see section 7.1.1 for definition)

7.3.1 Deaths

During the FSU reporting period there was one death reported. This occurred in the compassionate use program due to a subdural hematoma. A second death is reported after the FSU reporting period (9/30/2010). This death occurred on (b) (6). A patient in study E22-303 was found dead by a roadside after leaving a hospital emergency room. No deaths were reported in **clinical pharmacology** studies or **Study 304**. A brief synopsis of these two deaths is provided as “Death 1” and “Death 2” below.

Death #1- Compassionate Use Program (subject D-23129-3227-033-100): A 58 yo female at time of enrollment, the patient had been treated with ezogabine for approximated 9.5 years. She was taking 100mg twice a day at the time of death. A downward course of medical events began when the patient had a spontaneous subarachnoid hemorrhage in (b) (6) at the age of 67 years. An anterior communicating artery aneurysm was clipped. Post operatively the patient suffered two subdural hematomas, one apparently spontaneously and one after a fall at a "rest home". Following a craniotomy for the second subdural hematoma the patient remained poorly responsive (Glasgow coma scale 3-4 non sedated) and a decision was made to withdrawal ventilator support. The record indicates ezogabine was among the discharge medications to the "rest home".

Death #2- Study VRX-RET-E22-303 (subject 15201): A 33 year old Hispanic male was treated with ezogabine for approximately 4 years at the time of death. The patient apparently had a seizure in public while en-route to visit his sister. He was seen in a hospital emergency room. The patient's family was searching for him and found that he had departed the hospital emergency room but his belongings remained behind, including medications and documents. His condition upon leaving the hospital is not known. The family subsequently learned that the patient had spent the night after leaving the hospital at a fire station. While at the fire station the patient is reported to have been conversant. The family continued to search for the patient and he was found dead in a drain at the side of the road on (b) (6) The patient last dose of ezogabine was taken on the morning of (b) (6)

Brief Program overview: There were a total of 17 deaths in the ezogabine development program. There were 13 treatment emergent deaths in clinical trials and the compassionate use program. There were 4 deaths in pretreatment or post treatment intervals. A tabular report of deaths by safety interval is shown in table 11.

Table 11 Number of Deaths and Exposure for Patients who Received Ezogabine for the Overall Epilepsy Program (does not include death outside of ezogabine treatment)

Safety Population	Treatment Group	Exposure in Patient-Years	All Fatal Events	Fatal Events/ 1000 PY	SUDEP[b]	SUDEP/ 1000 PY
ISS Cut-off 31 Dec 08 Overall	Ezogabine	1400	10	7.1	8	5.7
120-Day cut-off Overall	Ezogabine	1556[a]	12[c]	7.7	8	5.1
Final Safety cut-off Overall	Ezogabine	1821[a]	13[c]	7.1	8	4.4

a. Actual exposure numbers are available for the All Phase II/III Combined through the respective cut-off date.
Exposure for the compassionate use program is an estimate.
b. Includes all patients that meet criteria for possible or probable SUDEP irrespective of reported

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preferred term, and includes an additional case adjudicated by the FDA as a possible SUDEP.
c. Includes one death that was reported after the cut-off.
PY=patient-years

Reviewer Comment: The deaths in the FSU interval do not appear to be related to ezogabine treatment. In the second case there may have been seizure due to cessation of anticonvulsant medication. The reason for the patient lapse of normal self care and medication is unclear.

7.3.2 Nonfatal Serious Adverse Events

All Phase II/III Group (see section 7.1.1 for definition)

During the FSU reporting period a total of 13 patients reported a first TESAE bringing the current total to 243 (18%) of patients. The cumulative total at the conclusion of the 120 day safety update from the previous submission was 230 (16.8%) patients reporting an SAE, thus there was an increase in the final interval of 1%. Sponsor table of TESAE reported by at least 3 patients in the "All Phase II/III combined group" is shown below (table 12). Grey shaded rows represent an increase in the interval from initial submission 120 day safety update and the "Final Safety Update".

Table 12 TESAE Reported by at Least 2 Patients (Safety Population: All Phase II/III Combined)

	Number (%) of Patients EZG (N=1365)		
Preferred Term	**ISS Integrated Data Cut-off: 30 June 2008**	**120-Day Safety Data Cut-off: 2 October 2009**	**Final Safety Data Cut-off: 30 September 2010**
Any SAE	**216 (15.8)**	**230 (16.8)**	**243 (17.8)**
Convulsion	33 (2.4)	35 (2.6)	36 (2.6)
Psychotic disorder	9 (0.7)	9 (0.7)	11 (0.8)
Confusional state	8 (0.6)	7 (0.5) a	7 (0.5)
Status epilepticus	8 (0.6)	8 (0.6)	10 (0.7)
Complex partial seizures	7 (0.5)	7 (0.5)	7 (0.5)
Epilepsy (increased seizure frequency)	6 (0.4)	7 (0.5)	6 (0.4)b
Dizziness	5 (0.4)	5 (0.4)	6 (0.4)
Chest pain	5 (0.4)	5 (0.4)	5 (0.4)
Grand mal convulsion	5 (0.4)	6 (0.4)	8 (0.6)
Somnolence	4 (0.3)	4 (0.3)	4 (0.3)
Headache	4 (0.3)	4 (0.3)	4 (0.3)
Conversion disorder	4 (0.3)	4 (0.3)	4 (0.3)
Pneumonia	4 (0.3)	5 (0.4)	5 (0.4)
Urinary retention	4 (0.3)	4 (0.3)	4 (0.3)
Hyponatremia	4 (0.3)	5 (0.4)	5 (0.4)
Pregnancy	4 (0.3)	4 (0.3)	2 (0.1)c
Coma	3 (0.2)	3 (0.2)	3 (0.2)

	Number (%) of Patients EZG (N=1365)		
Preferred Term	**ISS Integrated Data Cut-off: 30 June 2008**	**120-Day Safety Data Cut-off: 2 October 2009**	**Final Safety Data Cut-off: 30 September 2010**
Mental status changes	3 (0.2)	3 (0.2)	3 (0.2)
Drug toxicity	3 (0.2)	3 (0.2)	5 (0.4)
Overdose	3 (0.2)	3 (0.2)	3 (0.2)
Abdominal pain	3 (0.2)	3 (0.2)	3 (0.2)
Diarrhea	3 (0.2)	3 (0.2)	3 (0.2)
Nausea	3 (0.2)	3 (0.2)	4 (0.3)
Vomiting	3 (0.2)	3 (0.2)	4 (0.3)
Fatigue	3 (0.2)	3 (0.2)	3 (0.2)
Urinary tract infection	3 (0.2)	3 (0.2)	3 (0.2)
Renal colic	3 (0.2)	3 (0.2)	3 (0.2)
Cholelithiasis	3 (0.2)	3 (0.2)	3 (0.2)
Transaminases increased	3 (0.2)	3 (0.2)	3 (0.2)
Vertigo	3 (0.2)	3 (0.2)	3 (0.2)
Head injury	2 (0.1)	3 (0.2)	3 (0.2)
Suicidal ideation	2 (0.1)	2 (0.1)	3 (0.2)
Non-cardiac chest pain	2 (0.1)	2 (0.1)	3 (0.2)
Ankle fracture	1 (<0.1)	1 (<0.1)	2 (0.1)
Partial seizures	1 (<0.1)	1 (<0.1)	2 (0.1)
Radius fracture	1 (<0.1)	1 (<0.1)	2 (0.1)
Lobar pneumonia	1 (<0.1)	1 (<0.1)	2 (0.1)
Deep vein thrombosis	1 (<0.1)	1 (<0.1)	2 (0.1)

Note: those events highlighted in gray have a higher incidence than 120-Day SU.
a. For Patient 303-14-001416: the AE of confusional state was recorded as serious in the ISS data, but in the updated 120-day 303 dataset, the AE of confusional state was recorded to be not serious.
b. For Patient 304-040113: the AE of epilepsy occurred at the time of transitioning from Study 302 to 304. After queries, several terms were collapsed to reflect "increase seizure worsening" which had been reported just prior to beginning Study 304.
c. As pregnancy was not considered an SAE per protocol, the coding for 2 patients was changed in the dataset. Thus, there are 2 fewer pregnancies reported as SAEs in the FSU.

The sponsor table (above) indicates 13 SAEs occurred during the interval of the FSU. A search of the AE.xpt database of the FSU identifies 20 patients reporting TESAEs. 12 of these twenty patients had no prior report of SAEs in the AE.xpt dataset from the 120 day Safety Update of the initial NDA submission. Eight patients had prior SAEs identified. One patient, in study 303, case 5203 had an SAE of lobar pneumonia on 9/11/2009, which is before the interval of the FSU, however this report is included in the sponsor narratives of "SAEs in Clinical Pharmacology and All Phase II/III Studies". The reviewer speculates that this may be the 13th case noted in the sponsor total of first SAE reports. A table of the twenty patients reporting SAEs in FSU interval is included below (table 13).

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Table 13 Tabular presentation of SAEs in the "All Phase II/III Group" FSU Interval

Tabular presentation of SAEs in the "All Phase II/III Group" Final Update Interval								
Subject ID	SAE 1st or previous event	Age	SEX	Treatment duration	Dose	PT (not all reported same date)	Comment	Special interest
112	First	23	F	1389	900	APPENDICITIS PERFORATED		N
1101	First	62	M	1412	1200	LUMBAR RADICULOPATHY		N
5203	*	58	M	1000	1050	LOBAR PNEUMONIA	Had UR in initial review on PBO, Lobar pneumonia on	N
5405	First	59	F	851	1200	RADIUS FRACTURE		N
15203	First	40	M	878	1200	DRUG TOXICITY	may be related to ezo, patient also on PHT, VPA , levels non-toxic, may be due to patient medication error. Symptoms resolved with dose unchanged in hospital.	N
20216	First	30	F	964	1200	ANKLE FRACTURE	fx due to fall, no CNS effects reported, no seizure	N
25106	First	56	M	1114	1200	PSYCHOTIC DISORDER	underlying brain injury, dyscontrol	Y
25205	First	42	M	1162	1200	STATUS EPILEPTICUS	concomitant PHT levels low Y	Y
25504	First	52	F	1158	1200	PSYCHOTIC DISORDER / SUICIDAL IDEATION	psychotic symptoms and suicidality after 3 years on treatment, an indication that widow of risk is not confined to drug initiation. Pt at higher risk due to prior (no dx) psychiatric dysfunction	Y
25506	First	47	M	728	750	HALLUCINATION / DEEP VEIN THROMBOSIS / PNEUMONIA MYCOPLASMAL	hallucination is an event of interest, not an AE term for this patient. No report of blood dyscrasia	Y
70205	First	55	M	1212	600	RIB FRACTURE	unrelated	N
90505	First	60	M	984	900	ACUTE ABDOMEN	hospitalization but no intervention, possible cholelithiasis, discharged and remained on ezogabine	N
90515	First	37	F	870	900	UPPER LIMB FRACTURE	tripped and fell, fx arm, remained on ezogabine	N
10206	Prior	50	F	1519	1200	DRUG TOXICITY	multimodal CNS adverse effects due to AED polypharmacy	N

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25201	Prior	36	M	1250	900	INTERVERTEBRAL DISC PROTRUSION		N
25203	Prior	29	F	1022	?	GRAND MAL CONVULSION	seizure occurred the day following ezo cessation (abrupt)	Y
25406	Prior	49	F	1207	900	NON-CARDIAC CHEST PAIN		N
30401	Prior	47	F	1505	?	CONVULSION	no case report	Y
40405	Prior	45	M	1177	950	DIZZINESS, NAUSEA, CONVULSION, VOMITING,	A mix of seizures and AED adverse effects during concomitant AED changes.	Y
40901	Prior	65	F	1184	600	PARTIAL SEIZURES, GRAND MAL CONVULSION, DEPRESSED LEVEL OF CONSCIOUSNESS	Withdrew from study due to fatigue, seizure breakthrough following this long treatment interval is of uncertain relation to the ezogabine treatment.	Y
50302	Prior	46	F	1038 -1084	1050	STATUS EPILEPTICUS, PAIN IN EXTREMITY, PERIPHERAL ISCHEMIA	interval of status epileptics after approximately 2.2 years of stable dose. The relation to the status episode is unclear and cannot be differentiated from the natural history of the patient epilepsy	Y

*9/11/2009 report in AE dataset did not include lobar pneumonia, not present after dataset cut off but present in sponsor narratives.

Clinical Pharmacology Studies

Study RTG114137

In Study RTG114137, **1 subject** (Subject 32) had an SAE of psychotic disorder approximately 3 weeks after beginning ezogabine. This subject did recount an impulsive suicide attempt 14 years before during a fight with his girlfriend. At a subsequent evaluation and there was some consideration of treating him for bipolar disorder. This case was included in the initial ezogabine NDA medical review page 172.

RTG113214

There were no SAEs in this study

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RTG113215

Two subjects reported serious adverse events in this study. One in part A and one in Part B.

Subject 15103

This subject a 29 year old male was participating in Part A of the study. Part A was a single dose study of 480mg MR release formulation and one dose of ezogabine IR 400mg, in sequence with 5 to 7 day washout. This event occurred following the 5th dose of ezogabine, 28 days after the start of study drug. The subject developed severe acute confusional state and moderate amnesia. The events are stated to be disabling. On examination by the investigator the subject was unresponsive to verbal commands and appeared pale. Blood pressure and 12 lead ECG were normal. The subject was placed on telemetry and repeat ECGs were within normal limits. The patient recovered from the event in 5 to 10 minutes with partial amnesia. The amnesia resolved after approximately one hour. The subject was re-examined three hours post dose and appeared normal and answered all questions appropriately. At that the subject stated he only remembered people were surrounding him and had partial understanding of their questions but was unable to answer. The subject was kept an extra night for observation. The subject was discharged from the unit the following day in stable condition. The patient was on no concomitant medications, and had no past medical or family history of neurologic disorders.

At the time of this event the patient had received his 5th and final dose out of a sequence of five doses of ezogabine. The first four doses of ezogabine were each 480mg MR release formulations. These were administered approximately once weekly followed by a 1 week washout period. The 5th dose was a 400mg IR formulation and as noted the event occurred 24 minutes after administered with duration of approximately one hour.

Subject 15602

This subject, a 34 year old male was participating in part B of the study. In part B there is multiple dose treatment with ezogabine with dose escalation. The subject had received ezogabine for 17 days and achieved a dose of 480mg BID when he developed nausea, vomiting and dark stools (but did not report the events). Laboratory studies 3 days later revealed hemoglobin of 8.5mg/dl (normal range 12.5 - 16.5) and hematocrit result of 26.9% (normal range 37.5 - 49.5). Repeat results on [redacted] (b) (6) revealed hemoglobin 8.2 mg/dl and hematocrit 26.0% (an AE of “anemia” was entered) . The subject was questioned after the decreased hemoglobin and hematocrit was noted. Treatment with study drug was

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discontinued on 24 May following the 8:00 am dose and the subject was withdrawn from the study. He was sent to the ER for evaluation and admitted to the hospital with possible GI bleed on (b) (6).

Subsequently the subject was hospitalized and hemoglobin and hematocrit had further dropped to 7.7 mg/dl and 24.5%, respectively. The subject was found on endoscopy to have a clean based duodenal ulcer with no active bleeding. Biopsies were positive for *Helicobacteria pylori* and chronic inflammation. Subject received omperazole, amoxicillin trihydrate, pantoprazole, clarithromycin and sodium chloride for *H.pylori* treatment. His hemoglobin and hematocrit result climbed to 9.4 mg/dl and 29.8% during his hospitalization and in the days following his endoscopy. He did not require a transfusion.

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Reviewer Comment (All Phase II/III Group and Clinical Pharmacology Studies)**:** no notable spike in SAE frequency overall or indication of a previously unobserved signal of serious adverse events in this safety database update. One notable case of psychotic symptoms occurred in a healthy volunteer in the urine handling study RTG114137, this case was reported in the safety review of the initial NDA submission and is noted hear for completeness but does not contribute new insight into the ezogabine risk profile. The SAE of subject 15103 in the modified release formulation study has features that may be due to a complex partial seizure and subsequent post ictal state. This subject had only 4 prior doses of ezogabine spread over an interval of 28 days, leaving little opportunity to accommodate to the drug. The nature of this event is uncertain; it may have been an interval of drug induced central nervous system depression or alternatively a non-motor complex partial seizure with post ictal state.

7.3.3 Dropouts and/or Discontinuations

All Phase II/III Group

During the FSU reporting period, a total of 17 patients withdrew due to adverse events bringing the overall total to 454 (33%) patients and increase of 1.3% over the 120 day safety update of the initial NDA submission. The sponsor table below (table 14) shows the cumulative occurrence of study withdrawals by each safety interval and preferred term. The rows shaded in grey represent preferred terms associated with additional withdrawals in the FSU.

Table 14 Dropouts & Discontinuations, All Phase II/III Combined Group- number at each safety cutoff

	Number (%) of Patients		
	EZG Total (N=1365)		
Preferred Term	**ISS Integrated Data Cut-off: 30 June 2008**	**120-Day Safety Data Cut-off: 2 October 2009**	**Final Safety Data Cut-off: 30 September 2010**
Any event leading to Withdrawal	**418 (30.6)**	**437 (32.0)**	**454 (33.3)**
Dizziness	71 (5.2)	74 (5.4)	77 (5.6)
Somnolence	58 (4.2)	60 (4.4)	62 (4.5)
Confusional state	49 (3.6)	49 (3.6)	49 (3.6)

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Fatigue	43 (3.2)	45 (3.3)	49 (3.6)
Disturbance of attention	27 (2.0)	26 (1.9) a	27 (2.0)
Coordination abnormal	26 (1.9)	27 (2.0)	28 (2.1)
Tremor	25 (1.8)	25 (1.8)	25 (1.8)
Vertigo	24 (1.8)	24 (1.8)	24 (1.8)
Headache	23 (1.7)	23 (1.7)	23 (1.7)
Convulsion	22 (1.6)	22 (1.6)	22 (1.6)
Memory impairment	20 (1.5)	20 (1.5)	21 (1.5)
Speech disorder	17 (1.2)	18 (1.3)	18 (1.3)
Dysarthria	17 (1.2)	17 (1.2)	18 (1.3)
Nausea	15 (1.1)	17 (1.2)	17 (1.2)
Diplopia	16 (1.2)	16 (1.2)	16 (1.2)
Aphasia	16 (1.2)	16 (1.2)	16 (1.2)
Anxiety	13 (1.0)	14 (1.0)	14 (1.0)
Balance disorder	13 (1.0)	13 (1.0)	13 (1.0)
Psychotic disorder	13 (1.0)	13 (1.0)	15 (1.1)
Asthenia	13 (1.0)	13 (1.0)	13 (1.0)
Gait disturbance	13 (1.0)	13 (1.0)	13 (1.0)

Note: those events highlighted in gray have a higher incidence than the 120-Day SU.
a. For Patient 304-654-65403 the AE of disturbance of attention AE was recorded with an action of "withdrawal "for the ISS. The data for the 120 day update shows the same AE as action taken NONE.

Search of the AE.xpt database of the FSU identifies patients who withdrew in the reporting interval after 10/2/2009. These patients are shown in table 15. The sponsor narrative report reveals 1 additional patient who withdrew from the study, although the adverse event leading to withdrawal occurred before the FSU calendar interval.

Table 15 Clinical Details, Study Withdrawals from All Phase II/III entered during FSU interval

Clinical Details, Study Withdrawals from All Phase II/III entered during Final Safety Update interval								
Subject ID	**Withdrawal in Final or prior interval**	**Age**	**Sex**	**Duration on EZO**	**Dose at Withdrawal**	**Preferred term**	**Comment**	**Event of special interest**
10206	Final	50	F	1519	1200	DRUG TOXICITY	multimodal CNS adverse effects due to AED	NO

Reference ID: 2957637

Clinical Details, Study Withdrawals from All Phase II/III entered during Final Safety Update interval								
Subject ID	**Withdrawal in Final or prior interval**	**Age**	**Sex**	**Duration on EZO**	**Dose at Withdrawal**	**Preferred term**	**Comment**	**Event of special interest**
							polypharmacy	
20222	Final	33	F	805	1200	SUICIDAL IDEATION	Suicidal ideation, no prior psych history noted.	YES
25106	Final	56	M	1114	1200	PSYCHOTIC DISORDER	underlying brain injury, dyscontrol	YES
25504	Final	52	F	1158	1200	PSYCHOTIC DISORDER, SUICIDAL IDEATION	Psychotic symptoms and suicidality after 3 years on treatment, an indication that widow of risk is not confined to drug initiation. Pt at higher risk due to prior (no dx) psychiatric dysfunction	YES
50302	Final	46	F	1084	1050	STATUS EPILEPTICUS, DIZZINESS	interval of status epileptics after approximately 2.2 years of stable dose. The relation to the status episode is unclear and cannot be differentiated from the natural history of the patient epilepsy	YES
60205	Final	36	F	1336	?	PREGNANCY	normal birth reported but perinatal Fetoplacental insufficiency.	NO
3303	Prior	28	F	280	1050	FATIGUE	persistent fatigue	NO
25506	Prior	47	M	620	750	HALLUCINATION	anxiety noted as medical history in 1998	YES
40119	Prior	58	F	165	600	DIZZINESS	may have withdrawn due to unsatisfactory response	NO
40127	Prior	60	M	230	1050	AMNESIA	persistent poor memory, unsatisfactory response	NO
40138	Prior	33	M	127	?	BRADYPHRENIA, DIZZINESS, PALPITATIONS, TIC, FATIGUE	occasional tic, generalized CNS toxicity symptoms	NO
40901	Prior	65	F	979	600	FATIGUE	Withdrew from study due to fatigue, seizure breakthrough following this long treatment interval is of uncertain relation to the ezogabine treatment.	NO
50119	Prior	24	F	411	1200	SOMNOLENCE	persistent somnolence	NO
65407	Prior	63	M	485	600	SOMNOLENCE	persistent somnolence	NO
80108	Prior	42	F	53	750	DISTURBANCE IN	some improvement over time but insufficient	NO

Reference ID: 2957637

Clinical Details, Study Withdrawals from All Phase II/III entered during Final Safety Update interval								
Subject ID	**Withdrawal in Final or prior interval**	**Age**	**Sex**	**Duration on EZO**	**Dose at Withdrawal**	**Preferred term**	**Comment**	**Event of special interest**
						ATTENTION, MEMORY IMPAIRMENT, COGNITIVE DISORDER, DYSPHASIA	to remain on ezogabine treatment	
90207	Prior	43	F	475	1200	AMNESIA	short term memory loss, resolved with dechallenge	NO

Clinical Pharmacology Studies

RTG 114137

Table 16 RTG 114137 Study Withdrawals

RTG 114137 Study Withdrawals						
Subject	Dose at Withdrawal	Event	SAE	comment	CNS	Psychotic symptoms
1	900	Dysarthria, confusional state, immobility	No	45 m yo on 750mg EZO. 10 minutes after receiving the Day 21 evening dose, the subject was reported to have developed a short episode of dysarthria, followed 31 minutes later by confusional state, and inability to move. These events resolved within the hour The patient resumed treatment the following day without a similar episode however he was subsequently withdrawn from study.	Y	
4	900	Drug hypersensitivity (allergic reaction to	No	47 yo f, 20 days after starting, at a dose of 750mg/ day patient reported headache, on day 23 patient developed allergic reaction- content of allergic reaction not provided but responded to	N	

Reference ID: 2957637

RTG 114137 Study Withdrawals						
Subject	Dose at Withdrawal	Event	SAE	comment	CNS	Psychotic symptoms
		study drug), headache		acetaminophen and diphenhydramine.		
9	300	Urticaria	No	42 yo Asian f, developed urticarial rash and was discontinued. No data on rash resolution.	N	
10	750	Asthenia, altered state of consciousness	No	44 yo caucasian m, developed an episode of altered consciousness and weakness on day 20 of treatment, 22 minutes after the evening dose of 250mg. The event resolved in 42 minutes.	Y	
14	600	Confusional state, dysarthria, dizziness	No	53 yo caucasian f developed intermittent confusional state on day 10 of treatment on hour after 200mg dose. Treatment continued but 2 days later an episode of dysarthria occurred 1 hour after 200mg dose, duration 11 minutes, and then resolved. The following day 1 hour after 200mg dose developed intermittent dizziness. Intermittent confusion, dizziness continued until withdrawal 19 days after start treatment. Resolution on day 20.	Y	
15	600	Dizziness	No	57 yo caucasian f, developed dizziness on day 8 after 200mg morning dose.	Y	
28	600	Influenza-like illness	No	45 yo m developed flu like illness 9 days into treatment on 600mg EZO/day. Subsequently subject found to have gonococcal urethritis.	N	
30	600	Increased hepatic enzyme	No	43 yo African American male developed flu like illness and elevation of hepatic transaminases 12 days after start of EZO. Max ALT 3 x ULN, Max AST 5 x ULN. Total Bili remained WNL.	N	
32	900	Psychotic disorder	Yes	Acute psychosis, day 24, 40 minutes after 300mg dose. Discussed in initial NDA safety review		Y

RTG113214

Reference ID: 2957637

There were no treatment-emergent adverse events (TEAEs) leading to withdrawal in this study

RTG113215

Study RTG113215, 2 subjects reported an AE leading to withdrawal in Part A and total of 7 subjects reported an AE leading to withdrawal in Part B, see section 7.1.1 for patient ezogabine dosing.

Table 17 RTG113215 Adverse Events Leading to Study Withdrawal

RTG113215 Adverse Events Leading to Study Withdrawal						
Subject	Daily Dose at Withdrawal	Event	SAE	comment	CNS	Psychotic symptom
15103	400mg IR	Confusion , amnesia	Y	Severe confusional state- fully discussed in section 7.3.2	Y	
15116	480mg MR	Viral syndrome	N	Viral syndrome	N	
15602	1280mg	Duodenal ulcer	Y	Duodenal ulcer, fully discussed in 7.3.2	N	
15610	640mg	Rash	N	Mild generalized rash	N	
15613	1280mg	Somnolence / confusion	N	55 yo African American f ,22 days after start of ezogabine experienced somnolence and confusion after her evening dose of study drug. Both symptoms resolved in 3 days	Y	
15614	960mg	Confusion, paranoid thinking, auditory hallucination	N	30 yo African American f, developed episodes of confusion, intermittent paranoid thinking and auditory hallucination. The first event of confusion preceded the paranoid thinking and hallucination. The paranoid thinking developed 14 days after start of ezogabine treatment, on 960mg daily.		Y
15617	960mg	Auditory hallucination, paranoia, anxiety, dizziness	N	30 yo caucasian f developed episodes of dizziness and anxiety beginning on day 10 of ezogabine treatment while on 640mg / day, 19 days after start of ezogabine the		Y

Reference ID: 2957637

RTG113215 Adverse Events Leading to Study Withdrawal						
Subject	Daily Dose at Withdrawal	Event	SAE	comment	CNS	Psychotic symptom
				patient began experiencing intermittent auditory hallucinations a few hours after study drug dosing. This event was followed 30 minutes later by paranoid feelings and an hour later by anxiety. All symptoms resolved within two days.		
15618	320mg	Anxiety	N	39 yo m developed Anxiety 4 days after beginning ezogabine	Y	N
15633	640mg	Rash	N	22 yo m developed generalized pruritis 9 days after beginning ezogabine and generalized rash 2 days later. Rash resolved in 4 days	N	N

Reviewer Comment: In the "All Phase II/III Combined Grouping", compassionate use study and clinical pharmacology studies contributing to the FSU there were 35 adverse events leading to study withdrawal. Eighteen (18) of these were due to a range of central nervous system adverse (CNS) effects, 6 due to psychotic symptoms (although a CNS effect it is reported as a distinct event), and 3 due to rash.

In the multiple dose Clinical Pharmacology Studies there were 65 participating healthy subjects. Sixteen of these subjects experienced adverse events leading to study withdrawal. Six events were due to CNS adverse effects, 3 due to psychotic symptoms and 3 due to rash.

The profile of adverse events leading to withdrawal is similar to those in the initial NDA submission with predominance of CNS and psychiatric symptoms. The occurrence of psychotic symptoms in healthy subjects participating in the clinical pharmacology studies indicates that ezogabine may produce these adverse effects independently of a background central nervous system disorder or concomitant anticonvulsant medications. The dosage escalation was more rapid in the clinical pharmacology studies than in labeling, which underscores the increased risk for psychiatric adverse events in accelerated dose escalation.

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7.3.4 Significant Adverse Events

Adverse events are not pooled in this section in this review.

7.3.5 Submission Specific Primary Safety Concerns

Renal and Urinary Disorders

All Phase II/III Group

During the FSU reporting period, 13 patients reported renal/urinary TEAEs for the first time bringing the overall total to 364 (27%). There were no new SAEs or TEAEs leading to withdrawal during the FSU interval.

These new reports occurred under the following preferred terms: 7 reports “urinary tract infection”, 3 reports “ urinary hesitation”, 2 reports, “dysuria”, 3 reports “urinary retention”, 1 report “Hematuria”, 1 report, “chromaturia”, 2 reports “Leukocyturia”, 1 report “Nephrolithiasis”, 1 report “Urine flow decreased” ,

Voiding Dysfunction and Urinary Retention

During the FSU reporting period, 8 patients reported voiding dysfunction and urinary retention-related TEAEs for the first time bringing the overall total to 126 (9%); 3 patients reported urinary hesitation, urinary retention, and micturition urgency for the first time; 1 patient reported urinary incontinence, benign prostatic hyperplasia, and bladder pain for the first time. These are shown in the sponsor table below (table 18).

Table 18 Adverse Events of Voiding Dysfunction and Urinary RetentionReported in 2 or More Patients or Increasing From the ISS (Safety Population: All Phase II/III Combined)

Preferred Term	Number (%) of Patients EZG (N=1365)

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	ISS Integrated Data Cut-off: 30 June 2008	120-Day Safety Data Cut-off: 2 October 2009	Final Safety Data Cut-off: 30 September 2010
Any event	**115 (8.4)**	**118 (8.6)**	**126 (9.2)**
Urinary hesitation	42 (3.1)	42 (3.1)	45 (3.3)
Urinary retention	26 (1.9)	26 (1.9)	29 (2.1)
Residual urine volume	15 (1.1)	16 (1.2)	16 (1.2)
Urine flow decreased	8 (0.6)	8 (0.6)	9 (0.7)
Micturition frequency decreased	6 (0.4)	6 (0.4)	6 (0.4)
Urinary incontinence [a]	6 (0.4)	5 (0.4)	6 (0.4)
Oliguria	5 (0.4)	5 (0.4)	5 (0.4)
Bladder disorder	4 (0.3)	4 (0.3)	4 (0.3)
Micturition disorder	4 (0.3)	4 (0.3)	4 (0.3)
Micturition urgency	4 (0.3)	4 (0.3)	7 (0.5)
Bladder spasm	3 (0.2)	3 (0.2)	3 (0.2)
Hypertonic bladder	2 (0.1)	2 (0.1)	2 (0.1)
Neurogenic bladder	2 (0.1)	2 (0.1)	2 (0.1)
Strangury	1 (<0.1)	2 (0.1)	2 (0.1)
Benign prostatic hyperplasia	0	1 (<0.1)	2 (0.1)
Bladder pain	1 (<0.1)	1 (<0.1)	2 (0.1)
Note: those events highlighted in gray have a higher incidence than the 120-Day SU.			

Three new adverse events of urinary retention are noted during the FSU reporting interval. None of these are reported as serious adverse events or study withdrawals. One event, case 1506, narrative presented below, occurred in the initial submission 120 day safety update but is reported in the FSU. In order to identify the remaining two cases the adverse event datasets from the initial submission 120 day safety update and the FSU are compared to find reports of the AE term "urinary retention" that are present in the FSU but not in the 120 day safety update. Two are identified. First (patient 000801, study 303), a 47 year old male, has an event of "urinary retention" entered on (b) (6) Although this occurs in the NDA 22345 ISS (integrated summary of safety) interval the event is entered in the FSU. The event occurs on day 761 of ezogabine treatment on a dose of 1200mg / day. The second (patient 020110, study 303) and final reported event of "urinary retention" occurs in a 26 year old female on day 889 of ezogabine treatment at a dose of 1200mg / day.

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In one entry of urinary retention the report is noted to be of severe intensity. This patient was presented in the initial NDA submission 120 day safety update as an SAE due to splenic hemorrhage. In addition, urinary retention had occurred 14 days prior to the splenic hemorrhage and was not considered as an SAE at the time of occurrence and was not discussed in the splenic hemorrhage SAE narrative. The urinary retention was considered a severe event and the splenic hemorrhage SAE narrative is updated in the FSU to include the urinary retention. In addition this case of urinary retention was not captured in the listing of PVR (post void residual) values associated with patients who had a PT of "urinary retention" (table 69- initial submission review). The only PVR available was at baseline, approximately 2 years and 4 months before the adverse event of urinary retention. A brief update narrative is presented below.

Patient 303-01506: a 20-year-old Caucasian male taking ezogabine 900 mg/day in combination with other AEDs. On 06 Sep 2009 (Day 845), the patient reported urinary retention of severe intensity. As a result a Foley catheter was inserted. On (b) (6) the patient was diagnosed with splenic hemorrhage during a visit to the emergency room on (b) (6). At that visit he requested his Foley catheter be removed. While hospitalized for the event of splenic hemorrhage, a consultation request was placed with urology. In addition, the hospital recommended obtaining the patient's past urology records to review the evaluation resulting in the need for the urethral catheter. The urologist added Flomax to help him with the urinary retention. While hospitalized, the catheter was left in place. Neither PVR ultrasound nor AUA symptom index at the time of the event were obtained. Following the hospitalization, the patient's urinary catheter was removed and the event of urinary retention resolved on 01 Oct 2009 (Day 870). The patient continued in the study. The investigator assessed urinary retention as non serious and probably related to the study medication.

American Urological Association (AUA) Symptom Index

Shift Table

The AUA symptom index reveals that 121/664 (18%) patients with AUA SI scores in the "mild" range at baseline had shifts to "moderate" or "severe" post-baseline. This shift compares to 108 of 664 (16%) patients who had a shift from "mild" at baseline to moderate or severe post baseline at the 120 day safety update.

Post-Void Residual Volume

During the FSU reporting period, Post-Void Residual Volume (PVR) values of potential clinical concern (PCC) were reported for 15 patients post-baseline bringing the overall total to 70/642 (11%). Nine of these 15 new patients with PVR in the range of PCC had PVR values of potential clinical concern at baseline.

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Reviewer Comment: In the "All Phase II/III Combined Grouping" new reports of voiding dysfunction occur in this reporting interval. At this point in the open label extension studies these patients have been on ezogabine treatment for an extended period of time. The events of "urinary retention" occur in three patients after treatment for 761 days, 845 days and 889 days, in two male and one female patient. One male patient is 20 years old and the female patient is 26 years old. These two patients are unlikely to have pre-existing cause for urinary retention. There were also three new events of "urinary hesitation" and one new event of urine flow decreased. The events of "urinary retention" support the concern that there is persistent risk of voiding dysfunction after ezogabine treatment for several years.

Urinary Tract Infections and Related Signs and Symptoms

During the FSU reporting period, 7 patients reported urinary tract infection (UTI) -related TEAE for the first time bringing the overall total to 202 (15%), shown in the sponsor table below (table 19). Rows highlighted in grey indicate preferred terms with an increase during the FSU.

Table 19 Adverse Events of Urinary Tract Infections and Related Signs and Symptoms Reported in 2 or More Patients (Safety Population: All Phase II/III Combined)

Preferred Term	Number (%) of Patients EZG (N=1365)		
	ISS Integrated Data Cut-off: 30 June 2008	120-Day Safety Data Cut-off: 2 October 2009	Final Safety Data Cut-off: 30 September 2010
Any event	**191 (14.0)**	**195 (14.3)**	**202 (14.8)**
Urinary tract infection	105 (7.7)	107 (7.8)	114 (8.4)
Urine analysis abnormal	35 (2.6)	35 (2.6)	35 (2.6)
Dysuria	31 (2.3)	31 (2.3)	33 (2.4)
Leukocyturia	12 (0.9)	13 (1.0)	15 (1.1)
Cystitis	8 (0.6)	10 (0.7)	11 (0.8)
Bacteriuria	7 (0.5)	7 (0.5)	8 (0.6)
Bacteria urine	5 (0.4)	5 (0.4)	5 (0.4)
Bacteria urine identified	4 (0.3)	4 (0.3)	4 (0.3)
Kidney infection	2 (0.1)	2 (0.1)	2 (0.1)

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Pyelonephritis	2 (0.1)	2 (0.1)	2 (0.1)
Urinary tract infection bacterial	2 (0.1)	2 (0.1)	2 (0.1)
Urethral pain	2 (0.1)	2 (0.1)	2 (0.1)
Urinary tract pain	2 (0.1)	2 (0.1)	2 (0.1)
White blood cells urine	2 (0.1)	2 (0.1)	2 (0.1)
Asymptomatic bacteriuria	1 (<0.1)	1 (<0.1)	2 (0.1)
Note: those events highlighted in gray have a higher incidence than the 120-Day SU.			

Reviewer Comment: In the "All Phase II/III Combined Grouping" the risk of urinary tract infection is persistent through long duration ezogabine treatment. Similar to the observations of the initial NDA submission, the event of urinary tract infection is frequent.

Urinary Crystals and Nephrolithiasis

During the FSU reporting period, 1 patient (nephrolithiasis, Patient 303- 20212) reported a urinary crystal event for the first time. An event reported during the ISS reporting period had been overlooked and is reported here also (microlithiasis, Patient 303-20214). These 2 events bring the total or urinary crystal events to 25 (2%), see sponsor table below (table 20).

Table 20 Adverse Events Relating to Urinary Crystals Reported in Any Treatment Group (Safety Population: All Phase II/III Combined)

Preferred Term	Number (%) of Patients EZG		
	(N=1365)		
	ISS Integrated Data Cut-off:	120-Day Safety Data Cut-off:	Final Safety Data Cut-off:
	30 June 2008	2 October 2009	30 September 2010
Any event	**22 (1.6)**	**23 (1.7)**	**25 (1.8)**
Nephrolithiasis	9 (0.7)	10 (0.7)	11 (0.8)
Renal colic	7 (0.5)	7 (0.5)	7 (0.5)
Crystalluria	2 (0.1)	2 (0.1)	2 (0.1)
Crystal urine present	2 (0.1)	3 (0.2)	3 (0.2)

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Urine analysis abnormal	2 (0.1)	2 (0.1)	2 (0.1)
Calculus ureteric	1 (<0.1)	1 (<0.1)	1 (<0.1)
Crystal urine	1 (<0.1)	1 (<0.1)	1 (<0.1)
Microlithiasis	0	0	1 (<0.1)
Note: those events highlighted in gray have a higher incidence than the 120-Day SU.			

Reviewer Comment: In the "All Phase II/III Combined Grouping" during the FSU there is only one additional event related to urine crystal formation. This is not entered as an SAE or withdrawal, no additional information is available.

Clinical Pharmacology Studies (all Renal and Urinary Disorders)

Study RTG114137

The Renal – Urinary adverse events in study RTG114137 were 6 cases of chromaturia and two cases of Pollakiuria.

Study RTG113214

There were no adverse events of "Renal and Urinary Disorders" in this single dose study with maximum dose of 400mg, 5 day washout between dose.

Study RTG113215

All Renal / Urinary events occurred in part B of this study. In review, Part B was a multiple ascending dose study of 5 week duration with maximum dose 1280mg / day, whereas Part A was a single dose study with each dose followed by a 5 to 7 day washout. There were a total of 18 Renal / Urinary events which occurred in 10 unique patients. The adverse events are shown in the table 21. Urinary hesitation, a manifestation of voiding dysfunction will be examined in detail. The occurrences of urinary hesitation occurred across a range from low to high dose. Six patients, 3 male and 3 female experienced 7 events of urinary hesitation Two subjects had urinary hesitation at 320mg daily, 1 at 640mg daily, 2 at 960mg daily and 1 at 1280mg daily. The mean age of subjects with urinary hesitation was 38.5 years with 5 patients younger than 40 years and one 23 year old male.

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Table 21 Subjects in Study RTG113215 with adverse events of "Renal and Urinary Disorders"

Subjects in Study RTG113215 with adverse events of "Renal and Urinary Disorders"				
Subject ID	age	Sex	PT (preferred term)	Treatment Group
15611	27	M	Chromaturia	1 x 320mg qd
15619	45	M	Chromaturia	1 x 320mg bid
15626	39	M	Dysuria	1 x 200mg IR tid (Group 2)
15630	38	F	Dysuria	1 x 480mg bid
15626	39	M	Micturition frequency decreased	1 x 160mg bid
15619	45	M	Pollakiuria	1 x 320mg bid
15620	40	M	Pollakiuria	1 x 160mg bid
15620	40	M	Pollakiuria	1 x 320mg bid
15606	23	M	Urinary hesitation	1 x 320mg qd
15613	55	F	Urinary hesitation	1 x 480mg bid
15616	39	F	Urinary hesitation	1 x 640mg bid
15616	39	F	Urinary hesitation	4 x 160mg bid
15624	37	M	Urinary hesitation	1 x 160mg bid
15626	39	M	Urinary hesitation	1 x 480mg bid
15630	38	F	Urinary hesitation	1 x 320mg bid
15632	26	M	Urine odour abnormal	1 x 320mg qd

Reviewer Comment: In the clinical pharmacology studies the most frequent Renal / Urinary events occur in the longest duration study with the highest maximum dose (Study RTG113215). The majority of Renal / Urinary events were in the category of voiding dysfunction. There were 7 events of urinary hesitation and one event of "micturition frequency decreased". There were two events of dysuria. These events occurred in healthy volunteers and are consistent with prior observations in ezogabine treatment but also demonstrate the events of voiding dysfunction are no restricted to the epilepsy population.

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Hallucinations and Psychosis

All Phase II/III Combined Grouping:

During the FSU reporting period, there were 4 patients who had not previously reported a hallucination/psychosis-related TEAE through the 120-Day reporting period reported a hallucination/psychosis-related TEAE. Two of these events were SAEs. When combined with the 85 patients who reported hallucination/psychosis-related TEAEs through the 120-Day reporting period, a total of 89 (7%) patients reported hallucination/psychosis-related TEAEs. During the FSU reporting period, 2 patients reported psychotic disorder for the first time, while hallucination; hallucination, visual; and delusion were reported by 1 patient each for the first time. See table 22.

SAEs

The two "hallucination and psychosis" SAEs occurred in Patient 304-25106 and Patient 304-25504. When combined with the 19 patients who reported hallucination/psychosis-related TESAEs through the 120-Day reporting period, a total of 21 (2%) patients reported hallucination/psychosis-related TEAEs. Brief narratives for these patients are provided below.

Patient 304-25504: a 52-year-old Caucasian female with a previous event of acute psychological dysfunction was receiving 1200 mg/day of open-label ezogabine. She was admitted to the hospital on [redacted] (b) (6)) after 3 days of "bizarre" behavior and auditory hallucinations, diagnosed as psychosis with delusions and suicidal intent, which manifested as refusal to take antiepileptic medications and attempting to get run over by motor vehicles. There were no apparent seizures prior to or during this event, but a sleep-deprived electroencephalogram (EEG) was abnormal and consistent with potential localization -related epilepsy. Ezogabine was discontinued; the patient recovered and was discharged from the hospital on [redacted] (b) (6) The investigator assessed the events as life-threatening and probably related to the study medication. The suicidal intent was believed to be likely related to the pre-existing psychological dysfunction that had become aggravated with ezogabine.

Patient 304-25106, a 56-year-old Caucasian male with a history of anger control problems, acquired brain injury and intellectual impairment, was receiving 1200 mg/day of open-label ezogabine. He was first evaluated in March 2010 (~Day 1047) due to episodes of altered mental status. Over approximately 3 months, he had episodes of paranoia, auditory hallucinations, delusions and abnormal behavior. He was admitted on day [redacted] (b) (6) and transferred to a psychiatric long-term

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unit, where he demonstrated no further behavioral issues, anger, or confusion. Early tapering of ezogabine was begun on [redacted] (b) (6) and he was discharged on [redacted] (b) (6) The behavioral disturbances were considered to be mixed, with evidence of post-ictal delirium suggestive of seizure activity, with a likely depressive illness. The subject was lost to follow-up on 25 May 2010. Thus the outcome and the resolution date were unknown.

Table 22 Adverse Events of Psychosis and Hallucinations Reported by 2 or More Patients (Safety Population: All Phase II/III Combined)

Adverse Events of Psychosis and Hallucinations Reported by 2 or More Patients (Safety Population: All Phase II/III Combined)			
	Number (%) of Patients		
Preferred Term	**EZG (N=1365)**		
	ISS Integrated Data Cut-off: 30 June 2008	**120-Day Safety Data Cut-off: 2 October 2009**	**Final Safety Data Cut-off: 30 September 2010**
Any event	**83 (6.1)**	**85 (6.2)**	**89 (6.5)**
Hallucination	21 (1.5)	22 (1.6)	23 (1.7)
Psychotic disorder	17 (1.2)	17 (1.2)	19 (1.4)
Hallucination, visual	15 (1.1)	17 (1.2)	18 (1.3)
Hallucination, auditory	6 (0.4)	6 (0.4)	6 (0.4)
Agitation	6 (0.4)	6 (0.4)	6 (0.4)
Euphoric mood	6 (0.4)	6 (0.4)	6 (0.4)
Mood altered	6 (0.4)	6 (0.4)	6 (0.4)
Delusional disorder, persecutory type	3 (0.2)	3 (0.2)	3 (0.2)
Depersonalization	3 (0.2)	3 (0.2)	3 (0.2)
Paranoia	3 (0.2)	3 (0.2)	3 (0.2)
Delirium	2 (0.1)	2 (0.1)	2 (0.1)
Delusion	2 (0.1)	2 (0.1)	3 (0.2)

Clinical Pharmacology Studies

Reference ID: 2957637

Study RTG114137: There was one SAE and study withdrawal of a patient due to psychosis. This subject did recount an impulsive suicide attempt 14 years before during a fight with his girlfriend. At a subsequent evaluation and there was some consideration of treating him for bipolar disorder. This case was included in the initial ezogabine NDA clinical review page 172. There were two AEs due to hallucination.

Study RTG113214: There were no SAEs or AEs of "Hallucination and Psychosis" in this clinical pharmacology study.

Study RTG113215: Two patients experience adverse events of "Hallucination, auditory" and four patients had AEs of "hallucination, visual".

Reviewer Comment (All Phase II/III Group and Clinical Pharmacology Studies)**:** Two patients in the open label extension studies had SAEs due to psychotic symptoms, in one patient there was a positive dechallenge. In the clinical pharmacology studies one healthy control subject had an SAE due to psychotic symptoms (covered fully in the initial NDA safety review) also with a positive dechallenge.

In all of the clinical pharmacology studies 8 patients had adverse events of "hallucination", "hallucination, auditory" or "hallucination, visual". The occurrences of psychotic symptoms in the healthy subjects of the clinical pharmacology studies provides evidence that the underlying central nervous system pathology present in the epilepsy population is not necessary for to support these symptoms. Evidence of this phenomenon was also seen in the safety population of the initial NDA review.

Suicidality

During the FSU reporting period, a total of 2 patients who had not previously reported a TEAE related to suicidality through the 120-Day reporting period had suicidality-related TEAE (both reported suicidal ideation). When combined with the 10 patients who reported suicidality-related TEAEs through the 120-Day reporting period, a total of 12 (<1%) patients reported suicidality-related TEAEs, see sponsor table below (table 23). One of these episodes of suicidal ideation was considered a TESAE raising the total suicidality related SAEs to 10.

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Table 23 Completed Suicide, Suicidality, and Self-Injurious Behavior (Safety Population: All Phase II/III Combined)

Completed Suicide, Suicidality, and Self-Injurious Behavior (Safety Population: All Phase II/III Combined)			
	Number (%) of Patients		
Preferred Term	**EZG (N=1365)**		
	ISS Integrated Data Cut-off: 30 June 2008	**120-Day Safety Data Cut-off: 2 October 2009**	**Final Safety Data Cut-off: 30 September 2010**
Any event	**10 (0.7)**	**10 (0.7)**	**12 (0.9)**
Suicide attempt	2 (0.1)	2 (0.1)	2 (0.1)
Suicidal ideation	2 (0.1)	2 (0.1)	4 (0.3)
Overdose	4 (0.3)	4 (0.3)	4 (0.3)
Accidental overdose	2 (0.1)	2 (0.1)	2 (0.1)
Intentional overdose	1 (<0.1)	1 (<0.1)	1 (<0.1)

Both of the new events of suicidal ideation resulted in study withdrawal increasing the total to 6, the total number of cases withdrawn due to suicidality related events in the All phase II/III combined group.

The two update events of suicidal ideation are reviewed. The first (303-020222) is later denied by the patient and confounded by 3 concomitant AEDs. The second (304-25504), on day 1158 of ezogabine treatment was an episode with concurrent hallucinations with psychotic features and suicidal ideation. The content of the patient suicidal ideation was to discontinue anti-epilepsy treatment and attempt to get run over by motor vehicles on a highway. This second patient also had laboratory abnormalities during hospitalization which resulted from these behavioral changes. Out-of-range blood hematology and chemistry laboratory test results included C-reactive protein of 36 mg/L (n=<5.0), total bilirubin and conjugated bilirubin of 26 µmol/L (n=<20) and 17 µmol/L (n=<4) respectively, aspartate transaminase of 46 U/L (n=<31), and lymphocytes of 0.83 x 10^9/L (n=1-4) However no abnormalities of transaminases or bilirubin are noted before or in follow up to this episode. This patient is also included above in the discussion of "*Hallucinations and psychosis*".

Clinical pharmacology studies

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215- no events

214- no events

137- no events

Reviewer Comment (All Phase II/III Group and Clinical Pharmacology Studies)**:** The first case of suicidal ideation occurs while on three concomitant AEDs which confound causality. The second event of suicidal ideation appears to be associated with a concurrent medical illness. Suicidality is covered in current anticonvulsant class labeling.

Seizure Worsening and Status Epilepticus

All Phase II/III Group

There were 6 epilepsy related SAEs added during the FSU interval. These are shown in the table below. In three of the six events there are confounding actions occurring such as background AED changes or low background AED levels. One of the events has no case report in the submission (30401). The event of status epilepticus (50302) occurs approximately 2.2 years after beginning ezogabine treatment thus the natural history of this patient's epilepsy cannot be distinguished from an effect of ezogabine treatment. In all cases the epilepsy related events occur greater than 1000 days after starting ezogabine treatment and may represent the natural history of epilepsy.

During the FSU reporting period, 1 patient reported a seizure-related TEAE leading to withdrawal. The adverse event of status epileptics occurred after approximately 2.2 years of stable dose. The relation to the status episode is unclear and cannot be differentiated from the natural history of the patient epilepsy. See table 24.

Table 24 Tabular presentation of Epilepsy related SAEs in the "All Phase II/III Group", FSU Interval

Tabular presentation of Epilepsy related SAEs in the "All Phase II/III Group", Final Update Interval

Reference ID: 2957637

Subject ID	Age	SEX	Treatment duration	Dose	PT (not all reported same date)	Comment	SAE leading to Withdrawal
25205	42	M	1162	1200	STATUS EPILEPTICUS	concomitant PHT levels low	N
25203	29	F	1022	?	GRAND MAL CONVULSION	seizure occurred the day following ezo cessation (abrupt)	N
30401	47	F	1505	?	CONVULSION	no case report	N
40405	45	M	1177	950	DIZZINESS, NAUSEA, CONVULSION, VOMITING,	A mix of seizures and AED adverse effects during concomitant AED changes.	N
40901	65	F	1184	600	PARTIAL SEIZURES, GRAND MAL CONVULSION, DEPRESSED LEVEL OF CONSCIOUSNESS	Withdrew from study due to fatigue, seizure breakthrough following this long treatment interval is of uncertain relation to the ezogabine treatment.	N
50302	46	F	1038 -1084	1050	STATUS EPILEPTICUS, PAIN IN EXTREMITY, PERIPHERAL ISCHEMIA	Interval of status epileptics after approximately 2.2 years of stable dose. The relation to the status episode is unclear and cannot be differentiated from the natural history of the patient epilepsy	Y

The sponsor provides a comparative table of epilepsy related adverse events shown in the table below (table 25). Ten patients experienced epilepsy related events for the first time in the FSU interval. Four of these events were “convulsion”, 5 events were “tremor”, 2 were “status epilepticus”, 2 were “Grand mal convulsion”, and 2 were “Partial seizures”.

Table 25 Epilepsy related adverse events, all phase II/III

Preferred term	**Number (%) of patients Ezogabine N=1365**		
	ISS Integrated Data Cut-off: 30 June 2008	**120-Day Safety Data Cut-off: 2 October 2009**	**Final Safety Data Cut-off: 30 September 2010**
Any event	**186 (13.6)**	**197 (14.4)**	**207 (15.2)**
Convulsion	99 (7.3)	108 (7.9)	112 (8.2)
Myoclonus	19 (1.4)	19 (1.4)	19 (1.4)

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Tremor	15 (1.1)	15 (1.1)	20 (1.5)
Epilepsy	13 (1.0)	15 (1.1)	14 (1.0) [a]
Syncope	12 (0.9)	12 (0.9)	12 (0.9)
Complex partial seizures	10 (0.7)	10 (0.7)	10 (0.7)
Status epilepticus	8 (0.6)	8 (0.6)	10 (0.7)
Grand mal convulsion	7 (0.5)	8 (0.6)	10 (0.7)
Postictal state	4 (0.3)	4 (0.3)	4 (0.3)
Simple partial seizures	3 (0.2)	3 (0.2)	3 (0.2)
Epileptic aura	2 (0.1)	2 (0.1)	2 (0.1)
Loss of consciousness	2 (0.1)	2 (0.1)	2 (0.1)
Postictal headache	2 (0.1)	2 (0.1)	2 (0.1)
Partial seizures with secondary generalization	1 (<0.1)	2 (0.1)	2 (0.1)
Partial seizures	1 (<0.1)	1 (<0.1)	3 (0.2)

[a] For Patient 304-040113: the AE of epilepsy occurred at the time of transitioning from Study 302 to 304. After queries, several terms were collapsed to reflect "increase seizure worsening" which had been reported just prior to beginning Study 304.

Note: those events highlighted in gray have a higher incidence than the 120-Day SU.

Clinical Pharmacology Studies

Study RTG113214- no epilepsy related events occurred during the conduct of this study.

Study RTG113215 – The only epilepsy related terms that occurred in the adverse event dataset of this study were two events of tremor, one with a verbatim term of shakiness. Neither event was recorded as an SAE or study withdrawal.

There was also an event not recorded under an epilepsy related AE term. Subject 15103 had an event coded as "acute confusional state" and "amnesia" which had features which emulated a complex partial seizure and subsequent post ictal state. Highlights of the case narrative are presented in section 7.3.2. This event prompted a re-examination of the placebo controlled dataset for pro-convulsant signal, presented below prior to "Reviewer comment".

Study RTG114137- The only epilepsy related terms that occurred in the adverse event dataset of this study were two events of tremor. Neither event was recorded as an SAE or study withdrawal.

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Controlled Trial Dataset Re-examination

The observation of events experienced by subject 15103 in study RTG113215 prompts a re-examination of the placebo controlled dataset (studies 205, 301, 302) for an ezogabine related pro-convulsant safety signal. Convulsion is a common adverse event in the clinical trial database; in placebo controlled phase 2-3 trials the PT (preferred term) convulsion was more frequent in the placebo group compared to the ezogabine treatment group 4.4% and 3.8% respectively. A follow up examination of the controlled dataset to compare the frequency of a full profile (13 terms) of epilepsy related PTs between placebo and ezogabine treatment is performed. The following epilepsy related PTs are chosen for the search: convulsion, atonic seizure, epilepsy, myoclonic epilepsy, partial seizures, status epilepticus, tonic convulsion, complex partial seizures, psychomotor seizures, temporal lobe seizures, grand mal convulsion, petit mal epilepsy, generalized non-convulsive epilepsy. This search reveals that 21 (4.9%) of patients in the placebo group and 38 (4.7%) patients in the ezogabine treatment group experienced one of these epilepsy related events. The greater frequency of epileptiform events in the placebo group points away from a conclusion that ezogabine is pro-convulsant, however the potentially epileptiform event (subject 15103) in a healthy subject following a single, 400mg IR dose of ezogabine reinforces the need that patients follow the labeled titration schedule

Reviewer Comment (All Phase II/III Combined Grouping and Clinical Pharmacology Studies)**:** Epilepsy related events continue to occur in the long term open label studies. This is not unexpected in an epilepsy population; those events which occur are difficult to distinguish from the natural history of the underlying disease process. Re-examination of the controlled trial dataset is triggered by the observation of events experienced by subject 15103. In this re-examination, epileptiform events are identified using 13 epilepsy related terms. The pooled events captured by this search reveal a greater frequency of epileptiform events in the placebo group.

In the FSU there is no seizure type subset that appears to emerge in an increased frequency. Overall frequency of these events does not appear to change in the FSU interval compared to the 120 day safety update interval. There is one case of possible absence seizure in a healthy volunteer (15103 discussed in section 7.3.2) after his 5th dose of ezogabine where each single dose is separated by approximately 1 week. The first 4 doses were 480mg of a modified release form and the 5th dose was 400mg of ezogabine IR. This case triggers a concern for development of seizure like events following a high single dose in patients naive to ezogabine; however the true physiology of the event is unknown. This event reinforces the need that patients follow the labeled titration schedule

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Neutropenia and Severe Infections

All Phase II/III

One patient (study 303- 001101) experienced a first time AE of neutrophil count decreased in the FSU interval. This patient had no infection related adverse events. There were 9 unique patients who experienced 11 infection related adverse events. The majority of the infection related events were "urinary tract infections" 7/11 (63%). See sponsor comparative table of events by safety interval below (table 26). An additional 3 were preferred terms indirectly related to "urinary tract infections", and only one, a lobar pneumonia was an infection event not related to the urinary tract.

Table 26 Neutropenia or Infection Related Adverse Events in More than 2 Patients (Safety Population: All Phase II/III Combined)

Neutropenia or Infection Related Adverse Events in More than 2 Patients (Safety Population: All Phase II/III Combined)			
Preferred Term	**Number (%) of Patients EZG (N=1365)**		
Table 37	**ISS Integrated Data Cut-off: 30 June 2008**	**120-Day Safety Data Cut-off: 2 October 2009**	**Final Safety Data Cut-off: 30 September 2010**
Any event	**175 (12.8)**	**182 (13.3)**	**192 (14.1)**
Infection events			
Urinary tract infection	105 (7.7)	107 (7.8)	114 (8.4)
Pneumonia	13 (1.0)	15 (1.1)	15 (1.1)
Cystitis	8 (0.6)	10 (0.7)	11 (0.8)
Bacteriuria	7 (0.5)	7 (0.5)	8 (0.6)
Bronchopneumonia	3 (0.2)	3 (0.2)	3 (0.2)
Kidney infection	2 (0.1)	2 (0.1)	2 (0.1)
Lobar pneumonia	2 (0.1)	2 (0.1)	3 (0.1)
Primary pneumonia atypical	2 (0.1)	2 (0.1)	2 (0.1)
Pyelonephritis	2 (0.1)	2 (0.1)	2 (0.1)

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Urinary tract infection bacterial	2 (0.1)	2 (0.1)	2 (0.1)
Asymptomatic bacteriuria	1 (<0.1)	1 (<0.1)	2 (0.1)
Blood and Lymphatic events			
Leukopenia	19 (1.4)	20 (1.5)	20 (1.5)
Neutropenia	9 (0.7)	10 (0.7)	10 (0.7)
Investigations			
Bacteria urine	5 (0.4)	5 (0.4)	5 (0.4)
Bacteria urine identified	4 (0.3)	4 (0.3)	4 (0.3)
Hematology test abnormal	3 (0.2)	3 (0.2)	3 (0.2)
White blood cell count increased	3 (0.2)	3 (0.2)	3 (0.2)
Lymphocyte count decreased	2 (0.1)	2 (0.1)	2 (0.1)
Neutrophil count decreased	2 (0.1)	2 (0.1)	3 (0.2)
White blood cell count decreased	2 (1.1)	3 (0.2)	3(0.2)

The hematologic dataset of section 7.4.1 reveals there were 3 new unique patients in the FSU with cytopenias in the PCC range (potential clinical concern), two with leukopenia and one with neutropenia. None of these patients had an infection related adverse event.

Clinical Pharmacology Studies

RTG113214: one AE related to infection occurred in this study. A subject had an AE of “folliculitis”. There was no AE due to a blood dyscrasia related preferred term. The hematology dataset was examined. There were two patients with low reticulocytes, two patients with a low platelet count one with a low absolute neutrophil count. These counts are unlikely related to ezogabine due to the maximum five dose exposure over approximately one month.

RTG113215: There were 5 AEs in this study related to infection, 3 are noted to be viral infection, one pharyngitis and one folliculitis, none are entered as SAEs, one subject with viral infection had study drug withdrawn. There were no adverse events due to “Blood and lymphatic system disorder” SOC terms in the adverse event dataset.There were two patients who developed a low absolute neutrophil count and one who developed a low white blood cell count in the range of “potential clinical importance” during the study. These occurred in part B, the sustained multiple dose section of the study. These are show with study day and ezogabine dose in the table below (table 27).

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Table 27 Study RTG113215: Subjects with Hematologic Values of Potential Clinical Importance in Part B

Study RTG113215: Subjects with Hematologic Values of Potential Clinical Importance in Part B						
Subject #	Study Part / group	Treatment	Study Day	Hematologic Parameter (UNITS)	Value	Normal Range
15606	B/1	1 x 640mg QD	8	ANC (GI/L)	1.2	1.7 - 8.1
			14		1.0	1.7 - 8.1
		1 x 320mg + 1 x 640mg QD	21		1.1	1.7 - 8.1
			28		1.1	1.7 - 8.1
		1 x 640mg QD	8	WBC Count (GI/L)	2.6	4 - 10.8
			14		2.3	4 - 10.8
		1 x 320mg + 1 x 640mg QD	21		2.5	4 - 10.8
			28		2.6	4 - 10.8
15611	B/1	1 x 640mg QD	8	ANC (GI/L)	1.2	1.7 - 8.1
15621	B/1	Screening	0	ANC (GI/L)	1.4	1.7 - 8.1
		1 x 640mg QD	8		1.4	1.7 - 8.1
		1 x 640mg QD	14		1.4	1.7 - 8.1
		1 x 320mg + 1 x 640mg QD	21		1.3	1.7 - 8.1
		4 x 320mg QD	28		1.1	1.7 - 8.1
		4 x 320mg QD	28		1.1	1.7 - 8.1

Study RTG114137: Six subjects had AEs recorded for infection events. Three patients had entries for tinea pedis, and one each for folliculitis, rhinitis, and urethritis-gonococcal. None of these infection events was entered as an SAE and none were withdrawn from the study.

No subject had abnormal hematology values that were flagged as being of potential clinical importance (PCI) during the ezogabine/retigabine 300 mg, 450 mg, 600 mg and 900 mg treatment periods. During the 750 mg treatment period at Day 15 pre-dose, decreased lymphocyte counts were reported in two subjects (6%), decreased total neutrophil counts in three subjects (10%), a decreased platelet count in one subject (3%) and a decreased white blood cell count in one subject (3%). None of these values was considered clinically significant or reported as an AE.

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Reviewer comment (All Phase II/III Combined Grouping and Clinical Pharmacology Studies): The observations of infections and cytopenias in the FSU are similar in frequency and severity to those seen in the initial NDA safety review.

Cardiac Rhythm Abnormalities

All Phase II/III Combined

During the FSU reporting period, a total of 5 patients who had not previously reported a TEAE related to cardiac rhythm/conduction abnormalities through the initial submission 120-Day reporting period experienced a first time TEAE related to cardiac rhythm/conduction abnormalities. These five patients bring the total cardiac rhythm/conduction abnormalities to 121 (9%) events reported in this group through the FSU interval. None of the new cardiac rhythm/conduction abnormalities were reported as SAEs, 1 of the patients with a cardiac rhythm/conduction abnormality was withdrawn from the study. The event was "palpitations". Cardiac rhythm/conduction abnormalities are shown in the sponsor table below (table 28). Those preferred terms with new entries during the FSU are highlighted in grey.

During the FSU reporting period, no events related to QTc prolongation were reported.

Table 28 Cardiac Rhythm/Conduction Abnormalities Reported in at least 2 Patients (Safety Population: All Phase II/III Combined)

Cardiac Rhythm/Conduction Abnormalities Reported in at least 2 Patients (Safety Population: All Phase II/III Combined)			
	Number (%) of Patients		
Preferred Term	**EZG (N=1365)**		
	ISS Integrated Data Cut-off: 30 June 2008	**120-Day Safety Data Cut-off: 2 October 2009**	**Final Safety Data Cut-off: 30 September 2010**
Any Event	**111 (8.1)**	**116 (8.5)**	**121 (8.9)**
Chest pain	38 (2.8)	41 (3.0)	42 (3.1)
Palpitations	18 (1.3)	19 (1.4)	19 (1.4)
Syncope	12 (0.9)	12 (0.9)	12 (0.9)

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Chest Discomfort	6 (0.4)	6 (0.4)	6 (0.4)
ECG QT prolonged	4 (0.3)	4 (0.3)	4 (0.3)
Heart rate irregular	4 (0.3)	4 (0.3)	4 (0.3)
Tachycardia	3 (0.2)	4 (0.3)	5 (0.4)
Arrhythmia	2 (0.1)	2 (0.1)	2 (0.1)
AV Block first degree	2 (0.1)	2 (0.1)	2 (0.1)
AV Block second degree	2 (0.1)	2 (0.1)	2 (0.1)
Bradycardia	2 (0.1)	2 (0.1)	2 (0.1)
Sinus Bradycardia	2 (0.1)	2 (0.1)	3 (0.2)
Supraventricular tachycardia	2 (0.1)	2 (0.1)	2 (0.1)
Ventricular extrasystoles	2 (0.1)	2 (0.1)	4 (0.3)
ECG ST-T change	2 (0.1)	2 (0.1)	2 (0.1)
Heart rate increased	2 (0.1)	2 (0.1)	2 (0.1)
Loss of consciousness	2 (0.1)	2 (0.1)	2 (0.1)
Syncope vasovagal	2 (0.1)	2 (0.1)	2 (0.1)
Note: those events highlighted in gray have a higher incidence than the 120-Day SU.			

QT interval

Adverse events: There were no events of Torsades de pointes or Electrocardiogram QT prolonged in the “All Phase II/III” group during the FSU reporting period.

Table 29 Findings for QTc of Potential Clinical Concern (Safety Population: All Phase II/III Combined)

Findings for QTc of Potential Clinical Concern (Safety Population: All Phase II/III Combined)			
	Number of Patients/Number of Patients Evaluable (%)		
	RTG (N=1365)		
QTc Bazett’s	**ISS Integrated Data Cut-off: 30 June 2008**	**120-Day Safety Data Cut-off: 2 October 2009**	**Final Safety Data Cut-off: 30 September 2010**
Increase >30 msec from baseline	253/1213 (20.9)	272/1213 (22.4)	278/1213 (22.9)
Increase >30 msec and ≤60 msec from baseline	246/1213 (20.3)	265/1213 (21.8)	271/1213 (22.3)

Increase >60 msec from baseline	22/1213 (1.8)	22/1213 (1.8)	24/1213 (2.0)
Post-baseline ≥450 msec[a]	56/1213 (4.6)	63/1213 (5.2)	71/1213 (5.9)
Post-baseline ≥480 msec[a]	6/1213 (<1.0)[b]	6/1213 (<1.0)[b]	6/1213 (<1.0)[b]
Post-baseline ≥500 msec[a]	1/1213 (<0.1)[c]	1/1213 (<0.1)[c]	1/1213 (<0.1)[c]
QTc Fridericia's			
Increase >30 msec from baseline	198/1213 (16.3)	213/1213 (17.6)	218/1213 (18.0)
Increase >30 msec and ≤60 msec from baseline	196/1213 (16.2)	211/1213(17.4)	216/1213 (17.8)
Increase >60 msec from baseline	12/1213 (1.0)	12/1213 (1.0)	14/1213 (1.2)
Post-baseline ≥450 msec[a]	18/1213 (1.5)	20/1213 (1.6)	21/1213 (1.7)
Post-baseline ≥480 msec[a]	3/1213 (<1.0)[d]	3/1213 (<1.0)[d]	3/1213 (<1.0)[d]
Post-baseline ≥500 msec[a]	0	0	0

a. And baseline < this value or missing.
b. Three of these patients had PCC values at baseline.
c. This patient also had a PCC value at baseline.
d. One patient also had a high value at baseline.
Data are for any post-baseline finding. A patient may be counted more than once, if they had ECG parameters that met different criteria across various time points.

Using Fridericia's criteria in the FSU: (a patient may be counted more than once, as noted in the table above)

5 additional patients had an increase > 30msec from baseline.
5 additional patients had an increase >30 msec and ≤60 msec from baseline.
2 additional patients had an increase >60 msec from baseline.
1 additional patient had a post baseline QT ≥450 msec

Clinical Pharmacology Studies

Study RTG113214

Adverse events: There were no events of Torsades de pointes or Electrocardiogram QT prolonged during study RTG113214.

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ECG: No subject had a QTcF value greater than or equal to 450msec post dose. There was no change from baseline QTcF > 30msec.

Study RTG113215

Adverse events: There were no events of Torsades de pointes or Electrocardiogram QT prolonged during study RTG113215

ECG:

Category of QTc Interval Data for Subjects with QTc ≥450msec by Treatment and Time

In part B, group 1, there was 1 subject observed to have a QT, in the range >450 to ≤480 msec during ezogabine treatment using both QTcB & QTcF correction. In part B, group 2, 2 subjects were observed to have a QT, in the range >450 to ≤480 msec during ezogabine treatment using both QTcB & QTcF correction. In group 2, these observations were seen only in the IR (immediate release) group.

Frequency of Maximum Change from Baseline QTcB and QTcF Values by Prespecified Categories:

In study part A group one, 4 subjects had a QTcB prolongation >30 to ≤60 msec and one subject had a QTcF >30 to ≤60 msec. In study part A group 3, 3 subjects had a QTcB prolongation >30 to ≤60 msec, no subjects had a QTcF >30 to ≤60 msec. In part B, group 1, two subjects had QTcB & QTcF prolongation >30 to ≤60 msec. In part B, group 2, 3 subjects had a QTcB prolongation >30 to ≤60 msec, no subjects had a QTcF >30 to ≤60 msec. No subjects in either part of the study had QT prolongation >60 msec using either QTcB or QTcF.

Study RTG114137

Adverse events: There were no events of Torsades de pointes or Electrocardiogram QT prolonged during study RTG114137.

ECG: No subject had a QTcF or QTcB value greater than or equal to 450msec at any post dose time point during the ezogabine treatment period. No subject had a QTcF or QTcB change from baseline greater than 60 msec at any post dose time point during the ezogabine treatment period. Changes from baseline greater than or equal to 30 msec were

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reported in one subject (3%) prior to 300 mg dosing on Day 1, one subject (3%) prior to 750 mg dosing on Day 15 and two subjects (7%) prior to 750 mg dosing on Day 18. These changes were all less than 60 msec.

Reviewer Comment (All Phase II/III Combined Grouping and Clinical Pharmacology Studies): During the FSU there were no observed occurrences of cardiac rhythm or conduction disorder of sufficient magnitude to indicate labeling change. The results were similar to those presented in the original ISS and 120-Day Safety Update.

Gall Bladder Effects

A study using isolated guinea pig gall bladder demonstrated that ezogabine caused concentration-dependently relaxation of pre-contracted segments of guinea pig gall bladder smooth muscle. In addition, in preclinical studies in dogs, an unusual hepatic lesion was seen in the area underlying the gall bladder. This is believed to be a compression injury following observed (ultrasound) pre and post prandial gall bladder enlargement in the dogs of up to ~300% (pre) and ~900% (post). These findings support the potential existence of potassium channels in gall bladder tissue, and that activation of these channels can lead to hypomotility of the gall bladder.

All Phase II/III Combined Grouping

There were no SAEs or AE leading to withdrawal due to hepatobiliary disorders in the “All Phase II/III” studies. There were no new AEs in the SOC “Hepatobiliary disorders” in the FSU for “All Phase II/III” studies.

Clinical Pharmacology Studies

Study RTG113214

There are no adverse events in the SOC “Hepatobiliary disorders” in study RTG113214

Study RTG113215

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Due to the concern that ezogabine may impair gall bladder contractility Study RTG113215 included an evaluation of repeat dose ezogabine on gall bladder volume of healthy subjects.

Study Design: The study was designed with two parts, part A to investigate the bioavailability of the prototype MR formulations administered in the fed and fasted state as a single dose relative to administration of the IR, market image formulation, in the fed and fasted state. The second part (part B) was designed to determine if there are any dose dependent changes in the absorption of retigabine from the selected MR formulation as assessed by pharmacokinetic linearity over the dose range 320 mg to 1280 mg qd and 160 mg to 640 mg bid when administered to healthy volunteers. It is the multiple dose, part B, which contains the evaluation of gall bladder volume. Both part A and part B are open-label, randomised studies.

In part B subjects were divided into two groups (16 patients/ group) to receive an escalating dosage of ezogabine delivered as either a single daily dose or a twice a day regimen. Dosing was started in both groups at 320mg daily and there was weekly dose escalation of 320 mg at the end of each week up to a maximum of 1280 mg/day (1 x 640 mg bid or 2 x 640 mg qd). Subjects continued treatment of (1 x 640 mg bid or 2 x 640 mg qd) for three days and had a PK assessment on day 25 then transition to a day 25 dose delivered as multiples of the lowest strength capsule. On day 29 the retigabine treatment was switched to the IR formulation. All the subjects received the Retigabine IR daily dose of 600 mg as Retigabine IR 200 mg TID. This treatment regimen continued for three days with PK assessment on day 31.

Gall bladder volumes were assessed once by ultrasound each week during escalation of the modified release formulation such that volume assessments will occur at baseline and at daily doses of 320mg, 640mg, 960mg, and 1280mg, on day -1, 6, 13, 20, and 24 respectively. The ultrasound was performed after an overnight fast and before the morning ezogabine dose. Gall bladder sonography information is collected on 32 patients in part B of this study. Twenty nine patients had sonographic measurements at all designated intervals, 2 patients had measurements at days -1, 5 and 12, and 1 patient measurement at baseline and day 5 only.

Gall Bladder Volume Analysis

There were 153 gall bladder volume measurements performed on the 32 subjects in study part B. These values were analyzed to determine if there was a trend of increasing gall bladder volume during sustained ezogabine treatment with incrementally increasing dose. A least squares linear regression was performed on the values obtained from each patient. A pearson product-moment correlation coefficient for the regression line was also calculated. The y value was the gall

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bladder volume with an x value of days. The interval between study days was not uniform. The interval between day -1 and day 5 was six days while the interval between days 5 to 12 and 12 to 19 was 7 days. The final interval between days 19 and 23 was 4 days. Each interval however did represent an increased stratum of ezogabine dosing. Thirteen patients had a bladder volume / study day slope which was positive and sixteen patients had a bladder volume / study day slope which was negative. The minimum and maximum slope values were -0.75 and 0.74 respectively. The mean slope of the positive group was 0.24 while the mean for the negative slope group was -0.3. The symmetry of values for the positive and negative slope groups suggests that there is no signal for increasing bladder volume over time.

Although the symmetric positive to negative range of slope values points away from a true signal of increase of bladder volume during exposure to retigabine, those subjects with a positive slope of linear regression are further examined. Subjects who have a linear regression with positive slope are identified. Thirteen of 32 subjects (41%) have linear regression results with positive slope, figure 2. As previously noted the maximum positive value for slope is 0.74. None of those subjects with a positive slope of linear regression had a value (r) which exceeded the critical value for 0.05 level of significance (all non-significant).

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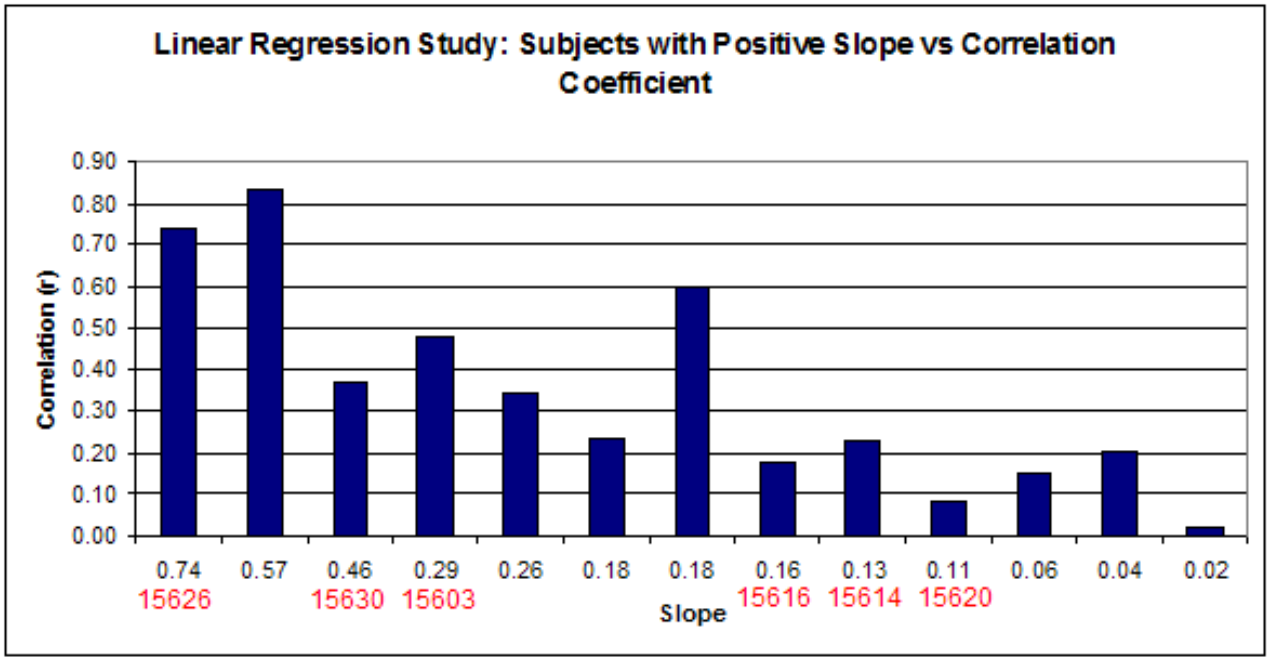
Figure 2 RTG113215: 13 Patients with Positive slope of Linear Regression for Gall Bladder volume vs Study day (baseline, 4 follow up measures), Correspondence between Slope and R (correlation Coefficient). Six patients with abnormally high gall bladder volume are noted by red patient ID number under corresponding bar.



Note: Six subjects with abnormally elevated gall bladder volumes are identified by subject ID number in red under slope / correlation bar.

Further analysis is conducted by examining all subjects with any gall bladder volume greater than normal (> 30ml[1]). Six subjects are identified, shown in table 30. All subjects with an abnormally high gall bladder volume measurement also had

1 Greenberger Norton J, Paumgartner Gustav, "Chapter 305. Diseases of the Gallbladder and Bile Ducts" (Chapter). Fauci AS, Braunwald E, Kasper DL, Hauser SL, Longo DL, Jameson JL, Loscalzo J: Harrison's Principles of Internal Medicine, 17e: http://www.accessmedicine.com/content.aspx?aID=2874111.

a positive slope of linear regression (gall bladder volume vs study day, figure 2). Three (3) subjects had a single elevated gall bladder volume value bracketed in time by normal values. One subject had an elevated final (day 24) value with normal preceding values. One patient had above normal and increasing values at the last two measurements (day 20 and 24). One subject had an elevated baseline and final value. The subject with a trend in the last two values was the only one with a profile suggestive of an ezogabine mediated gall bladder effect. This subject (15626), had a positive linear regression slope of .74, with r=0.74 (ns), a baseline volume of 9 ml and subsequent treatment values of 31ml, 22 ml, 31ml and 32 ml at days 6, 13, 20 and 24 respectively. The values at day 6, 20 and 24 exceeded normal by a maximum of 2 ml. The maximum gall bladder volume seen in this study was 49 ml, an excess over normal of 19 ml which occurred in subject 15620, this was an isolated value surrounded by normal values. The second highest value was 46 ml which occurred in subject 15630 on day 24. This value was preceded by a normal value (13 ml) on day 20.

Table 30 Subjects in Gall Bladder volume Study with measurement > 30ml.

6 Subjects With One Or More Above Normal Gall Bladder Volume Measurement								
Subject	Gall Bladder vol.	Study Day	Subject	Gall Bladder vol.	Study Day	Subject	Gall Bladder vol.	Study Day
15603	20	-1	**15616**	34	-1	***15626***	9	-1
15603	20	5	15616	15	6	15626	31	6
15603	33	12	15616	21	13	15626	22	13
15603	30	19	15616	23	20	15626	31	20
15603	23	23	15616	36	24	15626	32	24
Slope / R	0.29	0.48	Slope / R	0.16	0.18	Slope / R	0.74	0.74
15614	22	-1	**15620**	19	-1	***15630***	24	-1
15614	25	5	15620	22	6	15630	23	6
15614	19	12	15620	49	13	15630	26	13
15614	33	19	15620	29	20	15630	13	20
15614	21	23	15620	17	24	15630	46	24
Slope / R	0.13	0.23	Slope / R	0.11	0.08	Slope / R	0.46	0.37
Large font italic = abdominal pain								

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Subject 15615; abdominal pain study days 4 to 8	
Gall Bladder volume	Study Day
18	-1
15	5
18	12
23	19
19	23

Analysis of Abdominal and GB volume: Subject **15614** had an AE of abdominal pain in the interval between study day 12 and study day 19 when mildly abnormal gall bladder volume was noted. Subject **15615** had 4 days of abdominal pain beginning study day 4 although no abnormal gall bladder volume noted, see above table (table 30). Subject **15626** had abdominal pain noted on study day 20 only. This subject had the strongest positive slope and correlation between gall bladder volume and time on ezogabine. A mildly abnormal gall bladder volume is noted on day 20, see table above. Subject **15630** had an event of abdominal pain of two days duration in the interval between last normal gall bladder volume and final volume measurement which was 16 ml above normal. Subject **15630** had a two day episode of abdominal pain in the interval between a normal volume measurement on day 20 and abnormal gall bladder volume of 46ml on day 24. Overall 3 of the 6 subjects with an abnormally high gall bladder volume experienced abdominal pain, although the pain did not correspond to the date of increased gall bladder volume in all cases.

Analysis of GB Volume and Voiding Dysfunction: Subject **15626** who had the largest positive slope of gall bladder volume linear regression and the largest correlation coefficient, also suffered abdominal pain on a day of abnormally large gall bladder volume, in addition this subject had adverse events of voiding dysfunction on day 2, and 18. Both of these days were in an interval between normal and abnormal gall bladder volume where the volume may have been rising. The abdominal pain on day 20 was also in an interval when gall bladder volume was abnormal. Subject **15620** had two events of voiding dysfunction (Pollakiuria) on study days 5 and 11. The event on study day 11 corresponds to an interval where gall bladder volume may have also been rising. Subject **15630** had an AE of urinary hesitation on study day 12. Gall bladder volume on that day was normal however; a gall bladder volume of 46 ml occurred on study day 24. Subject **15616** had an elevated gall bladder volume at baseline and day 24 and an AE of urinary hesitation on day 24 and 30.

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Differential Occurrence of Abdominal Pain AE (adverse event): Abnormally large gall bladder volume is noted in 19% of the healthy subjects of study RTG113215 on at least one measurement. 50% of the patients with abnormally large gall bladder volume suffered an AE of abdominal pain while (9/26) 35% of patients with normal gall bladder volume had an adverse event of abdominal pain. Also, 66% of the subjects with an abnormally increased gall bladder volume had an AE of voiding dysfunction. None of the subjects with abnormal gall bladder volume or a gall bladder volume trend line of concern (subject 15615, 15601) had gastrointestinal AEs entered as serious or leading to study withdrawal.

Differential Occurrence of Increased Gall bladder Volume and Voiding dysfunction: 66% (4/6) of subjects with an abnormal gall bladder volume had an AE of voiding dysfunction while 14% (4/28) subjects with no report of abnormal bladder volume had an adverse event of voiding dysfunction.

Sex / Age 4/5 subjects with increased gall bladder volume and abdominal pain were female, age range = 25 to 38 and there was one male age 39. There were no adverse events in the Hepatobiliary Disorders SOC in study RTG113215.

RTG114137

There are no adverse events in the SOC “Hepatobiliary disorders” in study RTG114137.

Re-examination of the Controlled Trial and All Phase II/III Combined Group Datasets for Preferred Terms “Abdominal Pain” and “hepatobiliary” Adverse events

Abnormal gall bladder emptying may be a contributing factor in the development of gallstone disease so the occurrence of the terms “cholelithiasis”, “cholecystitis”, “biliary colic” and “bile duct obstruction”, “abdominal pain”, and “abdominal pain upper” in the controlled clinical trials and “all phase II/III Combined Group” clinical trials group were re-examined[2].

Controlled trials

Abdominal Pain

2 Erpecum KJ, Henegouwen GP, Stolk MFJ, Hopman WPM, Jansen JBMJ, Lamers CBHW. Fasting gallbladder volume, postprandial emptying and cholecystokinin release in gallstone patients and normal subjects. Journal of Hepatology 1992;14:194-202.

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In Phase II/III controlled trials there was abdominal pain reported in 4% (17/427) placebo assigned patients and 2% (16/813) ezogabine treated patients. There were two withdrawals from the treatment group and one from placebo. There were two patients with abdominal pain entered as SAEs from the placebo treatment group.

Study withdrawal due to abdominal pain: patient (study 301) 3401 developed intermittent abdominal pain on day 3 along with dizziness and was withdrawn. Patient (study 301) experience mild abdominal pain beginning day 5 of treatment until day 12 along with vertigo. The pain is reported as mild. Patient (study 301) 3901 developed abdominal pain during transition from PBO to ezogabine, approximately 24 days after beginning treatment with ezogabine. This patient also developed urinary retention, the source of the abdominal pain is not determined. A final patient (study 301) 5104 developed abdominal pain on study day 12 in addition to stiffness in shoulders, nausea and vertigo. The pain was reported as mild.

Abdominal pain upper

In controlled trials abdominal pain upper was reported in 1.6% (7/427) placebo patients and 2% (16/813) ezogabine treated patients. In the ezogabine treated patients there was no dose response. One event in the placebo group was entered as an SAE. There were two withdrawals, one from placebo and one from the ezogabine treatment group.

Withdrawal patient (study 205) 1046 had abdominal distension and pain reported as mild.

Hepatobiliary disorders

Five preferred terms appear in controlled trials within the SOC hepatobiliary disorders. These are “biliary colic”, “cholecystitis”, “hepatic function abnormal”, “hyperbilrubinemia”, and “jaundice”. The terms “biliary colic” and “cholecystitis” are retained for analysis because the remaining terms are less specific for gall bladder dysfunction.

In controlled trials cholecystitis was reported in 0.7% (3/427) placebo patients and 0.1% (1/813) ezogabine treated patients. There were two events in the placebo group entered as SAEs and none in the ezogabine treatment group. There were no withdrawals for cholecystitis.

There were no events of “cholelithiasis” in the controlled clinical trials.

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In controlled trials biliary colic was reported in no placebo patients and 0.1% (1/813) ezogabine treated patients. This event was entered as an SAE but did not lead to withdrawal. This patient 1017 (study 205), was a 34 year old female who had a prior history of cholelithiasis approximately three years before this event. The event occurred on day 48 of treatment at a dose of 1200mg ezogabine. The patient had an emergency cholecystectomy the following day.

All Phase II/III Group

Biliary Colic

There was one case of biliary colic in the open label extension of study 303. Patient **15106** reported right upper quadrant pain with nausea and vomiting on study day 233 at an ezogabine dose of 1050mg / day. A cholecystectomy was performed due to this pain on study day 548.

Abdominal Pain

There are 83 instances in 50 patients. In 3 unique patients the event was reported as an SAE. 54% (45/83) of these events occurred in the first three months with median of 77 days and a maximum of 758 days.

SAE Patient reviews

50604 (study 302): this is a 40 yo female who developed abdominal pain on day 7 of ezogabine treatment at a dose of 300mg a day. On day 25 of treatment this patient was hospitalized with **cholelithiasis** and had a cholecystectomy. There is no history of prior cholelithiasis noted.

00009 (study 200/201): This is an 18 yo female who developed an episode of abdominal pain on day 77 of treatment at 900mg/ day.

0171 (study 212): this is a 26 yo female who reported abdominal pain which resulted in hospitalization on day 231 of treatment at 1200mg / day ezogabine. A renal / abdominal ultrasound was within normal limits. The pain was diagnosed as non-specific.

Abdominal Pain Upper

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There were 77 instances in 45 patients. There was one withdrawal but no SAEs. The single withdrawal, patient **1046** is reported in "controlled trials" above. 54% (42/77) of these events occurred in the first three months with a median of 80 days and a maximum of 1189 days.

Bile duct obstruction

One patient **015212** (study 303) a 41 yo female developed abdominal colic in the region of the right hypochondrium on day 188 of ezogabine treatment at a dose of 1200mg / day. Abdominal ulatrasound revealed "vesicular lithiasis and 9mm dilation of the choledochus. Patient was treated medically and continued ezogabine treatment.

Cholecystitis and Cholelithiasis

Six patients developed Cholecystitis and Cholelithiasis during ezogabine treatment in the "All phase II/III Combined grouping". Five of these events were entered as SAEs and one of the SAEs was withdrawn from the study. One patient, **50604** had an AE of "abdominal pain" and details are provided above.

> **01416** (study 303): this is a 70 year old male developed urinary hesitancy and pain under the ribs on day 279 of ezogabine treatment at a dose of 1200mg/ day. The patient had an exploratory laparotomy and was found to have a 3 cm stone in the gallbladder with an intra-hepatic abscess.
> **55503** (study 304): this is a 30 yo female who developed abdominal pain and had a subsequent diagnosis of cholecystitis on day 917 of treatment with ezogabine 900mg / day. The patient had a cholecystectomy on day 972.
> **00019** (study 208): this 40 yo female developed abdominal pain and was determined to have cholelithiasis on study day 1153 at a dose of 300mg/ day.
> **65408** (study 304): 38 yo f who was found to have cholelithiasis on day 250 of treatment with ezogabine 900mg/ day. The narrative does not report the symptoms that precipitated the ultrasound evaluation. The gall bladder revealed minor chronic cholecystitis.

Reviewer Comment (All Phase II/III Combined Group, Gall Bladder volume study and Complete safety database re-evaluation): Study RTG113215 offers new insight into the effect of ezogabine on the gall bladder. 32 subjects with increasing dose of ezogabine had periodic sonographic gall bladder volume measurements over an interval of 24 days. These observations generated five (volume / time) data points in most subjects. In order to determine if these data points showed an increase in the gall bladder volume over time, a least squares linear regression line was generated for each subject. The outcome

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of interest was therefore a positive slope of volume vs time. Thirteen subjects had a positive value for the slope of this line.

None of the 13 subject with a positive slope of linear regression had a significant correlation value. In the subject who had the highest value for slope and r (correlation) the maximum gall bladder volume was 2 ml greater than normal. In those with a positive value for slope of linear regression, the mean value of slope was 0.24. The symmetric range of positive and negative slope found for the linear regression lines indicates there is no trend for increase in gall bladder volume in 32 healthy subjects during a 4 week course of increasing dose of ezogabine from 320mg to 1280mg.

Subjects with a gall bladder volume greater than 30 ml were considered abnormal. Six such subjects were identified. There were two subjects who each had a single gall bladder volume which was notably greater than normal, one 16 ml > normal and one 19 ml > normal. These were isolated values otherwise bracketed by normal values in the two subjects. The values did not occur in an increasing tread over time. In one of these subjects there was a slope of 0.46 with r=0.37, the other had a slope of 0.11 with an r=0.08.

Although there does not appear to be meaningful signal for increased gall bladder volume with increasing duration and dose of ezogabine treatment, the observation that occurrences of abnormal gall bladder volume were seen only in subject with a positive slope of linear regression is notable. In the ezogabine phase 3 clinical trials there was a small subset of patients with similar occurrences of isolated, unpredictable high urinary bladder volumes. These sporadic high gall bladder volume values may be related in mechanism to the similar observations seen in the urinary bladder. This was explored in the differential occurrence of increased gall bladder volume and voiding dysfunction noted above. The results of the analysis suggest a bias toward the occurrence of voiding dysfunction in subjects who had an abnormally high gall bladder volume measurement.

Ezogabine may have a common mechanism that results in both gall bladder and urinary bladder contractile dysfunction. The clinical outcome in urinary bladder dysfunction is voiding dysfunction and in the most severe cases, urinary retention. The clinical outcome in gall bladder dysfunction is less clear, although abnormal gallbladder emptying may contribute to gallstone disease. Abdominal pain and biliary colic may be expected in disorders of gall bladder contractility but in study RTG113215 there was only a small differential occurrence of abdominal pain between the subjects with elevated gall bladder volume and those with no abnormal elevation and there were no AEs of “biliary colic”, “cholecystitis” or “cholelithiasis”. In the ezogabine phase II / III controlled trials; abdominal pain and cholecystitis were notably more frequent in the placebo group than in ezogabine treated patients. There was one case of biliary colic in the ezogabine

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treatment group; however this patient had a prior history of cholelithiasis. In the ezogabine “All Phase II/III Combined Grouping” there were 3 patients who suffered an event of “cholelithiasis” and 3 patient who suffered and event of “cholecystitis” (5 of these six patients have case reports are described above). These six occurrences in a long duration open label trial do not reach a level of evidence to indicate a safety signal due to the common occurrence of gall bladder disease in the general population.

The re-examination of the controlled and “All Phase II/III” trials group does not reveal a clear signal for clinical sequelae of gall bladder contractility dysfunction. In conclusion, ezogabine may have an influence on gall bladder contractility but there is currently insufficient evidence of clinically related sequelae to change labeling. Focused pharmacovigilance is appropriate and is currently planned by the sponsor.

7.4 Supportive Safety Results

7.4.1 Common Adverse Events

All Phase II/III Combined Grouping

During the FSU reporting period, 7 patients reported a TEAE for the first time; making a total of 1242 (91%) patients who reported a TEAE. The types and incidences of TEAEs were similar to those reported in the original ISS and 120-Day Safety Update.

During the FSU reporting period, 10 patients reported headache for the first time, 8 patients reported influenza, 7 reported somnolence and urinary tract infection, and 6 reported Nasopharyngitis, see table below (table 31). All other TEAEs had 4 or fewer patients reporting those TEAEs for the first time.

Table 31 Adverse Events Reported by at Least 5% of Patients (Safety Population: All Phase II/III Combined)

Adverse Events Reported by at Least 5% of Patients (Safety Population: All Phase II/III Combined)		
	Number (%) of Patients	

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	EZG (N=1365)			
Preferred Term	**ISS Integrated Data Cut-off: 30 June 2008**	**120-Day Safety Data Cut-off: 2 October 2009**	**Final Safety Data Cut-off: 30 September 2010**	**Increase during 120 update to FSU interval**
Any event	**1225 (89.7)**	**1235 (90.5)**	**1242 (91.0)**	**7**
Dizziness	431 (31.6)	439 (32.2)	442 (32.4)	3
Somnolence	389 (28.5)	397 (29.1)	404 (29.6)	5
Headache	279 (20.4)	287 (21.0)	297 (21.8)	10
Fatigue	245 (17.9)	251 (18.4)	252 (18.5)	1
Tremor	176 (12.9)	180 (13.2)	182 (13.3)	2
Confusional state	163 (11.9)	163 (11.9)	163 (11.9)	0
Coordination abnormal	138 (10.1)	141 (10.3)	142 (10.4)	1
Nausea	128 (9.4)	133 (9.7)	134 (9.8)	1
Memory impairment	121 (8.9)	123 (9.0)	126 (9.2)	3
Vertigo	121 (8.9)	122 (8.9)	124 (9.1)	2
Diplopia	112 (8.2)	114 (8.4)	114 (8.4)	0
Urinary tract infection	105 (7.7)	107 (7.8)	114 (8.4)	7
Convulsion	99 (7.3)	108 (7.9)	112 (8.2)	4
Disturbance in attention	106 (7.8)	107 (7.8)	108 (7.9)	1
Asthenia	96 (7.0)	97 (7.1)	98 (7.2)	1
Dysarthria	89 (6.5)	92 (6.7)	94 (6.9)	2
Vision blurred	92 (6.7)	93 (6.8)	93 (6.8)	0
Nasopharyngitis	76 (5.6)	86 (6.3)	92 (6.7)	6
Speech disorder	90 (6.6)	90 (6.6)	91 (6.7)	1
Gait disturbance	82 (6.0)	84 (6.2)	85 (6.2)	1
Influenza	70 (5.1)	75 (5.5)	83 (6.1)	8
Diarrhea	76 (5.6)	81 (5.9)	83 (6.1)	2
Balance disorder	76 (5.6)	76 (5.6)	77 (5.6)	1
Aphasia	73 (5.3)	75 (5.5)	76 (5.6)	1
Vomiting	69 (5.1)	72 (5.3)	75 (5.5)	3
Paraesthesia	70 (5.1)	71 (5.2)	74 (5.4)	3
Anxiety	68 (5.0)	71 (5.2)	73 (5.3)	2
Constipation	66 (4.8)	68 (5.0)	72 (5.3)	4
Upper respiratory tract	64 (4.7)	68 (5.0)	71 (5.2)	3

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Adverse Events Reported by at Least 5% of Patients (Safety Population: All Phase II/III Combined)				
	Number (%) of Patients			
	EZG (N=1365)			
Preferred Term	ISS Integrated Data Cut-off: 30 June 2008	120-Day Safety Data Cut-off: 2 October 2009	Final Safety Data Cut-off: 30 September 2010	Increase during 120 update to FSU interval
infection				
Back pain	61 (4.5)	65 (4.8)	69 (5.1)	4
Note: those events highlighted in gray have a higher incidence than the 120-Day SU.				

Clinical Pharmacology Studies

Study RTG113214: There were 5 adverse events experience by 4 patients in this study. The events were headache, tonsilllar hypertrophy, folliculitis, skin laceration, and euphoric mood.

Study RTG113215

In the single dose component (part A) of the study there were 82 non-serious adverse events in 33 patients. Those most common, with more than 3 instances each were somnolence (14 instances), dizziness (12 instances), headache (11 instances), euphoric mood (7 instances) and fatigue (4 instances)

In the multiple dose component (part B) of this study there were 494 non-serious adverse events in 31 patients. These 494 events spanned 96 preferred terms. There were 27 preferred terms with greater than 3 occurrences. These are shown below in table 32. The most common ten preferred terms in order of frequency are dizziness, headache, somnolence, constipation, disturbance in attention, dry mouth, fatigue, euphoric mood, abdominal pain, and confusional state.

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Table 32 Non-Serious AE of Study RTG 113215

Common Adverse Events in Study RTG113215	
Preferred Term	**Occurrences**
Dizziness	50
Headache	46
Somnolence	36
Constipation	25
Disturbance in attention	24
Dry mouth	17
Fatigue	17
Euphoric mood	16
Abdominal pain	15
Confusional state	15
Memory impairment	15
Vision blurred	13
Nausea	12
Dermatitis contact	11
Abnormal dreams	10
Paraesthesia	9
Anxiety	7
Aphasia	7
Urinary hesitation	7
Back pain	6
Hallucination, visual	6
Acne	5
Chest pain	5
Hot flush	5
Nightmare	5
Pruritus	5
Myalgia	4

Study RTG114137

Reference ID: 2957637

In this study there were 241 adverse events in 31 patients. These events spanned 81 preferred terms. There were 24 terms with greater than 2 occurrences during the study. These are shown in table 33 below. The most common ten preferred terms are dizziness, euphoric mood, headache, somnolence, memory impairment, confusional state, Paraesthesia oral, dysarthria, nausea and chromaturia.

Table 33 Non-Serious AE of Study RTG114137

Common Adverse Events in Study RTG 114137	
Preferred Term	**Occurrences**
Dizziness	22
Euphoric mood	16
Headache	16
Somnolence	14
Memory impairment	9
Confusional state	8
Paraesthesia oral	8
Dysarthria	7
Nausea	7
Chromaturia	6
Disturbance in attention	6
Dry mouth	5
Heterophoria	5
Paraesthesia	5
Constipation	4
Coordination abnormal	4
Fatigue	4
Vision blurred	4
Abdominal pain	3
Arthralgia	3
Dermatitis contact	3
Diarrhoea	3

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Common Adverse Events in Study RTG 114137	
Preferred Term	**Occurrences**
Tinea pedis	3
Xerosis	3

Reviewer Comment: the profile of common adverse events is similar to those seen in the safety dataset of the initial ezogabine medical review.

7.4.2 Laboratory Findings

All Phase II/III Group

Due to the small proportion of additional data points in the FSU interval compared to the contribution of Phase II/III safety dataset of the initial NDA submission, central tendency and shifts are not re-examined for the All Phase II/III safety FSU dataset. Frequency of PCC values at baseline compared to post baseline will be examined for the Final Safety Data cut off interval.

Hematologic

All Phase II/III Combined Grouping

Table 34 Hematology Values of Potential Clinical Concern (Safety Population: All Phase II/III Combined)

Hematology Values of Potential Clinical Concern (Safety Population: All Phase II/III Combined)			
	Percentage of Patients (n/N)		
	ISS Integrated Data Cut-off: 30 June 2008	120-Day Safety Data Cut-off: 2 October 2009	Final Safety Data Cut-off: 30 September 2010
Hemoglobin			

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PCC low Baseline Post-Baseline	 <1.0 (8/1340) 1.2 (15/1301)	 <1.0 (8/1340) 1.2 (15/1301)	 <1.0 (8/1340) 1.2 (15/1301)
Hematocrit			
PCC low Baseline Post-Baseline	 <1.0 (11/1329) 1.2 (15/1300)	 <1.0 (11/1329) 1.2 (15/1300)	 <1.0 (11/1329) 1.2 (15/1300)
White Blood Cells			
PCC low Baseline	1.4 (19/1340)	1.4 (19/1340)	1.4 (19/1340)
Post-Baseline	3.6 (47/1301)	3.8 (49/1301)	3.9 (51/1301)
PCC high Baseline Post-Baseline	 <1.0 (2/1340) <1.0 (10/1301)	 <1.0 (2/1340) <1.0 (11/1301)	 <1.0 (2/1340) <1.0 (11/1301)
Neutrophils (absolute)			
PCC low Baseline	11.5 (152/1317)	11.5 (152/1317)	11.5 (152/1317)
Post-Baseline	19.2 (245/1277)	19.8 (253/1277)	19.9 (254/1277)
Eosinophils (absolute)			
PCC high Baseline Post-baseline	 1.1 (14/1290) 1.4 (18/1255)	 1.1 (14/1290) 1.4 (18/1255)	 1.1 (14/1290) 1.4 (18/1255)
Platelets			
PCC low Baseline Post-Baseline	 <1.0 (10/1333) 1.2 (16/1300)	 <1.0 (10/1333) 1.3 (17/1300)	 <1.0 (10/1333) 1.3 (17/1300)
PCC high Baseline Post-Baseline	 <1.0 (4/1333) 1.1 (14/1300)	 <1.0 (4/1333) 1.1 (14/1300)	 <1.0 (4/1333) 1.1 (14/1300)

There were no new adverse events noted for neutropenia or leukopenia in the FSU.
There were no new Serious Adverse Events noted for hematologic events in the FSU
There were no new adverse events leading to study withdrawal due to hematologic events in the FSU

Reference ID: 2957637

The occurrence of PCC values for Hemoglobin, Hematocrit, WBCs, Neutrophils, Eosinophils, and Platelets are examined and reveal additional patient reports only for WBCs and Neutrophils. In the interval from the initial submission 120 day safety cut off to the Final Safety Database cutoff there were two additional patients who had reports of low PCC value for WBCs (study 304- patients 60219, 70109) and one additional patient (Study 304-40137) who had a report of low PCC value for neutrophils. None of these patients had an adverse event entry for an infection or cytopenia.

Clinical Pharmacology Studies

Study RTG113214

Abnormalities of hematology values in this study are very unlikely to reveal true safety signal. In this study the subject receives only 5 single ezogabine doses over approximately 25 days, each dose separated by a 5 day washout.

Study RTG113215

Abnormalities of Hematology values from Part A of this study are very unlikely to reveal true safety signal. In part A the subject receives only 5 single ezogabine doses over approximately one month, each dose separated by a 5 to 7 day washout.

In part B there was one subject 15602 (1 x 480mg BID) had an SAE reported for “anemia”. This etiology of the anemia was due to a gastrointestinal hemorrhage, although the anemia was not considered to be related to study drug, the subject was withdrawn from study treatment.

Table 35 Subjects with Clinical Laboratory Values or Potential Clinical Importance (PCI) in Part B (Study RTG113215)

Subjects with Clinical Laboratory Values or Potential Clinical Importance (PCI) in Part B (Study RTG113215)						
Subject No.	Part/ Group	Treatment	Study Day	Parameters (Units)	Value	Normal Range
Hematology						
15606	B/1	1 x 640mg QD	8	ANC (GI/L)	1.2	1.7 - 8.1

Reference ID: 2957637

Subjects with Clinical Laboratory Values or Potential Clinical Importance (PCI) in Part B (Study RTG113215)						
Subject No.	Part/ Group	Treatment	Study Day	Parameters (Units)	Value	Normal Range
			14		1.0	1.7 - 8.1
		1 x 320mg + 1 x 640mg QD	21		1.1	1.7 - 8.1
			28		1.1	1.7 - 8.1
		1 x 640mg QD	8	WBC Count (GI/L)	2.6	4 - 10.8
			14		2.3	4 - 10.8
		1 x 320mg + 1 x 640mg QD	21		2.5	4 - 10.8
			28		2.6	4 - 10.8
15611	B/1	1 x 640mg QD	8	ANC (GI/L)	1.2	1.7 - 8.1
15621	B/1	Screening	0	ANC (GI/L)	1.4	1.7 - 8.1
		1 x 640mg QD	8		1.4	1.7 - 8.1
		1 x 640mg QD	14		1.4	1.7 - 8.1
		1 x 320mg + 1 x 640mg QD	21		1.3	1.7 - 8.1
		4 x 320mg QD	28		1.1	1.7 - 8.1
		4 x 320mg QD	28		1.1	1.7 - 8.1

Study RTG114137

The reviewer screened the laboratory dataset to identify values that may indicate bone marrow suppression. Values for hematocrit, platelet count, lymphocyte count, absolute neutrophil count (ANC), and WBC count below the normal protocol assigned range were identified and shown in table 36 below. Those subjects with below normal values for these hematologic parameters were captured. The profile of the values in these patients were examined for the timing and severity of the nadir in addition to the rate of recovery, primarily to see if recovery was achieved by the follow up lab testing. The profile was also examined to identify if the screening value was low. In those with an abnormal screening value the nadir was examined but unless severe there is no comment.

Reference ID: 2957637

Table 36 Subjects with abnormal low values for key hematologic parameters (31 subject in total achieved an ezogabine treatment of 750mg/ day)

Subjects with abnormal low values for key hematologic parameters (31 subject in total achieved an ezogabine treatment of 750mg/ day)					
Hct		**PLT**	n= 94 to 150 GI/L	**Lymphs**	n= 0.8 to 3.3 GI/L
Subject ID	comment	Subject ID	comment	Subject ID	comment
5, 15, 20, 25	All subjects had low values at screening	22	Normal screening, values of 94, 95, 92, 98 (x 1000) during treatment with rebound to normal at follow up	26	Low at 1 treatment measure only then normalizes while continued on 250mg TID. Nadir 0.5 GI/L
		30	Nadir of 87k during treatment, rebound to normal at follow up	30	Nadir during treatment = 0.6 GI/L , rebounds at follow up

Neutrophil count (ANC)	n= 1.8 to 7.8 GI/L	**WBC**	N= 4.0 to 12.0 GI/L
Subject ID	Comment	Subject ID	comment
2	Low at screening	2	Low screen
17	Nadir 1.6 GI/L, rebounds at follow up	12	Nadir 3.93 GI/L, rebounds at follow up
18	Low screen with further decrease during treatment nadir = 1.3 GI/L	18	Nadir 3.45 GI/L rebounds at follow up in 2 weeks.
21	Nadir = 1.4 GI/L, normal at follow up	20	Nadir 3.93 GI/L
26	Low pre-treatment	25	Nadir 3.52 GI/L
31	Low screen	26	Low screen

Reference ID: 2957637

		30	Nadir 3.56 GI/L
		31	Nadir 3.92 GI/L
	6.5% (2/31) subjects who reached the 750mg / day dose had an ANC change from normal to below normal during treatment		19% (6/31) subjects who reached the 750mg/day dose had a change in WBC from normal to below normal during treatment. (in this case not in PCC (potential clinical concern) range.

Reviewer Comment (All Phase II/III Combined Grouping and Clinical Pharmacology Studies)**:** The PCC values from the "All Phase II/III Combined Grouping" do not provide evidence for a new safety signal for blood dyscrasia. The data from the clinical pharmacology studies demonstrate the capacity to depress neutrophils and WBC counts in healthy subjects as was seen in the epilepsy patient trials. The clinical pharmacology data reveals 2 patients (6.5%) with PCC (potential clinical concern) values for ANC and Platelet count during treatment with ezogabine. There were no PCC values for WBC count. These data reinforce the need for continued pharmacovigilance for blood dyscrasia but no change from the current position in labeling.

Clinical Chemistry

All Phase II/III Combined Grouping

There were no new serious adverse events or adverse events with an associated Clinical Chemistry preferred term leading to study withdrawal in the FSU

There were no new adverse events noted for hyperkalemia in the FSU.

There were no new adverse events noted for the preferred terms "BLOOD POTASSIUM INCREASED". HEPATIC ENZYME INCREASED, LIVER FUNCTION TEST ABNORMAL, or TRANSAMINASES INCREASED,

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The frequency of PCC values at baseline compared to post baseline for Sodium, Potassium, Chloride, Bicarbonate, Urea, Creatinine, Uric Acid, Glucose, Protein, Calcium and Cholesterol are examined. In the interval from the initial submission 120 day safety cut off to the Final Safety Database cutoff additional unique patient reports in the PCC range are noted for Sodium (PCC low), Potassium (PCC high), Chloride (PCC low), Bicarbonate (PCC low), Glucose (PCC low) and Cholesterol (PCC high) in the Final Safety Data interval. The changes are shown in table 37 below.

Table 37 Final Safety Database cutoff, parameters where additional unique patient reports in the PCC range are noted

Final Safety Database cutoff, parameters where additional unique patient reports in the PCC range are noted			
	Percentage of Patients (n/N)		
	ISS Integrated Data Cut-off: 30 June 2008	120-Day Safety Data Cut-off: 2 October 2009	Final Safety Data Cut-off: 30 September 2010
Sodium			
PCC low Baseline Post Baseline	 2.2 (30/1336) 4.1 (53/1302)	 2.2 (30/1336) 4.1 (53/1302)	 2.2 (30/1336) 4.1 (54/1302)
Potassium			
PCC high Baseline Post Baseline	 <1.0 (7/1333) 2.3 (30/1299)	 <1.0 (7/1333) 2.5 (32/1299)	 <1.0 (7/1333) 2.5 (33/1299)
Chloride			
PCC low Baseline Post Baseline	 4.1 (54/1305) 6.7 (85/1270)	 4.1 (54/1305) 7.2 (91/1270)	 4.1 (54/1305) 7.3 (93/1270)
PCC high Baseline Post Baseline	 4.8 (62/1305) 9.8 (125/1270)	 4.8 (62/1305) 10.2 (129/1270)	 4.8 (62/1305) 10.5 (133/1270)
Bicarbonate			
PCC low Baseline Post Baseline	 7.9 (61/777) 12.6 (95/755)	 7.9 (61/777) 13.5 (102/755)	 7.9 (61/777) 13.9 (105/755)

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Glucose			
PCC low Baseline Post Baseline	 1.0 (14/1334) 2.5 (32/1300)	 1.0 (14/1334) 2.7 (35/1300)	 1.0 (14/1334) 2.9 (38/1300)
Cholesterol			
PCC high Baseline	20.9 (274/1311)	20.9 (274/1311)	20.9 (274/1311)
(≤1.0 mg/dL) Post Baseline	28.1 (359/1276)	29.0 (370/1276)	29.5 (376/1276)

Reviewer Comment: there is no evidence of a new safety signal seen upon examination of the PCC values for clinical chemistry parameters or by occurrence of clinical chemistry adverse event terms in the FSU interval. In the initial NDA safety review there was some concern that a signal for hyperkalemia may be present. The updated PCC values do not add additional evidence to support this concern.

Hepatic Function

All Phase II/III Combined Grouping

Aspartate aminotransferase (AST), Alanine aminotransferase (ALT), alkaline phosphatase, total bilirubin

There were no new patient reports of elevations of AST, ALT, Alkaline phosphatase, or total bilirubin into the PCC range during the Final Safety Data interval

There were no new adverse events reports entered for the preferred terms “ALANINE AMINOTRANSFERASE INCREASED”, “ASPARTATE AMINOTRANSFERASE INCREASED”, “BLOOD ALKALINE PHOSPHATASE INCREASED”, “BLOOD BILIRUBIN INCREASED”.

Reviewer Comment: there is no evidence of a new safety signal for hepatic dysfunction seen upon examination of the PCC values for hepatic function parameters or by occurrence of hepatic function adverse events in the FSU interval.

Clinical Pharmacology Studies- Clinical Chemistry and Hepatic Function

Reference ID: 2957637

Study RTG113214:

There were no AEs reported due to abnormalities on clinical laboratory evaluations in the study.

Isolated out range clinical chemistry results of potential clinical significance were reported in three subjects (#2, #5 and #8). The 3 out of range were an increase of glycemia, and increase of AST and one increased value of potassium. None of these isolated out of range were considered clinically significant

Study RTG113215:
Abnormalities of Clinical Chemistry values from Part A of this study are very unlikely to reveal a new valid safety signal due to short exposure to ezogabine. In part A the subject receives only 5 single ezogabine doses over approximately one month, each dose separated by a 5 to 7 day washout.

Part B

Mean changes from baseline in clinical chemistry and hepatic function values were observed; however, none of the mean changes appeared to be clinically significant. No significant urinalysis results or changes were observed for Part B.

Adverse Events:

The following 2 subjects had clinical laboratory abnormalities reported as AEs during Part B, Group 1.
• Subject 15617 (ezogabine: 1 x 320mg + 1 x 640mg QD) had a single episode of moderate 'hepatic enzyme increased' reported as an AE. This AE was not considered to be related to study drug. This subject had high AST (342 IU/L) and ALT (160 IU/L) values at follow-up that also met the definition of PCI (potential clinical importance) values.
• Subject 15611 (ezogabine: 1 x 320mg QD) had intermittent mild 'chromaturia' reported as an AE. The AE was considered by the investigator to be related to study drug. Urinalysis values for this subject were normal.

The following subject had clinical laboratory abnormalities reported as AEs during Part B, Group 2.
• Subject 15619 (1 x 320mg BID) had a single episode of mild 'chromaturia' reported as an AE. The AE was considered by the investigator to be related to study drug. Urinalysis values for this subject were normal.

Values of Potential Clinical Importance (PCI)

Reference ID: 2957637

Table 38 Subjects with Clinical Laboratory Values or Potential Clinical Importance (PCI) in Part B (Study RTG113215)

Subjects with Clinical Laboratory Values or Potential Clinical Importance (PCI) in Part B (Study RTG113215)						
Subject No.	Part/ Group	Treatment	Study Day	Parameters (Units)	Value	Normal Range
Clinical Chemistry						
15617	B/1	None	Follow-up	ALT (IU/L)	160	9 - 52
				AST (IU/L)	342	14 - 36
15627	B/1	1 x 320mg + 1 x 640mg QD	21	Potassium (mmol/L)	6	3.5 - 5.1
15625	B/2	None	Screening	Potassium (mmol/L)	5.9	3.5 - 5.1

Study RTG114137:

No subject had abnormal clinical chemistry values that were flagged as of potential clinical concern during the ezogabine 300 mg, 450 mg, 600 mg and 900 mg treatment periods. During the 750 mg treatment period at Day 15 pre-dose, elevated Alanine transaminase (ALT) was reported in 1 (3%) subject, elevated aspartate aminotransferase (AST) in 1 (3%) subject and elevated glucose in 2 (6%) subjects. The AST and glucose values were not considered clinically significant by the Investigator.

The elevated ALT value in Subject 30 was reported as an AE of increased hepatic enzyme, which led to withdrawal from the study. On Day 13 the subject experienced flu-like symptoms which resolved on Day 15. On that same day, Day 15 of dosing, laboratory results revealed moderate elevated liver enzymes (non-serious). Study medication was discontinued after the Day 15 dose and the highest recorded ALT value was 247 IU/L on Day 16, which was approximately 4 x upper limit of normal (ULN). The ALT value returned to normal at the Follow-up visit on Study Day 28, at which time the AE was considered resolved, see table below.

There was an additional clinical chemistry AE during the Follow-up phase, which was an abnormal liver function test in Subject 27. The last dose that this subject received was 750 mg per day. At the Follow-up visit 9 days after the final dose,

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an ALT value of PCI was reported as an AE (188 IU/L; normal range 5–60 IU/L). The highest ALT value, 226 IU/L, was recorded at an unscheduled visit 2 days later. Subsequently, ALT values decreased over time and then returned to normal with a value of 53 IU/L, 42 days after the onset of the AE. Other liver function test parameters recorded at the time of the AE were as follows: AST 64 IU/L (normal range: 5–40 IU/L), alkaline phosphatase 108 IU/L (normal range: 38–126 IU/L) and total bilirubin 13.68 µmol/L (normal range: 3.42–23.94 µmol/L). Hepatitis A, B and C serologies were negative.

Reviewer Comment: there is no evidence of a new safety signal for clinical chemistry values or hepatic dysfunction seen upon examination of the PCC values for adverse events in the FSU interval. None of the hepatic function abnormalities breached the Hy's law threshold and transaminase values trended rapidly back to normal after medication discontinuation (except subject 15617 where the abnormality is first noted in follow up). There was a single elevated potassium in an ezogabine treated patient in RTG113215 part B, an elevation of similar magnitude was observed in one subject at screening (no treatment).

7.4.3 Vital Signs

All Phase II/III Combined Grouping

Table 39 Vital Signs Changes of Potential Clinical Concern (Safety Population: All Phase II/III Combined)

Vital Signs Changes of Potential Clinical Concern (Safety Population: All Phase II/III Combined)			
	n/N (%) of Patients Meeting Criteria at Any Post-Baseline Timepoint		
Vital Sign Parameter and Position (alphabetical order)	ISS Integrated Data Cut-off: 30 June 2008	120-Day Safety Data Cut-off: 2 October 2009	Final Safety Data Cut-off: 30 September 2010
Diastolic hypertension - sitting	8/534 (1.5)	8/534 (1.5)	8/534 (1.5)
Diastolic hypotension - sitting	14/534 (2.6)	14/534 (2.6)	14/534 (2.6)
Diastolic hypertension - standing	25/1267 (2.0)	30/1267 (2.4)	32/1267 (2.5)
Diastolic hypotension - standing	37/1267 (2.9)	38/1267 (3.0)	41/1267 (3.2)
Diastolic hypertension - supine	7/795 (0.9)	11/795 (1.4)	12/795 (1.5)
Diastolic hypotension - supine	32/795 (4.0)	36/795 (4.5)	41/795 (5.2)
Pulse - Bradycardia - sitting	8/534 (1.5)	8/534 (1.5)	8/534 (1.5)

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Pulse - Tachycardia - sitting	20/534 (3.7)	20/534 (3.7)	20/534 (3.7)
Pulse - Bradycardia - standing	7/1297 (0.6)	9/1267 (0.7)	10/1267 (0.8)
Pulse - Tachycardia - standing	97/1297 (7.7)	105/1267 (8.3)	107/1267 (8.4)
Pulse - Bradycardia - supine	11/795 (1.4)	13/795 (1.6)	16/795 (2.0)
Pulse - Tachycardia - supine	24/795 (3.0)	25/795 (3.1)	28/795 (3.5)
Systolic hypertension - sitting	20/534 (3.7)	20/534 (3.7)	20/534 (3.7)
Systolic hypotension - sitting	33/534 (6.2)	33/534 (6.2)	33/534 (6.2)
Systolic hypertension - standing	41/1267 (3.2))	49/1267 (3.9)	52/1267 (4.1)
Systolic hypotension - standing	69/1267 (5.4)	71/1267 (5.6)	73/1267 (5.8)
Systolic hypertension - supine	26/795 (3.3)	31/795 (3.9)	34/795 (4.3)
Systolic hypotension - supine	40/795 (5.0)	44/795 (5.5)	45/795 (5.7)

Clinical Pharmacology Studies

Study RTG113214:

No vital sign values of potential clinical importance were reported in this small study in which 8 subjects received 5 single doses of ezogabine followed by a 5 day washout.

Study RTG113215:

Part A: Overall, 10 subjects had at least one vital sign values of PCI during Part A. Of those, 2 had high systolic blood pressure, 4 had high diastolic blood pressure, and 5 had a high heart rate. However, none of these values were considered to be clinically significant or reported as an AE and all but one resolved prior to follow-up.

Part B: Overall, 4 subjects had at least one vital sign value of PCI. Of those, 2 subjects had high diastolic blood pressure. However, none of these values were isolated episodes and therefore none was considered to be clinically significant or reported as an AE and all resolved prior to follow-up.

Study RTG114137:

No subject had any changes in vital signs that were reported as AEs.

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The vital sign dataset is reviewed. There are three instances of values in the range of potential clinical importance. On in subject 7 where a diastolic blood pressure measurement in the high range is noted, value 101 mmHg (n=100mmHg). The second is a case of elevated heart rate in subject 32 where heart rate is high on study day 24 (ezogabine dose 250mg TID), value 121 (n=110), a third, also in subject 32 on study day 11 (ezogabine dose 200mg TID) with a low systolic blood pressure reading, value 67 mmHg (n=85 mmHg).

Reviewer Comment (All Phase II/III Grouping and Clinical Pharmacology Studies): In study RTG114137 there was a subject with a notable decline in systolic blood pressure during treatment however as seen in review of the original NDA safety dataset there are instances of both depressed and elevated blood pressure and heart rate. In the All Phase II/III Combined Grouping there were 3 additional patients with instances of systolic hypertension (standing) and 2 additional patients with instances of systolic hypotension (standing). There were 2 additional patients with instances of diastolic hypertension (standing) and 3 additional patients with diastolic hypotension (standing), table 39. These observations indicate a broad confidence band for blood pressure measurements with changes in blood pressure in the direction of both elevation and reduction with no systematic shift in either direction evident.

7.4.4 Electrocardiograms (ECGs)

QT parameters are covered in the cardiac section of 7.3.5 (Submission Specific Primary Safety Concerns)

All Phase II/III Combined Grouping

Other ECG parameters assessed for outlier values of PCC (heart rate and PR and QRS intervals) were observed at frequencies similar to those observed in the original ISS and 120-Day Safety Update.

• Heart rate decreases meeting PCC criteria (<50 bpm and decrease from baseline ≥15 bpm) were recorded at least once in 19/1214 (1.6%) ezogabine-treated patients.
• Heart rate increases meeting PCC criteria (>100 bpm and increase from baseline ≥15 bpm) were recorded at least once in 31/1214 (2.6%) of ezogabine-treated patients.
• PR interval changes meeting PCC criteria (≥210 msec and increased from baseline) were recorded at least once in 58/1212 (4.8%) ezogabine-treated patients.

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• Lastly, QRS interval changes meeting PCC criteria (≥120 msec and increased from baseline) were recorded at least once in 16/1213 (1.3%) ezogabine-treated patients.

Clinical Pharmacology Studies

Study RTG113214: No treatment related ECG abnormalities are reported.

Study RTG113215

Part A: No significant mean changes or dose-related trends in ECGs were observed

Part B: No significant mean changes or dose-related trends in ECGs were observed

One subject had low heart rate values recorded. While on MR2 (modified release) 640mg daily the patient had heart rate values of 54 and 48 beats per minute noted.

Study RTG114137

No subject had any changes in 12-lead ECG intervals that were reported as AEs.

One subject had an abnormal ECG trace that was considered clinically significant; this was in the ezogabine 600 mg treatment session. This finding was a junctional rhythm in Subject 10. However, rare occurrence of junctional rhythm had been seen in this subject's Holter analysis of continuous ECG data acquired **on Day -2** (baseline, data on file), considered by the Investigator to be non-disqualifying (subject was subsequently enrolled). The follow-up visit finding was asymptomatic and converted to sinus rhythm within a short period of time. Vital signs were normal during this period. The subject was placed on continuous telemetry monitoring and review of these data over 36 h showed no change in frequency of episodes of junctional rhythm after dosing. This was clinically stable. The finding was judged not to represent a significant change from baseline and was not reported as an AE.

Reviewer Comment (All Phase II/III Grouping and Clinical Pharmacology Studies): The clinical pharmacology studies do not reveal new signal for abnormalities in heart rate, PR and QRS intervals. The All Phase II/III Combined Grouping reveals abnormalities in these parameters of the same order as the initial ISS and 120 day safety update.

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7.4.5 Special Safety Studies/Clinical Trials

Due to the concern that ezogabine may impair gall bladder contractility Study RTG113215 included an evaluation of repeat dose ezogabine on gall bladder volume of healthy subjects. This is discussed in section 7.3.5, "Gall Bladder Effects"

7.4.6 Immunogenicity

Refer to Page 233, initial NDA 22345 Clinical Review

7.5 Other Safety Explorations

7.5.1 Dose Dependency for Adverse Events

No further data extracted in this review, see page 233 initial NDA 22345 Clinical Review

7.5.2 Time Dependency for Adverse Events

No further data extracted in this review, see page 236 initial NDA 22345 Clinical Review

7.5.3 Drug-Demographic Interactions

No further data extracted in this review, see page 237 initial NDA 22345 Clinical Review

7.5.4 Drug-Disease Interactions

No further data extracted in this review, see page 245 initial NDA 22345 Clinical Review

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7.5.5 Drug-Drug Interactions

No further data extracted in this review, see page 247 initial NDA 22345 Clinical Review

7.6 Additional Safety Evaluations

7.6.1 Human Carcinogenicity

See discussion of (b) (4) mutagenicity in section 4.1, Chemistry Manufacturing and Controls.

7.6.2 Human Reproduction and Pregnancy Data

All Phase II/III Combined Grouping

As of the 2 October 2009 120-Day Safety Update cut-off date, a total of 13 pregnancies were reported in the ezogabine clinical development program.

Between the 120-Day cut-off and the FSU cut-off, **2 additional pregnancies** were reported (Table 43). One pregnancy occurred in Patient 60205 in Study 304 who had an AE of feto-placental insufficiency. The patient received ezogabine for approximately 10 days after conception. This pregnancy resulted in the birth by Cesarean-section of a 2300g, but otherwise healthy infant.

The second pregnancy occurred in Patient 303-03001 who had a history of spontaneous abortions. The patient was weaned off the study medication with the last dose on 03 June 2010 (Day 1274), and withdrew from the study on 04 June 2010 at her own request, as she wanted to try alternative marketed anti-epileptic medications. She had a positive home pregnancy test on 17 Aug 2010. The first day of the last menstrual period was reported as the first week of June. Five days after the positive pregnancy test, the pregnancy resulted in a spontaneous abortion.

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7.6.3 Pediatrics and Assessment of Effects on Growth

No additional studies in this submission

7.6.4 Overdose, Drug Abuse Potential, Withdrawal and Rebound

No additional studies in this submission

7.7 Additional Submissions / Safety Issues

This review captures all safety data from available submissions.

8 Postmarket Experience

As of the date of the NDA resubmission, ezogabine has not yet been launched in any country.

Reference ID: 2957637

9 Appendices

9.1 Literature Review/References

See footnotes.

9.2 Labeling Recommendations

Section 6.1 Clinical Trials, heading "Additional Adverse Reactions Observed During All Phase 2 and 3 Clinical Trials" is condensed with the elimination of the (b) (4) terminology. All terms from this section were re-examined and tested for inclusion considering the "importance", "seriousness", and "causality" of the events. The occurrence of the events compared to placebo in the controlled clinical trials was used a pointer for choice of inclusion. A table representing this analysis is shown below.

Table 40 All events listed in Label section 6.1 in Additional Adverse Reactions Observed analyzed by frequency in Controled trial database & importance-seriousness- likelihood of causality with RETAIN / DELETE conclusion

PT	PBO unique patients (427)	PBO %	Potiga Unique Patients (813)	Potiga %	Frequent / infrequent / rare in section 6.1	Importance -seriousness , causality	retain / delete
							(b) (4)
Encephalopathy	0	0.0	2	0.2	Infrequent	greater in treatment, causality high	retain
							(b) (4)
Euphoric mood	0	0.0	4	0.5	Infrequent	greater in Potiga, causality high	retain
Feeling drunk	0	0.0	7	0.9	Frequent	greater in Potiga, causality high, safety high	retain
							(b) (4)
Leukopenia	2	0.5	10	1.2	Frequent	greater in Potiga, causality suspect, safety high	retain
							(b) (4)

PT	PBO unique patients (427)	PBO %	Potiga Unique Patients (813)	Potiga %	Frequent / infrequent / rare in section 6.1	Importance -seriousness , causality	retain / delete
						safety low	
(b) (4)							
Nephrolithiasis	0	0.0	4	0.5	Infrequent	greater in Potiga, causality high, safety high	retain
Neutropenia	5	1.2	2	0.2	Infrequent	greater in PBO, causality suspect, safety high	retain
(b) (4)							
Pruritus	4	0.9	3	0.4	Frequent	greater PBO, causality suspect, safety moderate	retain
(b) (4)							
Rash	2	0.5	6	0.7	Frequent	greater in Potiga, causality suspect, safety high	retain
Renal colic	1	0.2	3	0.4	Infrequent	greater in Potiga, causality high, safety high	retain
Syncope	1	0.2	5	0.6	Infrequent	greater in Potiga, causality suspect, safety high	retain
Thrombocytopenia	1	0.2	2	0.2	Infrequent	equal PBO -Potiga, causality suspect, safety high	retain

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A total of 14 terms are retained for this section and placed in order of frequency, table of event frequency shown below.

Preferred term	# Events	# unique patients
(RASH)	81	56
(NYSTAGMUS)	85	55
(LEUKOPENIA)	61	27
DYSPNOEA	45	25
(MUSCLE SPASMS)	29	19
(ALOPECIA)	34	18
NEUTROPENIA)	27	14
(SYNCOPE)	18	13
(NEPHROLITHIASIS)	15	13
(RENAL COLIC)	18	9
(THROMBOCYTOPENIA)	19	8
(EUPHORIC MOOD)	14	7
Coma	3	3
(ENCEPHALOPATHY)	2	2

9.3 Advisory Committee Meeting

See section 9.3 initial NDA 22345 Clinical Review

Reference ID: 2957637

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/s/

STEVEN T DINSMORE
06/08/2011

NORMAN HERSHKOWITZ
06/08/2011

MEMORANDUM

DATE: November 13, 2010

FROM: Russell Katz, M.D.
Director
Division of Neurology Products/HFD-120

TO: File, NDA 22-345

SUBJECT: Recommendation for action on NDA 22-345, for the use of Potiga (ezogabine) as adjunctive treatment of partial seizures in adults

NDA 22-345, for the use of Potiga (ezogabine) as adjunctive treatment of partial seizures in adults, was submitted by Valeant Pharmaceuticals North America, on 10/30/09. According to the sponsor, ezogabine stabilizes neuronal KCNQ channels in the open position, and is presumably the first potassium channel opener developed for the treatment of epilepsy. The application contains the results of three randomized, placebo controlled trials, as well as the requisite safety data.

The application has been reviewed by Dr. Ohidul Siddiqui, statistician, Dr. Steven Dinsmore, medical officer, Dr. Chong M. Kim, medical officer of the Agency's Division of Reproductive and Urologic Products, the Agency's Interdisciplinary Review Team for QT Studies, Dr. Edward Fisher, pharmacology reviewer, Dr. Lois Free, pharmacology supervisor, Drs. Tara Turner, Zachary Oleszczuk, and Manizeh Siahpoushan, Division of Medication Error Prevention and Analysis (DMEPA), Barbara Fuller, Division of Risk Management, Dr. Antoine El-Hage and Jyoti Patel, Division of Scientific Investigations, Dr. Mohan Sapru, chemist, Office of New Drug Quality Assurance (ONDQA), Dr. John Duan, ONDQA, biopharmaceutics, Dr. Mohammad Atiar Rahman, animal carcinogenicity statistician, Dr. Katherine Bonson, Controlled Substances Staff, Dr. Jane Bai, Office of Clinical Pharmacology Safety Review Team, Dr. Ling Chen, statistician, Office of Translational Sciences, Dr. Ta-Chen Wu, Office of Clinical Pharmacology, and Dr. Norman Hershkowitz, neurology team leader and Cross Discipline Team Leader (CDTL). The DNP review staff recommends that the sponsor be sent a Complete Response letter. In this memo, I will briefly review the relevant data, and offer the division's recommendation for action on this NDA, along with the rationale for that recommendation.

Effectiveness

As noted above, the sponsor has submitted the results of three controlled trials that they believe establish substantial evidence of effectiveness for Potiga as adjunctive treatment for partial seizures in adults. I will briefly review these studies.

Study 205

This was a multi-national, parallel group trial in which patients were randomized to receive either placebo, or ezogabine 600 mg/day, 900 mg/day, or 1200 mg/day, given in a TID regimen, added on to a regimen of one or two anti-epilepsy drugs (AEDs). The study was performed in Australia, Belgium, Croatia, Czech Republic, Finland, France, Germany, Israel, Italy, Netherlands, New Zealand, Norway, Poland, Portugal, Slovakia, Spain, Sweden, the UK, and the US. From about 5% (1200 mg/day) to 8% (600 mg/day) of patients were enrolled in the US.

The study consisted of an 8 week prospective baseline, an 8 week titration phase, and an 8 week maintenance phase. The primary outcome was the percent change from baseline in the 28 day partial seizure frequency.

The following chart displays the disposition of patients in this study:

	Pla	600 mg/d	900 mg/d	1200 mg/d
Randomized	97	101	95	106
Completed	75 (77%)	75 (74%)	67 (70.5%)	62 (58.5%)
D/C due to				
Adverse event	12 (12.5%)	21 (21%)	21 (22%)	33 (31%)

The following chart displays the results of the analysis of the primary outcome.

Median Percent Change From Baseline in 28 Day Partial Seizure Frequency

	Placebo	600 mg/d	900 mg/d	1200 mg/d
N	96	99	95	106
% Change	-13.1%	-23.4%	-29.3%	-35.2%
P-value		0.2	0.04	<0.001

The following chart displays a comparison of the percentage of patients considered to be responders (at least a 50% decrease in the rate of partial seizures compared to baseline):

Percent of Responders (ITT Maintenance Phase)

	Placebo	600 mg/d	900 mg/d	1200 mg/d
N	78	83	74	68
% Responders	25.6%	27.7%	40.5 %	41.2%
P-value		0.85	0.057	0.01

Study 301

Study 301 was a multi-national, parallel group trial in which patients were randomized to receive either placebo or Potiga 1200 mg/day, given in a TID regimen. The study was conducted in Argentina, Brazil, Canada, Mexico, and the US. In this study, there was an 8 week prospective baseline, followed by a titration period of up to 6 weeks, and then a 12 week maintenance phase. About 50% of the patients were enrolled in the US.

The primary outcome was as in Study 205.

The following chart displays the disposition of patients in this study:

	Pla	1200 mg/d
Randomized	152	154
Completed	127 (84%)	97 (63%)
D/C due to		
Adverse event	13 (8.6%)	41 (27%)

The following chart displays the results of the primary outcome.

Median Percent Change in 28 day Partial Seizure Frequency

	Placebo	1200 mg/d
N	150	151
% Change	-17.5%	-44.3%
P-value		<0.001

The following chart displays a comparison of the percentage of patients considered to be responders (at least a 50% decrease in the rate of partial seizures compared to baseline):

Percent of Responders (ITT Maintenance Phase)

	Placebo	1200 mg/d
N	137	68
% Responders	22.6%	55.5%
P-value		<0.001

The median percent change in the 28-day partial seizure frequency in the US/Canada was -19.6% in the placebo group (N=81) and -29% in the Potiga 1200 mg/day group (N=85).

Study 302

This was a multi-national, parallel group trial in which patients were randomized to receive either placebo or ezogabine 600 mg/day or 900 mg/day, given as a TID regimen. In this study, there was an 8 week prospective baseline period, followed by a titration phase of up to 4 weeks, and followed by a 12 week maintenance phase. The study was conducted in Australia, Belgium, France, Germany, Hungary, Israel, Poland, Russia, South Africa, the UK, Ukraine, and the US (N=3). The primary outcome was as in the other 2 studies.

The following chart displays the disposition of patients in this study:

	Pla	600 mg/d	900 mg/d
Randomized	179	181	179
Completed	153 (85.5%)	135 (75%)	121 (68%)
D/C due to			
Adverse event	14 (8%)	26 (14%)	46 (26%)

The following chart displays the results of the analysis of the primary outcome.

Median Percent Change From Baseline in 28 Day Partial Seizure Frequency

	Placebo	600 mg/d	900 mg/d
N	176	179	175
% Change	-15.9%	-27.9%	-39.9%
P-value		0.007	<0.001

The following chart displays a comparison of the percentage of patients considered to be responders (at least a 50% decrease in the rate of partial seizures compared to baseline):

Percent of Responders (ITT Maintenance Phase)

	Placebo	600 mg/d	900 mg/d
N	164	158	149
% Responders	18.9%	38.6%	47%
P-value		<0.001	<0.001

Safety

A total of 2168 patients/subjects have been exposed to at least one dose of ezogabine in the development program. A total of 1365 patients with epilepsy have been treated with ezogabine in all Phase 2 and 3 studies, and a total of 2034 patients with epilepsy have been exposed to at least one dose of ezogabine.

The mean duration of treatment of patients with epilepsy in Phase 2 and 3 studies was 303 days, with the median exposure being 235 days. In Phase 2/3 epilepsy studies, 779 patients were treated for at least 6 months, and 483 received treatment for at least one year.

A total of 295 patients received at least 600 mg/day for at least 1 year, and 657 patients have received at least 600 mg/day for at least 6 months. A total of 156 patients have received a daily dose of at least 900 mg for at least one year, and a total of 52 patients have received a daily dose of at least 1200 mg for at least one year; a total of 134 patients have received a daily dose of at least 1200 mg for at least 6 months.

Deaths

In trials of patients with epilepsy, there were 10/1365 patients (0.7%) treated with ezogabine who died. In the controlled trials, a total of 2/813 (0.2%) of ezogabine-treated patients died compared to 3/427 (0.7%) of placebo patients. There was no death that could directly be attributed to treatment with ezogabine.

A total of 6 of the deaths in the ezogabine-treated patients were considered either possibly or probably Sudden Unexplained Death in Epilepsy (SUDEP). The calculated rate of SUDEP in this development program was about 4.4 deaths/1000 patient years. As noted by Dr. Dinsmore, the range of estimates of SUDEP described in the literature ranges from 0.09 deaths/1000 patient years in a population of patients with newly diagnosed epilepsy to 9.3 deaths/1000 patient years in a study of patients referred to epilepsy surgery centers; the average rate (to the extent that such an average is in any way meaningful) is about 3.6 deaths/1000 patient years.

Serious Adverse Events (SAEs)

In controlled studies of patients with epilepsy, a total of 72 patients (about 9%) treated with ezogabine experienced at least one SAE, compared to about 6% in the placebo group. The following table presents percentages of patients in the controlled trials who experienced various SAEs at an incidence of >1% in the 1200 mg group:

Event	Pla	Ezo 600	Ezo 900	Ezo 1200
N	427	281	273	259
Psychotic disorder	0	0	<1	1.9
Convulsion	1.2	1.8	<1	1.9

Several SAEs occurred in 2 patients each in the 1200 mg/day group (nausea, encephalopathy, confusional state and suicidal ideation).

In all Phase 2/3 studies in patients with epilepsy, there were a total of 216/1365 (16%) of patients who reported at least one SAE. The only SAE reported at an incidence of 1% or greater was “convulsion”, which was reported in 33 patients (2.4%).

In other studies (bipolar disorder, post-herpetic neuropathic pain [PHN], compassionate epilepsy, clinical pharmacology, and abuse potential studies), a total of 18 patients reported at least one SAE. Of these, there were 2 cases of atrial fibrillation in the PHN study, one case of extrasystoles in a clinical pharmacology study, and one case each of cardiac arrest/asystole and ventricular tachycardia in the abuse potential study. These will be discussed later in a section discussing cardiac toxicity.

Discontinuations

A total of 25% of epilepsy patients and 11% of placebo patients discontinued treatment in the epilepsy controlled trials. The following chart displays the percentages of the more important/frequent AEs that led to discontinuation in the epilepsy controlled trials.

Event	Pla	600	900	1200
N	427	281	273	259
Any AE Leading to D/C	10.5	17.4	25.3	31.3
Dizziness	1.2	3.2	5.9	8.1
Confusional state	<1	1.4	2.9	7.7
Somnolence	<1	2.5	4.8	3.1
Fatigue	<1	3.2	4.4	2.3
Vertigo	<1	1.8	1.8	2.3
Coordination abnl	<1	<1	1.8	3.5
Attention Disturbance	0	1.1	1.8	2.3
Headache	<1	1.1	1.8	2.3
Tremor	0	<1	1.5	2.7
Dysarthria	0	1.1	<1	2.3
Convulsion	1.6	<1	<1	2.3

In all Phase 2/3 trials of patients with epilepsy, a total of 418/1365 (31%) of ezogabine treated patients discontinued treatment due to an AE. The most common AEs leading to discontinuation in Phase 2/3 studies were: dizziness, 5%; somnolence and confusional state, 4%; fatigue, 3%; disturbance of attention, 2%.

Common Adverse Events

The following table lists the incidence of the AEs seen in the controlled epilepsy trials.

Event	**Pla**	**600**	**900**	**1200**
N	427	281	273	259
Dizziness	9	14.6	23	32
Somnolence	12	15	24.5	26.6
Confusional State	2.6	4	7.7	16
Fatigue	6	16	15	13
Tremor	3	2.5	9.5	12.4
Coordination abnl	3	5	5	11.6
Blurred vision	2	2	4.4	10.4
Vertigo	2	8	8	9
Memory Impairment	2.6	2.5	5.5	9
Dysarthria	<1	3.6	2	8
Nausea	5	6	6	8.5
Diplopia	1.6	8	5.5	7
Disturbance in Attention	<1	6	5.5	6.6
Aphasia	<1	1	3	6.6
Gait disturbance	1	2	5	6
Paresthesia	2	2.5	1.5	5.4
Balance disorder	<1	3	3	5
Constipation	1.4	1.4	4	5
Disorientation	1	0.4	0.4	4.6
Anxiety	2	2.5	2	4.6
Influenza	2	3.6	1	4.6
Asthenia	2	4	5.5	4
Dysuria	1	1.4	2	4
Urinary hesitation	1	2	1	3.5
Amnesia	1	1	3	3
Dysphasia	0.5	1	1	3

Weight increased	1	2	3	3
Dyspepsia	1.6	2.5	1.5	3
Chromaturia	0	1	1.5	3
Psychotic disorder	0	0	0.4	2
Hematuria	1	2	1	1.5

A very similar pattern of AEs was seen in all Phase 2/3 epilepsy studies, as well as in the other studies performed with ezogabine.

As can be seen, many of these AEs were dose related. Most were rated as mild to moderate in intensity, and were generally tolerated and extinguished with continued treatment.

Dr. Dinsmore has performed extensive analyses to determine if dizziness, the most common AE, was related temporally to reports of (orthostatic) hypotension; there is no evidence of a correlation of the two events.

Psychiatric Events

As can be seen, there was a dose related increase in the number of patients in epilepsy controlled trials who discontinued treatment due to psychiatric events (in particular, confusion and disturbances in attention) as well as in the occurrence of psychiatric adverse events (memory impairment, disturbances in attention, anxiety, psychotic disorders, disorientation, and confusional state [the latter occurred in 16% of patients at the daily dose of 1200 mg]).

Dr. Dinsmore performed an analysis in which he combined various terms that could reasonably be considered to constitute psychotic symptoms (including hallucinations [visual, auditory], psychotic disorder, acute psychosis). In this analysis, a total of 0.5%, 1.4%, 1.8%, and 5% of patients in the placebo, 600 mg/d, 900 mg/d, and 1200 mg/d groups, respectively, experienced psychotic symptoms.

Laboratory findings

There were small mean decreases in total WBC and neutrophil counts with ezogabine treatment, as well as small mean increases in eosinophil counts. The following shift table displays the percent of patients (by dose) who had at least one value that became abnormal during treatment in the controlled epilepsy trials:

	Pla	600	900	1200
RBC Indices				
Normal to low				
Hct	14	16	23	18
WBC Indices				
Normal to low				
WBC	16	23	21	18
Lymphocytes	11	20	15	16
Normal to high				
WBC	2	1	2	5
Eosinophils				
(absolute)	1.5	2.6	2.7	4.5
(percent)	5.3	10.5	16	14

An examination of patients who had at least one value that met outlier criteria for values of potential clinical concern (PCC) revealed few, if any, differences in the percentage of patients on drug or placebo who met such criteria. There were a total of 10 ezogabine-treated patients with neutropenia; all but one had low neutrophils at baseline, and the other was on concomitant carbamazepine, was treated with folate and continued in the study.

Clinical chemistry

There were very small mean increases in serum sodium and three cases of patients with serum Na >153 and 7 patients with serum Na <127 at at least one visit. Of the latter, 6 were on concomitant medications that are known to cause hyponatremia. No patient discontinued treatment for changes in serum sodium.

There were no important shifts in the percentage of patients whose laboratory values shifted from normal at baseline to either high or low values with the following exceptions:

	Pla	600	900	1200
Renal fxn				
Normal to high				
Urea	2.2	5	7	8.5
Uric acid	1	2	3	3
Liver fxn				
Normal to high				
AST	6.4	10.7	8.9	11.6
ALT	5.2	14	15	18
T. Bili	1.5	3	5	13

As noted by Dr. Dinsmore, the increases in total bilirubin were considered to have been related to a problem in the assay.

Liver function

In epilepsy controlled trials, the percentages of patients with LFTs > 3 X Upper Limit of Normal (ULN) was 1%, 1.5%, 3.1%, and <1% in the placebo, 600 mg/d, 900 mg/d, and 1200 mg/d ezogabine groups, respectively. There were no differences in the percentage of patients who had LFTs between 5 and 10 X ULN among the treatment groups, including placebo. No patient was noted to have a combination of LFTs >3 XULN and total bilirubin >2 X ULN with a relatively normal Alk Phos, a pattern known to predict the capacity of a drug to cause liver failure in a percentage of patients who meet these criteria. There were no important differences in mean changes from baseline in any laboratory measures of liver function between placebo and any dose group of ezogabine.

However, as noted by Dr. Dinsmore, a total of 27 patients discontinued treatment with ezogabine due to LFT abnormalities.

Of these 27, 13 occurred in controlled trials: 6 in Study 201, a study in patients with diabetic neuropathy (6/120; 5%) and 7 in the epilepsy controlled trials (7/813; 0.9%).

The maximum multiple of the ULN for ALT elevation was 27 X ULN in one patient, who had a normal total bilirubin and alkaline phosphatase. Three other patients had ALT elevations of between 10 and 11 X ULN, also with no other associated laboratory abnormalities. Most of the other 27 patients had ALT elevations in the 3-5 X ULN range. As noted above, none of the 27 patients had an ALT of at least 3 XULN and a total bilirubin of greater than 2 X ULN (the highest total bilirubin documented in this cohort of 27 patients was 1.7 X ULN, accompanied by an ALT of 5 X ULN and alkaline phosphatase of 3.8 X ULN). In 23/27 patients, the abnormalities resolved upon discontinuation of treatment (in the other 4 patients, the data are not available).

One of the 27 patients had an ALT of 10.3 X ULN and a direct bilirubin of 2.4. This case is under discussion internally at the time of the writing of this memo. This patient was receiving 750 mg/day and was at Day 31 of treatment at the time of the documented abnormality; this also resolved with discontinuation of treatment.

Vital signs

There were small differences between placebo and ezogabine-treated patients in the percentage of patients who met outlier criteria for various measures of hypotension. The following chart displays these changes:

Percentage of patients meeting outlier criteria for blood pressure changes

	Pla	600	900	1200
Diastolic hypotension				
Standing	1.2	2.6	1.9	2.4
Supine	2.5	2.8	1.7	4.7
Orthostatic hypotension				
Diastolic	22.9	23.9	19.1	26.7
Systolic hypotension				
Sitting	1.1	4.1	4.4	1.9
Supine	4.3	4.5	3.5	6.0

(Data for Orthostatic hypotension was obtained from Studies 301 and 302; data for Diastolic and Systolic hypotension was obtained from Study 205)

A total of 4 SAEs were associated with reports of hypotension, but one occurred in the setting of sepsis and in one there was a history of hypotension. In only one of the cases was the hypotension considered the primary SAE.

Syncope

There were 5 cases of syncope in ezogabine-treated patients (one SAE), and 1 on placebo in the epilepsy controlled trials. There were a total of 14 cases of syncope in the database. Several of these patients had blood pressure measurements that revealed decreases of from 10-20 mm Hg from baseline, although these changes were not measured at the time of the event (in one patient, a BP of 89/61 was recorded presumably during, or very near, a 20 minute loss of consciousness; this event could have been a seizure).

Urinary symptoms

The urinary tract was noted to have been the site of ezogabine-induced toxicity in rodent toxicity studies. These animals developed distended bladders and some developed renal lesions thought to be secondary to urinary retention. The findings were considered to have been the result of the pharmacologic action of the drug on potassium channels. For this reason, specific monitoring of urinary function was undertaken in clinical trials, including measuring the American Urological Association Symptom Index (AUASI; see Dr. Dinsmore's review for a description of this scale), periodically in all controlled and open-label studies, and post-voiding residuals (PVRs) were to be assessed periodically in Study 301, 302, and in open-label studies.
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The following chart displays the percentages of patients experiencing at least one of the stated AEs referable to urinary complaints.

Event	Pla	600	900	1200
UTI	5	2	3	8
Dysuria	0.7	1.4	2	4
Urinary hesitation	1	2	1	3.5
Chromaturia	0.2	0.7	1.5	2.7
Abnormal UA	1	0.7	1	3
Residual Urine Volume	0.2	0	1.5	1.5

There were no important mean changes from baseline in the AUASI total scores.

There were a total of 5 SAEs in 4 patients treated with ezogabine compared to one SAE in a placebo patient referable to the urinary system in epilepsy controlled trials.

The 5 SAEs in the ezogabine-treated patients included a case of renal colic, urinary Retention, atonic bladder (all resolved with continued treatment) and renal failure and urinary incontinence, which resulted in discontinuation of drug.

The patient with renal failure was a 53 year old woman whose symptoms (myalgia, cough, polydipsia, and sweats) began on Day 23 of ezogabine 600 mg/day. The patient was noted to have elevated ALT (max 5 X ULN), AST (max 2.6 X ULN), creatinine (4 X ULN), BUN (max 3.75 X ULN), bilirubin (max 1.7 X ULN), and CRP. On Day 31, she was noted to have 1500 cc of cloudy urine on catheterization. The ezogabine was discontinued, and several days later her laboratory values were returning to normal.

The other patient who was withdrawn from treatment was a 34 year old woman who experienced “atonic urinary bladder” on Day 21 (although symptoms began on Day 15) of ezogabine 600 mg/day, and urinary incontinence on Day 63. Drug tapering was begun on Day 63 (her last day of ezogabine was about 3 weeks later), and her PVR was 159 ml on Day 63. Normal bladder sensation was reported to have been returning after discontinuation, although one PVR of 130 ml was noted about 5 weeks after her last dose.

A total of 4 other patients were withdrawn from treatment for signs/symptoms referable to the urinary system. Only one was related to urinary Retention, a 47 year old woman on 900 mg/day who experienced urinary retention on Day 29 of treatment. Tapering was initiated on Day 40, and her symptoms resolved on Day 41. A PVR was normal 13 days after her last dose.

In Phase 2/3 studies combined, the most common AEs referable to the urinary system were as follows:

UTI	7.7%
Urinary hesitation	3.1%
Urinalysis abnormal	2.6%
Dysuria	2.4%
Urinary Retention	1.9%
Hematuria	1.8%
Chromaturia	1.7%
Polyuria	1.6%
Residual urine volume	1.1%

There were a total of 18 patients who reported at least one SAE (8 of these discontinued treatment), and a total of 18 patients who discontinued treatment for AEs related to the urinary system (of these 18 patients, 10 had events that were not considered SAEs).

The following are brief descriptions of the patients in this group who discontinued treatment (and who have not already been discussed).

A 58 year old man who had urinary retention on Day 20 on 750 mg/day. He had a pre-void volume of 2200 ml, and a PVR of 572 ml, and a second of 245 ml. PVR was 0 three days after drug discontinuation.

A 22 year old woman on 600 mg/day developed fever, confusion, and somnolence on day 170. A diagnosis of urosepsis was made.

A 30 year old man developed agitation, urinary retention and an upper respiratory tract infection on day 81 of treatment (2 weeks of 1200 mg/day). A total of 1200 ml of urine were evacuated by catheter. Drug was stopped on day 83. The patient had several PVRs while on treatment that ranged up to 900 ml. The patient undertook self-catheterization after treatment discontinuation. An EMG on Day 116 revealed no EMG activity during bladder filling, and PVRs post-treatment were up to almost 900 ml at least up until day 223.

A 24 year old man developed vomiting and abdominal pain on day 166 of treatment with ezogabine 900 mg/day. A UA showed “inflammation’ (no infection). A pyelogram showed left hydronephrosis and hydroureter, but no obstruction. The patient fully recovered about 30 days after the last dose.

A 51 year old man was hospitalized for “nephropathy” on Day 455 of 900 mg/day. He had a slightly elevated BUN and creatinine, and recovered.

A 35 year old man had a PVR of 101 ml on day 501 of ezogabine 750 mg/day. He complained of straining on urination, and intermittently not being able to empty his bladder.

A 31 year old woman developed urinary Retention on day 171 of ezogabine 900 mg/day; a PVR was 104 ml on that day. A repeat PVR on Day 231 was 231 ml. She also complained of straining on urination and of a sensation of incomplete bladder emptying. She recovered .

A 38 year old woman developed urinary retention on day 582 of 900 mg/day of ezogabine. She had no documented abnormal PVRs.

A 62 year old woman had symptoms of urinary Retention on Day 43 of 600 mg/day of ezogabine. On day 63, she had a PVR of 330 ml. Drug taper began on day 65. She was ultimately determined to have had S1 root compression,

and had spinal surgery. On day 206 (126 days after discontinuation), she had a PVR of 19 ml.

A 45 year old woman had an increase in PVR from baseline of 173 ml on day 112 of 900 mg/day of ezogabine. She had several abnormal PVRs, including one of 150 ml on Day 505. She discontinued treatment on day 505 for unrelated reasons.

One healthy volunteer, a 21 year old man, in a study of modified release tablets developed moderately severe urinary retention. After 5 daily doses of 400 mg/day that followed a 6 week washout that had been preceded by 3 single doses 7 days apart, he developed difficulty in voiding (hadn't voided in 14 hours) and abdominal discomfort. He was catheterized with withdrawal of about 1000 ml.

A 76 year old woman in a study of patients with post-herpetic neuralgia developed urinary retention on Day 20 at dose 150 mg TID . A PVR on day 11 was 106. Her last dose of drug was on Day 24, and a PVR on day 30 was 354 ml. She was taking concomitant amitriptyline.

A total of 27 patients had at least one adverse event listed as urinary retention who had a dose of ezogabine reported at the time of the AE. Dr. Dinsmore has examined all PVR data for these patients. Only 11 of these patients had a PVR recorded on the date of the event. Examination of the PVR data from these patients does not reveal a clear pattern of changes that would qualify PVR as a useful measurement to predict the onset of urinary retention. The data that are available do not provide useful information in this regard. For example, 7 patients with an event of urinary retention had a PVR 1 month prior to the event; in 5 of these, the PVR was less than what it had been at baseline. At least half of the PVRs on the date of an event were normal in the 11 patients for whom this data are available. The data presented do not establish that PVR is useful as a predictive tool.

A total of 16 of the cases of Retention occurred in the first 6 month of treatment, but cases occurred as late as about 900 days of treatment.

About 106 patients were treated for at least 18 months, and 6 cases were seen in this cohort. A total of 2 cases occurred after about 840 days, and about 31 patients received treatment for this duration.

Cardiac

There were no important differences in the incidence of cardiac related AEs or conduction abnormalities between placebo and any dose of ezogabine in the

controlled epilepsy studies, nor were there more SAEs or discontinuations due to cardiac events in the ezogabine group compared to the placebo patients.

In all Phase 2/3 epilepsy studies, there were 7 SAEs related to cardiac events: 5 events of chest pain (4 after at least 149 days on drug, one at day 5). There were a total of 7 discontinuations due to cardiac events: 2 cases of ventricular extrasystole, and 1 case each of syncope, ventricular tachycardia, asystole, extrasystole, and chest discomfort.

In all Phase 2/3 epilepsy studies, the following events were reported in at least 0.5% of patients:

Chest pain	2.8%
Palpitations	1.3%
Syncope	0.9%

There were several cases worth noting.

1) A 34 year old woman in an abuse potential study suffered what was reported as “cardiac arrest” about 2 hours after a single 900 mg dose of ezogabine. The event lasted 25 seconds and resolved spontaneously. A stress echo later was negative, as were relevant laboratory measures.
2) A 41 year old man in the same abuse potential study had asymptomatic brief episodes of ventricular tachycardia 21/2 hours after a single dose of 900 mg. The episodes consisted of two 5 beat runs, followed several minutes later by 3 more runs of between 3-8 beats, and then several minutes later by a run of 19 beats.
3) A healthy male volunteer in a Phase 1 multiple dose study receiving 300 mg q 12 hours (day 9 of treatment) was noted on telemetry to have a 3 beat run of ventricular tachycardia while sleeping. Six days later he experienced a vasovagal episode. The next day, he was noted, on telemetry, to have another 3 beat run of “wide complex ectopy”.

In a study of patients with post-herpetic neuralgia, there were 4 cases of atrial fibrillation that were considered SAEs and resulted in drug discontinuation.

1) A 73 year old woman developed palpitations on 150 mg TID of ezogabine about 20 days after initiation of treatment. The next day, she was admitted to the hospital with atrial fibrillation with a rapid ventricular response. Drug was discontinued. She had a history of “borderline” hypertension and a non-symptomatic heart murmur, and treatment with amlodipine for hypertension was initiated one week before her symptoms.
2) An 84 year old man who developed fatigue, shortness of breath, lightheadedness, dizziness, and palpitations about 2 weeks after initiation

of treatment with 200 mg TID. He presented 2 weeks later, and was noted to be in atrial fibrillation (HR of 112). An angiogram revealed total occlusion of the LAD (he had no history of heart disease but had a 20 year history of smoking).

3) A 77 year old man developed nausea, vomiting and fever after receiving ezogabine for about 2 weeks (dose at time of event was 150 mg TID). An EKG revealed atrial fibrillation with a ventricular rate of 115 bpm. He was noted to be in heart failure, and a diagnosis of clostridium difficile was also made.
4) An 84 year old woman experienced palpitations about 3 weeks after starting treatment with ezogabine (200 mg TID). She was noted to have atrial fibrillation with a rapid ventricular response (HR 125 bpm). She had a history of diabetes, and a chest X-ray revealed cardiomegaly and COPD.

In this study, 120 patients received ezogabine and 60 received placebo. The incidence of atrial fibrillation was therefore 3.3% on drug, and 0% on placebo. The average age of the patients in this study was 63 years.

The sponsor performed a thorough QT study, in which they evaluated an ezogabine dose of 1200 mg/day, placebo, and moxifloxacin (positive control). The study enrolled 120 healthy volunteers, and the maximum mean difference between placebo and drug for QT prolongation was 7.7 msec, with an upper bound of the 90% confidence interval for the drug-placebo difference in QT of 11.9 msec. As noted by the Interdisciplinary QT Review Team, the study suffered from several flaws (e.g., the rising phase of the moxifloxacin arm was not adequately evaluated, higher doses of ezogabine [that would be expected to result in relevant plasma levels in patients with renal/hepatic disease] were not evaluated).

EKGs performed during the controlled epilepsy studies revealed inconsistent findings.

The greatest differences from placebo in QT interval were seen at weeks 12 and 18, in an inconsistent pattern, as depicted below, in msecs:

	Pla	600	900	1200
Week 12	1.4	2.1	16.7	14.8
Week 18	3.6	11.3	10.6	3.3

The following chart displays the percentage of patients with various changes from baseline in QT interval:

	Pla	600	900	1200
> 30 msec	8%	10%	12%	12%
> 30 msec and < 60 msec	8%	10%	11%	12%

There were no meaningful changes between placebo and any ezogabine dose in PR interval, QRS interval, or heart rate. There were essentially no differences in the percentage of patients with QT intervals of >450 msec in the placebo and ezogabine groups.

Chemistry

The sponsor has proposed to market the following tablet strengths: 50 mg, (b) (4) 200 mg, 300 mg, and 400 mg. They have performed a bioequivalence study comparing the 400 mg studied and to-be-marketed tablets, and they are bioequivalent. The sponsor has requested a waiver of the requirement for bioequivalence studies comparing the studied and to-be-marketed tablets for all of the lower strengths. Dr. Duan has concluded that waivers can be granted for all strengths except the (b) (4) to-be-marketed tablet, because the (b) (4) . The sponsor proposes that strengths less than 300 mg would be used only for titration.

Non-clinical toxicology

The sponsor has identified 3 mutagenic impurities in the final product: (b) (4), a (b) (4) and known mutagen (b) (4), a (b) (4) and (b) (4) another (b) (4) All three are positive in the Ames assay. The sponsor has set a specification for (b) (4) that limits the exposure to these two impurities combined to (b) (4) micrograms/day, below the acceptable maximum limit of 1.5 micrograms/day for the total amount of structurally related genotoxins. However, the sponsor first set a limit of (b) (4) for (b) (4) then (b) (4) and most recently they have proposed an upper limit of (b) (4) for (b) (4) However, even at a limit of (b) (4), the amount of (b) (4) to which a patient would be exposed at a dose of 1200 mg/day would be about (b) (4) the acceptable upper limit.

In order to address the mutagenic potential of (b) (4) and to determine if its carcinogenic potential is accurately predicted by the positive Ames test result, the sponsor performed an additional combination in vivo micronucleus/comet assay.

This assay is designed to assess the compound's "…potential to induce structural chromosome damage and/or aneuploidy in polychromatic erythrocytes from bone marrow and DNA strand breaks…in the liver of rats.", according to Dr. Fisher (page 118 of his review). (b) (4) was negative in this assay.

However, as noted by Drs. Fisher and Freed, there is considerable debate about the ability of this assay to predict the carcinogenic potential of compounds more reliably than the Ames assay. Apparently, the results of the comet assay are highly dependent on numerous "biological and technical variables" according to Dr. Fisher, and it is acknowledged that the two assays (comet and Ames) measure different endpoints.

Ezogabine was negative in a two year rat carcinogenicity study, although at the highest dose tested (50 mg/kg/day) the exposure to ezogabine was only ½ that seen clinically at the 1200 mg/day dose. A lifetime carcinogenicity study could not be performed in mouse due to bladder toxicity, so a neonatal mouse carcinogenicity study was performed, a model thought to be sensitive to genotoxic compounds, according to Dr. Fisher. In this study, there was a small, dose related increase in lung neoplasms. In neither carcinogenicity study was (b) (4) present in amounts adequate to assess its carcinogenic potential.

It is also important to note that in the in vitro chromosomal aberration assay, ezogabine was noted to cause dose related abnormalities.

Pharmacokinetics

Ezogabine is extensively metabolized, primarily via N-acetylation (to form NAMR, an acetylated metabolite) and glucuronidation, both of ezogabine (presumably to numerous glucuronidated metabolites)and NAMR. About 85% of the administered dose is recovered in the urine, with 36% of the administered dose recovered as unchanged parent. Metabolites account for about 90% of the total radioactivity in the plasma. The elimination half lives of both ezogabine and NAMR are about 7-11 hours. Ezogabine is not a substrate, inhibitor, or inducer of CYP450 isozymes, or of P-glycoprotein.

Dr. Wu recommends that the sponsor, in Phase 4, investigate the potential of ezogabine to inhibit CYP2B6, and perform an in vitro study to determine if ezogabine is a substrate for major transporters in the kidney.

Controlled Substance Review

The CSS recommends that ezogabine be placed in Schedule (b) (4) of the Controlled Substances Act, a conclusion with which the sponsor agrees. At the time of this writing, however, this recommendation has not been officially forwarded by the Agency to the Drug Enforcement Agency (DEA) for final scheduling.

Dr. Bonson of the CSS also recommends that the sponsor, in Phase 4, perform a study in animals to better characterize whether or not ezogabine can produce physical dependence. The sponsor did not perform adequate studies in humans to address this question.

Advisory Committee meeting

Primarily because of Potiga's capacity to cause urinary retention, this application was discussed at a meeting of the Peripheral and Central Nervous Systems Advisory Committee (PCNS AC) on August 11, 2010. The standing committee was supplemented with experts in epilepsy and urology.

The committee voted unanimously that the sponsor had provided substantial evidence of effectiveness for ezogabine as adjunctive treatment for adults with partial seizures. By a vote of 11 Yes, 0 No, and 2 Abstentions, the committee voted that the risk of urinary retention could be mitigated by appropriate patient monitoring, and that, in general, adequate monitoring could consist of patient education and routine clinical vigilance, but that in the typical case sophisticated urologic monitoring was unnecessary.
They did offer the view that for patients who could not reliably report symptoms of urinary retention (for example, patients with cognitive impairment), a urologic consultation might be helpful. They voted unanimously that specific monitoring for urinary stones or infections was not required.

The committee also recommended that the sponsor perform, in Phase 4, urodynamic studies to try to identify the mechanism of urinary retention, and that patients under the age of 12 not be treated with ezogabine until these studies were performed. They agreed that there were no other safety issues that would preclude approval.

SUMMARY

The sponsor has submitted the results of three controlled trials that appear to be adequate and well-controlled, and that evaluate doses of 600, 900, and 1200 mg/day of ezogabine, given in a three times a day regimen as adjunctive therapy in the treatment of adults with partial seizures. The review team has identified no issues that would undermine the conclusion that ezogabine is effective in this setting. Although in only one study was the effect at 600 mg/day statistically significantly superior to placebo (Study 302), there was a clear numerical improvement in the 600 mg/day group compared to placebo in the other study in which it was examined (Study 205), and that study was considerably smaller than Study 302. In our view, then, the data establish that the 600 mg/day dose is effective, but that the 900 mg/day dose is clearly more effective (a conclusion based on two trials, and on the two outcomes described in those studies). Only

one study directly compared the effectiveness of 900 mg and 1200 mg/day. In this study, there is a minimal increase in the effectiveness of the 1200 mg/day dose compared to the 900 mg/day dose on the primary outcome, but not numerically on the Percent of Responders (although in this latter analysis, only the 1200 mg/d-placebo contrast reached statistical significance).

In addition, the sponsor has submitted safety data in over 2000 patients with epilepsy.

As noted earlier, the results of animal studies identified the urinary tract as a target for toxicity. For this reason, the Agency required the sponsor to specifically monitor patients for signs/symptoms of urinary retention. As described in this memo, and in more detail in Dr. Dinsmore's review, the data clearly establish ezogabine's capacity to produce urinary retention that in most, though not all, cases was shown to be reversible.

The data suggest that there is no reliable way to adequately predict the onset of urinary retention, and the AC agreed.

The sponsor has proposed that the risk can be adequately managed not only with monitoring (and, of course, appropriate product labeling), but by providing a Medication Guide to alert patients to the signs/symptoms that may occur. The committee agreed with this approach, and the division does as well.

Other potentially important safety issues include the occurrence of arrhythmias, especially atrial fibrillation, which seemed to be most prominent in a study of patients with post-herpetic neuralgia. The study population in this study differed from the populations enrolled in the efficacy studies primarily in mean age (63 vs about 36 years), and the presence of an increased incidence of concomitant medical conditions.

Ezogabine clearly has the capacity to produce, in some patients, increases in LFTs, some of considerable elevation. Although a few patients experienced mild elevations in total bilirubin, no patient met criteria for a Hy's law case. All LFT elevations resolved with discontinuation of drug, and ezogabine's capacity to increase LFTs can be managed with appropriate product labeling.

In addition, ezogabine clearly causes significant psychiatric adverse events, and clearly in a dose related fashion. These events caused some patients to discontinue treatment, and generally these symptoms resolved with drug discontinuation. Nonetheless, this seems to be a prominent aspect of ezogabine's adverse reaction profile, and should be prominently described in product labeling. In our view, it is one main reason to recommend 900 mg/day as the primary recommended dose.

Ezogabine appears to produce a mild increase in the QT interval, a finding that can be adequately managed with appropriate labeling.

As noted above, the sponsor has documented, through dissolution data, that all dosage strengths that they wish to market, (b) (4) will perform similarly to the corresponding strengths that they studied. (b) (4)

(b) (4)

As noted previously, the sponsor proposes a specification for (b) (4) an impurity found to be positive in the Ames assay, of (b) (4) This specification would permit daily exposure to (b) (4) of about (b) (4) the acceptable upper limit of exposure for a genotoxic impurity. The sponsor argues that (b) (4) has been shown to be not mutagenic, based on the results of the negative comet assay.

According to Drs. Fisher and Freed, there is considerable controversy about the meaning of a negative comet assay in the face of a positive Ames assay. In their view (and there is considerable literature that agrees), the specific conditions of the comet assay have a critical influence on its interpretation, and, in any event, they evaluate different genotoxicity endpoints (strand breaks for the comet assay and point mutations for the Ames). Suffice it to say, the negative comet assay here cannot be reliably interpreted to overcome the concern raised by the

positive Ames assay. Even though the mouse carcinogenicity assay documented only a small carcinogenic signal, neither it nor the rat carcinogenicity assay adequately examined the capacity of (b) (4) to cause cancer. For this reason, it is possible that the carcinogenicity signal might be considerably stronger if adequate levels of (b) (4) were studied.

The sponsor has recently informed us that they will be examining alternate synthetic routes for ezogabine, at least one of which, according to our chemists, is likely to produce no (b) (4)

The presence of a genotoxic impurity, shown to be positive in the Ames assay, at multiples of the allowable upper limit of daily exposure, is a critical issue. However, this result needs to be assessed in the context of a fairly strong mutagenicity signal seen for the parent compound in the in vitro chromosomal aberration assay. That is, one could argue that the relatively rather large signal produced by the parent poses a more significant risk than the relatively (presumed) small risk imposed by the highest acceptable level of (b) (4) at the newly proposed specification of (b) (4)

Under these conditions, it could be argued that a way forward at this time would be to approve the application, with a Post Marketing Requirement (PMR) imposed on the sponsor to make all reasonable efforts to reduce the level of the impurity in the final product to an acceptable level (as noted above, our chemists believe that a plan already proposed by the sponsor would be expected to result in no detectable levels of (b) (4) Such an approach could be considered reasonable, because epilepsy is a serious disease for which additional treatments are necessary, and because, assuming the sponsor meets the deadlines imposed by a PMR, patients would be exposed to elevated levels of (b) (4) for a limited time (the time it took to produce drug with acceptable amounts of (b) (4) perhaps months).

This issue has been extensively discussed with the review team. Our view is that, although the above described approach is reasonable, it would be more compelling if any documented advantage of ezogabine compared to other available anticonvulsants had been shown, either regarding effectiveness or safety; of course, none has been shown.

Regarding the issue of the “swamping” of the relatively small risk posed by the proposed levels of (b) (4) by the apparent larger risk posed by the parent compound, I would note the following.

First, the batches used in the in vitro chromosomal aberration studies included unknown levels of (b) (4) it is at least possible, therefore, that the signal seen in those studies was due, at least in part, to (b) (4)

Further, although the proposed levels of (b) (4) in the drug product only (b) (4) exceed the acceptable limit of 1.5 micrograms/day, it is impossible to conclude that the relatively large signal of risk for the parent compound seen in the in vitro study does, in fact, pose a greater risk than the amount of (b) (4) to which patients would be exposed under the new specification. That is, there is no reliable way to compare the degrees of risk posed by the parent and (b) (4)

In addition, the abnormalities detected by the in vitro assay for the parent (clastogenic potential) are different from those detected in the Ames assay for (b) (4) (again, point mutations). Therefore, even if the risk from (b) (4) is quantitatively lower than that from the parent (again, this is unknown), the risks are qualitatively different, and, presumably, independent. This argues for reducing the risk due to any possible genotoxic compound; clearly, this cannot be done for the parent compound.

We agree that patients with epilepsy need more treatments, and we also assume that some patients will respond to a given anticonvulsant and not to others even in the absence of evidence documenting this. If we could be assured that the sponsor could adequately address this issue (either produce a synthesis that can bring the levels of (b) (4) to below 1.5 mcg/day, or fail in all reasonable efforts to bring it down below (b) (4); in the latter case, we would accept the limit of (b) (4) in a relatively short period of time, we would recommend approval at this time.

However, we have no absolute reassurance that this can be achieved. We are hopeful that this **can** be successfully resolved relatively quickly, but the possibility exists that the time it will take to produce a product in which the level of (b) (4) is acceptable may be prolonged. For this reason, we believe that the sponsor should be required to reduce the amount of (b) (4) in the final product before the drug is approved, and, as noted, we believe that the sponsor should be able to alter the synthetic route in a way that will definitively mitigate the risk in a relatively short period of time. It is, of course, possible that the sponsor, despite all reasonable efforts, will not be able to reduce the amount of (b) (4) any further than (b) (4) If this is true, as noted above, we would recommend approving the application (with appropriate labeling), with a post-marketing requirement that they directly assess the carcinogenic potential of (b) (4) in an appropriate in vivo model.

For the reason stated above, then, we recommend that the Agency issue a Complete Response (CR) letter.

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/s/

RUSSELL G KATZ
11/29/2010

Cross-Discipline Team Leader Review

Date	11/30/10
From	Norman Hershkowitz, MD, PhD
Subject	Cross-Discipline Team Leader Review
NDA/BLA # **Supplement#**	22345 (000)
Applicant	Valeant Pharmaceuticals
Date of Submission	10/30/09
PDUFA Goal Date	11/30/10
Proprietary Name / Established (USAN) names	Potiga/ezogabine
Dosage forms / Strength	50 mg, (b) (4) 200 mg, 300 mg and 400 mg strength tablets
Proposed Indication(s)	Adjunctive treatment of partial onset seizures in adults.
Recommended:	Complete Response

Cross Discipline Team Leader Review Template

1. Introduction

Ezogabine is a new molecular entity that has been submitted for the approval as adjunctive treatment in partial seizures in adults. There are well over 10 agents presently approved for this indication. This drug may posses a unique mechanism of action. Unlike others presently labeled, it appears to enhance neuronal voltage-gated potassium channels (predominantly KCNQ2 and KCNQ3). This action is referred to as a "potassium channel opener," and it should theoretically should stabilize neuronal excitability and exert an anticonvulsant effect. However, like some other anticonvulsants, ezogabine also seems to enhance GABA currents in neurons.

2. Background

During the developmental of this drug a strong signal for the induction of urinary retention was observed in non-clinical studies. Because of this, the Sponsor was asked to add urinary function monitoring (see below) during the developmental program, to both protect patients and collect additional data on risk. An Advisory Committee was convened, largely because of this being the first in its pharmacologic class ("potassium channel opener") and because of concerns over bladder toxicity, with reported serious cases identified in the clinical database. This adverse reaction appears to be unique amongst the anticonvulsant class of agents.

3. CMC

The Sposnor plans to market 50 mg, (b) (4) 200 mg, 300 mg and 400 mg strength tablets.

General CMC Review

One important issue was identified by the CMC and pharm/tox reviewer regarding the issue of impurities. Genetic testing of the batches of the drug indicated it to be potentially mutagenic, based upon a positive Ames test. This is thought, at least in part, to be potentially caused by the presence of mutagenic impurities, two of which, additively, are being maintained in the to-be-marketed product at adequately low levels based upon standards. The third ((b) (4) far exceeded the required limits (approximately (b) (4) based upon a recommended dose of 1200 mg daily). As the Sponsor believed that it was difficult to reduce levels of (b) (4) levels, they attempted an additional analysis using the comet assay. This assay indicated that (b) (4) was relatively safe. DNP's pharm/tox reviewers do not consider the comet assay as a truly validated measure of mutagenicity. Moreover, although carcinogenicity studies proved to be relatively negative, they were not very reassuring to DNP's pharm/tox reviewers, as the (b) (4)

impurity was lower in the these studies then that of which patients will be exposed to with the to-be-marketed product. Moreover, while the carcinogenicity studies were read as negative, they show a weak carcinogenicity signal. During a meeting on November 4, 2010 the Sponsor informed the Division that they would be able to reduce the (b) (4) impurity to approximately (b) (4) the limit. CMC believed that this could be further reduced. The issue was raised that there are presently many anticonvulsants available for this indication and, except for its unique mechanisms, this anticonvulsant does not stand out to have any unique qualities when compared to others (e.g. it is no more efficacious then others approved by the division). For this reason the division did not feel compelled to approve the agent until levels were further lowered. The decision at that time was to issue a CR letter and request that the Sposnor reduce the levels further. A latter submission by the Sposnor on November 15 agreed to lower the impurity to approximately (b) (4) the upper limit (based upon a therapeutic dose of 1200 mg/day) with a promise to attempt further reduction at latter times. This was discussed by the review team on November 16, and there was a relative consensus that by agreeing to this the Division would lose leverage in actuating the Sponsor's agreement in lowering the impurity. I would also add that I was concerned that such an agreement may result in inadequate supply of the drug, because of the limited batches available with this impurity profile, and this could potentially result in a spot shortages, as the Sponsor may not presently be equipped to produce the product at the quantities required: i.e. many batches would have to be discarded which do not show the required impurity profile. Spot shortages, can be a safety concern. The final consensus was for a CR action, although a minority in the group noted that they could vote for approval at this time, but were aligned with the final CR decision.

No other CMC issues were identified.

ONDQA Biopharmaceutics Review

Dr. John Duan performed the ONDQA review.

Dr. Duan intends in granting a bio-waiver for the 50 mg, 200mg and 300 mg strength. (b) (4)

4. Nonclinical Pharmacology/Toxicology

As noted above this agent acts predominately on the KCNQ potassium channel, although it has some GABA facilitating effect. Accordingly, ezogabine has shown to have anticonvulsant activity in a number of animal seizure models.

Of inertest, it is not believed to act on the cardiac isoform of this potassium channel and has been shown to have minimal effecting animal cardiac studies. While Ezogabine bound to hERG channel, it did so only at high concentrations. The Sponsor demonstrated little effect in non-clinical studies on cardiac tissue, except at very high concentrations when it produced a prolongation in the QT interval and decrease in heart rate.

Although not present in the heart, this potassium channel isoform is present in vascular smooth muscle and therefore may exhibit a potential for lowering blood pressure. Mild to moderate blood pressure lowering effect was noted in some, but not all, animal studies. Lack of concomitant EKG changes in these studies was interpreted as suggesting that this effect was not cardiac in origin.

The effect on this potassium channel may also influence urinary bladder and Gal Bladder emptying as well, i.e. it may decrease voiding in these organs.

Thus, urinary bladder distention, bladder necrosis and kidney damage was demonstrated in a repeated dosing studies in a number of species (rodents and dogs). These changes were likely a result of reduced urinary bladder function and increased pressure in the urinary system. Juvenile animals appeared to be more sensitive to this effect.

With regard to gallbladder effects, focal liver damage was observed in the vicinity of the gallbladder in dogs but not rodent species.

The predominant dose limiting toxicity observed in animals is that of neurotoxicity (hypoactivity, ataxia tremors, prostration, etc), which is similar to other anticonvulsants.

Neutrophil changes were observed in dogs when admistered ezogabine's active N-acetyl metabolite (NAMR). There where both increases and decreases noted in circulating neutrophils associated with some end organ inflammatory changes (e.g. brain and heart). These appeared to resolve on drug discontinuation. As this was not seen in rodents, the pharmacology reviewer interpreted this as a species specific immunologic response to a "foreign metabolite."

Reproductive and developmental studies according the pharm/tox reviwer were "fairly unremarkable." Treatment of pregnant females throughout organogenesis resulted in low birth

weight and some "fetal skeletal variations" in progeny. Treatment throughout pregnancy and lactation resulted in decreased offspring survival, body weight gain, and reflex development. The pharm/tox reviewer recommend Category C, and I agree.

Genetic testing of the batches of the drug indicated it to be potentially mutagenic based upon a positive Ames test (see above section on CMC). This is thought, at least in part, to be potentially caused by the presence of mutagenic impurities, two of which, together, are being maintained in the to-be-marketed product at adequately low levels based upon standards. The third (b) (4) base upon that which the Sposnor intends to market exceeds the required limits (see the CMC Section above).

5. Clinical Pharmacology/Biopharmaceutics

General PK Review

The principal Clinical Pharmacology Review was performed by Dr. Tai-Chen Wu.

Ezogabine is largely metabolized into an N-glucuronide. It is also metabolized into N-acetyl metabolite (NAMR), which is believed to have anticonvulsant activity, but is less potent then the parent drug. There is no evidence for hepatic oxidative metabolism of ezogabine or NAMR by cytochrome P450 enzymes. The Ezogabine is 80% protein bound and NAMR is 45% protein bound. Ezogabine is predominately eliminated through the kidneys with about 34% being unchanged.

Ezogabine exhibits linear exposure throughout its expected therapeutic range. Absorption demonstrated two peaks (Tmax at 0.67 to 1.5 and 1.7 to 4 hours) with a $T_{1/2}$ of 9-14 hours.

AUC values in elderly subjects were approximately 40-50% higher and the half-life was approximately 30% of that of younger subjects. The PK reviewer advises that the label recommends dose reduction to approximately two-thirds of the target dose, although this is not recommended by the Sposnor. I concur with the PK reviewer.

Because of reduced elimination in patients with hepatic impairment, the PK reviewer recommends a dose reduction to two-thirds of the target dose be considered for patients with moderate hepatic impairment based on PK property. Greater reductions are recommended (one-half of targeted dose) in severe hepatic impairment. I concur.

Because of reduction in AUC in renally impaired patients, the PK reviewer agrees with the Sposnor in their recommendation to reduce the initial and maintenance dose of ezogabine by 50% in patients with creatinine clearance <50 ml/min. They, however, note that there is a 50% reduction in the Cmax in patients with end stage renal disease who are on dialysis. In this case 50% reduction in dose is also recommended by our reviewers in the label, but with a

notation that caution should practiced as the "effect of hemodialysis on ezogabine clearance has not been established." I agree with the labeling of the reduced dose, but, perhaps, the label should note that the reduction in Cmax in dialyzed patients.

In their dose-response review, the PK reviewer notes that "there appears a significant relationship and seems to reach a plateau at 1200mg/day." They don't specifically seem to address whether there is a difference between the 900 mg/day and 1200 mg/day does. The PK review only included studies 301 and 302, but failed to include 205. I believe there is some evidence in the latter study that 1200 mg/day may be marginally for effective, on average then 900 mg/day (see efficacy), but there is also a substantial increase in adverse events in this dosage step.

The PK reviewer recommends the following PMRs:

- An *in vitro* study to evaluate to evaluate the potential for ezogabine to inhibit CYP2B6.
- An *in vitro* study to evaluate whether ezogabine is a substrate for major transporters in the kidney.

6. Clinical Microbiology

Not applicable.

7. Clinical/Statistical- Efficacy

Dr. Steven Dinsmore performed the clinical efficacy review and Dr. Ohid Siddiqui performed the statistical review.

Three trials were submitted for the division's consideration. Trial 205 was a "phase 2b" dose finding trial, and trials 301 and 302 were considered phase 3 pivotal trials. All trials were randomized, double-blind, placebo-controlled, international, multicenter, parallel-arm trials that examined the therapeutic effect of ezogabine adjunctive therapy in adults with partial onset epilepsy. They all used an 8 week prospective baseline phase followed by a titration phase. The titration was followed by a maintenance period of 8 week duration in trial 205 and 12 week period in trials 301 and 302. Design features of the study are presented in the table below, which is modified from the FDA's statistical review. All dosages were admistered in a TID regimen. A single back titration to 1050 mg/day was allowed in study 301 if patients could not tolerate 1200 mg/day dose.

	Study 205	Study 301	Study 302
Phase/Sponsor	IIb/Wyeth	III/Valeant	III/Valeant
Treatment Group	600, 900, 1200 mg/day, PBO	1200 mg/day, PBO	600, 900 mg/day, PBO
Duration of Double-blind	16 weeks	18 weeks	16 weeks
Duration of Titration	8 weeks	6 weeks	4 weeks
Duration of Maintenance	8 weeks	12 weeks	12 weeks
Age of Subjects	16-70 years old	18 to 75 years old	18 to 75 years old

The primary endpoint was the percent change from baseline seizure frequency as calculated from the 28-day total partial seizure frequency. The primary analysis set included a typical modified intent to treat set: i.e. patients, who received at least one dose of study drug, had a baseline seizure evaluation and at least one seizure evaluation on treatment (including titration and maintenance phase). The primary analysis in study 205 was a rank analysis of covariance (ANCOVA). The primary analysis in studies 301 and 302 was a non-parametric stratified rank analysis of covariance (ANCOVA).

Secondary endpoint evaluations included: 1) quartile distribution of change in seizure frequency from baseline, 2) number of patients who achieve total seizure freedom, 3) time without seizures, 4) potential exacerbation of pre-existing seizures or the development of new seizure types, 5) median percent change in 28-day total seizures in the maintenance phase, 6) responder rate in the double-blind phase as determined by patients with ≥ 50% reduction from baseline and 7) Investigator CGI.

Withdrawals for any reason and for reasons of adverse events appeared to be dose dependent within and between trials with approximately 15% to 22 %, 25% to 28 %, 31 to 34% and 39% withdrawing from placebo, 600 mg/day, 900 mg/day and 1200 mg/day for any reasons, respectively. Approximately one-half to two-thirds of withdrawals were from adverse events, being higher in high dose groups. Demographics (race, sex, age and US vs. non-US) were generally well distributed across treatment groups. Studies 205 and 302 contained a predominant non-US study populations (>92% and >98%, respectively). Half patients studied in trial 301 were from the US.

The table below, derived from the FDA statistical analysis, presents data from all three studies. All doses resulted in a trend for therapeutic effect, but statistical significance was reproducible only at the 900 and 1200 mg/day dose. Thus, only one of two studies was statistically significant at the 600 mg/day dose: study 205 failed to demonstrate statistical significance at this dose. However, the study 205 examined many fewer patients, then did the study 302, compromising its statistical power. Nonetheless, the magnitude of effect at 600 mg dose was approximately the same in both studies. A dose response was apparent between all doses within studies. The difference in the magnitude of the treatment effect (drug-placebo) from

600 mg/day to 900 mg/day was 10% and 12%. There, however, was only one study (study 205) were an in-study comparison was possible between doses of 900 mg/day and 1200 mg/day, and in that case the difference in treatment effect was about 6%. This suggests a dose response throughout the doses studied, but perhaps with a small degree of flattening when increased from 900 mg/day to 1200 mg/day.

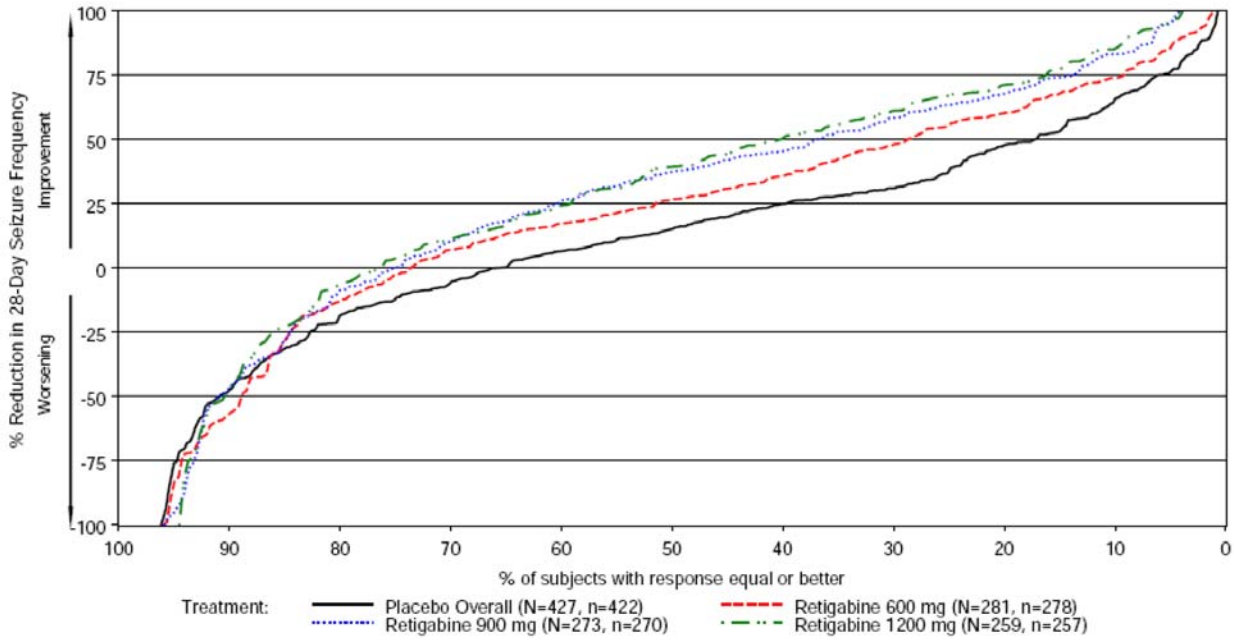
Percent Change from Baseline in Total Partial Seizure Frequency ITT Double-Blind Population for Studies 205, 301 and 302

	Placebo	ezogabine 600 mg/day	ezogabine 900 mg/day	ezogabine 1200 mg/day
Study 205				
n	96	99	95	106
Median	-13.1	-23.4	-29.3	-35.2
Range	-100, 533	-100, 1703	-100, 298	-100, 375
P-value	-	0.199	0.043	<0.001
Study 301				
n	150	-	-	151
Median	-17.5	-	-	-44.3
Range	-90, 628	-	-	-100, 302
P-value	-	-	-	<0.001
Study 302				
n	176	179	175	-
Median	-15.9	-27.9	-39.9	-
Range	-100, 1712	-94, 250	-100, 226	-
P-value	-	0.007	<0.001	-

The p-values presented are from non-parametric rank ANCOVA models.

Cumulative distribution functions (see figure below), which combines data from all the studies, is consistent with an increase in therapeutic effect from 600 mg/day to 900 mg/day. The 900 mg/day to 1200 mg/day difference is not as great, but it should be noted that the data comes from multiple studies

Distribution Profile of Total Partial Seizure Frequency (Double-Blind Phase) –
ITT Double-Blind Population: Studies 205, 301 and 302



GCP compliance issues were identified at one site in study 205 (out of a total of 73). The Sponsor performed a sensitivity analysis and according to Dr. Siddiqui, this revealed similar magnitudes of effects for all treatment groups. However, DSI (see below) concluded from their inspections that overall performance of studies were adeqaute.

Secondary endpoints such as responder rate, quartile distribution, and CGI tended to track with the primary endpoint. Off interest, CGI in one study (302) did not always track with seizure control. This may be related to the sensitivity of this measure or the increase in adverse reaction produced at higher doses.

The FDA statistical reviewer was able to reproduce all calculations performed by the Sponsor on primary and secondary endpoints as well as performing a sensitivity analysis that excluded the six sites, considered to have some degree of irregularities in study 205. Dr. Siddiqui also performed additional sensitivity analyses, which constituted other analysis methods used in epilepsy trials. These included: 1) ANCOVA analysis on the observed total partial seizure frequency at post baseline, and 2) ANCOVA on the log-transformed total partial seizure frequency at post baseline. All analyses, according to Dr Siddiqui were consistent with the conclusions of efficacy at all studied doses. Dr. Siddiqui also compared effects at US site (including Canada) with non-US sites (Mexico and South America) in study 301. He notes that "difference between treatment groups on the primary efficacy results for the mITT

population favored ezogabine in both geographic regions; although, he also notes a greater effect at Mex / S. American site (treatment difference of 39%) as compared to the US site (treatment difference of 9.3%).

The statistics reviewer performed subgroup analysis across age and sex groups and concluded no differences. My examination of Dr. Siddiqui data suggest a consistent slightly greater effect observed in female then males, perhaps representing differences in body mass. There were insufficient numbers of non-Caucasians groups to perform any meaningful analysis.

The FDA statistical reviewer concluded that "the findings of the three studies confirmed that ezogabine (600, 900, and 1200 mg/day) is an effective, add-on therapy in the treatment of partial seizures." Dr. Dinsmore and I agree with this. I would also add that while the increase in efficacy from 600 to 900 mg/day is clear there appears to smaller increase in efficacy from 900 to 1200 mg/days. This lesser increase in effectiveness must be weighed against the increase in adverse reaction (See Safety) and should be noted in the label. Dr. Dinsmore expressed a similar view.

8. Safety

Dr. Dinsmore performed the safety medical review.

Exposure

The safety database was derived from a total of 44 studies, which includes 1365 patients with ezogabine exposure in phase 2 and 3 epilepsy studies (including 1240 patients studied in the double blind placebo controlled trials with 813 drugs and 427 placebo patients) and 669 subjects in other studies (clinical pharmacology). Some additional patients received ezogabine in bipolar post-herpetic neuralgia studies. As per Dr. Dinsmore's calculation the total unique exposure to ezogabine was 2168. From examination of the data from the combined phase 2/3 exposures that Dr. Dinsmore's presents in his review, it can be gleaned that 779 patients were exposed for greater then 6 months and 483 patients exposed for greater then one year. As per the data presented by Dr. Dinsmore, approximately one half of the 6 month exposure is at doses of 900 to <1200 and one quarter of patients were exposed dose ranges each of 600 to $\leq$ 900 and $\geq$ 1200. The Sponsor is recommending doses of 600, 900 and 1200 mg/day. Such exposures are adeqaute. All prior values were based upon data presented in the original ISS. While no additional patients were exposed to drug at the safety update, the duration of exposures increased. Thus, there were 586 patients exposed for a period of greater then 1 year at the time of the safety update.

Most exposures were in Caucasians between ages 18 and 64. Male and female exposure was generally well balanced. Study 305, because of the site where the study was performed, contained 25% Hispanic patients. As Dr. Dinsmore notes, the study program allows for limited insight into generalization with regard to race, as there were generally a small percent of

patients in certain racial categories (e.g. 2.5% Black and 4.8% Hispanic). Demographics were generally well distributed between treatment groups in the controlled trials.

Deaths

Dr. Dinsmore notes that there were a total of 10 deaths, of 1365 patients (0.7%), in the epilepsy development program. Two of these occurred greater then 30 days after the last drug exposure. There were 3 deaths in the placebo group, out of 427 patients studied (0.7%), and 2 deaths, out of 813 studied (0.2%), in the ezogabine groups in the controlled phase of the epilepsy trials.

Two deaths were, according to Dr. Dinsmore, a result of identifiable medical causes. One death was from metastatic cancer, but with no informtion as to whether the cancer was present before or after ezogabine. The other was that of a 57 year old who died of diabetic ketoacidosis, but no previous history of diabetes. Other deaths (n=7) appeared to be attributable, as either possible or probable, to SUDEP, with one exception. The exception consisted of a 34 year old female who died of a "cardiovascular cause" While this patient was young she was noted to be "morbidly obese" and an autopsy revealed rather advanced coronary artery disease. This death was categorized as "SUDEP cannot be excluded." The Sponsor calculates that the rate of SUDEP in their database to be 4.4/1000 patient-years (not including the single death that was placed in the category of "cannot be excluded"). Dr. Dinsmore notes that the Sposnor compared this rate to the literature, which varied from 0.09 (newly diagnosed epilepsy) too 9.3 (refractory patients who are surgery candidates). Dr. Dinsmore notes that while the rate is high in the database, in that it closer to surgical candidates, the rate is not unreasonable as patients who are selected are relatively refractory. I agree and would also add that it is not that different from other similar epilepsy trials as analyzed by the FDA. These are described in the lamictal label. Rates in such trials varied from 3.5 to 4.0 per 1000 patient years.

Two additional deaths were added in the safety update, one from multiple myeloma and one from a subdural hematoma.

The non-SUDEP deaths do not fit an obvious pattern that might suggest drug causality.

Non-Fatal Serious Adverse Events

In placebo controlled trials approximately 6% and 9% of patients in the placebo and total ezogabine groups, respectively, experienced serious adverse events. This increased to 16% for patients receiving drug in all phase 2 and 3 epilepsy trials (i.e. including long term open label exposure). The most common serious adverse event in both controlled and open label epilepsy database were related to seizures. Rate of seizure reporting was 1.2 % and 1.5% in placebo and ezogabine dose groups in the controlled trial database, respectively, with 2.4% of patients reported to suffer from seizures in the complete phase 2/3 database. The difference between

placebo and control is not great, although one might have expected a reduction. Nonetheless, this may represent an ascertainment error, with more patients on drug reporting AEs to their doctors because of other toxicities and consequently a slightly higher rate of seizures. Moreover, no signal is apparent for all seizures reported as any adverse event (not just serious) (see below). Also formal seizure counts, as part of the efficacy measure, are likely a better determinate of seizure rate, and suggest, if anything, a reduction in seizures.

Psychotic disorder was the second most common event. In this case there was a difference with placebo and drug treatment groups, with no patients reported to have psychotic disorder as an SAE in the placebo group and 1.5% of patients reported in the drug group in the controlled database; 1.0% were reported with this event in the compete phase 2/3 seizure database. There appeared also to be a suggestion of dose response for this effect. This appears rather significant. This will be discussed further in a special section below, but it is noteworthy that the Sposnor has included this in the Warnings and Precautions section of the labeling to which I agree.

Other less frequent, but still common, serious adverse events observed included nausea, fatigue, drug toxicity, encephalopathy, dizziness, myoclonus, confusional state and suicidal ideation. The complete epilepsy database exhibited similar SAEs profile, but with the addition of some other notable events of dizziness, chest pain, somnolence, headache, conversion disorder, urinary retention, hyponatremia, coma, metal status changes, vertigo, urinary tack infection , renal colic, cholelithiasis, and increased transaminase. Many of these will be described in the label, but drug attribution for some are unlikely likely due to other causes (e.g. hyponatremia confounded with other causal medications and chest pain was a common event that occurred at similar rates in drug and placebo groups). Some of the more important serious events will further discussed in sections below.

Few SAEs are reported for other studies (i.e. Clinical Pharmacology). However, considering the mechanism of this drug, Dr. Dinsmore points out two interesting events occurring in abuse studies that examined patients with a prior drug history of drug abuse, where telemetry was preformed: 1) A 41 year old with 5, 3 to 8 and one 19 beat run runs of ventricular tachycardia without any associated symptoms ; 2) Cardiac arrest/asystole in a 34 year old female that involved a 25 second period of asystole in a patient with a pre-drug history of marked sinus bradycardia (44 BPM), which spontaneously resolved . Both events occurred at relatively high single dose exposures (single doe of 900 mg). In an additional multiple dose PK study, one patient was noted to have ventricular tachycardia in the form of recurrent episodes of 3 beat runs and some dizziness and “vaso-vagal episode” and other general symptoms of poor tolerance such as somnolence, and coordination problems. These cases, along with additional cases of atrial fibrillation (2 of which were described as serious) identified in an ongoing study on post-herpetic neuralgia will be discussed further below. But, as will be seen, this reviwer concludes that there are to many confounders in the atrial fibrillation cases. The single prolonged case of ventricular tachycardia and the asystole will be included in the overdosage section, although these are isolated cases and there may be some confounders (i.e. history of drug abuse in both and bradycardia in one).

Dropouts and/or Discontinuations

Adverse events resulted in discontinuation in 11% of patients in the placebo group and 25% of patients in the ezogabine group in all controlled epilepsy trials and 31% of patients in all phase 2 and 3 experience (including open label). This effect exhibited a dose response relation in the controlled trials, with 11%, 17%, 25%, and 31% discontinuing in the placebo, 600, 900, and 1200 mg/day groups, respectively. The most frequent causes of discontinuations in controlled studies were neurologic in nature. Thus, adverse events associated with discontinuations where treatment difference (drug-placebo) for the total ezogabine group was > 2.0% were dizziness, confusional state, somnolence, and fatigue. However, vertigo coordination abnormal, disturbances of attention, headache, tremor and dysarthria also ranked high (treatment difference between 1 and 2%). Many of these events are common to the anticonvulsant class of medications. Most of these adverse events exhibited a dose dependency. Dropout in the complete phase 2/3 trials were of similar nature. Notable dropouts included those related to potential urinary toxicity (see below), including 5 cases of urinary retention, 1 atonic urinary bladder, 1 hematauria, 1 hydronephrosis, 1 micturition frequency decreased, 1 nephritis, 1 nephropathy toxic, and 1 renal failure. Dr. Dinsmore describes 22 cases of patients dropping out because of liver function abnormality. This will be discussed below. Also noted was 1 suicide attempt in all phase II/III studies which is in keeping with a concern addressed by class labeling for anticonvulsants. There was 1 case of WBC count decreased, 1 case of aplastic anemia, and 1 case of bone marrow failure reported, which will be discussed below.

Common Adverse Events

Adverse events in the controlled database were observed in 75% of patents in the placebo group and 81% for all ezogabine treated patients. There was some degree of dose dependency but with a shallow slope (e.g.74% to 88% in 600 to 1200 mg/day). Incidence of Adverse Drug Reactions Reported in ≥ 2% of Patients Treated with 600, 900, or 1200 mg/day Ezogabine and Numerically Greater Than Placebo for the control study population are presented in the table below (transcribed for Dr. Dinsmore's review). Most of the treatment emergent adverse events reported by ezogabine-treated patients were mild to moderate in intensity. Of note, the majority of common adverse events are neurologic and neuropsychiatric. This is rather common for the anticonvulsant class of medication. There is a particularly high treatment effect (>10 % at any dose) for dizziness, somnolence confusional state, fatigue and tremor. Most common effects appeared to be dose dependent.

Preferred Term	Number (%) of Patients			
	Placebo (N=427)	ezogabine 600 mg/day (N=281)	ezogabine 900 mg/day (N=273)	ezogabine 1200mg/day (N=259)
Dizziness	38 (8.9)	41 (14.6)	64 (23.4)	84 (32.4)
Somnolence	51 (11.9)	43 (15.3)	67 (24.5)	69 (26.6)
Confusional state	11 (2.6)	12 (4.3)	21 (7.7)	42 (16.2)
Fatigue	25 (5.9)	45 (16.0)	40 (14.7)	34 (13.1)
Tremor	12 (2.8)	7 (2.5)	26 (9.5)	32 (12.4)
Coordination abnormal	12 (2.8)	14 (5.0)	14 (5.1)	30 (11.6)
Blurred vision	9 (2.1)	5 (1.8)	12 (4.4)	27 (10.4)
Vertigo	9 (2.1)	22 (7.8)	21 (7.7)	24 (9.3)
Memory impairment	11 (2.6)	7 (2.5)	15 (5.5)	24 (9.3)
Dysarthria	3 (<1.0)	10 (3.6)	5 (1.8)	21 (8.1)
Nausea	22 (5.2)	18 (6.4)	17 (6.2)	22 (8.5)
Diplopia	7 (1.6)	22 (7.8)	15 (5.5)	19 (7.3)
Disturbance in attention	4 (<1.0)	17 (6.0)	15 (5.5)	17 (6.6)
Aphasia	4 (<1.0)	3 (1.1)	9 (3.3)	17 (6.6)
Gait disturbance	5 (1.2)	6 (2.1)	13 (4.8)	15 (5.8)
Paraesthesia	9 (2.1)	7 (2.5)	4 (1.5)	14 (5.4)
Balance disorder	3 (<1.0)	8 (2.8)	8 (2.9)	13 (5.0)
Constipation	6 (1.4)	4 (1.4)	11 (4.0)	13 (5.0)
Disorientation	3 (0.7)	1 (0.4)	1 (0.4)	12 (4.6)
Anxiety	8 (1.9)	7 (2.5)	5 (1.8)	12 (4.6)
Influenza	9 (2.1)	10 (3.6)	3 (1.1)	12 (4.6)
Asthenia	8 (1.9)	12 (4.3)	15 (5.5)	11 (4.2)
Dysuria	3 (0.7)	4 (1.4)	5 (1.8)	10 (3.9)
Urinary hesitation	4 (0.9)	6 (2.1)	3 (1.1)	9 (3.5)
Amnesia	3 (0.7)	2 (0.7)	9 (3.3)	8 (3.1)
Dysphasia	2 (0.5)	3 (1.1)	3 (1.1)	7 (2.7)
Weight increased	5 (1.2)	6 (2.1)	9 (3.3)	7 (2.7)
Dyspepsia	7 (1.6)	7 (2.5)	4 (1.5)	7 (2.7)
Chromaturia	1 (.0.2)	2 (0.7)	4 (1.5)	7 (2.7)
Psychotic disorder	0	0	1 (0.4)	6 (2.3)
Hematuria	3 (0.7)	6 (2.1)	3 (1.1)	4 (1.5)

Other adverse events reported in the Pivotal Controlled Trials grouping of studies in <2% of patients treated with ezogabine and numerically greater than placebo were increased appetite, hallucinations, myoclonus, hypokinesia, dry mouth, dysphagia, hyperhidrosis urinary retention, malaise, increased liver function tests, and peripheral edema. Events observed in the complete phase 2/3 trials were similar to that observed in the control trials.

While increase in weight is observed an adverse event, it was also observed in central analysis of weights and appeared dose dependent. Thus, in controlled trials the 16 week mean weight measurements were increased in the placebo, 600 mg/day, 900 mg/day and 1200 mg/day groups by 0.2 kg, 1.2 kg, 1.6 and 2.7 kg, respectively. Because of its apparent predictability and dose dependence Dr. Dinsmore and I recommend that this specific informtion be included in the label.

Laboratory Value Changes

Generally laboratory values remained unchanged with some exceptions.

Liver function changes as well are described below.

Although no changes in central tendency are noted there was a small increase in hyperkalemic outliers in controlled trials. Dr. Dinsmore notes that this is "not conclusive for causality," but should be noted in the labeling. In examining his data, I am not fully convinced that this is a true effect. When compared to other electrolytes, the number of placebo potassium outliers, which is what is used for comparison, appears unusually small and no obvious dose dependency is apparent.

Adverse Events of Special interest

Urinary Track disorders

Along with Dr. Dinsmore's review DRUP was asked to review the informtion on urologic complications. Dr. Kim performed that review.

In the early phases of ezogabine's drug development, a very predictable finding of bladder toxicity was observed in animal studies (see above). As a result the Sponsor was requested to carefully monitor bladder function. The monitoring included scheduled post-voiding residuals as well as directed questions according to the American Urological Association Symptom Index (AUA SI).

Dr. Dinsmore notes that during the double-blind phase of the randomized controlled trials, renal and urinary disorder AEs were reported for greater proportions of patients in the Total ezogabine group than the placebo group (17% versus 12.9%). The most common renal and urinary disorder reported adverse events in the ezogabine vs. placebo group (total drug group vs. placebo, respectively) were urinary tract infection (4.3% vs. 4.7%), dysuria (2.3% versus 0.7%), urinary hesitation (2.2% versus 0.9%), chromaturia (1.6% versus 0.2%), hematuria (1.6% versus 0.7%) and urine analysis abnormal (1.6% versus 0.9%). Other symptoms that exhibited a small treatment effect (i.e. at least 1% on drug and greater then placebo in controlled trial) included, but were not limited to nephrolithiasis, renal colic, urinary retention and residual urine volume. In the controlled epilepsy database there were 4 urinary serious adverse events that included renal colic, urinary retention, atonic bladder and atonic bladder/urinary incontinence and 5 adverse events that resulted in drug discontinuation (UTI, renal failure, hematauria, atonic bladder, urinary retention nephritis; 2 overlapping with SAEs) in the ezogabine group as compared to 1 SAEs (urinary retention) and 3 discontinuations (polyuria, polyuria/urinary retention and renal colic) in the placebo group, respectively.

No differences between placebo and ezogabine treatment groups were obvious in the AUA SI in the controlled trials.

Dr. Dinsmore also notes that in the complete phase 2/3 epilepsy database urinary track database adverse events were as follows: Urinary tract infection (8%), urinalysis abnormal (3%), dysuria (2%), urinary retention (2%), hematuria (2%), chromaturia (2%), polyuria (2%) and residual urine volume present (1%); all other renal and urinary AEs were reported by <1% of ezogabine-treated patients. There were a large number of serious adverse event reports referable to the urinary tack (n=29) in the phase 2/3 database. These consisted of events including urinary retention (n=8), residual urine volume (n=1), renal colic (n=3), atonic bladder (n=1), UTI (n=4), urosepsis (n-1), hydronephrosis (n=1), renal failure acute. Post voiding residuals in cases of urinary retention in this database varied from about 100 cc to 1,000 cc. Dr. Dinsmore notes that one case was associated with hydronephrosis, hydroureter, pyelocaliceal dilation or swollen kidney without identifiable obstructive process on diagnostic imaging, indicating that this indeed may be drug induced alteration in bladder function. These symptoms generally resolved with drug discontinuation. Off note, some events were classified as serious and some resulted in drug discontinuation. Dr. Dinsmore's analysis was also unable to demonstrate a close relationship between baselines, pre-drug, PVR and the likelihood of developing retention. There appeared to be no evidence that sex was a risk factor. Age was not generally a risk factor although there was a small tendency that patients over 50 years of age were at a slightly greater risk. As noted, PVRs were monitored throughout the studies. Changes in PVR did not appear to predict impending retention in this database.

Dr. Dinsmore performed an exploration of the complete database to examine factors associated with urinary retention. He identified 25 cases of urinary retention in the complete safety database. He demonstrated that 16 (59%) of the urinary retention events occur in the first six months, 5 (18.5%) in the first month; however, cases were seen as far as 2.5 years after the initiation of drug. Dr. Dinsmore also explored dose dependency of this effect. His analysis did not identify an obvious dose relationship, with events occurring at doses as low as 300 mg/day. However, when our urology consultant performed an analysis, combining all urinary retention preferred terms, (e.g. not only 'retention" but "impaired," "hesitation," atonic and frequency) a potential dose-response was apparent. There was no association between degree of post voiding residuals and dose as well.

Dr Kim (DRUP) essentially agreed with DNP's review in that he concluded that Ezogabine resulted in an increased risk of voiding dysfunction, including urinary retention. The DRUP reviewer notes that urinary retention occurred despite monitoring.

Dr Kim also notes that there was a tendency for increased "amorphous material" to be reported in patients on drug, as compared placebo. There was also a tendency for more stone formation to be observed in patients on drug then placebo, but no stone was identified as being composed of drug, which is largely excreted in the urine. He does not believe hat there is a clear signal for ezogabine stone formation. An advisory committee examined all these issues; the results of their deliberations can be found in the section Advisory Committee Meeting below, but they also did not conclude a predictable association between stone formation and ezogabine.

Seizures

The Sposnor and Dr. Dinsmore performed an analysis of seizure like events associated with treatment. As may be expected for the present population, the preferred term "convulsions were observed the same or less in drug treatment groups. The term myoclonic appeared more frequent in drug then in placebo (e.g. compare 0% in placebo and 1.1% in drug). This should, and is, included in the label. A calculation of relative risks based upon seizure related adverse events of seizures, performed by Dr. Dinsmore, demonstrated that the 95% confidence interval for every dose in the controlled trial subsumed a relative risk of 1.0. Except for the issue of myoclonus, the adverse event reporting appears consistent with the therapeutic effect of this drug and not with a risk for increased adverse events.

Psychiatric and Cognitive Effects

Dr. Dinsmore performed his own analysis of psychiatric events search terms (e.g. anxiety, disorientation, psychosis, depression thinking abnormal acute psychosis etc). He also performed analyses where he differentiated terms related to psychotic type behavior (e.g. hallucinations and psychosis) with that of other psychiatric symptoms (e.g. disorientation and anxiety).

In general, there appeared to be a dose-response relation between all psychiatric events and drug dose in the controlled trials with 6.3%, 5.7%, 7.0% and 16.6% of patients experiencing a psychiatric event in the placebo, 600 mg/day, 900 mg/day and 1200 mg/day groups, respectively. The most common events occurring in the controlled trials at the high dose (1200 mg/day) were anxiety, disorientation, psychotic disorder and hallucinations, where the observed treatment effect (drug - placebo) was 2.5%, 3.9%, 2.3% and 1.5%, respectively. Psychiatric events led to 8 withdraws and 2 SAEs (both SAEs were also study withdrawal) out of 427 patients in the placebo group compared to 28 withdraws and 8 SAEs (1 SAE was also a study withdrawal) out of 813 patients in the ezogabine treatment groups. Dr. Dinsmore performed a more focused review on psychotic type behavior (e.g. terms related to hallucinations or psychosis). In this case there was a very dramatic dose response relation when all such terms were combined with 0.5%, 1.4%, 1.8% and 5.0% of patients experiencing these symptoms in the placebo, 600 mg/day, and 900 mg/day and 1200 mg/day dose groups, respectively. Within this group there were 12 withdrawals in the drug group and 0 in the placebo. Dechallenge data was examined for the patients whom discontinued treatment. This revealed recovery occurred after 9 to 25 days. Some patients experiencing psychotic symptoms had a prior psychiatric history. A similar picture was observed in the full phase 2/3 epilepsy database, which included open labeled studies. Dr. Dinsmore points out that one study, where a rapid up–titration regimen was used, had a remarkably high incidence of psychotic type behavior. Thus 5 patients out of 27 discontinued because of psychotic like behavior. Dr. Dinsmore concludes that this study strongly indicates that the rate of up-titration is a factor in the induction of a psychotic like state. I agree. Psychosis was observed not only in seizure

patients, but in one normal patients, perhaps supporting the view that this does not represent a simple post-ictal psychosis type phenomenon.

Dr. Dinsmore concluded that behavioral toxicity is a very significant effect of the drug and should be discussed in the Warnings section of the label. I agree. The Sposnor has included it in the Warnings.

No cases of suicide were noted. One case of attempted suicide and another of suicidal ideation was observed in the drug group in the controlled trials. This may be compared to 2 cases of suicidal ideation in the placebo group. On the whole, this is not adeqaute by itself to permit a definitive statement regarding suicide, this drug, however, will receive the FDA class labeling as a result of our prior meta-analysis of previous combined controlled data on other anticonvulsants.

Ezogabine produced a common and obvious effect on cognition, which was dose dependent. Thus, a treatment effect (drug-placebo) of the adverse events of memory, speech abnormalities and confusion were reported in the high dose group in 21.3%, 14.6% and 16.8%, respectively. Few of these events were considered serious; however, in the high dose group approximately 7% of patients withdrew because of confusion. This informtion will be contained in the Warnings and Precautions section of the label.

Cardiac effects

Mean blood pressure and mean changes in orthostatic did not seem to be influenced by Ezogabine. Dr. Dinsmore notes sporadic cases of hypotension. I believe that these data are too variable and the differences between drug and placebo too small to conclude an effect on blood pressure or orthostasis. An outlier analysis performed by Dr. Dinsmore further supported the difficulty in attributing changes in blood pressure. Thus, drops in standing systolic blood pressure over baseline >20 mm Hg were observed in 22%, 25%, 21% and 24% of individuals patients receiving placebo, 600 mg/day, 900 mg/day and 1200 mg/day, respectively. There was a very small hypotensive effect in Dr Dinsmore's central analysis that appeared to be dose dependent, and involved mean drops in standing systolic blood pressure of 1.2 to 2.6 mmHg. This might be labeled, although admittedly the signal is very small.

Dr. Dinsmore notes little difference in general cardiac adverse events in drug as compared to placebo in randomized control trials in epilepsy. There was a slight difference in syncope between placebo and drug in the randomized control database (2/427 in placebo and 5/ 813 in the drug group). While this difference does not account for that large of a difference all cases of syncope were observed at the two higher doses. There were also 12 of 1365 cases of syncope in the total phase 2/3 database. Dr. Dinsmore notes 2 of these were reported as serious, with one, which he believes representing a seizure and in another there was inadequate informtion. Dr. Dinsmore examined the database for other cardiac reported events associated with these syncope cases and notes that no other cardiac symptoms were reported to be associated with these cases. He did note that some patients had a tendency for a general drop in blood pressure (10-20 mg Hg), not necessarily during the event. It is difficult to

definitively find causality with blood pressure as these pressure changes, which were sporadic and not necessarily linked to the event. In all, this may not be adeqaute for labeling, but should be followed as part of post-marketing vigilance.

The most notable cases of cardiac arrhythmias were observed in non-epilepsy studies. Two included exposure to high doses in patients with histories of drug abuse who were otherwise healthy and included, whom was dosed while on telemetry: 1) a 34 year old women with a 25 second period of asystole in a patient with a history of bradycardia, 2) a 41 year old male with runs of ventricular tachycardia (three 3 to 8 beats and one 19 beats). With these single isolated cases, it is difficult to attribute causality, but it is noteworthy that they occurred with a rather high single dosage. These cases will be described in the overdosage section of the label.

It is also noteworthy that 4 cases of a total of 813 patients in a randomized placebo control study on post heraptic neuralgia experienced atrial fibrillation in the drug treatment group while none (out of 427) were reported for the placebo group. It should be noted that this data was not part of the original NDA submission, as the trial was ongoing, but where requested during the ongoing NDA review. All cases occurred in the elderly and at least three had risk factors or an acute illness that may have led to a predilection toward atrial fibrillation. Dr. Dinsmore believes that these cases are a potential risk of the drug. This was discussed at team meetings and it was felt that there is presently inadequate data for certainty of drug causality as the patients whom developed this were elderly and had other risk factors. This being the case there should be some form of post-marketing pharmacovigilance for this and other cardiovascular adverse events.

The Sposnor performed a randomized-controlled, double-blinded, active and placebo, 3-arm (ezogabine, placebo, or moxifloxacin) parallel study in 120 healthy subjects. The highest dose examined in this study was the highest therapeutic dose of 400 mg TID. This was done for reasons of tolerance. Indeed many patients were unable to tolerate that dose. The largest upper bounds of the 2-sided 90% CI for the mean difference in QTcF between ezogabine 400 mg TID group and placebo was above 11.9 msec ms. The largest lower bounds of the two-sided 90% CI for the ΔΔQTcF for moxifloxacin was greater than 5 ms. No clinically relevant effect was observed on the PR and QRS interval. Off note, Dr. Dinsmore observed a subtle suggestion of a dose response in the RCT for QTcF for 30 msec outliers with placebo being 7.9% and 1200 mg daily being 12.1%. No cases of Torsades were observed in the database. QT prolongation, and its potential clinical significance, will be noted in the label. The IRT team notes that this informtion should be included in the label and that "QT interval should be monitored when POTIGA is prescribed with medicines known to increase QT interval and in patients with congenital long QT syndrome, heart failure, ventricular hypertrophy, hypokalemia, or hypomagnesemia."

Hepatic and Biliary Effects

Controlled studies showed a slight disproportional percent of liver function test elevations reported as an "adverse reaction" in drug treated groups. Thus, "all hepatic function" increases

were observed in 1.4 % of patients in placebo and 3.1 % in all drug treated groups. While this increase was not seen in reported AST (placebo 0.5% and drug 0.2%) it was in ALT (placebo 0.2% and drug 0.6%). Moreover, in the combined phase 2/3 database 14 of 1365 (1.0%) exhibited increase of ALT greater then 3 X the upper limit of normal (ULN) cases in 9 (0.7%) cases of greater then 5X ULN. 11 cases of ALT with increases > 3 ULN were noted to have drug discontinued following the ALT elevation and all were noted to exhibit a trend toward "normalization" afterwards. With two exceptions, which will be discussed below, elevations of transaminase were not associated with elevations in bilirubin. In one case a 48 year old female, described above in the discussion on urinary retention, presented with viral symptoms. She was noted to have ALT and total bilirubin elevation of 5.2 X ULN and 1.66 X ULN, respectively. This patient, however also experienced Alkaline Phosphatase increases by about three fold the ULN. She was discovered to have urinary retention with 1500 cc and renal. The combination of this occurring in the background of a potential urinary track infection, which can lead to elevations in bilirubin, and associated with elevations in Alkaline phosphatase, makes it unlikely that it represent as "near" Hy's Law case. The second case was that of a patient with elevated AST and ALT, the latter which was 10 times the ULN, which was associated with normal Alkaline Phosphatase. The total bilirubin was in the upper limits of normal, but the indirect bilirubin was 2.4 time the ULN. This case was discussed with Dr. John Senior, who noted that this does not represent a Hy's law case. One must use total bilirubin. The significance of the elevation of the indirect is unknown, but it could represent an alteration in the way bilirubin is metabolized.

Central analysis revealed small increases in ALT and AST which were not necessarily dose dependent. There is, however, a consistent increase in bilirubin, which the Sponsor notes is a result the interference of ezogabine and its NAMR metabolite with the analytic method used to measure bilirubin. Shift analysis revealed a similar trend. This interference with the bilirubin assay should be noted in the label; the Sposnor has included it.

Of an additional interest is the fact that non-clinical trials, at least in one species, suggested that there was a potential for cholestasis, through a mechanism involving reduced gallbladder contraction. Dr. Dinsmore performed an analysis of this by examining related adverse events and could not find an association. The above data on liver did demonstrate one case with elevated bilirubin and alkaline phosphatase. These, however, are not sufficient to conclude that ezogabine produces cholestasis.

The label notes elevated liver function test in the adverse events section, which I believe is appropriate. Hepatobiliary reactions should, however, be a subject of post-marketing pharmacovigilance.

Blood Dyscrasias

Nonclinical studies revealed a question of a potential signal for neutropenia in dogs with sub-chronic (13 week) treatment (see Pharmacology/Toxicology section above). This signal was not observed rodents.

Dr. Dinsmore examined all adverse events reported under the rubric of "blood and lymphatic events." While sporadic events were noted, there was no definitive trend. Thus, for example, while leucopenia, in the randomized control trials, was reported as an adverse event more commonly in the combined drug group then placebo group (1.2% vs. 0.4%, respectively), this was reversed for neutropenia (0.2% and 1.2, respectively). Also, one case of pancytopenia was observed in the placebo group and none in the drug group. Two of the hematologic events were labeled as serious, with one in the drug and one in the placebo group. The one labeled as serious in the drug treated groups started out with a low neutrophil count (1.1) and dropped to a critical level (0.9) but returned to baseline values with continued drug treatment and the initiation of folate. This case is really noncontributory, considering the small relative drop, it may have simply represented laboratory variability. The controlled trial outlier evaluation also reflected the absence of an obvious effect. Examination by Dr. Dinsmore, of this data revealed little or no difference in outliers when the combined dosage groups where compared to that of the placebo for total White Cells and Neutrophils. Moreover, although there appeared to be a potential small effect of drug when high dose outliers alone was compared to placebo, this effect vanished when one considered the incidence of baseline outliers, which was more common in the drug treated group. Dr. Dinsmore also examined individual cases for low neutrophils in the high dose group, and confirmed, in all but one case, the low count can be attributed to low baseline levels. In the one exception, the patient appeared to be continued on Ezogabine and started on folate (perhaps to reverse the folate waisting effect of carbamazepine, which was a concomitant medication), and appeared experience subsequent improvement. In central analysis very small changes in mean and median, over placebo, were observed at all doses in a non-dose dependent fashion for WBCs and Neutrophils. Thus, for the WBCs these changes were approximately 6% from baseline value decline over placebo. This small change might be considered in the adverse event section of the label.

One hematologic case was categorized as serious, labeled as a case of "aplastic anemia." This patient exhibited low total white blood cell count (3.6) and borderline low neutrophil (1.67) count at baseline. This patient presented with pneumonia, after 2 months of treatment and was hospitalized. At this time the cell count was high, but during hospitalization the total WBCs and Neutrophils were observed to drop (2.2 and 1.2). A bone marrow biopsy was read as "hypocellular." HCT and other blood elements were also noted to drop during this hospitalization. Nonetheless, the patient was continued, after discharge, on ezogabine for 2 months with continued low cell count, but no further downward trend. The patient was subsequently withdrawn from drug and 2 months after discontinuation was noted to have a continued low white cell count (2.3) low, but almost normal HCT. Dr. Dinsmore notes this case is confounded by the lack of de-challenge the acute infection, immediately followed by the cellular reaction. I would add that it is difficult to consider this an aplastic anemia, considering the stabilization of counts, albeit low, with continued treatment. Two additional serious cases are noted by Dr. Dinsmore that is described as neutropenia. Both cases started

with already low blood counts with one having only a small change in total count and the other resolving with continued drug use.

It is noteworthy that many anticonvulsants produce a dose dependent lowering of cell counts, which accounts for the high rates in the placebo groups. This background signal adds noise to the analysis, but Dr. Dinsmore concludes no increase in serious events, but the drug may have potential for some degree of bone marrow suppression, similar to other anticonvulsants, which I believe should be noted in the adverse section of the label.

There were small, but likely insignificant, reductions in the hematocrit.

9. Advisory Committee Meeting

An Advisory Committee was held on 8/11/10. The principal motivation for convening the committee was that ezogabine was considered first in its class (potassium opener anticonvulsant) and there were concerns about the strong animal and clinical signal for urinary retention. The committee consisted of the core PCNS members along with selected experts in epilepsy and urology.

The Committee unanimously agreed (13 yes, 0 No and 0 abstain) that there was substantial evidence of the effectiveness for ezogabine in the adjunctive treatment of partial onset seizures in adults. An overwhelming majority of members believed that urinary retention, which is considered a significant safety issue, can be mitigated with patient monitoring. (11 yes, 0 no and 2 abstain). As to how such monitoring should proceed was debated. Generally there appeared consensus that clinicians should use the clinical interview, patient education and possibly other instruments (symptom index) to monitor. One recommendation was made to use the AUA symptom index. However, it was noted that this was not predictive in studies. The panel discussed that perhaps in complicated cases (e.g. patients with neurologic disease that may effect urinary voiding and cognitively impaired patients) that urologic consultation may be useful. One urologist suggested spot urine residuals are helpful. The Committee unanimously agreed (0 yes, 13 No and 0 abstain) that monitoring was not required for infections or urolithiasis. The committee also agreed that additional populations at risk of urinary complications include old (>65 years of age) and children under 12. They suggested that children under 12 should not be studied until urodynamic studies are performed (see the discussion on PMR). The committee members agreed that there are no other serious safety issues that they are aware of that would preclude approval.

10. Pediatrics

The issues of PREA requirements were presented to the PeRC. There was mutual agreement with this division that:

- Pediatric studies in patients <1 month should be waived as partial seizures cannot always be adequately diagnosed or identified in this population.
- Development in children 1 month to <12 years should be deferred till more experience is obtained from an older population. The advisory committee also expressed a similar reserve and additionally suggested that such studies not be started till urodynamic studies are performed (see above). It is noteworthy that non-clinical studies indicated greater urinary morbidity in juvenile as compared to adult animals. Moreover, it is believed that this population would have difficulty in communicating any urinary symptoms to guardians and investigator, which may put them at high risk for irreparable urinary bladder and potentially kidney injury.

11. Other Relevant Regulatory Issues

DSI performed inspections at two sites in each of the two phase 3 trials, for a total of 4 inspections. Two were performed at domestic and 2 at foreign sites. Dr. Tony El Hage wrote the final review and concluded that "overall the data submitted from these sites are acceptable in support of the pending application."

The proprietary name of Ezogabine was approved. (b) (4) The Division agreed with this conclusion. The established name was subsequently changed to "ezogabine."

CSS recommended that ezogabine be Scheduled as a (b) (4) Human abuse studies indicated a number of subjects reporting euphoric mood, hallucinations and somnolence. Other studies confirmed this effect. There was a general consensus for such labeling. The Sposnor suggested a number of withdrawal phenomena, such as confusional state, psychosis, dizziness headache, hematuria, etc, be included in the label. Dr. Dinsmore performed a careful analysis of these cases and determined that the study was not adequately performed to separate out drug from withdrawal effects. I recommend not including such informtion in the label. CSS would like to require a PMR/PMC to investigate potential withdrawal symptoms in animals. The specifics for such a study has not yet been worked out.

12. Labeling

See final label in the CR letter.

13. Recommendations/Risk Benefit Assessment

Considering the findings of effectiveness and risks, approval is recommended from a clinical perspective. Thus, while there are risks associated with the use of this drug (e.g. urologic and psychiatric), the effectiveness for this drug, in this serious disease, outweighs such risks.

Moreover, risks can be mitigated through patient and physician education and monitoring. A REMS has been established to accomplish this end (see below) However, because of CMC-Carcinogenicity issues, described above, the division is recommending a complete response.

REMS

This division and the advisory committee recommended a REMS. The Sposnor has included MedGuide that describes Urologic and suicidal ideation issues in the first section of "most important informtion." Other significant adverse reactions are described elsewhere. The material is generally adeqaute but requires editing. Also included is a communication plan that consists of "Dear Health Professional Letters" to Neurologists, Urologists, ER physicians and Pharmacists. This informtion would also be included in a website. Except for editing, this plan seems appropriate.

Post-Marketing Requirements

Clinical team recommends two post-marketing requirements:

- *Urodynamic study*: While Ezogabine's effect on the bladder is assumed to be mediated by its ability to open potassium channels and to therefore relax the detrusor muscle, this mechanism has not been established in human subjects. The urologists on the advisory committee were impressed by the unpredictable nature of the urinary retention adverse events in the Ezogabine clinical trials, and believed that an understanding of the mechanism of this drug's direct effect on the lower urinary track function in humans might provide a better strategy for risk management. The currently proposed mechanism of action is largely focused on motor function of the bladder smooth muscle; however, one urologist on the advisory committee speculated that the variable presentation of urinary retention may be consistent with an effect on the sensory and not the motor arm of bladder function control. To clarify this issue the advisory committee recommended that urodynamic studies be performed as a post-marketing requirement. Therefore, we request that such studies be performed in patients with epilepsy and should include patients of different ages and in both sexes. Pre- and post- drug urodynamic measures should be carefully collected. Blinding, as well as randomization between active drug and a placebo control arm, is recommended. Urodynamic measurements should include, although not necessarily be limited to, uroflowmetry, multichannel cystometry, electromyography (EMG), and subjective sensory reporting.
- *Prospective Cohort Study of Patients Starting on Ezogabine as compared to those on Other Anticonvulsants.* The Sponsor has proposed a cohort study to better

define the risk of urinary retention and how it may vary with demographics (e.g. age), comorbidities that influence voiding (BPH, Multiple Sclerosis) and concomitant medications that may influence voiding. Using the (b) (4) database they will compare patients started on Ezogabine with those started on other anticonvulsants for the incidence of urinary retention. The study will analyze approximately 1,000 to 2,000 Ezogabine exposed patients, based upon different assumptions. The Division agrees with the performance of this study.

Clinical Pharmacology has the following recommended PMCS:

- An *in vitro* study to evaluate to evaluate the potential for ezogabine to inhibit CYP2B6.
- An *in vitro* study to evaluate whether ezogabine is a substrate for major transporters in the kidney.

CSS

- Animal studies to examine for possible withdrawal symptoms that may be in indiactive of physical dependence.

Pharmacovigilance

A number of suggestions are made by me for requiring pharmacovigilance. These include:1) the hepatobiliary system, 2) cardiovascular system.

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

/s/

NORMAN HERSHKOWITZ
11/30/2010

Deputy Office Director Decisional Memo; NDA 22-345

Date	11/30/2010
From	Ellis F. Unger, M.D., Deputy Director, ODE-I
Subject	Deputy Office Director Decisional Memo
NDA#	22-345
Applicant Name	Valeant Pharmaceuticals North America
Date of Submission	10/30/2009
PDUFA Goal Date	11/30/2010 (extended by major amendment)
Proprietary Name / Established (USAN) Name	Potiga ezogabine
Dosage Forms / Strength	Oral / 50, (b) (4) 200, 300, and 400 mg
Indication sought	…as adjunctive treatment for patients 18 years of age and older with partial onset seizures with or without secondary generalization.
Action:	*Complete Response*

Material Reviewed/Consulted – Action Package, including:	
Project Manager	Stephanie Keefe
Medical Officer Review	Steven Dinsmore
Consultant, Division of Reproductive and Urologic Products	Chong M. Kim, Mark Hirsch
PharmaCometric Review	Joo-Yeon Lee, Yaning Wang
Pharmacogenomic Review	Li Zhang, Issam Zineh
Statistical Review	Ohidul Siddiqui, Ling Chen, Kun Jin
Pharmacology Toxicology	Edward Fisher, Lois Freed
Chemistry Manufacturing and Controls	Mohan Sapru, Martha Heimann, Ramesh Sood
Statistical Review and Evaluation of Carcinogenicity Study	Mohammad Atiar Rahman
Biopharmaceutics	Mohan Sapru, John Duna, Patrick Marroum
Clinical Pharmacology	Ta-Chen Wu, Kristina Dimova, Angela Men
Clinical Pharmacology Safety Review	Peifan Bai, Darrell Abernethy
Environmental Assessment	Mohan Sapru
Division of Scientific Investigations	Antoine El-Hage, Jyoti Patel, Cynthia Kleppinger, Tejashri Purohit-Sheth
Division of Medication Error Prevention and Analysis, Office of Surveillance and Epidemiology	Tara Turner, Zachary Oleszczuk, Manizeh Siahpoushan, Kellie Taylor
Division of Risk Management, Office of Surveillance and Epidemiology	Barbara Fuller, Reema Jain, Mary Dempsey, LaShawn Griffiths, Sharon Mills, Claudia Karwoski, Kendra Worthy, Reema Jain, Jodi Duckhorn, Kate Heinrich
Controlled Substances Staff	Katherine Bonson, Ling Chen, Michael Klein, Silvia Calderon
QT Effects, Interdisciplinary Review Team for QT Studies	Hao Zhu, Jiang Liu, Qianyu Dang, Joanne Zhang, Suchitra Balakrishnan
Cross-Discipline Team Leader	Norman Hershkowitz
Director, Division of Neurology Products	Russell Katz

Action:

The Division of Neurology Products is recommending a Complete Response action on this application, and I concur with their recommendation.

Background:

Ezogabine is a small-molecule, first-in-class, neuronal potassium channel opener. Its purported mechanism of action involves stabilization and enhancement of potassium currents, and therefore differs from that of approved antiepileptic drugs (AEDs). Ezogabine is thought to have little effect on cardiac potassium channels. The proposed use is for adjunctive treatment of partial onset seizures in patients 18 years of age and older.

Despite the availability of the numerous AEDs for partial onset seizures, there remains a need for new drugs, as some 30% of patients are refractory to conventional treatments and continue to have inadequate seizure control.

Ezogabine has not been approved by any regulatory authority, although a marketing application is pending in the EU.

Chemistry Manufacturing and Controls (CMC):

The applicant has proposed marketing of 50-, (b) (4) 200-, 300-, and 400-mg strength tablets. They performed a bioequivalence study comparing the 400-mg tablet used in the clinical development program with the 400-mg to-be-marketed tablet, and found them bioequivalent. The applicant requested a waiver for bioequivalence studies for the lower strengths of the to-be-marketed tablets, based on dissolution data. Dr. Duan has concluded that waivers can be granted for all but the (b) (4), because (b) (4) Although the applicant noted that strengths less than 300 mg would only be used for titration, ezogabine doses should be reduced by one-third to one-half in patients with significant renal or hepatic impairment, and patients 65 and older, and in such patients, 100 mg could be administered TID as the maintenance dose. (b) (4)

Pharmacology/Toxicology:

The review found the application not approvable, because of the presence of (b) (4) a genotoxic impurity, at a level that would exceed the acceptable daily dose of a genotoxic impurity (b) (4) at all proposed therapeutic doses.

The drug substance initially tested positive in Ames assays, which led the applicant to test for the presence of impurities. They identified 3 impurities of concern in the final product (based on structural alert and/or Ames assay data): (b) (4) and known Ames-positive mutagen, and two (b) (4), (b) (4), both clearly Ames-positive as tested by the applicant. The applicant was able to reduce the specification limits of (b) (4) to acceptable levels (combined, total daily intake (b) (4)); however, they provided a

specification for (b) (4) of no more than (NMT) (b) (4) At the maximum proposed daily dose of 1200 mg, this would correspond to a daily exposure of (b) (4) exceeding the acceptable limit by more than (b) (4) of magnitude. They justified the (b) (4) specification on the basis of 3 factors, each considered below: 1) a lower specification was not achievable; 2) use of an individual TTC (Threshold of Toxicological Concern) approach; and 3) a negative *in vivo* Comet assay.

1) Specification below (b) (4) not achievable: Without explaining their original assertion that a specification of less than (b) (4) was not achievable, the applicant lowered the specification to (b) (4), and subsequently (very recently) to (b) (4) But even at (b) (4) the daily (b) (4) exposure at the maximum proposed dose (1200 mg/day) would be approximately (b) (4) the acceptable limit. The applicant believes they can eliminate (b) (4) entirely by altering the synthesis of the active drug, but has yet to submit data that support this approach.

2) Individual TTC approach: The applicant attempted to qualify the specification limit of NMT (b) (4) for (b) (4) based on extrapolation from published carcinogenicity data on structurally similar molecules. Having considered the applicant's arguments and the published data, however, the review team had a number of concerns. Ultimately, they concluded that the approach was unacceptable, as discussed in the reviews of Dr. Fisher and Freed.

3) Negative Comet assay: The applicant performed an additional *in vivo* combined micronucleus and Comet assay in order to address the mutagenic potential of (b) (4) and to determine if its carcinogenic potential is accurately predicted by the positive Ames assay. The *in* vivo combined assay was designed to assess (b) (4)s potential to induce structural chromosome damage in polychromatic erythrocytes from bone marrow and DNA strand breaks in rat hepatocytes. For both evaluations, (b) (4) was administered orally. Cyclophosphamide served as the positive control for the micronucleus assay, and ethyl methane sulphonate served as the positive control for the Comet assay. Although there was notable variability across the slide sections in the Comet assay, it was judged to be negative by both the applicant and review staff.

   If one takes the view that a negative Comet assay provides adequate reassurance on genotoxicity, even in light of Ames-positivity, then the concern regarding the (b) (4) specification for (b) (4) is moot. It is important, therefore, to consider the strengths and limitations of the Comet assay as presently understood.

   As noted by Drs. Fisher and Freed, there is considerable debate regarding the ability of the Comet assay to predict the carcinogenic potential of compounds more reliably than the Ames assay, and apparently some debate regarding the adequacy of validation of the assay for routine regulatory use. The Comet assay may not be able to detect mutagens that do not produce strand breaks or alkali-labile lesions. The reliability of the Comet assay appears to be dependent on a number of biological and technical factors, according to Dr. Fisher, and it is understood that the assay measures different endpoints than the Ames test. There are other individuals, however, who consider the Comet assay to be adequately validated.

   Thus, there are various opinions, some strongly held, as to whether a negative Comet assay has adequate negative predictive value to negate or dismiss a positive Ames test. After a careful weighing of the various factors, however, the review team opined that the

negative Comet assay should not take precedence over a positive Ames test, such that the specification of NMT (b) (4) for (b) (4) was deemed unacceptable.

It is also noteworthy that ezogabine was positive in a chromosomal aberration assay, *in vitro*.

Carcinogenicity

Because of ezogabine's toxicity (see below), the doses used in the carcinogenicity studies were necessarily limited. Ezogabine was negative in a two-year rat carcinogenicity study, although exposure at the highest dose tested (50 mg/kg/day) was only one-half of that expected under clinical use at a daily dose of 1200 mg. A lifetime mouse carcinogenicity study could not be performed because of urinary bladder toxicity, and so a neonatal mouse carcinogenicity study was performed – a model thought to be sensitive to genotoxic compounds, according to Dr. Fisher. In this study, there was a small, dose-related increase in lung neoplasms. Unfortunately, (b) (4) was not present in amounts adequate to assess its carcinogenic potential in either carcinogenicity study.

Toxicology

Ezogabine caused notable dose-limiting central nervous system (CNS) toxicity in mice, rats, and dogs. Findings included hypoactivity, decreased muscle tone, ataxia, prostration, tremors, convulsions, and myoclonus. Toxicity was greater in neonatal and/or juvenile rodents than adult animals.

KCNQ channels are expressed in urinary bladder smooth muscle cells as well as in neurons, and ezogabine hyperpolarizes the resting membrane potential of isolated rat bladder smooth muscle cells *in vitro*. In animal models of hypertrophic and neurogenic bladder, ezogabine was shown to decrease the frequency of spontaneous bladder contractions and block micturition, respectively. In repeat-dose studies, urinary bladder toxicity was observed in all species when examined. Toxicity was attributed to diminished peristalsis (hypotonic detruser muscle), leading to bladder distention, and ultimately obstructive uropathy, with renal pelvic dilatation, papillary necrosis, tubular dilatation, degeneration, and regeneration. Toxicity was evident at doses as low as 50 mg/kg (area under the curve [AUC] ~5 mcg·h/mL) in repeat-dose studies in adult mice. In the dose range-finding study for the neonatal mouse carcinogenicity study, pathologic bladder findings were observed at doses ≥2 mg/kg.

Ezogabine was found to cause relaxation of the gallbladder smooth muscle *in vitro*, and gallbladder dilatation *in vivo* (by abdominal ultrasound). In chronic dog studies, ezogabine caused localized hepatic damage subjacent to the gallbladder, thought to be caused by mechanical compression. Affected hepatic tissue demonstrated focal pressure necrosis, fibrosis, fibroplasia, mononuclear inflammatory cell infiltration, pigment deposition, and hemorrhage.

Clinical Pharmacology:

Ezogabine is generally rapidly absorbed with two concentration peaks (T_{max} at 0.67 to 1.5 hours; also 1.7 to 4 hours). Steady-state exposure (C_{max} and AUC) increased dose-proportionally and linearly at doses up to 400 mg TID. Clearance and half-life were dose-independent, with a half-life of 9 to 14 hours.

Ezogabine's steady-state volume of distribution is 2-3 L/kg, suggesting wide distribution. The parent drug is 80% protein-bound (mainly to albumin); NAMR (the N-acetyl metabolite of ezogabine) is 45% protein-bound.

Ezogabine is eliminated predominately through the kidneys, and approximately 34% is eliminated unchanged in the urine. The drug is metabolized extensively through formation of NAMR and N-glucuronides of both ezogabine and NAMR. There is no evidence of hepatic oxidative metabolism of ezogabine or NAMR via CYP450 enzymes.

In subjects over 65 years of age, plasma AUC values were approximately 40-50% higher than in younger subjects. The review team concluded that the label should recommend dose-reduction by one-third in patients aged 65 and over.

Because of reduced elimination in patients with hepatic impairment, the review team recommended dose-reduction by one-third in patients with moderate hepatic impairment, and by one-half in patients with severe hepatic impairment.

In patients with creatinine clearance <50 mL/min, the initial and maintenance doses of ezogabine should be reduced by 50%. Experience in patients on dialysis was inadequate to draw any useful conclusions, and the label should note this.

Site Inspections:

GCP compliance issues were identified at one site in study 205 (out of a total of 73). The Sponsor performed a sensitivity analysis and according to Dr. Siddiqui, this revealed similar magnitudes of effects for all treatment groups. DSI (see below), however, concluded from their inspections that overall performance of studies were adequate.

Evidence of Effectiveness:

The applicant submitted the results of three randomized controlled clinical trials in support of efficacy.

Trial 205 was classified as a phase 2 dose-finding trial; trials 301 and 302 were considered the phase 3 pivotal trials. All were international, randomized, double-blind, placebo-controlled, parallel-arm trials that examined the therapeutic effect of ezogabine as adjunctive therapy in adults with partial onset epilepsy (simple partial seizures and/or complex partial seizures with or without secondary generalization). Subjects with simple partial seizures as their only seizure type were eligible if seizures had a motor component.

All trials included a prospective baseline period, followed by titration and maintenance phases; subjects had to experience ≥4 seizures per 28 days during the prospective baseline period for enrollment.

For trial 205, subjects were eligible if receiving up to 2 AEDs at stable doses, whereas in trials 301 and 302, patients could be receiving up to 3 AEDs at stable doses for at least 1 month prior to screening and throughout the study treatment period.

Some key features of the trials are presented in Table 1. All test drugs were to be administered on a TID basis. A single back-titration to 1050 mg/day was permitted in study 301 for subjects unable to tolerate 1200 mg/day. Only Trial 302 had substantial US representation.

Table 1: Major features of efficacy trials

	Study 205	**Study 301**	**Study 302**
phase	2b	3	3
sponsor	Wyeth	Valeant	Valeant
treatment groups (daily dose)	600, 900, 1200 mg/day, placebo	1200 mg/day, placebo	600, 900 mg/day, placebo
approximate *n* per treatment group	100	180	150
baseline period	8 weeks	8 weeks	8 weeks
duration of double-blind period	16 weeks	18 weeks	16 weeks
duration of titration	8 weeks	6 weeks	4 weeks
duration of maintenance	8 weeks	12 weeks	12 weeks
age of subjects	16 to 70	18 to 75	18 to 75
Number of background AEDs	≤2	≤3	≤3
locations	Australia, Belgium, Croatia, Czech Republic, Finland, France, Germany, Israel, Italy, Netherlands, New Zealand, Norway, Poland, Portugal, Slovakia, Spain, Sweden, UK, US	Argentina, Brazil, Canada, Mexico, US	Australia, Belgium, France, Germany, Hungary, Israel, Poland, Russia, South Africa, UK, Ukraine, US
percent US subjects	7%	<1%	49%

For all 3 trials, the primary endpoint was the percent change from baseline seizure frequency as calculated from the 28-day total partial seizure frequency. For subjects who discontinued treatment prematurely, the number of seizures reported up to the time of discontinuation was used to calculate the seizure frequency. Subjects who did not have any post-baseline data were excluded from the primary analyses.

- In Trial 205, the primary analysis set was a modified intent-to-treat population of all randomized patients who received ≥1 dose of study drug, had a baseline seizure evaluation and ≥1 seizure evaluation on treatment. A rank analysis of covariance (ANCOVA) was used to analyze the primary endpoint data, with the rank of the baseline monthly seizure rate as a covariate and treatment and center as factors in the model.

- In Trials 301 and 302, the primary analysis set was a modified intent-to-treat population of all randomized patients who received at least one dose of study drug. The primary analysis was a non-parametric rank analysis of covariance, stratified by geographic region and baseline seizure frequency.

Numerous secondary endpoints were considered, but in essence they were merely alternative ways of considering seizures: 1) quartile distribution of change in seizure frequency from

baseline; 2) number of patients who achieve total seizure freedom; 3) time without seizures; 4) potential exacerbation of pre-existing seizures or the development of new seizure types; 5) median percent change in 28-day total seizures in the maintenance phase; and 6) responder rate in the double-blind phase as determined by patients with ≥50% reduction from baseline. There was no formal statistical plan to consider multiplicity, making interpretation difficult.

Table 2 summarizes the efficacy data from all three studies. FDA analyses are in agreement with those of the applicant. All comparisons to placebo are statistically significant, except for the 600 mg/day group in trial 205 (which does show a trend, however). It is not clear from the statistical review how multiplicity was considered in trials with more than one active treatment group.

Table 2: Median % change from baseline in total partial seizure frequency; trials 205, 301, and 302

	Placebo	ezogabine 600 mg/day	ezogabine 900 mg/day	ezogabine 1200 mg/day
Trial 205				
n	96	99	95	106
median	-13.1	-23.4	-29.3	-35.2
range	-100, 533	-100, 1703	-100, 298	-100, 375
*p-value	-	0.20	0.043	<0.001
Trial 301				
n	150	-	-	151
median	-17.5	-	-	-44.3
range	-90, 628	-	-	-100, 302
*p-value	-	-	-	<0.001
Trial 302				
n	176	179	175	-
median	-15.9	-27.9	-39.9	-
range	-100, 1712	-94, 250	-100, 226	-
*p-value	-	0.007	<0.001	-

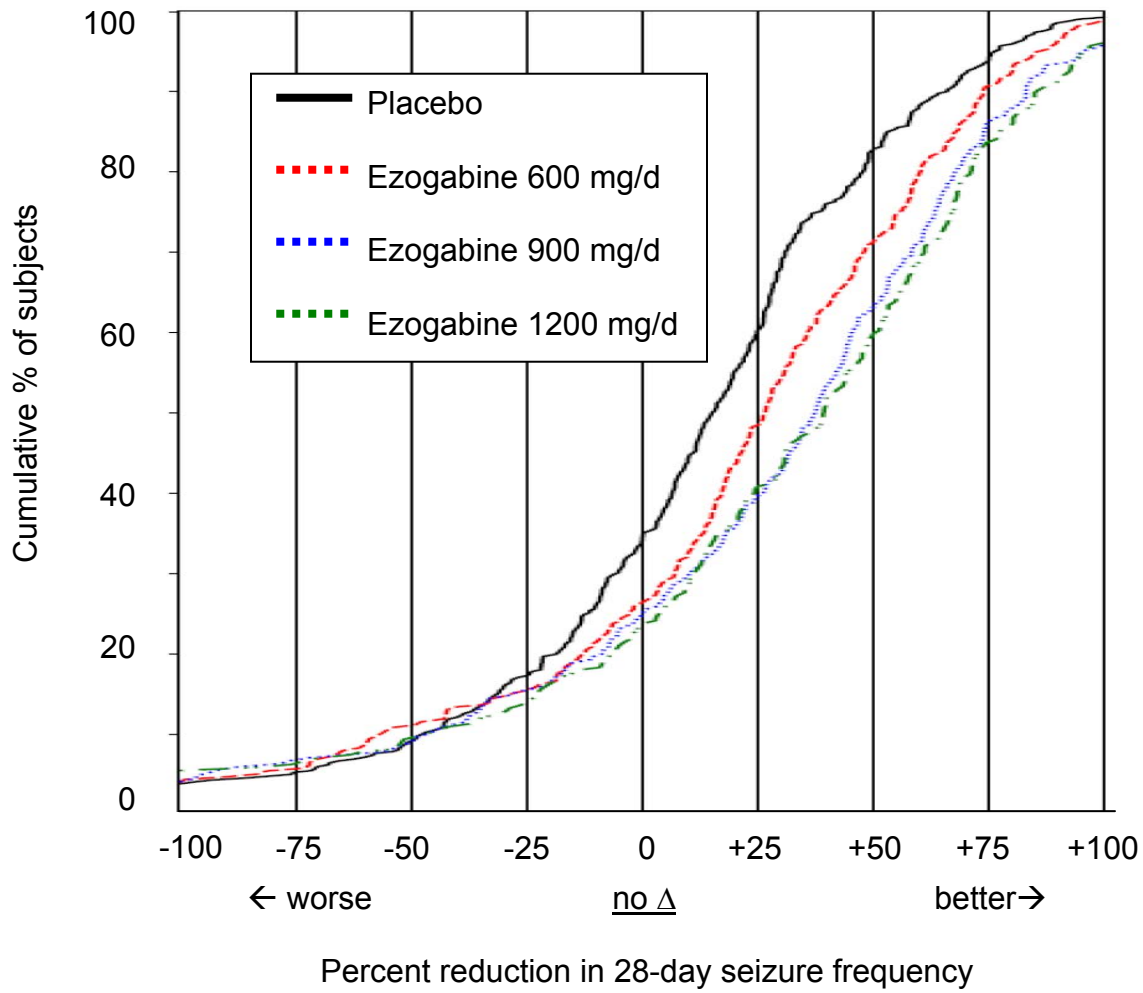
*p-values from non-parametric rank ANCOVA models

The data provide a reasonable if not compelling evidence of a dose-response. Trials 205 and 302 evaluated 2 or 3 ezogabine doses against placebo, and there is fairly clear evidence of a dose-response in both (although in trial 205, the difference between the lowest dose and placebo was not statistically significant). If one succumbs to the temptation to compare results across trials, the dose-response seems fairly well-characterized, although there are some important assumptions and limitations inherent in doing this.

The applicant combined the same-dose treatment groups across the 3 trials and provided a cumulative distribution function (rotated and flipped on its axis to enhance comprehension), Figure 1. If the cross-trial comparisons are valid, the data show that increasing the daily dose from 600 to 900 mg is associated with a gain in efficacy, whereas the additional benefit gained

by increasing the daily dose from 900 to 1200 mg is negligible. As will be described below, this is important, because many of the adverse events were strongly dose-related.

Figure 1: Cumulative distribution function of change in total partial seizure frequency (double-blind phase) – ITT Population: Studies 205, 301 and 302



Dr. Siddiqui, the statistical reviewer, agreed with the applicant's calculations on the primary and secondary endpoints, as well as with sensitivity analysis that excluded 6 sites considered to have irregularities in trial 205. Dr. Siddiqui also performed additional sensitivity analyses, including ANCOVA analyses on the observed total partial seizure frequency, post-baseline; and ANCOVA analyses on the log-transformed total partial seizure frequency, post-baseline. These analyses were consistent with the principal conclusions of efficacy.

The dropout rates during the double-blind phase in the three trials were relatively high and appeared to be dose-dependent, ranging from 15 to 22%, 25 to 28%, 31 to 34%, and 39% in the placebo, 600, 900, and 1200 mg/day groups in the various trials. The majority of withdrawals were related to adverse events, particularly in higher-dose groups.

In view of the high dropout rates, the statistical reviewer conducted two sensitivity analyses across trials 205, 301, and 302. In the first analysis, seizure data from titration phase were used for patients who dropped out and lacked subsequent data. In the second analysis, subjects who dropped out during the titration phase were assigned non-responder status. The findings were consistent with the protocol-specified analyses.

Subgroup analyses by age and sex found no important differences. Treatment effects in trial 301 were analyzed by region: results at North American sites (US plus Canada) were compared to results at other sites (Mexico and South America). Although an ezogabine treatment effect was apparent in both geographic regions, the treatment effect at North American sites (9%) was far less than at Mexican and South American sites (39%). There were insufficient numbers of non-Caucasians groups to perform any meaningful analysis.

The statistical reviewer concluded that "the findings of the three studies confirmed that ezogabine (600, 900, and 1200 mg/day) is an effective, add-on therapy in the treatment of partial seizures," and the clinical reviewer and cross-discipline team leader agreed. As noted above, however, there is essentially no gain in efficacy realized by increasing the daily dose from 900 to 1200 mg, a fact that must be weighed against the dose-relatedness of adverse reactions.

Safety:

Exposure

The safety database in the original submission included 2168 subjects exposed to at least one dose of ezogabine. This number includes 1365 subjects with epilepsy in the phase 2 and 3 trials, 669 subjects in clinical pharmacology studies, and 135 subjects with post-herpetic neuralgia or bipolar disorder. Table 3 summarizes the durations of therapy for the salient dose regimens of ezogabine used in phase 2 and 3 trials of epilepsy:

Table 3: Duration of ezogabine exposure in phase 2 and 3 epilepsy trials

	Ezogabine dose		
duration	**≥ 600 mg**	**≥ 900 mg**	**≥ 1200 mg**
> 3 months	1195	782	227
> 6 months	765	540	156
> 12 months	453	318	100

The exposure exceeds recommendations in the ICH E1 Guideline for drugs intended for long-term treatment of non-life-threatening conditions (>300 subjects for 6 months; >100 subjects for 1 year; >1500 overall).

In phase 2 and 3 trials, mean and median durations of treatment were 303 and 235 days, respectively. Most subjects were Caucasians between the ages of 18 and 64. Both sexes were well-represented. Blacks were underrepresented in the database (only 2.5% of subjects).

Deaths

Ten (10) of 1365 ezogabine-treated subjects (0.7%) died in the epilepsy trials. In the controlled phase of epilepsy trials, 2/813 (0.2%) of ezogabine-treated patients died compared to 3/427 (0.7%) of placebo patients. In the opinion of the review staff, no deaths were directly attributable to ezogabine.

A total of 6 of the deaths in the ezogabine-treated patients were considered either possibly or probably Sudden Unexplained Death in Epilepsy (SUDEP). One additional death occurred in a morbidly obese 34 year-old female who had advanced coronary artery disease on autopsy. This death was classified as "SUDEP cannot be excluded." The calculated rate of SUDEP in this development program was 4.4 deaths/1000 patient years. As noted by Dr. Dinsmore, the applicant estimated from the literature that the rate of SUDEP ranges from 0.09 deaths/1000 patient-years in studies of patients with newly diagnosed epilepsy to 9.3 deaths/1000 patient years in a study of refractory patients referred to epilepsy surgery centers. Dr. Hershkowitz opined that the rate of SUDEP in the development program seems to be in line with expectations, given that patients who are selected for study are relatively refractory. He added that the rate is similar to those of contemporary epilepsy trials analyzed by the Division. In those trials, rates of SUDEP have ranged from 3.5 to 4.0 events per 1000 patient-years.

Dropouts and Discontinuations

Overall, subjects who received ezogabine were more than twice as likely to discontinue as subjects who received placebo. In all controlled epilepsy trials, 25% and 11% of subjects in the ezogabine and placebo groups discontinued, respectively, and 31% of all ezogabine-treated subjects in all phase 2 and 3 trials ultimately discontinued. Adverse events were the principal reason for discontinuation, and discontinuations were dose-related, with 17, 25, and 31% of subjects discontinuing in the 600, 900, and 1200 mg/day groups, respectively.

Safety Concerns of Special Interest

Urinary Tract Disorders

As noted above, ezogabine affects potassium channels in urinary bladder muscle, and toxicity was observed in non-clinical studies. In the clinical trials, therefore, urinary tract adverse events were sought as adverse events of interest. In addition, some trials included assessment of the 7-question American Urological Association Symptom Index score and determination of post-void residual bladder volumes by ultrasound.

During the double-blind phase of randomized controlled trials, renal and urinary tract adverse events were reported in greater proportions of subjects who received ezogabine than placebo: 17% versus 13%, respectively; relative risk = 1.3.

Notable urinary tract adverse events in the development program (ezogabine vs. placebo, respectively) were dysuria (2.3% versus 0.7%), hesitation (2.2% versus 0.9%), chromaturia (1.6% versus 0.2%), hematuria (1.6% versus 0.7%) and abnormal urinalysis (1.6% versus 0.9%). Urinary retention was reported in 0.9% and 0.5% of subjects in the ezogabine and placebo groups, respectively. Urinary tract infection was the most common adverse event in this group, but was reported more frequently in patients who received placebo (4.3% vs. 4.7%, for ezogabine and placebo, respectively).

Analyses of the American Urological Association Symptom Index score did not show any clear trends. As Dr. Dinsmore pointed out, this is not unexpected, given that the overwhelming majority of subjects had no urinary tract symptoms at all.

There were 4 serious adverse events in the urinary system in the ezogabine group (renal colic, urinary retention, atonic bladder, and atonic bladder/urinary incontinence) compared to 1 in the placebo group (urinary retention). For the overall phase 2/3 safety database, there were 22 SAEs in 17 ezogabine-treated subjects referable to the urinary system. Urinary retention was the most frequent SAE (n=8). Of note, the median age of these subjects (37) and sex (50% male) match the demographics of the safety database as a whole. Thus, the data do not suggest that particular demographic groups are more vulnerable to urinary retention, a finding that, if present, could have provided a means to mitigate risk.

Six (6) urological adverse events led to drug discontinuation of ezogabine-treated subjects in the controlled trials (urinary tract infection, renal failure, hematauria, atonic bladder, urinary retention, nephritis) compared to 3 in placebo-treated subjects (polyuria, polyuria/urinary retention, and renal colic). In the overall phase 2/3 trial database, there were 17 withdrawals for urinary tract adverse events. One subject developed an obstructive uropathy picture without identifiable obstruction, suggesting drug-induced alteration in bladder function.

A striking finding, as Dr. Dinsmore notes, is that 25% of patients treated with ezogabine in phase 2/3 epilepsy trials reported at least one urological adverse event. Urinary tract infection (7.7%) was the most commonly reported urological adverse event, followed in decreasing frequency by hesitation (3.1%), abnormal urinalysis (2.6%), dysuria (2.4%), urinary retention (1.9%), hematuria (1.8%), chromaturia (1.7%), polyuria (1.6%), and residual urine volume present (1.1%). It is also noteworthy that these adverse events occurred despite heightened monitoring and awareness in a clinical trial environment.

There was no relationship between baseline post-voiding residual (PVR) or change in PVR and the likelihood of developing urinary retention. Sex was not a risk factor. Age was generally not a risk factor, although subjects over the age of 50 appeared to be at slightly greater risk. At the advisory committee meeting, there was some concern regarding the apparent lack of understanding of the mechanism(s) underlying the urinary adverse events, and some committee members suggested post-marketing urodynamic studies to provide mechanistic insight.

Dr. Dinsmore assessed the timing of the 25 cases of urinary retention identified in the safety database, finding that 18% of cases occurred within the first month, and 59% occurred within the first six months; however, cases were observed as late as 2.5 years after initiation of ezogabine. His analyses did not identify an obvious relationship to dose, with events occurring at doses as low as 300 mg/day. Conversely, analyses by Dr Kim, a consultant from the Division of Reproductive and Urological Products, suggested a dose-response.

Dr Kim noted that ezogabine is crystallogenic: nearly 40% of ezogabine is excreted unchanged in the urine, and the drug is insoluble at physiologic urinary pH. Urinary crystals and “amorphous material” were found more frequently in ezogabine-treated patients, and analyses using mass spectrometry identified peaks corresponding to the known molecular weight of ezogabine and its dimers. Although there was a trend towards more frequent stone formation in subjects on ezogabine than on placebo, no stone was identified as being composed of drug. The consultant opined that ezogabine crystalluria poses a theoretical risk of renal injury secondary to intratubular precipitation and urolithiasis, but noted that such findings were not

reported in the phase 3 trials, and the data do not provide a clear signal for ezogabine stone formation.

Psychiatric and Cognitive Symptoms

Dr. Dinsmore analyzed psychiatric and cognitive symptoms in the randomized controlled trials using a range of preferred terms (e.g., “anxiety,” “disorientation,” “hallucination,” “psychosis,” “depression,” “abnormal behavior,” “euphoric mood,” etc.). There was no apparent difference in the overall frequency of these events between the two lower doses of ezogabine (5.7 and 7.0% in the ezogabine 600 and 900 mg/day groups, respectively) and placebo (6.3%). For subjects in the 1200 mg/day ezogabine group, however, the frequency was 16.6%. Psychiatric adverse events led to 28 withdraws in 813 patients in ezogabine-treated subjects (3.4%), versus 8 withdraws in 427 patients (1.9%) in the placebo group.

With a more focused search on psychotic symptoms (“hallucination,” “psychotic disorder,” and “psychosis”), however, there was a clear dose-relationship with 0.5, 1.4, 1.8, and 5.0% of patients experiencing these symptoms in the placebo and ezogabine 600, 900, and 1200 mg/day groups, respectively. The applicant’s findings were similar, although their numbers were slightly higher: they found events related to hallucination or psychosis in <1, 2, 3, and 7% of patients in the placebo and ezogabine 600, 900, and 1200 mg/day groups, respectively.

The applicant also noted that these adverse events appeared within the first 8 weeks of treatment in all dose-groups, with most reported within 4 to 8 weeks. When examined by study phase, over half the events were reported during titration (19/32), and the actual dose at the time of symptom onset was generally <1200 mg/day.

Consistent with the applicant’s conclusions, Dr. Dinsmore pointed out that one of the phase 2 studies, study 209, included a rapid up-titration of ezogabine dose, and there was striking incidence of psychotic symptoms, with 5 of 27 subjects discontinuing because of psychotic-like behaviors. Thus, the rate of up-titration appears to be an important factor in the induction of psychotic symptoms. Moreover, one healthy volunteer experienced brief but severe psychosis in a phase 1 study, suggesting that ezogabine-induced psychosis is not simply a postictal or interictal phenomenon. Plainly, neuropsychiatric symptoms constitute a significant untoward effect of ezogabine, and they are to be discussed in the Warnings and Precautions section of labeling. They should also be discussed in the Medication Guide, as knowledge of the potential for such symptoms could impact patients’ decisions to start the drug, and such knowledge would also be important for patients who take the drug.

No cases of suicide were reported in the development program. One case of attempted suicide and another of suicidal ideation were observed in the drug group in the controlled trials, compared to 2 cases of suicidal ideation in the placebo group. Clearly these data are not adequate to permit a robust determination of risk. Thus, ezogabine will receive the FDA class labeling based on results of the Division’s meta-analysis of controlled studies of other AEDs.

Cardiovascular Effects

Dizziness was the most common adverse event reported in the pivotal controlled trials, reported in 23% of all ezogabine-treated subjects versus 9% of placebo. One of the potassium channels opened by ezogabine is present in vascular smooth muscle, such that there is a theoretical potential for blood pressure-lowering effects that could lead to dizziness. An outlier analysis performed by Dr. Dinsmore, however, did not support the concept that dizziness was blood

pressure-related. Specifically, decreases of 20 mmHg in standing systolic blood pressure over baseline were observed in similar fractions of subjects in all treatment groups: 22, 25, 21, and 24% of subjects receiving placebo, ezogabine 600, 900, and 1200 mg/day, respectively.

Two notable cardiac arrhythmias were observed in non-epilepsy studies in subjects exposed to high doses of ezogabine. The subjects had histories of drug abuse but were otherwise healthy: 1) a 34 year-old women with a history of bradycardia experienced asystole for 25 seconds with syncope, 1.8 hours after receiving a single 900-mg dose of ezogabine. Electrolytes were normal; a subsequent stress echo was negative. 2) a 41 year-old male had 4 runs of non-sustained ventricular tachycardia, as long as 9 beats in length.

The review team noted that these isolated cases make it difficult to attribute causality to the drug; in particular, the review team thought that having a history of bradycardia confounds the episode of asystole. I disagree with that logic, however. Bradycardia is common in younger women; true asystole is not. The episode corresponded fairly well in time with T_{max}, and it is difficult to find other reasons why the subject would have had asystole at that point in time. (Apparently, this was not a vasovagal episode associated with phlebotomy.) In other words, the event incriminates the drug beyond a reasonable doubt. The important point is that the event occurred after a 900-mg dose, whereas the highest dose recommended in labeling will be 400 mg, given TID. This case will be described in the overdosage section of the label. The episodes of non-sustained ventricular tachycardia in the 41 year-old male are not particularly troubling in my opinion, as this arrhythmia is commonly observed in asymptomatic individuals without known heart disease.

During the review process, the review team expressed considerable consternation regarding cases of atrial fibrillation reported in a randomized, placebo-controlled study of ezogabine in post-herpetic neuralgia. There were 4 cases of atrial fibrillation in 125 subjects randomized to ezogabine (3.2%), versus no cases in 62 subjects in the placebo group. Careful review of the cases showed that each subject had risk factors for atrial fibrillation, and given that the subject population was generally elderly (mean age 63), atrial fibrillation is actually expected. In any case, with the small number of events (and the 2:1 randomization), it would be difficult to conclude that the imbalance is anything more that a chance finding. As noted above, however, the drug's mechanism of action involves potassium channels, and adverse events associated with high doses of the drug, although unexpected, could be drug-related.

The applicant performed a thorough QT study in 120 healthy subjects. The highest dose examined was 400 mg TID, because higher doses were not thought to be tolerable; in fact, only 26 of 38 subjects tolerated the target dose. The mean difference in QTcF (Fridericia correction) between ezogabine 400 mg TID and placebo (placebo-subtracted change from baseline, $\Delta\Delta$QTcF), was 7.7 msec, and the upper bound of the 90% CI was 11.9 msec, observed 3 hours after dosing. The largest lower bound of the two-sided 90% CI for the $\Delta\Delta$QTcF for moxifloxacin was greater than 5 ms. The Interdisciplinary Review Team for QT Studies noted that the study suffered from several problems (i.e., the rising phase of the moxifloxacin arm was not adequately evaluated, and supratherapeutic concentrations of ezogabine were not studied because of tolerance issues).

Electrocardiograms were performed during the controlled epilepsy studies, but the results of the analyses revealed inconsistent findings.

The greatest differences from placebo in QT interval (msec) were observed at Weeks 12 and 18, in an inconsistent pattern:

	Placebo (n=427)	600 mg/d (n=281)	900 mg/d (n=273)	1200 mg/d (n=259)
Week 12	1.4	2.1	16.7	14.8
Week 18	3.6	11.3	10.6	3.3

An outlier analysis of the percentage of subjects with changes in QTcF interval from baseline:

	Placebo (n=403)	600 mg/d (n=266)	900 mg/d (n=255)	1200 mg/d (n=232)
> 30 msec	8%	10%	12%	12%
>30 and ≤60 msec	8%	10%	11%	12%

There were no meaningful changes between placebo and any ezogabine dose in PR interval, QRS interval, or heart rate. There were no differences in the percentage of patients with QT intervals of >450 msec between the placebo and ezogabine groups (approximately 1% in each group).

The Interdisciplinary Review Team suggested that the label include a general statement to the effect that the "QT interval should be monitored when POTIGA is prescribed with medicines known to increase QT interval and in patients with congenital long QT syndrome, heart failure, ventricular hypertrophy, hypokalemia, or hypomagnesemia," and such language will be included in labeling.

Hepatic and Biliary Effects

It was hypothesized that ezogabine's potassium channel effects could affect gallbladder smooth muscle in the same manner as it affects urinary bladder smooth muscle, and in dogs, ezogabine was found to cause pathologic changes in the liver subjacent to the gallbladder, thought to be related to this mechanism.

In the ezogabine clinical development program, however, the numbers of adverse events referable to gallbladder were small, and were similar in the ezogabine and placebo groups.

In the epilepsy controlled trials, liver function test (LFT) elevations reported as an adverse event were slightly more frequent in subjects who received ezogabine (3.1%) than placebo (1.4%).

The percentages of patients with LFTs > 3 X upper limit of normal (ULN) were 1%, 1.5%, 3.1%, and <1% in the placebo, 600, 900, and 1200 mg/day ezogabine groups, respectively. There were no differences in the percentage of patients with LFTs between 5 and 10X ULN. There were no Hy's law cases.

As noted by Dr. Dinsmore, however, 27 ezogabine-treated subjects discontinued treatment secondary to LFT abnormalities: 13 were in controlled trials, including 7 in epilepsy trials (7/813;

0.9%). One had an alanine aminotransferase (ALT) of 10X ULN and a direct bilirubin of 2.4, a case that remains under consideration at the time of writing of this memorandum. Three (3) other subjects had ALT elevations greater than 10X ULN, without other laboratory abnormalities. In 23 of 27 subjects, the abnormalities resolved upon discontinuation of treatment (in the other 4 patients, the data are not available).

Central analysis showed small increases in ALT and aspartate aminotransferase (AST) that were not dose-dependent. There was a consistent increase in bilirubin that the applicant attributed to interference of ezogabine and its NAMR metabolite with the analytic method used to measure bilirubin. Interference with the bilirubin assay is to be noted in the label.

Blood Dyscrasias

Neutropenia was identified as a potential safety signal in a canine toxicity study where NAMR was administered, prompting evaluation of neutropenia and infections in the ezogabine clinical program. No clear signal emerged. The applicant generated a query of "neutropenia or infection-related adverse events," and found a similar frequency between the placebo and ezogabine groups (approximately 7%). Whereas leucopenia was reported at a higher frequency in ezogabine-treated subjects than placebo (1.2% versus 0.5%), the opposite was true for neutropenia (0.2% versus 1.2%). Also, there was 1 case of pancytopenia reported in the placebo group, and none in the ezogabine group. Taken together, there does not appear to be a clear trend for neutropenia.

Abuse Potential

The Controlled Substance Staff concluded that ezogabine is a central nervous system depressant with an abuse potential similar to drugs in Schedule (b) (4) of the Controlled Substances Act (CSA). They recommended that ezogabine be placed in Schedule (b) (4) of the Controlled Substances Act, a conclusion with which the applicant agreed. At the time of this writing, however, this recommendation has not been officially forwarded by the Agency to the Drug Enforcement Agency (DEA) for final scheduling.

Risk Evaluation and Mitigation Strategy (REMS):

The applicant included a REMS consisting of a Medication Guide and communication plan. As submitted, the Medication Guide highlighted the risk of suicide and urological problems. The risk of neuropsychiatric symptoms should be added to the Medication Guide, as this is important information for potential users of the drug to consider before accepting a prescription, as well as important information for users of the drug. The division and the advisory committee were in agreement regarding the general plan for a REMS. The Division of Risk Management deferred comment on the sponsor's REMS proposal and communication plan until the applicant submits a satisfactory response to the Complete Response letter.

Risk Assessment of Established and Proprietary Names:

The Division of Medication Error Prevention and Analysis (DMEPA) identified a concern with the originally proposed established name, (b) (4) because of orthographic and phonetic similarities and potential name confusion with (b) (4) (the established name for (b) (4) The Division agreed with DMEPA's concern, and suggested that the applicant petition the United States Adopted Names (USAN) Council for a new established name. The applicant

pursued two alternative names; the established name (b) (4) was eventually rescinded in favor of a new USAN-designated established name: “ezogabine.”

Because DMEPA does not have authority over established names, they do not typically comment on a negative finding regarding their potential to function as a source of medication error. In this case, however, because the originally proposed established name was changed in light of a safety concern, DMEPA commented for the administrative record. They found no overt risks with the new established name “ezogabine.”

DMEPA had no objection to the proprietary name “Potiga” after a careful review.

Advisory Committee:

Primarily because of Potiga’s capacity to cause urinary retention, the application was referred to a meeting of the Peripheral and Central Nervous Systems Advisory Committee (PCNS AC) on August 11, 2010. The standing committee was supplemented with experts in epilepsy and urology.

The committee voted unanimously that the applicant had provided substantial evidence of effectiveness for ezogabine as adjunctive treatment for adults with partial seizures. By a vote of 11 “yes,” 0 “no,” and 2 abstentions, the committee voted that the risk of urinary retention could be mitigated by appropriate patient monitoring, and that, in general, adequate monitoring could consist of patient education and routine clinical vigilance. They opined that for the typical patient, sophisticated urologic monitoring was unnecessary, and that specific monitoring for urinary stones or infections was not required.

They did offer the view that for patients who could not reliably report symptoms of urinary retention (for example, patients with cognitive impairment), urologic consultation could be helpful.

The committee also recommended that the applicant perform, in phase 4, urodynamic studies to try to identify the mechanism of urinary retention, and that patients under the age of 12 should not be treated with ezogabine until these studies are performed. They agreed that there were no other safety issues that would preclude approval.

Postmarketing Requirements and Commitments:

The clinical review team recommends post-marketing *requirements* for a urodynamic study and for a prospective cohort study of patients starting on ezogabine as compared to those on other AEDs.

The clinical pharmacology review staff recommends post-marketing *commitments* for an *in vitro* study to evaluate to evaluate the potential for ezogabine to inhibit CYP2B6, as well as an *in vitro* study to evaluate whether ezogabine is a substrate for major transporters in the kidney.

The Controlled Substances Staff requested a post-marketing animal study to better characterize whether or not ezogabine can produce physical dependence. The applicant did not perform adequate studies in humans to address this issue.

Conclusions:

The applicant submitted three randomized, double-blind, placebo-controlled trials that provide evidence of effectiveness for ezogabine for the proposed indication: adjunctive therapy for the treatment of adults with partial seizures. The effect size was comparable to that shown for newer AEDs. The results were, for the most part, statistically persuasive and robust to exploration (the exception was the 600-mg daily dose in trial 205, where there was a trend favoring efficacy, but the results were not statistically significant).

A key question regarding efficacy is the extent to which the highest daily dose studied (1200-mg) should be encouraged or discouraged in labeling. One trial (205) compared the 900- and 1200-mg doses directly, and found only a minimal difference on the primary outcome measure. Examination of the cumulative distribution function for percent reduction in 28-day seizure frequency (Figure 1) makes a strong case that essentially nothing is gained by increasing the daily dose from 900 to 1200 mg. Conversely, adverse events are clearly more frequent at the higher dose.

The review team thought there was a reasonable case for including the 1200-mg daily dose in labeling, despite the minimal gain in efficacy, and I agree with their view. My logic is that 1) seizures are medically important events; 2) patients should be able to develop some sense of whether or not they derive greater seizure control from the higher dose; 3) patients will be cognizant of the side effects; and 4) those side effects are, by-and-large, reversible. In other words, patients should recognize if they are deriving benefit and recognize if they are harmed, and harm should be reversible. The possible exception here is urinary retention, which occurred in the clinical trials despite considerable attention directed towards its detection. In "real world" use, urinary retention, and more importantly, renal damage, could pose greater risks. The applicant proposed to manage this risk with monitoring, appropriate product labeling, and by providing a Medication Guide to patients. This approach seems rational, and the planned prospective cohort study could help resolve the magnitude of risk.

The safety database exceeds ICH E1 guidelines and includes data in over 2000 patients with epilepsy.

Ezogabine plainly causes significant dose-related neuropsychiatric adverse events, which (fortunately) resolve upon discontinuation. These symptoms will be prominently described in labeling, and should be included in the Medication Guide.

The Division was particularly concerned about the risk of arrhythmias, particularly atrial fibrillation. As noted above, atrial fibrillation was reported in a study of ezogabine for post-herpetic neuralgia, in a patient population of relatively advanced age (mean age 63 years). There were 4 cases of atrial fibrillation in 125 subjects randomized to ezogabine (3.2%), versus none in 62 subjects in the placebo group. Given that the number of cases is small, that randomization was 2:1, and that atrial fibrillation is relatively common in this older patient population, much of the concern seems unwarranted. Had there been a single case of atrial fibrillation in the placebo group, there would have been no concern here at all. Conversely, the single case of asystole in a young volunteer seems important to highlight in labeling, as noted above. Ezogabine appears to produce a slight increase in QT, an effect that should be adequately managed in labeling.

Ezogabine produced considerable increases in hepatic transaminases. Although a few patients experienced mild elevations in total bilirubin, there were no Hy's law cases. All transaminase

elevations resolved after discontinuation of ezogabine, and its capacity to increase transaminases can be managed through labeling.

As noted above, using dissolution data, the applicant has shown that all of the dosage strengths they wish to market will be bioequivalent to the corresponding strengths they studied in the clinical trials, with the exception of the (b) (4) dose. Dr. Katz's memorandum deals with this issue in detail. Based on the present state of knowledge, if the product were to be approved, the proposed (b) (4) tablet should not be part of that approval. (b) (4)

The (b) (4) impurity issue is discussed extensively above and in the review memoranda of Drs. Dinsmore, Freed, and Katz. The crux of the issue is that the review team does not believe that the negative Comet assay can overcome the concern raised by the positive Ames assay, and I cannot disagree with the experts on the review team.

One argument that can be made is that (b) (4) impurity at (b) (4) poses a relatively small risk compared to the fairly strong mutagenicity signal observed for the parent compound in the chromosomal aberration assay, such that it is unreasonable to place too much concern on the (b) (4) risk. That argument is based, however, on an assumption that the two risks are additive. If the risks of these agents were, in fact, synergistic, it would argue that their concentrations should be reduced to levels as low as reasonably practicable. In the absence of data, the review team thought that the latter principle was applicable in this case.

The sponsor recently informed the Division that they will be developing alternate synthetic pathways for ezogabine, and may be able to eliminate (b) (4) entirely.

As noted by Dr. Katz, one could argue that the application should be approved now, with a post-marketing requirement to reduce (b) (4) to an acceptable level. This pathway does not seem unreasonable, because epilepsy is a serious disease for which additional treatments are needed, and patients would be exposed to unacceptable concentrations of (b) (4) only until the sponsor fulfilled their post-marketing commitment.

After considerable discussion, however, the Division concluded that a better approach is to require reduction of (b) (4) to acceptable levels *before* approval. If the applicant had shown a compelling advantage of ezogabine relative to existing AEDs, there would be a stronger case for approving the marketing application now, and mandating reduction of the (b) (4) concentration as a post-marketing requirement. Importantly, the applicant has not provided any data to support the concept that another synthetic pathway is feasible – on either a small or large scale.

Finally, as Dr. Katz notes, we are concerned that patients with epilepsy need more treatments, and, although we have no proof, we might even assume that ezogabine would constitute a therapeutic advance for some patients who respond poorly to existing agents. If gaining approval of this AED *now* – a few months early – could help a handful of patients with epilepsy, that advantage must be weighed against the risk of having a product on the market with an unacceptably high concentration of (b) (4) an Ames-positive mutagen. We believe that the (b) (4) issue will be better addressed by having the applicant rectify the problem prior to approval.

We hope, the applicant can develop a new synthetic process that lowers levels to <1.5 mcg/day. If they are unable to accomplish this, they could gain approval with a post-marketing requirement to assess the carcinogenic potential of (b) (4) directly in an *in vivo* animal model.

For the reasons stated above, I am issuing a Complete Response letter on this application.

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

/s/

ELLIS F UNGER
11/30/2010

CLINICAL REVIEW

Application Type	NDA
Application Number(s)	22-345
Priority or Standard	Standard
Submit Date(s)	10/30/09
Received Date(s)	10/30/09
PDUFA Goal Date	8/30/2010
Division / Office	DNP/OND1
Reviewer Name(s)	Steven T. Dinsmore, DO
Review Completion Date	October 15, 2010
Established Name	Ezogabine
Trade Name	Potiga
Therapeutic Class	Anticonvulsant
Applicant	Valeant Pharmaceuticals
Formulation(s)	Immediate release, film coated tablets
Dosing Regimen	Three times daily oral administration
Indication(s)	Adjunctive treatment of Partial onset seizures
Intended Population(s)	18 years of age and older

Template Version: March 6, 2009

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1 Recommendations/Risk Benefit Assessment

1.1 Recommendation on Regulatory Action

Ezogabine is safe and effective at doses of 600mg to 1200mg and is recommended for approval on the basis of this medical review.

1.2 Risk Benefit Assessment

Efficacy is established based on three adequate and well controlled studies, one phase 2b, study 205, where the 900mg/day (300mg TID) and 1200mg/day (400mg TID) are statistically superior to placebo and two phase 3 studies, study 301 and 302. Study 301 establishes 1200mg/day (400mg TID) as superior to placebo; study 302 establishes 600mg/day (200mg TID) and 900mg/day (300mmg TID) are superior to placebo in reduction of seizure frequency. The primary efficacy endpoint in all studies is percent change from baseline in 28-day total partial seizure frequency during the double-blind phase in the ITT double-blind population.

Review of safety reveals an excess of TEAE over placebo by 6%. Dizziness and somnolence were the TEAE of greatest frequency, headache and fatigue followed. The deaths were not above the rate seen in other anticonvulsant development programs and the rate was not greater than in the placebo group. The common adverse event profile was similar to common adverse events seen in the use of approved anticonvulsant drugs. The common adverse events include dizziness, headache, fatigue, disturbance in attention, somnolence, and nausea. The exposure to ezogabine in development is in an acceptable range however this exposure cannot anticipate less common adverse events when ezogabine treatment is applied more broadly. Ezogabine had several adverse events of special interest which include: voiding dysfunction, possibly urinary tract calculi, prolongation of the QT interval, and frequent neuropsychiatric effects (dizziness, somnolence, impairment of attention, psychotic symptoms) and elevation of hepatic transaminases. No Hy's law cases were identified in clinical trials.

Although there is a prominent adverse event profile this agent has the potential to add to treatment where incomplete treatment response continues. The novel adverse event of voiding dysfunction has not been life threatening and has been reversible in all but one case which has been partially reversible. It appears that if the voiding dysfunction is identified early, permanent sequelae is very unlikely. Practitioners will need to be aware of the novel serious adverse effects of urinary retention and psychosis. Because adverse event rate rises more rapidly than the therapeutic benefit when increasing from 900mg to the 1200mg dose, an initial target dose of 900mg with further escalation to 1200mg if directed by individual response, is suggested. Overall the benefit of an additional, effective, anticonvulsant medication and vigilance in risk minimization are adequate to counter balance the adverse effect profile of ezogabine.

1.3 Recommendations for Postmarket Risk Evaluation and Mitigation Strategies

The reviewed agrees with the sponsor plans presented in the submission for the following:

- Voiding dysfunction
  - Medication guide

    - Post voiding dysfunction AE questionnaire
    - Education
        - Provider education via web site, educational meetings and a medical information letter
        - Pharmacist launch communication to include safety information from the package insert
- Suicidality
    - Medication guide
- QT effects
    - Education
        - Provider education via website
        - Medical information letter
        - Pharmacist launch communication to include safety information from the package insert with specific detail on at risk patients

1.4 Recommendations for Postmarket Requirements and Commitments

- Voiding dysfunction
    - PMR – the sponsor has proposed a study based on a prospective cohort design using data on treated epilepsy patients with the Healthcore INc. Research Database. This is a novel approach to capture events of voiding dysfunction, from an enhanced medical and pharmacy claims database.

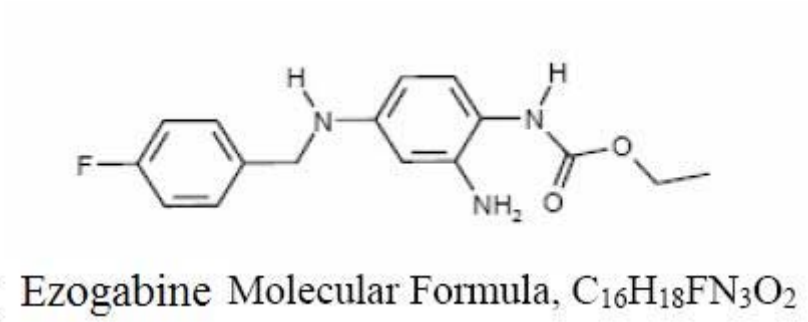
2 Introduction and Regulatory Background

2.1 Product Information

Ezogabine was first identified as an analogue of the analgesic compound flupirtine in the late 1980s and was demonstrated to have broad spectrum activity in studies conducted at the US (United States) National Institute of Health, designed to identify novel anticonvulsant agents using a battery of rodent seizure models

Ezogabine, a new molecular entity, has a primary pharmacological activity that is unlike currently available antiepileptic drugs (AEDs) and which is mediated through its ability to enhance the neuronal K+ current mediated by the Kv7 subfamily of voltage-gated potassium (KCNQ) channels, predominantly KCNQ2 and KCNQ3.

2.1.1 Molecular Formula



Ezogabine Molecular Formula, $C_{16}H_{18}FN_3O_2$

The established name ezogabine was changed because of similarity to an established name of another product used in the treatment of neurologic disease (b) (4) On February 24, 2010 the USAN Council adopted the name ezogabine as the USAN for what was formerly ezogabine and the adoption of ezogabine was rescinded. The proprietary name for ezogabine is Potiga™.

The proposed indication for Potiga™ is adjunctive treatment for patients 18 years of age and older with partial onset seizures with or without secondary generalization.

POTIGA should be given orally in 3 divided doses daily, with or without food. POTIGA Tablets should be swallowed whole. In order to minimize the risk of adverse reactions, patients should be titrated to an effective dosage of POTIGA. The initial dose should be 100 mg 3 times daily (300 mg/day). POTIGA should be increased at weekly intervals by a maximum of 150 mg/day, given as 3 divided doses, up to a recommended maximum dose of 600 to 900mg daily. Dosage may be increased to 1,200 mg/day based on individual patient response and tolerability. POTIGA is supplied for oral administration as 50-, (b) (4) 200-, 300-, and 400-mg film-coated immediate-release tablets.

2.2 Tables of Currently Available Treatments for Proposed Indications

Table 1 Anticonvulsants in common clinical use for the treatment of partial epilepsy

Phenobarbital
primidone
Phenytoin
Carbamazepine
Valproic acid
Gabapentin
Lamotrigine
Topiramate
Tiagabine
Levetiracetam

Oxcarbazepine
Zonisamide
Pregabalin
lacosamide

2.3 Availability of Proposed Active Ingredient in the United States

The active moiety (ezogabine) is a NCE (new chemical entity) and not currently marketed in any country

2.4 Important Safety Issues With Consideration to Related Drugs

Ezogabine is extensively metabolized in humans. A substantial fraction of the ezogabine dose is converted to inactive N-glucuronides. Ezogabine is also metabolized to an N-acetyl metabolite that is also subsequently glucuronidated. The N-acetyl metabolite of ezogabine has antiepileptic activity, but is less potent than ezogabine in animal seizure models.

There is no evidence for hepatic oxidative metabolism of ezogabine or the N-acetyl metabolite of ezogabine by cytochrome P450 enzymes. Therefore coadministration with inhibitors or inducers of cytochrome P450 enzymes is unlikely to affect the pharmacokinetics of ezogabine or the N-acetyl metabolite of ezogabine.

In addition, ezogabine and the N-acetyl metabolite of ezogabine did not induce CYP1A2 or CYP3A4/5 in human primary hepatocytes. Therefore ezogabine is unlikely to affect the pharmacokinetics of substrates of the major cytochrome P450 isoenzymes through inhibition or induction mechanisms.

For more detailed discussion refer to section 7.5.5.

2.5 Summary of Presubmission Regulatory Activity Related to Submission

Corporate Background of ezogabine:

The development history of ezogabine has included several changes in corporate sponsorship. Ezogabine was originally discovered by ASTA Medica and its former subsidiary, AWD GmbH, in Germany. Following completion of single and multiple dose Phase 1 human studies, ASTA Medica entered into a joint venture with Wyeth Research, Collegeville, Pennsylvania, USA, in 1997. Under Wyeth's sponsorship, IND 53,590 was submitted to FDA on August 14, 1997 to support clinical studies to assess ezogabine as a possible treatment for epilepsy. A number of Phase 1 and Phase 2 clinical studies were conducted before Wyeth discontinued its clinical development program as the result of a strategic re-evaluation of its product portfolio. All rights for ezogabine reverted to ASTA Medica in late 2001. In the following year (2002), the name of the company owning ezogabine changed from ASTA Medica AG to VIATRIS GmbH

& Co. KG. In 2004, VIATRIS licensed ezogabine to Xcel Pharmaceuticals. Although Xcel developed the final Phase 3 program, before commencement of the international Phase 3 studies, Valeant Pharmaceuticals acquired Xcel (2005), including the rights to ezogabine. Valeant continued the dialogue with FDA and finalized Phase 3 study protocols via FDA's special protocol assessment procedure and subsequently completed the Phase 3 studies. In the summer of 2008, shortly after completion of the Phase 3 studies, Valeant formed a development and commercialization partnership for ezogabine with GlaxoSmithKline.

EOP2 meeting, November 2, 2004

Issues of note in the end of phase II meeting of November 2, 2004 were as follows:

PK in special populations: In addition to the characterization of PK in subjects with renal impairment, hepatic impairment and the elderly, the division recommended the sponsor evaluate whether there are differences in pharmacokinetics due to ethnicity. The division indicated that it may be useful to genotype for UDPGT and NAT. It was also suggested that the sponsor provide for review and comments on plans for population pharmacokinetic exposure-response study design and analysis in the phase III studies. It was also recommended that the sponsor conduct a food effect study on the highest strength intended for market. A thorough characterization of ezogabine on QT was recommended.

Study Endpoint: In original design, studies 301 & 301 would utilize an RRatio to normalize data. A more traditional approach was recommended such as simple frequency or log transformed frequency. It was also recommended that both the 600mg and 900mg dose be examined in study 302.

Acceptance of studies: it was affirmed that study 205 did meet the requirements of an adequate and well controlled clinical trial of the safety and efficacy of ezogabine as adjunctive therapy for the treatment of partial onset seizures in adults.

Ezogabine and cardiac effect: plan to study QT was built into studies 301 and 302. Modifications were recommended to add elements of routine QT studies into studies 301 and 302 such as multiple time points (over 24 hours), averaging of repeated measures at each time point. There was concern over the safety of a positive control in the epilepsy population.

Bladder toxicity: the division requested safety monitoring protocols to include American Urological Association Symptom Index, chemical and microscopic urinalysis testing at every safety follow up, post voiding sonographic bladder residuals and consultation with urology during the study.

Bilirubin elevation: review of elevated bilirubin events to ascertain that they do not represent episodes of hepatic toxicity.

Examination for pro-convulsive effect: examine for new seizure types and incidence of status epilepticus following treatment.

Pre NDA, Preliminary Response to Briefing Packet Questions

Acceptance of Studies and Format: The sponsor reaffirmed with the division that studies 205, 301 and 302 are acceptable as basis for approval. In addition attention was directed to the issue that study 205 was written in a format that did not comply with current (2007) ICH format. The sponsor indicated plan to prepare an ICH format version of the study 205 report to be harmonized with the report format for studies 301 and 302 for the NDA submission. The division indicated acceptance.

Population pharmacokinetic strategy: The sponsor proposed a sample collection cutoff date of 10/31/07 which would allow inclusion of 100% of subjects from Study 301 (150) and 80% of subjects from study 302 (270). Overall more than 85% of Phase III program will contribute plasma concentration data for the analysis. The division requested in addition to standard model diagnostic plots, individual plots for a representative number of subjects. Each individual plot was requested to include observed concentrations, the individual prediction line and the population prediction line. In the report, tables were requested to include model parameter names and units. For example, oral clearance should be presented as CL/F (L/h) and not as THETA(1).

Exposure: the sponsor anticipated the numbers of patients exposed, in addition to dose and duration to meet ICH guidelines. This was acceptable to the division.

2.6 Other Relevant Background Information

3 Ethics and Good Clinical Practices

3.1 Submission Quality and Integrity

Overall eCTD format was followed and fully functional. There were items which needed additional refinement occasional link to incorrect target or links only to face page of study rather than specific subsection.

Some inaccuracies or incomplete case narratives noted that are important for full understanding of case. For example a case of death 00059, study 214, narrative indicates morbid obesity advanced coronary disease but no note of LAD lesion which is in case report. Also case 00387 of study 212 indicates a maximum ALT of 471 IU/L whereas the dataset indicates a maximum of 619 IU/L on a different date. Most case narratives of hepatic transaminases elevation did not include associated alkaline phosphatase or total bilirubin which are critical laboratory values for determination of case severity.

A most onerous example of an incomplete narrative of an SAE, aplastic anemia, is case 02 of study 3065A1-216. In this case there were no complete CBC results in the narrative but were only found by tedious examination of the 89 page case report form. There were no laboratory results from the patient hospitalization including a bone marrow biopsy result which is critical for the diagnosis of aplastic anemia. There was an indication of baseline hematopoietic deficiency in the narrative with no laboratory values to substantiate this statement.

3.2 Compliance with Good Clinical Practices

Study 205, site 021. The sponsor notes that during the course of document review at one site (Site 021 where 20 patients were enrolled), multiple Good Clinical Practice (GCP) non-compliance issues were identified, relating to Principal Investigator oversight, informed consent procedures and study documentation see appendix 9.8.

DSI Audits: DSI audits were request for sites from the phase III studies 301 and 302.

Study 301: Two sites from study 301 were selected initially, site # 001 and site # 107. Site 001 had the largest US enrollment; although no protocol violations the magnitude of enrolment was the basis of the audit. Site # 107 located in Monterrey Mexico was selected initially on the basis of two protocol violations and position as second largest enrollment in Mexico. Risk to the DSI investigator staff was subsequently factored into the decision to audit this site in light of the State Department Travel Warning concerning Mexico, with Monterrey specifically noted. The statistical consultant was asked to analyze the efficacy results with site #107 excluded. The consultant found no major change in the significance level with the exclusion of site 107. An alternate site # 014 was selected on the basis of 2nd largest US enrollment, 3 screening failures and 10 discontinuations.

Study 302: Two sites from study 302 were selected. Site # 401 was selected on the basis of largest enrollment, 38 patients (7.1%), of the study 302. Site # 853 was selected on the basis of two operational protocol violations- insufficient baseline seizures for inclusion into the study, location in a world region where FDA has limited experience with the overall reliability and integrity of clinical trial sites and magnitude of enrollment which positions this site as the 3rd largest in study 302.

DSI Inspection Results

Study 301

Site #001: 26 (22 unique subjects 4 rescreened) Subjects were screened with 16 reported as screen failures. 4 subjects terminated for non-compliance or adverse events. Sixteen subjects were randomized and completed the study. At the conclusion of the inspection, a 4 item Form FDA 483 was issued to the primary investigator. The medical records reviewed disclosed minor protocol violations and discrepancies between source documents and what was recorded in the case report forms. The DSI

assessment of data integrity concluded "Although regulatory violations were noted, the findings are unlikely to affect data integrity as they appear to be isolated occurrences and not systemic in nature. The remaining data generated from site #001 are considered reliable and appear acceptable in support of the application."

Site #014: At this site, a total of 17 subjects were screened, three (3) subjects reported as screen failures were re-screened and 2 were accepted into the study. Fourteen (14) subjects were randomized and 7 subjects completed the study. a two item Form FDA 483 was issued to the primary investigator. The investigation found protocol violations and discrepancies in the types and number of seizures due to transcription errors and non-reporting of one adverse event. The DSI assessment of data integrity concluded "Although regulatory violations were noted, the findings are not likely to affect data integrity. The remaining data from site #014 are considered reliable and appear acceptable in support of the pending application."

Study 302

Site #401: At this site, a total of 43 subjects were screened, 4 subjects were reported as screen failures, 38 subjects were randomized into the study, 18 subjects were discontinued and 24 subjects completed the study. Two subjects withdrew from the study: one had positive pregnancy test after the first dose, the second experienced a generalized rash. A one item Form FDA 483 was issued. The investigation found that 3 subjects were enrolled into the study contrary to protocol inclusion criteria. The DSI assessment of data integrity concluded "Although regulatory violations were noted, the findings are unlikely to affect data integrity. The remaining data generated from the site are considered reliable and appear acceptable in support of the application."

Site 853: At this site, a total of 26 subjects were screened, 2 subjects were reported as screen failures, 24 subjects were randomized and 19 subjects completed the study. Six (6) subjects withdrew from the study and the reasons were documented. The medical records reviewed disclosed no adverse findings that would negatively on the reliability of the data. In general, the records reviewed were found to be organized and the data verifiable, no form 483 was issued. The DSI assessment of data integrity concluded "The data from this site are considered reliable and appear acceptable in support of the pending application."

The sponsor was also inspected because Potiga (ezogabine) is a new molecular entity. The inspection audited Protocols VRX-RET-E22-301 and #302 and focused on two clinical investigators. The field investigator and headquarter representative joined the EMA team to review the firm's various operating procedures (SOPs) in accordance with the Sponsor/Monitor/Contract Research Organization (CRO) compliance program, including the monitoring SOPs. A Form FDA 483 was issued at the conclusion of the inspection for the failure to:

- Provide the clinical investigators with information needed to conduct the study in terms of additional safety procedures requested by the agency.

- Obtain, retain and provide upon request information regarding curriculum vitae or statement of the qualifications of investigators and selection of monitors.
- Provide training documentation of staff involved in the study.
- Submit an addendum to the protocol instead of granting 34 waivers for subjects not meeting inclusion/exclusion criteria.
- Ensure adequate monitoring at certain sites.

The DSI assessment of data integrity concluded "In general, the records and documents reviewed were found to be in order and verifiable. Although regulatory violations were noted as above, these do not appear systemic in nature and are unlikely to impact data reliability. The data generated appear to be acceptable in support of this application.

Reviewer Comment: Although regulatory violations were identified at 3 investigator sites and at the sponsor these were sporadic, not of a systemic nature and are unlikely to impact overall data reliability.

3.3 Financial Disclosures

The studies listed below are identified as the "covered clinical studies" for the purposes of the rule; i.e. within this marketing application, Valeant Pharmaceuticals, North America relies on the following studies to establish that the product is effective, table 2.

The development of ezogabine has involved several sponsors. Study 3065A1-205 (table 2) was conducted by Wyeth-Ayerst Research (Wyeth), prior to acquisition of ezogabine by Valeant Pharmaceuticals in 2005. Accordingly, a separate Form FDA 3454 is being submitted for this study, which was not sponsored by the applicant. A second Form FDA 3454 is provided for the remaining covered studies, which were sponsored by Valeant.

Table 2 Covered Clinical Studies for Establishment of Efficacy

Protocol No.	Protocol Title	Sponsor	Overall Study Start/Completion Dates
3065A1-205-AU/EU/US	A Randomized, Double-blind, Placebo-controlled, Parallel-group, Multicenter, Dose-ranging, Efficacy and Safety Study of Ezogabine (D-23129; GKE-841) Administered as Add-on Therapy in Patients With Partial Epilepsy	Wyeth-Ayerst Research	20 JUL 1999 30 MAY 2001
VRX-RETE22-301	A Randomized, Double-Blind, Placebo-Controlled, Multicenter, Parallel-Group Phase 3 Study to Determine the Efficacy and Safety of Ezogabine (1200mg/day) Used as Adjunctive Therapy in Refractory Epilepsy Patients with Partial-Onset Seizures	Valeant Pharmaceuticals	31 AUG 2005 10 JAN 2008
VRX-RETE22-	A Randomized, Double-Blind, Placebo-	Valeant	19 DEC 2005

Protocol No.	Protocol Title	Sponsor	Overall Study Start/Completion Dates
302	Controlled, Multicenter, Parallel-Group Phase 3 Study to Determine the Efficacy and Safety of Two Doses of Ezogabine (900 mg/day [300mg TID] and 600 mg/day [200 mg TID]) Used as Adjunctive Therapy in Refractory Epilepsy Patients with Partial-Onset Seizures	Pharmaceuticals	09 APR 2008
VRX-RETE22-105	Comparative, Randomized, Open-Label, Single-Dose, 2-Way Crossover Bioavailability, Safety and Tolerability Study of a 400 mg dose of Ezogabine Administered as the Clinical Trials Formulation and the Market Image Formulation in Healthy Adult Male Subjects	Valeant Pharmaceuticals	10 DEC 2007 21 DEC 2007

The sponsor (Valeant) has defined the overall duration of the clinical study as the time period beginning with the date of enrolment of the first patient entered into the clinical study at the first site until the date of the last patient assessment at the last site of a covered clinical study. However, to the extent investigators have provided financial disclosure information via questionnaires, they were asked to do so based on site-specific (or if shorter, their individual) study start and completion dates.

Study 301 and 302

The sponsor (Valeant) relied upon investigator financial interest information provided by the investigators through questionnaires. Financial interest was collected on investigators in Study VRX-RET-E22-105 at the start of the study. Financial interest was collected on investigators in VRX-RET-E22-301 and VRX-RET-E22-302 at the start of the study and again at study completion. If, according to their written commitment to Valeant, investigators filed questionnaires of updated financial interest information to account for any changes in the 1-year period following study completion, these additional questionnaires were relied on as well.

Study 205

Wyeth-Ayerst Research (Wyeth) collected information from some investigators on their financial interest by requesting their response via questionnaire. If according to their written commitment to Wyeth, investigators filed questionnaires of updated financial interest information to account for any changes in the 1-year period following study completion. Where financial interest on investigators had not been collected by Wyeth, Valeant Pharmaceuticals exercised due diligence and retrospectively requested via questionnaire the investigators financial interest with the previous sponsor, Wyeth, or with Valeant.

The sponsor relied on the financial interest questionnaire to acquire data on significant equity interest ($50,000 threshold), payment of other sorts ($25,000) threshold, and proprietary interest in the tested product. A list of all principle and subinvestigators is provided for each study. No investigator is identified with a disclosable financial interest

however there are several investigators for study 205 and 302 whose financial disclosure information was not obtainable. These investigators are identified in table 3. In addition to those investigators of study 302 whose disclosure information could not be obtained there were 11 investigators not show in the table who were listed by mistake as subinvestigators. The 4 subinvestigators who were participants in study 302 but whose financial disclosure information could not be obtained are indicated by the sponsor as no longer at the site. In study 205 there were 26 investigators involving 12 sites whose financial disclosure information is not available. The reasons indicated by the sponsor include, unable to locate, no longer at site, no response, and in one case the investigator is deceased.

Table 3 List of Investigators from Whom Required Information Could Not Be Obtained, study 205 and study 302

PI / Subinvestigator	Investigator Name	Site	# patients	% of study
Study 205				
(b) (6)				
PI	Julian Alvarez Tejerina	053	3	<1%
(b) (6)		004	1	<1%
		017	2	<1%
		020	1	<1%
		028	4	1%
		065	15	4%
		070	1	<1%
		075	13	3%
		076	4	1%
		080	2	<1%
		101	3	<1%
Study 302				
(b) (6)		803	11	2

In order to determine the impact of potential financial conflict of those whose disclosure information is unavailable the investigator site, size of patient enrollment and percent contribution to the study of this enrollment is examined. These relationships are seen in table 3. In study 301 there is one site where 4 sub investigators have undetermined financial disclosure. This site contributed 11 patients representing 2% of the study total enrollment. If one or more of these investigators is compromised the overall influence on the study is limited and unlikely to influence study outcome.

In study 205 there were 12 sites involved where the disclosure of investigators is not obtained. The largest site enrolled 15 subjects, representing 4% of study enrollment, the second largest enrolled 13 subjects, representing 3% of study enrollment and the third largest enrolled 8 subjects representing 2%% of overall study enrollment. The remaining 9 sites combined enrolled 21 patients representing 5.3% of overall study enrollment. None of the remaining 9 sites enrolled greater than 4 patients. The financial disclosure status and influence of these study 205 investigators is uncertain. The impact of this uncertainty is attenuated by the maximum single site contribution of the largest three enrollments to 4%, (site 065), 3% (site 075) and 2% (site 054). This conclusion is draw because it is unlikely that all non-disclosed investigators have a financial conflict. It is more likely that only a few have conflict, scattered among these sites. If a conflict were to exist, the influence of a subinvestigator at the site is likely to be diluted by the remaining investigators at the site. The investigators of greatest concern are the principle investigators; in this case (b) (6) at site (b) (6) has influence that could not exceed 2% of the study enrollment. The influence of the only remaining non-disclosed principle investigator is limited to the recruitment of 3 patients representing less than 1% of overall study enrollment.

4 Significant Efficacy/Safety Issues Related to Other Review Disciplines

4.1 Chemistry Manufacturing and Controls

An (b) (4) ((b) (4) that is genotoxic is retained in the final drug product. The CMC review does not recommend approval unless the high levels of (b) (4) in the active pharmaceutical ingredient is satisfactorily address. Discussion continues between FDA and the sponsor at the time of this writing 8/30/10.

4.2 Clinical Microbiology

No relevant specialty contribution for this product

4.3 Preclinical Pharmacology/Toxicology

The complete review is not submitted at time of this writing on 8/30/10 but the entry below contains discussion with the pharmacology – toxicology review on issues of importance to date.

Cardiac: ezogabine, at high concentrations, produced some hERG inhibition in vitro and prolonged QT slightly in a perfused guinea pig heart preparation, there was no evidence of EKG effects in vivo. However, decreases in blood pressure and heart rate were seen in several in vivo studies which were thought to be related to a relaxant effect on vascular smooth muscle.

Urinary tract / CNS: studies in juvenile rats treated from for approximately 2 weeks beginning on postnatal day 7 at doses from 0.2 to 54 mg/kg, increased mortality occurred at ≥ 2 mg/kg. In those animals found dead or electively euthanized early during the study, distended urinary bladders and concurrent secondary dilation of the renal pelvis were observed. Microscopically, the urinary bladder was dilated with thin walled mucosal and muscular layers. Secondary renal pelvic dilation and dilatation of the cortical proximal convoluted tubules were observed in multiple animals. Dilation of the ureter was also observed in some. Physical obstruction due to intraluminal crystals or debris was not found. It was thought that the urinary bladder distention induced secondary uremia and a moribund state. The etiology was thought to involve the neurogenic effect of ezogabine on the detrusor muscle in the urinary bladder causing inhibition of bladder contractility. Adverse clinical signs consisting of moribundity, coolness to the touch, and immobility were observed. Myoclonus and immobility were also observed in a number of animals, indicating increased sensitivity to CNS effects in young animals as well. The LOAEL for these effects (bladder and CNS) in adult rats is about 10X greater.

Similar or related effects were seen in adult rats, mice, and dogs. In adult rats, histopathological alterations of the urinary bladder included luminal ectasia, congestion of submucosal vessels, ulcerations and associated diffuse hyperplasia of the bladder mucosa. These observations were thought to be consistent with increased urine pressure in the bladder resulting from inhibition of micturition produced by the effect of ezogabine on bladder smooth muscle. The bladder effects were more pronounced in mice, where microscopic observations included distension, intraluminal debris/uroliths, edema, necrosis, epithelial hyperplasia, erosion, and ulceration; and secondary effects in the kidneys were seen including pelvic dilation, papillary necrosis, tubular degeneration/regeneration and tubular dilation. Bladder findings in adult dogs included degeneration and necrosis of the urinary bladder smooth muscle.

Hematologic: Some suppression of bone marrow granulocyte lineage was seen.

4.4 Clinical Pharmacology

Completed review not submitted for integration into the review at the time of this writing 8/30/10.

4.4.1 Mechanism of Action

See section 4.4

4.4.2 Pharmacodynamics

See section 4.4

4.4.3 Pharmacokinetics

See section 4.4

5 Sources of Clinical Data

5.1 Tables of Studies/Clinical Trials

		Clinical Studies Providing Safety Information for Ezogabine and Overview of Analysis Sets for Integrated Summaries				
Study	**Status of Study**	**Type of Study**	**RCT Analysis Set (3studies)**	**All Phase II/III Combined Analysis Set (13 studies)**	**Integrated Phase I Analysis Set (21 studies)**	**Presented Separately (10 studies)**
Phase I single-dose studies						
3065A1-100	Completed	Healthy subject PK			X	
3065A1-103	Completed	Comp. BA/BE			X1	
3065A1-105	Completed	Intrinsic factor PK			X	
3065A1-106	Completed	BA/PK			X	
3065A1-108	Completed	Healthy subject PK			X	
3065A1-110	Completed	Comp. BA/BE			X	
3065A1-120	Completed	Comp. BA/BE			X1	
3065A1-121	Completed	Bioanalytical			X	
3065A1-123	Completed	BA			X	
VRX-RET-E22-104	Completed	BA			X	
VRX-RET-E22-105	Completed	Comp. BA/BE			X	
VRX-RET-E22-SR101	Completed	Comp. BA/BE			X1	
3065A1-104	Completed	BA				X2
3065A1-117	Completed	Healthy subject PK				X2
VRX-RET-E22-101	Completed	Intrinsic factor PK				X3
VRX-RET-E22-102	Completed	Intrinsic factor PK				X3
VRX-RET-E22-107	Completed	Extrinsic factor PK				X3
VRX-RET-E22-108	Completed	Abuse potential				X3
Phase I multiple-dose studies						

		Clinical Studies Providing Safety Information for Ezogabine and Overview of Analysis Sets for Integrated Summaries				
Study	**Status of Study**	**Type of Study**	**RCT Analysis Set (3studies)**	**All Phase II/III Combined Analysis Set (13 studies)**	**Integrated Phase I Analysis Set (21 studies)**	**Presented Separately (10 studies)**
3065A1-101	Completed	Healthy subject PK			X	
3065A1-102	Completed	Healthy subject PK			X	
3065A1-107	Completed	Healthy subject PK			X	
3065A1-109	Completed	Extrinsic factor PK			X	
3065A1-112	Completed	Extrinsic factor PK			X	
3065A1-113	Completed	Extrinsic factor PK			X	
3065A1-115	Completed	Intrinsic factor PK			X	
VRX-RET-E22-103	Completed	Healthy subject PD and PD/PK			X	
VRX-RET-E22-106	Completed	Extrinsic factor PK			X	
VRX-RET-E22-MR103	Ongoing	PK				X
Phase IIa studies						
3065A1-200/2015	Completed	Safety and PK		X		
3065A1-202	Completed	Safety and PK		X		
3065A1-209	Completed	Safety and tolerability		X		
3065A1-214	Completed	Safety and tolerability		X		
Extension Studies from Phase IIa						
D-23129/8017	Completed	Safety and tolerability		X		
3065A1-208	Completed	Safety and tolerability		X		
3065A1-216	Completed	Safety and tolerability		X		
Phase IIb studies						
3065A1-205	Completed	Efficacy and safety	X	X		
Phase III studies						
VRX-RET-E22-301	Completed	Efficacy and safety	X	X		
VRX-RET-E22-302	Completed	Efficacy and safety	X	X		
Extension Studies from Phase IIb/III						
3065A1-212	Completed	Safety and tolerability		X		
VRX-RET-E22-303	Ongoing	Safety and tolerability		X		
VRX-RET-	Ongoing	Safety and		X		

		Clinical Studies Providing Safety Information for Ezogabine and Overview of Analysis Sets for Integrated Summaries				
Study	**Status of Study**	**Type of Study**	**RCT Analysis Set (3studies)**	**All Phase II/III Combined Analysis Set (13 studies)**	**Integrated Phase I Analysis Set (21 studies)**	**Presented Separately (10 studies)**
E22-304		tolerability				
Other Phase II/III studies						
VRX-RET-E22-NP201	Completed	Efficacy and safety in post-herpetic neuralgia (PHN)				X,5
D-23129-3227	Ongoing	Compassionate use - safety and tolerability				X
D-23129-8040	Completed	Safety and tolerability in bipolar disorder				X5

1. Only the IR treatment arms in these studies were included in the integrated data analyses.
2. Excluded from the integrated analysis because study drug received was a slow-release (SR) formulation (3065A1-104) or an intravenous (IV) formulation (3065A1-117).
3. Excluded from the integrated analysis because the populations studied differ from both healthy volunteers and patients with epilepsy (VRX-RET-E22-101 [renal insufficiency], VRX-RET-E22-102 [hepatic impairment], VRXRET- E22-107 [co-administration with alcohol] and VRX-RET-E22-108 [abuse liability]).
5. Excluded from the integrated analysis because study was not in epilepsy patients

Urology Consultation

The identification of novel urologic safety issues prompted submission of a consult to the Division of Reproductive and Urologic Products (DRUP). The consultants asked to provide insight and guidance on the issues of urinary retention / voiding dysfunction and urinary crystals / stone formation.

5.2 Review Strategy

The submission was in eCTD format which allowed review of sponsor narrative ISE and ISS and analysis using individual study and ISS datasets.

Efficacy

RCT trials 205, 301 and 302 were reviewed as support for efficacy.

Safety

The RCT trials were used where a placebo control would be most informative. All phase II/III trial group was used in a complementary form when observation of longer duration and a larger exposure population would prove more useful. A list of the trials may be seen in table 37. Section 7.3 analysis utilized primarily sponsor narrative and tables as sources for analysis and discussion of Deaths, SAEs, discontinuations and AEs. In section 7.4. for common adverse events a mix of reanalysis of the AE dataset and sponsor ISS was used. Dizziness in particular was reanalyzed using the AE and vital signs dataset to determine if this frequent AE was related to orthostatic blood

pressure challenge. The remainder of section 7.4, laboratory findings, vital signs, ECGs and special safety studies were reviewed utilizing the ISS analysis datasets. Section 7.5, other safety explorations utilized a mix of dataset analysis and sponsor submission.

5.3 Discussion of Individual Studies/Clinical Trials

Study 205

Protocol: 3065A1-205-AU/EU/US
Title of study: A randomized, double-blind, placebo-controlled, parallel-group, multicenter, dose-ranging, efficacy and safety study of ezogabine (D-23129; GKE-841) administered as add-on therapy in patients with partial epilepsy.
Study center(s): 73 active sites in 19 countries (6 Australia, 3 Belgium, 1 Croatia, 5 Czech Republic, 4 Finland, 7 France, 5 Germany, 3 Israel, 7 Italy, 2 Netherlands, 2 New Zealand, 1 Norway, 6 Poland, 1 Portugal, 3 Slovakia, 6 Spain, 2 Sweden, 4 United Kingdom, 5 USA)
Publication Porter RJ, Partiot A, Sachdeo
Studied period: 2 years. First subject enrolled: June 1999, First subject dosed: 22 Sep 1999, Last subject last dose: 29 May 2001.
Objectives: The primary objective was to evaluate the efficacy and safety of 3 times daily (TID) administration of 3 different doses (200, 300, and 400 mg) of ezogabine compared with placebo, all of which were administered as add-on therapy in patients with partial epilepsy who were receiving 1 or 2 of the following established treatments: valproic acid, carbamazepine, phenytoin, topiramate, lamotrigine, gabapentin, oxcarbazepine, benzodiazepines, or barbiturates and vagal nerve stimulation.
Methodology: This was a randomized, double-blind, placebo-controlled, multicenter, dose-ranging study of efficacy and safety in patients with epilepsy currently treated with one or two anti-epileptic drugs (AEDs). Patients were randomized to 4 parallel groups. The study consisted of 5 phases: an 8-week screening and baseline phase, during which patients were evaluated for seizure frequency; an 8-week titration phase; an 8-week maintenance phase, during which patients received the dose reached at the end of the titration phase; and a 5-week interim phase, during which the ezogabine dose was adjusted to 300 mg TID for all patients, figure 1. Seizures were captured by patients' diaries and classified by the investigator.
Number of subjects (planned and analyzed): A total of 360 patients were planned, 399 were randomized; 397 were analyzed for safety; and 396 were analyzed for efficacy (ITT population).
Diagnosis and main criteria for inclusion: Patients enrolled were men or women aged 16 to 70 years, diagnosed with partial epilepsy with simple partial seizures with a motor component, or complex partial seizures with or without secondary generalization. They were required to have ≥ 4 partial seizures on average per month during the 2 months prior to randomization. Patients, who were seizure-free for more than 30 consecutive days during the screening phase, were not eligible.
Test product, dose and mode of administration: Ezogabine was supplied in 3 capsule strengths (50, 100, and 200 mg) and administered orally.

Reference therapy, dose and mode of administration: The reference therapy was placebo administered orally TID as matching capsules.
Statistical methods: Efficacy: The primary efficacy endpoint was the percent change in monthly total partial seizure rate from baseline phase (8-week baseline phase) to the double-blind therapy phase (including all titration and maintenance phase data). Secondary efficacy assessments included assessments of percent change in monthly total partial seizure rate from baseline phase to other therapy phases; the responder rate, with a responder defined as a patient who has at least a 50% reduction in monthly rate of seizures, and the frequencies of types of seizures.

The percentage change in monthly total partial seizure rate was analyzed by using a rank analysis of covariance (ANCOVA) with the rank of the baseline monthly seizure rate as a covariate and treatment and center as factors in the model. The dose-response was studied by using appropriate contrasts in the ANCOVA according to a closed test procedure for a monotonic trend (two-sided, $\alpha = 5\%$). In addition, Hodges-Lehmann estimates and two-sided 95% confidence intervals are provided for the pairwise comparisons.

Harmonized analysis study 205

Further *post-hoc* analyses were conducted by Valeant in order to harmonize the statistical methodology with those applied in Studies 301 and 302. The patient populations characterized for these additional *post-hoc* analyses were:

- ITT (FDA) population was defined as all randomized patients who received at least one dose of study drug and had one post-baseline seizure assessment recorded in the double-blind phase (titration and maintenance phase combined).

- The ITT (EMEA) population was defined as all randomized patients who received at least one dose of study drug in the maintenance phase and had at least one seizure measurement (whether or not they had a seizure) recorded in the maintenance phase.

The relevant endpoints and associated *post-hoc* analyses are identified in the side-by-side comparisons below:

Original Analysis (WYETH)	
ITT Population • ≥1 dose study drug • Baseline seizure evaluation • On-therapy seizure evaluation Primary Analysis Methods for key endpoints: % change partial seizure frequency: Rank ANCOVA with treatment and pooled centers as factors and seizure rate as covariate Response Rate: Logistic regression with treatment and pooled centers as factors	Analyses of change from baseline to Maintenance phase were performed on the ITT population. Patients included in these analyses must have met the following criteria: • ≥1 dose study drug in maintenance • Baseline seizure evaluation • Maintenance seizure evaluation
Valeant *Post-Hoc* analyses to assess the effects of dropouts during titration on the key endpoints from baseline to maintenance phase	
ITT Identical to ITT used in original analysis Primary Analysis Methods for key endpoints same as for ITT All patients included in the ITT population were included in the analyses assessing change from baseline to maintenance phase. However, a range of algorithms were applied to impute data for patients who dropped out during titration phase.	
Valeant *Post-Hoc* (Harmonized) analyses to assess the original results using analogous statistical methods to those used in contemporary Valeant Studies 301 and 302	
ITT(FDA): Identical to ITT used in original analysis Primary Analysis Methods for key endpoints: % change partial seizure frequency: Non-parametric rank ANCOVA stratified by baseline seizure rate (4-8 v >8) Response Rate: Fisher's Exact test	ITT(EMEA): • ≥1 dose study drug in maintenance • Baseline seizure evaluation • Maintenance seizure evaluation Primary Analysis Methods for key endpoints same as for ITT (FDA)
Valeant *Post-Hoc* analyses to provide side-by-side summaries of Study 205 data which were not included in the original or amended clinical study reports	
ITT (Double-Blind) • ≥1 dose study drug • Baseline seizure evaluation	ITT (Maintenance) • Identical to ITT (EMEA)

Figure 1 Study 205 Dosing Schematic

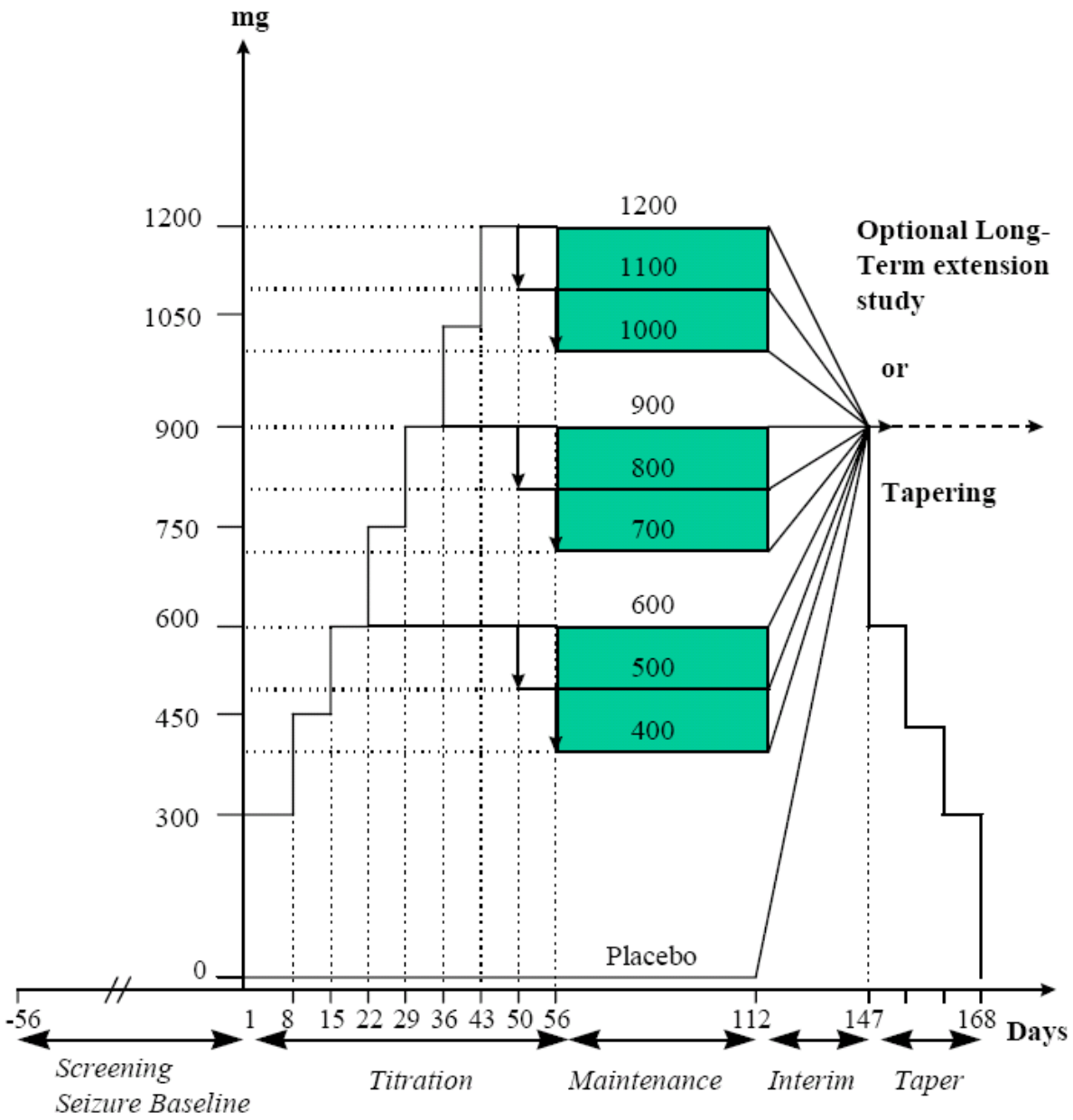


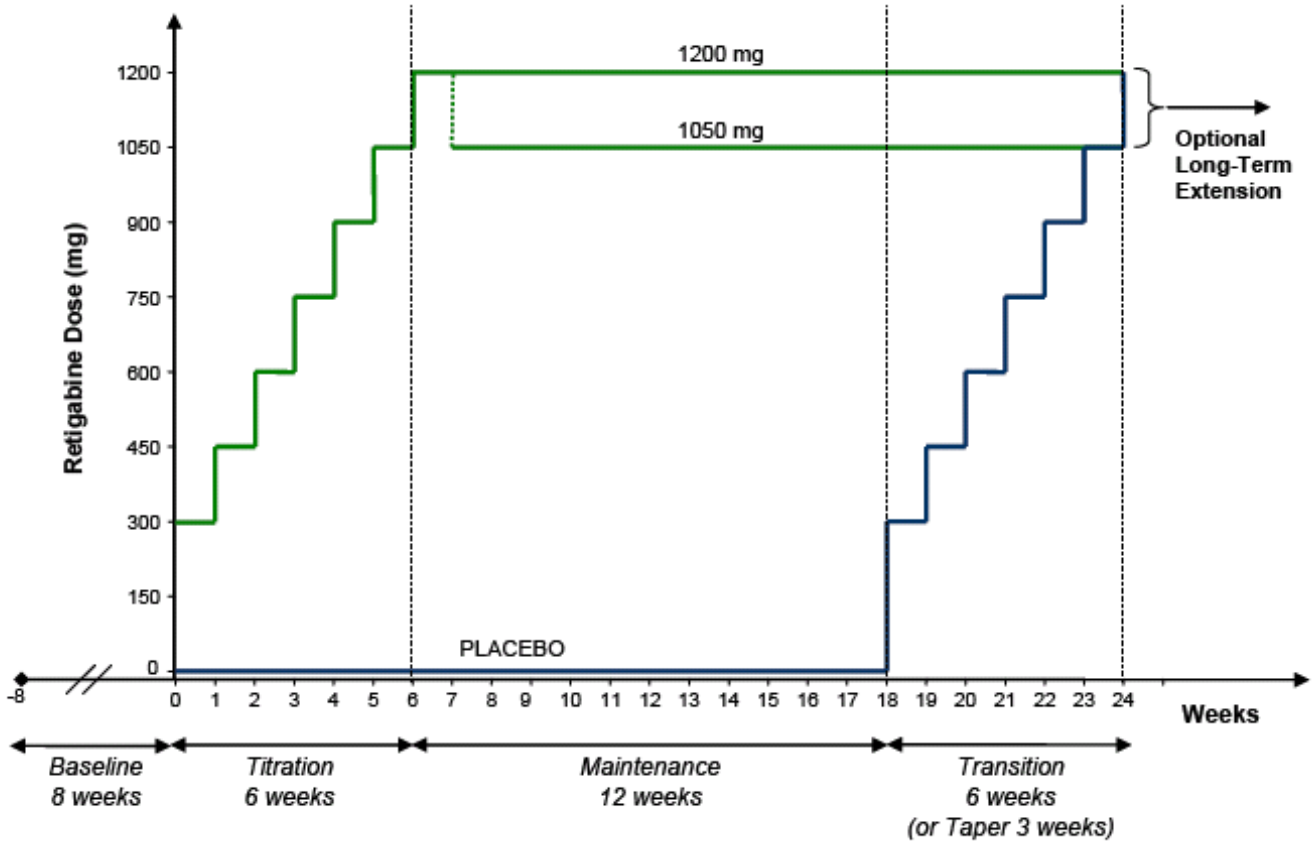
Figure 1: Dosing steps for all phases of the study
Dose reduction may take place as early as day 44

Study 301

Protocol no: VRX-RET-E22-301

Title of study: A randomized, double-blind, placebo-controlled, multicenter, parallel-group phase 3 study to determine the efficacy and safety of ezogabine (1200 mg/day) used as adjunctive therapy in refractory epilepsy patients with partial-onset seizures
Study center(s): 53 clinical centers in the US (34), Canada (4), Mexico (6), Argentina (5), and Brazil (4)
Study Period: 2 years: First patient screened: 31 August 2005, First patient dosed: 16 November 2005, Last patient completed: 10 January 2008.
Methods: This was a randomized, double-blind, placebo-controlled, multicenter, parallel-group Phase 3 study to assess the efficacy and safety of ezogabine (1200 mg/day; 400 mg TID]) compared to placebo in patients with epilepsy who were receiving 1, 2, or 3 AEDs. Use of a vagal nerve stimulator (VNS) was also allowed in addition to as many as 3 AEDs. The study consisted of a screening visit, an 8-week baseline phase to evaluate seizure frequency; a 6-week titration phase; a 12-week maintenance phase; and a 6-week transition phase or a 3-week tapering phase, see figure 2. During the titration phase, patients were titrated from 300 mg/day to 1200 mg/day (400 mg TID) on blinded study drug, with weekly increases in doses of 150 mg/day over the course of 6 weeks. Patients who were unable to tolerate dose escalation were discontinued from the study. During the maintenance phase, patients who were unable to tolerate the 1200 mg/day (400 mg TID) dose were allowed to reduce their dose to 1050 mg/day at the Week 7 visit only and were to continue on that dose for the remainder of the maintenance phase. The double-blind period consisted of the titration phase plus the maintenance phase for purposes of efficacy assessments. Patients who successfully completed the maintenance phase were invited to participate in an open-label extension study VRX-RET-E22-303.
Number of subjects (planned and analyzed): Planned: 280 patients (140 per arm). Analyzed: 305 patients (152 placebo, 153 ezogabine) in the safety population and in the intent-to-treat (ITT) FDA population; 256 patients (137 placebo, 119 ezogabine).
Diagnosis and main criteria for inclusion: Eligible patients were 18-75 years of age, had a diagnosis of refractory epilepsy with simple partial or complex partial seizures with or without secondary generalization (International League Against Epilepsy [ILAE] classification), had a 28-day partial seizure frequency of ≥4 seizures over an 8-week period, and did not have a consecutive period of 21 days without seizures. Refractory epilepsy was defined by diagnosis of epilepsy for 2 years or longer, with partial seizures despite having been treated in the past with at least 2 approved AEDs either alone or together at adequate doses for sufficient length of time in the opinion of the investigator.
Test product, dose and mode of administration: Ezogabine 50-mg, 100-mg, 300-mg tablets TID by mouth for a final total dose of 1200 mg/day (400 mg TID).
Reference therapy, dose and mode of administration: Matching placebo tablets TID by mouth.
Statistical methods: The primary efficacy analysis for the FDA review was the comparison of the median percent change in the 28-day total partial seizure frequency from baseline to the double-blind treatment period in the intent-to-treat FDA (ITT) population. .A non-parametric stratified rank analysis of covariance (ANCOVA) was used as the primary analysis to compare the percent change in total partial seizure frequency of the ezogabine and placebo treatment groups.

Figure 2 Study 301 Dosing Schematic



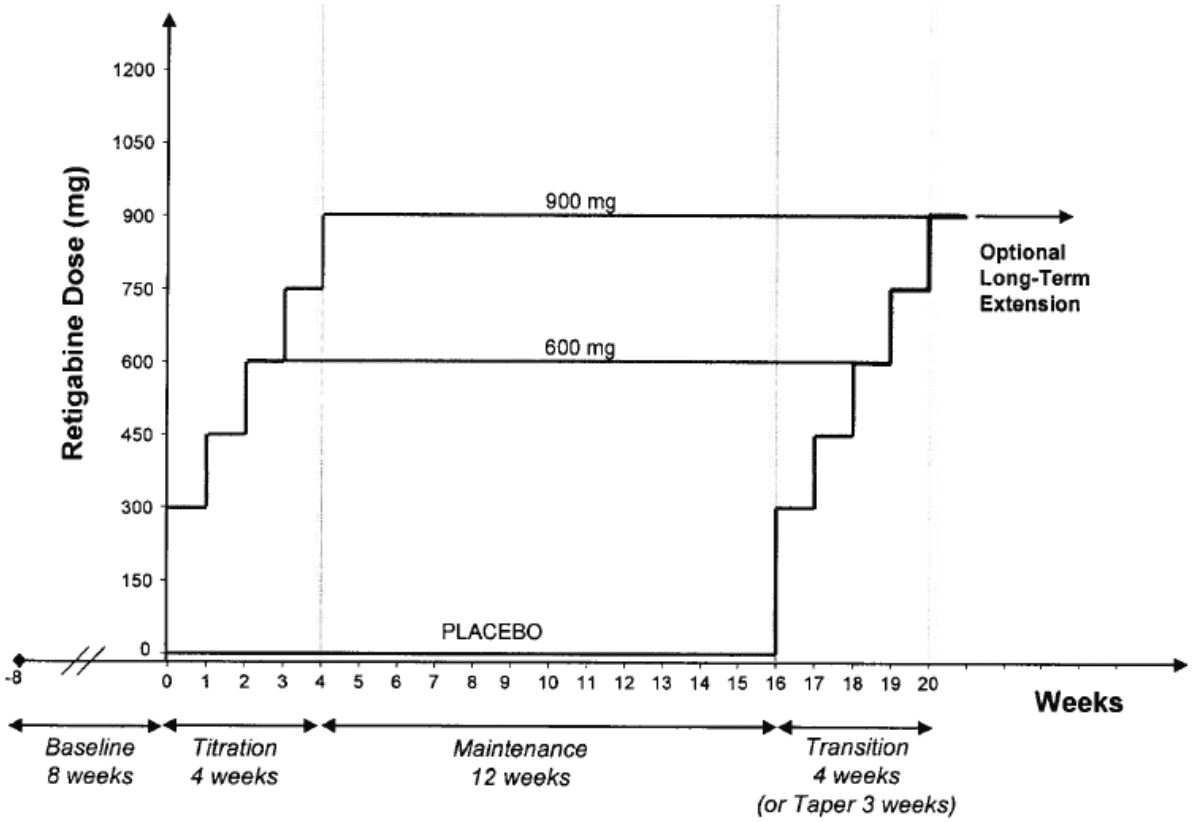
Study 302

Protocol: VRX-RET-E22-302
Title of study: A randomized, double-blind, placebo-controlled, multicenter, parallel-group Phase 3 study to determine the efficacy and safety of two doses of ezogabine (900 mg/day [300 mg TID] and 600 mg/day [200 mg TID]) used as adjunctive therapy in refractory epilepsy patients with partial-onset seizures.
Study Centers: 71 sites screened patients in Australia (5), Belgium (4), France (4), Germany (7), Hungary (3), Israel (8), Poland (8), Russia (5), South Africa (9), Spain (6), United Kingdom (5), Ukraine (5), and United States (2).
Study Period: 2 Years, First patient dosed: 13 February 2006, Last patient last visit: 09 April 2008
Objective: Primary- To demonstrate a superior change in total partial seizure frequency per 4 weeks from baseline to the double blind period (titration through maintenance) in patients treated with ezogabine dosed at 900 mg/day, in 3 equally divided doses (300 mg TID), compared to placebo. Secondary- To explore the change in total partial seizure frequency per 4 weeks from baseline and the proportion of the responders experiencing a ≥50% reduction in total partial seizure frequency in patients treated with

ezogabine dosed at 600 mg/day, in 3 equally divided doses (200 mg TID), compared to placebo.
Methods: This was a randomized, double-blind, placebo-controlled, multicenter, parallel-group Phase 3 study to assess the efficacy and safety of ezogabine dosed at 600 mg/day (200 mg TID) or 900 mg/day (300 mg TID) compared to placebo in patients with epilepsy who are receiving 1, 2, or 3 AEDs. Use of a vagal nerve stimulator (VNS) was also allowed in addition to as many as 3 AEDs.

The study consisted of a screening visit, an 8-week baseline phase to evaluate seizure frequency; a 4-week titration phase; a 12-week maintenance phase; and a 4-week transition phase or a 3-week tapering phase, figure 3. During the titration phase patients were titrated from 300 mg/day to 600 or 900 mg/day, with weekly increases in dose of 150 mg/day over the course of 2 to 4 weeks. Patients who were unable to tolerate the dose escalation were discontinued from the study. The double-blind period consisted of the titration phase plus the maintenance phase for purposes of efficacy assessments. Patients who successfully completed the maintenance phase were invited to participate in an open-label extension study (VRX-RET-E22-304, Study 304).
Number of Subjects Planned and Analyzed: Planned: 510 patients (170 per arm). Analyzed: 538 (179 placebo, 181 ezogabine 600 mg, 178 ezogabine 900 mg) for safety and intent-to-treat (ITT).
Diagnosis and main criteria for inclusion: Eligible patients were 18-75 years of age, had a diagnosis of refractory epilepsy with simple partial or complex partial seizures with or without secondary generalization (International League Against Epilepsy [ILAE] classification), had a 28-day partial seizure frequency of ≥4 seizures over an 8-week period, and did not have a consecutive period of 21 days without seizures. Refractory epilepsy was defined by diagnosis of epilepsy for 2 years or longer, with partial seizures despite having been treated in the past with at least 2 approved AEDs either alone or together at adequate doses for sufficient length of time in the opinion of the investigator.
Test product, dose and mode of administration: Ezogabine 50 -mg, 100-mg tablets TID by mouth for a final total dose of 600 mg/day or 900 mg/day.
Reference therapy, dose and mode of administration: Matching placebo tablets TID by mouth.
Statistical methods: The primary efficacy analysis for the FDA review was the comparison of the median percent change in the 28-day total partial seizure frequency from baseline to the double-blind treatment period in the intent-to-treat FDA (ITT) population. A non-parametric stratified rank analysis of covariance (ANCOVA) was used as the primary analysis to compare the percent change in total partial seizure frequency of the ezogabine and placebo treatment groups.

Figure 3 Study 302 Dosing Schematic



6 Review of Efficacy

Efficacy Summary

6.1 Indication

The indication proposed for ezogabine in this application is “adjunctive treatment for patients 18 years of age and older with partial onset seizures with or without secondary generalization.

6.1.1 Methods

There were three primary efficacy studies; **205, 301 and 302.**

Study 205 the primary objective was defined according to the key primary efficacy Variable: The percentage change in total partial seizure frequency per 28 days from baseline to the double-blind phase.

Study 205 patients were randomized 1:1:1:1 to one of four parallel groups: placebo, 600mg/day ezogabine, 900 mg/day ezogabine, or 1200 mg/day ezogabine. A sample size of 82 patients per group was calculated, based on 90% power for each active

treatment group to show a 20% difference in response from placebo (30% in active group vs. 10% in placebo group), with a two-sided significance level of 0.05. A sample size of 90 patients per group, i.e., a total of 360 patients, was planned in order to compensate for patients who did not meet the ITT criteria. A total of 399 patients were actually randomized.

Studies 301 and 302; the primary objectives were defined according to two key primary efficacy variables: The primary objective for FDA review was the evaluation of the percent change in the 28-day total partial seizure frequency from baseline to the double-blind phase (titration and maintenance phases combined).

The sample size calculations for both Study 301 and Study 302 were based on the percentage of responders observed in Study 205. For Study 301, a total of 250 evaluable patients (125 per arm, 1:1 randomization) were required in order to detect a 17% difference in responder rates between ezogabine 1200 mg/day and placebo with 85% power and a two-sided significance level of 5%. The assumed 10% attrition rate between randomization and the first post-dose seizure evaluation required that a total of 280 patients (140 per treatment arm) be randomized in order to satisfy the evaluable sample size requirements. A total of 306 patients were actually randomized.

For Study 302, a total of 453 evaluable patients (151 in each of the three treatment arms, 1:1:1 randomization) were required in order to detect a 16% difference in responder rates between ezogabine 900 mg/day and placebo with 85% power and a two-sided significance level of 5%. The assumed 10% attrition rate between randomization and the first post-dose evaluation assessment required that a total of approximately 510 patients (170 per treatment arm) be randomized in order to satisfy the evaluable sample size requirements. A total of 539 patients were actually randomized.

6.1.2 Demographics

Study 205

Patients were on average 37 years (range 14 to 66 years) with a mean duration of epilepsy of approximately 20 years (table 4). The majority (96%) of patients were Caucasian. The median baseline seizure rate was 8 to 10 seizures/month across all treatment groups. In the majority (70%) of patients, ezogabine was added to two other AEDs. No overall differences were seen between treatment groups in any of the demographic or baseline characteristics with the exception of the slightly higher median baseline seizure rate for the ezogabine 1200 mg/day dose group (10.4) compared to the other dose groups (7.9 to 8.5). Demographic and baseline characteristics of the patients who were evaluable for efficacy did not differ appreciably from those of the total population

Table 4 Demographics and Other Baseline Characteristics (Safety Population: Study 205)

	Placebo	EZO	EZO	EZO	Total

	N=96	600 mg/day N=100	900 mg/day N=95	1200 mg/day N=106	N=397
Age, years					
mean ± SD	34.5 ± 10.3	36.8 ± 10.9	37.0 ± 10.1	38.3 ± 11.9	36.7 ± 10.9
Sex, n (%)					
Male	48 (50)	54 (54)	48 (51)	55 (52)	205 (52)
Female	48 (50)	46 (46)	47 (49)	51 (48)	192 (48)
Race, n (%)					
White/Caucasian	89 (93)	98 (98)	92 (97)	103 (97)	382 (96)
Black	2 (2)	1 (1)	1 (1)	0	4 (1)
Hispanic	0	0	0	0	0
Asian	1 (1)	0	1 (1)	1 (<1)	3 (<1)
Other	4 (4)	1 (1)	1 (1)	2 (2)	8 (2)
Baseline Seizure Frequency					
Median	8.5	8.5	7.9	10.4	8.8
Number of AEDs, n (%)					
1	33 (34)	26 (26)	26 (27)	31 (29)	116 (29)
2	62 (65)	72 (72)	69 (73)	74 (70)	277 (70)
3	1 (1)	2 (2)	0	1 (<1)	4 (1)
Duration of Illness, years					
mean ± SD	20.7 ± 11.0	20.7 ± 11.8	19.6 ± 12.0	20.2 ± 11.3	20.3 ± 11.5

Study 301

Demographic data based on the Safety population indicated that patients (54% female, 46% male) were on average 37 years (range 18 to 71 years) with a mean duration of epilepsy of approximately 23 years, table 5. The majority (55%) of patients were Caucasian and a large minority (28%) were Hispanic. The median baseline seizure rate was 11 to 12 seizures/month and baseline seizure severity scores (CGI-Severity) were reported for the greatest percentage of patients in the marked (33%) to moderately severe (48%) categories.

The mean number of previous AEDs tried and failed in the 3 years prior to study entry was 2.5. Overall, approximately 50% of patients were taking two or more AEDs (52% ezogabine versus 46% placebo) with another 34% (28% ezogabine versus 40% placebo) taking three background AEDs.

The most frequently used AEDs for the overall safety population were carbamazepine (38%), lamotrigine (34%), phenytoin (22%) and levetiracetam (21%); the proportions were balanced across treatment groups. Vagal nerve stimulation was used by 10% of all patients (8% ezogabine versus 11% placebo) in addition to their background AEDs.

Table 5 Demographics and Other Baseline Characteristics (Safety Population: Study 301)

	Placebo N=152	EZO 1200 mg/day N=153	Total N=305
Age, years			
mean ± SD	36.7 ± 11.63	37.7 ± 12.55	37.2 ± 12.09

Sex, n (%)			
Male	72 (47.4)	68 (44.4)	140 (45.9)
Female	80 (52.6)	85 (55.6)	165 (54.1)
Race, n (%)			
White/Caucasian	78 (51.3)	90 (58.8)	168 (55.1)
Black	15 (9.9)	15 (9.8)	30 (9.8)
Hispanic	47 (30.9)	39 (25.5)	86 (28.2)
Asian	1 (0.7)	1 (0.7)	2 (0.7)
Other	11 (7.2)	8 (5.2)	19 (6.2)
Baseline Seizure Frequency			
n	150	151	n/a
Median	11.3	12.1	n/a
Previous AEDs tried and failed			
n	121	124	245
mean ± SD	2.5 ± 1.64	2.6 ± 1.52	2.5 ± 1.58
Number of AEDs, n (%)			
1	21 (13.8)	32 (20.9)	53 (17.4)
2	70 (46.1)	79 (51.6)	149 (48.9)
3	61 (40.1)	42 (27.5)	103 (33.8)
Vagal nerve stimulator used?			
Yes	17 (11.2)	12 (7.8)	29 (9.5)
No	135 (88.8)	141 (92.2)	276 (90.5)
Duration of Illness, years			
mean ± SD	23.1 ± 12.77	23.7 ± 13.00	23.4 ± 12.87
Note: All data are for Safety population, with the exception of baseline seizure rates, which are for the ITT double-blind population			

Study 302

Demographic data based on the Safety population indicated that patients (52% women and 48% male) were on average 38 years (range 18 to 74 years) with a mean duration of epilepsy of 22.6 years table 6. The majority (95%) of patients were Caucasian. The median baseline seizure rate was 9 to 10 seizures/month and baseline seizure severity scores (CGI-Severity) were reported for the greatest percentage of patients in the marked (30%) to moderately severe (51%) categories.

The mean number of previous AEDs tried and failed in the 3 years prior to study entry was 2.4. Overall approximately 49% of patients (49% placebo, 42% ezogabine 600 mg and 56% ezogabine 900 mg) were taking two or more AEDs with another 28% (29% placebo, 31% ezogabine 600 mg and 25% ezogabine 900 mg) taking three background AEDs. The most frequently used AEDs for the overall safety population were carbamazepine (48%), lamotrigine (27%), valproic acid (26%) and levetiracetam (23%).

Table 6 Demographics and Other Baseline Characteristics (Safety Population: Study 302)

302- demo	**Placebo N=179**	**EZO 600 mg/day N=181**	**EZO 900 mg/day N=178**	**Total N=538**
Age, years				
mean ± SD	37.7 ± 11.75	37.5 ± 12.02	37.7 ± 12.77	37.6 ± 12.16

302- demo	Placebo N=179	EZO 600 mg/day N=181	EZO 900 mg/day N=178	Total N=538
Sex, n (%)				
Male	89 (49.7)	76 (42.0)	93 (52.2)	258 (48.0)
Female	90 (50.3)	105 (58.0)	85 (47.8)	280 (52.0)
Race, n (%)				
White/Caucasian	169 (94.4)	173 (95.6)	170 (95.5)	512 (95.2)
Black	2 (1.1)	2 (1.1)	1 (0.6)	5 (0.9)
Hispanic	0	0	0	0
Asian	3 (1.7)	0	2 (1.1)	5 (0.9)
Other	5 (2.8)	6 (3.3)	5 (2.8)	16 (3.0)
Baseline Seizure Frequency				
n	176	179	175	n/a
Median	9.3	9.5	10.3	n/a
Previous AEDs tried and failed				
n	139	156	149	444
mean ± SD	2.5 ± 1.36	2.4 ± 1.44	2.4± 1.43	2.4 ± 1.41
Number of AEDs, n (%)				
1	40 (22.3)	49 (27.1)	35 (19.7)	124 (23.0)
2	87 (48.6)	76 (42.0)	99 (55.6)	262 (48.7)
3	52 (29.1)	56 (30.9)	44 (24.7)	152 (28.3)
Vagal nerve stimulator used?				
Yes	6 (3.4)	4 (2.2)	4 (2.2)	14 (2.6)
No	173 (96.6)	177 (97.8)	174 (97.8)	524 (97.4)
Duration of Illness, years				
mean ± SD	22.8 ±11.84	22.5 ± 13.02	22.5 ± 12.71	22.6 ± 12.51
Note: All data are for safety population, with the exception of baseline seizure rates, which are for the ITT double-blind population				

Reviewer Comment: Gender, race age, number of concomitant AEDs and duration of illness were not different from placebo and there were no large differences between studies with the exception of race. Studies 205 and 302 were almost completely Caucasian while study 301 had 9.8% black and 28.2% Hispanic. Overall the pivotal trials are informative primarily on efficacy in Caucasians with some applicability to the Hispanic population.

6.1.3 Subject Disposition

Study 205

A total of 399 patients were enrolled and randomized into Study 205. A total of 396 patients were analyzed for efficacy (ITT population) - one patient in the 600 mg/day group who had no seizure counts recorded during the treatment period was excluded from the ITT population. Two hundred and seventy-nine (279) patients completed the maintenance phase.

There was a dose-related trend in the proportion of patients who discontinued treatment during the study (21.9% placebo, 28% 600 mg/day, 33.7% 900 mg/day and 42.5% 1200 mg/day) (Table 5). The most common primary reason for withdrawal was due to adverse events (12.5% placebo, 21% 600 mg/day, 22.1% 900 mg/day and 31.1% 1200 mg/day). A significant difference between treatment groups (overall) was observed for discontinuations due to adverse events (p=0.016), table 7.

Table 7 Study 205, patient disposition

	Number (%) of Patients				
	Placebo	RTG 600 mg/day	RTG 900 mg/day	RTG 1200 mg/day	Total
Population					
Randomized	97 (100)	101 (100)	95 (100)	106 (100)	399
Safety	96 (99)	100 (99)	95 (100)	106 (100)	397
IITT Population	96 (99)	99 (98)	95 (100)	106 (100)	396
Patient Disposition					
N (Safety Population)	96 (99)	100 (99)	95 (100)	106 (100)	n/a
Completed[a]	75 (77.3)	75 (74.3)	67 (70.5)	62 (58.5)	n/a
Discontinued	21 (21.9)	28 (28.0)	32 (33.7)	45 (42.5)	n/a
Reason for Discontinuation					
Adverse Event	12 (12.5)	21 (21.0)	21 (22.1)	33 (31.1)	n/a
Unsatisfactory response- efficacy	4 (4.2)	1 (1.0)	4 (4.2)	1 (0.9)	n/a
Lost to follow-up (failed to return)	0	0	1 (1.1)	0	n/a
Protocol violation	3 (3.1)	3 (3.0)	0	4 (3.9)	n/a
Patient request unrelated to study	1 (1.0)	2 (2.0)	4 (4.2)	4 (3.9)	n/a
Other event	1 (1.0)	1 (1.0)	2 (2.1)	3 (2.8)	n/a

a. Included patients who were treated at the maintenance dose for the planned duration but who were not necessarily protocol compliant

Study 301

A total of 280 patients (140 per arm) were planned. A total of 306 patients with partial onset seizures with or without secondary generalization were randomized, and 305 patients (152 placebo, 153 ezogabine) were included in the safety and intent-to-treat (ITT) double-blind phase population. A total of 256 patients (137 placebo and 119 ezogabine) were included in the ITT maintenance population and 224 patients (127 placebo and 97 ezogabine) completed the maintenance phase.

A total of 26.9% of patients discontinued the double-blind phase. The withdrawal rate for ezogabine 1200 mg/day was 36.6% (n=56) compared with 17.1% (n=26) for placebo. The most common primary reason for withdrawal was due to adverse events (ezogabine
26.8% versus 8.6% placebo), table 8.

Table 8 Patient disposition study 301

301	Number (%) of Patients		
	Placebo N=152	RTG 1200 mg/day N=153	Total N=305
Population			
Randomized	152	154d	306[d]
Safety	152	153	305
ITT Double-Blind Population	152	153	305
ITT Maintenance Population	137	119	256
Patient Disposition			
N (Safety Population)	152	153	305
Completed double-blind treatment[a]	127 (83.6)	97 (63.0)	224 (73.2)
Discontinued from treatment[b]	26 (17.1)	56 (36.6)	82 (26.9)
Reason for Discontinuation[c]			
Adverse event	13 (8.6)	41 (26.8)	54 (17.7)
Unsatisfactory response- efficacy	2 (1.3)	4 (2.6)	6 (2.0)
Lost to follow-up (failed to return)	2 (1.3)	1 (0.7)	3 (1.0)
Protocol violation	4 (2.6)	4 (2.6)	8 (2.6)
Patient request unrelated to study	1 (0.7)	0	1 (0.3)
Other	4 (2.6)	6 (3.9)	10 (3.3)

ITT Double-Blind Population patients who completed Visit 11 (Week 18) and at least 60 days of treatment in the maintenance phase
b. One patient discontinued per the investigator, however, the patient was defined as a 'completer'. The completers population was defined as patients in the ITT double-blind population who completed 12 weeks of the maintenance phase, i.e., completed Visit 11 (Week 18) and duration of maintenances phase was ≥60 days.
c. These are the primary reasons for discontinuation as collected in the CRF. There may have been more than one reason. d. One patient was randomized, but never received study drug.

Study 302

A total of 539 patients with partial onset seizures with or without secondary generalization were enrolled and randomized and 538 (179 placebo, 181 ezogabine 600 mg/day and 178 ezogabine 900 mg/day) were analyzed for Safety and the ITT double-blind population. A total of 471 patients (164 placebo, 158 ezogabine 600 mg/day and 149 ezogabine 900 mg/day) were included in the ITT maintenance population.

A total of 129 (24%) patients discontinued the double-blind phase. There was a dose related trend in the proportion of patients who discontinued treatment during the study (15% placebo, 25% ezogabine 600 mg/day and 32% ezogabine 900 mg/day). The most common primary reason for withdrawal was due to adverse events (7.8% placebo, 14.4% ezogabine 600 mg/day and 25.8% ezogabine 900 mg/day) table 9.

Table 9 Patient Disposition Study 302

	Number (%) of Patients			
	Placebo	RTG 600 mg/day	RTG 900 mg/day	Total
Population				
Randomized	179	181	179a	539

Safety	179	181	178	538
ITT Double-Blind Population	179	181	178	538
ITT Maintenance Population	164	158	149	471
Patient Disposition				
N (Safety Population)	179	181	178	538
Completed double-blind treatment[b]	153 (85.5)	135 (74.6)	121 (67.6)	409 (75.9)
Discontinued from treatment[c,d,f]	27 (15.1)	46 (25.4)	56 (31.5)	129 (24.0)
Reason for Discontinuation[c,e]				
Adverse event	14 (7.8)	26 (14.4)	46 (25.8)	86 (16.0)
Unsatisfactory response	5 (2.8)	0	0	5 (<1)
Lost to follow-up	2 (1.1)	4 (2.2)	1 (0.6)	7 (1.3)
Protocol violation	2 (1.1)	6 (3.3)	3 (1.7)	11 (2.0)
Patient request unrelated to study	1 (0.6)	5 (2.8)	3 (1.7)	9 (1.7)
Other	3 (1.7)	5 (2.8)	3 (1.7)	11 (2.0)

One patient was randomized but never received study drug.
b. Percent of Randomized patients
c. Percent of Safety population (patients who received at least 1 dose of study drug)
d. One patient in the 900 mg/day group discontinued during the transition phase thus is not included in this table
e. These are the primary reasons for discontinuation as collected in the CRF. There may have been more than one reason
f. One patient in the placebo group discontinued after being considered a 'completer'. The completers population was defined as the ITT double-blind patients who completed 12 weeks of the maintenance phase, i.e., completed Visit 9 (Week 16) (defined as having a non-missing visit date for Visit 9), and for whom the duration of the maintenance phase was ≥60 days

6.1.4 Analysis of Primary Endpoint(s)

For FDA review, the studies were designed to demonstrate a superior change in total partial seizure frequency per 4 weeks from baseline to the double-blind period (titration through maintenance).

In the three primary efficacy studies, seizure data were recorded on a diary by the patient or caregiver as appropriate. The investigator was responsible for accurately transferring and defining the patient-collected observations in accordance with the International Classification of Seizures categories and then entering the data into the study case report form. Patients with complex partial seizures (with or without secondary generalization) as well as those patients with simple partial seizures with a recognizable motor component were eligible for study inclusion.

Primary Efficacy Results (table 13)

Statistical Considerations

In Study 205 the primary objective was defined according to the key primary efficacy variable

• The percentage change in total partial seizure frequency per 28 days from baseline to the double-blind phase.

Study 205 patients were randomized 1:1:1:1 to one of four parallel groups: placebo, 600mg/day ezogabine, 900 mg/day ezogabine, or 1200 mg/day ezogabine. A sample size of 82 patients per group was calculated, based on 90% power for each active treatment group to show a 20% difference in response from placebo (30% in active group vs. 10% in placebo group), with a two-sided significance level of 0.05. This difference in response rates was based on the expected overall treatment response rates observed in Marson et al[1]. A sample size of 90 patients per group, i.e., a total of 360 patients, was planned in order to compensate for patients who did not meet the ITT criteria. A total of 399 patients were actually randomized.

In Studies 301 and 302 the primary objectives were defined according to two key primary efficacy variables.

• The primary objective for FDA review was the evaluation of the percent change in the 28-day total partial seizure frequency from baseline to the double-blind phase (titration and maintenance phases combined).

• The primary objective for European review (EMEA) was comparison of the percentage of responders (defined as those experiencing a ≥50% reduction in 28-day total partial seizure frequency) from baseline to maintenance phase.

The sample size calculations for both Study 301 and Study 302 were based on the percentage of responders observed in Study 205. For Study 301, a total of 250 evaluable patients (125 per arm, 1:1 randomization) were required in order to detect a 17% difference in responder rates between ezogabine 1200 mg/day and placebo with 85% power and a two-sided significance level of 5%. The assumed 10% attrition rate between randomization and the first post-dose seizure evaluation required that a total of 280 patients (140 per treatment arm) be randomized in order to satisfy the evaluable sample size requirements. A total of 306 patients were actually randomized.

For Study 302, a total of 453 evaluable patients (151 in each of the three treatment arms, 1:1:1 randomization) were required in order to detect a 16% difference in responder rates between ezogabine 900 mg/day and placebo with 85% power and a two-sided significance level of 5%. The assumed 10% attrition rate between randomization and the first post-dose evaluation assessment required that a total of approximately 510 patients (170 per treatment arm) be randomized in order to satisfy the evaluable sample size requirements. A total of 539 patients were actually randomized.

In Study 205, site-based randomization was used, via sealed envelopes containing patient treatment assignment allocated to each site, whereas in Studies 301 and 302 a central based randomization with an IVRS system was used. Patients in Studies 301

[1] Marson AG, Kadir ZA, Hutton JL, and Chadwick DW. The new antiepileptic drugs: a systematic review of their efficacy and tolerability. *Epilepsia*. 38(8):1997;859-880.

and 302 were randomized to treatment based upon two pre-specified stratification variables: baseline seizure frequency (≤8 versus >8) and region. In Study 301, the region stratification variable was US/Canada versus Mexico/South America. In Study 302, it was Central/Eastern Europe versus Rest of World.

Results of Individual Studies

Study 205

Percent change in 28 day total partial seizure frequency in the double blind phase

The analysis of percent change in 28-day total partial seizure frequency in the double blind phase between treatment groups indicated a statistically significant linear dose effect (p<0.001). The median change in monthly total partial seizures was -13%, -23%, -29%, and -35% in the placebo group and the ezogabine 600 mg/day, 900 mg/day, and 1200 mg/day dose groups, respectively (Table 10).

Table 10 Percent Change from Baseline in 28-Day Total Partial Seizure Frequency during the Double-Blind Phase (ITT Population: Study 205)

		RTG	RTG	RTG
	Placebo	**600 mg/day**	**900 mg/day**	**1200 mg/day**
N	96	99	95	106
n	96	99	95	106
Mean ± SD	-3.3 ± 75.03	8.5 ± 190.94	-14.1 ± 70.35	-23.5 ± 64.87
Median	-13.1	-23.4	-29.3	-35.2
Range	-100, 533	-100, 1703	-100, 298	-100, 375
Effect size (tmt - Placebo)		-10.3	-16.2	-22.1
P-value[a]	-	0.199	0.043	<0.001
P-value[b]	-	-	-	0.001
P-value[c]	-	0.156	0.0495	0.002

N=Number of patients in the population; n=number of patients with data
a. The p-values presented are from the original closed test using rank ANCOVA under the assumption of monotonicity.
b. The p-value presented is from the direct comparison vs. placebo using pre-specified statistical method rank ANCOVA but without the assumption of monotonicity.
c. **The p-values presented are from the harmonized analysis using the non-parametric rank ANCOVA analysis as described in section 5.3.**

Study 301

Percent change in 28 day total partial seizure frequency in the double blind phase

With respect to the primary analysis for FDA review, the percentage reduction in 28-day total partial seizure frequency from baseline to the double-blind phase was significantly greater for ezogabine 1200 mg/day compared with placebo (p<0.001; median -44.3% versus -17.5%), table 11.

Table 11 Percent Change from Baseline in 28-Day Total Partial Seizure Frequency (ITT Double-Blind Population: Study 301)

	Placebo	EZO 1200 mg/day
N	152	153
n[a]	150	151
Mean ± SD	1.6 ± 95.09	-25.1 ± 64.75
Median	-17.5	-44.3
Range	-90, 628	-100, 302
Effect size (tmt - Placebo)		-26.8
P-value[b]	-	<0.001

Change from baseline results only presented for patients with post-baseline data
a. Only baseline data for patients with post-baseline values are presented at baseline
b. **P-value for treatment comparison versus placebo using non-parametric rank ANCOVA stratified by baseline seizure category and region**.

Study 302

Percent change in 28 day total partial seizure frequency in the double blind phase

With respect to the primary analysis for FDA review, the percentage reduction in 28-day total partial seizure frequency from baseline to the double-blind phase was significantly different between ezogabine both in the 900 mg/day and 600 mg/day dose groups and placebo (p<0.001 and p=0.007 respectively; median -39.9% and -27.9% versus -15.9%), table 12.

Table 12 Percent Change from Baseline in 28-Day Total Partial Seizure Frequency (ITT Double-Blind Population: Study 302)

		RTG	RTG
	Placebo N=179	600 mg/day N=181	900 mg/day N=178
n	176	179	175
Mean ± SD	-1.1 ± 138.37	-20.4 ± 51.02	-27.8 ± 56.12
Median	-15.9	-27.9	-39.9
Range	-100, 1712	-94, 250	-100, 226
Effect size (tmt - Placebo)		-12	-24
P-value[a]	-	0.007	<0.001

a. P-value for treatment comparison using non-parametric rank ANCOVA stratified by baseline seizure category and region.

Comparison and Analyses of Results Across Studies

The results of the comparison of percent change in 28-day total partial seizure frequency from baseline to the double-blind treatment period (titration and maintenance phases combined) are summarized for the ITT double-blind population across Studies 205, 301 and 302 in table 13.

Ezogabine was superior to placebo in the primary efficacy analysis in all three primary efficacy studies. The 900 and 1200 mg/day doses were statistically superior to placebo in both studies in which they were tested (p≤0.0495 for all comparisons). The 600 mg/day dose was statistically superior to placebo in one of two studies (Study 302; p=0.007). Additionally, in Study 205, there was numerical improvement in the 600 mg/day dose over placebo (-23% versus -13% respectively; p=0.156).

Results in Study 205 support a linear dose response for ezogabine. Ezogabine 600 mg/day separated from placebo but this difference was not statistically significant. Both ezogabine 900 mg/day and 1200 mg/day statistically separated from placebo.

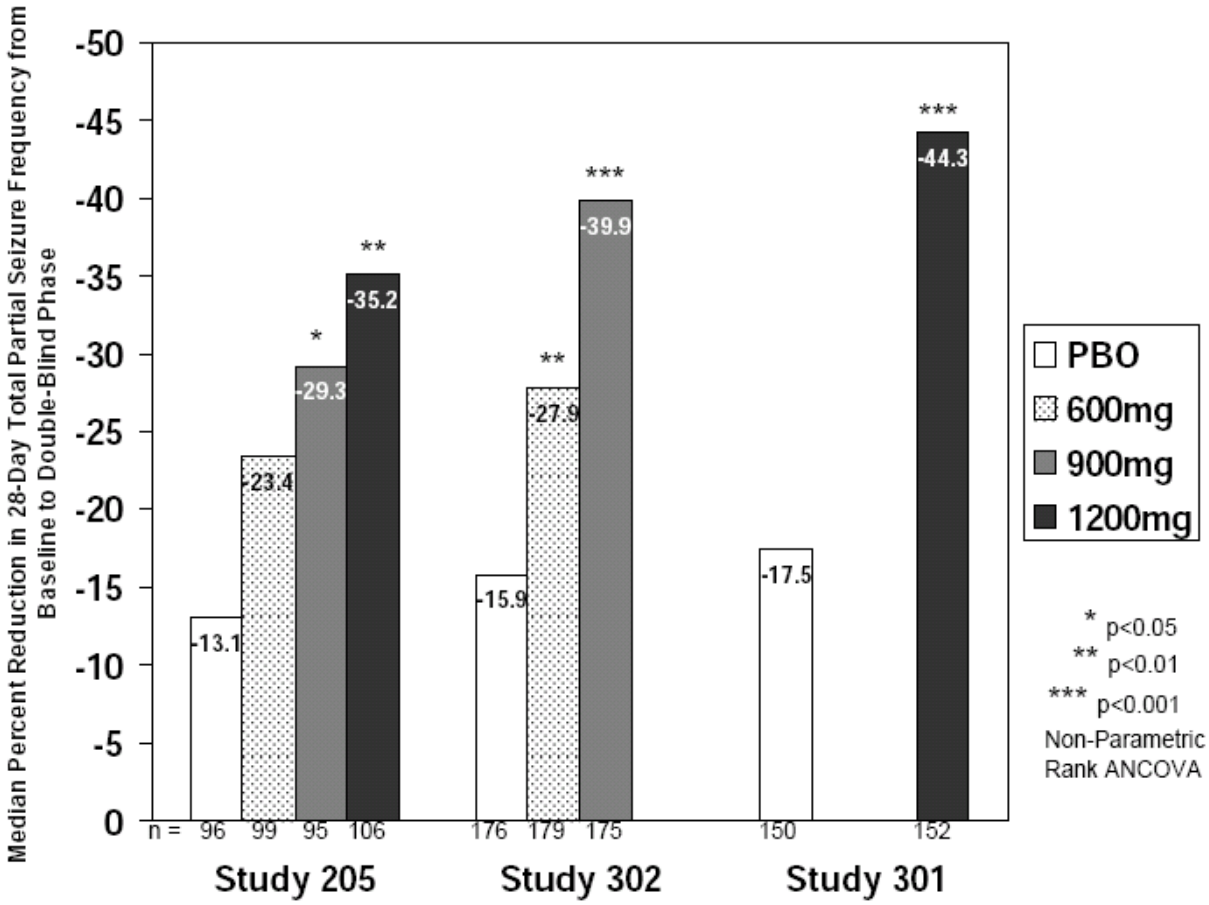
Table 13 Percent Change from Baseline in Total Partial Seizure Frequency (Double-Blind Phase) – ITT Population for Study 205 and ITT Double-Blind Population for Studies 301 and 302

	Placebo	RTG 600 mg/day	RTG 900 mg/day	RTG 1200 mg/day
Study 205				
N	96	99	95	106
n	96	99	95	106
Mean ± SD	-3.3 ± 75.03	8.5 ± 190.94	-14.1 ± 70.35	-23.5 ± 64.87
Median	-13.1	-23.4	-29.3	-35.2
Range	-100, 533	-100, 1703	-100, 298	-100, 375
P-value[a]	-	0.156	0.0495	0.002
P-value[b]	-	0.199	0.043	<0.001
P-value[c]	-	-	-	0.001
Study 301				
N	152	n/a	n/a	153
n	150	n/a	n/a	151
Mean ± SD	1.6 ± 95.09	n/a	n/a	-25.1 ± 64.75
Median	-17.5	n/a	n/a	-44.3
Range	-90, 628	n/a	n/a	-100, 302
P-valued	-	n/a	n/a	<0.001
Study 302				
N	179	181	178	n/a
n	176	179	175	n/a
Mean ± SD	-1.1 ± 138.37	-20.4 ± 51.02	-27.8 ± 56.12	n/a
Median	-15.9	-27.9	-39.9	n/a
Range	-100, 1712	-94, 250	-100, 226	n/a
P-value[d]	-	0.007	<0.001	n/a

n/a=not applicable (dose group not included in this study)
a. The p-values presented are from the *post-hoc* harmonized analysis using non-parametric rank ANCOVA.
b. The p-values presented are from the original closed test using rank ANCOVA under the assumption of monotonicity.
c. The p-value presented is from the direct comparison vs. placebo using pre-specified statistical method rank ANCOVA but without the assumption of monotonicity.
d. In Studies 301 and 302, the p-values are for the treatment comparison versus placebo using non-parametric rank ANCOVA.

Percent change from baseline in total partial seizure frequency for each of the three primary efficacy studies is presented graphically for the ITT double-blind population across Studies 205, 301, and 302 in figure 4.

Figure 4 Percent Change from Baseline in Total Partial Seizure Frequency (Double-Blind Phase) – ITT Population for Study 205 and ITT Double-Blind Population for Studies 301 and 302



Percent change from baseline in total partial seizure frequency in the ITT double blind population by dose; all RCT's integrated is show in table 14 and as a cumulative distribution function shown in figure 5.

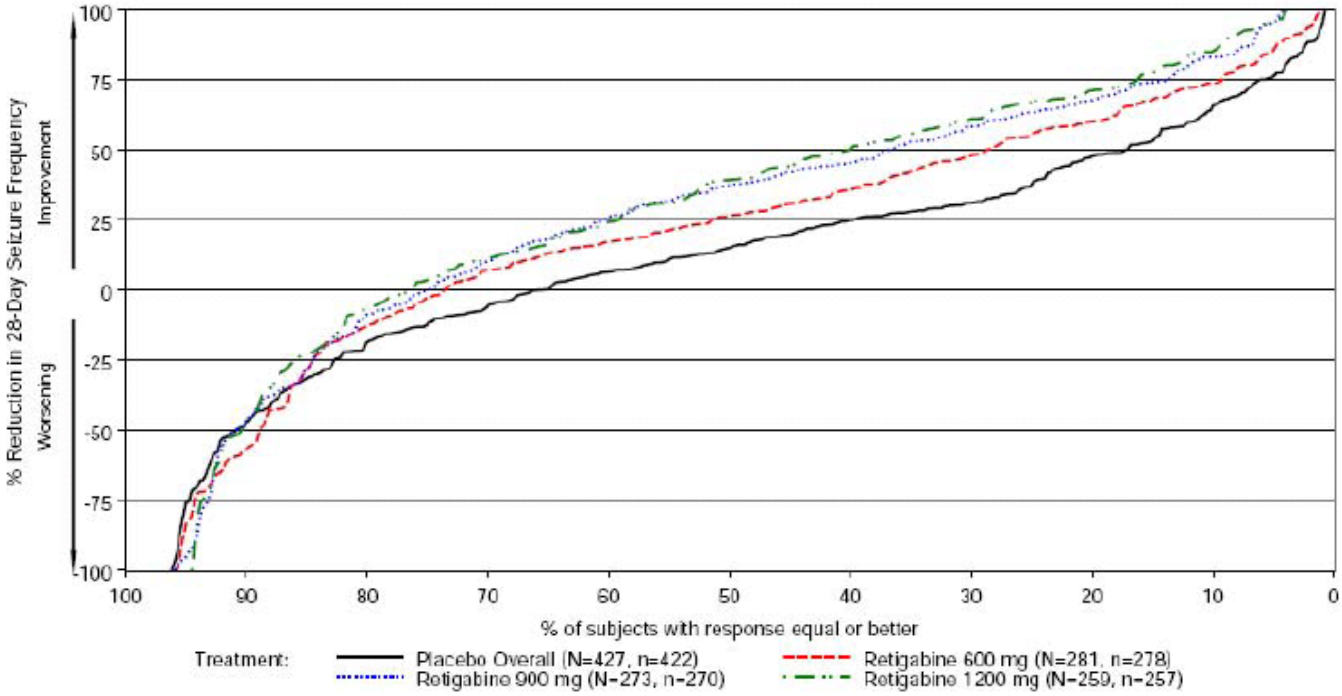
Table 14 Percent Change from Baseline in Total Partial Seizure Frequency (Double-Blind Phase) – ITT Double-Blind Population: Studies 205,301 and 302 Integrated

		RTG	RTG		RTG
	Placebo[a] N=275	**600 mg/day N=281**	**900 mg/day N=273**	**Placebo[b] N=248**	**1200 mg/day N=259**
Studies 205, 301 and 302 Integrated					
n	272	278	270	246	257
Mean ± SD	-1.9 ± 119.74	-10.1 ± 121.51	-23.0 ± 61.71	-0.3 ± 87.68	-24.4 ± 64.68
Median	-14.3	-26.4	-37.4	-14.9	-39.3
Range	-100, 1712	-100, 1703	-100, 298	-100, 628	-100, 375
P-value[c]	-	0.003	<0.001	-	<0.001

a. Consists of the placebo patients corresponding to the comparison with ezogabine 600 mg and 900 mg (Studies 205 and 302).
b. Consists of the placebo patients corresponding to the comparison with ezogabine 1200 mg (Studies 205 and 301).

c. Comparison vs placebo based on non-parametric rank ANCOVA.

Figure 5 Distribution Profile of Total Partial Seizure Frequency (Double-Blind Phase) – ITT Double-Blind Population: Studies 205, 301 and 302



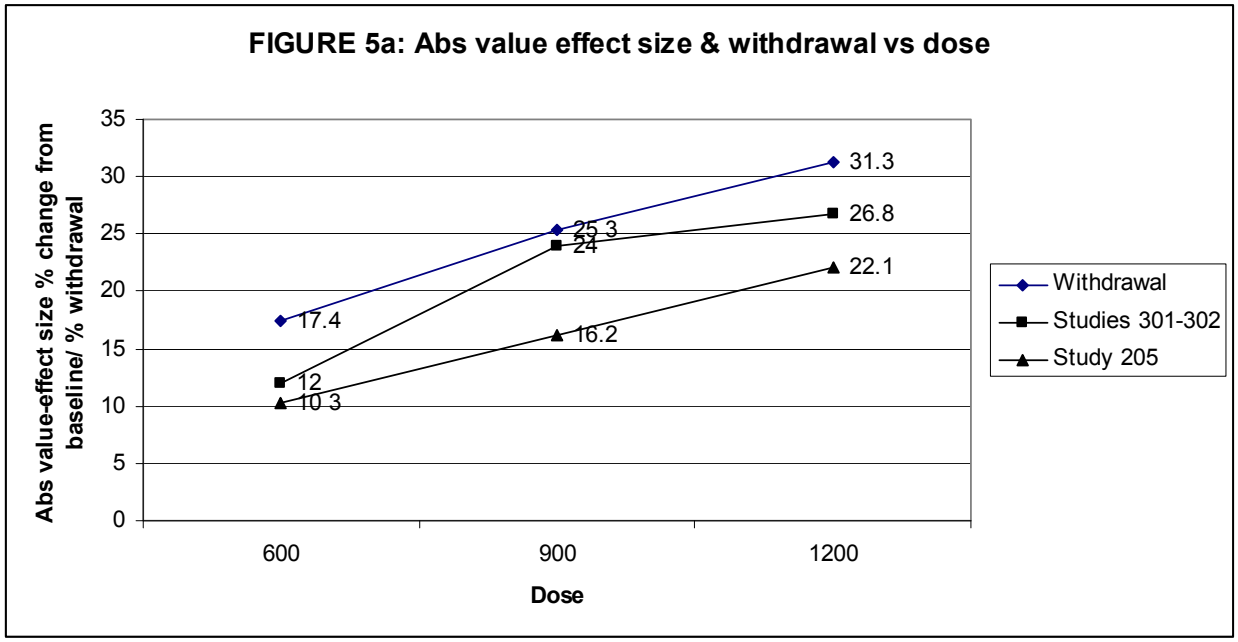
Therapeutic Effect vs Adverse effect

In study 205 the effect size of median % seizure reduction is linear across the dose range. If the dose is reduce to a proportion of 2, 3, 4 rather than 600, 900, 1200 then the slope of the study 205 effect size vs dose is 5.9 between the 600mg and 900mg dose and also 5.9 between the 900mg and 1200mg dose. If the effect size of % seizure reduction is examined across studies 301 and 302 for all doses (600mg, 900mg and 1200mg) the result is non-linear. The line segment between the 600mg and 900mg dose provided by study 302 has a slope of 12 using the technique of changing the x axis coordinate to a proportion of the dose as in study 205. The line segment between the 900mg dose provided by study 302 and 1200mg dose, provided by study 301 has a slope of 2.8.

A plot using study withdrawal by dose from the pooled RCT trials from table 57 can be used as an index of adverse effect by dose. This plot reveals a nearly linear increase in withdrawal rate from the 600mg to 1200mg dose.

When the plot of median % seizure reduction by ezogabine dose is compare to the study discontinuation by dose, the across study, 301 – 302 plot has a noteworthy flattening compared to the discontinuation rate whereas the study 205 plot demonstrates a parallel rise in effect size to discontinuation rate across the dose range, figure 5a. The across study measure is a less reliable indication of the full 600mg to

1200mg dose range but does indicate some attenuation of benefit between the 900mg and 1200mg dose contrasted to a steeper rise in discontinuation rate.



Reviewer Comment: Based on the percentage change in total partial seizure frequency per 28 days from baseline to the double blind phase of the ITT population study 205 shows a dose response at 900mg and 1200mg dosage with the 600mg dose non-significant from placebo. Based on the percentage change in total partial seizure frequency per 28 days from baseline to the double blind phase of the ITT population efficacy at 600mg, 900mg and 1200mg with a dose response is further supported by the results from study 301 and 301. In study 302 both the 600mg and 900mg dose have significant separation from placebo, while in study 301 the 1200mg dose also has significant separation from placebo. Taken together the three studies support a dose response with the observation of an increased effect size between the 600mg and 900mg dose with flattening of the effect dose response between 900mg and 1200mg.

The incidence of adverse effect is seen to increase between 900mg and 1200mg dose in study 205. The slope of the line representing study discontinuations increases between the 900mg and 1200mg dose compared to the 600mg and 900mg dose whereas the slope of the efficacy line between 600mg and 1200mg is attenuated in when examined across studies 301 and 302, figure 5a. This observation presents a question on the most appropriate therapeutic dose. Because of the escalation in adverse effects in the interval between the 900mg and 1200mg dose a target dose of 900mg should be recommended with further dose escalation to 1200mg if directed by clinical response.

6.1.5 Analysis of Secondary Endpoints(s)

Study 205

Percent change in 28-day total partial seizure frequency during maintenance

During the maintenance phase only, the median change from baseline in percent monthly seizure rates decreased by 23%, 30%, 36% and 44% in the placebo group and the ezogabine 600 mg/day, 900 mg/day, and 1200 mg/day dose groups respectively. The analyses using the original rank ANCOVA methodology under the assumption of monotonicity indicated a statistically significant difference between the ezogabine 1200 mg/day group and placebo (p=0.008), table 15.

Table 15 Percent Change from Baseline in 28-Day Total Partial Seizure Frequency during the Maintenance Phase (ITT Population: Study 205)

		RTG	RTG	RTG
	Placebo	**600 mg/day**	**900 mg/day**	**1200 mg/day**
N	78	83	74	68
Mean ± SD	-17.5 ± 52.6	0.5 ± 193.37	-23.1 ± 63.49	-25.6 ± 88.51
Median	-22.9	-30.4	-35.8	-43.7
Range	-100, 200	-100, 1653	-100, 292	-100, 503
P-value[a]	-	0.536	0.170	0.008
P-value[b]	-	-	-	0.012
P-value[c]	-	0.520	0.186	0.013

a. The p-values presented are from the original closed test using rank ANCOVA under the assumption of monotonicity.
b. The p-value presented is from the direct comparison vs. placebo using pre-specified statistical method rank ANCOVA but without the assumption of monotonicity .
c. The p-values presented are from the harmonized analysis using the non-parametric rank ANCOVA analysis.

Responder rates during double-blind phase

The responder rates during the double-blind phase were 16%, 23%, 32%, and 33% for the placebo group and the ezogabine 600 mg/day, 900 mg/day, and 1200 mg/day dose groups, respectively (Table 10). There was a significant separation from placebo for the 1200mg dose group, 15.6% and 33% respectively, p<0.0001. The results were consistent with the primary analysis for the percent change from baseline in seizure frequency, table 16.

Table 16 Responder Rates during the Double-Blind Phase Analysis: (ITT Population: Study 205)

	Number (%) of Patients			
		RTG	RTG	RTG
	Placebo	**600 mg/day**	**900 mg/day**	**1200 mg/day**
N	96	99	95	106
Responders	15 (15.6)	23 (23.2)	30 (31.6)	35 (33.0)
Non-responders	81 (84.4)	76 (76.8)	65 (68.4)	71 (67.0)
P-value[a]	-	0.189	0.008	0.001
P-value[b]	-	-	-	0.003

	Number (%) of Patients			
		RTG	RTG	RTG
	Placebo	600 mg/day	900 mg/day	1200 mg/day
P-value[c]	-	0.208	0.011	0.005

a. The p-values presented are from the original closed test using logistic regression under the assumption of Monotonicity.
b. The p-value is from the direct comparison vs. placebo using pre-specified statistical method logistic regression but without the assumption of monotonicity.
c. The p-values presented are from the harmonized analysis using the Fisher's Exact test.

Study 301

Change in total partial seizure frequency - maintenance phase

During the maintenance phase the median monthly seizure rates decreased by -54.5% for the ezogabine 1200 mg/day group compared to -18.9% for placebo (p<0.001), table 17 .

Table 17 Percent Change from Baseline in 28-day Total Partial Seizure Frequency (ITT Maintenance Population: Study 301)

	Placebo	EZO 1200 mg/day
N	137	119
Mean ± SD	-3.1 ± 135.74	-32 ±91.86
Median	-18.9	-54.5
Range	-100, 1382	-100, 660
P-value[a]	-	<0.001

a. P-value for treatment comparison versus placebo using non-parametric rank ANCOVA stratified by baseline seizure category and region

Responder rate during the double-blind phase

The responder rate during the double-blind phase was higher for ezogabine 1200 mg/day compared with placebo (44.4% versus 17.8%, p<0.001), table 18.

Table 18 Responder Rates (ITT Double-Blind Population: Study 301)

	Number (%) of Patients	
	Placebo N=152	EZO 1200 mg/day N=153
Responders	27 (17.8)	68 (44.4)
Non-responders[a]	125 (82.2)	85 (55.6)
P-value[b]		<0.001

Responders were defined as patients with ≥50% reduction in 28-day total partial seizure frequency
a. Patients without post-baseline data categorized as non-responders
b. P-value from Fisher's Exact test

Percent reduction in 28-day total partial seizure frequency by reduction category

The distribution in seizure frequency by quartile categories was assessed in both the double-blind and maintenance phase with double blind phase presented below, table 19.

There was a significant difference between treatment groups with respect to the over all profile for reduction in 28-day total partial seizures by quartile categories in the double blind phase with a greater percentage of the ezogabine group showing larger percentages of reduction in seizures compared with the placebo group (p<0.001)

A greater proportion of patients receiving ezogabine (18%) experienced a ≥75% reduction in seizure frequency compared to the placebo group (4%) in the double-blind phase. In addition, when compared to the placebo group, fewer patients in the ezogabine group experienced no change/increase in seizure frequency (26% ezogabine versus 36% placebo).

Table 19 Seizure Frequency by Quartiles (ITT Double-Blind Population: Study 301)

	Number (%) of Patients	
Reduction category	**Placebo N=152**	**EZO 1200 mg/day N=153**
75 to 100%	6 (3.9)	27 (17.6)
50 to <75%	21 (13.8)	41 (26.8)
25 to <50%	37 (24.3)	20 (13.1)
>0 to <25%	33 (21.7)	26 (17.0)
No reduction	55 (36.2)	39 (25.5)
P-value[a]		<0.001

Patients with no efficacy measure were reported in no-reduction category (2 patients in each group).
a. Cochrane-Mantel -Haenszel test

Study 302

Change in total partial seizure frequency percent change in 28-day total partial seizure frequency-maintenance phase

During the maintenance phase the median monthly seizure rates decreased by -35.3% (ezogabine 600 mg/day) and -44.3% (ezogabine 900 mg/day) compared to -17.4% in the placebo group (p=0.002 and <0.001 respectively), table 20.

Table 20 Percent Change from Baseline in 28-Day Total Partial Seizure Frequency (ITT Maintenance Population: Study 302)

	Placebo N=179	**EZO 600 mg/day N=181**	**EZO 900 mg/day N=178**
n	164	158	149
Mean ± SD	-5.1 ± 133.27	-25 ± 55.96	-30.9 ± 80.49
Median	-17.4	-35.3	-44.3
Range	-100, 1589	-100, 253	-100, 714
P-value[a]	-	0.002	<0.001

a. p-value for treatment comparison using non-parametric rank ANCOVA stratified by baseline seizure category and region.

Responder rate during the double-blind phase

The responder rates during the double-blind phase were significantly higher in both ezogabine dose groups (600 mg and 900 mg/day) compared to placebo (31.5% and 39.3% versus 17.3% respectively, p=0.002 and p<0.001 respectively), table 21.

Table 21 Responder Rates (ITT Double-blind Population: Study 302)

	Number (%) of Patients		
	Placebo N=179	**EZO 600 mg/day N=181**	**EZO 900 mg/day N=178**
Responders	31 (17.3)	57 (31.5)	70 (39.3)
Non-responders	148 (82.7)	124 (68.5)	108 (60.7)
P-value[a]		0.002	<0.001

Responders were defined as patients with ≥50% reduction in 28-day total partial seizure frequency. Patients without post-baseline data were categorized as non-responders.
a. P-value from Fisher's Exact test

Percent reduction in 28-day total partial seizure frequency by reduction category

The distribution in the reduction in seizure frequency by quartile categories was assessed in both the double-blind and maintenance phase with the double blind phase presented below, table 22.

There was a significant difference between treatment groups with respect to the overall profile for reduction in 28-day total partial seizures by quartile categories in the double blind phase with greater percentages of the ezogabine groups showing larger percentages of reduction in seizures compared with the placebo group (p=0.003 for the 600 mg/day group and p<0.001 for the 900 mg/day group.

A greater proportion of patients receiving ezogabine 600 mg/day and 900 mg/day experienced a ≥75% reduction in seizure frequency compared to the placebo group (8.8%, 15.2% and 6.7% respectively) in the double-blind phase. In addition, when compared to the placebo group, fewer patients in the ezogabine groups experienced no reduction/increase in seizure frequency (26.5% ezogabine 600 mg/day, 24.2% ezogabine 900 mg/day and 36.9% placebo). The results for the double-blind phase were supported when analyzed using decile categories.

Table 22 Seizure frequency by quartiles (ITT Double-blind Population: Study 302)

	Number (%) of Patients		
Reduction category	**Placebo N=179**	**RTG 600 mg/day N=181**	**RTG 900 mg/day N=178**
75 to 100%	12 (6.7)	16 (8.8)	27 (15.2)
50 to <75%	19 (10.6)	41 (22.7)	43 (24.2)

Reduction category	Number (%) of Patients		
	Placebo N=179	RTG 600 mg/day N=181	RTG 900 mg/day N=178
25 to <50%	39 (21.8)	38 (21.0)	41 (23.0)
>0 to <25%	43 (24.0)	38 (21.0)	24 (13.5)
No reduction	66 (36.9)	48 (26.5)	43 (24.2)
P-value[a]		0.003	<0.001
Patients without post-baseline data were placed in the no reduction / increase category a. P-value from Cochrane-Mantel-Haenszel test			

6.1.6 Other Endpoints

Clinician's Global Impression of Change

Study 205

The investigators were asked for their clinical global impression at the end of the maintenance phase. The CGI scores indicated that the proportions of patients considered at least minimally improved at the end of the maintenance phase were higher for the ezogabine groups than the placebo group (57% placebo, 74% 600 mg/day, 74% 900 mg/day, and 72% 1200 mg/day).

Pair-wise comparisons of the overall distribution of CGI scores were statistically significantly different in all ezogabine groups versus placebo ($p \leq 0.015$ for all three ezogabine doses)

Study 301

There were statistically significant treatment differences in favor of ezogabine compared with placebo for the mean CGI-I score at the end of the double-blind phase i.e., average score based on end of titration phase and end of maintenance phase, (2.9 versus 3.2 respectively, $p=0.02$) and in the maintenance phase (2.7 versus 3.2 respectively, $p=0.002$, CMH test.

Study 302

There were no statistically significant treatment differences between ezogabine dose groups (600 mg/day and 900 mg/day) versus placebo in the mean CGI-I score at the end of the double-blind phase (3.0, 3.2 versus 3.3 respectively). There were statistically significant treatment differences between ezogabine dose groups (600 mg/day and 900 mg/day) and placebo in the maintenance phase analysis (2.9, 2.9 versus 3.2 respectively, $p=0.001$ for both ezogabine dose comparisons versus placebo)

Number of seizure-free days

Study 205

There was no significant difference between treatment groups with respect to the number of seizure-free days per 28 days for each phase of the study (based on Hodges-Lehmamn estimates of differences between group median values) based on the ITT population analysis. However, between placebo and the ezogabine 1200 mg/day group, differences were observed when distributions were compared using rank ANCOVA (without multiplicity adjustment)

Percentage of seizure-free days

Study 301

There was a significant treatment difference in favor of ezogabine 1200 mg/day for the distribution of percentage of seizure-free days in both the double-blind and maintenance phases. The median percentage of seizure-free days during the double-blind phase was 84.1% ezogabine versus 77.3% placebo ($p<0.001$) and 86.9% versus 78.2% respectively ($p<0.001$) during the maintenance phase

Study 302

The distribution of percentage of seizure-free days during the double-blind phase between ezogabine (600 mg/day and 900 mg/day) and placebo was significant ($p=0.021$ for 600 mg/day comparison versus placebo and $p<0.001$ for 900 mg/day versus placebo). The median percentage values were 79.5%, 82.1% versus 77.8% respectively. The distribution of percentage of seizure-free days during the maintenance phase between ezogabine 600 mg/day and 900 mg/day and placebo was significant ($p=0.003$ for 600 mg comparison versus placebo and $p<0.001$ for 900 mg/day versus placebo)

6.1.7 Subpopulations

Primary Efficacy by Age Group

A dichotomized subgroup analysis in age categories above and below age 45 years (≤44 years and >44 years), based upon an approximation of the mid-point for the age range (14 to 74 years) in the patient population evaluated, was conducted for the primary efficacy endpoints. There were only 10 patients ≥65 years old and only 6 patients <18 years old; therefore efficacy analyses for the ≥65 years or <18 years age groups were not conducted due to the limitation of the data.

Percent Change from Baseline in 28-Day Total Partial Seizure Frequency by Age Group – ITT Double-Blind Population

Individual studies were examined and there was no significant treatment by age interaction demonstrated at any ezogabine dose tested. The response to treatment was not quantitatively or qualitatively affected by age. An integrated analysis was performed which revealed a statistically significant percent reduction from baseline in 28-Day total partial seizure rate at all doses of ezogabine within each age group category (≤44

years, >44 years). The placebo response rate was comparable across age group categories, table 23.

There was no significant treatment by age interaction demonstrated at any ezogabine dose tested. The response to treatment was not quantitatively or qualitatively affected by age.

Table 23 Percent Change from Baseline in 28-Day Total Partial Seizure Frequency by Age Group (Double-Blind Phase) – ITT Double-Blind Population: Studies 205, 301 and 302 Integrated

	Placebo[a]	RTG 600 mg/day	RTG 900 mg/day	Placebo[b]	RTG 1200 mg/day
≤44 years	**N=204**	**N=207**	**N=195**	**N=189**	**N=175**
n	201	206	194	188	173
Mean ± SD	-0.3 ± 135.05	-4.7 ±138.68	-20.2 ± 61.27	4.1 ± 96.33	-18.9 ± 65.91
Median	-13.7	-25.6	-34.6	-12.9	-31.9
Range	-100, 1712	-100, 1703	-100, 298	-92, 628	-100, 375
P-value[c]	-	0.034	<0.001	-	<0.001
>44 years	**N=71**	**N=74**	**N=78**	**N=59**	**N=84**
n	71	72	76	58	84
Mean ± SD	-6.3 ± 58.07	-25.3 ± 41.85	-30.0 ± 62.70	-14.5 ± 48.34	-35.8 ± 60.89
Median	-15.8	-27.4	-45.0	-21.2	-45.4
Range	-100, 203	-100, 126	-100, 224	-100, 203	-100, 302
P-value[c]	-	0.019	<0.001	-	<0.001

Only patients with baseline and post-baseline seizures were included in the analysis.
a. Consists of the placebo patients corresponding to the comparison with ezogabine 600 mg and 900 mg (Studies 205 and 302).
b. Consists of the placebo patients corresponding to the comparison with ezogabine 1200 mg (Studies 205 and 301).
c. Comparison vs placebo based on Rank Transformation Residual ANCOVA.

Primary Efficacy by Gender

Percent Change from Baseline in 28-Day Total Partial Seizure Frequency by Gender – ITT Double-Blind Population

In individual studies there was no significant treatment by gender interaction demonstrated at any ezogabine dose tested. The response to treatment was not quantitatively or qualitatively affected by gender.

For the integrated analysis in the double-blind phase, there was a statistically significant percent reduction from baseline in 28-day total partial seizure rate at all doses of ezogabine compared with placebo in female patients. The magnitude of effect increased with increasing doses of ezogabine.

In male patients there was a statistically significant percent reduction from baseline in 28-day total partial seizure rate at ezogabine 900 and 1200 mg/day. There was no significant treatment effect at ezogabine 600 mg/day although the effect at 600 mg/day was numerically superior to placebo. Of note in this analysis was the higher placebo response rate observed in male patients (-20%) compared to female patients (-9.2%)

that could contribute to the smaller treatment effect shown at the lowest ezogabine dose observed in males. The ezogabine results were -26% in both males and females, table 24.

There was no significant treatment by gender interaction demonstrated at any ezogabine dose tested. The response to treatment was not quantitatively or qualitatively affected by gender.

Table 24 Percent Change from Baseline in 28-Day Total Partial Seizure Frequency by Gender (Double-Blind Phase) – ITT Double-Blind Population (Studies 205, 301 and 302 Integrated)

	Placebo[a]	RTG 600 mg/day	RTG 900 mg/day	Placebo[b]	RTG 1200 mg/day
Male	**N=137**	**N=130**	**N=141**	**N=120**	**N=123**
n	136	129	139	119	122
Mean ± SD	-0.3 ± 156.38	1.6 ± 169.29	-21.4 ± 58.03	2.9 ± 101.28	-18.2 ± 64.25
Median	-20.0	-26.2	-33.8	-19.6	-30.7
Range	-100, 1712	-98, 1703	-100, 298	-100, 628	-100, 302
P-value[c]	-	0.245	0.017	-	0.012
Female	**N=138**	**N=151**	**N=132**	**N=128**	**N=136**
n	136	149	131	127	135
Mean ± SD	-3.5 ± 65.74	-20.1 ± 51.26	-24.7 ± 65.58	-3.3 ± 72.96	-30.1 ± 64.78
Median	-9.2	-26.6	-39.9	-12.0	-44.7
Range	-100, 533	-100, 182	-100, 250	-92, 533	-100, 375
P-value[c]	-	0.002	<0.001	-	<0.001

Only patients with baseline and post-baseline seizures were included in the analysis.
a. Consists of the placebo patients corresponding to the comparison with ezogabine 600 mg and 900 mg (Studies 205 and 302).
b. Consists of the placebo patients corresponding to the comparison with ezogabine 1200 mg (Studies 205 and 301).
c. Comparison vs placebo based on Rank Transformation Residual ANCOVA.

Primary Efficacy by Race

Percent Change from Baseline in 28-Day Total Partial Seizure Frequency by Race – ITT Double-Blind Population

Categories of race defined as White, Hispanic and Other, Study 301

Percent change from baseline in 28-day total partial seizure frequency is summarized for the ITT double-blind population by race (White/Caucasian, Hispanic and Others) for Study 301 in table 25. The majority of patients in Studies 205 and 302 were White/Caucasian (>95%), therefore the subgroup analysis by race was only performed for Study 301.

In Study 301, there was a statistically significant percent reduction from baseline in 28-day total partial seizure rate at ezogabine 1200 mg/day compared with placebo for all categories of race defined as White, Hispanic and Other. The magnitude of effect was somewhat greater in the non-White racial groups compared to the White racial group.

However there was no significant treatment by race (White and non-White) interaction demonstrated for ezogabine at 1200 mg/day. The response to treatment was not quantitatively or qualitatively affected by the racial groups that were assessed in this study.

Table 25 Percent Change from Baseline in 28-Day Total Partial Seizure Frequency by Race (Double-Blind Phase) – ITT Double-Blind Population (Study 301)

	Study 301	
	Placebo	**RTG 1200 mg/day**
White/Caucasian	**N=78**	**N=90**
n	77	89
Mean ± SD	-10.5 ± 45.78	-21.9 ± 65.02
Median	-19.0	-38.5
Range	-90, 162	-100, 302
P-valuea		0.011
Hispanic	**N=47**	**N=39**
n	47	39
Mean ± SD	4.7 ± 119.35	-37.2 ± 61.74
Median	-21.1	-51.6
Range	-89, 561	-100, 180
P-valuea		0.010
Other	**N=27**	**N=24**
n	26	23
Mean ± SD	32.0 ± 141.01	-16.5 ± 68.65
Median	-3.4	-28.9
Range	-83, 628	-90, 216
P-valuea		0.017
Only patients with baseline and post-baseline seizures were included in the analysis. a. Comparison vs placebo based on Rank Transformation Residual ANCOVA		

White/Caucasian patients vs Non-White patients, 1200mg dose group, Overall placebo and overall ezogabine

Percent change from baseline in 28-day total partial seizure frequency is summarized by White/Caucasian patients vs Non-White patients for the 1200 mg/day dose group, overall placebo and overall ezogabine group for the ITT double-blind population in table 26. This analysis was not performed for the ezogabine 600 mg/day and 900 mg/day dose groups and corresponding placebo group because the proportion of Non-Whites patients is small in both treatment groups.

In the integrated analysis for the double-blind phase, there was a statistically significant percent reduction from baseline in 28-day total partial seizure rate at ezogabine 1200 mg/day compared with placebo for both categories of race defined as Whites and non-Whites. The magnitude of effect was somewhat greater in the non-White racial group compared to the White racial group. This mainly reflected the fact that the majority of patients contributing to the non-White analysis comparison were from Study 301 where a larger magnitude of treatment effect was observed for the non-US patient group. The non-US patients were predominantly Hispanic patients.

There was no significant treatment by race (White and non-White) interaction demonstrated for ezogabine at 1200 mg/day and in the overall ezogabine doses analysis. The response to treatment was not quantitatively or qualitatively affected by the racial groups that were assessed.

Table 26 Percent Change from Baseline in 28-Day Total Partial Seizure Frequency by Race (Double-Blind Phase) – ITT Double-Blind Population (Studies 205, 301 and 302 Integrated)

	Placebo[a]	RTG 1200 mg/day	Overall Placebo	Overall RTG
White/Caucasian	**N=167**	**N=193**	**N=336**	**N=726**
n	166	192	332	719
Mean ± SD	-9.9 ± 48.90	-22.6 ± 64.91	-5.6 ± 106.15	-18.0 ± 90.72
Median	-15.1	-35.2	-16.0	-32.1
Range	-100, 203	-100, 375	-100, 1712	-100, 1703
P-value[b]	-	<0.001	-	<0.001
Non-White	**N=81**	**N=66**	**N= 91**	**N=87**
n	80	65	90	86
Mean ± SD	19.6 ± 135.10	-29.9 ± 64.18	17.7 ± 128.33	-27.5 ± 59.68
Median	-10.9	-47.6	-9.7	-42.6
Range	-89, 628	-100, 216	-89, 628	-100, 216
P-value[b]	-	<0.001	-	<0.001

Only patients with baseline and post-baseline seizures were included in the analysis.
a. Consists of the placebo patients corresponding to the comparison with ezogabine 1200 mg (Studies 205 and 301).
b. Comparison vs placebo based on Rank Transformation Residual ANCOVA

Primary Efficacy by Number of Background AEDs

Percent Change from Baseline in 28-Day Total Partial Seizure Frequency by Number of Background AEDs – ITT Double-Blind Population

Percent change from baseline in 28-day total partial seizure frequency is summarized by number of background AEDs for the ITT double-blind population in Table 78. In the integrated analysis for the double-blind phase, there were statistically significant treatment differences in the percent reduction from baseline in 28-day total partial seizure rate at ezogabine 900 and 1200 mg/day compared with placebo in all categories of number of background AEDs. The effects were not statistically significant for ezogabine 600 mg/day compared with placebo for patients receiving one AED at baseline (p=0.064) or ≥ 3 background AEDs (p=0.546).

The majority of patients in this subgroup analysis were in the category of two background AEDs at baseline. There was a significant treatment effect at all doses of ezogabine in this category.

In the overall analysis for treatment by number of background AED interaction the results showed no significant interaction by number of background AEDs received at baseline. In this analysis the response to treatment was not quantitatively or qualitatively affected by number of background AED usage.

	Placebo[a]	RTG 600 mg/day	RTG 900 mg/day	Placebo[b]	RTG 1200 mg/day
1 background AED	**N=73**	**N=76**	**N=62**	**N=53**	**N=60**
n	72	76	61	52	60
Mean ± SD	-11.6 ± 55.40	-25.3 ± 48.24	-36.5 ± 58.06	-20.1 ± 39.94	-39.3 ± 53.50
Median	-12.4	-30.2	-46.7	-20.4	-53.0
Range	-100, 208	-100, 148	-100, 226	-100, 93	-100, 129
P-value[c]		0.064	<0.001		0.004
2 background AEDs	**N=150**	**N=144**	**N=164**	**N=134**	**N=154**
n	148	141	162	134	153
Mean ± SD	3.7 ± 154.72	-2.4 ± 162.96	-18.5 ± 62.76	0.3 ± 94.10	-21.0 ± 66.99
Median	-15.7	-26.2	-31.0	-15.6	-33.8
Range	-100, 1712	-100, 1703	-100, 298	-92, 628	-100, 375
P-value[c]		0.011	0.003		<0.001
≥3 background AEDs[d]	**N=52**	**N=61**	**N=47**	**N=61**	**N=45**
n	52	61	47	60	44
Mean ± SD	-4.4 ± 51.84	-8.9 ± 53.47	-20.7 ± 61.41	15.5 ± 99.92	-16.0 ± 68.53
Median	-15.0	-20.8	-42.2	-6.7	-30.4
Range	-95, 225	-98, 250	-99, 185	-89, 561	-100, 216
P-value[c]		0.546	0.015		0.009

Only patients with baseline and post-baseline seizures were included in the analysis.
a. Consists of the placebo patients corresponding to the comparison with ezogabine 600 mg and 900 mg (Studies 205 and 302).
b. Consists of the placebo patients corresponding to the comparison with ezogabine 1200 mg (Studies 205 and 301).
c. Comparison vs placebo based on Rank Transformation Residual ANCOVA
d. AEDs were assessed for the ISS and ISE. In some cases there are differences between the numbers of AEDs identified from individual study reports.

Primary Efficacy by Seizure Type

Percent Change from Baseline in 28-Day Total Partial Seizure Frequency by Seizure Type – ITT Double-Blind Population

Partial Seizures

Percent change from baseline in 28-day total partial seizure frequency is summarized by baseline seizure type for the ITT double-blind population in table 27 .

For the integrated analyses by seizure subtype in the double-blind phase, there was a statistically significant percent reduction from baseline in 28-day total partial seizure rate at all doses of ezogabine in patients with simple partial seizures. Similar results were observed in the cohort of patients without simple partial seizures.

A similar significant treatment effect was seen at all ezogabine doses in patients with complex partial seizures. In the smaller cohort of patients without complex partial

seizures, ezogabine at 600 mg/day and 1200 mg/day was significantly different from placebo but the 900 mg/day dose was not.

Table 27 Percent Change from Baseline in 28-Day Total Partial Seizure Frequency, Simple and Complex Partial Seizures. (Double-Blind Phase) – ITT Double-Blind Population (Studies 205, 301 and 302 Integrated)

	Placebo[a]	RTG 600 mg/day	RTG 900 mg/day	Placebo[b]	RTG 1200 mg/day
Simple partial seizures					
Patients with simple partial seizures	N=77	N=100	N=81	N=81	N=82
n	74	100	81	81	80
Mean ± SD	18.4 ±205.55	-12.6 ±76.37	-12.1 ±70.83	6.5 ±100.43	-27.6 ±63.24
Median	-9.8	-26.9	-32.1	-11.1	-41.7
Range	-89, 1712	-94, 516	-100, 298	-77, 628	-100, 216
P-value[c]	-	0.014	0.005	-	<0.001
Patients without simple Partial Seizures	N=198	N=181	N=192	N=167	N=177
n	198	178	189	165	177
Mean ± SD	-9.5 ±62.08	-8.6 ±140.85	-27.6 ±56.95	-3.6 ±80.82	-23.0 ±65.45
Median	-15.1	-26.0	-38.4	-18.0	-38.5
Range	-100, 533	-100, 1703	-100, 250	-100, 561	-100, 375
P-value[c]	-	0.038	<0.001	-	<0.001
Complex partial seizures					
Patients with complex partial seizures	N=238	N=229	N=231	N=213	N=233
n	237	226	230	211	232
Mean ± SD	-9.1 ± 59.64	-9.1 ±128.41	-26.8 ±58.24	-1.8 ± 92.76	-27.4 ±59.33
Median	-16.1	-26.0	-40.0	-19.0	-39.3
Range	-100, 533	-100, 1703	-100, 250	-100, 628	-100, 375
P-value[c]	-	0.015	<0.001	-	<0.001
Patients without complex partial seizures	N=37	N=52	N=42	N=35	N=26
n	35	52	40	35	25
Mean ± SD	47.0 ±294.56	-14.1 ±86.18	-1.1 ±76.02	8.5 ±46.53	3.1 ±99.35
Median	-8.2	-28.3	-16.8	-4.4	-24.4
Range	-77, 1712	-90, 516	-100, 298	-76, 162	-100, 302
P-value[c]	-	0.031	0.315	-	0.025

Only patients with baseline and post-baseline seizures were included in the analysis.
a. Consists of the placebo patients corresponding to the comparison with ezogabine 600 mg and 900 mg (Studies 205 and 302).
b. Consists of the placebo patients corresponding to the comparison with ezogabine 1200 mg (Studies 205 and 301).
c. Comparison vs placebo based on Rank Transformation Residual ANCOVA

Secondarily Generalized Seizures

There were no statistically significant differences in the percent reduction from baseline in 28-day total partial seizure rate in the ITT double-blind population at any ezogabine dose compared with placebo for the cohort of patients with secondarily generalized seizures. There was numerical evidence for a reduction in seizure rate for ezogabine 600 and 900 mg/day compared with placebo. The treatment effect was similar between 1200 mg/day and placebo (-12.2% versus -11.4% respectively). In contrast there was a significant treatment effect at all doses of ezogabine in the cohort of patients without secondarily generalized seizures, table 28.

There was no significant treatment by secondarily generalized seizure type interaction at ezogabine doses of 600 and 900 mg/day. However, the treatment by secondarily generalized seizure subtype interaction was statistically significant at ezogabine 1200 mg/day.

Table 28 Percent Change from Baseline in 28-Day Total Partial Seizure Frequency, Secondarily Generalized Seizures (Double-Blind Phase) – ITT Double-Blind Population (Studies 205, 301 and 302 Integrated)

	Placebo[a]	RTG 600 mg/day	RTG 900 mg/day	Placebo[b]	RTG 1200 mg/day
Secondarily generalized seizures					
Patients with secondarily generalized seizures	N=82	N=101	N=98	N=80	N=85
n	80	101	96	80	84
Mean ± SD	5.5 ±196.91	2.0 ±181.01	-18.3 ±59.73	1.7 ±98.77	3.4±78.16
Median	-17.6	-27.9	-26.9	-11.4	-12.2
Range	-100, 1712	-92, 1703	-100, 298	-100, 628	-100, 302
P-value[c]	-	0.261	0.077	-	0.735
Patients without secondarily generalized seizures	N=193	N=180	N=175	N=168	N=174
n	192	177	174	166	173
Mean ± SD	-5.0 ±65.37	-17.0 ±67.01	-25.5 ±62.81	-1.3 ±82.11	-38.0 ±52.11
Median	-12.9	-25.9	-42.1	-15.6	-47.0
Range	-100, 533	-100, 516	-100, 250	-92, 561	-100, 375
P-value[c]		0.004	<0.001		<0.001

Only patients with baseline and post-baseline seizures were included in the analysis.
a. Consists of the placebo patients corresponding to the comparison with ezogabine 600 mg and 900 mg (Studies 205 and 302).
b. Consists of the placebo patients corresponding to the comparison with ezogabine 1200 mg (Studies 205 and 301).
c. Comparison vs placebo based on Rank Transformation Residual ANCOVA

Primary Efficacy by US Patients and Non-US Patients Subgroups

Percent change from baseline in 28-day total partial seizure frequency is summarized by US and Non-US patient's subgroups for the ITT double-blind population in table 24. In the integrated analyses for the double-blind phase, there was a statistically significant

percent reduction from baseline in 28-day total partial seizure rate for ezogabine 1200 mg/day compared with placebo for US patients. Most of the data for this analysis came from Study 301. When all US patients receiving any dose of ezogabine were combined in an assessment of treatment effect for ezogabine compared to placebo, the results were nearly identical with a strong trend towards statistical significance (p=0.055).

A statistically significant treatment effect was seen in non-US patients receiving ezogabine 1200 mg/day and in the assessment of all non-US patients receiving any dose of ezogabine.

The magnitude of response to ezogabine 1200 mg/day was similar in both US and non-US patients.

There was no significant treatment by US and non-US patients' interaction demonstrated for ezogabine 1200 mg/day and overall. The response to treatment was not quantitatively or qualitatively different across US and non-US patient categories. Although the response to treatment indicated by the magnitude of the median of the percent change from baseline is similar in US and non-US patients, the US placebo response is noted to be larger with a resultant decrease in effect size table 29.

Table 29 Percent Change from Baseline in 28-Day Total Partial Seizure Frequency by US Patients and Non-US Patients Subgroups (Double-Blind Phase) – ITT Double-Blind Population (Studies 205, 301 and 302 Integrated)

	Placebo[a]	RTG 1200 mg/day	Overall Placebo	Overall RTG
US Patients	**N=78**	**N=82**	**N=78**	**N=100**
n	76	82	76	99
Mean ± SD	-12.1 ± 56.40	-23.9 ± 63.45	-12.1 ± 56.40	-23.8 ± 63.68
Median	-22.7	-34.8	-22.7	-35.7
Range	-90, 316	-100, 302	-90, 316	-100, 302
P-value[b]	-	0.039	-	0.055
Non-US Patients	**N=170**	**N=177**	**N=349**	**N=713**
n	170	175	346	706
Mean ± SD	5.0 ± 98.20	-24.7 ± 65.43	1.9 ± 120.18	-18.3 ± 90.85
Median	-12.3	-39.3	-13.4	-32.6
Range	-100, 628	-100, 375	-100, 1712	-100, 1703
P-value[b]		<0.001		<0.001

Only patients with baseline and post-baseline seizures were included in the analysis.
a. Consists of the placebo patients corresponding to the comparison with ezogabine 1200 mg (Studies 205 and 301).
b. Comparison vs placebo based on Rank Transformation Residual ANCOVA

Reviewer Comment: The notable results of the subgroup analyses is the finding of non-significance in comparison to placebo of the secondarily generalized seizure subgroup. This is not contrary to proposed labeling but does provide an indication of the spectrum of ezogabine treatment response. Another notable observation is the difference in US vs non-US placebo response. This difference is of uncertain origin but underscores the consideration of cultural influence on response in clinical trials.

Overall the sub-group analyses for age (≤44 years vs. >44 years), gender, race (Whites vs. non- Whites), region (US vs. non-US), number of background AEDs at baseline (1, 2 or ≥3) and seizure subtypes (simple, partial, complex partial) indicate there are no significant differences in the magnitude or direction of response to treatment with ezogabine at any tested dose. With regards to the subgroup analysis by age there were too few elderly patients (n=10) to support an analysis of this subgroup.

6.1.8 Analysis of Clinical Information Relevant to Dosing Recommendations

Overview of Rationale for Dose Selection in the Clinical Development Program (taken from sponsor discussion section 1.4 ISE)

Early studies in healthy volunteers indicated that the maximum tolerated doses of ezogabine were up to 500 mg/day as a single dose and exceeded 600 mg/day in a dose titration regimen. However, it is recognized that patients with the disease under investigation are typically able to tolerate higher doses than healthy volunteers. In a series of preliminary Phase 2a efficacy studies, ezogabine was administered at increasing doses to patients with epilepsy to assess the safety and efficacy of ezogabine in this patient population. The first of these Phase 2a studies (Studies 200/201) employed a slow titration regimen initially up to a dose of 400 mg/day although this was subsequently amended in the protocol to higher doses (2400 mg/day).

The results from the first exploratory study with ezogabine (Study 200/201) indicated that a titration scheme of between 100 to 200 mg/week to a maintenance dose between 400 to 1200 mg/day was associated with the most effective therapeutic range based on responder rate analyses. A higher proportion of responders were observed at doses of 800 to 1200 mg/day (60%) relative to the proportion of responders at lower doses (31%). Four patients achieved doses greater than 1200 mg/day and in 1 patient a dose of 2400 mg/day was achieved. None of these patients were discontinued prematurely from study treatment. However none of these patients were classified as treatment responders. Based upon the small number of patients at doses >1200 mg/day, there was insufficient evidence to indicate improved benefit at doses above 1200 mg/day.

The second open-label, dose escalation study (Study 202) assessed administration of ezogabine doses up to 2000 mg/day. The efficacy findings further demonstrated increasing efficacy with increasing dose of ezogabine. Doses above 1200 mg daily were poorly tolerated. Ezogabine 1200 mg/day administered as a TID regimen was associated with efficacy and improved tolerability compared to a BID regimen.

Study 205 was designed to assess the dose response relationship of placebo and ezogabine doses of 600 mg/day, 900 mg/day and 1200 mg/day. A statistically significant linear dose response for ezogabine was demonstrated across the tested dose range (600, 900 and 1200 mg/day) in the pre-specified analysis. There was statistical and clinically relevant treatment differences shown with ezogabine 900 mg/day and 1200 mg/day compared with placebo in the double-blind phase when assessed according to median percent reduction in seizure frequency from baseline or

responder analysis (50% reduction in seizure frequency from baseline). While the 600 mg dose did not statistically separate from placebo, the 600 mg dose was numerically superior to placebo on the primary and key secondary efficacy endpoints including the responder rate analysis.

The clinical dose response observations presented in the forgoing paragraphs are also supported by a PK/PD assessment of percent change in total partial seizure frequency with an exposure response analysis. An exposure response relationship was evaluated using an inhibitory Emax model where AUC(0-τ) was the independent variable and the percent change from baseline in total partial seizure was the dependent variable. A total of 345 ezogabine-treated patients and 302 placebo-treated patients were included in the exposure-response analyses. A plot of the observed and predicted relationship between the median change from baseline in seizure frequency and median AUC(0-τ) values is presented in figure 6 while the model parameter estimates derived from fitting of the median data are shown in table 30.

Figure 6 Median Percent Changes from Baseline in Total Partial Seizure Frequency a Function of Ezogabine Median AUC

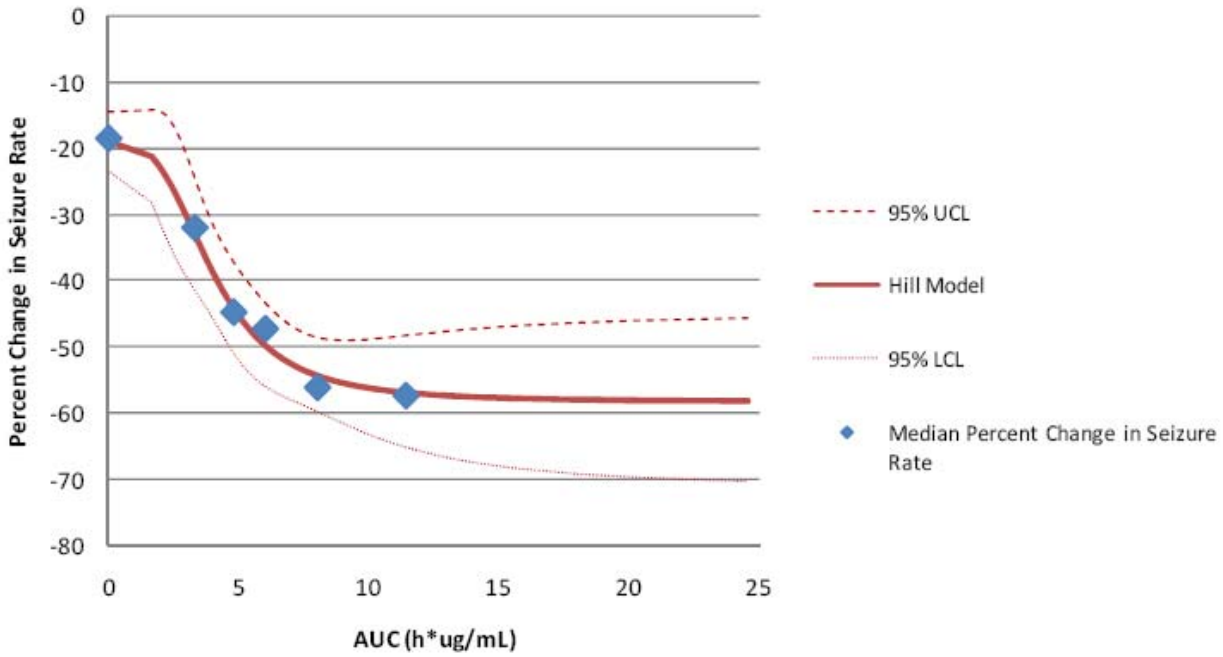


Table 30 Model Parameter Estimates derived from Modeling of the Median Percent Change in Total Partial Seizure Count by Ezogabine Median AUC using the Emax Model

Model Parameter	Parameter Estimate	Standard Error	95% Confidence Interval
*E*0	-16.4	6.00	(-30.5 to -2.18)
*E*max	-37.3	7.07	(-54.1 to -20.6)
EC50	3.85	0.379	(2.95 to 4.74)
ln Shape	1.90	0.534	(0.64 to 3.17)

From the PK/PD analyses, the predicted % reduction from baseline in total partial frequency for placebo (i.e., Eo) was approximately 16% (median data) which is consistent with the placebo response observed in Studies 301 and 302. The change from baseline in total partial seizure frequency increased with increasing systemic exposure to ezogabine up to a maximum of approximately 60% reduction in seizure frequency at ezogabine AUC(0-τ) values of ~10 ug.hr/mL and above. This value corresponds approximately to the median AUC(0-τ) value observed (9.67 ug.h/mL) for the 1200 mg/day dose group. The AUC(0-τ) associated with 50% of the maximum response was predicted to be ~4 ug.hr/mL which corresponds approximately to the median AUC(0-τ) (4.35 ug.h/mL) for the 600 mg/day dose group.

Reviewer Comment: The clinical dose response observations from studies 205, 301 and 302 indicate the dose recommendations in proposed labeling are in the appropriate range to obtain a desired anticonvulsant response while remaining in a window of patient tolerance. The validity of the dose in proposed labeling is further supported by the PK dose response analysis based on studies 301 and 302.

6.1.9 Discussion of Persistence of Efficacy and/or Tolerance Effects

Patients who completed Studies 205, 301 and 302 were eligible to enter long-term open-label ezogabine treatment protocols, Studies 212, 303 and 304 respectively. Long term efficacy data, with subject exposure ranging from 1 to 20 months is available from these three studies. A total of 365 patients including 114 patients in Study 212, 92 patients in Study 303 and 159 patients in Study 304 were exposed to ≥12 months of study drug during the open-label extension studies as of the 30 June 2008 data cut-off date. A total of 101 patients including 6 patients in Study 212, 29 patients in Study 303 and 66 patients in Study 304 were exposed to ≥20 months of study drug during the open-label extension studies as of the 30 June 2008 data cut-off date. A total of 57 patients received study drug for ≥18 months during open-label extension Study 212.

Percent Change in Monthly Total Partial Seizure Frequency

Patients Treated for at Least 12 Months

In patients who received at least 12 months of treatment in the open-label extension studies, the median percent change in monthly total partial seizure frequency was -56.9% overall (table 31). Results in individual open-label extension studies were -49.3% in Study 212, -63.4% in Study 303, and -59.6% in Study 304. While there was some variability between studies, in the overall population the percent change from baseline in total partial seizure frequency was relatively stable over the course of 12 months of treatment with ezogabine

Table 31 Percent Change from Baseline in Monthly Total Partial Seizure Frequency for Patients Treated with Ezogabine for at Least 12 Months During Open-Label Extension (Safety Population: Studies 212, 303 and 304)

	Study 212 N=114	Study 303 N=92	Study 304 N=159	All Patients N=365
n	114	92	159	365
Month 1				
Mean ± SD	-45.3 ± 63.82	-44.2 ± 52.37	-55.3 ± 39.94	-49.4 ± 51.67
Median	-62.3	-62.9	-59.3	-60.7
Range	-100, 312	-100, 124	-100, 116	-100, 312
Month 3				
Mean ± SD	-46.0 ± 48.77	-48.9 ± 46.63	-54.5 ± 36.96	-50.4 ± 43.47
Median	-53.4	-61.8	-62.0	-58.3
Range	-100, 248	-100, 117	-100, 116	-100, 248
Month 6				
Mean ± SD	-48.5 ± 42.79	-50.2 ± 42.56	-54.5 ± 36.83	-51.5 ± 40.22
Median	-57.7	-59.9	-59.6	-59.3
Range	-100, 201	-100, 101	-100, 118	-100, 201
Month 9				
Mean ± SD	-48.2 ± 40.16	-50.1 ± 42.36	-53.7 ± 36.23	-51.1 ± 39.05
Median	-52.5	-63.1	-60.5	-58.4
Range	-100, 194	-100, 94	-100, 110	-100, 194
Month 12				
Mean ± SD	-47.3 ± 41.91	-52.0 ± 39.66	-54.0 ± 34.75	-51.4 ± 38.36
Median	-49.3	-63.4	-59.6	-56.9
Range	-100, 227	-100, 103	-100, 117	-100, 227
N=number of patients in the population; number of patients with data. Note: Comparison to baseline period before double-blind phase of Studies 205, 301, and 302				

Patients treated for at Least 16 Months

In patients who received at least 16 months of treatment in the open-label extension studies, the median percent change in monthly total partial seizure frequency was -59.8% overall (table 32). Results in individual open-label extension studies were -51.3% in Study 212, -65.8% in Study 303, and -62.9% in Study 304. While there was some variability between studies, in the overall population the percent change from baseline in total partial seizure frequency was relatively stable over the course of 16 months of treatment with ezogabine.

Table 32 Percent Change from Baseline in Monthly Total Partial Seizure Frequency for Patients Treated with Ezogabine for at Least 16 Months During Open-Label Extension (Safety Population: Studies 212, 303 and 304)

	Study 212 N=77	Study 303 N=57	Study 304 N=113	All Patients N=247
n	77	57	113	247
Month 1				
Mean ± SD	-45.8 ± 68.77	-47.0 ± 47.69	-56.0 ± 42.08	-50.7 ± 53.00
Median	-62.7	-61.4	-59.3	-60.7
Range	-100, 312	-100, 124	-100, 116	-100, 312
Month 3				
Mean ± SD	-48.0 ± 48.84	-52.8 ± 41.01	-55.5 ± 38.31	-52.5 ± 42.41
Median	-54.4	-63.3	-63.8	-60.7
Range	-100, 248	-100, 110	-100, 116	-100, 248
Month 6				
Mean ± SD	-49.0 ± 43.48	-54.6 ± 34.26	-54.8 ± 39.42	-52.9 ± 39.57

	Study 212 N=77	Study 303 N=57	Study 304 N=113	All Patients N=247
n	77	57	113	247
Median	-57.4	-59.7	-59.6	-59.6
Range	-100, 201	-98, 50	-100, 118	-100, 201
Month 9				
Mean ± SD	-47.9 ± 41.17	-55.6 ± 32.73	-54.3 ± 39.01	-52.6 ± 38.35
Median	-53.4	-63.3	-61.1	-58.0
Range	-100, 194	-98, 50	-100, 110	-100, 194
Month 12				
Mean ± SD	-47.1 ± 43.71	-56.3 ± 32.25	-54.4 ± 37.53	-52.6 ± 38.50
Median	-49.3	-63.9	-61.0	-58.0
Range	-100, 227	-98, 41	-100, 117	-100, 227
Month 16				
Mean ± SD	-47.7 ± 44.71	-57.6 ± 33.21	-55.6 ± 35.06	-53.6 ± 38.01
Median	-51.3	-65.8	-62.9	-59.8
Range	-100, 246	-99, 34	-100, 78	-100, 246
N=number of patients in the population; number of patients with data. Note: Comparison to baseline period before double-blind phase of Studies 205, 301, and 302.				

Patients Treated for at Least 18 to 20 Months (studies 303 and 304)

A total of 57 out of 778 patients received at least 18 months of treatment in open-label extension Study 212. The data reflect the final data cut for patients in Study 212 until the study was stopped. A total of 29 out of 181 patients in Study 303 and 66 out of 375 patients in Study 304 received at least 20 months of treatment during the open-label extension studies as of the 30 June 2008 data cut-off date.

The median percent change in monthly total partial seizure frequency was -50.6% in patients who received at least 18 months of treatment in Study 212. In patients who received at least 20 months of treatment in Studies 303 and 304, the median percent change in monthly total partial seizure frequency was -68.2% overall, with rates in individual studies of -69.3% in Study 303 and -67.8% in Study 304 (table 33). While there was some variability between studies, the percent change from baseline in total partial seizure frequency was relatively stable over the course of 18 months of treatment with ezogabine in Study 212 and 20 months of treatment with ezogabine in Studies 303 and 304.

Table 33 Percent Change from Baseline in Monthly Total Partial Seizure Frequency for Patients Treated with Ezogabine for at Least 20 Months During Open-Label Extension (Safety Population: Studies 303 and 304

	Study 303 N=29	Study 304 N=66	All Patients N=95
n	29	66	95
Month 1			
Mean ± SD	-49.3 ± 39.98	-59.7 ± 40.45	-56.5 ± 40.38
Median	-55.4	-61.1	-60.7
Range	-100, 102	-100, 116	-100, 116
Month 3			
Mean ± SD	-54.5 ± 40.79	-58.4 ± 42.70	-57.2 ± 41.94
Median	-65.3	-68.0	-67.7

	Study 303 N=29	Study 304 N=66	All Patients N=95
n	29	66	95
Range	-95, 110	-100, 116	-100, 116
Month 6			
Mean ± SD	-58.7 ± 29.11	-57.6 ± 43.97	-57.9 ± 39.87
Median	-69.5	-70.2	-70.0
Range	-95, 14	-100, 118	-100, 118
Month 9			
Mean ± SD	-59.8 ± 27.15	-57.1 ± 43.72	-57.9 ± 39.28
Median	-68.9	-68.1	-68.3
Range	-95, 7	-100, 110	-100, 110
Month 12			
Mean ± SD	-60.5 ± 27.00	-57.2 ± 41.91	-58.2 ± 37.87
Median	-67.1	-65.2	-66.0
Range	-97, 8	-100, 117	-100, 117
Month 16			
Mean ± SD	-60.9 ± 29.81	-58.8 ± 38.33	-59.5 ± 35.80
Median	-68.0	-66.9	-67.6
Range	-97, 25	-100, 78	-100, 78
Month 20			
Mean ± SD	-62.4 ± 29.83	-60.8 ± 34.87	-61.3 ± 33.26
Median	-69.3	-67.8	-68.2
Range	-98, 39	-100, 63	-100, 63
N=number of patients in the population; number of patients with data. Note: Comparison to baseline period before double-blind phase of Studies 301 and 302.			

Reviewer Comment: The median percent change from baseline in 28 day total partial seizure frequency remained steady during the treatment interval of the open label studies 212, 303 and 304. These observations of sustained reduction of the percent change from baseline in the 28 day total partial seizure frequency do not reveal evidence of tolerance to the anticonvulsant effect of ezogabine during the 20 month period of open label treatment.

6.1.10 Additional Efficacy Issues/Analyses

Subgroup participation

There were only 10 patients ≥65 years included across the three primary efficacy studies. This small number of older participants limits generalizability of the clinical dose response findings from the primary efficacy studies to this age range.

7 Review of Safety

Safety Summary

7.1 Methods

7.1.1 Studies/Clinical Trials Used to Evaluate Safety

The clinical investigation of ezogabine included 44 clinical studies which contributed to the safety database. The studies and study composition are provided in this section and associated tables. Data from studies of similar design and patient populations were combined for integrated analysis as shown in section 7.1.3.

An overview of the studies from the development program included the following:

RCT (pivotal controlled trials): 1240 patients from Pivotal Controlled Trials are included in the ISS: 813 patients received ezogabine and 427 patients received placebo (Table 11). Of the 813 patients treated with ezogabine, 281 were assigned to 600 mg/day, 273 to 900 mg/day, and 259 to 1200 mg/day, table 34.

Table 34 Table 7.1-1 Pivotal Controlled trials

Table 7.1-1	Pivotal Controlled trials- Number of Patients					
Study	**Placebo**	**RTG 600 mg/day**	**RTG 900 mg/day**	**RTG 1200 mg/day**	**RTG Total**	**All Patients TOTAL**
3065 A1-205	96	100	95	106	301	397
VRX-RET-E22-301	152	0	0	153	153	305
VRX-RET-E22-302	179	181	178	0	359	538
Total	427	281	273	259	813	1240

All Phase II/III Trials Combined: Patients who received at least 1 dose of ezogabine in a Phase II or III study in epilepsy (except for Study 3227-CU) were included in the All Phase II/III Combined grouping, table 35. Patients who participated in both a double-blind and open-label extension study were counted only once within this analysis set. Patients who took placebo in a double-blind study and did not enter an open label extension were not included in this analysis set.

Table 35 Source and Number of Patients Included in the Integrated Summary of Safety (Safety Population: All Phase II/III Combined)

Table 7.1-2	Placebo	RTG	Total

		New Exposure1	Re-exposure2	
Placebo-controlled studies				
Double-blind phase				
3065 A1-205	96	301		397
VRX-RET-E22-301	152	153		305
VRX-RET-E22-302	179	359		538
Total	427	813		1240
Transition phase				
3065 A1-205		76		76
VRX-RET-E22-301		123		123
VRX-RET-E22-302		147		147
Total		346		346
Regimen-controlled studies				
3065 A1-214		73		73
Uncontrolled Trials				
3065 A1-200/201		46	0	
3065 A1-202		60	0	
3065 A1-208		0	47	
3065 A1-209		27	0	
3065 A1-212		03	222	
3065 A1-216		0	42	
D-23129-8017		0	23	
VRX-RET-E22-303		03	181	
VRX-RET-E22-304		03	375	
Total		133	890	
Total RTG		**1365**		

1. New exposure refers to patients who were receiving ezogabine for the first time during each specific study.
2. Re-exposure refers to patients who were re-exposed to ezogabine as a continuation of study medication during open-label extension study.
3. Patients had their first exposure to ezogabine during the transition phase of the parent study.

Clinical Pharmacology Studies: For the Integrated Clinical Pharmacology Grouping, subjects who received at least 1 dose of an IR formulation of ezogabine in any Clinical Pharmacology study (single- or multiple-dose) were included in the safety population

In total, 469 subjects received ezogabine IR in the 21 Clinical Pharmacology studies included in the integrated grouping. Six subjects received non-IR formulations and thus were not included in the integrated grouping. Subjects who received both IR and non-IR formulations in the integrated Clinical Pharmacology studies are counted once in the IR group only. A total of 194 subjects received ezogabine (either IR or non-IR) in the nonintegrated Clinical Pharmacology studies. An overall total of 669 subjects received ezogabine during the entire Clinical Pharmacology program, table 36.

Table 36 Source and Number Included in Entire Clinical Pharmacology Program

Table 7.1-3		
Study Number	**Total Number of Subjects1**	**Any RTG Exposures**
Integrated Studies		
3065 A1-100	16	16
3065 A1-101	48 (12 placebo)	36
3065 A1-102	45 (15 placebo)	30
3065 A1-103	12	122
3065 A1-105	48	48
3065 A1-106	24	24
3065 A1-107	9 (3 placebo)	6
3065 A1-108	6	6
3065 A1-109	29	29
3065 A1-110	23	23
3065 A1-112	21	20
3065 A1-113	15	15
3065 A1-115	37	37
3065 A1-120	12	12
3065 A1-121	5	5
3065 A1-123	12	12
VRX-RET-E22-103	120 (40 placebo, 40 MFX)	40
VRX-RET-E22-104	24	24
VRX-RET-E22-105	36	36
VRX-RET-E22-106	30	30
VRX-RET-E22-SR101	14	14
Total	**586**	**475**
Non-integrated studies		
3065 A1-104	24	24
3065 A1-117	15	15
VRX-RET-E22-101	373	37
VRX-RET-E22-102	24	24
VRX-RET-E22-107	24	24
VRX-RET-E22-108	36	34
VRX-RET-E22-MR103	36	36
Total	**196**	**194**
Total RTG exposure		**669**

1. Includes subjects exposed to control (placebo or active) and any ezogabine formulation (e.g. IR, MR, or IV)
2. Includes 6 subjects that received IR and 6 subjects who received MR.
3. Thirty-three subjects included in analysis; total exposed to RTG was 37.

7.1.2 Categorization of Adverse Events

Recoding to Medical Dictionary for Regulatory Activities (MedDRA): All adverse

events from studies integrated in the ISS were re-coded to MedDRA version 9.1. The six clinical pharmacology studies that were not integrated into ISS datasets were not converted to MEDRA 9.1.

Reviewer Comment: The definitions within RCT 302,301 and 205 are not identical in wording but result in alignment of definitions. In study 205 there is explicit statement that the AE was not present when the active phase of the study began or if present, had an increase in severity or frequency. Study 301 and 302 note that an AE can be a change in clinical status which has equivalent effect to the statement in study 205 indicating that the AE was not present prior to active phase. A change after entry into active phase is very similar to a change in clinical status. Study 205 has a shorter window for an event to be a valid AE than studies 301 and 302. In the former the window for valid AE begins on day of first capsule and ends 2 days after last intake of test capsule in contrast to studies 301 and 302 where the window of interest extends from enrollment to 30 days after last administration of study drug.

The AE definitions for study 303-304, are parallel to 301-302.

The definition for AE in studies 3065A1-200/201 (8001-8005) D23129-8017: does not include timeframe after test drug stopped.

3065A1-202 / 3065A1-208: same definition for AEs as pivotal trials in content but limits valid interval for AE to only active phase which is day 1 to day of last visit

Study 209 is a short treatment interval pre surgical trial, definition parallel to pivotal trials

Study 8040 does not define a valid interval for AEs but is otherwise definition is parallel to the pivotal trials. This is a short study with few patients, the lack of defined interval (beyond that of medication dosing) will not have a meaningful impact on study safety database.

Study NP201 is the same as RCT definitions.

Overall the AE definitions are sufficiently close in structure that the safety content of the safety database will be adequately homogenous.

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

Data from studies of similar design and patient populations were combined for integrated analysis, as described below and illustrated in table 37.

Pivotal Controlled Trials (RCT): this is the principal data set, which provides the primary information concerning the clinical safety of ezogabine. It comprises 3 randomized, double-blind, placebo-controlled trials with similar durations and primary outcome measures (Phase IIb study 205; Phase III studies 301 and 302).

Supplementary safety datasets are provided by the following groupings:

All Phase II/III Combined: this data set combines data from all 13 Phase II and Phase III epilepsy studies, and provides supporting evidence of the safety and tolerability of ezogabine in a larger population and over the longer term. It includes the 3 RCTs described above, together with 4 completed Phase IIa studies and 6 open label extension studies, 2 of which were ongoing at the time of the 120 day Safety Update. For patients who enrolled into extension studies, the data from the parent and extension study are linked so that their safety profile throughout the entire duration of exposure to active study medication (any dose of ezogabine) could be evaluated. For patients in double-blind studies who were on placebo, those who entered an open-label extension and thereby, switched to ezogabine are included in this dataset, whilst those who did not enter an open-label extension are excluded. For the All Phase II/III Studies, all data collected during treatment with ezogabine, including relevant follow-up, were combined into 1 category and not presented by dose, as investigators were allowed to adjust the regimen during the open-label extension studies according to their clinical judgment, including conversion to ezogabine monotherapy. Long-term safety with ezogabine was evaluated using this data set.

Integrated Clinical Pharmacology Studies: healthy subjects who received at least 1 dose of the immediate-release (IR) formulation of ezogabine were included in this data set (21 studies). For studies including both IR and other ezogabine formulations, only the IR treatment arms were included in the integrated safety analysis.

Data from those studies that were not integrated are described individually. The non-integrated studies are identified in table 37 below and include studies using a slow release or intravenous (IV) formulation, ongoing studies, studies in PHN or bipolar disorder patients or in non healthy volunteers (subjects with renal/hepatic impairment, coadministration with alcohol or recreational drug abusers).

Table 37 Clinical Studies Providing Safety Information for Ezogabine and Overview of Analysis Sets for Integrated Summaries

Table 7.1-5		Clinical Studies Providing Safety Information for Ezogabine and Overview of Analysis Sets for Integrated Summaries				
Study	**Status of Study**	**Type of Study**	**RCT Analysis Set (3studies)**	**All Phase II/III Combined Analysis Set (13 studies)**	**Integrated Phase I Analysis Set (21 studies)**	**Presented Separately (10 studies)**
Phase I single-dose studies						
3065A1-100	Completed	Healthy subject PK			X	
3065A1-103	Completed	Comp. BA/BE			X[1]	
3065A1-105	Completed	Intrinsic factor PK			X	
3065A1-106	Completed	BA/PK			X	
3065A1-108	Completed	Healthy subject PK			X	
3065A1-110	Completed	Comp. BA/BE			X	
3065A1-120	Completed	Comp. BA/BE			X[1]	
3065A1-121	Completed	Bioanalytical			X	

Table 7.1-5		Clinical Studies Providing Safety Information for Ezogabine and Overview of Analysis Sets for Integrated Summaries				
Study	**Status of Study**	**Type of Study**	**RCT Analysis Set (3studies)**	**All Phase II/III Combined Analysis Set (13 studies)**	**Integrated Phase I Analysis Set (21 studies)**	**Presented Separately (10 studies)**
3065A1-123	Completed	BA			X	
VRX-RET-E22-104	Completed	BA			X	
VRX-RET-E22-105	Completed	Comp. BA/BE			X	
VRX-RET-E22-SR101	Completed	Comp. BA/BE			X1	
3065A1-104	Completed	BA				X[2]
3065A1-117	Completed	Healthy subject PK				X[2]
VRX-RET-E22-101	Completed	Intrinsic factor PK				X[3]
VRX-RET-E22-102	Completed	Intrinsic factor PK				X[3]
VRX-RET-E22-107	Completed	Extrinsic factor PK				X[3]
VRX-RET-E22-108	Completed	Abuse potential				X[3]
Phase I multiple-dose studies						
3065A1-101	Completed	Healthy subject PK			X	
3065A1-102	Completed	Healthy subject PK			X	
3065A1-107	Completed	Healthy subject PK			X	
3065A1-109	Completed	Extrinsic factor PK			X	
3065A1-112	Completed	Extrinsic factor PK			X	
3065A1-113	Completed	Extrinsic factor PK			X	
3065A1-115	Completed	Intrinsic factor PK			X	
VRX-RET-E22-103	Completed	Healthy subject PD and PD/PK			X	
VRX-RET-E22-106	Completed	Extrinsic factor PK			X	
VRX-RET-E22-MR103	Ongoing	PK				X
Phase IIa studies						
3065A1-200/201	Completed	Safety and PK		X		
3065A1-202	Completed	Safety and PK		X		
3065A1-209	Completed	Safety and tolerability		X		
3065A1-214	Completed	Safety and tolerability		X		
Extension Studies from Phase IIa						
D-23129/8017	Completed	Safety and tolerability		X		
3065A1-208	Completed	Safety and tolerability		X		
3065A1-216	Completed	Safety and tolerability		X		
Phase IIb studies						
3065A1-205	Completed	Efficacy and safety	X	X		
Phase III studies						
VRX-RET-E22-301	Completed	Efficacy and safety	X	X		
VRX-RET-E22-302	Completed	Efficacy and safety	X	X		
Extension Studies from Phase IIb/III						
3065A1-212	Completed	Safety and tolerability		X		
VRX-RET-E22-303	Ongoing	Safety and tolerability		X		
VRX-RET-E22-304	Ongoing	Safety and tolerability		X		
Other Phase II/III studies						
VRX-RET-E22-NP201	Completed	Efficacy and safety in post-herpetic neuralgia (PHN)				X[5]
D-23129-3227	Ongoing	Compassionate use -				X

Table 7.1-5		Clinical Studies Providing Safety Information for Ezogabine and Overview of Analysis Sets for Integrated Summaries				
Study	**Status of Study**	**Type of Study**	**RCT Analysis Set (3studies)**	**All Phase II/III Combined Analysis Set (13 studies)**	**Integrated Phase I Analysis Set (21 studies)**	**Presented Separately (10 studies)**
		safety and tolerability				
D-23129-8040	Completed	Safety and tolerability in bipolar disorder				X[5]

1. Only the IR treatment arms in these studies were included in the integrated data analyses.
2. Excluded from the integrated analysis because study drug received was a slow-release (SR) formulation (3065A1-104) or an intravenous (IV) formulation (3065A1-117).
3. Excluded from the integrated analysis because the populations studied differ from both healthy volunteers and patients with epilepsy (VRX-RET-E22-101 [renal insufficiency], VRX-RET-E22-102 [hepatic impairment], VRXRET- E22-107 [co-administration with alcohol] and VRX-RET-E22-108 [abuse liability]).
5. Excluded from the integrated analysis because study was not in epilepsy patients

7.2 Adequacy of Safety Assessments

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

Overall Exposure to at Least One Dose of Ezogabine

As of the 31 December 2008 submission cut-off date, a total of 2034 unique patients (669 subjects from the clinical pharmacology studies and 1365 patients in Phase II and Phase III studies) were exposed to at least one dose of ezogabine in the epilepsy clinical development program, table 38. As of the 2 October 2009 120-Day Safety Update data cut-off date, no additional subjects have been exposed to ezogabine in the "All Phase II/III combined" study group described in the original ISS.

Additionally, 10 patients received ezogabine in completed bipolar disorder Study D-23129-8040. It is not known exactly how many patients received ezogabine in ongoing, double-blind PHN Study VRX-RET-E22-NP201; with 187 enrolled and a randomization scheme of ezogabine:placebo of 2:1, it would be expected that approximately 124 patients would be exposed to ezogabine. Thus, the overall total exposure to ezogabine as of the 31 December 2008 submission cut-off date is 2168.

Table 38 Enumeration of Unique Patients Exposed to Study Medication as of the 31 December 2008 submission cut-off date.

Table 7.2-1	Enumeration of Unique Patients Exposed to Study Medication	
	Number of Patients	
	Placebo	**RTG**
Total Unique Exposures in Clinical Pharmacology Studies	701	6692

Table 7.2-1	Enumeration of Unique Patients Exposed to Study Medication	
	Number of Patients	
	Placebo	RTG
Phase II and Phase III Study Groupings		
RCT (Studies 205, 301, and 302)	427	813
All Phase II and Phase III Combined		1365
Total All Epilepsy Phase II and Phase III Studies	427	1365
Total Unique Exposures in Epilepsy Clinical Development Program	497	2034
Other RTG Studies		
Study VRX-RET-E22-NP201, PHN3, 4	62	124
Study D-23129/8040, Bipolar Disorder	0	10
Total Unique Exposures to RTG	559	2168

1. Includes unique placebo exposure in parallel group studies (3065A1-101. 3065A1-102, 3065A1-107, and VRXRET- E22-103)
2. Includes unique RTG exposure numbers, regardless of formulation; patients may have also received control drug.
3. 31 December 2008 was the submission cut-off date.
4. Ongoing, double-blind study; numbers are estimates.

Exposure in Pivotal Controlled Trials

Mean exposure in ezogabine treated group in the longest treatment category >3 to 6 months was 72.4% (589 patients) compared to 85.5% (365 patients) in the placebo cohort. Mean exposure in treated patients was less than placebo by near 12 days when the mean of all ezogabine treatment groups is obtained. The median number of treatment days is identical in all ezogabine treatment groups and placebo, at 112 days.

Exposure in All Phase II/III combined trials

In the all phase 2/3 trials group 184 patients were exposed for >6 to 9 months, 112 patients were exposed to >9 to 12 months, and 184 patients were exposed for 18 to 24 months. For the entire group the mean number of days exposure was 302.7 with a median of 235. As of the 2 October 2009, the total exposure to ezogabine was approximately 1420 patient-years compared with 1131 patient years table 39.

Table 39 Exposure in All Phase II/III combined trials

	Number (%) of Patients	
	ISS Submission Cut-Off: 30 June 2008	120-Day Safety Data Cut-off: 2 October 2009
	RTG (N=1365)	RTG (N=1365)
Total time on drug		
≤ 1 week	50	50
1 week to 1 month	98	98
>1 month to 3 months	234	232

>3 months to 6 months	204	184
>6 month to 9 months	184	135
>9 months to 12 months	112	80
>12 months to 18 months	229	176
>18 months to 24 months	184	169
>24 months to 36 months	49	190
>36 months to 48 months	11	41
>48 months	10	10
Total time on drug, days		
Mean±SD	302.7±270.43	380.0±344.12
Median	235.0	261.0
Range	1, 1736	1, 1736
Total patient-days	413214	518,756
Total patient-years	1131.32	1420.28

Exposure to Ezogabine in Clinical Pharmacology Studies

In the Integrated Clinical Pharmacology Studies grouping, the total exposure to ezogabine was approximately 11 subject-years. The median exposure to ezogabine was 4.0 days, with a range of 1 to 29 days. For the all subjects in this grouping, exposure to ezogabine was for less than 1 month.

Exposure by Dose

In the combined Phase II/III trial grouping the ezogabine does range with the largest exposure to drug was in the 900mg to <1200 range with a mean exposure of 161.7 days compared to 12.6 days, 29.8 days, 94.7 days, and 137.5 days for the dose range of 0 to <300, 300 to <600, 600 to <900 and ≥1200 respectively.

Approximately 295 patients have been exposed to at least 600 mg/day ezogabine for at least 12 months in accordance with the International Conference on Harmonization (ICH) E1A guidance, and 657 have been exposed for at least 6 months,. For the dosage ≥1200mg 134 patients have been exposed for greater than six months and 52 patients have been exposed for greater than 12 months. As of the 2 October 2009, 453 patients have been exposed to 600 mg/day or more of ezogabine for at least 12 months and 765 have been exposed for a minimum of 6 months compared with the 295 patients and 657 patients, respectively, in the original application table 40.

Table 40 Summary of Total Exposure to Ezogabine by Dose Range (Safety Population: All Phase II/III Combined)

Table 7.2-3	Summary of Total Exposure to Ezogabine by Dose Range (Safety Population: All Phase II/III Combined)					
	RTG Dose (mg/day)					
Total time on drug, n	>0 to <300	300 to <600	600 to <900	900 to <1200	≥1200	Unknown
≤ 1 week	307	68	93	104	81	122
1 week to 1 month	186	1092	615	249	83	44
>1 month to 3 months	29	109	166	207	122	18

Table 7.2-3	Summary of Total Exposure to Ezogabine by Dose Range (Safety Population: All Phase II/III Combined)					
	RTG Dose (mg/day)					
>3 months to 6 months	5	31	202	191	78	7
>6 month to 9 months	0	13	61	102	45	1
>9 months to 12 months	0	4	38	79	37	0
>12 months to 18 months	0	5	56	99	40	0
>18 months to 24 months	1	2	22	42	8	0
>24 months to 36 months	0	3	5	9	2	0
>36 months to 48 months	0	0	4	4	2	0
>48 months	0	0	0	2	0	0
Total patient days	6636	39598	119483	175887	68464	2989
Mean±SD	12.6±28.11	29.8±60.71	94.7±153.37	161.7±198.0	137.5±167.89	15.6±29.06
Median	7.0	19.0	23.0	89.5	71.5	5.0
Range	1, 570	1, 837	1, 1427	1, 1665	1, 1370	1, 200
Total patients years	18.17	108.41	327.13	481.55	187.44	8.18
Total exposure at 120 day safety update, October 2, 2009						
≤ 1 week	337	67	91	102	80	128
1 week to 1 month	191	1091	602	242	76	40
>1 month to 3 months	29	112	157	190	105	13
>3 months to 6 months	5	30	188	171	71	3
>6 month to 9 months	0	13	52	93	32	1
>9 months to 12 months	0	4	38	73	24	0
>12 months to 18 months	0	5	63	93	45	0
>18 months to 24 months	1	3	37	63	35	0
>24 months to 36 months	0	3	30	52	17	0
>36 months to 48 months	0	0	5	8	3	0
>48 months	0	0	0	2	0	0
Total patient days	6910	40823	151377	223648	93627	2193
Mean±SD	12.3±27.26	30.7±62.85	119.9±202.18	205.4±257.90	191.9±245.29	11.9±26.07
Median	7.0	20.0	25.0	96.0	83.0	3.0
Range	1, 570	1, 837	1, 1427	1, 1665	1, 1370	1, 203
Total patients years	18.92	111.77	414.45	612.31	256.34	6.00
≤ 1 week	337	67	91	102	80	128
Key: shaded area captures subjects who have >600mg dose for >6 months, shaded in outlined cells captures >600mg dose for >12 months.						

Reviewer Comment: Sponsor has achieved ICH exposure guideline for minimum daily dose of 600mg requested in labeling. For the maximum dosage of ≥1200mg, 134 patients have been exposed for greater than six months and 52 patients have been exposed for greater than 12 months.

Demography of Exposure

Pivotal Controlled Trials

Gender, Age, Race

In each of the three randomized, controlled trials, there was no difference among treatment groups with respect to age or gender table 41. The mean age was 35 to 38 years, and slightly more than half of the subjects were female. The majority of subjects across all three studies were White/Caucasian. Study 301 included a greater percentage of Hispanic, Black and Other race subjects than Studies 205 and 302. The pooled RCT demographics shown in table 42 allow a more succinct overview of the study demographics. There were 3 subjects under 18 because the inclusion criteria for study 205 accepted ages 16 to 70 years old. Only 8 subjects 65 years or older were participants.

Table 41 Age, Gender, Race by Study, Dose Group

Table 7.2-4	Study 205				Study 301		Study 302		
	Placebo N=96	RTG 600 mg/day N=100	RTG 900 mg/day N=95	RTG 1200 mg/day N=106	Placebo N=152	RTG 1200 mg/day N=153	Placebo N=179	RTG 600 mg/day N=181	RTG 900 mg/day N=178
Age, years									
mean ± SD	34.5 ± 10.3	36.8 ± 10.9	37.0 ± 10.1	38.3 ± 11.9	36.7 ± 11.63	37.7 ± 12.55	37.7 ± 11.75	37.5 ± 12.02	37.7 ± 12.77
Sex, n (%)									
Female	48 (50)	46 (46)	47 (49)	51 (48)	80 (52.6)	85 (55.6)	90 (50.3)	105 (58.0)	85 (47.8)
Male	48 (50)	54 (54)	48 (51)	55 (52)	72 (47.4)	68 (44.4)	89 (49.7)	76 (42.0)	93 (52.2)
Race, n(%)									
White/ Caucasian	89 (93)	98 (98)	92 (97)	103 (97)	78 (51.3)	90 (58.8)	169 (94.4)	173 (95.6)	170 (95.5)
Black	2 (2)	1 (1)	1 (1)	0	15 (9.9)	15 (9.8)	2 (1.1)	2 (1.1)	1 (0.6)
Hispanic	0	0	0	0	47 (30.9)	39 (25.5)	0	0	0
Asian	1 (1)	0	1 (1)	1 (<1)	1 (0.7)	1 (0.7)	3 (1.7)	0	2 (1.1)
Other	4 (4)	1 (1)	1 (1)	2 (2)	11 (7.2)	8 (5.2)	5 (2.8)	6 (3.3)	5 (2.8)

Table 42 Summary of Demographic Characteristics, Pooled RCT Safety Population, Studies 205, 301, 302

Table 7.2-4a	Summary of Demographic Characteristics, Pooled RCT Safety Population, Studies 205, 301, 302				
	Placebo (N=427)	RTG 600 mg/day (N=281)	RTG 900 mg/day (N=273)	RTG 1200 mg/day (N=259)	RTG Total (N=813)
Age, years					
Mean±SD	36.8±11.41	37.4±11.61	37.6±11.92	38.1±12.29	37.7±11.92
Median	36.0	37.0	37.0	37.0	37.0

Table 7.2-4a	Summary of Demographic Characteristics, Pooled RCT Safety Population, Studies 205, 301, 302				
	Placebo (N=427)	**RTG 600 mg/day (N=281)**	**RTG 900 mg/day (N=273)**	**RTG 1200 mg/day (N=259)**	**RTG Total (N=813)**
Range	17, 74	18, 66	14, 69	17, 71	14, 71
Age category (years), n (%)					
<18	2 (<1.0)	0	1 (< 1.0)	2 (< 1.0)	3 (< 1.0)
18 to 64	423 (99.1)	279 (99.3)	271 (99.3)	252 (97.3)	802 (98.6)
≥65	2 (<1.0)	2 (<1.0)	1 (<1.0)	5 (1.9)	8 (<1.0)
Sex, n (%)					
Male	209 (48.9)	130 (46.3)	141 (51.6)	123 (47.5)	394 (48.5)
Female	218 (51.1)	151 (53.7)	132 (48.4)	136 (52.5)	419 (51.5)
Race, n (%)					
Caucasian	336 (78.7)	271 (96.4)	262 (96.0)	193 (74.5)	726 (89.3)
Black	19 (4.4)	3 (1.1)	2 (<1.0)	15 (5.8)	20 (2.5)
Hispanic	48 (11.2)	0	0	39 (15.1)	39 (4.8)
Asian	5 (1.2)	0	3 (1.1)	2 (<1.0)	5 (<1.0)
Other1	19 (4.4)	7 (2.5)	6 (2.2)	10 (3.9)	23 (2.8)

Reviewer Comment: There were no striking differences in distribution of demographic parameters of age, sex, or race between treatment arms of the individual studies. There was acceptable proximity to equality of distribution of these parameters between treatment arms. Study 301 was the only study with racial diversity, reflecting the greater population diversity in the United States from which 48% of the subjects were drawn. There was minimum contribution of studies 205 and 302 to diversity. When added to the non-caucasian subjects of study 301 the racial diversity of the pooled studies is quite limited in proportion to the total of subjects studied, yielding 2.5% Black and 4.8% Hispanic who received ezogabine, which allows limited insight into generalizability.

Concomitant AEDs

The Phase III studies could be considered as recruiting more refractory patient groups compared to the Phase 2 study (Study 205), based upon inclusion criteria with respect to concomitant AED use i.e., subjects were allowed up to three AEDs compared to only two AEDs in Study 205. The majority of subjects in Study 301 and Study 302 received ≥2 AEDs. In Study 205, the majority of subjects received 2 AEDs, table 43. In all 3 studies, carbamazepine was the most common background AED, table 44 to table 46. In study 205 the placebo group has a somewhat greater number of patients on one AED than the treatment groups. The distribution between 1 and 2 AED treatment is very similar among the treatment groups. There are only two vagal nerve stimulators used in study 205. Study 301 has only one ezogabine treatment group, 1200mg / day. This group has greater numbers of subjects in the 1 and 2 AED groups than the placebo cohort. The placebo cohort in this study has 40.1% of patients in the 3 concomitant AED category while the ezogabine treatment has 27.5% of subjects in the category receiving 3 concomitant AEDs. A total of 29 patients in this study had VNS (vagal nerve stimulators) with a fair balance between placebo and ezogabine treatment. Study 302 had a 600mg and 900mg / day treatment arms. The largest numbers for each treatment

arm, placebo and 2 ezogabine were in the 2 concomitant AED group, with the 900mg a day showing the largest at 55.6%. There were 14 VNS in study 302 with a roughly even division among each arm.

Table 43 Concomitant AED Number by Study / Dose

Table 7.2-5	Study 205				Study 301		Study 302		
	Placebo N=96	RTG 600 mg/day N=100	RTG 900 mg/day N=95	RTG 1200 mg/day N=106	Placebo N=152	RTG 1200 mg/day N=153	Placebo N=179	RTG 600 mg/day N=181	RTG 900 mg/day N=178
Concomitant AEDs									
0									
1	33 (34.4)	26 (26)	26 (27.4)	31 (29.2)	21 (13.8)	32 (20.9)	40 (22.3)	49 (27.1)	35 (19.7)
2	62 (64.6)	72 (72)	69 (72.6)	74 (69.8)	70 (46.1)	79 (51.6)	87 (48.6)	76 (42.0)	99 (55.6)
3	1 (1)	2 (2)	0 (0)	1 (<1)	61 (40.1)	42 (27.5)	52 (29.1)	56 (30.9)	44 (24.7)
VNS									
Yes		1 (1)	1 (1.1)		17 (11.2)	12 (7.8)	6 (3.4)	4 (2.2)	4 (2.2)
No		99 (99)	94 (98.9)		135 (88.8)	141 (92.2)	173 (96.6)	177 (97.8)	174 (97.8)

Reviewer Comment: there were no striking differences in distribution of concomitant AED number between treatment arms of any of the three studies. In those studies allowing up to 3 concomitant AEDs the majority of subjects were on 2 or more AEDs, maximum 84.%, minimum 72.9%. Study 205 allowed only 2 concomitant AEDs with the majority on 2, minimum 64.6% , maximum 72.6%. The majority of VN stimulators were present in study 301 where 29 subjects had these devices, while study 302 had 14 and study 205 only 2.

Concomitant AED Type

In study 205 the most common concomitant AEDs in use were the carboxamide derivatives, and within this group, carbamazepine. Among all of the non-study AEDs the use was distributed close to equally between the treatment arms with the only exception seen for barbiturate derivatives where the 200mg TID arm had 32% use with the next largest use seen in the placebo arm at 23% table 7.2-6.

Study 301 has acceptable proximity to equality of use among treatment arms between all of the concomitant AEDs. The majority AEDs in use were carbamazepine and lamotrigine, table 7.2-7.

Study 302 has acceptably equal distribution of concomitant AED use between treatment arms among all of the AEDs with modest divergence seen for the barbiturates and derivatives where the 200mg TID arm had almost double the use of the placebo arm, however the total numbers were small. This AED class accounted for 10% of all concomitant AEDs. There was also modest divergence for topiramate where the 200mg

TID arm had 22.1% use compared to 13.5% in the e300mg TID arm. The largest use of concomitant AED in this study was carbamazepine with a total of 47.8% of subjects in all arms on this agent, table 46.

Table 47 of concomitant AEDs for the pooled RCT studies reveals consistent numerical distribution of use for concomitant AEDs across the placebo and dose groups.

Table 44 Study 205, AED Type by Patients and Dose

Table 7.2-6

Study 205: NUMBER (%) OF PATIENTS RECEIVING NON-STUDY AED MEDICATIONS

MEDICATION CLASSIFICATION	Placebo (N = 96)	Retigabine 200 mg tid (N = 100)	Retigabine 300 mg tid (N = 95)	Retigabine 400 mg tid (N = 106)	FISHER'S EXACT P-VALUE
ANY CONCOMITANT MEDICATION	96 (100)	100 (100)	95 (100)	106 (100)	
ALL OTHER THERAPEUTIC PRODUCTS	8 (8)	8 (8)	3 (3)	6 (6)	0.406
ANTI-PARKINSON AGENTS	3 (3)	2 (2)	3 (3)	5 (5)	0.746
BARBITURATES AND DERIVATIVES	22 (23)	32 (32)	19 (20)	18 (17)	0.071
BENZODIAZEPINE DERIVATIVES	29 (30)	25 (25)	32 (34)	35 (33)	0.525
CARBONIC ANHYDRASE INHIBITORS	2 (2)		1 (1)	1 (<1)	0.558
CARBOXAMIDE DERIVATIVES	78 (81)	88 (88)	84 (88)	90 (85)	0.471
FATTY ACID DERIVATIVES	52 (54)	65 (65)	50 (53)	53 (50)	0.146
HYDANTOIN DERIVATIVES	30 (31)	35 (35)	32 (34)	34 (32)	0.945
OTHER ANTIEPILEPTICS	72 (75)	74 (74)	77 (81)	70 (66)	0.116
OTHER PERIPHERAL VASODILATORS		1 (1)			0.732
SUCCINIMIDE DERIVATIVES	1 (1)	2 (2)		3 (3)	0.526

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Table 45 Study 301, AED Type by Patients and Dose

Table 7.2-7 Study 301: Concomitant AEDs Reported for at Least 5% of Patients in Placebo or Retigabine Treatment Groups

ATC Drug Class Medication Preferred Term	Number (%) of patients Placebo (N=152)		RTG 400 mg TID (N=153)		Total (N=305)	
Barbiturates & derivatives	**17**	**(11.2)**	**19**	**(12.4)**	**36**	**(11.8)**
Phenobarbital	16	(10.5)	17	(11.1)	33	(10.8)
Benzodiazepine derivatives[a]	**56**	**(36.8)**	**55**	**(35.9)**	**111**	**(36.4)**
Clonazepam	22	(14.5)	21	(13.7)	43	(14.1)
Clobazam	18	(11.8)	18	(11.8)	36	(11.8)
Carboxamide derivatives	**86**	**(56.6)**	**78**	**(51.0)**	**164**	**(53.8)**
Carbamazepine	57	(37.5)	58	(37.9)	115	(37.7)
Oxcarbazepine	29	(19.1)	20	(13.1)	49	(16.1)
Fatty acid derivatives	**32**	**(21.1)**	**25**	**(16.3)**	**57**	**(18.7)**
Valproic acid	32	(21.1)	25	(16.3)	57	(18.7)
Hydantoin derivatives	**34**	**(22.4)**	**34**	**(22.2)**	**68**	**(22.3)**
Phenytoin	33	(21.7)	33	(21.6)	66	(21.6)
Other antiepileptics	**106**	**(69.7)**	**99**	**(64.7)**	**205**	**(67.2)**
Lamotrigine	52	(34.2)	52	(34.0)	104	(34.1)
Levetiracetam	32	(21.1)	31	(20.3)	63	(20.7)
Topiramate	29	(19.1)	26	(17.0)	55	(18.0)
Pregabalin	13	(8.6)	7	(4.6)	20	(6.6)
Zonisamide	11	(7.2)	8	(5.2)	19	(6.2)

[a] Includes benzodiazepines for non-epilepsy purposes or acute use in epilepsy (e.g. diazepam, lorazepam)

Note: table based on ≥5% of patients for the preferred term. ATC = anatomical therapeutic classification, RTG = retigabine; TID = three times daily

Table 46 Study 302 AED Type by Patients and Dose

Table 7.2-8 Study 302: Number of Patients Taking Background AEDs

ATC DRUG CLASS MEDICATION PREFERRED TERM	300MG TID (N=178)	200MG TID (N=181)	PLACEBO (N=179)	TOTAL (N=538)
BARBITURATES AND DERIVATIVES	18 (10.1%)	24 (13.3%)	12 (6.7%)	54 (10.0%)
PHENOBARBITAL	15 (8.4%)	19 (10.5%)	9 (5.0%)	43 (8.0%)
PRIMIDONE	2 (1.1%)	5 (2.8%)	3 (1.7%)	10 (1.9%)
PHENYTOIN	1 (0.6%)	0	0	1 (0.2%)
BARBITURATES, PLAIN	3 (1.7%)	4 (2.2%)	5 (2.8%)	12 (2.2%)
BENZOBARBITAL	3 (1.7%)	4 (2.2%)	5 (2.8%)	12 (2.2%)
BENZODIAZEPINE DERIVATIVES	24 (13.5%)	25 (13.8%)	25 (14.0%)	74 (13.8%)
CLOBAZAM	14 (7.9%)	17 (9.4%)	13 (7.3%)	44 (8.2%)
CLONAZEPAM	9 (5.1%)	6 (3.3%)	11 (6.1%)	26 (4.8%)
LORAZEPAM	1 (0.6%)	0	0	1 (0.2%)
DIAZEPAM	0	1 (0.6%)	0	1 (0.2%)
PHENAZEPAM	0	1 (0.6%)	0	1 (0.2%)
BENZODIAZEPINE DERIVATIVES	0	0	1 (0.6%)	1 (0.2%)
CARBOXAMIDE DERIVATIVES	116 (65.2%)	107 (59.1%)	109 (60.9%)	332 (61.7%)
CARBAMAZEPINE	94 (52.8%)	79 (43.6%)	84 (46.9%)	257 (47.8%)
OXCARBAZEPINE	22 (12.4%)	28 (15.5%)	26 (14.5%)	76 (14.1%)
FATTY ACID DERIVATIVES	49 (27.5%)	49 (27.1%)	63 (35.2%)	161 (29.9%)
VALPROIC ACID	47 (26.4%)	46 (25.4%)	60 (33.5%)	153 (28.4%)
TIAGABINE	3 (1.7%)	3 (1.7%)	7 (3.9%)	13 (2.4%)
HYDANTOIN DERIVATIVES	11 (6.2%)	15 (8.3%)	13 (7.3%)	39 (7.2%)
PHENYTOIN	11 (6.2%)	15 (8.3%)	13 (7.3%)	39 (7.2%)
OTHER ANTIEPILEPTICS	116 (65.2%)	110 (60.8%)	109 (60.9%)	335 (62.3%)
LAMOTRIGINE	49 (27.5%)	43 (23.8%)	53 (29.6%)	145 (27.0%)
LEVETIRACETAM	41 (23.0%)	44 (24.3%)	36 (20.1%)	121 (22.5%)
TOPIRAMATE	24 (13.5%)	40 (22.1%)	28 (15.6%)	92 (17.1%)
PREGABALIN	11 (6.2%)	5 (2.8%)	8 (4.5%)	24 (4.5%)
GABAPENTIN	9 (5.1%)	4 (2.2%)	7 (3.9%)	20 (3.7%)
ZONISAMIDE	8 (4.5%)	8 (4.4%)	4 (2.2%)	20 (3.7%)
SULTIAME	0	1 (0.6%)	1 (0.6%)	2 (0.4%)
ACETAZOLAMIDE	1 (0.6%)	0	0	1 (0.2%)
SUCCINIMIDE DERIVATIVES	0	0	1 (0.6%)	1 (0.2%)
ETHOSUXIMIDE	0	0	1 (0.6%)	1 (0.2%)

Table 47 Concomitant AEDs Reported in Greater than or equal to 5% of Patients in the Total RTG Group (Safety Population: RCT, Studies 205, 301, and 302)

Table 7.2-9	**Concomitant AEDs Reported in Greater than or equal to 5% of Patients in the Total RTG Group (Safety Population: RCT, Studies 205, 301, and 302)**				
Medication PT	**Number (%) of Patients**				
	Placebo (N=427)	**RTG 600 mg/day (N=281)**	**RTG 900 mg/day (N=273)**	**RTG 1200 mg/day (N=259)**	**RTG Total (N=813)**
Carbamazepine	201 (47.1)	146 (52.0)	161 (59.0)	130 (50.2)	437 (53.8)
Lamotrigine	125 (29.3)	63 (22.4)	71 (26.0)	78 (30.1)	212 (26.1)
Valproic acid	113 (26.5)	74 (26.3)	64 (23.4)	47 (18.1)	185 (22.8)
Topiramate	75 (17.6)	56 (19.9)	45 (16.5)	38 (14.7)	139 (17.1)
Leviteracetam	68 (15.9)	46 (16.4)	44 (16.1)	31 (12.0)	121 (14.9)
Phenytoin	60 (14.1)	29 (10.3)	19 (7.0)	48 (18.5)	94 (11.8)
Oxcarbazepine	58 (13.6)	34 (12.1)	30 (11.0)	25 (9.7)	89 (10.9)
Clobazam	39 (9.1)	23 (8.2)	19 (7.0)	24 (9.3)	66 (8.1)
Phenobarbital	28 (6.6)	20 (7.1)	21 (7.7)	18 (6.9)	59 (7.3)
Clonazepam	37 (8.7)	9 (3.2)	13 (4.8)	26 (10.0)	48 (5.9)

Table 7.2-9	Concomitant AEDs Reported in Greater than or equal to 5% of Patients in the Total RTG Group (Safety Population: RCT, Studies 205, 301, and 302)				
Medication PT	Number (%) of Patients				
	Placebo (N=427)	RTG 600 mg/day (N=281)	RTG 900 mg/day (N=273)	RTG 1200 mg/day (N=259)	RTG Total (N=813)
Gabapentin	12 (2.8)	17 (6.0)	17 (6.2)	11 (4.2)	45 (5.5)

Reviewer Comment: there were no striking differences in distribution of concomitant AED type between treatment arms within the three studies. There were also no large differences between uses of concomitant medication across dosage groups in the pooled RCT studies. These observations reduce the likelihood that unequal distribution of the concomitant AEDs will influence the effect of the study drug on epilepsy treatment.

7.2.2 Explorations for Dose Response

Analysis of Adverse Effect Dose-Response Relationship

Pharmacokinetic-pharmacodynamic (PK-PD) analyses were conducted to evaluate the relationship between predicted ezogabine steady-state systemic exposure (area under the curve over the dosing interval (AUC(0-τ)) and key efficacy / safety endpoints using data pooled from Studies 301 and 302.

Additional PK/PD analyses were conducted to investigate the relationship between AUC(0-τ) and the probability of efficacy (≥50% reduction from baseline in total partial seizure frequency) and the probability of occurrence of adverse events. This analysis showed that over the entire AUC(0-τ) range observed in Studies 301 and 302, the probability of ≥50% decrease from baseline in seizure frequency was higher than the probability of any of the AE occurring. The slope of the exposure-response relationship for probability of efficacy was similar to that for dizziness and coordination abnormal whereas the slope of the exposure response relationship for dysarthria, somnolence, tremor and vision blurred were less steep, indicating that these latter AEs were less sensitive to changes in exposure

A summary of the predicted response by dose level from the PK/PD analyses for efficacy and safety endpoints from Studies 301 and 302 is shown in table 1.

Table 48 Summary of Predicted Responses by Dose based on PK/PD Analyses for Efficacy and Safety Endpoints from Studies 301 and 302

Dose	Placebo	600 mg/day	900 mg/day	1200 mg/day
Median AUC(0-τ) (ug.h/mL)	0	4.35	6.78	9.67
Predicted % change in seizure frequency	-18.9	-40.9	-51.8	-55.9
Probability of >50% reduction in seizure frequency	0.24	0.37	0.44	0.54

Probability of Dizziness	0.09	0.17	0.22	0.30
Probability of Somnolence	0.13	0.18	0.22	0.27
Probability of Coordination Abnormal	0.02	0.04	0.06	0.10
Probability of Dysarthria	0.01	0.03	0.04	0.05
Probability of Tremor	0.04	0.06	0.07	0.09
Probability of Vision Blurred	0.02	0.04	0.05	0.06

Adverse Events, Intensity vs Dose

The majority of patients reported TEAEs with a maximum intensity of mild or moderate, table 2. The percentage of patients reporting TEAEs with a maximum intensity of moderate was comparable between the placebo and 600 mg/day ezogabine group (34% and 35%, respectively) but was higher with increasing ezogabine doses (42% and 47% in the 900 and 1200 mg/day groups, respectively). For a maximum intensity of severe, the percentage of patients was similar between the placebo and both the 600 and 900 mg/day groups (10%, 10%, and 12%, respectively), but higher in the 1200 mg/day (20%).

Table 49 TEAEs by Maximum Intensity (Safety Population: RCT, Studies 205, 301, and 302)

	Number (%) of Patients				
		RTG	RTG	RTG	RTG
AEs by Maximum Intensity	**Placebo (N=427)**	**600 mg/day(N= 281)**	**900 mg/day(N= 273)**	**1200 mg/day (N=259)**	**All Doses (N=813)**
Mild	131 (30.7)	83 (29.5)	77 (28.2)	55 (21.2)	215 (26.4)
Moderate	144 (33.7)	97 (34.5)	114 (41.8)	121 (46.7)	332 (40.8)
Severe	43 (10.1)	27 (9.6)	32 (11.7)	51 (19.7)	110 (13.5)

Reviewer Comment: Adverse events increase with increasing dose although only dizziness approaches the slope of the concentration – response curve. The table of adverse events by maximum intensity reveals a notable increase in events between the 900mg and 1200mg dose (8%), compared to the increase in severe adverse events between the 600mg and 900mg dose (2.1%). There is some evidence of diminishing return in efficacy with increase of adverse effect when moving from the 900mg to 1200mg a day dose.

7.2.3 Special Animal and/or In Vitro Testing

Following identification of the KCNQ (Kv7) family of potassium ion channels, RTG was identified as an opener (positive modulator or enhancer) of the KCNQ2-5, but not KCNQ1 isoforms of this family of K+ ion channels. The KCNQ2-5 genes encode a family of voltage-dependent ion channels that maintain cellular membrane potential, regulate neurotransmitter release, and control subthreshold electrical excitability in neurons. KCNQ1, an additional member of the KCNQ family, is primarily expressed in

the CVS. KNCQ2-5 channels are also found in peripheral hollow organs, including vascular smooth muscle, urinary bladder and intestine.

Pre clinical testing issues of concern has been directed by the effect of ezogabine on cellular membrane potential, including cardiac and cerebral electrophysiology, and the range of distribution of KNCQ2-5 channels, as noted above, in vascular smooth muscle, urinary bladder and intestine.

Central Nervous System

Behavioral alteration was explored in mice and rats as well as motor function change and proconvulsant activity.

Cardiovascular System

In vitro studies in cat myocytes were conducted to evaluate electrophysiologic properties. The effect of ezogabine on the large arteries of the rat were performed as well as studies on the electrophysiologic effect of ezogabine on a guinea pig heart model. In vivo studies of ezogabine were conducted to evaluate safety pharmacology in dogs and pigs.

Respiratory system

Two studies were conducted to determine the effects of ezogabine on the respiratory system in anaesthetized guinea pigs and in Beagle dogs.

Gastrointestinal System

In vitro study of guinea pig gallbladder contractility was performed as well as repeat dose toxicity studies in mouse and dog where the pharmacologic effect of ezogabine on gall bladder relaxation was examined.

Urinary and Renal System

This has emerged as a target system of importance due to the effect of ezogabine on bladder contractility. This as been identified in a rodent model where ezogabine results in an inhibition of micturition and bladder distention with secondary effects on the kidneys produced by increased urinary tract pressure. In vitro studies were performed on bladder muscle cells from rats and guinea pigs to better identify the effect of ezogabine.

Reviewer Comment: the sponsor nonclinical testing has been appropriately directed to study most relevant target tissue directed by the distribution of KNCQ2-5 channels, using in vitro and in vivo models.

7.2.4 Routine Clinical Testing

In reference to the pivotal controlled trials routine clinical testing was adequate for both general screening for adverse effects and for special assessment of unique adverse effects that were identified during development.

Safety assessments

Study 301 & 302: the safety assessment program for studies 301 and 302 differed only by a two week displacement in timing for those elements of the assessment that were not obtained at each visit. This was due to the 2 week longer duration of the titration phase of study 301; this is due to the two additional weeks needed to achieve the 1200mg dose in this study. The periodically obtained safety elements affected by this timing difference are the AUA symptom index (appendix 9.9), and bladder PVR (post void residual) ultrasound. Clinical laboratory studies and vital signs were obtained at final baseline, each double blind study visit and the final study visit after taper. 12 lead ECGs were obtained at final baseline visit in triplicate, all titration phase study visits and the first and last maintenance phase study visit, each transition phase to open label visit as well as final visit. Physical and neurologic exam are obtained at the same corresponding points in study 301 and 302 which are screening, final baseline, final maintenance and final study visit. In both studies 301 and 302 urinalysis is obtained at baseline, each titration and maintenance visit, transition phase (to open label) visits and final study visit. A pregnancy test is obtained in both studies at screening, final baseline, last titration phase, last maintenance phase, last transition phase (to open label) and final study visit.

In both studies 301 and 302 the hematology and clinical chemistry parameters obtained are as follows:

Hematology: hemoglobin, hematocrit, RBC count, WBC count with differential, and platelet count.

Blood chemistries: sodium, potassium, chloride, bicarbonate, glucose, cholesterol, creatinine, calcium, phosphorus, BUN, uric acid, total bilirubin, total protein, AST, ALT, and alkaline phosphatase levels.

Study 205: the safety assessment program for study 205 included clinical laboratory determinations at screening and final baseline visit, at all titration and maintenance phase visits (3-9) except visit 6, at open label extension visit 12 and final study visit. Vital signs including weight are obtained at every study visit. 12 lead ECG were obtained at screening, final baseline visit, study visit 7 and 9. Physical and neurologic exam were obtained at screening, maintenance visit 9, dose interim visit 11 and final study visit (at end open label or complete taper). AUA symptom index was obtained at baseline and maintenance visit 9. A holter monitor was obtained at screening and maintenance visit 9.

Reviewer Comment: All studies had adequate clinical laboratory testing to maintain surveillance for liver function study abnormalities and hematologic abnormalities. Clinical evaluation for urinary tract abnormalities was more robust in studies 301 and 302 with the addition of post void residual measurements at 4 time points both studies and 2 addition AUA symptom index sampling points compared to study 205. The phase III studies had adequate urinary tract monitoring for voiding dysfunction and urinary sediment issues of concern.

Cardiac monitoring in Study 301 and 302 included QT monitoring to supplemental study 103 "Thorough ECG Trial" with a PK sampling point correlated with the scheduled 12 lead ECG at all titration phase study visits, the first and last maintenance phase study visit, and final study visit. The program was adequate for monitoring the cardiac effects of this novel KCNQ (Kv7) K+ channel modulator.

7.2.5 Metabolic, Clearance, and Interaction Workup

The pharmacokinetics (PK) of ezogabine (RTG) were examined in more than 50 ADME studies in multiple species including mice, rats, rabbits, dogs, monkeys and minipigs. The species selection for PK studies included those species that were used in the primary pharmacology and toxicology studies of RTG (primarily mice, rats and dogs) mostly by the oral route thus supporting the proposed clinical route of administration.

Metabolism: Data on the metabolism of RTG and NAMR were obtained from in vivo studies in mice, rats, rabbits, dogs, and monkeys and from in vitro studies in tissue and/or tissue preparations from mice, rats, dogs, rabbits, monkeys and humans.

In vivo data on the metabolism of RTG and NAMR was obtained from studies in mice, rats, rabbits, and dogs. There were 19 in vivo studies covering the spectrum of metabolic analysis as shown in the list below:

1. Evaluation of the biotransformation of ezogabine in mice after a single oral dose of 8.25mg/kg. Plasma samples were obtained at .25 hrs, .5 hrs and 1 hour after administration
2. Evaluation of Metabolite profiles in plasma, urine and feces from two mouse strains (CD-1 and B6C3F1) following a single oral dose of 0.32 mg of [$_{14}$C]RTG per mouse (approx. 10.7 mg/kg, representing 11.74 MBq/kg or 317 µCi/kg).
3. Metabolite Profiles of Brain and Plasma Samples after a Single Oral Administration of 8.25 mg/kg [^{14}C]ezogabine to Rats.
4. Metabolite Profiles of Plasma and Milk Samples after a Single Oral Administration of 8.25 mg/kg [^{14}C]ezogabine to Lactating Rats
5. Glucuronidation of [14C]ezogabine in vitro in Human Liver Microsomes and in vivo in Rats and Dogs
6. Exploratory Investigations on the in vivo Metabolism of ezogabine D-23129 in Plasma of Rats and Dogs and on Metabolite Pharmacokinetics in Rats.

7. Exploratory investigations on the metabolism of RTG in rats and dogs receiving 82.5 mg/kg or 38.3 mg/kg RTG, respectively, as single and repeat oral doses were performed by HPLC and column-switching.
8. RTG and Metabolites: Kinetic Parameters of RTG, NAMR, FBI in Male Rats after Single. dose (SD) and Multi-dose (MD) Oral Administration (Week 4) of RTG at 82.5 mg/kg/day
9. Metabolite Profiles of [Aniline Ring-U-14C] ezogabine in Rats and Dogs after Oral Dosing of 8.25 mg/kg
10. Urinary and Fecal Metabolite Profiles in Male Rats After p.o. Single Dose Administration of 8.25 mg/kg [$_{14}$C]RTG
11. Collection of Samples for Identification of the Metabolites of $_{14}$C-Ezogabine after a Single Oral Dose to Rats. Drug-related radioactivity and RTG metabolism was investigated in plasma after oral administration of 8.25 mg/kg [$_{14}$C]RTG and approximately 7.6 mg/kg unlabelled RTG to male Sprague Dawley rats.
12. Percent of sample radioactivity as [$_{14}$C]-RTG or metabolites of [$_{14}$C]-RTG in pooled plasma (before and after SPE clean-up) after administration of a single oral dose of [$_{14}$C]-RTG (8.25 mg/kg) to male rats (Mean ± SD, N = 3)
13. Metabolism of [$_{14}$C]ezogabine in Rats and Dogs after Oral Dosing of 8.25 mg/kg. The *in vivo* metabolism of RTG in rats and dogs was investigated in different studies following a single oral dose of 8.25 mg/kg, representing a radioactive dose of 8.73 MBq/kg
14. Glucuronidation of ezogabine *in vitro* in Human Liver Microsomes and *in vivo* in Rats and Dogs
15. Exploratory Investigations on the *in vivo* Metabolism of ezogabine in Plasma of Rats and Dogs and on Metabolite Pharmacokinetics in Rats
16. Metabolite Profiles of [Aniline Ring-U-$_{14}$C]D-23129 in Rats and Dogs after Oral Dosing of 8.25 mg/kg
17. Metabolism of [$_{14}$C]D-23129 in Rats and Dogs after Oral Dosing of 8.25 mg/kg
18. Investigation of the Influence of D-23129 on Hepatic Drug Metabolizing Enzymes
19. Investigation of the Influence of D-23129 on Hepatic UDP-Glucuronosyltransferases

In vitro data: there were 9 studies covering the spectrum of metabolic analysis as shown in the list below:

1. In vitro Metabolism of [14C]Ezogabine in Caco-2 Cell Cultures
2. Ezogabine N-Glucuronidation and its Potential Role in Enterohepatic Circulation
3. Evaluation of *in vitro* Metabolism of Ezogabine and N-Acetyl Metabolite of Ezogabine in Rat, Rabbit, Dog, Monkey and Human Liver Microsomes and Hepatocytes
4. *In vitro* and *in vivo* metabolism of D-23129 in man.
5. The Preliminary Evaluation of GKE-841 (RTG) as a Reversible Inhibitor of Human P450 Enzymes
6. *In Vitro* Evaluation of Ezogabine and NAMR as Inhibitors of Human CYP2C8

7. *In Vitro* Evaluation of RTG and NAMR as Inducers of Cytochrome P450 Expression in Cultured Human Hepatocytes
8. The Effect of Imipramine or Lamotrigine on Ezogabine Glucuronidation in Human Liver Microsomes
9. The Effect of Valproic Acid on Ezogabine Glucuronidation in Human Liver Microsomes

P-gp

The interaction of ezogabine with P-gp was evaluated by examining evaluating diffusion in Caco-2 monolayers in the presence of known inhibitors verapamil and doxorubicin which did not influence the diffusion of ezogabine. Evaluation of the potential for ezogabine and NAMR to inhibit P-gp in a LLC-PK cell monolayer was also evaluated.

Drug Drug interaction

Ezogabine is extensively metabolized with a substantial fraction converted to inactive N-glucuronides. Ezogabine is also metabolized to an N-acetyl metabolite that is also subsequently glucuronidated. There is no evidence for hepatic oxidative metabolism of ezogabine ore the N-acetyl metabolite of ezogabine by cytochrome P450 enzymes.

Lamotrigine is predominantly metabolized by glucuronidation, similarly to ezogabine[2]. The metabolism of lamotrigine is susceptible to both enzyme inhibition and enzyme induction[3]. Phenobarbital is a potent nonspecific inducer of CYP and other hepatic enzymes including UDP-glucuronidases[4].

Study Number	Description	RTG Formulation
3065A1-109	Interaction with lamotrigine	IR
3065A1-112	Interaction with oral contraceptives	IR
3065A1-113	Interaction with phenobarbital	IR
VRX-RET-E22-106	Interaction with oral contraceptives	IR
VRX-RET-E22-107	Interaction with ethanol	IR

The sponsor has performed clinical studies to examine the interaction of ezogabine with lamotrigine, phenobarbital and oral contraceptives. In addition the sponsor identifies two internal studies of in vitro examination of the effect of Imipramine, lamotrigine and valproic acid on ezogabine glucuronidation. There was on study of the interaction of carbamazepine, sodium valproate, and phenytoin with ezogabine in a mouse model. In a rat model the interaction of carbamazepine, valproate and phenytoin was performed.

2 Cary Elwes RD, Binnie CD. Clinical pharmacokinetics of newer antiepileptic drugs: lamotrigine, vigabatrin, gabapentin, and oxcarbazepine. Clin Pharmacokinetics 1996; 30 (6): 403-15.
3 Cecilie Johannessen Landmark and Philip N Patsalos. Drug interactions involving the new second- and third generation antiepileptic drugs. Expert Rev. Neurother. 10(1), 119–140 (2010)
4 Anderson G. Pharmacogenetics ad enzyme induction / inhibition properties of antiepileptic drugs. Neurology 2004; 63(10) Supp 4

Reviewer Comment: the sponsor has performed an adequate assessment of metabolism, clearance and drug interaction.

7.3 Major Safety Results

7.3.1 Deaths

As of the 120 day safety update cut-off (October 2, 2009) there were 15 treatment-emergent deaths in the epilepsy clinical development program, (3/427 (0.7%) patients who received placebo and 12/1365 (0.9%) patients who received ezogabine) (table 50). Two of these deaths are recorded in the database as occurring greater than 30 days after the last known dose.

In the Pivotal Controlled Trials grouping, there were 3 deaths out of 427 patients in placebo (0.7%) and 2 deaths out of 813 patients in the Total RTG group (0.2%) (1 patient in the 600 mg/day group and 1 patient in the 1200 mg/day group).

Table 50 All Treatment Emergent Deaths in the Overall Ezogabine Program

Table 7.3-1	All Treatment Emergent Deaths in the Overall Ezogabine Program						
Treatment Group/Dose	**Study ID**	**Patient ID**	**Demographics (Age, Race, Sex)**	**Study drug Day /dose @ death**	**Adverse Event (Preferred Term)**	**SUDEP / Not**	**Comments**
Placebo							
NA	205	001100	22/C/M		Injury	Not SUDEP	Patient assaulted and beaten to death
NA	301	02805	57/C/F		Collapse of lung; respiratory failure	Not SUDEP	Fell during seizure and sustained injuries
NA	302	55504	31/C/M		SUDEP	Probable SUDEP	Found dead in bed; no autopsy
RTG (mg/day)							
675	208	00004	60/C/F	Day 462, 675mg/day	Metastatic neoplasm	Not SUDEP	Non small cell lung cancer to liver. DVT. Hb 7.7. UTI
800[1]	208	00013	39/C/F	Day 1448	Death	Probable SUDEP	Hx Renal Calculi, renal colic-hemorrhage in 10-2000. (b) (6) Found dead on kitchen floor; no autopsy
1050	214	00059	34/C/F	Day 23 1050mg	Cardiopulmonary failure; arteriosclerosis	SUDEP cannot be excluded	D (b) (6) Autopsy: morbid obesity; advanced cardiovascular disease. LAD

1200	301	02513	57/B/M	Day 18, 450mg/day- in titration	Diabetic ketoacidosis; bacteria urine identified	Not SUDEP	Glucose: 582; Autopsy: DKA (acetone, marked hyperglycemia); cardiovascular disease
600	302	55408	55/C/M	Day 75, 600mg/day	SUDEP	Probable SUDEP	Found dead in bed; no autopsy
900	304	55305	46/C/F	Day 155, 14 day after transition 600 to 900 in DB to OL	Sudden death	Possible SUDEP	Autopsy: likely died during seizure
1200**1**	304	25210	25/C/F	Day 469, Transition to 1200mg 35 days pre-death	SUDEP	Probable SUDEP	Found dead by family in morning; no autopsy.
900**1**	304	85111	42/C/M	Day 219, 900mg/day, OL	Asphyxia	Possible SUDEP	Reported to have experienced asphyxia during seizure; no autopsy
1200	CU	046126	24/C/M	Day 564 1200mg/day	SUDEP	Probable SUDEP	Found dead in bed; no autopsy
600	CU	015349	27/C/F	Day 981, 600mg/day	SUDEP	Probable SUDEP	Found dead in bed; no autopsy
120 day safety update							
950	304	055601	53/C/F	1032(Dx)/ 950mg/day OL	Multiple myeloma	Not SUDEP	None
600	CU	033-100	58/O/F	Day 3291+/200 mg/day	Subdural hematoma	Not SUDEP	Reported after (b) (6) -case report only SDH, D/C from hospital (b) (6)

1. Dosing records indicate last known dose of ezogabine was >30 days before event. Patient included on treatment emergent table because they likely continued ezogabine up until time of event based on clinical assessment.
Note: Study 304 and the CU program are ongoing.
B=Black or African-American; C=Caucasian or White; F=female; ID=identification; M=male

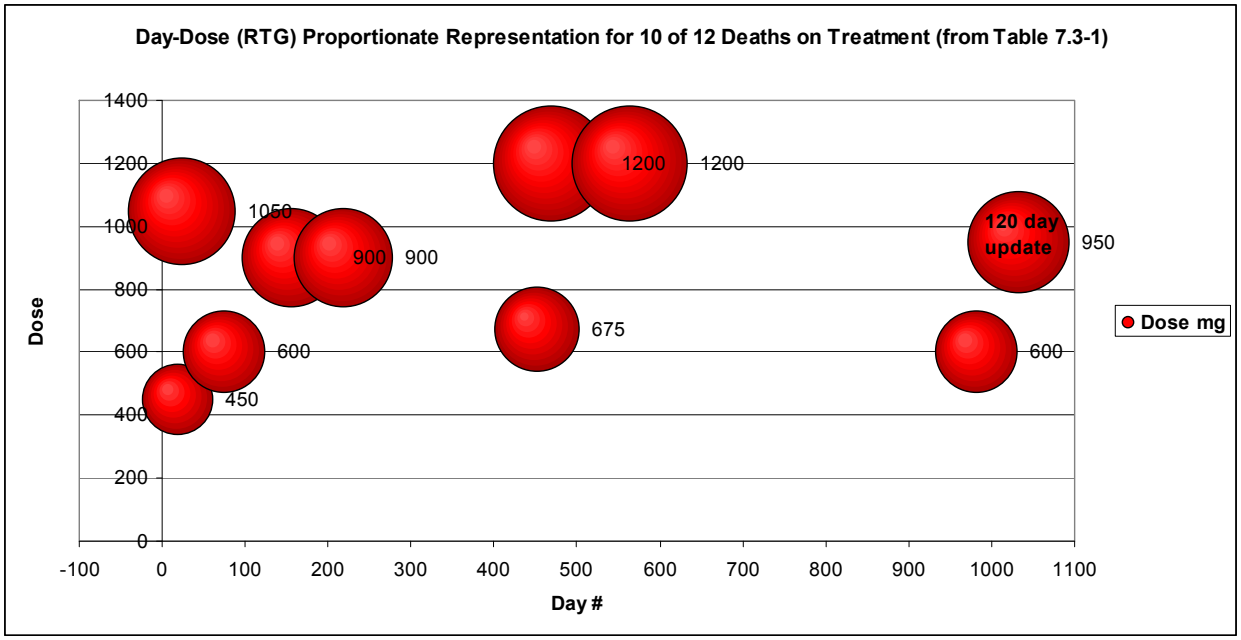


Figure 7 Day-Dose Graphic for 10 of 12 deaths on treatment

Two of the ten deaths on ezogabine were due to clearly identifiable medical causes, Case 0004 was due to a metastatic neoplasm, and there is no indication in the case narrative if the malignancy was thought to start before or after beginning ezogabine. Case 02513 was due to diabetic ketoacidosis in a 57 year old male. There is no indication in the case report that this patient had pre-existing diabetes. His concurrent medication list does not indicate diabetes treatment.

The narrative for case 00059 indicate a primary cardiovascular cause of death in a 34 year old female. The patient background reveals a significant cardiovascular risk factor of morbid obesity and advanced coronary artery disease on post mortem including an LAD lesion. There is no explicit statement of myocardial infarction from the post mortem report but features of terminal heart failure indicated by pulmonary edema and hepatic congestion. This case is reported by the sponsor as non SUDEP, however the young age of the patient and absence of explicit cause of sudden death do not allow SUDEP to be completely excluded. There are seven remaining cases which can be characterized as possible or probable SUDEP.

The day of death and dose at death are displayed graphically in figure 7. Two deaths are not included in the graphic, one from the original ISS which occurred on day 1448 but the ezogabine dose was not reported, a second (1 of 2 from the 120 day safety update) is not included which occurred beyond day 3291 from subdural hematoma where dose is unclear in the case report. In this graphic the diameter of the point (circle) is proportionate to the y axis dose; the day is represented on the X axis. This graphic is useful for screening for a pattern related to the dose or duration of exposure and none is seen.

The sponsor calculates a rate of possible, probable or definite SUDEP of 4.4/1000 patient years of exposure, however case 00059 needs to be moved to the category of possible of SUDEP raising the SUDEP rate to > than 4.4/1000 patient years. A question arises of whether this is a greater than expected SUDEP rate for this population and if so is the increase a drug related effect. The literature indicates a rate ranging from .09 cases of SUDEP per 1000 patient years in a prospective follow up of newly diagnosed epilepsy to 9.3 / 1000 patient years in a study of epilepsy surgery referrals with an average of 3.64 /1000 over 17 studies from clinical trials and epilepsy referral centers[5]. A graphic display of the range cases/1000 person-years can be seen in figure 8.

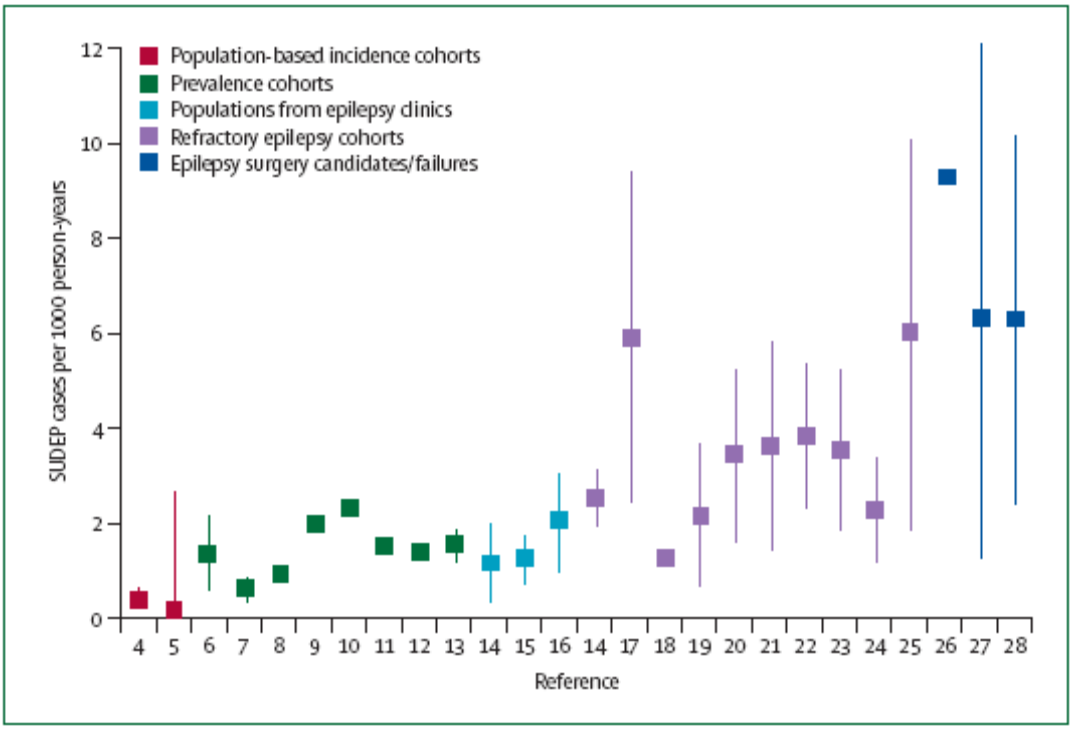


Figure 8: Incidence of SUDEP in 26 studies of different epilepsy populations[6]

120 Day Safety Update

During the 120-Day Safety Update reporting period (between 1 January 2009 and 2 October 2009), there were no deaths in Study 303 and one death (multiple myeloma, not sudden unexplained death in epilepsy [SUDEP]) in Study 304. Additionally, after the 120-Day Safety Update cut-off, there was one death in the compassionate use program (recurrent subdural hematoma, not SUDEP. When combined with the 13 treatment-emergent deaths (3 on placebo) reported in the original ISS, there were a total of 15 treatment-emergent deaths in the epilepsy program (3/427 [0.7%] patients who received placebo and 12/1365 [0.9] patients who received ezogabine).

5 Tomson T, Nashef L, Ryvline P. Sudden unexpected death in epilepsy:current knowledge and future directions. Lancet Neurol 2008;7:1021-31.
6 Tomson T, Nashef L, Ryvline P. Sudden unexpected death in epilepsy:current knowledge and future directions. Lancet Neurol 2008;7:1021-31.

Reviewer Comment: The occurrence of death in the development program does not reveal a relationship to the dose or duration of treatment. Four of the deaths are due to concurrent medical disorder with extremely low likelihood of relationship to study drug leaving a balance of 8 unexplained sudden deaths (SUDEP). The rate of SUDEP in this study is in the range of the highest rate cohorts in the medical literature, which are the epilepsy surgery candidates. This is a refractory population who may to some extent approximate the surgical candidate cohort, however it is uncertain if this rate (>4.4/1000 person years) is greater than expected.

7.3.2 Nonfatal Serious Adverse Events

Pivotal Controlled Trials –RCT (Studies 205, 301 and 302)

Approximately 6% and 9% of patients in the placebo and Total RTG groups, respectively, reported a TESAE. Among the ezogabine dose groups, TESAEs were reported for 8%, 7%, and 11% of the 600, 900, and 1200 mg/day groups, respectively. The most frequently reported TESAE was convulsion. This was seen in 1% (5 pts.) of placebo, 2% (5 pts.) in the 600mg treatment group, <1% (2pts) in the 900mg treatment group and 2% (5 pts) in the 1200mg/ day group. Psychotic disorder was the second most frequently reported TESAE, <1% (1pt) in the 900mg/day group and 2% (5 pts) in the 1200mg/day group. All other TESAEs were reported by no more than 2 (<1%) patients in any treatment group.

Reported at an incidence of <1%, but only reported in the ezogabine 1200 mg/day group, were TESAEs of nausea, encephalopathy, confusional state, and suicidal ideation (2 patients for each event). A TESAE of depression was reported by 2 patients taking placebo and by 1 patient taking ezogabine 1200 mg/day. A listing of all TESAEs reported by ≥2 patients in any treatment group is presented in table 51.

Table 51 Number (%) of Patients, TESAEs in RCT (Pivotal Controlled Trials)

Preferred Term	Table 7.3-2 Number (%) of Patients, TESAEs in RCT (Pivotal Controlled Trials)				
	Placebo (N=427)	**RTG 600 mg/day (N=281)**	**RTG 900 mg/day (N=273)**	**RTG 1200 mg/day (N=259)**	**RTG Total (N=813)**
Any SAE	**25 (5.9)**	**23 (8.2)**	**18 (6.6)**	**29 (11.2)**	**70 (8.6)**
Convulsion	5 (1.2)	5 (1.8)	2 (<1.0)	5 (1.9)	12 (1.5)
Psychotic disorder	0	0	1 (<1.0)	5 (1.9)	6 (<1.0)
Nausea	0	0	0	2 (<1.0)	2 (<1.0)
Fatigue	0	2 (<1.0)	0	0	2 (<1.0)
Drug toxicity	0	2 (<1.0)	0	0	2 (<1.0)
Encephalopathy	0	0	0	2 (<1.0)	2 (<1.0)
Dizziness	1 (<1.0)	0	2 (<1.0)	0	2 (<1.0)
Myoclonus	0	2 (<1.0)	0	0	2 (<1.0)
Confusional state	0	0	0	2 (<1.0)	2 (<1.0)
Suicidal ideation	0	0	0	2 (<1.0)	2 (<1.0)

Preferred Term	Table 7.3-2 Number (%) of Patients, TESAEs in RCT (Pivotal Controlled Trials)				
	Placebo (N=427)	**RTG 600 mg/day (N=281)**	**RTG 900 mg/day (N=273)**	**RTG 1200 mg/day (N=259)**	**RTG Total (N=813)**
Any SAE	**25 (5.9)**	**23 (8.2)**	**18 (6.6)**	**29 (11.2)**	**70 (8.6)**
Depression	2 (<1.0)	0	0	1 (<1.0)	1 (<1.0)
Epididymitis	2 (<1.0)	1 (<1.0)	0	0	1 (<1.0)
Abdominal pain	2 (<1.0)	0	0	0	0
Cholecystitis	2 (<1.0)	0	0	0	0

RCTs, SAE by study phase

During titration phase the 600mg/ day and 900mg/day dose had total SAE reports equal to placebo. In the 1200mg/day group the number of reports was twice (8%) that of placebo (4%) and all ezogabine treatment was 1% greater than placebo. In maintenance phase placebo had SAE reports from 3% of patients while in the 600mg/day group there were reports from 5% of patients, in the 900mg/day there were SAE reports from 4% of patients, in the 1200mg/day group 5% had SAEs and for all ezogabine treatment combined SAEs were reported in 4%. These data are displayed in tabular form in table 52 .

Table 52 Total SAE reports from number (%) of patients by treatment group

Table 7.3-3	Total SAE reports from number (%) of patients by treatment group	
Treatment group	Titration	Maintenance
Placebo	16/427 (4%)	11/383 (3%)
600mg	11/281 (4%)	11/243 (5%)
900mg	12/273 (4%)	8/226 (4%)
1200mg	20/259 (8%)	10/189 (5%)
All Ezogabine (all dose strata)	43/813 (5%)	29/658 (4%)

All Phase II/III Combined

In the All Phase II/III Combined grouping, TESAEs were reported by 16% (216/1365 subjects) of patients treated with ezogabine

Convulsion was the only TESAE reported by >2% of patients treated with ezogabine in the “All Phase II/III Combined” studies (33 patients, 2.4%). Psychotic disorder was the second most frequently reported SAE (9 patients, <1%), followed by confusional state (8 patients, <1%), status epilepticus (8 patients, <1%), and complex partial seizures (7 patients, <1%). All other TESAEs were reported for 6 (<1%) or fewer patients in these studies.

As of the 120-Day Safety Update reporting period, at least one TESAE was reported by 17% of patients who received ezogabine, table 53. A total of 14 patients who had not

previously reported a TESAE in the original ISS reported a TEAE between 1 July 08 and 2 October 09. When combined with the 216 patients who reported TESAEs in the original ISS, a total of 230 patients reported TESAEs in this study grouping. The types and incidences of TESAEs were similar to those reported in the original ISS.
During the 120-Day Safety Update reporting period, 2 patients reported convulsion as a TESAE for the first time. All other TESAEs had 1 or no patients reporting those TESAEs for the first time.

Table 53 TESAE by Preferred Term, All Phase II/III Combined

Preferred Term	Number (%) of Patients	
	RTG (N=1365)	
	ISS Integrated data Cut-Off: 30 June 2008	120-Day Safety Data Cut-off: 2 October 2009
Any SAE	**216 (15.8)**	**230 (16.8)**
Convulsion	33 (2.4)	35 (2.6)
Psychotic disorder	9 (0.7)	9 (0.7)
Confusional state	8 (<1.0)	7 (0.5) [a]
Status epilepticus	8 (0.6)	8(0.6)
Complex partial seizures	7 (0.5)	7 (0.5)
Epilepsy (increased seizure frequency)	6 (0.4)	7 (0.5)
Dizziness	5 (0.4)	5 (0.4)
Chest pain	5 (0.4)	5 (0.4)
Grand mal convulsion	5 (0.4)	6 (0.4)
Somnolence	4 (0.3)	4 (0.3)
Headache	4 (0.3)	4 (0.3)
Conversion disorder	4 (0.3)	4 (0.3)
Pneumonia	4 (0.3)	5 (0.4)
Urinary retention	4 (0.3)	4 (0.3)
Hyponatremia	4 (0.3)	5 (0.4)
Pregnancy	4 (0.3)	4 (0.3)
Coma	3 (0.2)	3 (0.2)
Mental status changes	3 (0.2)	3 (0.2)
Drug toxicity	3 (0.2)	3 (0.2)
Overdose	3 (0.2)	3 (0.2)
Abdominal pain	3 (0.2)	3 (0.2)
Diarrhea	3 (0.2)	3 (0.2)
Nausea	3 (0.2)	3 (0.2)
Vomiting	3 (0.2)	3 (0.2)
Fatigue	3 (0.2)	3 (0.2)
Urinary tract infection	3 (0.2)	3 (0.2)
Renal colic	3 (0.2)	3 (0.2)
Cholelithiasis	3 (0.2)	3 (0.2)
Transaminases increased	3 (0.2)	3 (0.2)
Vertigo	3 (0.2)	3 (0.2)
Head injury	2 (0.1)	3 (0.2)
Cerebrovascular accident	2 (0.1)	2 (0.1)
Coordination abnormal	2 (0.1)	2 (0.1)

Encephalopathy	2 (0.1)	2 (0.1)
Myoclonus	2 (0.1)	2 (0.1)
Depression	2 (0.1)	2 (0.1)
Hallucination	2 (0.1)	2 (0.1)
Suicidal ideation	2 (0.1)	2 (0.1)
Suicide attempt	2 (0.1)	2 (0.1)
Accidental overdose	2 (0.1)	2 (0.1)
Foot fracture	2 (0.1)	2 (0.1)
Bronchopneumonia	2 (0.1)	2 (0.1)
Gastritis	2 (0.1)	2 (0.1)
Gait disturbance	2 (0.1)	2 (0.1)
Non-cardiac chest pain	2 (0.1)	2 (0.1)
Hematuria	2 (0.1)	2 (0.1)
Tetany	2 (0.1)	2 (0.1)
Uterine leiomyoma	2 (0.1)	2 (0.1)
Liver function test abnormal	2 (0.1)	2 (0.1)
Trismus	2 (0.1)	2 (0.1)
Surgery	2 (0.1)	2 (0.1)
Diplopia	2 (0.1)	2 (0.1)
Dyspnea	2 (0.1)	2 (0.1)
Partial seizures with secondary generalizations	1 (<0.1)	2 (0.1)
Joint injury	1 (<0.1)	2 (0.1)
Sudden unexplained detain in epilepsy	1 (<0.1)	2 (0.1)
Biliary colic	1 (<0.1)	2 (0.1)
Cholecystitis	1 (<0.1)	2 (0.1)
Intervertebral disc protrusion	1 (<0.1)	2 (0.1)

Completed studies in Other Indications (Bipolar disorder D23129/8040)

No TESAEs reported in this study of 10 enrollees and 3 completers

Ongoing study in Post herpetic Neuropathic Pain, Study VRX-RET-E22-NP201

Study NP201 synopsis: this is a double blind, placebo controlled Phase 2a Proof of concept study to evaluate the efficacy of Maximally tolerated doses of ezogabine vs Placebo in Reducing pain associated with Post Herpetic Neuralgia. It is a multicenter study 46 centers in the US and 4 in South America. The trial consisted of a 21 day Screening Phase; a 1-week Baseline Phase; a double-blind Titration Phase up to 6 weeks to determine the MTD; a 4-week, double-blind Maintenance Phase; and a 3-week Taper Phase.

There were 187 patients randomized, 125 patients received ezogabine, 63 received placebo. Patients were to be stratified based on the number of PHN medications the patient was taking at the Baseline Visit (no medication or 1 medication); however, the stratification was instead based on the number of PHN medications the patients were taking at screening (0, 1, or ≥2 medications). The trial consisted of a 21-day Screening Phase; a 1-week Baseline Phase; a double-blind Titration Phase of up to 6 weeks to determine the MTD; a 4-week,

double-blind Maintenance Phase; and a 3-week Taper Phase. Once patients reached their MTD, they entered the Maintenance Phase. Once patients achieved their MTD during the Titration Period, they entered the Maintenance Phase.

Patients who met all eligibility criteria following the Screening and Baseline Phases were randomized at Day 0 to either ezogabine or placebo and entered the Titration Phase which lasted up to 6 weeks. During the Titration Phase, doses of ezogabine and matching placebo were escalated 1 dose level (150mg/day), once weekly in a blinded manner through a maximum of 6 dose levels, ranging from 150 mg/day to 900 mg/day. Patients who reached their MTD entered the Maintenance Phase, throughout which the dose of ezogabine or placebo was to remain fixed. However, if a patient experienced moderate-to-severe side effects, a decrease of 1 dose level was to be allowed during the first week of the Maintenance Phase.

Following the end of the Maintenance Phase, patients underwent final efficacy assessments prior to entering a 3-week Taper Phase. The ezogabine or placebo dose was reduced by one-third during each of the first 2 weeks of the Taper Phase; study medication was stopped no later than by the third week.

6 patients reported 10 TESAEs, reported in table 54, see section 7.3.5 “Submission Specific Primary Safety Concerns”, “ Cardiac Rhythm/Conduction Abnormalities” where there is discussion of 4 cases of atrial fibrillation compiled by the completion of this study, these cases, they are also presented in section 7.3.4 Significant Adverse Events-Cardiac.

Table 54 VRX-RET-E22-NP201 Ezogabine vs. Placebo in Post-Herpetic Neuralgia

Table 7.3-5	**VRX-RET-E22-NP201 Ezogabine vs. Placebo in Post-Herpetic Neuralgia**
Patient ID	**AE Preferred Term**
004-0004	Asthma
	Chronic obstructive pulmonary
	disease
016-0002	Atrial fibrillation
017-0006	Maculopathy
	Retinal detachment
025-0009	Clostridium difficile colitis
	Pneumonia
	Pulmonary embolism
042-0008	Atrial fibrillation
105-0012	Pneumonia

Study 3227-CU, Compassionate Use in Epilepsy

As of the submission cut-off date of 31 December 2008, out of 50 patients enrolled in Study 3227-CU, 5 patients reported a total of 7 non-fatal TESAEs: subluxation of hip, varicose vein surgery, lightheadedness, acute gastroenteritis, right side abdominal pain, hematuria, and community acquired pneumonia. All events resolved, or resolved with sequelae.

Clinical Pharmacology Studies

Five subjects reported single TESAEs in the Clinical Pharmacology studies (both integrated and non-integrated combined) (table 55). Two of the 469 (<1%) subjects in the Integrated Clinical Pharmacology Studies grouping reported a single TESAE (tooth abscess or hyperventilation).

Abuse potential Study VRX-RET-E22-108.

Two subjects experienced a TESAE (cardiac arrest/asystole and ventricular tachycardia) (CSR VRX-RET-E22-108). There was no evidence from telemetry recordings that either SAE was associated with QT changes. Both events resulted in withdraw from the study table 56.

Table 55 TESAEs in Clinical Pharmacology Studies (Safety Populations: All Clinical Pharmacology Studies [Integrated and Non-Integrated])

TESAEs in Clinical Pharmacology Studies (Safety Populations: All Clinical Pharmacology Studies [Integrated and Non-Integrated])						
Study	**Subject**	**RTG Dose**	**Preferred Term**	**Related?**	**Withdrawn ?**	**Outcome**
3065A1-107	0500006	400 mg BID	Extrasystoles	Y	Y	Recovered
3065A1-115	000047	Not reported	Tooth abscess	N	N	Recovered
3065 A1-117	00001	25 mg multiple dose	Hyperventilation	N	N	Recovered

Table 56 TESAEs in Abuse Potential Study

VRX-RET-E22-108	9077	900 mg single dose	Cardiac arrest/asystole	Y	Y	Recovered
VRX-RET-E22-108	9008	900 mg single dose	Ventricular tachycardia	Y	Y	Recovered

Salient features from the cases reports of cardiac rhythm disturbance, patients 0500061, and abuse potential study subjects 9077, 9008, these cases are presented here for reader convenience and again presented in relevant sections 7.3.4, Significant Adverse Effects- Cardiac and 7.3.5 “Submission Specific Safety Concerns”, Cardiac Rhythm/Conduction Abnormalities.

Subject 0500006; On [redacted] (b) (6) (Day 9), after having been titrated up to 300 mg every 12 hours, he was noted on telemetry to have a three beat run of wide complex tachycardia while sleeping. It resolved spontaneously without intervention. On [redacted] (b) (6) (Day 15), he reported intermittent episodes of feeling high and one episode of vasovagal while taking a shower. The event of feeling high resolved on [redacted] (b) (6) (Day 20). On [redacted] (b) (6) (Day 16), after having been titrated up to 400 mg every 12 hours, he reported a feeling of forgetfulness, sleepiness, non cardiac chest discomfort, palpitations, intermittent dizziness, intermittent lack of coordination, lightheadedness, chest tightness, blurred vision, and an altered mental state. On the same date, telemetry captured a three beat run of wide complex ectopy. The study drug was discontinued and he was observed on telemetry for seven additional days until the study was complete. No further events of cardiac ectopy occurred over the course of observation, so the patient was discharged to home.

Subject 9077: (female, 34 years of age) experienced an SAE of cardiac arrest 1.8 hours after receiving a single oral dose of ezogabine 900 mg. The subject had no significant findings on medical history or physical examination. The subject also had previous ECG findings of marked sinus bradycardia (down to 44 b/min on ECG assessments) and possible left atrial enlargement that were not considered clinically significant. The event consisted of a 25-second period (approximately) of asystole while in a semi-recumbent position, which resolved spontaneously. Five minutes after the event, the patient was conscious and able to speak. After the asystole, the heart rhythm returned to a junctional escape rhythm with a rate of between 50 and 60 beats/min. A cardiac stress echo test performed later in the hospital was within normal limits and all laboratory results, including electrolytes were within the normal reference ranges.

Subject 9008: (male, 41 years of age) exhibited asymptomatic episodes of brief nonsustained ventricular tachycardia on telemetry, 2.5 hours after receiving a single oral dose of ezogabine 900 mg. The subject had no clinically significant findings on medical history or physical examination. All previous ECGs and safety laboratory tests were normal. During the SAE, the subject experienced two 5 beat runs of wide complex ventricular tachycardia, and several minutes later experienced 3 more runs of ventricular tachycardia ranging from 3 to 8 beats, and finally several minutes after this experienced a longer run lasting 19 beats. The subject recovered without sequelae and was withdrawn from the study. A follow-up cardiology consultation showed normal results on ECG, echocardiogram, and stress test.

Summary: The pivotal controlled trial (RCT) grouping reveals an occurrence of 70 (8.6%) serious adverse events (SAE's) in the ezogabine treated subjects compared to 5.9% of the placebo group. In the all II/III combined group, any SAE

occurred in 216 (15.8%) of subjects. The top two preferred terms (PT) under which an SAE occurred were convulsion and psychotic disorder in both the RCTs and all phase II/III combined group. The PT convulsion as an SAE occurred in 12 (1.5%) of all ezogabine treated patients in the pivotal controlled trials and in 33 (2.4%) of all phase II and III trials combined. The PT psychotic disorder occurred in 6 (<1.0%) of ezogabine treated patients in the pivotal controlled trials and in 9 (<1%) of the all phase II and III trials combined. Among the remaining mix of SAEs there was no discernable difference between the dose ranges, all were less than 1% in occurrence. In the all phase II/III group, no SAE except convulsion occurred with a frequency greater than 1%.

In the pivotal controlled trial (RCT) grouping there was no clear dose response relationship to occurrence of serious adverse events (SAE). There were 23 (8.2) serious adverse events in the 600mg/day group, 18 (6.6) in the 900mg/day group and, 29 (11.2) in the 1200mg/day group, this outcome places the highest occurrence of SAEs in the highest dose group, the second highest in the lowest 600mg/day group and the lowest occurrence of SAEs in the middle or 900mg/day group. The occurrence of the highest SAE number in the highest dose group is supportive of a dose effect. The occurrence of the SAE, convulsion follows the same pattern.

When serious adverse events are examined within each study phase there is a trend for dose response in the titration phase with the 600mg/day and 900mg/day groups both showing 4% occurrence of SAEs and the 1200mg/day group showing an 8% occurrence of SAEs. In the maintenance phase no trend is observed. The 600mg/day group and 1200mg/day groups both have a 5% occurrence of SAEs. The mid-range, 900mg/day group has a lower 4% occurrence of SAEs. When serious adverse events are examined between study phases (titration-maintenance) there is evidence that SAEs decrease in the maintenance phase at the highest dose based on the occurrence of 8% SAEs at 1200mg/day in the titration phase and 5% occurrence of SAEs in maintenance phase. At the 900mg/day dose there is no difference between phases and at 600mg/day the maintenance phase has 1% higher occurrence of SAEs. The reduction in SAEs from titration to maintenance phase at the highest dose may be due to development of accommodation to the medication, which is seen commonly in use of anticonvulsants.

There were 5 SAEs reported by 5 subjects in the clinical pharmacology studies. Three of these were cardiac rhythm disturbances which is a cause of concern. In case 9077 (abuse potential study) the subject was a 34 yo female who experienced a 30 second period of asystole two hours after taking a 900mg dose of ezogabine. The patient (9077) had ezogabine and N-acetyl ezogabine levels obtained 15 minutes before the event, these were low relative to levels obtained previously where no adverse symptoms were observed. This subject also had bradycardia noted on ECG at screening and subsequent periods of the study. Case 9008 (abuse potential study) was a 41 yo male had two 5 beat runs of wide complex ventricular tachycardia approximately 2.5 hours following a 900mg dose

of ezogabine and subsequently 3 additional runs of ventricular tachycardia ranging in length from 3 to 8 beats. A final run of 19 beats was noted with no further abnormality. The patient was asymptomatic throughout. Both case 9077 and 9008 were participants in the abuse potential study and both had histories of multiple types of recreational drug use. Subject 0006 on two separate days, at 600mg/day and 800mg/day of ezogabine respectively had a three beat run of wide complex ventricular tachycardia. There was no hemodynamic compromise identified however the patent reported symptoms point to poor tolerance of the medication. Following titration to 400mg every 12 hours the patient reported feeling forgetful, sleepy, intermittently dizzy, intermittent poor coordination, lightheaded, chest tightness, blurred vision and an altered mental state.

In the post herpetic neuralgia study NP201 six patients reported 10 SAEs, two of these SAEs were atrial fibrillation, in two distinct patients. Case 016-0002 was a 73 yo female reported headache, poor balance, loss of appetite after reaching dose level 3, 150mg ezogabine three times daily. She subsequently requested discontinuation and was found by ECG to have atrial fibrillation the day following her last dose of ezogabine. She subsequently had successful cardioversion. Diagnostic evaluation revealed acute diastolic congestive heart failure. In the second case, subject 042-008, an 84 yo male, who had symptoms of shortness of breath, lightheadedness, dizziness, and palpitations for two weeks. He had discontinued his study medication about 6 days after developing this symptom complex at dose of 200mg TID (dose level 4). Eight days later at the scheduled study visit the patient was found to have atrial fibrillation. The patient was chemically cardioverted and on further evaluation found to have total occlusion of the left anterior descending coronary artery.

Reviewer Comment: review of the serious adverse events reveals the frequency of convulsion and cardiac dysrhythmia to be areas of concern. Both categories of adverse events are confounded and not clearly a safety signal for ezogabine. Convulsion is an event which will occur as a background event in a study of refractory epilepsy patients. There was a small gradient between placebo and all ezogabine treated patients in the pivotal controlled trials. Among the cardiac dysrhythmias, two of the cases of ventricular dysrhythmias occurred in the abuse potential study, this raise the possibility that these events are confounded by the physiologic effect of prior recreational drug exposure and differences in lifestyle form typical healthy subjects. Temporal relationship to the ezogabine dose adds weight to the events as ezogabine related. Only one case of ventricular dysrhythmias occurred in a healthy volunteer, a bioavailability study, in this case the events were least threatening, 2 three beat runs of ventricular tachycardia. Among the two cases of atrial fibrillation in study NP201 (post herpetic neuralgia) one is clearly confounded by serious coronary artery disease. The second case is however likely related to the study drug. There is a possible safety signal for cardiac rhythm disturbance; ezogabine relationship to convulsion may require post marketing scrutiny.

7.3.3 Dropouts and/or Discontinuations

Pivotal Controlled Trials –RCT (Studies 205, 301 and 302)

TEAEs led to discontinuation of 11% of patients in the placebo group and 25% of patients in the Total RTG group (table 57). Among the ezogabine dose groups, TEAEs leading to discontinuation were reported for 11%, 17%, 25%, and 31% of the placebo group, 600, 900, and 1200 mg/day groups, respectively.

The individual AEs that most frequently (>2% in Total RTG group) led to discontinuation were dizziness, confusional state, somnolence, and fatigue. There appeared to be a ezogabine dose relationship for discontinuations due to dizziness and confusional state as also shown in table 57.

Table 57 TEAEs Leading to Discontinuation Reported by >2% of Patients in Any Treatment Group By Preferred Term (Safety Population: RCT, Studies 205, 301, and 302)

	TEAEs Leading to Discontinuation Reported by >2% of Patients in Any Treatment Group By Preferred Term (Safety Population: RCT, Studies 205, 301, and 302)				
	Number (%) of Patients				
Preferred Term	**Placebo (N=427)**	**RTG 600 mg/day (N=281)**	**RTG 900 mg/day (N=273)**	**RTG 1200 mg/day (N=259)**	**RTG Total (N=813)**
Any event leading to d/c	**45 (10.5)**	**49 (17.4)**	**69 (25.3)**	**81 (31.3)**	**199 (24.5)**
Dizziness	5 (1.2)	9 (3.2)	16 (5.9)	21 (8.1)	46 (5.7)
Confusional state	4 (<1.0)	4 (1.4)	8 (2.9)	20 (7.7)	32 (3.9)
Somnolence	4 (<1.0)	7 (2.5)	13 (4.8)	8 (3.1)	28 (3.4)
Fatigue	1 (<1.0)	9 (3.2)	12 (4.4)	6 (2.3)	27 (3.3)
Vertigo	4 (<1.0)	5 (1.8)	5 (1.8)	6 (2.3)	16 (2.0)
Coordination abnormal	3 (<1.0)	2 (<1.0)	5 (1.8)	9 (3.5)	16 (2.0)
Disturbance in attention	0	3 (1.1)	5 (1.8)	6 (2.3)	14 (1.7)
Headache	2 (<1.0)	3 (1.1)	5 (1.8)	6 (2.3)	14 (1.7)
Tremor	0	1 (<1.0)	4 (1.5)	7 (2.7)	12 (1.5)
Dysarthria	0	3 (1.1)	1 (<1.0)	6 (2.3)	10 (1.2)
Convulsion	7 (1.6)	2 (<1.0)	1 (<1.0)	6 (2.3)	9 (1.1)

The pattern of distribution for the overall incidence of TEAEs leading to premature withdrawal by time to first occurrence was similar among treatment groups, table 58. During the first week of therapy, the overall incidence of TEAEs leading to premature withdrawal was 3% in the placebo group and ranged from 4% to 7% in the ezogabine groups. Overall incidence of onset of new events leading to premature withdrawal was lower in each treatment group during the second week of therapy and then increased during Weeks 2 to <4 and Weeks 4 to <8. Thereafter, the incidence of onset of new events leading to premature withdrawal declined in each treatment group, table 58.

Most of the TEAEs leading to premature withdrawal had first onset within the first 12 weeks of therapy (range: 93% [placebo] to 99% [ezogabine 900 mg]). In the total RTG group, of the 199 patients who withdrew due to AEs, 117 (59%) patients discontinued within the first 4 weeks of therapy and 191 (96%) within 12 weeks of therapy.

Table 58 Overall Incidence of TEAEs Leading to Premature Withdrawal by Time to First Occurrence (Safety Population: RCT, Studies 205, 301, and 302)- Any Event

	Overall Incidence of TEAEs Leading to Premature Withdrawal by Time to First Occurrence (Safety Population: RCT, Studies 205, 301, and 302)- Any Event				
	n/N (%) of Patients				
		RTG			
Time to first occurrence		**600**	**RTG**	**RTG**	**RTG**
(Days/Weeks)	**Placebo**	**mg/day**	**900 mg/day**	**1200 mg/day**	**Total**
1 to < 8 (up to Wk 1)	12/427 (2.8)	14/281 (5.0)	19/273 (7.0)	9/259 (3.5)	42/813 (5.2)
8 to < 14 (Wks 1 to <2)	2/418 (<1.0)	3/274 (1.1)	6/265 (2.3)	7/254 (2.8)	16/793 (2.0)
14 to < 28 (Wks 2 to <4)	9/411 (2.2)	16/270 (5.9)	20/262 (7.6)	23/249 (9.2)	59/781 (7.6)
28 to < 56 (Wks 4 to <8)	15/406 (3.7)	9/263 (3.4)	18/246 (7.3)	31/237 (13.1)	58/746 (7.8)
56 to <84 (Wks 8 to <12)	4/384 (1.0)	5/237 (2.1)	5/218 (2.3)	6/194 (3.1)	16/649 (2.5)
84 to < 182 (Wks 12 to <26)	3/366 (<1.0)	2/266 (<1.0)	1/205 (<1.0)	5/172 (2.9)	8/603 (1.3)
182 to < 273 (Wks 26 to <39)	0/14 (0)	0/2 (0)	0	0/10 (0)	0/12 (0)

Withdraw by study phase (RCT)

Titration Phase (table 59): examination of TESAEs in RCTs leading to withdraw in 1% or greater of total ezogabine treatment patients during titration phase reveals that central nervous system events are most prominent. Dizziness in the leading cause of withdraws, occurring in 4.7% of patients in the total ezogabine treatment, with a dose response noted. There were 5 (1.2%), 7(2.5%), 14(5.1%) and 17(6.6%) withdrawals in the placebo, 600mg, 900mg and 1200mg groups respectively. A dose response was also noted in withdrawal due to confusional state, coordination abnormal, disturbance in attention, and tremor. Non central nervous system TESAEs leading to withdraw in 1% or greater of total ezogabine treatment patients were headache, nausea, vision blurred, and diplopia. Events of special interest which occurred during titration phase but in frequency less than 1% of total ezogabine treatment were convulsion 6 (0.7%) of total ezogabine treatment with no dose response, hallucination, visual 2 (0.2%) and atonic urinary bladder 1(0.1%). There were no cases of transaminase increase or urinary retention.

Maintenance Phase (table 60): During maintenance phase there were only two preferred terms with TESAEs with a greater than 1% occurrence of the total ezogabine treatment group, these were dizziness and fatigue. There was a dose response seen in dizziness with 0, 2 (0.8%), 2 (0.9%), 3 (1.6%) cases in the placebo, 600mg, 900mg and 1200mg groups respectively. SAEs of dizziness as a percent of the total ezogabine treatment group decreased from 4.7% in titration phase to 1.1% in maintenance phase. Fatigue cases also decreased from 2.5% in titration phase to 1.1% in maintenance phase. There were occurrences of serious adverse events of special interest leading to withdrawal, these include hallucinations, visual with 3(0.5%) group, transaminases increased 2(0.3%) and urinary retention 1(0.2%) occurrences in the total ezogabine treatment group. There were no transaminase increased in the placebo group and there was 1 urinary retention in the placebo group. There were no urinary retention or transaminase increased SAEs to withdrawal in the titration phase, there was an increase in the occurrence of hallucination, visual from 2 (0.2%) in titration phase to 3(0.5%) in maintenance phase. There were no hallucinations, visual in either titration or maintenance phase in placebo group.

The spectrum and overall numbers of TESAEs leading to withdraw is greater in titration phase. As an example in the ezogabine treatment group, dizziness declines from 4.7% of withdrawals in titration phase to 1.1% in maintenance phase. Fatigue also decreases from 2.5% to 1.1%. 12 categories (preferred terms) of SAEs leading to withdrawal in greater than 1% of the total ezogabine group in titration phase drop to below 1.0% in maintenance phase. These events include confusional state, somnolence, coordination abnormal, vertigo, disturbance in attention, headache, tremor, dysarthria, memory impairment, speech disorder, nausea, vision blurred, and diplopia. One category of special interest, (hallucinations, visual) increased in frequency during maintenance phase. Atonic urinary bladder did not occur in maintenance phase but urinary retention did appear as one SAE to withdrawal. One case of transaminase increased, occurs in maintenance phase but none are present in titration.

Table 59 TESAEs leading to withdrawal by preferred term, Titration Phase, Pivotal Controlled Trials, study 205, 301, 302 combined

table of events in titration phase	placebo (n=427)	600 mg/day (n=281)	900 mg/day (n=273)	1200 mg/day (n=259)	total (n=813)
any event	30/427 (7.0%)	37 / 281 (13.2%)	51 / 273 (18.7%)	63 / 259 (24.3%)	151 / 813 (18.6%)
dizziness	5 / 427 (1.2%)	7 / 281 (2.5%)	14 / 273 (5.1%)	17 / 259 (6.6%)	38 / 813 (4.7%)
confusional state	4 / 427 (0.9%)	4 / 281 (1.4%)	6 / 273 (2.2%)	17 / 259 (6.6%)	27 / 813 (3.3%)
somnolence	2 / 427 (0.5%)	7 / 281 (2.5%)	12 / 273 (4.4%)	6 / 259 (2.3%)	25 / 813 (3.1%)
fatigue	1 / 427 (0.2%)	3 / 281 (1.1%)	12 / 273 (4.4%)	5 / 259 (1.9%)	20 / 813 (2.5%)
coordination abnormal	2 / 427 (0.5%)	2 / 281 (0.7%)	5 / 273 (1.8%)	9 / 259 (3.5%)	16 / 813 (2.0%)
vertigo	2 / 427 (0.5%)	5 / 281 (1.8%)	5 / 273 (1.8%)	4 / 259 (1.5%)	14 / 813 (1.7%)

table of events in titration phase	placebo (n=427)	600 mg/day (n=281)	900 mg/day (n=273)	1200 mg/day (n=259)	total (n=813)
disturbance in attention	0 / 427	1 / 281 (0.4%)	4 / 273 (1.5%)	5 / 259 (1.9%)	10 / 813 (1.2%)
headache	1 / 427 (0.2%)	2 / 281 (0.7%)	4 / 273 (1.5%)	4 / 259 (1.5%)	10 / 813 (1.2%)
tremor	0 / 427	1 / 281 (0.4%)	4 / 273 (1.5%)	5 / 259 (1.9%)	10 / 813 (1.2%)
dysarthria	0 / 427	3 / 281 (1.1%)	1 / 273 (0.4%)	5 / 259 (1.9%)	9 / 813 (1.1%)
memory impairment	0 / 427	2 / 281 (0.7%)	4 / 273 (1.5%)	3 / 259 (1.2%)	9 / 813 (1.1%)
speech disorder	0 / 427	1 / 281 (0.4%)	5 / 273 (1.8%)	3 / 259 (1.2%)	9 / 813 (1.1%)
nausea	2 / 427 (0.5%)	2 / 281 (0.7%)	4 / 273 (1.5%)	3 / 259 (1.2%)	9 / 813 (1.1%)
Vision blurred	0 / 427	0 / 281	5 / 273 (1.8%)	3 / 259 (1.2%)	8 / 813 (1.0%)
Diplopia	0 / 427	0 / 281	5 / 273 (1.8%)	4 / 259 (1.5%)	8 / 813 (1.0%)
convulsion	5 / 427 (1.2%)	1 / 281 (0.4%)	1 / 273 (0.4%)	4 / 259 (1.5%)	6 / 813 (0.7%)
hallucination, visual	0 / 427	0 / 281	0/273	2/259 (0.8%)	2/813 (0.2%)
Atonic urinary bladder	0 / 427	0 / 281	1 / 273 (0.4%)	0 / 259	1 / 813 (0.1%)

Table 60 TESAEs leading to withdrawal by preferred term, Maintenance Phase, Pivotal Controlled Trials, study 205, 301, 302 combined

table of events in maintenance phase	placebo (n=427)	600 mg/day (n=281)	900 mg/day (n=273)	1200 mg/day (n=259)	total (n=813)
any event	15 / 383 (3.9%)	15 / 243 (6.2%)	19 / 226 (8.4%)	19 / 189 (10.1%)	53 / 658 (8.1%)
dizziness	0 / 383	2 / 243 (0.8%)	2 / 226 (0.9%)	3 / 189 (1.6%)	7 / 658 (1.1%)
fatigue	0 / 383	6 / 243 (2.5%)	0 / 226	1 / 189 (0.5%)	7 / 658 (1.1%)
transaminases increased	0 / 383	0 / 243	1 / 226 (0.4%)	1 / 189 (0.5%)	2 / 658 (0.3%)
Urinary Retention	1 / 383 (0.3%)	0 / 243	1 / 226 (0.4%)	0 / 189	1 / 658 (0.2%)

Reviewer Comment: This comparative profile of TESAEs in RCTs leading to withdrawal in titration and maintenance phase suggests that the predominant central nervous system adverse events become less common due to development of tolerance or alternatively, the susceptible individuals are eliminated early due to dropout. Two adverse events of special interest, with one case each, transaminase increased and urinary retention emerges during maintenance phase. This suggests that sustained exposure to ezogabine may be needed before the adverse event is produced.

All Phase II/III Combined

In the All Phase II/III Combined studies, TEAEs leading to discontinuation were reported by 418 of 1365 (31%) ezogabine-treated patients. The most frequently reported TEAEs leading to discontinuation in the All Phase II/III Combined grouping were dizziness (71/1365, 5%), somnolence (58/1365, 4%), confusional state (49/1365, 4%), fatigue (43/1365, 3%), and disturbance of attention (27/1365, 2%). All other TEAEs leading to discontinuation were reported for <2% of patients.

Reviewer Comment: The profile of adverse events in the placebo controlled trials is similar to the all phase II/III group with nervous system and psychiatric related adverse effects most frequent. The high frequency events are in the spectrum seen commonly in anticonvulsant drugs, these include nervous and psychiatric disorders. This is reasonably expected due to the neural target of the anticonvulsant drugs. A typical gastrointestinal effect, nausea, is not seen in high numbers, eye disorders of diplopia and blurred vision are very likely secondary to the nervous system impact, rather than a primary ocular or ocular muscle phenomena.

7.3.4 Significant Adverse Events

Events In This Section Will Be Grouped By Medical Topic, then titled by event name.

Urology

Urinary Retention with Incomplete recovery, Case VRX-RET-E22-303-03505:

Only the most important elements of patient 03505 urinary retention safety report are presented in this section, however the summation of all IND safety reports is presented in appendix 9.7.

Patient # 03505 was a 30 yo Caucasian male on 1200mg ezogabine in open label continuation study developed psychomotor agitation, urinary retention and a respiratory infection. A foley catheter was inserted in the emergency room (January 3, 2008) and 1200ml of urine was evacuated and the patient was hospitalized. The case summary indicates a neuropsychiatric change captured by the following two sentences: *he reported heightened anxiety and anxiousness with large amplitude, involuntary, bilateral leg movement with the inability to sit still and feeling as if he needed to escape from the car. The patient was very agitated, crying and emotional which led to hospitalization and discontinuation of study drug treatment.*

Additional information received reveals the patient had experienced approximately 18 hours of progressive urinary retention before seeking treatment in the emergency department of a community hospital. At the time the patient was agitated and in acute distress.

Study drug was reduced to 1050 mg/day on (b) (6) (Day 55) and stopped on (b) (6) (Day 83). On (b) (6) (Day 71), a bladder ultrasound revealed 122 cc of retained urine and on (b) (6) (Day 81) another ultrasound revealed 900 cc of retained urine in his bladder.

After an initial urologic consultation the patient followed up with another (new) urologist for urodynamic studies performed on (b) (6) (approximately 11 weeks post event). The patient informed the urologist that four or five times a day, he would experience a "strong urge" to void but had difficulty urinating. His urine stream would "end prematurely" and "sputter". The urodynamic study demonstrated normal bladder compliance, but no EMG activity during filling of the bladder. The patient experienced a sensation of fullness upon filling and no leak was present during cough or valsalva maneuvers. However, the patient was unable to void (voided volume was Oml, PVR was 882ml. Detrusor contraction was not sustained. The findings were reported to be consistent with a neurogenic bladder.

(b) (6) (21 months post event): Additional information received from the PI confirmed the patient is stable with sequelae of self – catheterization

Renal Failure

Search of the case narratives for the term renal failure reveals two cases of renal failure. These are also found in the AE (adverse event dataset), one case (0448) captured by the term “renal failure” in the PTNAME column, the second captured by the term “renal failure acute” (study 208, case 000017). Case 3065 A1-05~000032~000448 is described below in “hepatic / urinary dual event” and in appendix 9.11. Case 3065 A1-208~020879~000017 will be described below.

3065 A1-208~020879~000017: a 21 yo female enrolled in study 3065 A1-208 an open label, long-term safety, tolerability and efficacy study. Ezogabine therapy began on 2/28/01. concomitant medication; patient had been on 1200mg ibuprofen BID for about six months. Approximately (b) (6) the patient developed right flank pain while on ezogabine 1200mg a day. This was treated with Bactrim as a urinary tract infection, however the patient developed an allergic reaction. The patient discontinued ezogabine on (b) (6). Pain continued until (b) (6) when she noted increasing right flank pain radiating to the anterior abdomen. Patient was hospitalized, it is noted that a CT of the kidneys was performed revealing swelling of the right kidney. Patient was begun on amoxicillin and Percocet and discharged from the hospital. Pain continued with vomiting. In addition the patient became anuric for 12 hours. Bladder catheter was placed yielding only a small amount of bloody urine.

Laboratory studies: WBC 16.1 cu/mm (units not given), BUN 23 mg/dl, creatinine 3.8mg/dl. Electrolytes normal. Patient hospitalized and subsequently treated with phenergan and Dilaudid. A renal ultrasound performed revealed symmetric kidney size at 11.8cm. There was mild fullness of the right kidney. Patient recovered and was discharged from hospital on (b) (6). the recovery course suggests a positive dechallenge.

Reviewer Comment: among the cases of urinary retention case 03505 is the only case with apparent permanent sequelae. The patient suffered a change in mental status/ psychosis which may have delayed his response to the developing urinary retention. It is possible that the delay resulted in the apparent permanent need for self catheterization. The history suggests the patient had significant head trauma from a motorcycle accident in light of the subsequently development of refractory epilepsy and treatment with a vagal nerve stimulator. There is no indication in the case narrative that the patient had a pre-existing psychiatric diagnosis. This intersection of the sequelae of severe brain trauma and psychosis during treatment with ezogabine raise the possibility that certain types of cerebral substrate may be more sensitive to the neuropsychiatric side effects of ezogabine.

Two cases of renal failure are identified, 0448 likely due to an obstructive uropathy due to bladder dysfunction, case 0017 is of uncertain cause. No renal calculi was identified. The patient became anuric but no excessive bladder volume was identified. This may have been an analgesic nephropathy.

Hematology

Aplastic Anemia, Patient 3065 A1-216~000001~000002 pateints)begins ezogabine on (b) (6) with a hemoglobin, platelets and absolute neutrophil count all in the low normal range and WBC count mildly depressed. Approximately two months after beginning ezogabine the patient develops a moderate depression of thrombocytes, granulocytes and erythrocytes with a reticulocytosis in the setting of an acute infectious illness. This temporal profile indicates the infection preceded the depression of hematopoiesis. The patient was hospitalized on (b) (6) for productive cough, vomiting, diarrhea, headache and sore throat and fever 102.8F. Bone marrow biopsy was performed with report stating “hypocellular” without further details. There is improvement in hemoglobin and WBC count and normalization of platelets over 4 days between (b) (6). During this interval the patient had pancytopenia but at no point did the patient meet criteria for severe aplastic anemia, table 61[7,8]. The patient was discharged on (b) (6) The patient was continued on ezogabine for an additional two months before study withdrawal. The last dose of ezogabine on (b) (6) was given three months following the event of (b) (6). A follow up CBC 2 months after last ezogabine dose reveals normal hemoglobin but moderately depressed WBC and platelet count.

7 Issaragrisil S et.al. and the Aplastic Anemia Study Group. Incidence of Aplastic Anemia in Bangkok. Blood 1991;77:p2166-2168
8 Montane E, et. al. Epidemiology of aplastic anemia: a prospective multicenter study. Haematologica 2008;93: p518-523.

Reviewer Comment: This case is most consisted with chronic background pancytopenia of uncertain etiology, based on history of prior history of depressed RBC, WBC and platelets in 1999 as well as low RBC and WBC at study baseline. This was likely exacerbated by an acute infectious illness on (b) (6). A responsive bone marrow is indicted by reticulocytosis noted on (b) (6) and a rapid rebound of platelets and partial rebound of RBC by (b) (6). The patient is maintained on ezogabine for an additional two months until study withdraw on (b) (6) due to continuation of bone marrow depression. Following ezogabine withdrawal there is a negative dechallenge, the granulocytic line and platelets remain depressed 2 months following withdrawal of ezogabine. .

A clear causal relationship to ezogabine is not established based on the negative dechallenge, mild baseline depression of RBC and WBC count and acute infectious illness at the time of pancytopenia onset.

Table 61 Hematology parameters by date of case 3065 A1-216~000001~000002

	Hb	Hct	RBC	WBC	Neurtophils	Lymphs.	Plt		ESR
NL	120-156g/l	0.35-0.46 L/L	3.9-5.2 10^12/L	3.8-10.8 10^9/L	1.52-8.1 10^9/L	0.6-4.9 10^9/L	130-400 10^9/L		
Baseline									
Date									
(b) (6)	120	.352	3.6	3.6	1.67	1.29	139		
Onset Acute Pneumonia									
	Hb	Hct	RBC	WBC	Granulocyte	Lymphs	Plts		
NL	12-16 g/dL	37-47 %	4.2-5.4 X 10 (6)	4.8-10.8 X 10(3)	1.4-.6.5 X 10 (3)	1.2-3.4 X 10 (3)	130-400 X10 (3)		
Date									
(b) (6)	10	26.8	2.69	7.2	5.9	0.5	117		
Hospitalization									
	Hb	Hct	RBC	WBC	Neutrophils	Lymphs	Plts	Reticulocyte uncorrected	
NL	12.5-16 g/dL	37-47%	4.2-5.4 m/mm3	4.0-10.5 k/mm3	1.8-7.8k/mm3	1.0-4.8k/mm3	140-440 k/mm3	0.3-2.8%	
(b) (6)	7.5	20.9	2.06	3.8	1.2	0.7	122	3.9	58mm/hr
	8.7	25	2.46	2.2			123		
	8.7	24.5	2.4	2.2			134		
	9.6	27.0	2.66	2.4			151		
Follow up 2 months after Study drug discontinued									
	Hb	Hct	RBC	WBC	Neutrophils	Lymphs	Plts		
NL	7.45-9.7 mmol/L	0.35-0.46 L/L	3.9-5.2 10^12/L	3.8-10.8 10^9/L			130-400 10^9/L		
(b) (6)	7.2	0.32	3.1	2.3			122		

Asystole: case VRX-RET-E22-108: Subject 9077: (female, 34 years of age) experienced an SAE of cardiac arrest 1.8 hours after receiving a single oral dose of ezogabine 900 mg. The subject had no significant findings on medical history or physical examination. The subject also had previous ECG findings of marked sinus bradycardia (down to 44 b/min on ECG assessments) and possible left atrial enlargement that were not considered clinically significant. The event consisted of a 25-second period (approximately) of asystole while in a semi-recumbent position, which resolved spontaneously. Five minutes after the event, the patient was conscious and able to speak. After the asystole, the heart rhythm returned to a junctional escape rhythm with a rate of between 50 and 60 beats/min. A cardiac stress echo test performed later in the hospital was within normal limits and all laboratory results, including electrolytes were within the normal reference ranges.

Ventricular Tachycardia: Case VRX-RET-E22-108: Subject 9008: (male, 41 years of age) exhibited asymptomatic episodes of brief nonsustained ventricular tachycardia on telemetry, 2.5 hours after receiving a single oral dose of ezogabine 900 mg. The subject had no clinically significant findings on medical history or physical examination. All previous ECGs and safety laboratory tests were normal. During the SAE, the subject experienced two 5 beat runs of wide complex ventricular tachycardia, and several minutes later experienced 3 more runs of ventricular tachycardia ranging from 3 to 8 beats, and finally several minutes after this experienced a longer run lasting 19 beats. The subject recovered without sequelae and was withdrawn from the study. A follow-up cardiology consultation showed normal results on ECG, echocardiogram, and stress test.

Ventricular Tachycardia: case 3065A1-107, Subject 0500006; On (b) (6) (Day 9), after having been titrated up to 300 mg every 12 hours, he was noted on telemetry to have a three beat run of wide complex tachycardia while sleeping. It resolved spontaneously without intervention. On (b) (6) (Day 15), he reported intermittent episodes of feeling high and a vasovagal episode while taking a shower. The event of feeling high resolved on (b) (6) (Day 20). On (b) (6) Day 16), after having been titrated up to 400 mg every 12 hours, he reported a feeling of forgetfulness, sleepiness, non cardiac chest discomfort, palpitations, intermittent dizziness, intermittent lack of coordination, lightheadedness, chest tightness, blurred vision, and an altered mental state. On the same date, telemetry captured a three beat run of wide complex ectopy. The study drug was discontinued and he was observed on telemetry for seven additional days until the study was complete. No further events of cardiac ectopy occurred over the course of observation, so the patient was discharged to home.

Atrial Fibrillation 4 cases Study NP201

These 4 cases are presented here to capture and highlight all high impact cases that influence risk and labeling, however they are also present later in the section 7.3.5 "Submission Specific Primary Safety Concerns", in the context of "Cardiac Rhythm/Conduction Abnormalities"

SAE & Withdrawal

Patient 016-002: A 73 year old female with a history of borderline hypertension and a non-symptomatic heart murmur was randomized to receive 150 mg of ezogabine TID and began taking study medication on 16 October 2008. She developed palpitation symptoms on 6 November. On (b) (6) she the subject had an onset of extreme tiredness, feeling off balance, loss of appetite, and dry mouth was admitted with a diagnosis of atrial fibrillation with rapid ventricular response. The patient commenced Norvasc (amlodipine) for hypertension approximately one week before presentation (b) (6) The event was considered an SAE and led to withdrawal from the study. The investigator considered the atrial fibrillation to be related to study drug.

Patient 042-008: An 84 year-old Caucasian male with a 20 year history of tobacco use and no history of atrial fibrillation or coronary disease was randomized to receive 200 mg of ezogabine TID and began taking study medication on 7 October 2008. On (b) (6) he presented with a 2 week history of fatigue, shortness of breath, lightheadedness, dizziness, and palpitations and was found to be in AF with a rate of 112 beats per minute. A coronary angiogram on (b) (6) revealed chronic total occlusion of the left anterior descending artery. The atrial fibrillation was considered serious, and the investigator did not consider it to be related to study medication.

AE (adverse event) Only

Patient 025-009: A 77 year-old Caucasian male with no prior cardiac history was randomized to receive 150 mg of ezogabine TID and began taking study medication on 23 September 2009. On (b) (6), he was admitted to the hospital intensive care unit due to nausea, vomiting and fever, but no diarrhea. Upon stool culture clostridium difficile colitis was diagnosed. An ECG on (b) (6) showed atrial fibrillation with a ventricular rate of 115 beats per minute. The investigator confirmed that the subject had no prior cardiac history and the atrial fibrillation and congestive heart failure were not considered serious adverse events.

Patient 042-0007: An 84-year-old Caucasian female with a history of diabetes, overactive bladder and osteoporosis was randomized to receive 200 mg of ezogabine TID and began taking study medication on 25 September 2008. On (b) (6) she presented to the emergency room with palpitations. ECG showed atrial fibrillation with rapid ventricular response, left axis deviation and minimal voltage criteria for left ventricular hypertrophy (LVH) with a ventricular rate of 125. Chest x-ray demonstrated cardiomegaly, COPD and right basilar atelectasis. The patient spontaneously converted back to sinus rhythm while in the emergency room and was

not admitted. The investigator considered the event of atrial fibrillation possibly related to the study medication.

Hepatic / Urinary Dual Adverse Event Case

Patient 3065 A1-205~000032~000448: a 53 yo female suffered with acute renal failure likely due to obstructive uropathy. First symptom occurred 23 days after beginning therapy while on 600mg ezogabine a day. The patient had myalgia, cough, polydipsia and sweats. Laboratory studies revealed increased ALT,AST, Creat, Bilirubin and CRP (328, normal range <12). Patient was hospitalized, on bladder catheterization found to have 1500ml cloudy urine. Ezogabine discontinued and patient discharged from hospital one week later. Patient on concomitant valproic acid 1000mg daily and carbamazepine 800mg daily. See appendix 9.11 for timeline of laboratory studies.

7.3.5 Submission Specific Primary Safety Concerns

Urinary Tract Disorders

Background

Effects of ezogabine on the urinary tract and bladder function were first noted in nonclinical safety studies. In these studies, rodents chronically exposed to ezogabine developed distended urinary bladders likely as a result of ezogabine-induced inhibition of bladder contraction. Some animals were observed to have renal lesions thought to be due to increased mechanical back pressure because of inability to empty their bladders. These effects on bladder function are thought to be due to the pharmacological action of ezogabine at specific KCNQ channels expressed in urinary bladder smooth muscle. The findings in the toxicology studies were investigated with in vitro studies in rodent bladder myocytes and models of bladder hyperexcitability. The in vitro studies also suggested that ezogabine could inhibit micturition.

The nonclinical safety findings have been extensively evaluated during the clinical program. The potential effect of ezogabine on urinary bladder function in humans has been assessed by tracking of renal and urinary AEs and serial collection of American Urological Association Symptom Index (AUA SI) scores and post-void residual bladder ultrasounds during the Phase III program. During a teleconference which took place in May 2007, FDA requested that urinary-bladder SAEs be evaluated by a qualified medical specialist.

In study 205 the AUA symptom index (appendix 9.9) was performed at study day 1 and visit 9 (day 112). In study 301 the AUA symptom index was performed on visit 3 (day 0), visit 6 (day 42), visit 10 (day 70), and visit 11 (day 126) and final visit 16 (day 154). Urinalysis was performed at day 0 and each visit during controlled trial and post void residual volume was performed at visit 3 (day 0), visit 9 (day 70), visit 11 (day 126) and visit 16 (day 154) –final. In study 302 the AUA symptom index was performed at visit 3

(day0), visit 7 (day 84), visit 9 (day112), and visit 13 (day140)-final. These parameters were also assessed periodically during the open label extension studies. The lower threshold defining abnormal residual urine volume, a value needed to provide context for the following discussion, is between 50ml and 100ml[9].

RCTs (Pivotal Controlled Trials)

During the double-blind phase of randomized controlled trials, renal and urinary disorders AEs were reported for greater proportions of patients in the Total RTG group than the placebo group (17% versus 12.9%). The relative risk of reporting a renal/urinary disorder in the Total RTG group was 1.32, with a 95% confidence interval of 0.986, 1.761. The relative risk of reporting an event in each of the dose groups was as follows: 600 mg/day group was 1.05 (95% CI 0.714, 1.543); 900 mg/day was 0.995 (95% CI 0.67, 1.478); and 1200 mg/day was 1.948 (95% CI 1.409, 2.695).

The most common renal and urinary disorder AEs in the Total RTG group were urinary tract infection (4.3% vs 4.7%), dysuria (2.3% versus 0.7%), urinary hesitation (2.2% versus 0.9%), chromaturia (1.6% versus 0.2%), hematuria (1.6% versus 0.7%) and urine analysis abnormal (1.6% versus 0.9%), table 62.

Table 62

	Adverse Events of Renal/Urinary Disorders Reported by 2 or more Patients in Any Treatment Group (Safety Population: RCT, Studies 205, 301, and 302)				
	Number (%) of Patients				
	Placebo N=427	**Ezogabine**			
Preferred Term		**600 mg/day (N=281)**	**900 mg/day (N=273)**	**1200 mg/day (N=259)**	**Total (N=813)**
Any event	**55 (12.9)**	**38 (13.5)**	**35 (12.8)**	**65 (25.1)**	**138 (17.0)**
Urinary tract infection	20 (4.7)	5 (1.8)	9 (3.3)	21 (8.1)	35 (4.3)
Dysuria	3 (0.7)	4 (1.4)	5 (1.8)	10 (3.9)	19 (2.3)
Urinary Hesitation	4 (0.9)	6 (2.1)	3 (1.1)	9 (3.5)	18 (2.2)
Chromaturia	1 (0.2)	2 (0.7)	4 (1.5)	7 (2.7)	13 (1.6)
Hematuria	3 (0.7)	6 (2.1)	3 (1.1)	4 (1.5)	13 (1.6)
Urine analysis abnormal	4 (0.9)	2 (0.7)	3 (1.1)	8 (3.1)	13 (1.6)
Polyuria	7 (1.6)	2 (0.7)	3 (1.1)	6 (2.3)	11 (1.4)
Residual urine volume	1 (0.2)	0	4 (1.5)	4 (1.5)	8 (1.0)
Urinary Retention	2 (0.5)	1 (0.4)	4 (1.5)	2 (0.8)	7 (0.9)
Nephrolithiasis	0	0	0	4 (1.5)	4 (0.5)
Bacteriuria	1 (0.2)	2 (0.7)	1 (0.4)	0	3 (0.4)
Leukocyturia	2 (0.5)	3 (1.1)	0	0	3 (0.4)
Proteinuria	3 (0.7)	3 (1.1)	0	0	3 (0.4)

9 Kelly CE. Evaluation of Voiding Dysfunction and Measurement of Bladder Volume. Rev Urol. *2004;6(suppl 1):S32-S3.*

	Adverse Events of Renal/Urinary Disorders Reported by 2 or more Patients in Any Treatment Group (Safety Population: RCT, Studies 205, 301, and 302)				
	Number (%) of Patients				
	Placebo N=427	Ezogabine			
Preferred Term		600 mg/day (N=281)	900 mg/day (N=273)	1200 mg/day (N=259)	Total (N=813)
Renal Colic	1 (0.2)	0	2 (0.7)	1 (0.4)	3 (0.4)
Urine flow decreased	2 (0.5)	1 (0.4)	0	1 (0.4)	2 (0.2)
Micturition frequency decreased	0	2 (0.7)	0	0	2 (0.2)
Micturition urgency	3 (0.7)	0	0	1 (0.4)	1 (0.1)
Pollakiuria	2 (0.5)	0	0	0	0
Urine sediment present	2 (0.5)	1 (0.4)	0	0	1 (0.1)

When the most common, UTI, Dysuria, and urinary hesitation, (reported in at least 2 %) AEs are examined by study phase, significant differentiation is seen only in the 1200mg/day group where urinary tract infection occurs 1.9 times as frequently and urinary hesitation emerges as an event occurring in greater than 2% (only in the 1200mg/day group) in the maintenance phase. This observation suggests latency in the emergence of these effects.

American Urologic Association Symptom Index (Appendix 9.9)

	Change from Baseline in American Urological Association Symptom Index Total Scores (Safety Population: RCT, Studies 205, 301, and 302)				
Statistic	Placebo (N=427)	RTG 600 mg/day (N=281)	RTG 900 mg/day (N=273)	RTG 1200 mg/day (N=259)	RTG Total (N=813)
Baseline phase Mean (SD) Change from Baseline to:	n=343 3.5 (5.0)	n=194 2.7 (4.7)	n=187 2.5 (3.8)	n=162 4.9 (6.5)	n=543 3.3 (5.1)
Week 2 Mean (SD)	n=2 -.0.5 (3.5)	n=4 -0.2 (3.4)	n=1 1	n=0 0	n=5 -1.4 (3.2)
Week 4 Mean (SD)	n=165 -0.4 (2.9)	n=163 0.2 (3.8)	n=153 0.1 (3.1)	n=4 0.8 (8.1)	n=320 0.2 (3.5)
Week 6 Mean±SD	n=139 -0.1 (4.1)	n=4 -1.8 (2.2)	n=3 2.7 (5.5)	n=117 -0.3 (5.3)	n=124 -0.2 (5.3)
Week 8 Mean (SD)	n=157 -0.5 (3.8)	n=148 0.5 (4.0)	n=129 0.1 (4.4)	n=4 1.5 (10.5)	n=281 0.4 (4.3)
Week 10 Mean (SD)	n=125 -0.2 (5.3)	n=2 5.5 (7.8)	n=4 -2.0 (4.2)	n=96 0.1 (5.8)	n=102 0.1 (5.8)
Week 12 Mean (SD)	n=5 0.0 (0)	n=1 2.0	n=3 6.0 (10.4)	n=7 -1.0 (1.7)	n=11 1.2 (5.8)
Week 14 Mean (SD)	n=3 0.3 (0.6)	n=0 0	n=1 -2.0	n=1 -14.0	n=2 -8.0 (8.5)
Week 16 Mean (SD)	n=155 -0.6 (3.0)	n=137 0.0 (3.6)	n=122 -0.3 (3.4)	n=12 2.3 (6.6)	n=271 -0.1 (3.7)

	Change from Baseline in American Urological Association Symptom Index Total Scores (Safety Population: RCT, Studies 205, 301, and 302)				
Statistic	Placebo (N=427)	RTG 600 mg/day (N=281)	RTG 900 mg/day (N=273)	RTG 1200 mg/day (N=259)	RTG Total (N=813)
Week 18 Mean (SD)	n=115 -0.5 (4.5)	n=4 0.3 (2.1)	n=2 1.0 (1.4)	n=81 -1.0 (5.6)	n=87 -0.9 (5.4)
Week 20 Mean (SD)	n=3 -2.3 (2.1)	n=1 0	n=1 0	n=5 1.0 (3.7)	n=7 0.7 (3.1)

Reviewer comment: the change of scores over time in the AUA index table is unrevealing. There are no noteworthy changes in score toward more severe. This is likely because the urinary tract adverse effects are not sufficiently frequent to alter the overall symptom scores of pooled observations.

Serious Adverse Events within the RCT grouping

Table 63 Serious Adverse Events Due to Renal/Urinary Disorders (Safety Population: RCT, Studies 205, 301, and 302)

Study	Patient ID	Age/Race/ Gender	Treatment Group mg/day (Actual Dose at time of AE)	Preferred Term	Day of onset	Resolved Y/N	Withdrawn Y/N
205	000125	39/C/M	900/(900)	Renal colic	43, 49	Y	N
			600				
205	000448	53/C/F	(600)	Renal failure	20	Y	Y
301	005203	55/C/M	Placebo	Urinary retention	25	Y	N
302	025108	31/C/F	900/(600)	Urinary retention	19	Y	N
302	025405	34/C/F	900/(600)	Atonic urinary bladder	21	Y	Y
			900 (unk)	Urinary incontinence	63	Y	

There were 5 SAEs relating to Renal/Urinary Disorders in 4 (<1%) patients in the Total RTG group compared to 1 (0.2%) SAE for a patient on placebo, table 63. One (0.4%) SAE of renal failure was reported in the 600 mg/day group; 1 (0.4%) SAE each of atonic urinary bladder, renal colic, urinary retention and urinary incontinence in the 900 mg/day group and zero events in the 1200 mg/day group. One (0.2%) SAE of urinary retention was reported in the placebo group. All patients recovered. One of the 5 patients was on placebo. One developed flank pain about 2 months after beginning study drug and was found to have a left ureteral lithiasis of calcium-oxalate phosphate-monohydrate. This patient completed the study. The next patient from the review suffered obstructive uropathy with acute renal failure. This resolved with a post obstructive diuresis. This same patient had an increase in transaminases and bilirubin (represents a dual renal and hepatic adverse effect). This case is presented in greater detail in the following

section on RCT study withdrawals. The patient recovered after medication withdrawal. The third study drug treatment patient suffered an inability to empty her bladder beginning on day 17 of treatment however during the course of treatment no abnormality of post void residual was identified. The fourth and final patient developed decreased sensation when needing to void on day 15 of study drug treatment, on day 21 the patient had the same disturbance of sensation with an abnormal urine dipstick which was positive for leukocytes ad traces of blood. This case is provided in greater detail below in the section of RCT discontinuations.

Table 64 Discontinuations Due to Renal/Urinary Disorders (Safety Population: RCT, Studies 205, 301, and 302)

Study	Patient ID	Age/Race/ Gender	Dose mg/day (Actual Dose at time of AE)	Preferred Term	Day of Onset	SAE (Y/N)	Resolved (Y/N)
302	070101	22/C/F	600 (600)	Urinary tract infection	77	N	Y
205	000448	53/C/F	600 (600)	Renal failure	20	Y	N
205	000647	22/C/F	Placebo	Renal colic	10	N	Y
301	001303	26/C/M	1200 (1050)	Hematuria	42	N	Y
301	020217	34/C/F	Placebo	Polyuria, Urinary retention	43, 44	N	Y
302	025405	34/C/F	900 (600)	Atonic urinary bladder	21	Y	Y
302	030301	48/C/F	900 (900)	Urinary retention	29	N	Y
302	040121	46/C/F	Placebo	Polyuria	47	N	Y
302	090509	49/C/M	600 (377.8)	Nephritis	81	N	Y

Following are brief narrative case reports of the SAEs (table 63) & Discontinuations (table 64) from the RCT (pivotal controlled trials) grouping in ezogabine treated patients, 8 patients.

Patient 00125: a 39 yo w male developed left lower back pain during titration phase of ezogabine (day 43). Patient was seen in the emergency room the same day and hospitalized for “swollen left kidney” described as severe. An ultrasound with contrast was performed the next day which revealed distal ureter lithiasis. Treatment included extracorporeal shock wave lithotripsy and pain management. A 1.5 mm fragment of the calculus was collected and analysis of the fragment revealed a calcium-oxalate-phosphate-monohydrate stone. A repeat episode of pain occurred after hospital discharge, a subsequent ultrasound and IVP revealed small dilation of the left pyelum-calyces region and proximal ureters without clear cause. The patient continued in the study.

Patient 25108: a 31 yo w female reported mild urinary retention that manifested as an occasional inability to empty her bladder on day 19 of ezogabine treatment, at a dose of 600mg a day. Urine dipstick was positive for blood but contrary to the dipstick the laboratory report indicated positive protein and negative blood. Patient continued study and entered maintenance phase on day 29 of treatment (900mg / day). Patient continued to experience intermittent symptoms of urinary retention. Approximately day 56 on the timeline a post void residual ultrasound was normal, premicturition volume 156ml and post void residual 1 ml. The subjective sensation of inability to completely empty bladder is not corroborated with an objective abnormality of bladder dysfunction.

Patient 0448 a 53 yo female suffered with acute renal failure likely due to obstructive uropathy. First symptom occurred 23 days after beginning therapy while on 600mg ezogabine a day. The patient had myalgia, cough, polydipsia and sweats. Laboratory studies revealed increased ALT,AST, Creat, Bilirubin and CRP (328, normal range <12). Patient was hospitalized, on bladder catheterization found to have 1500ml cloudy urine. Ezogabine discontinued and patient discharged from hospital one week later. Patient on concomitant valproic acid 1000mg daily and carbamazepine 800mg daily. See appendix 9.11 for timeline of laboratory studies.

Patient 25405 a 34 year old female on 600mg a day ezogabine at time of adverse event. The patient was on concomitant lamotrigine and levetiracetam and experienced atonic urinary bladder on day 21 of treatment and urinary incontinence on day 63 of treatment. First symptoms began day 15 of treatment, patient felt a decreased sensation when needing to urinate. During approximately the subsequent 15 weeks the patient reported abnormal bladder sensation and abnormal post void residual volumes. See table 65.

Table 65 Subject VRX-RET-E22-302-25405 table of adverse event

Date	Day	PVR (ml)	Bladder sensation	Urine dipstick	RTG dose	comment
(b) (6)	-1	29				
	21		Decreased sense of need to void	+ leukocytes, trace blood		
					300mg TID	Entered maintenance phase
	49	74				
	63	159	Urinary incontinence			Study drug discontinued, begins tapering
						Last dose of ezogabine
	88	70				
	104	83	Decreased sensation			
		Negative				20days after last ezogabine

(b) (6)						
		30	Return of normal bladder sensation			
		130				
		21	Reports normal bladder sensation			
		62				

Patient 070101: a 22 yo female participant of study 302 on 600mg/day of ezogabine, concomitant levetiracetam and lamotrigine experienced abnormal tandem gait and intention tremor on day 61 of treatment. She first reported UTI on day 42 of therapy and was treated with norfloxicin. The patient again reported mild UTI on day 77. All adverse events were resolved by day 92 while last dose of study drug was day 97.

Patient 01303 a 26 yo male participant in study 301 developed intermittent hematuria on day 42 of ezogabine treatment, 6, days after reaching a dose of 1050mg/day. Normal PVR results were obtained. Patient began tapering study during approximately day 70 and hematuria resolved day 72. Drug discontinued day 84.

Patient 30301 a 47 yo female participant of study 302 randomized to 300mg TID experienced urinary retention on day 29 of 900mg/day ezogabine treatment. The patient reported she had to push or strain more than half the time. The symptom resolved on day 41 while last day of study drug was day 53. Taper began day 40. Last study visit was day 66 and PVR was abnormal that day at 101ml.

Patient 90509 a 49 yo male developed hypokalemia, diarrhea, had chronic hyponatremia (concurrent carbamazepine). Patient also given diagnosis of nephritis but no specific medical data provided, narrative indicates that diarrhea and nephritis resolved 18 days after last dose of ezogabine. Dose at time of onset 400mg/day.

Reviewer Comment: Review of the RCT data supports a urinary tract safety signal for urinary tract infection and possibly a disorder of bladder contractility.

All Phase II/III Combined

During the Phase II/III Combined studies, 25% of patients treated with ezogabine reported renal and urinary disorder AEs. Urinary tract infection (8%) was the most commonly reported AE. Other common AEs reflected the Pivotal Controlled Trials group: urinary hesitation (3%), urinalysis abnormal (3%), dysuria (2%), urinary retention (2%), hematuria (2%), chromaturia (2%), polyuria (2%) and residual urine volume present (1%). All other renal and urinary AEs were reported by <1% of ezogabine-treated patients, table 66.

As with the Pivotal Controlled Trials grouping, renal/Urinary events were reported most frequently during the first 8 weeks of treatment although there were sporadic reports with decreasing frequency beyond 8 weeks.

Table 66

	Adverse Events of Renal/Urinary Disorders Reported by 2 or more Patients (Safety Population: All Phase II/III Combined)
Preferred Term	**Number (%) of Patients RTG**
	(N=1365)
Any event	**346 (25.3)**
Urinary tract infection	105 (7.7)
Urinary hesitation	42 (3.1)
Urinalysis abnormal	35 (2.6)
Dysuria	33 (2.4)
Urinary retention	26 (1.9)
Hematuria	24 (1.8)
Chromaturia	23 (1.7)
Polyuria	22 (1.6)
Residual urine volume	15 (1.1)
Blood urine present	12 (0.9)
Leukocyturia	12 (0.9)
Proteinuria	12 (0.9)
Nephrolithiasis	9 (0.7)
Urine flow decreased	8 (0.6)
Cystitis	8 (0.6)
Bacteriuria	7 (0.5)
Urinary sediment present	7 (0.5)
Renal colic	7 (0.5)
Micturition frequency decreased	6 (0.4)
Urinary incontinence	6 (0.4)
Oliguria	5 (0.4)
Bacteria urine	5 (0.4)
Bacteria urine identified	4 (0.3)
Bilirubinuria	4 (0.3)
Bladder disorder	4 (0.3)
Costovertebral angle tenderness	4 (0.3)
Micturition disorder	4 (0.3)
Micturition urgency	4 (0.3)
Bladder spasm	3 (0.2)
Pollakiuria	3 (0.2)
Red blood cells urine	3 (0.2)
Crystalluria	2 (0.1)
Hypertonic bladder	2 (0.1)
Neurogenic bladder	2 (0.1)
Urethral pain	2 (0.1)
Urinary tract disorder	2 (0.1)
Urinary tract pain	2 (0.1)
Urine abnormality	2 (0.1)
Kidney infection	2 (0.1)
Pyelonephritis	2 (0.1)
Urinary tract infection bacterial	2 (0.1)
Blood creatinine increased	2 (0.1)
Crystal urine present	2 (0.1)
Protein urine	2 (0.1)
Red blood cells urine positive	2 (0.1)
White blood cells urine	2 (0.1)

Table 67 Table of all SAEs, and Withdrawals Due to Renal/Urinary Disorders derived from "Phase 2/3 DB safety analysis" of the Adverse event dataset including 120 day safety update*.

Protocol	SUBJID	Age/sex/race	PTNAME	Day of onset after EZO	EZO Dose at AE	SAE	With-drawal
VRX-RET-E22-303	103	20/F/C	URINARY TRACT INFECTION	97	1200	Y	N
VRX-RET-E22-301	103	20/F/C	HAEMATURIA	43	918.8	Y	N
VRX-RET-E22-301	3901	58/M/C	URINARY RETENTION	28	714.3	Y	Y
VRX-RET-E22-301	10607	31/F/H	URINARY TRACT INFECTION	137	1400	Y	N
VRX-RET-E22-302	25509	47/F/C	URINARY TRACT INFECTION	118	600	Y	N
3065 A1-205	125	39/M/C	RENAL COLIC	43	900	Y	N
3065 A1-205	448	53/F/C	RENAL FAILURE	20	600	Y	Y
VRX-RET-E22-302	25108	31/F/C	URINARY RETENTION	19	600	Y	N
VRX-RET-E22-302	25405	34/F/C	ATONIC URINARY BLADDER	21	600	Y	Y
VRX-RET-E22-302	25405	34/F/C	URINARY INCONTINENCE	63	.	Y	Y
3065 A1-208	13	39/F/C	HAEMATURIA	560	700	Y	N
3065 A1-208	13	39/F/C	HAEMATURIA	681	600	Y	N
3065 A1-208	13	39/F/C	RENAL COLIC	681	600	Y	N
3065 A1-208	17	18/F/C	RENAL FAILURE ACUTE	986	1200	Y	N
VRX-RET-E22-303	103	20/F/C	URINARY TRACT INFECTION	97	1200	Y	N
3065 A1-212	184	33/M/C	RENAL COLIC	266	1150	Y	N
3065 A1-212	693	22/F/C	UROSEPSIS	170	600	Y	Y
VRX-RET-E22-303	902	39/M/C	URINARY RETENTION	698	900	Y	N
VRX-RET-E22-303	902	39/M/C	URINARY RETENTION	872	600	Y	N
VRX-RET-E22-303	3505	30/M/C	URINARY RETENTION	81	1050	Y	Y
VRX-RET-E22-304	50710	24/M/C	HYDRONEPHROSIS	166	900	Y	Y
VRX-RET-E22-304	60306	52/M/C	NEPHROPATHY TOXIC	455	600	Y	Y
VRX-RET-E22-302	070101	22/C/F	URINARY TRACT INFECTION	77	600	N	Y
VRX-RET-E22-301	001303	26/C/M	HEMATURIA	42	1050	N	Y
VRX-RET-E22-302	030301	48/C/F	URINARY RETENTION	29	900	N	Y
VRX-RET-E22-302	090509	49/C/F	NEPHRITIS	81	377.8	N	Y
3065 A1-212	000528	39/C/M	URINARY TRACT INFECTION	206	800	N	Y
VRX-RET-E22-304	070201	36/C/M	URINARY RETENTION	501	750	N	Y
VRX-RET-E22-304	070310	31/C/F	URINARY RETENTION	171	900	N	Y
VRX-RET-E22-304	65408	38/F/C	URINARY RETENTION	582	900	N	Y
VRX-RET-E22-302	25107	62/F/C	NERVE ROOT COMPRESSION*	43	600	N	Y
VRX-RET-E22-304	50102	45/F/C	RESIDUAL URINE VOLUME	57	900	N	Y

*Events which occurred during transition phase to open label remain listed under the DB study 301 or 302 rather than extension studies 303 or 304.

Brief Narrative of cases from table 67:(note, patient case narratives 00125, 00448, 25108, 25405, 70101, 01303, 30301, and 90509 are provided above in RCT SAE and discontinuations)

Patient 000103: a 20 yo w F on placebo during DB phase entered OL study. On day 170 of study (day 97 of EZO treatment), while taking ezogabine 350mg TID patient experienced nausea, vomiting, and a sharp, stabbing pain that originated in her left flank and progressed to her entire abdomen. On day 172 computed tomography revealed bilateral hydroureteronephrosis that was more prominent on the left side. The delayed kidney, ureter, and bladder x-ray study showed unobstructed contrast filling of the left kidney and ureter. A foley catheter was placed due to voiding difficulties and bladder irrigation produced clear urine and resolution of pain. All recent post void residual urine volumes had been within normal limits. Lab results revealed a gonococcal infection and the patient was treated with levofloxacin. The patient was discharged on hospital day 5 and remained in the study. Medication list while in hospital reveal multiple analgesics to treat pain and vaginitis.

Patient 03901: a 58 yo w M experienced urinary retention on day 20 of ezogabine treatment. The patient experienced severe oliguria and mild abdominal pain with on ezogabine 250mg TID. PVR ultrasound revealed a pre-void volume of 2187ml and an initial postvoid residual of 572ml and a second post void residual of 245ml. Previous PVR ultrasound results were within normal limits. On exam prostate slightly enlarged, benign and non-tender. Three days after last dose of study medication PVR was 0ml.

Patient 10607: 31 yo Hispanic F while in transition phase to OL developed pain over the left flank associated with dysuria, urinary urgency, nausea and vomiting. On day 138 of treatment, taking ezogabine 400mg TID the patient was diagnosed with a UTI or urinary colic by her physician. On day 141 of treatment an excretory urinary exam was determined to be abnormal, revealing pyelocaliceal dilatation with evidence of ureteral stones without bladder disease. The patient recovered on day 147 and continued in the study.

Patient 25509: 46 yo w F while on ezogabine 200mg TID developed a severe urinary tract infection on treatment day 118. The event had a prodrome of headache severe nausea and vomiting. Patient was hospitalized, febrile and dehydrated. During hospitalization no urine testing was performed and patient was discharged after five hours. UA at outpatient clinic day 118 revealed out of range values for red blood cells 9-14/HPF, blood 2+, and white blood cells too numerous to count. On that day, the patient complained of a sore back accompanied by fever and rigors for the previous three days. Urine microscopy revealed white cells, red cells, epithelial cells and bacteria. The patient had been on oral antibiotics prior to obtaining a urine culture that was reported as negative. The patient was diagnosed with a urinary tract infection and hospitalized the same day. (Day 123), the patient was discharged home on a course of oral amoxicillin. On day 126, the patient reported that her symptoms had subsided.

Patient 00013: a 41 yo w F developed renal colic after approximately 2 years of therapy patient developed renal colic and gross hematuria. Patient had two instances of

hematuria about 4 months apart occurring on a background of “basement membrane disease” there is also a family history of renal calculi.

Patient 00017: a 21 yo wF on ezogabine 1200mg a day for approximately 6.5 months developed right flank pain, nausea and vomiting. CT scan showed right kidney swollen with possibility of “some blockage”. KUB showed no stone but stent placed I right ureter. Final diagnosis was ATN/ Acute renal failure due to NSAID treatment.

Patient 00184: a 33 yo w M in OL ezogabine treatment at a dose of 1050mg/ day was hospitalized for left renal colic on day 266 of treatment. An abdominal ultrasound and IV pyelogram were both negative for abnormalities. The patients experience a persistent increase in partial seizures approximately day 233, and discontinued study drug on day 364.

Patient 00693: 22 yo w F on OL ezogabine 600mg / day developed fever 39C, confusion and somnolence. Study report indicates only a diagnosis of urospesis. Patient subsequently discontinued medication.

Patient 00902: 39 yo w M while in OL treatment on 900mg a day, approximately day 528 of treatment patient had change in mental status, he was found wandering and taken to the emergency room. He was reported to have questionable hallucinations. He also had abrasion and ecchymosis on right side of head. CT brain negative for hemorrhage. During hospitalization a urology consult was obtained, and a bladder scan revealed a PVR of 700 ml. A foley catheter was placed. The urologist opinion was that the urinary retention may have been due to an obstructive voiding problem. Previous PVR volumes were normal. On day 700 of treatment the patient admitted with a flurry of seizures and urinary retention.

Patient 03505: a 30 yo w M developed psychomotor agitation, urinary retention and URI. In the hospital a foley catheter was inserted and 1200 ml urine evacuated. The patient had been on 1200mg ezogabine / day for approximately 2 weeks at the time of this hospitalization. At time of admission (day 55) ezogabine was reduced to 1050mg /day then stopped on day 83. On day 71 bladder ultrasound revealed 122 ml of retained urine while on day 81 there was 900ml of retained urine. Patient was referred to a urologist and a course of self catheterization was initiated. On day 223 the patient voiding diary revealed that he spontaneously voided 340ml per void and had 280 ml per catheterization during the week. A urodynamic study on 3/24/2008 (day 116) revealed no EMG activity during filling of the bladder. He had a sensation of fullness but was unable to void with a PVR of 882 ml. Due to the critical nature of this voiding dysfunction AE the complete text of the IND safety report is provided in Appendix 9.7

Patient 50710: 24 yo w M developed abdominal pain and vomiting on 900mg / day of ezogabine 166 of treatment during open label study. Computed tomography of the abdomen revealed a round lesion in the area of the left uretero-vesicular junction with dilatation of the left collecting system. A urine culture was negative but urinalysis revealed inflammation. Antibiotic therapy was started with quinolone, cefuroxime, and ciprofloxacin. On 28 Oct 2007 (day 169), retrograde pyelography revealed the presence

of left hydronephrosis and hydroureter, but no evidence of an obstructive ureteral lesion. Cystoscopy conducted the same day revealed a normal urethra, mild hyperemia in the trigonum area, and the left orifice was described as raised, protruding, and edematous. Patient developed a mild elevation of creatinine during his hospitalization at 1.39 mg/dL (ULN = 1.30 mg/dL). Urinalysis on 31 Oct 2007 (day 172) was positive for protein and blood, with 4-12 WBC and 31-50 red blood cells per high-powered field. Bladder postvoid residual volume was 0 mL. Full recover approximately 30 days after last dose of ezogabine

Patient 60306: 51 yo w M. hospitalized for drug-related nephropathy while on ezogabine 900mg / day, and he began tapering study drug on 12 Dec 2007 (Day 455). Urinalysis was also intermittently positive for traces of protein and ketones. Patient had developed mild elevation of BUN and creatine. Creatinine 1.07 x ULN, BUN 1.29 ULN.

Patient 70201: a 35 yo w M was found to have a PVR of 101 ml on day 501 on treatment, taking 750 mg ezogabine / day. The patient also had positive changes in several questions on the AUA symptom index. He indicated he had a sensation of not emptying his bladder completely (less than 1 time in 5), stopped and started several times when urinating (more than half the time), and had to strain to begin urination (more than half the time). These answers had changed from the previous time, 15 Jan 2007, when he answered “not at all” to the 3 questions. The patient previous PVR obtained 10 months before had shown an increase (67ml).

Patient 70310: 31 yo w F developed urinary retention during OL treatment day 171 while on ezogabine 900mg a day. Baseline post-void residual (PVR) bladder ultrasound on 02 Jul 2007 was normal, with 69 ml of residual volume. A PVR bladder ultrasound on 10 Jan 2008 (Day 171) revealed an abnormal residual urine volume of 104 ml. Follow-up PVR bladder ultrasounds on 10 Mar 2008 (Day 231) and 06 May 2008 (Day 288) remained abnormal, with PVR urine volume of 231 ml and 80 ml, respectively. On 06 May 2008, using AUA Symptom Index, the patient indicated that more than half the time, she stopped and started again when urinating or had to strain to begin urination, and almost always had a sensation of incomplete bladder emptying.

Patient 00528: 39 yo w M on OL ezogabine treatment at 900mg a day experienced urinary tract infection, day 206 of treatment. UA showed 15-25 s-leucocytes and 15-25s erythrocytes. Patient also experienced multiple episodes of clonic seizures and tapered study drug on day 206 of treatment.

Patient 65408: 38 yo w F developed urinary retention on 3/27/09 day 582. Patient seizure control began to deteriorate and she also developed episodes of moderately sever lightheadedness and nausea. Due to these adverse events the patient began tapering ezogabine. No further information provided on the urinary retention in case report. Patient did have previous SAE for choliathiasis on day 274. Incision of the gall bladder revealed minor chronic cholecystitis. Review of PVR dataset reveals no abnormal PVR values. Maximum value was 34 ml on 9/18/08.

Patient 25107: 62 yo w F, on day 43 of study maintenance phase taking 600mg of ezogabine experienced symptoms of urinary retention which included strain when passing urine and relief when urine was passed. On day 63 a bladder ultrasound revealed a premicturition volume of 857 ml with a PVR of 330ml. Patient began taper of study drug on day 65. On 3/20/07, 13 (day 91) days after last ezogabine dose a CT of the spine revealed a posterolateral disc extrusion indenting anterior thecal sac on the right at level L5/L1 with compression of the right S1 nerve root. There was mild to moderate central spinal canal stenosis at L3/4 and L4/5, in addition there were 'a couple of very small intra-renal calculi visualized at the mid pole of the left kidney". On day 135, 57 days after last ezogabine the patient had spinal surgery. On day 206, 126 days after final ezogabine an ultrasound revealed premicturition volume of 242ml with PVR 19ml, however there is no PVR or urinary symptom data presented for the interval day 65 to day 206.

Patient 50102: 45 yo w F had PVR change from baseline PVR of 173 ml on day 112 of treatment while on 900mg of ezogabine. There were no symptoms listed on the AUA symptom index taken the same day. Patient continued in study and had subsequent PVR measurements on day 168, day 231 and day 505 with results of 200ml. 95ml and 150ml respectively. The patient remained asymptomatic but withdrew from study on day 505 due to unrelated AE.

The category of serious adverse event and withdrawals from the Phase II/III combined reveals 7 (8 instances) cases of urinary retention containing 4 males and 3 females with an onset minimum of day 19 and maximum of day 872. the ezogabine dose ranges from 714.3 to 1050mg a day. The age ranges from a minimum of 31 years old to a maximum of 58 years, table 67.

Healthy Volunteer

Subject 019 (VRX-RET-E22-MR103): This study was an open label study to evaluate PK , safety and tolerability following single and multiple dose administration of two different modified release formulations compared to single dose administration of one immediate release formulation. 21 yo w M, healthy volunteer was dismissed from the study after administration of Ezogabine, 2 × 200 mg MR tablets (400mg in one dose daily) (Formulation 8), because of moderately severe urinary retention.

The urinary retention even occurred in period 4 of study MR103. There was a 6 week washout period between the end of period 3 and start of period 4. Period 4 was scheduled to be a 14 day trial of 2 x 200mg, formulation 8 of ezogabine delivered as a single 400mg dose or 200mg twice a day. The subjects are in confinement for monitoring during period 4. The case narrative of patient 019 does not disclose which delivery program the patient was assigned. On day five, after receiving daily ezogabine 400mg for 5 days the patient was unable to void for 14 hours and had lower abdominal discomfort and pain.

The patient was taken to an ER where he was catheterized using a Foley's catheter and approximately 1000ccs of urine was drained. The subject returned to the research clinic on the same day for observation. He was able to void normally after the procedure, and was then dismissed later the same day (+dechallenge). The patient had a follow up ultrasound of the bladder at a time / date unspecified after the event. This revealed a normal prostatic size. There was a pre-void volume of 307ml and post-void 15ml.

Post Herpetic Neuralgia (VRX-RET-E22-NP201)

Patient 025-003: 76 yo w F taking ezogabine in combination with Amitriptyline developed urinary retention on day 20 dose level 3. PVR was 106 on day 11. Last day study drug was day 24 with PVR on day 30 354ml.

Reviewer Comment: The 26 cases captured from SAEs and discontinuations in table 67 above are reviewed in the foregoing section. **Review of these cases reveals clear episodes of urinary retention.** There are also cases of subjective sense of hesitation or difficulty emptying bladder which, although not associated with measured retention may be a prodrome to retention. The cases of greatest interest and concern are those which reveal hydronephrosis, hydroureter, pyelocaliceal dilation or swollen kidney without an identifiable stone or obstructive process on diagnostic imaging. There was 1 case of hydronephrosis with a positive dechallenge (50710), this case also had a hydroureter. There was one case of hydroureter (00103), this patient remained in the study with the event possibly due to a gonococcal infection. There was one case of pyelocaliceal dilatation (10607), this patient continued in study. There was one case of swollen kidney with no evidence of obstruction (00017), this patient developed acute renal failure attributed to NSAID nephropathy and remained in the study.

These events suggest that a functional obstruction may develop without stone formation. The event in the healthy volunteer reveals that impaired bladder emptying may develop quite rapidly, in as few as 5 days of treatment. The occurrence of spontaneous resolution with continuation in the study of patient 10607 suggest that the events of obstruction, whether functional or due to stone formation may be transient. Case 00103 is confounded by the presence of a gonococcal infection; however this patient had hydroureteronephrosis without an identified obstructive process and no evidence of voiding abnormality. This observation coupled with the features of case 10607 and healthy volunteer 019 raise the possibility of rapidly developing, transient, functional urinary tract obstruction, of uncertain etiology.

Predictability of Urinary Retention

Identification of parameters that may predict the occurrence of urinary retention is desirable to aid in monitoring and prevention of the adverse effects of voiding dysfunction and infection. Several parameters are examined for predictive properties; these include post void residual volume (PVR), duration of ezogabine treatment, ezogabine dose, baseline PVR value, age and sex.

The “All phase II/III combined analysis set” of the adverse event database (ae.xpt) is searched to capture the preferred term “urinary retention”. This search yields 35 instances of the PTNAME “urinary retention” treated with ezogabine at the time of adverse event. Duplicate entries from these 35 cases are eliminated to yield 28 unique cases of urinary retention. An additional case of urinary retention is identified under the adverse event term “renal failure”, however this patient had bladder volume of 1500ml and required catheterization for bladder drainage. This case raised the total number to 29 cases. Post void residual volumes from the PVR dataset (pvr.xpt) are matched, where available, to those patients who were in studies 301, 302, 303, 304. Each available PVR value is placed on a timeline of months before or after the event date of “urinary retention” to create a grid of patient timelines with PVR values plotted in monthly increments preceding and following the event of “urinary retention”, table 69.

Urinary retention event dates are obtained from the ae.xpt database while the PVR values are obtained from the pvr.xpt dataset. The diagnosis of urinary retention may be a clinical diagnosis with no objective measurement of bladder function on the event date. As an example this is the situation is for patient 30301 who has an adverse event of “urinary retention” on 11/15/06 but the available PVR values are obtained on 10/17/06 and 12/22/06. In the case of patient 30301 the week 4 visit date fell on 11/14/06 with the AE reported the following day. In addition in study 302 the bladder ultrasound examinations are scheduled for week 8 and 16 during maintenance phase. Only 11 unique patients with the adverse event of “urinary retention” have a recorded PVR value on the date of the event.

Overall the PVR grid reveals that the PVR values have little or no relationship to the event of urinary retention. Examination of the interval 3 months prior to an event of urinary retention reveal only 2 of 9 available values show a positive change from baseline. It is possible that more frequent PVR measurements would capture an increase in PVR value more proximate to the event of urinary retention however there is a practical limit to the frequency of obtaining these measurements in the community practice setting.

Urinary Retention by Duration of Treatment

From all adverse events of the preferred term “ urinary retention” in the SAFE23OL safety dataset, 27 instances in 25 unique patients who have an adverse event start date following the date of first ezogabine dose are identified. The difference between the ezogabine start date and adverse event date is calculated and the distribution is examined to determine if there is a relationship between the occurrence of urinary retention and duration of treatment. This is shown in figure 10. Examination of the distribution reveals that 16 (59%) of the urinary retention events occur in the first six months, 5 (18.5%) in the first month. The median of occurrence is at 134 days with a mean of 284 days with a range from 1 to 996 days. This distribution indicates a majority of cases occur in the first six months but cases may be seen as long as 2.5 years after initiation of treatment. Unfortunately this analysis indicates that although frequency of

occurrence is greater in the early (6 month) interval after treatment initiation, there is no reliable point that defines where there is no further risk of urinary retention.

Risk of Urinary Retention related to ezogabine dose

In 24 of the 27 instances of urinary retention on ezogabine there is a recorded ezogabine dose on the day of adverse event. Examination of the distribution of urinary retention events by dose does not reveal a dose response. There a fairly even distribution of events among low, middle and high dose groups. This distribution may be seen in table 68.

Table 68 distribution of urinary retention events by total daily ezogabine dose

Total daily dose (mg) subject was taking at time of imputed adverse event start date*	Number of patients
300	1
600	4
714.3	1
750	2
900	8
1050	2
1200	5
1280	1

* from “Analysis Data Definition”

In 11 patients on ezogabine treatment there is an ezogabine dose and a PVR value recorded on the day of the urinary retention. In this small sample the relationship between ezogabine dose and PVR value may be examined. In this subset there is no clear dose response. Comparison of the medians and means as well as a plot of grand mean is shown in figure 9, where the 1200mg dose in the two instances of occurrence is associated with a smaller change from baseline PVR than the 2 instances of 750mg dose.

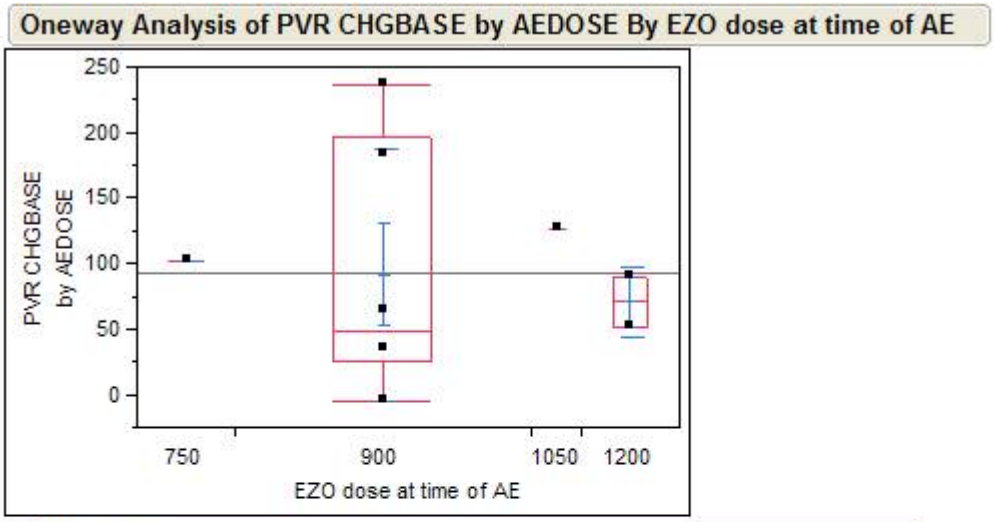
Risk of Urinary Retention related to baseline PVR value.

There are 23 unique patients on ezogabine at the time of urinary retention who also have a baseline PVR value identified. The distribution of baseline values is examined as well as the baseline values of all subjects in the RCTs with available baseline values (n=842). The median baseline PVR value in those with urinary retention adverse event is 27ml with a mean of 42ml and a range of 0 to 188ml. In the all controlled trial group (including those with urinary retention) the median is 7ml, with a mean of 21ml and a range of 0 to 774ml. This subtle difference in the baseline PVR values of the controlled trial group and the subset who suffered an adverse event of urinary retention does not appear to be of sufficient magnitude to be predictive.

Risk of Urinary retention by age and sex

26 unique patients on ezogabine at the time of urinary retention adverse event are examined to determine age distribution. The distribution is similar to the distribution in the all RCT study, ezogabine treatment patients have a small disproportionality above age 50, figure 11. In the group of 26 unique patients who had an adverse event of urinary retention while on ezogabine treatment there were 13 male and 13 female patients.

Figure 9 Change from baseline PVR across dose range in 11 cases of urinary retention



Quantiles

Level	Minimum	10%	25%	Median	75%	90%	Maximum
750	102	102	102	102	102	102	102
900	-5	-5	25	49	196.5	237	237
1050	126	126	126	126	126	126	126
1200	52	52	52	71	90	90	90

Means and Std Deviations

Level	Number	Mean	Std Dev	Std Err Mean	Lower 95%	Upper 95%
750	2	102.000	0.0000	0.000	102.0	102.00
900	6	91.333	95.9701	39.180	-9.4	192.05
1050	1	126.000	.	.	.	.
1200	2	71.000	26.8701	19.000	-170.4	312.42

Table 69 Distribution Of PVR Value Obtained Before And After Event Of Urinary Retention 27 Unique Subjects From 41 Events Where PT Is Urinary Retention; Patient Is On Ezogabine Treatment At Time Of Event. (extracted from AE.xpt dataset)

SUBJID	Base line												Event							comment
00448													1500ml, C							53 yo F, 205, 600mg, TTO - 25 day, obstructive uropathy, renal failure. NO PVR, Withdrawal
3505	24 OL												1200ml (d 55) ER 1/23/08 C	122 2/8/ 08	900 ml 2/18 /08					30 yo M, 303, 1050mg, 11/30/07 -1/23/08, Withdrawal from study
30301	38												No measure, strain push	101 ml						48 yo F, 302, 900mg, 10/18/06 – 11/15/06 Withdrawn from study
65408	7	10						34					Narrative - UR mod severity							38 yo F, 304 ,750mg 8/24/07-3/27/09. Withdrawn from study
70201	0			67									101ml, AUA not emptying							36 yo M,304,750mg 5/29/06 – 10/11/07. Withdrawn from study
70310	69											30	104			231		80		31 yo F, 304,900mg 7/24/07 -1/10/08. Withdrawn
00902	37	37					17						700ml 3/4/08 C						44	39 yo, M, 303,900mg 4/6/06 to 3/4/08, SAE
00902	37	37	17										990ml 8/24/08 C						44	39 yo, M, 303,600mg, 4/6/06 to 8/24/08, SAE
103	0																		11	
202	2									0							4		62	
801	27		122		15								210							
2508	55																			
2512	50													40		118				
3602	21			11								6								
5402	2												92	67					91	
5405	6											5	58						23	
10202	155						7				15									
25108	0														1			2	2	
25215	30												156		83			35	68	
25407	33													28		7			0	
30301	38												101							

SUBJID	Base line													Event							comment
50603	13	139	92									29									
60214	30																				
65408	7	10					34														
70110	188											26		183		90		215			
70201	0	0			67									102							
70310	69			27								30		104		231					Discontinued @ +3 mo
85403	33									215		100		270		63		0			Improve while on ezo
months		**≥12**	**11**	**10**	**9**	**8**	**7**	**6**	**5**	**4**	**3**	**2**	**1**	**0**	**1**	**2**	**3**	**4**	**5**	**≥6**	
		Months Preceding Urinary Retention (UR)													**Months following UR**						

Shaded Patients 3505, 30301, 65408, 70201, 70310 and 00902 were entered as "Urinary Retention" serious adverse events (SAE), Patient 00448 was entered as "Renal Failure). Bold capital C in event indicates patient had catheterization to drain bladder.

Figure 10 Duration of Ezogabine treatment (in days) to AE "urinary retention" in 27 instances identified from AE safety dataset where start and adverse event date identified

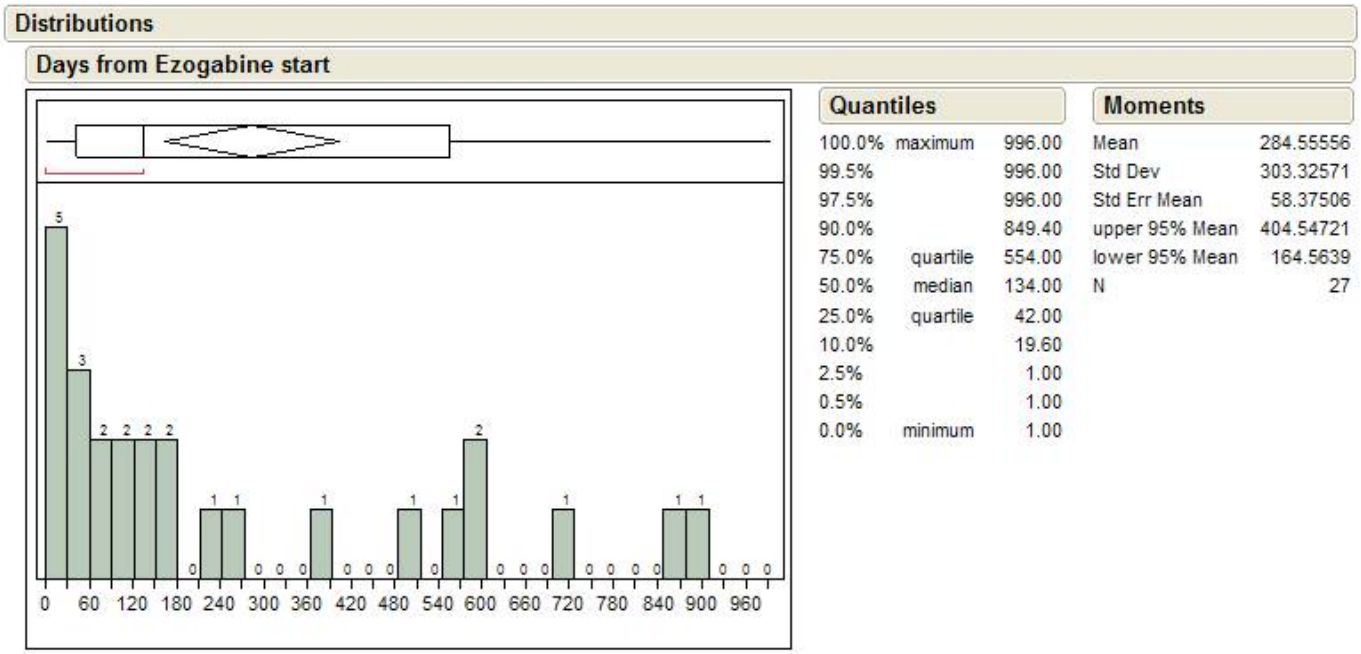
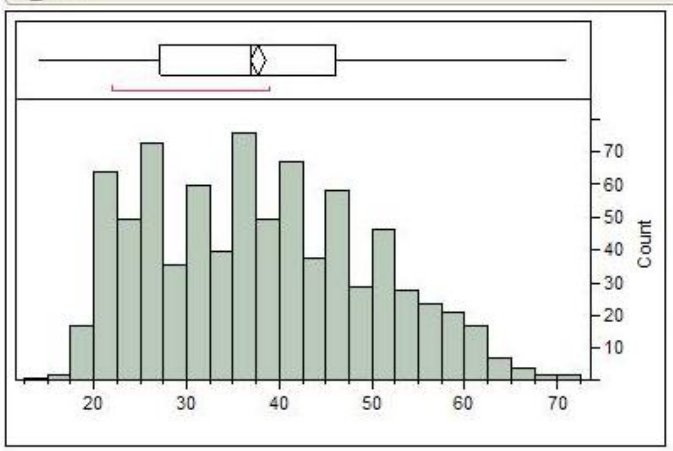


Figure 11 Graphic comparison of age distribution of EZO treated patients with urinary retention compared to overall EZO treated patients in RCT group.

Age distribution all EZO treatment in PCT

Distributions

C_AGE



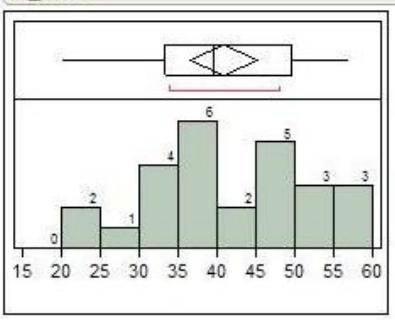
Quantiles		
100.0%	maximum	71.000
99.5%		68.860
97.5%		62.000
90.0%		54.000
75.0%	quartile	46.000
50.0%	median	37.000
25.0%	quartile	27.000
10.0%		22.000
2.5%		19.350
0.5%		18.000
0.0%	minimum	14.000

Moments	
Mean	37.681427
Std Dev	11.923013
Std Err Mean	0.4181583
upper 95% Mean	38.502226
lower 95% Mean	36.860628
N	813

Age distribution of 26 unique EZO treated patients with AE "urinary retention"

Distributions

C_AGE



Quantiles		
100.0%	maximum	57.000
99.5%		57.000
97.5%		57.000
90.0%		55.300
75.0%	quartile	49.500
50.0%	median	39.500
25.0%	quartile	33.250
10.0%		24.200
2.5%		20.000
0.5%		20.000
0.0%	minimum	20.000

Moments	
Mean	40.923077
Std Dev	10.891917
Std Err Mean	2.1360806
upper 95% Mean	45.322417
lower 95% Mean	36.523737
N	26

Reviewer Comment: Examination of the parameters associated with PVR values including duration of ezogabine treatment, ezogabine dose, baseline PVR values, and sex, do not show associations that will be helpful in securely predicting an occurrence of urinary retention. There is a subtle shift in age toward 45 and older compared to the age within the ezogabine treated overall pivotal controlled trials group.

Urologic Consultation

Voiding Dysfunction: The urologic consultation team concurs with the clinical team that there is increased risk of voiding dysfunction including urinary retention with ezogabine therapy. The time to onset of urinary retention is unpredictable.

Urinary Crystals and Stone Formation: the consultation team concluded that the composition of the urinary crystals is not identified and cases of Nephrolithiasis are poorly documented with no clear evidence implicating ezogabine in urinary tract stone formation.

Seizure Worsening and Status Epilepticus

Epilepsy worsening is a concern in anticonvulsant development programs, high doses of some anticonvulsant agents may be associated with CNS stimulation. The sponsor has entered a focused section in the ISS on seizure worsening and status epilepticus in the section of safety topics of interest.

Background: The primary mechanism of action of ezogabine is activation of the KCNQ channels, which has been extensively evaluated in multiple in vitro and in vivo systems. Single and repeat oral or i.v. administration of ezogabine induced a number of clinical signs suggestive of CNS stimulation that were marked at high oral doses or following i.v. administration. Findings in repeat-dose toxicity studies of limb tremor and convulsions at high dose levels were considered to potentially result from the extended pharmacology of ezogabine. Proconvulsant activity was only observed in the ezogabine toxicity studies at dose/exposure levels that were approximately 10-fold greater than those associated with anti-epileptic activity in the nonclinical rodent efficacy studies; proconvulsant activity was not seen in nonclinical efficacy studies with ezogabine at doses in the rodent therapeutic range.

Seizure frequency was determined from a daily seizure diary, in which patients recorded the nature and frequency of their seizures. It should be noted that because the assessment of efficacy was based on the evaluation of seizure frequency, seizures were to be documented as AEs only under specific circumstances (e.g., unusual type of seizure, increase in frequency of seizures, SAEs, event led to discontinuation). Seizures were coded as follows:

- Partial seizures: simple partial seizures, complex partial seizures, flurries and partial evolving to secondarily generalized.

- Generalized or unclassified seizures: absence seizures, myoclonic seizures, tonic clonic seizures, tonic seizures, atonic seizures, partial status epilepticus, convulsive epilepticus, and unclassified seizures

AE preferred terms were searched in the Pivotal Controlled Trials and All Phase II/III Combined groups. Adverse event preferred terms searched for seizures and related events were the following: sudden death (verbatim: during the seizure), back pain (verbatim: shakiness), acquired epileptic, clonus, complex partial, complex partial

seizures, convulsion, epilepsy, epileptic aura, grand mal convulsion, loss of consciousness, myoclonus, partial seizures, partial seizures with secondary, petit mal epilepsy, poor quality sleep, post-ictal headache, postictal state, simple partial seizures, status epilepticus, syncope, tongue biting, tremor, unresponsive to stimuli.

RCT

Results for the randomized controlled trials are seen in table 70, the largest numerical value for seizure related preferred term was for convulsion followed by myoclonus and syncope. The numerical hierarchy for terms below syncope in order of events yields occurrences no greater than 2 subjects or 0.2%, and are therefore less informative. The AE convulsion occurred in 19 (4.4%) of placebo, 6 (2.1%) of the 600mg/ day group, 9 (3.3%) of the 900mg/day dose group, 16 (6.2%) of the 1200mg/day dose group and 31 (3.8%) of the total ezogabine treatment group. The AE myoclonus occurred in none (0) of the placebo group, 3 (1.1%) of the 600mg/ day group, 4 (1.5%) of the 900mg/day dose group, 2 (0.8%) of the 1200mg/day dose group and 9 (1.1%) of the total ezogabine treatment group. The AE syncope occurred in 1 (0.2%) of the placebo group, none (0) of the 600mg/ day group, 3 (1.1%) of the 900mg/day dose group, 2 (0.8%)of the 1200mg/day dose group and 5 (0.6%) of the total ezogabine treatment group.

Table 70 Seizures and Related Events (Safety Population: RCT, Studies 205, 301, and 302)

	Seizures and Related Events (Safety Population: RCT, Studies 205, 301, and 302)				
	Number (%) of patients				
	Placebo N=427	**Ezogabine**			
Preferred term		**600 mg/day N=281**	**900 mg/day N=273**	**1200 mg/day N=259**	**Total N=813**
Any event	**26 (6.1)**	**13 (4.6)**	**21 (7.7)**	**25 (9.7)**	**59 (7.3)**
Convulsion	19 (4.4)	6 (2.1)	9 (3.3)	16 (6.2)	31 (3.8)
Myoclonus	0	3 (1.1)	4 (1.5)	2 (0.8)	9 (1.1)
Syncope	1 (0.2)	0	3 (1.1)	2 (0.8)	5 (0.6)
Grand mal convulsion	0	1 (0.4)	1 (0.4)	0	2 (0.2)
Complex partial seizures	1 (0.2)	0	2 (0.7)	0	2 (0.2)
Simple partial seizures	0	1 (0.4)	0	1 (0.4)	2 (0.2)
Status epilepticus	0	0	1 (0.4)	1 (0.4)	2 (0.2)
Epileptic aura	1 (0.2)	1 (0.4)	0	1 (0.4)	2 (0.2)
Tremor	0	0	1 (0.4)	1 (0.4)	2 (0.2)
Epilepsy	1 (0.2)	0	1 (0.4)	0	1 (0.1)
Poor quality sleep	0	0	0	1 (0.4)	1 (0.1)
Postictal state	4 (0.9)	1 (0.4)	0	0	1 (0.1)
Tongue biting	0	0	1 (0.4)	0	1 (0.1)

The relative risk of experiencing seizure related AE in all patients who received ezogabine in the randomized controlled trials was 1.2 ranging from 0.8 to 1.6, table 71. The 95% CIs included 1.0 at all doses.

Table 71 Relative Risk Ratios and 95% Confidence Intervals for Seizure Worsening (any seizure related AE) and Status Epilepticus, Pivotal Controlled Trials grouping

	EZOGABINE (600 MG/DAY) / PLACEBO	EZOGABINE (900 MG/DAY) / PLACEBO	EZOGABINE (1200 MG/DAY) / PLACEBO	EZOGABINE (TOTAL) / PLACEBO
RELATIVE RISK RATIO	0.760	1.263	1.585	1.192
95% CI	[0.397, 1.453]	[0.726, 2.200]	[0.936, 2.685]	[0.763, 1.862]

Seizures Related to Study Phase

Seizures were more frequently reported during the titration phase than during the maintenance phase in all treatment groups. There were more seizure-related events in the Total RTG group (42 patients, 5%) than in placebo (18 patients, 4%) during titration; the proportion of patients experiencing seizure events (mix of all epilepsy related terms) was 4.2%, 3%, 6% and 7% in the placebo, 600 mg/day, 900 and 1200 mg/day groups, respectively. During the maintenance phase, which represents a time of stable dosing, seizure-related events were reported in 3% of patients in the placebo, 600 and 900 mg/day group, and 4% in the 1200mg/day group. Thus, although seizure-related AEs appear to be dose-related, with the most seizures occurring in the 1200mg/day group, there was decrease in the actual number of events during the maintenance phase versus titration phase.

Seizure Related SAEs

Convulsion and myoclonus were the only seizure-related SAEs reported for more than 2 patients in any treatment group. Seizure-related SAEs were reported for 2% (7/427) of patients in the placebo group and 2% of patients (19/813) in the Total RTG group. Serious AEs of myoclonus was reported in 2 patients (1%) in the 600 mg/day group, and none in placebo. Overall, the rate of seizure-related events reported as SAEs was similar between the placebo and ezogabine groups.

Seizure Related Discontinuations

Epilepsy (verbatim term ‘epilepsy worsened’) was an SAE for 1 patient in the placebo group (Patient 301-010204) and led to discontinuation for 1 patient in the 900mg/day group (Patient 302-085309). Status epilepticus was an SAE that led to discontinuation for 1 patient (Patient 301-001308) in the 1200mg/day group. Complex partial seizures were an SAE for 1 patient in the placebo group (Patient 205-001481) and led to discontinuation for 2 patients in the 900mg/day group (Patients 302-05521 and 302-080105). Grand mal convulsion was an SAE for 1 patient in the 600mg/day group (Patient 205-000002) and 1 patient in the 900mg/day group (Patient 205-000109).

All Phase II/III Combined Studies

In the All Phase II/III Combined studies, seizure related AEs were reported for 14% of ezogabine patients, and convulsion was the most common seizure-related AE (7%), table 72. All other seizure-related AEs in the All Phase II/III Combined ezogabine group were reported for ≤1% of patients.

Table 72 Seizures and Related Events (Safety Population: All Phase II/III Combined) Show to ≥0.5%

	Seizures and Related Events (Safety Population: All Phase II/III Combined) Show to ≥0.5%
Preferred term	**Number (%) of patients Ezogabine N=1365**
Any event	**186 (13.6)**
Convulsion	99 (7.3)
Myoclonus	19 (1.4)
Tremor	15 (1.1)
Epilepsy	13 (1.0)
Syncope	12 (0.9)
Complex partial seizures	10 (0.7)
Status epilpeticus	8 (0.6)
Grand mal convulsion	7 (0.5)

Reviewer Comment: The actual content of the term AE term “convulsion” is variable and may not be the same event from investigator to investigator and thus is a noisy term for drawing conclusions. However there is a noticeable dose response for the frequency of this event at 4.4%, 2.1%, 3.3% and 6.2% in the placebo, 600mg, 900mg, and 1200mg dose respectively. In addition the relative risk ratio calculated by the sponsor also has a dose response with a 1.6 RR in the 1200mg group. The high placebo rate of 4.4% for the AE, convulsion reduces the significance of the dose response that is observed.

Blood Dyscrasias

Background

A potential signal for neutropenia was identified in a 13-week oral capsule toxicity study of the ezogabine metabolite NAMR in dogs (m2.4). In a follow-on study, dogs were orally dosed for 13 weeks at 3, 10 or 30 mg/kg QD or 10 mg/kg TID NAMR. At the high dose (30 mg/kg QD or 10 mg/kg TID), lower neutrophil counts were observed in some interim and terminally sacrificed animals. However, high neutrophil counts were also often observed. Bone marrow myeloid hyperplasia and thymic necrosis were seen in some interim-sacrificed animals. At the two higher doses, thymic atrophy and granulocytic hyperplasia in the bone marrow were observed in some moribund animals. Based on the NAMR repeat-dose toxicity data in the dog alone, there might be the potential for hematological effects at the human therapeutic dose of ezogabine. In the

rat, at doses of up to 120 mg/kg NAMR over 13 weeks, there were no similar findings on neutrophils or myeloid tissue. Specific immunotoxicological investigations on peripheral blood leukocytes and natural killer cell activity found no NAMR-related effects.

RCT

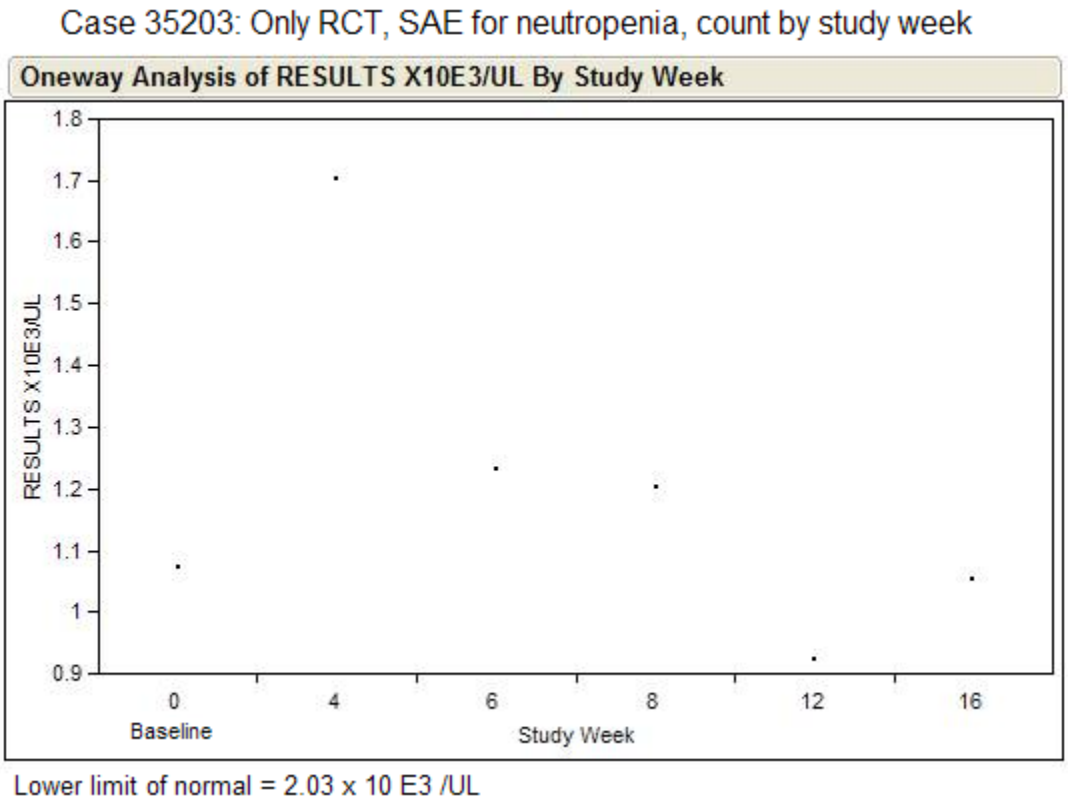
Table 73 Leukopenia, Neutropenia and Pancytopenia Related Adverse Events (Safety Population: RCT, Studies 205, 301, and 302)

Preferred Term	Number (%) of Patients				
	Placebo N=427	Ezogabine			
		600 mg/day (N=281)	900 mg/day (N=273)	1200 mg/day (N=259)	Total (N=813)
Leukopenia	2 (0.5)	6 (2.1)	1 (0.4)	3 (1.2)	10 (1.2)
Neutropenia	5 (1.2)	1 (0.4)	0	1 (0.4)	2 (0.2)
Pancytopenia	1 (0.2)	0	0	0	0

In the RCTs there were 7 adverse events of neutropenia, 2 in ezogabine treatment and 5 in the placebo treatment group. Within these 7 adverse events there were 2 SAEs of neutropenia, one in placebo, one in the treatment group.

The SAE in the ezogabine treatment group (case 35203) began the study with a neutrophil count in the range of PCC (1.07×10^3 /UL). The neutrophil count dropped into the severe neutropenia range at week 12. Folic acid treatment was begun and ezogabine treatment was continued followed by improvement in neutrophil count.

Table 74 Case 35203: ANC x 10^3 /ul, SAE for Neutropenia by week during double blind interval.



All Phase II/III Combined Group

Within the All Phase II/III Combined Group there were 10 (0.7%) unique patients with neutropenia adverse events and no additional SAEs or study withdrawals.

Leukopenia

RCT

In the RCTs there were 12 adverse events of leukopenia, 2 (0.5%) in placebo and 10 (1.2%) in ezogabine treatment. There were no SAEs or study withdrawals for leukopenia in the RCT group.

All Phase II/III Combined Group

Within the All Phase II/III Combined Group there were 10 (0.7%) unique patients with leukopenia adverse events. There were no SAEs or study withdrawals.

Pancytopenia

In the RCTs there were two adverse events of pancytopenia, one occurred in placebo and one occurred before the first dose of ezogabine

Within the All Phase II/III Combined Group there were no additional cases of pancytopenia.

Reviewer Comment: There is no compelling signal for blood dyscrasias. There is a small separation between placebo and ezogabine treatment for Leukopenia (0.7%) and neutropenia (0.4%) The single SAE for neutropenia in the ezogabine treatment group entered the study with a level of neutropenia that actually improved at several study visits. There were also no cases with evidence of causality among the 10 cases of severe neutropenia (<1 x 10^3 cells / ul, ANC) identified from RCTs weeks 2 to 18. (table36)

The analysis is continued with the additional related discussion of hematology means, shift analysis and outliers with final conclusions in the hematology outlier reviewer comments of section 7.4.2.

Cardiac Rhythm/Conduction Abnormalities

Background

The sponsor review of the preclinical cardiac pharmacology for ezogabine would suggest that neither ezogabine nor NAMR exhibit pro-arrhythmic effects. In a conscious dog model, 12 animals given daily doses of up to 38 mg/kg for one week showed no ECG effects at any level. ECGs were within normal limits for all animals. In another dog study, intravenous doses of ezogabine given until the appearance of dose limiting side effects, yielded no arrhythmias or signs of arrhythmogenic potential (including QTc changes) on ECG tracing (m2.4).

In vitro cardiac pharmacology studies have also indicated that neither ezogabine nor NAMR produced prolonged action potential durations in cat cardiac myocytes and dog Purkinje fibers. In addition, neither ezogabine nor NAMR prolonged QT intervals in isolated guinea pig hearts at ezogabine concentrations up to 30 μM (equivalent to a supratherapeutic human concentration). It was not until a very high concentration of 100 μM (approximately 15 times the expected peak therapeutic concentration in humans), that a 17% increase in the QT interval and a 47% decrease in the heart rate were noted. In vitro ion channel studies have demonstrated that the IC50 for ezogabine inhibition of the KCNQ1/KCNE1 and hERG channels in the myocardium is at least 100 μM. The IC50 for NAMR for hERG inhibition is greater than 1000 uM (m2.4).

RCT

Events of cardiac rhythm/conduction abnormalities were reported sporadically throughout the duration of the studies and were not clustered in any particular phase of treatment or specific length of exposure. The frequency of overall events was greater in the total ezogabine group than in the placebo group by a small margin, 4.6% vs 4.0%.

There was no dose response noted in any category of rhythm/conduction abnormalities in the RCT studies, table 75.

Table 75 Cardiac Rhythm/Conduction Abnormalities Reported in at least 2 Patients in any Treatment Group (Safety Population: RCT, Studies 205, 301, and 302)

	Number (%) of Patients				
Preferred Term	**Placebo N=427 (%)**	**Ezogabine**			
		600 mg/day N=281	**900 mg/day N=273**	**1200 mg/day N=259**	**RTG Total N=813**
Any Event	17 (4.0)	14 (5.0)	15 (5.5)	8 (3.1)	37 (4.6)
Palpitations	3 (0.7)	3 (1.1)	2 (0.7)	1 (0.4)	6 (0.7)
Sinus Bradycardia	0	2 (0.7)	0	0	2 (0.2)
Chest Pain	3 (0.7)	5 (1.8)	2 (0.7)	2 (0.8)	9 (1.1)
Heart rate irregular	0	0	2 (0.7)	0	2 (0.2)
Syncope	1 (0.2)	0	3 (1.1)	2 (0.8)	5 (0.6)
ECG QT correct interval prolonged	2 (0.5)	0	0	0	0

SAEs : There were 2 SAEs related to cardiac rhythm/conduction abnormalities in the placebo group (1AV block-withdrawn and 1 ventricular asystole) There were 2 SAEs in the treatment group, 1 chest pain , 1 syncope (seizure likely).

Discontinuations: 9 patients discontinued 2 in the placebo group, 7 in the treatment group. 3 of the seven ezogabine treated patients were withdrawn due to palpitations, one due to tachycardia, one ST depression, one irregular heart beat, and one syncope.

Conduction abnormalities were reported more frequently in the placebo group (6 events, 1.4%) than in the Total RTG group (2 events, 0.2%),table 76.

Table 76 Conduction Abnormalities Reported In At Least 1 Patient In Any Treatment Group (Safety Population: RCT, Studies 205, 301, 302)

	Number (%) of Patients				
Preferred Term	**Placebo N=427 (%)**	**Ezogabine**			
		600 mg/day N=281	**900 mg/day N=273**	**1200 mg/day N=259**	**RTG Total N=813**
Atrioventricular block	1 (0.2)	0	0	0	0
First degree AV block	0	1 (0.4)	0	0	1 (0.1)
ECG PR Prolongation	1 (0.2)	0	0	0	0
ECG QT interval corrected prolonged	2 (0.5)	0	0	0	0
ECG QT Prolonged	1 (0.2)	1 (0.4)	0	0	1 (0.1)
ECG QT shortened	1 (0.2)	0	0	0	0
Total events	6	2	0	0	2

All Phase II/III

7 SAEs, 5 due to chest pain, 4 of 5 after 149 days or greater duration of treatment, one occurred on day 5; case report implies baseline T wave inversion reported to patient, this preceded the experience of chest pain. No evidence of ischemia on cardiac enzymes, ECG unchanged since 2005 (study in 2007). SAE for bradyarrymthia, study 208 absence seizure with bradycardia and several sinus pauses after increase in ezogabine has quality of true drug effect.

7 discontinuations due to cardiac rhythm/conduction abnormalities, 3 were also SAEs. 1 syncope, 1 ventricular tachycardia –study 108, 1 asystole, study 108, 1 extrasystole, 1 chest discomfort. 2 ventricular extrasystoles, 0044 healthy, PVC didn't feel well at 600mg.

	Cardiac Rhythm/Conduction Abnormalities Reported in at least 2 Patients (Safety Population: All Phase II/III Combined)
	Number (%) of Patients
	RTG
Preferred Term	**(N=1365)**
Any Event	**111 (8.1)**
Chest pain	38 (2.8)
Palpitations	18 (1.3)
Syncope	12 (0.9)
Chest Discomfort	6 (0.4)
ECG QT prolonged	4 (0.3)
Heart rate irregular	4 (0.3)
Tachycardia	3 (0.2)
Arrhythmia	2 (0.1)
AV Block first degree	2 (0.1)
AV Block second degree	2 (0.1)
Bradycardia	2 (0.1)
Sinus Bradycardia	2 (0.1)
Supraventricular tachycardia	2 (0.1)
Ventricular extrasystoles	2 (0.1)
ECG ST-T change	2 (0.1)
Heart rate increased	2 (0.1)
Loss of consciousness	2 (0.1)
Syncope vasovagal	2 (0.1)

	Arrhythmias Reported in at least 1 Patient (Safety Population: All Phase II/III Combined)
	Number (%) of Patients
Preferred Term	**RTG**
	(N=1365)
Any Event	**21 (1.6)**
Heart rate irregular	4 (0.3)
Tachycardia	3 (0.2)
Arrhythmia	2 (0.1)
Bradycardia	2 (0.1)
Sinus Bradycardia	2 (0.1)

Supraventricular tachycardia	2 (0.1)
Heart rate increased	2 (0.1)
Ventricular extrasystoles	2 (0.1)
Atrial Fibrillation	1 (<0.1)
Sinus Tachycardia	1 (<0.1)

Syncope serious adverse events (SAEs): case 03101- study 301 is a likely seizure, 20min LOC followed by confusion, also several small seizures at ER. Case 00004 healthy subject of study 106 had syncope 17 min post dose resolved 2 min, this has quality of true drug effect. Case 25214 study 304- only reports fainting episode on day 72. no additional medical data.

Two events of arrhythmia occurred in study E22-108, the abuse potential study, one a 30 second cardiac arrest, the second, several episodes of ventricular tachycardia. These are presented in greater detail in section 7.3.4, significant adverse events-cardiac.

120 day Safety Update Relevant Cardiac Findings

All Phase II/III Combined Safety Grouping

In the "All Phase II/III combined" group where additional safety data is available from ongoing OL extension studies 303 and 304 revealed only minor change in cardiac events from the initial ISS. There were 5 additional adverse events, but no serious adverse events (SAE) in the category of "Cardiac Rhythm/ Conduction Abnormalities". These were 3 chest pain, 1 palpations, and 1 tachycardia table 77.

Table 77 Cardiac Rhythm/Conduction Abnormalities Reported in at Least 2 Patients (All Phase II/III Combined)

	Number (%) of Patients	
Preferred Term	**RTG (N=1365)**	
	ISS Integrated data Cut-Off: 30 June 2008	**120-Day Safety Data Cut-off: 2 October 2009**
Any Event	**111 (8.1)**	**116 (8.5)**
Chest pain	38 (2.8)	41 (3.0)
Palpitations	18 (1.3)	19 (1.4)
Syncope	12 (0.9)	12 (0.9)
Chest Discomfort	6 (0.4)	6 (0.4)
ECG QT prolonged	4 (0.3)	4 (0.3)
Heart rate irregular	4 (0.3)	4 (0.3)
Tachycardia	3 (0.2)	4 (0.3)
Arrhythmia	2 (0.1)	2 (0.1)
AV Block first degree	2 (0.1)	2 (0.1)
AV Block second degree	2 (0.1)	2 (0.1)
Bradycardia	2 (0.1)	2 (0.1)
Sinus Bradycardia	2 (0.1)	2 (0.1)
Supraventricular tachycardia	2 (0.1)	2 (0.1)

	Number (%) of Patients	
Preferred Term	**RTG (N=1365)**	
	ISS Integrated data Cut-Off: 30 June 2008	**120-Day Safety Data Cut-off: 2 October 2009**
Ventricular extrasystoles	2 (0.1)	2 (0.1)
ECG ST-T change	2 (0.1)	2 (0.1)
Heart rate increased	2 (0.1)	2 (0.1)
Loss of consciousness	2 (0.1)	2 (0.1)
Syncope vasovagal	2 (0.1)	2 (0.1)

Study NP201 (post herpetic neuralgia)

The completed safety database of study NP201 of ezogabine in post-herpetic neuralgia did contain noteworthy cardiac rhythm events. There were 4 cases of atrial fibrillation (2 as SAE and 2 AE) in the ezogabine treatment group and none in the placebo group. The 2 SAE cases were included in the discussion of serious adverse events, section 7.3.2. In review, the two cases of SAE and withdrawal from study were as follows, first an 84 yo male one 600mg a day of ezogabine developed shortness of breath approximately 1 month after beginning ezogabine and was subsequently found to have atrial fibrillation with a rate of 112 beats/ min. A coronary angiogram done to investigate the new onset atrial fibrillation revealed serious coronary artery disease with an occlusion of the left anterior descending artery. In the second case a 73 yo female with borderline hypertension developed fatigue and loss of appetite and dry mouth approximately 3 weeks after beginning ezogabine. She discontinued medication and had an early termination clinic visit the following day. At this visit atrial fibrillation was identified with a ventricular rate of 127 beats/min. the subject was hospitalized and found to have mild renal insufficiency, moderate elevation of hepatic transaminases (3 x ULN) , hyperglycemia (glu 272mg/dl) and mild hyponatremia. The subject was chemically cardioverted to sinus rhythm.

As noted there were a total of 4 cases of atrial fibrillation, the remaining two cases were not entered as serious adverse events (SAE) or a withdrawal from study. These will be briefly reviewed. In the first the patient was a 77 yo male with no prior cardiac history who was hospitalized approximately 2 weeks after beginning ezogabine for nausea, vomiting and fever without diarrhea. He had achieved an ezogabine dose of 450mg a day. During the hospitalization an ECG revealed atrial fibrillation with a rate of 115 beats / min. this subject proceeded to have a complex course of with a diagnosis of C. difficile colitis. hospital discharge and readmission due to a left lower lobe pneumonia. On readmission the patient was in sinus tachycardia with frequent PVCs. During the second hospitalization a pulmonary embolus was diagnosed. The patient again resumed atrial fibrillation with no entry in the record to indicate if the rhythm was later corrected. The second case of atrial fibrillation which entered the safety dataset as an adverse event but not in the category of a serious adverse event or withdrawal was an 84 yo female who presented to an emergency room with palpations approximately 3 weeks after beginning ezogabine and achieving a dose of 200mg TID. In the ER an ECG revealed

atrial fibrillation with a rapid ventricular response. The patient spontaneously converted to sinus rhythm while in the emergency room and was not admitted to the hospital.

Reviewer Comment: Review of events in the all phase II/III safety group does not reveal a compelling cardiac safety signal. There are two cases of concern from the abuse potential study which were quite serious, one had a mitigating circumstance of baseline bradycardia which may have been related to her severe sinus pause / asystole and the second, a case of spontaneous ventricular tachycardia, maximum run of 19 beats is unexplained. There is no evidence that this malignant cardiac dysrhythmia is manifest by an increase in sudden death in this development program. The rate of SUDEP in the clinical trials does not exceed the rate reported in the medical literature for the epilepsy population. **These two cases should be entered into labeling as an event seen in clinical trials.**

The 4 case of atrial fibrillation in study NP201 represent a possible safety signal in this special population. These 4 cases occurred in an ezogabine treatment population of 120 patients and none occurred in the placebo group (60 patients). Comparatively there was only 1 case in the ezogabine treatment group of the pivotal controlled trials treatment group of 813 patients and none in the placebo group of this trial population (427 patients). This represents an occurrence of 3.3% in the post herpetic neuralgia study ezogabine treatment group and none in placebo, a study with a mean age of participants of 63 years. In the pivotal controlled trials group there was an occurrence of only .12% where the mean age was 38 years. **This raises the possibility of a safety signal for induction of atrial fibrillation in the elderly population which should be included in adverse event seen in clinical trials section of labeling**.

Ezogabine Effects on Gall Bladder

Background

In dogs, ezogabine was found to cause changes in the liver included a subcapsular loss and alteration of hepatocytes in lobes adjacent to the gall bladder, sponsor reports: (D-3129/9321020031; D-23129/3000896861; D-23129/3000912148). These findings are believed to be related to localized pressure induced by an enlarged gall bladder resulting from RTG/KCNQ mediated relaxation of smooth muscle. The effects of ezogabine on the gall bladder in the dog did not affect the release of bile.

It was hypothesized that ezogabine could affect smooth muscle in the gall bladder in the same manner that it affects urinary bladder smooth muscle. The inhibition or reduction in gall bladder contractility would then be expected to result in gall bladder enlargement. Subsequent study demonstrated that ezogabine, through its effects on the KCNQ channels, could inhibit the contraction of gall bladder smooth muscle strips (precontracted by histamine application) and reduce the sensitivity of gall bladder smooth muscle strips to histamine-induced contraction.

RCT

Equal numbers of patients reported abnormalities of gall bladder function in the Total RTG and placebo groups. There were 3 SAEs in the placebo group: 2 patients with cholecystitis and 1 patient with hepatic function abnormal; 1 patient in the 1200 mg/day group was an SAE of biliary colic.

All Phase II/III

	Hepatobiliary Abnormalities Reported (Safety Population: All Phase II/III Combined)
	Number (%) of Patients
	RTG
Preferred Term	**(N=1365)**
Hepatic neoplasm	1 (<0.1)
Cholelithiasis	3 (0.2)
Cholecystitis	2 (0.1)
Hyperbilirubinemia	3 (0.2)
Jaundice	1 (<0.1)
Hepatic pain	3 (0.2)
Biliary colic	2 (0.1)
Bile duct obstruction	1 (<0.1)
Cholecystectomy	1 (<0.1)

There were 7 SAEs reported under the SOC of hepatobiliary disorders: 3 (0.2%) events of cholelithiasis and 1 (<1%) each of bile duct obstruction, biliary colic, cholecystitis and hepatitis. In addition, there was 1 SAE of cholecystectomy reported under the SOC of Surgical and Medical Procedures.

Reviewer Comment: the potential for gall bladder dysfunction based on mechanism is of concern, the numbers presented in RCT and all phase II/III are small and do not reveal a safety signal concerning disorders related to gallbladder contractility.

Ezogabine Effects on Liver -

The overall occurrence of liver function study adverse events is presented in table 78 with detailed review of individual cases to follow.

Table 78 Hepatic Enzyme Adverse Events (Safety Population: RCT, Studies 205, 301, and 302)

Preferred Term	**Number (%) of Patients**				
	Placebo N=427	**Ezogabine**			
		600 mg/day N=281	**900 mg/day N=273**	**1200 mg/day N=259**	**Total N=813**
Any hepatic enzyme event	**6 (1.4)**	**6 (2.1)**	**9 (3.3)**	**9 (3.5)**	**24 (3.0)**
GGT increased	2 (0.5)	0	5 (1.8)	3 (1.2)	8 (1.0)
ALT increased	1 (0.2)	1 (0.4)	1 (0.4)	3 (1.2)	5 (0.6)
Liver function test abnormal	0	2 (0.7)	2 (0.7)	1 (0.4)	5 (0.6)

AST increased	2 (0.5)	0	1 (0.4)	1 (0.4)	2 (0.2)
Hepatic enzyme increased	0	2 (0.7)	0	0	2 (0.2)
Transaminases increased	0	0	1 (0.4)	1 (0.4)	2 (0.2)
Hepatic function abnormal	1 (0.2)	1 (0.4)	0	0	1 (0.1)
Blood alk phos abnormal	0	0	0	1 (0.4)	1 (0.1)
Blood alk phos increased	2 (0.5)	0	0	0	0

Brief Synopsis of All SAEs & Withdrawals Based on Liver Function Abnormalities
(The following cases are obtained by a word search using hepatic function search terms of the individual case reports from the initial ISS & 120 day safety report. This approach is undertaken capture all possible cases with any hepatic or liver function search term from within the "deaths, SAEs, discontinuations" narrative case reports. This yields a collection of cases which do not reconcile in numbers with the sponsor table of safety-RCT population in the above table because in some cases the keyword is captured from within the narrative rather than as a term of entry into the AE (adverse event) dataset.

304- 50711: This 32-year-old Caucasian female, with a history of partial epilepsy, laparotomy due to paraovarian cyst, and hepatitis B, was part of an open label ezogabine study. She was taking ezogabine in combination with topiramate, gabapentin, and clonazepam when she developed elevated liver enzymes and drug induced hepatitis that led to hospitalization on [redacted] (b) (6)) and on [redacted] (b) (6). Baseline aminotransferase levels normal. Dx drug induced hepatitis. Patient last dose of ezogabine was on day 225. Patient discharged from hospital on day 243 but readmitted on day 251 due to lack of improvement. AST and ALT peaked on day 252 with values of 571 IU/L and 1017 IU/L respectively. Liver function improvement began on day 257. LFTs normalized by [redacted] (b) (6) approximately 10 weeks after onset of abnormality (not shown in case table below). Although no elevation of bilirubin the transaminase elevation was very severe with a long latency to recovery after discontinuation. The role of the background hepatitis B is uncertain. The sponsor has not indicated if the hepatitis B was a single phase or a chronic hepatitis B which could increase hepatic sensitivity. There is no indication in the sponsor narrative that there was an acute hepatitis B overlapping with the transaminases elevation.

Case 50711					
Date	**ALK PHOS (ULN=100 IU/L)**	**ALT (ULN=37 IU/L)**	**ALT ULN**	**AST (ULN=36 IU/L)**	**T. Bili (ULN=20.52 mmol/L)**
[redacted] (b) (6)	58	10	0.3	12	3.42
	53	10	0.3	12	1.71
	56	18	0.5	20	1.71
	59	15	0.4	15	3.42
	56	10	0.3	13	5.13
	54	11	0.3	11	1.71
	58	9	0.2	14	1.71
	56	8	0.2	11	1.71
	54	10	0.3	14	3.42
	55	15	0.4	12	6.84
	54	13	0.4	13	6.84
	50	15	0.4	13	5.13
	56	14	0.4	15	5.13

(b) (6)	49	20	0.5	18	6.84
	57	40	1.1	31	6.84
	56	52	1.4	30	8.55
	62	146	3.9	75	10.26
	69	242	6.5	110	3.42
	124	1000	27.0	535	6.84

Patient 0448 a 53 yo female suffered with acute renal failure likely due to obstructive uropathy. First symptom occurred 23 days after beginning therapy while on 600mg ezogabine a day. The patient had myalgia, cough, polydipsia and sweats. Laboratory studies revealed increased ALT,AST, Creat, Bilirubin and CRP (328, normal range <12). Patient was hospitalized, on bladder catheterization found to have 1500ml cloudy urine. Ezogabine discontinued and patient discharged from hospital one week later. Patient on concomitant valproic acid 1000mg daily and carbamazepine 800mg daily. See appendix 9.11 for the full timeline and profile of laboratory studies. This patient is also discussed in SAE section

E22-106-000005: a 44 yo WF healthy volunteer in oral contraceptive study, taking 750mg/day ezogabine in period 3 of study, after approximately 16 days of exposure to ezogabine. She noted palpitations. Subsequently had chills and **macular rash** on legs abdomen and back. The following day she noted mild joint pain, muscle weakness and headache, feeling hot and had elevated body temperature (not provided). Max **AST 183** (4.6 ULN), Max **ALT 226** (4.3 ULN). Study drug discontinued. Fever subsided 2 days later. ALT returned to normal 29 days after onset.

202-20210-100011: a 57 yo WF at visit 20 while on ezogabine 400mg day and depakote 750mg daily the patient was found to have elevated ALT to 164 IU/L, and AST 101 IU/L. ezogabine was taper and discontinued and depakote was reduced. Viral hepatitis screen was negative. Three weeks after discontinuation of ezogabine and reduction of Depakote for one week, hepatic enzyme values continued to increase. Depakote was then discontinued. Approximate one month after discontinuation of Depakote the patient lever enzymes returned to normal. This case is confounded by the concomitant depakote. The time line of recover, following removal of Depakote is evidence that the valproic acid was more likely causative of this drug induced hepatitis. The maximum ALT noted at visit (b) (6) is 4.9 ULN, The maximum T. Bilirubin noted, 11.97 umol/L occurs on visit date (b) (6) with a value of 10.26 on (b) (6) the date corresponding to maximum ALT.

Case 100011						
date	**ALK PHOS (ULN=100 IU/L)**	**T. Bili (ULN=20.52 mmol/L)**	**date**	**ALT (ULN=37 IU/L)**	**ALT ULN**	**AST (ULN=36 IU/L)**
(b) (6)	111	6.84	(b) (6)	19	0.5	28
	102	6.84		21	0.6	28
	80	8.55		18	0.5	28
	87	5.13		32	0.9	36
	89	10.26		39	1.1	45
	111	10.26		54	1.5	79
	106	11.97		105	2.8	174

Case 100011						
date	ALK PHOS (ULN=100 IU/L)	T. Bili (ULN=20.52 mmol/L)		ALT (ULN=37 IU/L)	ALT ULN	AST (ULN=36 IU/L)
(b) (6)	97	11.97		101	2.7	164
	103	10.26		128	3.5	150
				156	4.2	215
				182	4.9	341

208-20877-00016: a 49 yo WF after 96 days of ezogabine treatment, while in OL 200mg / day developed elevated ALT and AST, maximum values on day 109 were **ALT 95 IU/L (2.6 ULN) and AST 84 IU/L**, with bilirubin on day 109 6.84 mmol/l but maximum of 20.52 (1 ULN) on (b) (6), which was approximately day 144. ALT on (b) (6) had returned to normal at 28 IU/L. The elevation of bilirubin to exactly the upper limit of normal a month after max ALT is puzzling.

212-00067-00387: a 20 yo BM in OL extension to study 205 developed elevation of ALT and AST with maximum value of 155.8 IU/L and 471.5 IU/L (8.8 ULN) on day 148 of treatment. Patient was in OL study at the time on 900mg / day. Hepatic enzymes were found to be normalized approximately 59 days after withdrawal.

Case 212-00067-00387 Liver Function Values and Visit Date					
Visit Date	Alk Phos (ULN=145 IU/L)	ALT (ULN= 48 IU/L)	*ALT ULN*	AST (ULN= 45 IU/L)	T. Bili (ULN= 20.52 umol/L)
(b) (6)	89	9	0.2	15	6
	92	619	12.9	199	6
	104	542	11.3	161	8
	104	422	8.8	135	6
	104	364	7.6	133	12
	85	48	1.0	25	6

E22-303-03006: a 33 yo WM, began study 301 in placebo, started ezogabine in OL on day 168. ALT found elevated on day 309 while taking 1100mg ezogabine a day. No value given for day 309 corresponding to (b) (6). Available values are 56 IU/L on (b) (6) and 55 IU/L on (b) (6). ezogabine taper began on day 336. Maximum elevation from available data is 1.2 ULN for ALT. This is a very mild hepatic function abnormality of uncertain significance.

NP201-043-0003: 52 yo WM has PMH of HTN, peptic ulcer and hepatitis of unknown etiology was participating in post herpetic neuralgia study. Patient began study drug treatment on (b) (6) wit first mild elevation of transaminases noted on (b) (6). Patient continued in study and reached MTD on (b) (6) at Dose level 4, 200mg TID. On (b) (6) (day 46 of treatment) the patient had moderate elevation of transaminases levels. The patient was discontinued due to this abnormality with last dose of ezogabine on day 50. On repeat lab test of (b) (6) values had returned to

normal. Patient maximum ALT of 107 IU/L (2.5 ULN) on (b) (6) with AST of 120 IU/L (3.3 ULN). Total bilirubin and alkaline phosphatase remained within normal limits.

NP201-021-0003: 68 yo WF , in PHN study. Max ALT 167 IU/L (4.9 ULN) on day 59 of study, ezogabine then discontinued. Total Bilirubin and alk. Phos remained WNL. ALT value normalized in approximately 3 weeks.

NP201-042-0002: 65 yo WF in PHN study, found to have elevated ALT and AST on day 31 (b) (6) in study at dose level 5, 750mg/day. ALT= 245 IU/L, AST= 116 IU/L, Max values occurred 4 days later 9/16/08) , ALT = 349 (10.3 ULN), AST 130 IU/L, total bilirubin 21 umol/L, (ULN= 21 umol/L) Alk Phos 58 IU/L (ULN= remained within normal limits but there was indirect bilirubin increase to 2.4 ULN on (b) (6) Liver function values normalized approximately 3 weeks after ezogabine discontinuation. This is serious drug induced hepatitis with no confounding cause. Although indirect bilirubin level reached 2.4 ULN (17 µmol/L) , total bilirubin level remained within normal limits. Patient was apparently asymptomatic.

NP201-042-0005: a 60 yo WM in PHN study on day 44 of study while taking 450mg ezogabine daily was found to have elevated liver function studies. The patient discontinued study medication with normalization of liver function in approximately 4 weeks. Maximum ALT of 480 IU/L (11.2 ULN) and AST of 429 IU/L (11.9 ULN) with T. bilirubin of 21 (1 ULN) umol/L . This is a serious drug induced hepatitis with no confounding cause but did not reach crisis proportion of 2 x elevation of T. Bilirubin. Patient was apparently asymptomatic. (

NP201-007-0010: a 71 yo WM with hx of HTN and Hypercholesterolemia who was found to have elevated liver function profile on day 43 of ezogabine treatment, receiving 750mg/day at time of event. Study medication was discontinued. Maximum ALT 129 IU/L (3.7 ULN) , AST 57 IU/L (1.6 ULN), T. Bilirubin WNL. ALT continued at 2 ULN 4 weeks after discontinuation. This is a moderate hepatitis , likely study drug induced, the patient was on confounding impastation and a testosterone replacement.

301-00035-03506: a 42 yo WF, developed abnormal liver function profile on ezogabine 1050mg/day on day 141 of study 301. Patient felt mildly sedated but not acutely ill. Last dose ezogabine on (b) (6) Hepatic enzymes trending down but not normalized at last measurement 2 weeks after discontinuation.

Case 03506						
Date	**ALK PHOS (ULN=100 IU/L)**	**ALT (ULN= 37 IU/L)**	**ALT ULN**	**AST (ULN= 36 IU/L)**	**T. Bili (ULN=20.52 mmol/L**	**T.Bili ULN**
(b) (6)	52	51	1.4	39	5.13	0.3
	54	25	0.7	20	3.42	0.2
	55	26	0.7	24	10.26	0.5
	55	23	0.6	31	11.97	0.6
	51	19	0.5	19	11.97	0.6
	48	19	0.5	20	10.26	0.5

Case 03506						
Date	ALK PHOS (ULN=100 IU/L)	ALT (ULN= 37 IU/L)	ALT ULN	AST (ULN= 36 IU/L)	T. Bili (ULN=20.52 mmol/L	T.Bili ULN
(b) (6)	49	15	0.4	32	11.97	0.6
	46	15	0.4	20	11.97	0.6
	49	22	0.6	25	10.26	0.5
	41	59	1.6	39	10.26	0.5
	49	379	10.2	228	15.39	0.8
	60	273	7.4	102	6.84	0.3
	48	115	3.1	56		

301-00105-10511: A 52 yo Hispanic F developed liver function abnormalities on day 42 of treatment with ezogabine while taking 1050mg / day. Patient reported dizziness, language disturbance and increased somnolence, dose was reduced on day 49. On day 56 liver function are improved but remain elevated. Patient was withdrawn from study on day 57. Patient on concomitant valproic acid and topiramate.

Case 10511					
Date	ALK PHOS (ULN=100 IU/L)	ALT (ULN=37 IU/L)	ALT ULN	AST (AST=36 IU/L)	T. BILI (ULN=20.52 umol/L
(b) (6)	101	24	0.6	32	5.13
	107	22	0.6	26	5.13
	120	24	0.6	27	5.13
	95	21	0.6	25	6.84
	88	132	3.6	147	8.55
	94	220	5.9	180	8.55
	111	152	4.1	93	8.55
	96	74	2.0	58	8.55
	93	17	0.5	21	6.84

303-00152-15210: 43 yo Hispanic F. in open label ezogabine treatment experienced increased hepatic transaminases one Day 168 of treatment. Patient also had rash on arms and legs. Patient WBC also low at 2.5K but had been low since baseline. Safety dataset indicates that ezogabine at adverse event date was 1200mg/day. This case of drug induced hepatitis did not reach critical levels with elevation of bilirubin, this case was associated with a rash possibly indicating a broader spectrum of immunologic reaction. The patient was discontinued from the study. ALT and AST returned to normal range when measured 20 days after beginning ezogabine taper and 7 days after last medication dose.

Case 15210					
Date	ALK PHOS (ULN=100 IU/L)	ALT (ULN=37 IU/L)	ALT ULN	AST (ULN=36 IU/L)	T. Bili (ULN= 20.52 umol/L)
(b) (6)	57	14	0.4	14	3.42
	57	15	0.4	17	3.42
	60	14	0.4	15	3.42

Case 15210					
Date	ALK PHOS (ULN=100 IU/L)	ALT (ULN=37 IU/L)	ALT ULN	AST (ULN=36 IU/L)	T. Bili (ULN= 20.52 umol/L)
(b) (6)	59	15	0.4	13	3.42
	62	18	0.5	17	5.13
	59	20	0.5	14	5.13
	59	18	0.5	15	5.13
	73	15	0.4	14	3.42
	59	16	0.4	12	6.84
	54	12	0.3	14	6.84
	56	13	0.4	12	6.84
	60	20	0.5	16	8.55
	84	262	7.1	137	10.26
	81	59	1.6	26	6.84

302-00602-60214: a 33 yo WM developed moderated elevation of ALT and AST, in this case AST exceeded ALT elevation. Peak elevation occurred on (b) (6) (day 86) when patient was withdrawn from study ALT = 102 IU/L (2.1 ULN), AST = 300 IU/L (6.7 ULN). After complete cessation of ezogabine ALT normalized and AST near normal in 2 weeks. No elevation of Total Bilirubin occurred.

304-00853-85314: a 61 yo WM developed elevated hepatic transaminases during open label ezogabine treatment. On (b) (6) (day 247 study) patient had peak elevations and was discontinued from the study.

Case 85314						
Date	ALK PHOS (ULN=145)	ALT (ULN=48)	ALT ULN	AST (ULN=45)	T. Bili (ULN=20.52)	BILI ULN
(b) (4)	68	120	2.5	70	10.26	0.5
	89	88	1.8	53	8.55	0.4
	91	91	1.9	60	8.55	0.4
	99	120	2.5	77	10.26	0.5
	101	86	1.8	52	11.97	0.6
	95	74	1.5	51	10.26	0.5
	90	99	2.1	90	8.55	0.4
	104	88	1.8	72	5.13	0.3
	100	94	2.0	67	10.26	0.5
	89	102	2.1	87	20.52	1.0
	84	282	5.9	246	23.94	1.2
	98	250	5.2	198	8.55	0.4
	92	165	3.4	115	10.26	0.5

NP201-016-0003: a 70 yo WF in study of ezogabine in post herpetic neuralgia was on treatment for 16 days, but 8 days on (b) (6) at 450mg/day when an increase in LDH and total bilirubin was identified. ALT and AST remained within normal limits, total bilirubin had maximum at 1 umol/l over the upper limit of normal (21umol/L). LDH maximum was equal to the upper limit of normal. All values within normal limits 3 days after discontinuation.

301-00102-10211: a 22 yo Hispanic F, in study 301 placebo transitioned to OL ezogabine. On (b) (6) while on 1200mg ezogabine a day approximately six weeks after start of ezogabine the patient was found to have elevated liver function profile. The narrative report indicates that the patient continued into open label extension but no further information on course of event provided. The safety dataset stops entries at (b) (6) indicating that patient discontinued study. AE dataset has blank where study withdrawal would be indicated. No indication of events after (b) (6) while liver transaminases remained elevated. AE dataset indicates action take, study drug reduced but no further narrative or dataset information on recovery. There is no report of an elevation of bilirubin but no information on recovery.

Case 10211					
Date	ALK PHOS (ULN=100 IU/L)	ALT (ULN=37 IU/L)	ALT ULN	AST (ULN=36 IU/L)	T. Bili (ULN=20.52umol/L)
(b) (6)	92	23	0.6	21	5.13
	112	17	0.5	17	5.13
	101	22	0.6	23	3.42
	112	18	0.5	20	5.13
	101	23	0.6	22	3.42
	110	19	0.5	21	3.42
	109	21	0.6	21	3.42
	94	27	0.7	27	1.71
	122	20	0.5	18	5.13
	107	17	0.5	21	3.42
	105	31	0.8	32	5.13
	115	55	1.5	39	6.84
	119	261	7.1	190	6.84
	123	289	7.8	144	10.26
	135	283	7.6	170	6.84

216-00001-00003: a 45 yo WF on OL ezogabine 1200mg / day First elevation of liver function noted on day 84 of study. Patient continued in study until (b) (6) when she was withdrawn. Narrative indicates that liver function abnormality peaked on day 115 with AST 94 IU/L and ALT 137 IU/L. total bilirubin levels not provided. This represents a mild drug induced hepatitis with max ALT approximately 3.5 ULN.

302-00252-25213: a 49 yo WF in study 302 randomized to ezogabine 900mg a day had AE of diarrhea, constipation and vomiting which required two hospitalizations. Patient began abdominal pain and distension about 3 weeks after beginning ezogabine. Patient was withdrawn from study with last study drug on day 63 , (b) (6). Liver function normalized on study of (b) (6). This may have been a drug induced hepatitis. There was a background illness with features of gastroenteritis of uncertain origin and relationship to the elevated liver transaminases.

Case 25213					
Date	ALK PHOS (ULN=100 IU/L)	ALT (ULN=37 IU/L)	ALT ULN	AST (ULN= 36 IU/L)	T. Bili (ULN=20.52umol/L)

Case 25213					
Date	ALK PHOS (ULN=100 IU/L)	ALT (ULN=37 IU/L)	ALT ULN	AST (ULN= 36 IU/L)	T. Bili (ULN=20.52umol/L)
(b) (6)	139	15	0.4	18	3.42
	151	25	0.7	24	3.42
	156	21	0.6	16	3.42
	154	26	0.7	23	6.84
	144	188	5.1	102	8.55
	141	22	0.6	21	3.42

304-00501-50107: a 54 yo WF began ezogabine in transition to OL study 304 on day 117. On day 144 patient began taking 600mg /day. On day 159 (b) (6) patient found to have abnormal liver function studies (also 19 days after beginning treatment with escitalopram for depression). Patient was discontinued from study with last dose of ezogabine on (b) (6) No further lab data available but narrative report reveals abnormal liver function tests resolved on (b) (6) This is likely a drug induced hepatitis but without elevation of bilirubin levels.

Case 50107					
Date	ALK PHOS (ULN= 100 IU/L)	ALT (ULN= 37 IU/L)	ALT ULN	AST (ULN=36 IU/L)	T. Bili (ULN=20.52umol/L)
(b) (6)	105	25	0.7	29	10.26
	92	25	0.7	26	8.55
	105	32	0.9	38	8.55
	94	28	0.8	30	8.55
	101	28	0.8	36	8.55
	141	20	0.5	28	5.13
	139	29	0.8	37	8.55
	117	23	0.6	31	11.97
	137	85	2.3	76	18.81
	168	274	7.4	208	18.81
	209	300	8.1	227	13.68

E22-MR103 001-006: 60 yo WF healthy volunteer for study of modified release form of ezogabine. Elevation of liver function studies noted on day 7 of period 4 (daily dosing for 14 days) and study drug discontinued. Hepatitis panel negative. Although patient exposed to study drug in previous periods there was a 5 week wash out following period 3. Patient had a rapid development of hepatic enzyme elevation, following 7 days of treatment. Ezogabine dose during period 4 is 200mg BID. Liver functions normalized 11 days after medication discontinued. No data on total bilirubin provided. ALT max 328 IU/L (8.9 ULN). Alk Phos elevation to less than 1.5 ULN at peak. This was a rapid onset hepatic drug reaction in a healthy volunteer , no bilirubin data provided. Recover was also rapid.

Case E22-MR103 / 001-006					
Date	Study Period Dosing Day	AST (U/L)	ALT (U/L)	GGT (U/L)	Alk. Phos (U/L)

Case E22-MR103 / 001-006					
Date	Study Period Dosing Day	AST (U/L)	ALT (U/L)	GGT (U/L)	Alk. Phos (U/L)
(b) (6)	Screening	21	38	--	94
	P1 Check-in	21	32	--	93
	P1 Discharge	31	40	--	91
	P2 Check-in	18	27	--	93
	P2 Discharge	21	25	--	92
	P3 Check-in	19	24	--	94
	P3 Discharge	31	35	--	94
	P4 Check-in	16	17	--	92
	P4 D7	163	328	--	185
	P4 D7 Repeat	68	237	222	174
	P4 Follow-up	35	130	191	162
	P4 Follow-up	20	35	114	126
	P4 Follow-up	23	39	98	118
		--	16	55	--
		--	--	26	--
Normal range		<31	<36 [5-37] for the test on (b) (6)	<36 [7-32] for the tests on (b) (6)	35-122

212-00078-00541: a 29 yo WM in study 212, on 900mg ezogabine a day developed increased GGT on day 176 that peaked on day 475 at 235 IU/L. On day 321 (b) (6) patient developed increased level of ALT that resolved on day 475. The patient had nausea and vertigo on day 482. The GGT elevation is of uncertain origin but also non specific. The increase in ALT in June of 2001 peaks on (b) (6) the resolves after dose reduction. Patient subsequently withdrew from study 3 months later. This is a mild elevation of transaminase of uncertain origin.

Case 00541					
Date	ALK PHOS (ULN=145 IU/L)	ALT (ULN=48 IU/L)	ALT ULN	AST (ULN= 45 U/L)	T. Bili (ULN= 20.52)
(b) (6)	98	47	1.0	26	11
	114	43	0.9	17	9
	91	38	0.8	16	9
	107	38	0.8	18	11
	103	60	1.3	30	14
	119	61	1.3	35	10
	108	68	1.4	30	9

Case 00541					
Date	ALK PHOS (ULN=145 IU/L)	ALT (ULN=48 IU/L)	ALT ULN	AST (ULN= 45 U/L)	T. Bili (ULN= 20.52)
(b) (6)	117	38	0.8	24	13
	107	42	0.9	21	7
	101	46	1.0	22	15

304-00401-40142: 55 yo WF enrolled in study 302 in placebo arm, subsequently transitioned to OL treatment in study 304 beginning ezogabine on (b) (6) Approximately 3 months after starting ezogabine treatment at 600mg a day the patient had increase in ALT to 1.5 ULN, the following month level went to 4.2 ULN with AST about 2.5 ULN. Total Bilirubin remained normal. Medication taper to discontinuation began on (b) (6) with last dose on (b) (6). On (b) (6) transaminase values trending toward normal (one week after cessation).

Case 40142					
Date	ALK PHOS (ULN= 100 IU/L)	ALT (ULN= 37 IU/L)	ALT ULN	AST (ULN= 36 IU/L)	T. Bili (ULN= 20.52mmol/L)
(b) (6)	66	20	0.5	20	5.13
	71	19	0.5	20	3.42
	64	22	0.6	22	3.42
	66	22	0.6	21	3.42
	67	21	0.6	25	5.13
	89	25	0.7	26	5.13
	79	25	0.7	26	5.13
	64	21	0.6	21	5.13
	81	27	0.7	28	8.55
	73	25	0.7	25	8.55
	73	30	0.8	28	10.26
	79	55	1.5	40	10.26
	90	154	4.2	98	10.26
	88	171	4.6	124	8.55
	90	80	2.2	54	5.13

304-00852-85201: 34 yo WM with elevated ALT and AST (seen in table below) at screening and during placebo treatment in study 302 began OL treatment with ezogabine 900mg / day on (b) (6). Following treatment the transaminases elevated further, subsequently ezogabine tapered on (b) (6) with discontinuation on (b) (6) One week after discontinuation ALT trending toward normal with value lower than at screening.

Case 85201					
Date	ALK PHOS (ULN=145 IU/L)	ALT (ULN=48 IU/L)	ALT ULN	AST (ULN=45 IU/L)	T. Bili (ULN=20.52 mmol/L)
(b) (6)	110	83	1.7	130	17.1
	87	26	0.5	42	10.26

(b) (6)	88	41	0.9	54	11.97
	78	23	0.5	44	6.84
	94	20	0.4	51	5.13
	93	88	1.8	215	22.23
	125	63	1.3	120	18.81
	109	100	2.1	164	13.68
	92	43	0.9	55	8.55
	87	38	0.8	74	8.55
	104	74	1.5	113	17.1
	94	25	0.5	53	13.68
	127	112	2.3	141	13.68
	108	146	3.0	170	8.55
	116	62	1.3	54	6.84

304-00852-85206: 24 yo WF enrolled in placebo arm of study 302 began OL treatment in study 304 on (b) (6) with 900mmg ezogabine a day. Due to increase transaminases patient began study taper on (b) (6) with last dose taken on (b) (6). transaminases normalized on last laboratory study of (b) (6). No symptoms or prodrome reported.

Case 85206					
Date	ALK PHOS (ULN=145 IU/L)	ALT (ULN=48 IU/L)	ALT ULN	AST (ULN=45 IU/L)	T. Bili (ULN=20.52 mmol/L)
(b) (6)	57	27	0.7	17	5.13
	58	18	0.5	14	6.84
	67	21	0.6	13	6.84
	66	19	0.5	12	5.13
	57	16	0.4	13	6.84
	64	14	0.4	13	5.13
	64	20	0.5	15	10.26
	67	20	0.5	13	5.13
	58	19	0.5	14	8.55
	78	20	0.5	15	6.84
	59	168	4.5	74	8.55
	58	186	5.0	75	8.55
	63	318	8.6	110	8.55
	66	33	0.9	17	5.13

Reviewer Comment: 27 cases of liver function abnormality are presented above drawn from SAEs or discontinuations in the ezogabine safety database. In one of the 27 there was a significant elevation of total bilirubin to 1.7 ULN but this occurred on a background of an infectious illness. In one case the ALT level was elevated to an extreme range of 27 ULN but total bilirubin remained within normal limits. In the remainder of cases there was less extreme elevation of aminotransferases. In all cases the levels improved or normalized after discontinuation of ezogabine. In two cases there was an associated, non serious rash which raises the possibility of drug induced hepatitis occurring in the broader context of a systemic immune response. There were six cases of elevated transaminases levels in the post herpetic neuralgia study (NP201).

The 6 SAEs / discontinuations which occurred in study NP201 were in a total ezogabine treatment population of 120 patients compared to 7 SAE / discontinuations in the pivotal controlled trials of safety population of 813 patients. This represents an incidence of 5% in the study NP201 population compared to 0.86% in the ezogabine treated population in the pivotal controlled trials. The mean age of patients in study NP201 was 63 years and the mean age in the pivotal controlled trials was 37.2 years. The mean age of NP201 SAE / discontinuations for liver function abnormalities was 64.3 years compared to 44.6 years in the same category from the pivotal controlled trials ezogabine safety group. These SAE / discontinuation rates compared to study population age **suggest the older population may be at greater risk for drug induced hepatic dysfunction.**

Review of the SAEs / discontinuations for hepatic laboratory abnormalities reveals that ezogabine has the capacity to induce hepatic transaminases elevation, which may represent hepatocellular injury. This capacity has not reached a magnitude of hepatic injury which breaches the hepatic reserve for bilirubin uptake and excretion (Hy's Law screen (p 205); however these cases indicate a need for recognition of this capacity in labeling and increased pharmacovigilance in the post marketing interval to detect more severe cases, should they occur. This may be especially true for the population over age 60 which did not have a large representation in epilepsy clinical trials but had a disproportionate representation of cases in the small NP201 trial. Proposed labeling recognized the elevation of liver function tests in " Clinical Trials Experience" – " other adverse reactions seen", based on current evidence this is an appropriate strength of labeling, however based on the observations of liver function abnormalities in study NP201 increased post marketing pharmacovigilance should be initiated.

Speech and Cognitive/Memory Effects

	Adverse Events Relating to Speech and Cognitive/Memory Effects (Safety Population: RCT, Studies 205, 301, and 302)				
	Number (%) of Patients				
		RTG	**RTG**	**RTG**	**RTG**
Preferred Term1	**Placebo (N=427)**	**600 mg/day (N=281)**	**900 mg/day (N=273)**	**1200 mg/day (N=259)**	**Total (N=813)**
Cognitive events	32 (7.5))	33 (11.7)	57 (20.9)	90 (34.7)	180 (22.1)
Confusion type	14 (3.3)	13 (4.6)	22 (8.1)	52 (20.1)	87 (10.7)
Memory type	20 (4.7)	23 (8.2)	39 (14.3)	50 (19.3)	112(13.8)
Processing type	0	2 (0.7)	4 (1.5)	4 (1.5)	10 (1.2)
Speech (speech abnormalities grouped)	11 (2.6)	21 (7.5)	32 (11.7)	62 (23.9)	115 (14.1)

Conclusion: There was an apparent relationship between AE incidence and randomized ezogabine dose for overall cognitive events, confusion and memory type of events and also for adverse events related to speech. There also appeared to be a relationship between speech and cognitive events with 57% (66/115) of patients who reported a speech event also experiencing a cognitive event.

Psychotic Symptoms

Psychiatric adverse reactions related to psychosis are the concern of this section. Search terms are chosen for examination of the adverse event dataset by selecting verbatim terms which are related to psychosis (Psychotic Symptoms), (table A, appendix 9.14). These terms are then mapped to their respective preferred terms (PT), (table B appendix 9.14). Additional search terms that have an association with psychotic symptoms are selected from all preferred terms from within the SOC term "psychiatric disorders" associated with two or more withdrawals from study, (table C, appendix 9.14). Among these terms, withdrawal due to confusional state is the most common. This term is not retained as a search term because of lack of specificity for psychiatric reactions and may be due to non-specific sedative effects of study medication. Insomnia was also not included as a severe psychiatric search term although there were 25 occurrences and 3 withdrawals in the RCT dataset. The combined search terms (PTs) chosen to capture psychotic symptoms are displayed in (Table D, appendix 9.14).

The search terms are subsequently divided into two sets, the first set, actually a subset of the broad table D set. This is conceptually a focused "psychotic symptom" subset, directly related by the content of the search words which are psychotic features. This subset contains only the preferred terms "psychotic disorder", "acute psychosis", "hallucination", "hallucination, visual", and "hallucination, auditory".

The second set is the full search term set seen in table D whose purpose is to capture psychotic symptoms which may not be coded by the more specific psychosis related preferred terms in the focused subset.

RCT

The table D search terms are used to capture events from the AE (adverse event) dataset. The subsets of events from the double blind treatment interval (titration and maintenance) phase are selected using the PH23 dataset indicator. This search yields 158 events. The events are analyzed to remove duplicate entries associated with each preferred term category and are shown in table 79. The number of cases entered in the row titled "any event" is also adjusted to remove duplicate entries which may occur in different preferred term categories.

Table 79 Psychotic Symptom adverse events by Dose derived from 30 Preferred Term Search to Capture Major Psychiatric Events. (RCT)

Preferred Term-	**PBO**		**600mg/ day**		**900mg/ day**		**1200mg/ day**		**Total**	
	N=427	**%**	**N=281**	**%**	**N=273**	**%**	**N=259**	**%**	**N=813**	**%**
ANY EVENT (unique patients)	27	6.3	16	5.7	19	7.0	43	16.6	78	9.6
ANXIETY	8	1.9	7	2.5	5	1.8	12	4.6	24	3.0
DISORIENTATION	3	0.7	1	0.4	1	0.4	12	4.6	14	1.7

Preferred Term-	PBO		600mg/ day		900mg/ day		1200mg/ day		Total	
	N=427	%	N=281	%	N=273	%	N=259	%	N=813	%
HALLUCINATION, VISUAL	0	0.0	2	0.7	2	0.7	4	1.5	8	1.0
PSYCHOTIC DISORDER	0	0.0	0	0.0	1	0.4	6	2.3	7	0.9
DEPRESSION	14	3.3	1	0.4	3	1.1	2	0.8	6	0.7
ABNORMAL BEHAVIOUR	1	0.2	1	0.4		0.0	4	1.5	5	0.6
HALLUCINATION	1	0.2	1	0.4	2	0.7	2	0.8	5	0.6
EUPHORIC MOOD	0	0.0	1	0.4	2	0.7	1	0.4	4	0.5
AFFECT LABILITY	0	0.0	0	0.0	1	0.4	2	0.8	3	0.4
BRADYPHRENIA	0	0.0	0	0.0	3	1.1	0	0.0	3	0.4
AGGRESSION	3	0.7	2	0.7	0	0.0	0	0.0	2	0.2
HALLUCINATION, AUDITORY	1	0.2	1	0.4	0	0.0	1	0.4	2	0.2
SUICIDAL IDEATION	0	0.0	0	0.0	0	0.0	2	0.8	2	0.2
ACUTE PSYCHOSIS	0	0.0	1	0.4	0	0.0	0	0.0	1	0.1
DEPERSONALISATION	0	0.0	0	0.0	1	0.4	0	0.0	1	0.1
ILLUSION	0	0.0	0	0.0	1	0.4	0	0.0	1	0.1
PARANOIA	0	0.0	0	0.0	0	0.0	1	0.4	1	0.1
THINKING ABNORMAL	0	0.0	1	0.4	0	0.0	0	0.0	1	0.1
AGITATION	1	0.2	0	0.0	0	0.0	0	0.0	0	0.0

A total of 158 event are captured which are generated by 105 unique patients. There were 27 unique events in the placebo group and 78 in the ezogabine treatment group with the frequency of ezogabine treatment exceeding placebo by 3.3% in the analysis or alternatively the ezogabine event rate is 1.5 times the placebo adverse event rate. The percent of events for the total ezogabine treatment exceeded placebo for all psychiatric adverse events except depression where total placebo exceeded total ezogabine events by 2.6%. There was a dose response noted for the terms psychotic disorder and hallucination with ezogabine treatment in excess of placebo at all doses. There were no placebo entries for psychotic disorder or hallucination-visual compared to 6 and 4 ezogabine cases respectively. **There were 8 withdraws and 2 SAEs (both SAEs were also study withdrawal) in the placebo group compared to 28 withdraws and 8 SAEs (1 SAE was not also a study withdrawal) in the ezogabine treatment groups.** This observation supports the conclusion that ezogabine is causative of these psychotic symptoms.

The core terms for hallucination and psychosis including hallucination, hallucination-visual, psychotic disorder, hallucination-auditory, and acute psychosis are examined separately from the larger body of search terms, table 80. This evaluation reveals a separation between placebo and total ezogabine adverse events that is larger than the corresponding categories in table 79 which included all search terms. The findings of the “Psychotic Symptoms” analysis, table 79, are compared to the findings of the focused “psychotic symptom” analysis, table 80. Any event placebo and total ezogabine treatment reveals a smaller separation between placebo and ezogabine treatment, 6.3% vs 9.6% respectively in the larger “psychotic symptom” analysis than in the focused (5 term) “psychotic symptom” analysis where total placebo and ezogabine events are 0.5% and 2.7% respectively. The adverse event rate in the focused subgroup is approximately 5 times greater in total ezogabine treatment than in the total placebo treatment group. This observation suggests that there is a more specific

relationship between the "psychotic symptoms" encompassed by the focused list of terms than in the broad list of search terms table 79. This conclusion is also supported by the observation that the only two terms with a dose response are included in the "focused" group.

Table 80 Psychotic Symptom adverse events by Dose, Derived from "Focused" Search Term Subset. (RCT)

Preferred Term-	PBO		600mg/ day		900mg/ day		1200mg/ day		Total	
	N=427	%	N=281	%	N=273	%	N=259	%	N=813	%
ANY EVENT	2	0.5	4	1.4	5	1.8	13	5.0	22	2.7
HALLUCINATION, VISUAL		0.0	2	0.7	2	0.7	4	1.5	8	1.0
PSYCHOTIC DISORDER*		0.0		0.0	1	0.4	6	2.3	7	0.9
HALLUCINATION	1	0.2	1	0.4	2	0.7	2	0.8	5	0.6
HALLUCINATION, AUDITORY	1	0.2	1	0.4		0.0	1	0.4	2	0.2
ACUTE PSYCHOSIS		0.0	1	0.4		0.0			1	0.1
Shaded row sections represent dose response values										
*verbatim terms for "psychotic disorder" for the 7 ezogabine patients include; psychosis, psychosis to observation transient postictal psychotic disorders, psychosis (hallucination), exacerbation of chronic interictal psychosis, postictal psychotic episode.										

Within the focused "Psychotic Symptoms", terms, table 80 there were 12 (1.5%) withdrawals in the ezogabine treatment group and 0 in the placebo group. Among the broader search term group (table D, appendix 9.14**) there were 28 (3.4%) study withdrawals in the ezogabine treatment group and 8 (1.9%) in the placebo group.** Based on study withdrawals the larger search analysis does not yield a significantly different placebo-ezogabine separation (both 1.5%) than the focused analysis which is restricted to 5 psychosis terms, however in the "focused" group there are 0 placebo events which increases the weight of the ezogabine cases. Within the overall adverse events the "focused" subset (**table 80**) better distinguishes between ezogabine and placebo treatment.

The individual case reports of the 12 focused "Psychotic Symptom" withdrawals are reviewed, 4 of these have features consistent with a diffuse cerebral dysfunction that may be seen in drug intoxication. In two cases a post ictal psychosis was present and in the remaining 6 cases the psychiatric adverse event emerged as a discrete event unrelated to diffuse cerebral dysfunction (appendix 9.14). In the cases consistent with drug intoxication / diffuse cerebral dysfunction the recovery after drug discontinuation occurred in 3 days or less. In the 6 "drug effect" cases, recovery data is only provided in two. One of these had a 9 day recovery and the second a 25 day recovery.

Among the 28 withdrawals in the broad "Pyschotic Symptom" search term group, 9 had a prior psychiatric history identified (source: medical history dataset). One withdrawal was associated with hospitalization in this group (11%) whereas there were 3 hospitalizations at time of withdrawal from within the 19 subjects (16%) who did not have a prior psychiatric history. If hospitalization is considered an index of reaction

severity this observation does not support a difference in severity of event between those with and without a past psychiatric history. Among the 11 placebo patients withdrawn from the broad "Pyschotic Symptom" search term group there was only one who had an identified past psychiatric history and this patient did not have a hospitalization associated with study withdrawal. In the placebo group there was one hospitalization at time of withdrawal which occurred in a patient with no prior psychiatric history.

In the 30 term event analysis (broad "psychiatric symptoms" search term group) the occurrence of past psychiatric history was 9% among those with psychiatric adverse events in the placebo group compared to 30% of those with a psychiatric adverse event in the ezogabine treatment group. This indicates that a "Psychotic Symptom" adverse event may be more likely to occur in a patient with prior psychiatric history.

Reviewer Comment: Examination of the RCT safety dataset for core "Psychotic Symptom" preferred terms (hallucination, hallucination-visual, hallucination-auditory, psychotic disorder, and acute psychosis) reveals a 2.7% occurrence of these events in ezogabine treatment patients compared to 0.5% of patients in the placebo group, table 80. Further review of the SAEs / withdrawals reveals features of a discrete drug related effect in 6 patients with insufficient data to comment on the rate of recovery in these patients. There is an intuitive concern that a history of prior psychiatric disorder would increase risk of more severe "Psychotic Symptom" adverse effect but this is not supported by the observation that hospitalization is more frequent in those with no psychiatric history. However a "Psychotic Symptom" adverse effect may be more likely in those with a past psychiatric history. The examination results in a conclusion that the occurrence of "Psychotic Symptom" adverse event is a safety signal in ezogabine treatment, it appears to be an independently emergent effect (not associated with concurrent drug intoxication terms) in approximately half of the events and may occur in the context of drug intoxication or post ictal state in the remaining half.

All Phase II/III events

The search terms of table D are applied to the "All phase II/III combined analysis set". There are 439 "Psychotic Symptom" adverse events identified and 70 unique patient study withdrawals. Among the ezogabine treated study withdrawals all adverse event terms with an occurrence greater than two patients are presented in table 81. The most frequent adverse event was anxiety. The most frequent reasons for withdrawal were psychotic disorder and anxiety both with 13 withdraws, however these 13 withdrawals represents 72% of those with an AE of psychotic disorder and 17% of those with an AE of anxiety.

Table 81 "Psychotic Symptom" Adverse Events Derived from 30 Preferred Term Search to Capture Psychiatric Events. (All phase II/III combined analysis set)

Preferred term	AE Unique patients	AE % 1365	Unique patients withdrawal	Withdrawal as % of AE patients (PTNAME)
PSYCHOTIC DISORDER	18	1.3	13	72.2
ANXIETY	78	5.7	13	16.7
DISORIENTATION	32	2.3	7	21.9
HALLUCINATION, VISUAL	16	1.2	5	31.3
ABNORMAL BEHAVIOUR	12	0.9	3	25.0
HALLUCINATION	23	1.7	3	13.0
HYPOMANIA	4	0.3	2	50.0
BRADYPHRENIA	13	1.0	3	23.1
CONVERSION DISORDER	7	0.5	3	42.9
DELIRIUM	2	0.1	2	100.0
THINKING ABNORMAL	8	0.6	3	37.5

Study 3065 A1-209 is given special note here as part of the "All phase II/III combined analysis set". There were five study withdrawals all due to psychotic symptoms. This was a study with rapid dose titration, see table 81b for full presentation of the patients and dose schedule. This study is discussed more fully in the following section on the relation between psychotic features and rate of titration.

One of the most intense psychotic reactions in the "All Phase II/III combined" studies occurred in a patient with previous psychiatric history. This patient in study 303 (case 10508), had an SAE and study withdrawal due to major depression. This reaction was considered more intense based on the duration of the reaction which was ongoing 3 weeks after ezogabine discontinuation and the intensity of the reaction which included auditory and visual hallucinations, delusion and catatonia.

Relation between psychotic symptoms and rate of titration

The relation between psychotic symptoms and rate of titration is illustrated by study 209 where dose escalation was evaluated in sequential groups to achieve doses of 300, 400 or 600mg QID (four times a day), with rapid titration. In this study there were 5 study withdrawals. These five withdrawals comprised 18.5% of the 27 enrolled patients. All of the withdrawals were due to psychosis. Two of the adverse effects were recorded as hallucination, one due to psychotic disorder and two due to delusion, however all were identified in the narrative case report as "psychosis". The relationship to the rate of titration is presented in table 81b below which reveals that the minimum rate of exposure to ezogabine in the interval up to the adverse event was near twice the titration rate in proposed labeling. At the time of the adverse event patients were on

ezogabine treatment alone with background AEDs discontinued for 24 hours. This raises the confounding issue of the role that background AED withdrawal might play in the resultant adverse event; however there is no report of seizure in the case narratives of these patients and no statement that these events appeared to be post ictal psychosis.

Table 81b Study 209, titration rate of subjects with psychotic symptoms and study withdrawal

Patient ID (study group)	Full Days of treatment prior to AE	Cumulative dose in mg of ezogabine during full treatment days prior to AE	Multiple of proposed labeled dose during full treatment days	Day of AE	Cumulative dose in mg ezogabine prior to AE	Multiple of proposed label dose prior to AE	Adverse event
019	<1			1	800mg	2.7	Severe paranoid psychosis
025	1	600mg	2	2	1100mg	1.8	Paranoid psychosis
018	1	1200mg	4	2	2600mg	4.3	Severe psychosis
030	2	1400mg	2.3	3	1700mg	1.9	Paranoid psychosis
017	2	2500mg	8.3	3	2800mg	3.1	Delusional psychotic disorder

Study 209 overview: This was a pilot, open label, sequential group study to determine the dose of ezogabine to be used in a larger monotherapy study in patients scheduled for surgical treatment of epilepsy. Inclusion criteria included cessation of background AEDs. Long acting barbiturates, bromide, and benzodiazepines were discontinued 14 days before the first ezogabine exposure. Other AEDs were discontinued 24 hours before ezogabine exposure. Patients were assigned to study groups, each with a different daily ezogabine dose schedule, the schedule of ezogabine administration to each of the 5 withdrawal patients is provided in the **lower portion of this table.**

Subject 017

02 Sep 99	2:50 pm	400 mg
	9:03 pm	400 mg
03 Sep 99	3:00 am	400 mg
	9:00 am	400 mg
	3:00 pm	500 mg
	9:00 pm	400 mg
04 Sep 99	3:10 am	300 mg

Subject 018

16 Sep 99	8:45 am	400 mg
	3:30 pm	400 mg
	9:00 pm	400 mg
17 Sep 99	2:45 am	400 mg
	8:45 am	500 mg
	2:45 pm	500 mg

Subject 019			Subject 025		
20 Sep 99	9:30 am	400 mg	07 Feb 00	12:00 pm	200 mg
	3:00 pm	400 mg		4:00 pm	200 mg
				8:00 pm	200 mg
			08 Feb 00	0:00 pm	200 mg
				6:00 am	300 mg

Subject 030		
11 May 00	12:00 pm	200 mg
	6:00 pm	200 mg
12 May 00	00:00 pm	200 mg
	6:00 am	200 mg
	12:00 pm	300 mg
	6:00 am	300 mg
13 May 00	00:00 pm	300 mg

A case of a brief but severe psychosis not part of the "All Phase II/III analysis set" occurred in a healthy volunteer participating in study 106. This study is in the "Integrated Pharmacology Analysis Set". The subject was a healthy patient in a PK study of ezogabine and norethindrone (case 00022). This patient achieved a dose of 900mg in 12 days. In the dose escalation of proposed labeling an individual will receive 450mg at day 12. The day after reaching the 900mg dose the patient was found in her room "screaming and crying stating she had been split in half and was bleeding." This occurred 9 minutes after her morning 300mg dose of study drug. The titration rate in this case was 33% more rapid than the labeled titration rate.

There was another instance of psychotic episode in a healthy volunteer, also, not associated with the "All Phase II/III analysis set". This study was an open label, randomized, up titration study to assess the effect of urine sampling handling on safety results of urine, study RTG114137. In this case the titration rate was only modestly accelerated over the rate proposed in current labeling. A subject reached a dose of 900mg at the beginning of week 4, where in proposed labeling a dose of 750mg would be achieved. This subject (report # 2010VX000835) was a healthy volunteer who also had a previous history of suicidal gesture and possibly bipolar disorder. The subject had psychotic symptoms 40 minutes after his second 300mg dose of day 24 (this day scheduled for 900mg total daily dose). He began to talk incoherently, became extremely agitated and attempted to break glass windows and a mirror. He referred to wanting to commit suicide. This event occurred in a situation with both an accelerated titration rate and a background of previous psychiatric history which both show evidence of increasing the likelihood of a psychoactive adverse event. This event resulted in the discontinuation of study RTG114137, the sponsor report indicates "*The principal investigator indicated that the site did not feel comfortable continuing to dose subjects further, based on this event and similar (although less extreme) cases of hallucination, ataxia, confusional state at higher doses that were reported by other subjects*"

Psychoactive effect in rapid titration is further explored in the discussion of drug abuse potential where 171 of the 234 "euphoria" related events are produced by 2 of the 21 pharmacology studies, in these studies titration was notably accelerated.

Reviewer comment: Examination of the "Psychotic Symptom" related events in the RCT and "All phase II/III combined" is performed. Two analysis are performed for the RCTs, a focused examination of 5 core "Psychotic Symptom" search terms and a 30 term search derived from verbatim terms related to psychosis and any term in the SOC "psychiatric disorders" associated with 2 or more study withdrawals. Confusional state and insomnia were then excluded from the search due to lack of precision.

Five core terms were included in the RCT analysis which included psychotic disorder, acute psychosis, hallucination, hallucination-visual, and hallucination-auditory. There was separation between the total numbers of adverse events occurring in placebo compared to the ezogabine treatment groups. There was also separation between the discontinuations in the placebo and ezogabine treatment group with none occurring in the placebo group and 12 withdrawals in the ezogabine treatment group.

The 5 core "Psychotic Symptom" terms revealed a greater placebo –ezogabine difference in adverse event occurence than the results of the 30 term "Psychotic Symptom" search. In the 30 term analysis the adverse event as a percent of the total ezogabine treatment group was 1.5 times greater than the placebo group. In the 5 core term analysis the total ezogabine treatment group adverse events were 5 times greater than the placebo group- when the adverse events are derived as a percent of the total treatment group. In the 30 term search the percentage of adverse events in placebo vs ezogabine treatment were 6.3% vs 9.6% compared to 0.5% vs 2.7% in the core terms. All withdrawals associated with hospitalization occurred exclusively in the 5 core "Psychotic Symptom" search terms with no hospitalizations added by the additional 25 terms in the expanded search term group. This indicates the 5 core "Psychotic Symptom" terms are associated with more severe events.

Examination of the case narratives of the SAEs and study withdrawals reveals 13 (1.0%) cases of psychiatric reactions in 1365 patients; although one case represents an overdose where the patient had taken a 900mg single dose of ezogabine rather than divided into three doses. Further examinations of the clinical pharmacology studies and a special study of urine sample handling in healthy volunteers reveal an overall picture where the most severe cases were seen in settings of rapid titration and possibly prior psychiatric history.

Conclusion: Ezogabine is significantly psychoactive when delivered at accelerated titration rates and / or in select sensitive individuals. At the extreme ezogabine is seen to produce psychotic symptoms. Individuals with prior psychiatric history may be more sensitive to this property of ezogabine. In proposed labeling psychiatric disorders are noted in section 5.4 of warnings and precautions; however the conditions of high dose and rapid titration which are more commonly associated with the emergence of psychotic symptoms are not

presented. These conditions should be added to section 5.4 of warnings and precautions: *Psychosis and/or hallucinations were reported in 3% of patients on POTIGA, versus <1% for patients on placebo; 2% of patients discontinued POTIGA because of psychotic symptoms. These reactions are related to dose and accelerated titration.*

Suicidal Behavior

Based on the independent adjudication, in randomized controlled trials, there were 2 events in 813 ezogabine-treated patients of completed suicide, suicidality, or self injurious behavior compared with 2 events in 427 placebo-treated patients. Specifically, ezogabine-treated patients demonstrated 0 suicides and 2 events of suicidality (1 suicide attempt and 1 suicidal ideation). Placebo-treated patients had 0 suicides and 2 events of suicidality (both suicidal ideation).

The rate of suicidal thoughts and behavior reported in the placebo-controlled trials of ezogabine was similar to placebo. The rate of 1.6 patients with events per 1000 patients treated with ezogabine was consistent with that reported in the Agency's meta-analysis of 11 approved AEDs (3.6 patients with events per 1000 patients with epilepsy).

Reviewer Comment: there is no evidence of a signal for increased suicidality in the ezogabine treatment group of the RCTs.

7.4 Supportive Safety Results

7.4.1 Common Adverse Events

Overview

All Phase II/III Combined studies & Clinical Pharmacology Studies

The 6 most commonly reported TEAEs among ezogabine-treated patients were dizziness, headache, fatigue, disturbance in attention, somnolence, and nausea, reported by 11 to 32% of patients. All other AEs were reported by less than 10% of patients in the total ezogabine treatment group (in the Pivotal Controlled Trials grouping). The incidence of headache was similar in placebo and ezogabine-treated patients; the other 3 most commonly reported TEAEs were reported at a higher incidence in ezogabine-treated patients.

Most of the TEAEs reported by ezogabine-treated patients were mild or moderate in intensity; among the ezogabine dose groups, patients in the 1200 mg/day group had the highest proportion of TEAEs reported as severe (20% in the Pivotal Controlled Trials grouping).

The AE data from "All Phase II/III Combined" studies suggested that the incidence of AEs did not increase notably with longer exposure to ezogabine and that the profile (e.g., intensity) was similar.

Pivotal Controlled Trials (Studies 205, 301, and 302)

The incidence of TEAEs was 75% in the placebo group and 81% in the total ezogabine treatment group. TEAEs with the highest incidence in the total ezogabine treatment group were dizziness (23%), somnolence (22%), headache (15%), and fatigue (15%); these events were reported by 9%, 12%, 16%, and 6%, respectively, of placebo-treated patients.

There were 3 TEAEs with a treatment difference ≥5% for patients in each of the three ezogabine dose groups compared with placebo: dizziness, fatigue, and vertigo.

A TEAE was considered to be a dose-related ADR (adverse drug reaction) if the incidence was greater in the total ezogabine treatment group than in the placebo group and the incidence increased with each increasing ezogabine randomized dose. In the Pivotal Controlled Trials, there was an apparent relationship between AE incidence and randomized ezogabine dose for the following events: dizziness, somnolence, confusional state, tremor, coordination abnormal, memory impairment, vision blurred, speech disorder, gait disturbance, aphasia, balance disorder, and constipation.

Although the incidences were at least 2-fold greater in patients who received ezogabine versus placebo, there did not appear to be a dose relationship for fatigue, vertigo, diplopia, disturbance of attention, asthenia, or dysarthria.

The most commonly reported AEs generally were reported more frequently during the titration phase than during the longer maintenance phase in both the placebo and ezogabine treatment groups.

All Phase II/III Combined studies

In All Phase II/III Combined studies, the most common AEs were similar to those seen with ezogabine in Pivotal Controlled Trials. Incidence rates for the more common AEs were similar to or slightly higher than those for the Total RTG group (and generally comparable to those for the highest ezogabine dose group) in Pivotal Controlled Trials, suggesting that AEs did not increase notably with longer exposure to ezogabine. The AE profile was also similar with respect to intensity, relatedness, and time to first occurrence.

Pivotal controlled Trials (studies 205,301,302)

At least one TEAE was reported by 75% of patients in the placebo group and 81% of patients in the Total RTG group. Among patients in the ezogabine dose groups, at least one TEAE was reported by 74%, 82%, and 88% of the 600, 900, and 1200 mg/day dose groups, respectively.

In the total ezogabine treatment group, dizziness and somnolence were the TEAEs with the highest incidence (23% and 22%, respectively); headache and fatigue were the other AEs reported by >10% of the Total RTG group (15% each). Among these 4 TEAEs, a greater proportion of patients in the total ezogabine treatment group than in the placebo group reported dizziness (23% versus 9%), somnolence (22% versus 12%), and fatigue (15% versus 6%). Headache was reported by similar proportions of patients in the total ezogabine treatment group and placebo groups (15% and 16%, respectively), table 82.

Among the most common events, there were 4 TEAEs with a treatment difference ≥5% for patients in each of the 3 ezogabine dose groups compared with placebo: dizziness, fatigue, vertigo, and disturbance in attention.

Table 82 Incidence of Adverse Drug Reactions Reported in Greater than or equal to 2% of Patients Treated With 600, 900, or 1200 mg/day Ezogabine and Numerically Greater Than Placebo (Safety Population: RCT, Studies 205, 301 and 302)

Preferred Term	Placebo (N=427)	600 mg/day (N=281)	900 mg/day (N=273)	1200 mg/day (N=259)	Total EZO (N=813)	Total EZO %
Dizziness	38 (8.9)	41 (14.6)	64 (23.4)	84 (32.4)	189	23.2
Somnolence	51 (11.9)	43 (15.3)	67 (24.5)	69 (26.6)	179	22
Fatigue	25 (5.9)	45 (16.0)	40 (14.7)	34 (13.1)	119	14.6
Confusional state	11 (2.6)	12 (4.3)	21 (7.7)	42 (16.2)	75	9.2
Vertigo	9 (2.1)	22 (7.8)	21 (7.7)	24 (9.3)	67	8.2
Tremor	12 (2.8)	7 (2.5)	26 (9.5)	32 (12.4)	65	8.0
Coordination abnormal	12 (2.8)	14 (5.0)	14 (5.1)	30 (11.6)	58	7.1
Nausea	22 (5.2)	18 (6.4)	17 (6.2)	22 (8.5)	57	7.0
Diplopia	7 (1.6)	22 (7.8)	15 (5.5)	19 (7.3)	56	6.9
Disturbance in attention	4 (<1.0)	17 (6.0)	15 (5.5)	17 (6.6)	49	6.0
Memory impairment	11 (2.6)	7 (2.5)	15 (5.5)	24 (9.3)	46	5.7
Blurred vision	9 (2.1)	5 (1.8)	12 (4.4)	27 (10.4)	44	5.4
Asthenia	8 (1.9)	12 (4.3)	15 (5.5)	11 (4.2)	38	4.7
Dysarthria	3 (<1.0)	10 (3.6)	5 (1.8)	21 (8.1)	36	4.4
Gait disturbance	5 (1.2)	6 (2.1)	13 (4.8)	15 (5.8)	34	4.2
Aphasia	4 (<1.0)	3 (1.1)	9 (3.3)	17 (6.6)	29	3.6
Balance disorder	3 (<1.0)	8 (2.8)	8 (2.9)	13 (5.0)	29	3.6
Constipation	6 (1.4)	4 (1.4)	11 (4.0)	13 (5.0)	28	3.4
Paraesthesia	9 (2.1)	7 (2.5)	4 (1.5)	14 (5.4)	27	3.3
Influenza	9 (2.1)	10 (3.6)	3 (1.1)	12 (4.6)	25	3.1
Anxiety	8 (1.9)	7 (2.5)	5 (1.8)	12 (4.6)	24	3.0
Weight increased	5 (1.2)	6 (2.1)	9 (3.3)	7 (2.7)	22	2.7
Amnesia	3 (0.7)	2 (0.7)	9 (3.3)	8 (3.1)	19	2.3
Dysuria	3 (0.7)	4 (1.4)	5 (1.8)	10 (3.9)	19	2.3
Dyspepsia	7 (1.6)	7 (2.5)	4 (1.5)	7 (2.7)	18	2.2
Urinary hesitation	4 (0.9)	6 (2.1)	3 (1.1)	9 (3.5)	18	2.2

Preferred Term	Placebo (N=427)	600 mg/day (N=281)	900 mg/day (N=273)	1200 mg/day (N=259)	Total EZO (N=813)	Total EZO %
Disorientation	3 (0.7)	1 (0.4)	1 (0.4)	12 (4.6)	14	1.7
Chromaturia	1 (.0.2)	2 (0.7)	4 (1.5)	7 (2.7)	13	1.6
Dysphasia	2 (0.5)	3 (1.1)	3 (1.1)	7 (2.7)	13	1.6
Hematuria	3 (0.7)	6 (2.1)	3 (1.1)	4 (1.5)	13	1.6
Psychotic disorder	0	0	1 (0.4)	6 (2.3)	7	0.9

All Phase II/III Combined

At least one TEAE was reported by 90% of patients who received ezogabine in the “All Phase II/III Combined” studies. As with the total ezogabine treatment group in the Pivotal Controlled Trials grouping, the most frequently reported TEAEs by preferred term in the “All Phase II/III Combined studies” were dizziness (32%), somnolence (29%), headache (20%), and fatigue (18%), tremor (13%), confusional state (12%), and coordination abnormal (10%); all other AEs were reported in <10% of patients.

Integrated Clinical Pharmacology Studies

At least one TEAE was reported by 75% of ezogabine-treated subjects in the Integrated Clinical Pharmacology Studies grouping. Dizziness, headache, fatigue, disturbance in attention, somnolence, and nausea were the TEAEs with the highest incidence (32%, 26%, 23%, 14%, 13%, and 11%, respectively). All other AEs were reported in <10% of patients. Other AEs commonly reported (≥5%) in these studies that were reported less often in the All Phase II/III Combined grouping were euphoric mood (9%) and hypoesthesia oral (8%), both of which were reported in <1% of the All Phase II/III Combined grouping. Feeling drunk was reported in 6% of ezogabine-treated subjects in the Integrated Clinical Pharmacology Studies grouping and in 2% of ezogabine-treated patients in the All Phase II/III Combined grouping. Events of euphoric mood and feeling drunk are discussed further in section 7.6.4 subheading “Integrated Pharmacology Studies”

120 Day Update

As of the 120-Day Safety Update reporting period, at least one TEAE was reported by 91% of patients who received ezogabine.

A total of 10 patients who had not previously reported a TEAE in the original ISS reported one during the 120-Day Safety Update reporting period; making a total of 1235 patients (91%) who reported a TEAE in this study grouping, table 83. The types and incidences of TEAEs were similar to those reported in the original ISS.

Table 83 Adverse Events Reported by at Least 5% of Patients (All Phase II/III Combined) ISS / 120 safety update compared

	Number (%) of Patients	
	RTG (N=1365)	
Preferred Term	**ISS Integrated data Cut-Off: 30 June 2008**	**120-Day Safety Data Cut-off: 2 October 2009**
Any event	**1225 (89.7)**	**1235 (90.5)**
Dizziness	431 (31.6)	439 (32.2)
Somnolence	389 (28.5)	397 (29.1)
Headache	279 (20.4)	287 (21.0)
Fatigue	245 (17.9)	251 (18.4)
Tremor	176 (12.9)	180 (13.2)
Confusional state	163 (11.9)	163 (11.9)
Coordination abnormal	138 (10.1)	141 (10.3)
Nausea	128 (9.4)	133 (9.7)
Memory impairment	121 (8.9)	123 (9.0)
Vertigo	121 (8.9)	122 (8.9)
Diplopia	112 (8.2)	114 (8.4)
Disturbance in attention	106 (7.8)	107 (7.8)
Urinary tract infection	105 (7.7)	107 (7.8)
Convulsion	99 (7.3)	108 (7.9)
Asthenia	96 (7.0)	97 (7.1)
Vision blurred	92 (6.7)	93 (6.8)
Speech disorder	90 (6.6)	90 (6.6)
Dysarthria	89 (6.5)	92 (6.7)
Gait disturbance	82 (6.0)	84 (6.2)
Balance disorder	76 (5.6)	76 (5.6)
Diarrhea	76 (5.6)	81 (5.9)
Nasopharyngitis	76 (5.6)	86 (6.3)
Aphasia	73 (5.3)	75 (5.5)
Paraesthesia	70 (5.1)	71 (5.2)
Influenza	70 (5.1)	75 (5.5)
Vomiting	69 (5.1)	72 (5.3)
Anxiety	68 (5.0)	71 (5.2)
Note: those events highlighted in gray have a higher incidence than the original ISS.		

Reviewer Comment: 31 adverse drug reactions are identified. Dizziness occurred in 32.4% of subjects treated with 1200mg/day of ezogabine compared to 8.9% of placebo and is explored more extensively below to determine if there is a relationship to altered cerebral perfusion due to orthostatic blood pressure change.

Dizziness

Dizziness was the most common adverse events reported in the pivotal controlled trials. This occurred in 23.2% of all ezogabine treated patients and 8.9% of

placebo. There was also a dose related increase in the report of dizziness reaching a maximum of 32.4% in the ezogabine 1200mg/day group.

Dizziness Related To Blood Pressure

Four analyses are presented in to determine if the dizziness AEs are a result of orthostatic hypotension (postural challenge to blood pressure). The full analyses are presented in appendix 9.12. In each analysis a change from baseline of greater than -20mmHg systolic blood pressure is chosen as the critical level of blood pressure change. This is the generally accepted standard of clinically significant blood pressure drop associated with a postural challenge. In the study 301 and 302 vital sign database there is a direct entry of orthostatic blood pressure "systolic", this measurement represents the systolic blood pressure change (delta BP) between supine and standing position at each visit. Study 205 has only blood pressure measured in sitting and standing position, recorded as diastolic BP sitting or standing and systolic BP sitting or standing at each visit.

Analysis 1 of the term dizziness associated with SAE there were six cases identified, one in placebo and 5 in ezogabine treatment. Among the 5 ezogabine cases two were clearly unrelated to ezogabine treatment, in two cases causality uncertain but possible and in one case the SAE of dizziness was very likely due to ezogabine treatment. This was case 40119, also discussed below, a case identified in analysis 3.

Analysis 2, examines the interaction of events of blood pressure decline ≥-20mmHg change from baseline captured from the vital sign table during titration and maintenance phase of study 301 and 302 with the AE "dizziness" in the PTNAME column of the AE dataset. The subject ID of those subjects identified from the vital signs dataset with an incident of orthostatic blood pressure decline ≥-20mmHg change from baseline is matched with the AE dataset of all dizziness (PTNAME). The frequency of matched IDs is obtained for placebo and ezogabine groups. The date of adverse event is also examined for proximity to the date of the low blood pressure event.

In both studies 301 and 302 there is an increase in the number of instances of threshold orthostatic hypotension (≤-20mmhg) events associated with a dizziness adverse event in the ezogabine treatment patients compared to the placebo treatment groups. These findings suggest a relation between decline in orthostatic systolic blood pressure value and some of the instances of the adverse event "dizziness". In study 301 there are 5 instances in 4 unique patients in the placebo group compared to 24 instances in13 unique patients in the 1200mg ezogabine treatment group. In the placebo group there were 3 events where the temporal proximity of the orthostatic event and the dizziness event were within 30 days while in the ezogabine 1200mg group there were 8 such associations. Overall in the titration and maintenance intervals of study 301 there were 112 instances of the AE "dizziness" occurring in 61 patients.

In study 302 there was only one instance of match between "dizziness" and an orthostatic systolic blood pressure drop ≥-20mmhg in the placebo group. In the 600mg treatment group there were 8 instances in 6 patients where there was a match between

orthostatic drop and the AD “dizziness”. The 900mg group had 12 instances in 6 patients of such a match. In the 600mg group 4 of the instances of orthostatic systolic blood pressure drop and “dizziness” occurred inside of a 30 day interval. The 900mg had 9 such occurrence within a 30 day interval. Overall in the titration and maintenance intervals of study 302 there were 134 instances of the AE “dizziness” occurring in 79 unique patients.

Analysis 3, in analysis 3, studies 205, 301 and 302 are examined for incidents of postural blood pressure decline ≥-20mmHg change from baseline during titration and maintenance phase of the study. The overall frequency of events during the entire titration-maintenance interval in the treatment and placebo groups is compared and taken as an index of the propensity for ezogabine to cause orthostatic blood pressure drop which may result in a subjective experience of dizziness. The incidents of decline ≥-20mmHg from baseline may occur more than once in a single patient. The percent of patients with an incident of blood pressure decline from baseline greater than the -20mmhg threshold is also examined.

Based on examination of standing systolic blood pressure change from baseline in study 205 and orthostatic systolic blood pressure change in studies 301 and 302 there is no signal for the development of orthostatic blood pressure instability due to ezogabine treatment. In study 205 the highest dose ezogabine groups had smaller deviations of median and mean from the baseline values. In study 301 the percent of patients with instances of ≥-20mmhg decline from baseline was smaller in the 1200mg ezogabine group than in placebo although the number of instances was greater and the range was noticeably greater due to several outliers (maximum -63mmhg). The difference in medians and means in placebo compared to ezogabine was small. In study 302 the percent of patients with decline ≥-20mmhg decline from baseline was smaller in the ezogabine 600mg and 900mg group compared to placebo, there were also fewer instances of this degree of decline in ezogabine treatment compared to placebo. There was a small increase in the medians (both -25 mmhg compared to placebo -22mmhg) of ezogabine treatment compared to placebo but the mean of the 600mg group was smaller than placebo.

Analysis 4, examination of change from baseline ≥-20mmhg at a specific study phase, mid titration, did not reveal a compelling difference in the incidence of change from baseline ≥-20mmhg between the placebo and ezogabine treatment group. As in analysis 2 the question in analysis 4 is “dizziness” due to diminished cerebral perfusion. In this analysis a specific exam of mid titration of studies 205, 301 and 302 is performed to determine if there is an increase in low blood pressure events during the introductory period of ezogabine.

Reviewer Comment: Overall the data do not support a signal for destabilization of blood pressure upon postural challenge as a clinically meaningful cause of the AE “dizziness”, although analysis 2 (interaction of low BP events and dizziness-AE dataset) reveal more frequent interactions in ezogabine treatment groups than placebo. There is only a single causal case of dizziness related to orthostatic hypotension due to

ezogabine identified. This finding indicates that in rare cases or due to idiosyncratic cause, ezogabine may induce significant orthostatic hypotension.

Onset and Duration of Dizziness (RCT)

In the double blind titration and maintenance interval there were 370 instances of dizziness generated by 189 unique ezogabine treated patients. In 87 instances no adverse event end date was recorded. 46 patients were discontinued from the study with an AE of dizziness.

Those who were withdrawn had a median onset of dizziness on day 22 with a mean of day 29. Of those not withdrawn the median day of dizziness onset was 32 with a mean of 38.

Within the 370 instances of dizziness, 242 (65%) occurred during titration, while 121 (33%) instances occurred during maintenance phase and 5 during taper phase. In those instances during titration phase where an adverse event is recorded as recovered, the median duration of the adverse event is 5 days, range 0 to 188 with a mean of 22 days.

In 121 instances which occurred during maintenance phase where an adverse event is recorded as recovered, the median duration of the adverse event is 0 days with a range of 0 to 136 and mean of 8 days.

Recovered / not recovered: There were 75 instances generated by 64 unique patients entered as event ongoing. There were two patients with no entry for adverse event outcome. Among those entered as not recovered there were no SAE's or study withdrawals.

In 293 instances, generated by 147 unique patients, the outcome is noted as recovered. Within these 147 unique patients 55 had multiple entries for the adverse event dizziness. These were not individually reviewed to determine the reason for multiple entry but several were sampled to examine the basis for the multiple entry. The three largest multiple entries were 10, 9 and 8. All had unique dates for the adverse event but in all 27 instances the date of recovery was coded as the date of adverse event onset (0 day recovery). Among these 293 instances there was no adverse event end date recorded in 11. **Among those 282 instances where the adverse event end date is noted the median duration of the event was 1 day (range 0 to 188 days) with a mean of 17 days.** In 237 (84%) of 282 instances of dizziness recovery occurs within 30 days while 24 (8.5%) of 282 events recovery occurs in greater than 60 days.

There were 368 of 370 instances where the AE outcome is recorded. In 293 of 368 (80%) recovery is entered as the outcome.

Reviewer Comment: In the RCT's 46 patients discontinued from the study due to dizziness but among patients with adverse event entries of dizziness 80% go on to recover. The majority of instances occur during titration phase. This analysis indicates that dizziness tends to occur in the early phase of ezogabine exposure. The duration of

the adverse effect appears to be short in the majority of those who are able to tolerate the event without study dropout. The observation that 64 patients had an ongoing event and that 8.5% of instances have a greater than 60 day recovery indicates that dizziness may persist in a subset of patients.

Somnolence (RCT)

In the double blind titration and maintenance intervals there were 293 instances of the adverse event “somnolence” generated by 179 unique patients. 28 patients discontinued from the study due to somnolence. Adverse event end date is not recorded in 115 of the 293 instances. These 115 instances are generated by 87 unique patients. In 113 of these instances the event is entered as ongoing.

There were 178 (61%) instances generated by 136 unique patients where the adverse event outcome is entered as recovered. These 178 instances had a median duration of 19.5 days, range 0 to 154 days with a mean of 34 days.

236 instances generated by 154 unique patients occurred in titration phase. In this group among those where the adverse event outcome was recovered the median duration of the event was 20 days, range 0 to 154 days with a mean of 35 days.

55 instances generated by 39 unique patients occurred in maintenance phase. In those instances where the adverse event outcome was recovered, the median duration of the event was 27 days, range 0 to 106 with a mean of 30 days.

Reviewer Comment: In the RCT’s 28 patients discontinued from the study due to somnolence but among patients with adverse event entries of somnolence 61% go on to recover within the double blind phase. Among those in this group the median recovery time is 20 days with a mean of 35 days. 81% of instances occur during titration phase. The majority occurrence of somnolence in titration phase and indicates that there is accommodation to this effect as ezogabine exposure continues. The 59% of instances where recovery is not entered as event outcome and the range up to 154 days of event duration in those who do recover indicates that in a substantial number of cases somnolence may be persistent.

7.4.2 Laboratory Findings

Hematology and Clinical Chemistry

Sponsor outlier Criteria Tables

Table 84 CBC Outlier Criteria Table

Parameter	Standard Unit	Reference range	Values of PCC	
			Low value	High value

Hemoglobin	g/L	M: 130-175 F: 113-156	M: ≤100 F: ≤90	NA
Hematocrit	L/L	M: 0.40-0.54 F: 0.35-0.47	M: ≤0.32 F: ≤0.28	NA
RBC	m/mm3	M: 4.4-5.9 F: 4.0-5.6	NA	NA
WBC	GI/L	4.1-12.3	≤2.8	≥16
Platelets	GI/L	140-370	≤100	≥550

Table 85 Differential Outlier Criteria Table

Differential WBC Counts	Reference Range GI/L	Values of PCC	
		Low value	High value
Neutrophils	2.03-7.71589	≤1.8	NA
Bands		NA	NA
Lymphocytes	0.8-2.8	NA	NA
Monocytes	0.3-1.3	NA	NA
Eosinophils	0.0-0.4	NA	>0.8
Basophils	0.0-0.2	NA	NA

Table 86 Clinical Chemistry Outlier Criteria Table

Clinical Chemistry	Standard Unit	Reference Range	Values of PCC	
			Low value	High value
Total Bilirubin	umol/L		NA	≥34.2
AST (SGOT)	U/L	0-41	NA	≥3 x ULN ≥5 x ULN ≥10 x ULN
ALT (SGPT)	U/L	0-45	NA	≥3 x ULN ≥5 x ULN ≥10 x ULN
Alkaline Phosphate	U/L	30-125 (19-59y) 29-149 (60+y)	NA	≥3 x ULN
Creatinine	umol/L	35.36-106.08	NA	≥176.8
Urea	mmol/L	1.43-8.57	NA	≥14.28
Sodium	mmol/L	132-147	≤127	≥153
Potassium	mmol/L	3.5-5.5	≤3.0	≥6.0
Chloride	mEq/L	98-110	≤92	≥112
Bicarbonate	mmol/L	22-32	≤18	≥36
Uric Acid	umol/L	W 214.128-475.84	NA	M>654.28 F>594.8
Protein (total)	g/L	60-85	<45	>100
Glucose	mmol/L	3.60815-7.71589	≤2.7755	≥11.102
Calcium	mmol/L	2.0958 – 2.56985	≤1.8962	≥2.86925
Phosphate	mg/dL	2.7-4.8 (13-59y) 2.1-5.0 (60+y)	≤2.2 (13-59y) ≤1.9 (≥60y)	≥5.5 (13-59y) ≥5.6 (≥60y)
Cholesterol	mmol/L	3.3618-5.172	≤1.6809	≥6.465

Central Tendency and Change from Baseline - RCT (Pivotal Controlled Trials)

Hematology

See Appendix 9.13.1 for full Hematology Central Tendency Analysis

Reviewer Comment: There were small negative mean changes from baseline in WBC and Neutrophils that do not reach sufficient magnitude to indicate a signal for depression of these hematologic parameters. There were small positive mean changes from baseline over placebo noted for eosinophils with a maximum of 0.11GI/L seen at week 10 at dose 900mg/day. The increased exposure, at weeks 12, 14 16 and 18 do not reveal an association of increasing eosinophil count over time, some values show a small negative change. This profile mean change in eosinophil count from baseline does not indicate a signal for treatment related eosinophilia.

Clinical Chemistry

Sodium (Na+)

Reviewer Comment: Although there is a small change toward positive value of change from baseline serum Na+ in the 1200mg dose group, there is no evidence that this is resulting in an increase in individual severe abnormal Na+ values in this dose group; however an examination for Na+ outliers in the chemistry dataset is performed in the outlier analysis section.

Potassium (K+)

Reviewer comment: examination of the mean and median change from baseline for serum K+ between placebo and ezogabine treatment patient or between placebo and each dose group individually reveal no difference between placebo and treatment. There are small but not clinically notable differences between placebo and each dose group mean, although medians are all 0.

Bicarbonate (HCO_3)

Reviewer Comment: there are no meaningful differences between the median and mean bicarbonate change from baseline in the placebo and ezogabine treatment groups.

Chloride (Cl)

Reviewer Comment: there is no noteworthy clinical difference in the changes from baseline between the placebo and ezogabine treatment groups for chloride measurements.

Renal Function

There were no clear differences between the placebo group and the ezogabine groups for any renal function indices (creatinine, urea and uric acid) at baseline and there were no meaningful changes over time for creatinine. Slight increases in urea and uric acid

were apparent in ezogabine groups from Week 2 but did not appear to increase further over time and were more apparent in the ezogabine 1200 mg/day group, table 87.

Table 87 Renal function parameters, Urea, Creatinine, Uric acid, group means change from baseline for placebo, 600mg, 900mg, 1200mg, presented by weeks 2-18.

	Number of Patients Urea (MMOL/L)				
	Placebo N=427	**RTG 600 mg/day N=281**	**RTG 900 mg/day N=273**	**RTG 1200 mg/day N=259**	**RTG Total N=813**
Total Population **Baseline mean(±SD)**	426 **4.50 (1.401)**	280 **4.53 (1.505)**	273 **4.50 (1.447)**	257 **4.29 (1.253)**	810 **4.44 (1.412)**
Change from Baseline, mean(±SD)					
Week 2	0.04 (1.095)	0.63 (2.936)	0.35 (1.162)	0.43 (1.046)	0.47 (1.955)
Week 4	0.08 (1.098)	0.58 (1.231)	0.55 (1.324)	0.71 (1.094)	0.61 (1.222)
Week 6	-0.06 (1.037)	0.50 (1.159)	0.67 (1.316)	0.69 (1.198)	0.62 (1.226)
Week 8	-0.04 (1.181)	0.38 (1.242)	0.55 (1.280)	0.84 (1.208)	0.57 (1.257)
Week 12	0.02 (1.108)	0.45 (1.276)	0.59 (1.254)	0.83 (1.138)	0.56 (1.251)
Week 16	-0.00 (1.131)	0.29 (1.211)	0.57 (1.319)	0.74 (1.172)	0.46 (1.259)
Week 18	-0.02 (1.207)	0.65 (1.268)	0.21 (1.558)	1.07 (1.390)	0.98 (1.398)
	Number of Patients Creatinine (UMOL/L)				
Total Population **Baseline mean(±SD)**	425 **70.4 (15.33)**	279 **68.8 (15.24)**	271 **68.0 (14.23)**	257 **69.0 (16.05)**	807 **68.6 (15.16)**
Change from Baseline, mean(±SD)					
Week 2	0.4 (8.91)	6.4 (91.39)	0.9 (8.60)	0.5 (9.09)	2.7 (54.42)
Week 4	0.6 (8.62)	0.4 (12.52)	1.0 (18.22)	1.0 (9.01)	0.8 (13.81)
Week 6	1.2 (13.97)	0.1 (9.03)	1.6 (9.44)	0.8 (10.10)	0.8 (9.51)
Week 8	0.4 (9.64)	0.3 (8.28)	1.0 (9.37)	0.6 (9.17)	0.6 (8.92)
Week 12	-0.0 (8.89)	1.6 (10.28)	1.5 (11.13)	1.0 (9.52)	1.5 (10.50)
Week 16	-0.3 (8.87)	0.0 (8.52)	1.8 (8.46)	1.2 (9.31)	0.9 (8.63)
Week 18	1.3 (11.31)	-0.1 (4.72)	-2.8 (3.98)	2.0 (12.64)	1.5 (11.86)
	Number of Patients Uric Acid(UMOL/L)				
Total Population **Baseline mean(±SD)**	426 **237.8 (80.10)**	280 **232.4 (74.25)**	273 **232.7 (76.27)**	257 **233.0 (80.25)**	810 **232.7 (76.78)**
Change from Baseline, mean(±SD)					
Week 2	-1.5 (44.84)	1.3 (40.97)	-0.2 (36.07)	2.9 (40.45)	1.3 (39.21)
Week 4	0.6 (45.03)	1.1 (37.13)	1.8 (35.37)	-0.0 (37.43)	1.0 (36.60)
Week 6	-1.8 (45.67)	4.8 (38.51)	3.7 (37.09)	2.3 (40.76)	3.6 (38.73)
Week 8	-0.4 (50.12)	1.3 (34.07)	3.4 (37.25)	3.9 (40.98)	2.8 (37.28)
Week 12	-1.1 (55.71)	4.6 (38.97)	1.9 (41.31)	5.2 (36.06)	3.6 (39.45)
Week 16	-6.6 (49.11)	3.8 (40.99)	3.2 (38.16)	5.1 (39.31)	3.7 (39.55)
Week 18	-4.3 (34.19)	-4.4 (29.17)	-6.4 (36.42)	3.8 (46.92)	2.5 (45.02)

Liver Function

Mean AST showed a slight increase from baseline (up to 5 IU/L) in the ezogabine groups that was apparent from Week 2 but did not appear to increase further over time, and there was no evidence of a dose relationship. Similarly, mean ALT showed a slight increase from baseline (by ~ 1 to 3 IU/L) in the ezogabine groups that was apparent from Week 4 but did not appear to increase further over time, and there was no evidence of a dose relationship. Mean total bilirubin showed an increase from baseline (up to 5 IU/L) in the ezogabine groups that was apparent from Week 2 but did not appear to increase further over time, and there was no evidence of a dose Relationship. Changes from baseline in AST, ALT and Total Bilirubin also reflected this pattern, table 88.

Table 88 Baseline AST, ALT, and Total Bilirubin, and Change in AST, ALT, and Total Bilirubin from Baseline

	Number of Patients AST(IU/L)				
	Placebo N=427	**RTG 600 mg/day N=281**	**RTG 900 mg/day N=273**	**RTG 1200 mg/day N=259**	**RTG Total N=813**
Total Population **Baseline mean(±SD)**	426 **20.2 (11.10)**	280 **19.2 (6.93)**	273 **19.9 (9.13)**	257 **20.4 (8.22)**	810 **19.8 (8.14)**
Change from Baseline, mean(±SD)					
Week 2	0.1 (10.40)	0.8 (6.16)	1.5 (18.31)	0.9 (15.51)	1.1 (14.17)
Week 4	-0.3 (9.99)	2.1 (12.84)	1.1 (9.53)	0.9 (8.48)	1.4 (10.51)
Week 6	0.5 (9.89)	1.9 (10.32)	2.5 (14.70)	2.5 (14.28)	2.3 (13.15)
Week 8	0.4 (11.21)	1.4 (7.76)	1.8 (12.59)	2.3 (9.99)	1.8 (10.24)
Week 12	0.0 (8.51)	2.9 (10.62)	3.9 (23.43)	0.6 (12.18)	3.0 (17.15)
Week 16	0.5 (11.54)	2.2 (6.71)	2.1 (11.70)	-1.1 (11.50)	1.7 (9.76)
Week 18	0.1 (8.17)	-1.1 (13.92)	0.1 (8.59)	2.8 (8.69)	2.3 (9.14)
	ALT (IU/L)				
Baseline mean(±SD)	**21.0 (11.22)**	**19.9 (10.20)**	**21.0 (11.60)**	**20.9 (13.55)**	**20.6 (11.81)**
Change from Baseline, mean(±SD)					
Week 2	0.6 (17.06)	0.4 (9.12)	1.3 (15.53)	0.3 (14.34)	0.7 (13.21)
Week 4	-0.6 (8.08)	3.3 (19.48)	1.2 (9.73)	1.5 (12.02)	2.0 (14.48)
Week 6	0.4 (8.79)	2.0 (13.34)	3.3 (22.52)	3.8 (18.37)	3.0 (18.34)
Week 8	0.2 (9.22)	2.2 (12.72)	2.9 (13.70)	3.6 (14.67)	2.9 (13.65)
Week 12	0.2 (8.12)	3.9 (15.27)	5.2 (20.05)	1.5 (17.52)	4.0 (17.68)
Week 16	0.1 (11.06)	2.5 (10.62)	3.8 (16.52)	-1.0 (14.49)	2.5 (13.89)
Week 18	-0.2 (8.54)	-0.1 (15.77)	-1.0 (4.00)	4.0 (12.95)	3.4 (12.80)
	Total Bilirubin (UMOL/L)				
Baseline mean(±SD)	**6.32 (2.780)**	**6.59 (2.815)**	**6.45 (2.591)**	**6.66 (3.201)**	**6.56 (2.871)**
Change from Baseline, mean(±SD)					
Week 2	0.01 (2.169)	1.99 (2.927)	2.17 (2.771)	2.08 (2.853)	2.08 (2.850)
Week 4	-0.13 (2.253)	3.06 (3.880)	3.35 (3.849)	3.68 (3.724)	3.35 (3.824)

Week 6	0.14 (3.180)	3.23 (3.509)	4.64 (3.793)	5.57 (5.251)	4.42 (4.318)
Week 8	-0.03 (2.279)	2.99 (3.148)	4.88 (3.642)	6.41 (5.251)	4.65 (4.271)
Week 12	-0.08 (2.484)	3.03 (3.294)	4.49 (3.446)	8.59 (6.380)	4.46 (4.384)
Week 16	-0.27 (2.383)	2.60 (3.368)	4.45 (3.469)	9.04 (6.078)	4.25 (4.425)
Week 18	0.04 (2.240)	1.61 (3.760)	4.53 (4.589)	4.91 (4.696)	4.66 (4.668)

ALT Reviewer Comment: examination of mean ALT change from baseline of ezogabine dose group compared to placebo median and means reveal a small increase in the treatment groups compared to placebo. Examination of the change from baseline ALT of each dose group compared to placebo stratified by week reveals a small positive increase in the treatment groups compared to placebo. In this examination there is no clear dose response or increase with duration of exposure see appendix 9.13.1.3.

AST Reviewer Comment: Group median and mean AST values are examined. Examination of placebo compared to combined ezogabine dose groups, weeks 2 to 18 (entire interval combined) reveal a small increase in median and mean AST values from baseline in the combined ezogabine dose groups compared to placebo. Examination of the individual 600mg, 900mg and 1200mg dose groups compared to placebo also reveals a very small increase in median and mean of ezogabine compared to placebo. appendix 9.13.1.3. The analysis of change from baseline on a week by week basis for placebo and the individual 600mg, 900mg and 1200mg dose groups also reveals a small increase in means at multiple points in the treatment groups compared to the placebo. There is no noted dose response and there is no trend of increase with longer duration of exposure, table 88.

Total Bilirubin Reviewer Comment: There is a noticeable increase in mean and median total bilirubin values for the ezogabine treatment groups compared to placebo. The sponsor explains this increase in bilirubin is due to false elevations due to ezogabine and the N-acetyl metabolite interference with the standard clinical laboratory diazo method used in bilirubin assays[10]. Evaluation of values of potential clinical concern (PCC) reveals only one PCC value (USUBJID 3065 A1-205~000019~000248) in the double blind trial interval weeks 2-18. This value is 45umol/l. This subject has no recorded AE related to hepatic dysfunction, there are several entries, all for diplopia, table 99. This subject has no abnormal hepatic transaminases. The increase in mean bilirubin values does not appear to be associated with an increase in critically high bilirubin values.

Metabolism Indices: (glucose, total protein, calcium, phosphorus, cholesterol)

Glucose

10 NDA 22345, ISS p238.

Median and mean change in blood glucose in studies 205, 301 and 302 comparing pooled treatment to pooled placebo are examined across the span of all visits weeks 2 to 18 in figure 64 and 65, In figure 65 the mean and median change in studies 205, 301 and 302 comparing dose groups to placebo are examined. In figures 66 and 67 week 4 alone is examined in the same fashion as figure 66.

Reviewer Comment: although the median and mean of change from baseline for glucose revealed larger values than other metabolic indices, examination of the placebo and ezogabine group medians and means as well as the examination of individual dose group medians and means at weeks 4 and 12 reveal only small changes in mean and median values that are not clinically meaningful.

Conclusion: There were no clear differences between patients receiving placebo and patients receiving ezogabine for any metabolism indices and no meaningful changes over time. The largest mean changes from baseline compared to placebo occur in the glucose values. These do not reach a magnitude sufficiently large to consider clinically meaningful.

Shift Analysis (RCT, studies 205, 301,302)

Clinical Chemistry

Electrolytes

The proportions of patients with a shift from normal to low or from normal to high values of sodium, potassium, chloride, and bicarbonate were similar between the placebo- and ezogabine-treated groups, with the exception of sodium and potassium showing greater then twice and three times the percent shift to high compared to placebo respectively, in the 900mg dose group. There was also greater shift in bicarbonate from normal to low by almost 10% in the 1200mg dose group, table 89. These observations are noteworthy but do not clearly indicate a safety signal in light of means and outliers reviewed above.

Renal function

The proportions of patients with a shift from normal to high values of urea were slightly higher in the ezogabine-treated patients compared with placebo, with evidence of a dose relationship, table 89. The proportions of patients with a shift from normal to low or from normal to high creatinine and uric acid were not meaningfully different between the placebo- and ezogabine-treated groups.

Liver Function

Generally, a higher proportion of patients showed shifts from normal to high AST and ALT (than shifts to low), table 89. For AST, the proportions of patients with a shift from normal to high were slightly higher in the ezogabine-treated patients compared with placebo, although there was no evidence of a dose relationship. However, for ALT there

was an indication of a dose relationship for the incidence of shifts from normal to high, which was reported in 5% of patients receiving placebo and in 14%, 15%, and 18% of patients receiving ezogabine 600, 900, and 1200 mg/day, respectively. For total bilirubin, there was an indication of a dose relationship for the incidence of shifts from normal to high, which was reported in 2% of patients receiving placebo and in 3%, 5%, and 13% of patients receiving ezogabine 600, 900, and 1200 mg/day, respectively. As noted earlier, in the case of bilirubin, this is likely a result of assay interference.

Metabolism Indices

The proportions of patients with shifts from normal to low, or from normal to high for glucose, total protein, calcium, phosphorus, and cholesterol were similar in the placebo and ezogabine-treated groups, without evidence of a dose relationship, table 89. A higher proportion of patients showed shifts from normal to high cholesterol (than shifts to low), and a slightly higher proportion of patients showed shifts from normal to low glucose and calcium (than shifts to high).

Table 89 Shifts to Abnormal Values for Clinical Chemistry (Safety Population: RCT, Studies 205, 301, and 302) Key: B= Baseline, P-B = post baseline

	Percentage of Patients (n/N)				
	Placebo (N=427)	RTG 600 mg/day (N=281)	RTG 900 mg/day (N=273)	RTG 1200 mg/day (N=259)	RTG Total (N=813)
Electrolytes					
Normal at B to Low P-B					
Sodium	5.4	6.5	4.2	6.1	5.6
Potassium	4.3	<1.0	2.0	2.1	1.6
Chloride	4.2	5.7	4.1	6.5	5.4
Bicarbonate	32.3	24.8	22.4	41.6	29.4
Normal at B to High P-B					
Sodium	4.1	5.7	9.2	2.2	5.7
Potassium	1.8	2.7	6.4	<1.0	3.3
Chloride	3.4	7.8	8.3	2.6	6.3
Bicarbonate	21.4	17.1	18.4	17.8	17.7
Renal Function					
Normal at B to Low P-B					
Urea	1.0	0	<1.0	0	<1.0
Creatinine	2.5	1.5	1.2	2.9	1.8
Uric acid	12.1	11.5	11.6	12.2	11.8
Normal at B to High P-B					
Urea	2.2	5.0	7.0	8.5	6.8
Creatinine	1.7	1.9	1.2	<1.0	1.3
Uric acid	1.2	2.3	3.0	2.8	2.7
Liver Function					
Normal at B to Low P-B					
AST	3.9	3.2	1.6	<1.0	1.9
ALT	1.3	1.6	2.0	<1.0	1.4
Alkaline phosphatase	3.4	4.0	4.1	2.5	3.6
Total bilirubin	11.5	0	<1.0	<1.0	<1.0

Normal at B to High P-B					
AST	6.4	10.7	8.9	11.6	10.4
ALT	5.2	14.1	15.2	18.1	15.7
Alkaline phosphatase	5.8	7.5	5.5	5.0	6.0
Total bilirubin	1.5	3.1	4.8	12.8	6.8
Metabolism Indices					
Normal at B to Low P-B					
Glucose	10.7	5.4	7.3	8.5	7.0
Total protein	1.5	<1.0	1.2	<1.0	<1.0
Calcium	11.1	9.4	7.2	10.8	9.1
Phosphorus	4.5	4.2	4.4	3.9	4.2
Cholesterol	7.0	6.0	7.5	6.6	6.7
Normal at B to High P-B					
Glucose	1.8	3.5	2.8	4.7	3.7
Total protein	3.0	1.5	2.0	2.1	1.9
Calcium	3.0	3.9	2.8	<1.0	2.4
Phosphorus	3.3	4.2	4.4	3.1	3.9
Cholesterol	23.4	34.0	32.3	25.5	30.4

Hematology

The magnitude of shift from baseline in ezogabine compared to placebo in most hematologic parameters is small. There are several parameters were the gradient of change between placebo and ezogabine treatment is noticeably greater than the majority of parameters. These occur in red blood cell counts, white blood cell counts, lymphocyte counts and eosinophil counts. In the measurement of RBC, WBC and Lymphocyte counts the shift is negative. Eosinophils show a positive shift (increasing). Table 90 displays the shifts in percentage of patients for hematologic parameters. Those parameters with a negative value shift >5% compared to placebo are RBC and hematocrit at ezogabine 900mg/day, WBC at ezogabine 600mg/day and 900mg/day, lymphocytes at ezogabine 600mg/day and total ezogabine. Eosinophils reveal a shift >5% compared to placebo at all doses of ezogabine dosage with a maximum at 900mg/day.

Table 90 Shifts to Abnormal Values for Hematology Labs (Safety Population:

RCT, Studies 205, 301, and 302) Key: B= Baseline, P-B = post baseline

	Percentage of Patients (n/N)				
	Placebo (N=427)	RTG 600 mg/day (N=281)	RTG 900 mg/day (N=273)	RTG 1200 mg/day (N=259)	RTG Total (N=813)
Red Blood Cell Indices					
Normal at B to Low P-B					
Red blood cells	6.6	10.4	12.1	6.3	9.7
Hemoglobin	7.4	7.7	11.3	9.8	9.6
Hematocrit	13.9	15.7	23.2	18.3	19.0
Normal at B to High P-B					
Red blood cells	<1.0	0.0	0.0	0.0	0.0
Hemoglobin	1.6	<1.0	2.1	<1.0	1.1
Hematocrit	<1.0	0.0	<1.0	<1.0	<1.0
White Blood Cell Indices					
Normal at B to Low P-B					
White blood cells	15.9	22.6	21.2	17.6	20.6
Neutrophils (absolute)	17.3	19.7	17.1	19.0	18.6
Neutrophils (%)	10.5	7.7	6.3	6.5	6.8
Bands (absolute)	0	0	0	0	0
Bands (%)	0	0	0	0	0
Lymphocytes (absolute)	11.2	20.2	15.0	15.7	17.0
Lymphocytes (%)	6.7	12.9	8.9	11.1	11.0
Monocytes (absolute)	10.6	11.1	8.0	12.8	10.6
Monocytes (%)	10.6	10.7	9.5	9.8	10.0
Eosinophils (absolute)	0.0	0.0	0.0	0.0	0.0
Eosinophils (%)	0.0	0.0	0.0	0.0	0.0
Basophils (absolute)	0.0	0.0	0.0	0.0	0.0
Basophils (%)	0.0	0.0	0.0	0.0	0.0
Normal at B to High P-B					
White blood cells	2.0	1.3	1.7	4.9	2.5
Neutrophils (absolute)	4.0	4.8	3.8	4.5	4.4
Neutrophils (%)	7.8	11.8	8.8	8.3	9.7
Bands (absolute)	10.0	0	0	9.1	4.3
Bands (%)	10.0	0	0	9.1	4.3
Lymphocytes (absolute)	4.9	<1.0	<1.0	<1.0	<1.0
Lymphocytes (%)	11.1	3.7	3.8	5.6	4.3
Monocytes (absolute)	6.1	5.3	4.6	5.3	5.1
Monocytes (%)	7.3	8.3	10.3	7.1	8.6
Eosinophils (absolute)	1.5	2.6	2.7	4.5	3.3
Eosinophils (%)	5.3	10.5	16.0	14.1	13.5
Basophils (absolute)	0.0	<1.0	1.5	1.2	1.0
Basophils (%)	<1.0	<1.0	1.2	0	<1.0
Platelets					
Normal at B to Low P-B	4.4	2.4	4.3	3.7	3.5
Normal at B to High P-B	1.8	1.6	1.6	2.1	1.7

Reviewer Comment: The observations of the hematology shift analysis are concordant with those seen in the central tendency analysis for WBC and eosinophils. RBC and hematocrit show a >5% shift over placebo for only the 900mg/day dose while lymphocytes also have a >5% shift over placebo for only the 900mg/day dose. WBC

show a shift of >5% for both 600mg/day and 900mg/day. None of these parameters has a high magnitude shift at all doses or shows a dose response. Eosinophil percentage reveals a >5% shift over placebo at all doses but does not show a consistent increase with ezogabine dose (dose response). Absolute eosinophil count shows a maximum shift over placebo of 3% at 1200mg/day ezogabine, however there is a weak dose response noted with 1.1% greater than placebo at 600mg/day, 1.2% greater than placebo at 900mg/day and 3% greater than placebo at 1200mg/day. This trend in isolation does not rise to the level of evidence to conclude a safety signal for eosinophilia and is not noted to be a harbinger of multiorgan hypersensitivity syndrome based on the serious adverse events in the clinical development program but may be an area for surveillance in the post marking lifecycle of ezogabine.

Outlier Analysis (RCT, studies 205, 301, 302)

Hematology Outlier Analysis – RCT (Pivotal Controlled Trials)- table 92

Hemoglobin; Examination of hemoglobin measurements for occurrence of values of clinical concern (low range) in ezogabine treatment patients compared to placebo reveals no frequency of occurrence in ezogabine treatment groups greater than placebo.

WBC: examination of frequency of low WBC counts in the range of clinical concern in placebo compared to ezogabine treatment groups reveals the occurrence to be less in the ezogabine 600mg/day and 900mg/day group than placebo, however the 1200mg/day ezogabine group has an excess of 1.1% greater than placebo. There is no increase over placebo in the category of high values of WBC of clinical concern.

Neutrophils: examination of frequency of low neutrophil counts in the range of potential clinical concern in placebo compared to ezogabine treatment groups reveals that the ezogabine 600mg/day treatment group has an excess of 1.1% over placebo, 900mg/day has an occurrence of values of potential clinical concern 5% less than placebo and the ezogabine 1200mg/day group has an excess over placebo of 5.9%. it is noted that the ezogabine 1200mg/day treatment group at baseline had an excess over placebo of 5.5% which accounts for 93% of the post baseline excess of the 1200mg ezogabine group. The more severe category of potential clinical concern, neutropenia (absolute neutrophil count <1.0) occurred in 1.0% of placebo and 1.2% of the ezogabine treatment group (10 patients).

The group of 10 unique neutropenia patients is examined further to explore the details of the neutropenia event. Details of interest include the presence or absence of pretreatment low neutrophil counts, the duration of neutropenia, the visit week/dose of ezogabine and recovery. All but 1 case had screening or 1st day dosing low neutrophil count, neutropenia or count in range of potential clinical concern PCC. In the single case of sporadic neutropenia at week 4 there was no intervention and subsequent neutrophil counts normalized. There was no withdrawal in this group due to neutropenia although there was one withdrawal in the group of 10 due to disturbance in attention and dizziness, a second withdrawal due to anxiety and tremor and a third withdrawal

due to pregnancy. This totals to 3 withdrawals. In another case there are no records entered after visit # 6 but no case report in the withdrawal section of case narratives. In the remaining 6 patients all continued in the study. There was an SAE due to neutropenia but the patient continued into the study and showed improvement after treatment with folate. This same subject was on concomitant CBZ, table 91.

Table 91 Ten patients with neutropenia < $1x10^3mm^3$,identified in studies 205,301,302 weeks 2 to 18.

SUBJID	NEUTROPHIL COUNT	Week/s of occurrence	Ezogabine dose	Comment/ Recovery / action
000786	0.99	0	0	Neutropenia prior to EZO treatment. Withdrawn at visit 4 due to disturbance in attention and dizziness
000997	0.672	4	600mg	Isolated measurement resolved with drug continuation.
002102	0.7 (nadir) Confusing- at screening?	.83 on day of first dose, 1.4 (PCC) at screening	Day of first dose (0) to 1200mg	Baseline neutropenia and low to neutropenia through duration of study into open label continuation
002703	1.24	PCC week 0- (day following first EZO dose, then weeks 2 – 6.	300mg, max 2 doses	PCC at study initiation, short latency indicates not likely due to study drug, continued in study, discontinued due to pregnancy- died (b) (6) days after last dose Define PCC in legend.
010701	0.97 Confusing- at screening?	14	1200mg	PCC at screening and week 0, nadir wk 14 continued into OL study. Neutrophil count recovered, but at 4 of 7 OL visits count in range of PCC.
020102	0.73-0.99	0-6	1200mg	Leukopenia at baseline Continued in study to week 6. 5 of 7 values in range of leukopenia, 2 of 7 in PCC
020412	0.67	6	1050mg	Neutrophil count of PCC at baseline. Withdrawn from study due to SAE of anxiety & tremor
000507	0.699- 0.993	0, 2, 8, 12, 16, first two OL visits. The remaining in	Max 900mg reduced to 300mg week 2	PCC at screening, SAE Week 2, dizziness & ataxia, dose reduced from 900mg to 300mg/day. Pt then

		PCC until 2 months into OL		continued into OL study
035203	0.92	12	600mg	SAE for neutropenia. Neutrophil count of PCC at baseline (1.07). On concomitant CBZ. Improved with folic acid treatment. Patient continued to OL.
025104	0.92	Screening, 0	0	Neutropenia at screening, continued into study with improvement

Eosinophils: examination of frequency of high eosinophil counts in the range of potential clinical concern in placebo compared to ezogabine treatment groups reveals only the 1200mg/day group has a 0.1% excess over placebo over the placebo group.

Table 92 Hematology Values of Potential Clinical Concern (Safety Population: RCT, Studies 205, 301, and 302) Key: B= Baseline, P-B = post baseline

		Percentage of Patients (n/N)				
		Placebo (N=427)	RTG 600 mg/day (N=281)	RTG 900 mg/day (N=273)	RTG 1200 mg/day (N=259)	RTG Total (N=813)
Hemoglobin						
PCC Low	B	1.4 (6/425)	<1.0 (1/280)	0	0	<1.0 (1/811)
	P-B	1.2 (5/413)	1.8 (5/271)	<1.0 (1/261)	<1.0 (1/251)	<1.0 (7/783)
Hematocrit						
PCC low	B	1.2 (5/424)	0	0	0	0
	P-B	1.7 (7/412)	1.5 (4/271)	<1.0 (1/261)	0	<1.0 (5/783)
White blood cells						
PCC low	B	<1.0 (2/425)	<1.0 (2/280)	0	2.3 (6/258)	1.0 (8/811)
	P-B	2.9 (12/413)	2.6 (7/271)	1.1 (3/261)	4.0 (10/251)	2.6 (20/783)
PCC High	B	0	<1.0 (1/280)	0	0	<1.0 (1/811)
	P-B	<1.0 (2/413)	0	0	<1.0 (2/251)	<1.0 (2/783)
Neutrophils (absolute)						
PCC low	B	8.5 (36/424)	8.2 (23/280)	4.0 (11/273)	14.0 (36/258)	8.6 (70/811)
	P-B	16.5 (68/413)	17.7 (48/271)	11.5 (30/261)	22.4 (56/250)	17.1 (134/782)
Eosinophils (absolute)						
PCC high	B	1.2 (5/424)	<1.0 (2/280)	<1.0 (2/273)	<1.0 (2/258)	<1.0 (6/811)
	P-B	1.5 (6/413)	1.1 (3/271)	<1.0 (2/261)	1.6 (4/250)	1.2 (9/782)
Platelets						
PCC low	B	<1.0 (3/423)	<1.0 (2/278)	<1.0 (1/272)	<1.0 (1/256)	<1.0 (4/806)
	P-B	1.7 (7/413)	1.8 (5/271)	1.1 (3/261)	0	1.0 (8/783)
PCC high	B	<1.0 (1/423)	<1.0 (1/278)	<1.0 (2/272)	0	<1.0 (3/806)
	P-B	0	<1.0 (2/271)	<1.0 (2/261)	1.2 (3/251)	<1.0 (7/783)
No values of PCC were defined for red blood cells, lymphocytes, monocytes, or basophils.						

Reviewer Comment: The hematology laboratory values of potential clinical concern (outlier analysis) reveal WBC and neutrophils at the 1200mg dose to have a notable increase in occurrence of low PCC values over placebo. Those cases of low neutrophil values in the range of severe neutropenia are examined. The exam reveals that all but one of the 10 cases had neutropenia or neutrophil count in the range of PCC at baseline. In the single case with normal neutrophil counts then sporadic incursion into the range of neutropenia the patient was on concomitant carbamazepine, treated with folate and had subsequent improvement with continuation of ezogabine. A portion of the occurrence of low neutrophil values in excess of placebo can be accounted for by the high baseline occurrence in ezogabine treatment group over placebo. The converging evidence of an ezogabine effect on total WBC count and neutrophil count observed in analysis of central tendency, post baseline shift and outlier analysis indicate the presence of a moderate safety signal. This signal is noted in proposed labeling under "Blood and Lymphatic System Disorders" within "Additional Adverse Reactions Observed During All Phase 2/3 Clinical studies" – Blood and Lymphatic System Disorders- Frequent: leukopenia, Infrequent: Neutropenia.

Electrolyte Outlier Analysis

Sponsor's table of values of PCC within the electrolyte section of chemistry table 93:

Table 93 Electrolyte Values of Potential Clinical Concern (Safety Population: RCT, Studies 205, 301, and 302) Key: B= Baseline, P-B = post baseline

	Percentage of Patients (n/N)				
	Placebo (N=427)	**RTG 600 mg/day (N=281)**	**RTG 900 mg/day (N=273)**	**RTG 1200 mg/day (N=259)**	**RTG Total (N=813)**
Sodium					
PCC low					
B	1.4 (6/426)	3.6 (10/280)	1.5 (4/273)	1.2 (3/257)	2.1 (17/810)
P-B	3.1 (13/413)	5.1 (14/272)	2.7 (7/261)	2.8 (7/250)	3.6 (28/783)
PCC high					
B	0	0	0	0	0
P-B	<1.0 (1/413)	<1.0 (2/272)	<1.0 (2/261)	<1.0 (1/250)	<1.0 (5/783)
Potassium					
PCC low					
B	0	<1.0 (1/279)	0	0	<1.0 (1/807)
P-B	0	<1.0 (1/272)	<1.0 (1/260)	0	<1.0 (2/782)
PCC high					
B	0	<1.0 (2/279)	1.1 (3/271)	0	<1.0 (5/807)
P-B	<1.0 (1/413)	1.1 (3/272)	2.7 (7/260)	<1.0 (2/250)	1.5 (12/782)
Chloride					
PCC low					
B	3.8 (16/426)	3.6 (10/280)	4.4 (12/273)	2.3 (6/257)	3.5 (28/810)
P-B	5.6 (23/413)	7.7 (21/272)	6.5 (17/261)	6.8 (17/251)	7.0 (55/784)
PCC high					
B	3.3 (14/426)	4.6 (13/280)	3.3 (9/273)	3.5 (9/257)	3.8 (31/810)
P-B	4.6 (19/413)	9.9 (27/272)	10.0 (26/261)	4.8 (12/251)	8.3 (65/784)
Bicarbonate					
PCC low					
B	4.0 (13/329)	5.0 (9/180)	3.4 (6/176)	6.6 (10/151)	4.9 (25/507)

	Percentage of Patients (n/N)				
	Placebo (N=427)	**RTG 600 mg/day (N=281)**	**RTG 900 mg/day (N=273)**	**RTG 1200 mg/day (N=259)**	**RTG Total (N=813)**
P-B	13.2 (42/318)	5.7 (10/175)	5.4 (9/168)	15.5 (23/148)	8.6 (42/491)
PCC high					
B	<1.0 (1/329)	0	<1.0 (1/176)	0	<1.0 (1/507)
P-B	<1.0 (3/318)	0	1.2 (2/168)	0	<1.0 (2/491)

Based on table 93 above in the placebo and ezogabine groups, a small proportion of patients had values of PCC for sodium at baseline. The incidence of post baseline sodium values of PCC was similar between placebo and ezogabine. The incidence of potassium values of PCC appeared slightly higher in patients receiving ezogabine. However, there was no evidence of an ezogabine dose relationship. The proportion of patients with high or low values of PCC for chloride at baseline was similar between treatment groups. More patients on ezogabine had high or low PCC values for chloride post baseline, however there was no evidence of a dose relationship. The proportion of patients with PCC values for low bicarbonate at baseline was similar between placebo and ezogabine treatment groups. The incidence of PCC low bicarbonate post-baseline increased in all treatment groups, but was most common on placebo.

Reviewer analysis of Electrolyte Outliers

Na+ (sodium)

Changes from baseline which were greater than 2 standard deviations from the mean were captured (> ±8mmol/l). Among all change from baseline > ±8mmol/l there were three resultant high values in the range of PCC (potential clinical concern) with serum sodium results of 153 mmol/l, 154 mmol/l and 158 mmol/l. There were 9 result values in the low range of PCC table recorded from 7 unique patients, table 94. Synopsis from these 10 cases are presented below.

Table 94 Patients identified with Na+ values in PCC range extracted from the subset of subjects with change from baseline Na+ values (all doses, weeks 2-18) greater then 2 standard deviations from the mean of all change from baseline

Concomitant AED	USUBJID	EZO dose	week	Serum Na+, mmol/l
Valproic acid, topiramate	3065 A1-205~000094~001358	600mg	16	153
clonazepam, valproic acid, lamotrigine, diazepam, tranxene,	3065 A1-205~000077~001141	1100mg	16	154
Carbamazepine,	VRX-RET-E22-302~000702~070201	900mg assigned treatment		158
Oxcarbazepine, phenobarbital	VRX-RET-E22-302~000401~040124	900mg	6	127
maliasin,	3065 A1-205~000019~000250	1200mg assigned	16	126

phenytoin		treatment	
oxcarbazepine levetiracetam clobazam	VRX-RET-E22-302~000703~070311	900mg	124
Carbamazepine, clobazam	3065 A1-205~000021~000304	900mg assigned treatment	123
Carbamazepine, phenobarbital	VRX-RET-E22-302~000853~085313	600mg	123
Oxcarbazepine, lamotrigine	VRX-RET-E22-302~000554~055413	600mg	122
carbamazepine levetiracetam clobazam	VRX-RET-E22-302~000505~050510	528.6mg	121

Patient 3065 A1-205~000094~001358 had serum Na+ recorded at weeks 2,4,6,8,12,and 16. Only week 16 level was in the range of PCC. There was no sustained progression over time. The AE database is screened to determine if there was any associated AE proximate to the date of the recorded abnormal serum Na+. The PT “renal colic” occurs on 3/13/01 approximately 2 weeks after the recording of elevated serum sodium.

Patient 3065 A1-205~000077~001141 had serum Na+ recorded at weeks 2,4,6,8,12,and 16. only week 16 value was in the range of PCC. There was no clear progression over time. The AE database is screened to determine if there was any associated AE proximate to the date of the recorded abnormal serum Na+. The AE database is screened to determine if there was any associated AE proximate to the date of the recorded abnormal serum Na+. The PT “ urinary tract infection” is noted approximately three weeks before the event of the PCC value of serum Na+. Serum Na+ is outside the reference range at a value of 148mmol/l at the start of the AE.

Patient VRX-RET-E22-302~000702~070201 The very highest sodium level (158mmol/l) was found in subject USUBJID= VRX-RET-E22-302~000702~070201 at visit week 12. This subject was found to have elevated serum Na+ at visit week 2. The remaining recorded visits in the serum sodium database were weeks 4, 6, 8, and 16. At these evaluations the serum Na+ was normal. This subject ID is then used as a row selector for the AE database with 20 AE events identified. None of the events in PTNAME are related to hypernatremia and only one event occurs within three weeks of an elevated serum Na+ measurement, this event “pain in extremity” is not related to hyponatremia. None of the 20 AEs is noted to be a serious adverse event (SAE) although an event which occurs 14 months after the last hypernatremia is urinary retention, an event of special interest. This patient is on concomitant carbamazepine which may cause hyponatremia.

Patient VRX-RET-E22-302~000401~040124 had serum Na+ recorded at weeks 2,4,6,8,12,and 16. Only week 6 value was in the range of PCC. There was no clear progression with increasing duration of exposure. The AE database is screened to determine if there was any associated AE proximate to the date of the recorded abnormal serum Na+. Only one AE is found, “laboratory value abnormal” on 5/2/07, the

concurrent ezogabine dose is 900mg. This patient is on concomitant which may cause hyponatremia.

Patient 3065 A1-205~000019~000250 had serum Na+ recorded at weeks 2,4,6,8,12,and 16. only week 16 value was in the range of PCC. There was no clear trend of progressive decline of serum Na+ with increasing duration of ezogabine exposure. The AE database is screened to determine if there was any associated AE proximate to the date of the recorded abnormal serum Na+. There is no AE entry for this patient in the AE database.

Patient VRX-RET-E22-302~000703~070311 had serum Na+ recorded at weeks 2,4,6,8, and 12 with values in the range of low PCC at weeks 2, 4 and 8. Baseline serum Na+ was in the low reference range, 133mmol/l. The AE database is screened to determine if there was any associated AE proximate to the date of the recorded abnormal serum Na+. The PT “amnesia” and “disturbance in attention” is noted on 9/5/07 while the low serum Na+ values in the PCC range occur on 08/08/2007, 08/21/2007, and 09/17/2007. The nadir of serum Na+, 123mmol/l occurs on 8/8/07, and a value of 126mmol/l on 9/17/07. The hyponatremia may have caused these mental impairment events. This patient is on oxcarbazepine which may cause hyponatremia.

Patient 3065 A1-205~000021~000304 had serum Na+ recorded at weeks 2,4,6,8, and 12 with values in the range of low PCC at weeks 2 and 8. Baseline serum Na+ was in the low reference range, 133mmol/l. There is no clear trend of decreasing Na+ with increasing exposure. The AE database is screened to determine if there was any associated AE proximate to the date of the recorded abnormal serum Na+. There is no entry in the AE database for this patient. This patient is on carbamazepine which may cause hyponatremia.

Patient VRX-RET-E22-302~000853~085313 had serum Na+ recorded at weeks 2,4,6,8,12 and 16 with values in the range of PCC low at week 6 and below reference range at weeks 2 – 8. Baseline serum Na+ was in the low reference range, 132mmol/l. There is a trend of improving serum Na+ from weeks 6 to 16. The AE database is screened to determine if there was any associated AE proximate to the date of the recorded abnormal serum Na+. The PT “diplopia” is noted on 12/27/06 the same date as the entry for the hyponatremia. The dose of ezogabine on the date of event is 600mg. The patient was on concomitant carbamazepine which may be the cause of hyponatremia.

Patient VRX-RET-E22-302~000554~055413 had serum Na+ recorded at weeks 2,4,6,8,12 and 16 with values in the range of PCC low at weeks 2,6,12, and 16 and below reference range at week 8. Baseline serum Na+ was in the low reference range 130mmol/l at week 8. The AE database is screened to determine if there was any associated AE proximate to the date of the recorded abnormal serum Na+. There is an AE with PT “fear” on 4/22/07 and an AE with PT “pyrexia” entered on 5/17/07, the ezogabine dose on these dates is 600mg. 04/22/2007 and 05/17/2007 correspond to two of the hyponatremia dates, the PT “fear” may be a cognitive event due to hyponatremia, however the PT “pyrexia” may be causative to the hyponatremia through

the mechanism of infection. The patient is on concomitant oxcarbazepine which may be a cause of hyponatremia.

Patient VRX-RET-E22-302~000505~050510 had serum Na+ recorded at weeks 2,4,6,8,12 and 16 with values in the range of PCC low at week 12. There is no clear trend of declining Na+ with increasing duration of exposure. The AE database is screened to determine if there was any associated AE proximate to the date of the recorded abnormal serum Na+. There is an entry of PT “dizziness” with and AE start date of 8/15/07 corresponding to the recorded date of serum Na+ of 121mmol/l. The hyponatremia may be related to the adverse event of dizziness. The ezogabine dose on the recorded adverse event start date is 528.6mg. carbamazepine is noted as a background AED which may be a cause of hyponatremia.

Reviewer Comment: in this overview from the group of patients with a change from baseline Na+ at any point in the controlled study greater then 2 standard deviations from the mean of all change from baseline, 3 patients with severe hypernatremia and 7 patients with severe hyponatremia were identified. Of the three patients with hypernatremia none had evidence of relation of ezogabine exposure duration to the hyponatremia and none had an adverse event or withdrawal attributable to the hypernatremia. Among those patients with hyponatremia 6 of the 7 seven cases were confounded by concomitant medication which may cause hyponatremia. In the single unconfounded case there was no evidence of progressive decline in serum Na+ with increased duration of ezogabine exposure. This single case is unexplained.

K+ (Potassium)

An independent examination of the outliers in the PCC range for potassium is performed table 95. This reveals a total of 17 occurrences of elevated potassium in 12 patients. The 12 patient total agrees with the sponsor table 93 above. The individual outlier cases are examined in the discussion below.

Table 95 Occurrences Of K+ PCC Values Among Placebo, 600mg, 900mg And 1200mg Doses In RCT.

Placebo		600		900		1200	
PCC threshold	# Subjects (N Rows)	PCC threshold	# Subjects (N Rows)	PCC threshold	# Subjects (N Rows)	PCC threshold	# Subjects (N Rows)
		<=3mmol/L	1	<=3mmol/L	1		
>=6mmol/L	1	>=6mmol/L	4	>=6mmol/L	11	>=6mmol/L	2

Outliers by duration exposure- weeks

Table 96 K+, all occurrences of high or low PCC values, subject ID, result, week and PCC threshold.

USUBJID	RESULTS	WEEK	SIGCRIT

PBO			
VRX-RET-E22-302~000805~080502	6	2	>=6mmol/L
600			
VRX-RET-E22-302~000401~040102	8	6	>=6mmol/L
VRX-RET-E22-302~000602~060216	6.1	8	>=6mmol/L
VRX-RET-E22-302~000853~085312	6.4	8	>=6mmol/L
VRX-RET-E22-302~000853~085312	6.7	12	>=6mmol/L
VRX-RET-E22-302~000905~090509	2.1	12	<=3mmol/L
900			
VRX-RET-E22-302~000401~040108	2.8	2	<=3mmol/L
3065 A1-205~000021~000295	6.9	4	>=6mmol/L
VRX-RET-E22-302~000603~060306	6.2	4	>=6mmol/L
3065 A1-205~000065~001004	6.6	6	>=6mmol/L
3065 A1-205~000081~001191	6.2	6	>=6mmol/L
VRX-RET-E22-302~000851~085103	6.2	6	>=6mmol/L
3065 A1-205~000081~001191	6.4	8	>=6mmol/L
VRX-RET-E22-302~000603~060306	6.4	8	>=6mmol/L
VRX-RET-E22-302~000851~085103	6.3	8	>=6mmol/L
VRX-RET-E22-302~000603~060312	6.4	10	>=6mmol/L
3065 A1-205~000078~001469	6	12	>=6mmol/L
VRX-RET-E22-302~000603~060306	6.1	12	>=6mmol/L
1200			
VRX-RET-E22-301~000153~015304	6	4	>=6mmol/L
3065 A1-205~000052~000659	6.4	6	>=6mmol/L

Examination of patients with K+ values in the range of PCC reveal one occurrence in the placebo group, 5 occurrences in 4 unique patients in the 600mg treatment group. 4 of the 5 occurrences in the 600mg group are critically high values and one is a critically low value. In the 900mg group there are 11 PCC values in 8 patients, 10 are high critical values, and one is low. In the 1200mg group there are two PCC values in two patients, both critically high values, table 96.

Examination of high PCC values by week of occurrence does not reveal a trend associated with duration of exposure within each dose group. When all dose groups pooled there is a predominance of events at week six or later in 14 of 16 high PCC events. There are only 2 low PCC events one a 2 weeks and one at 12 weeks, thus revealing no pattern, table 96.

There is no clear dose response, only 2 high PCC events at 1200mg a day and 11 at 900mg. There are 12 unique patients with potassium values in the high PCC range and 1 in placebo. There are two unique patients with potassium values in the low PCC range and none in placebo. In the high PCC range this represents a 12:1 ratio of ezogabine to placebo events which is disproportionately large compared to the approximately 1.9:1 ratio of ezogabine to placebo patients. The bias toward hyperkalemia, 12 cases compared to 2 cases of hypokalemia in the PCC range suggests this is a signal for hypokalemia rather that patient variability. The 12 cases of hyperkalemia in the PCC range represents 1.5% of the 813 ezogabine treatment patients in the double blind treatment phase.

The AE database was screened to capture adverse event entries under subject ID with K+ (potassium) PCC values. 109 adverse events were captured from the 15 unique USUBJID (patients) of the PCC outlier subjects. Two of these adverse events have likely relationship to the aberrant K+ values. One is an event of hypokalemia, this AE is recorded for a patient with a K+ value of 2.1mmol/l. This individual also has two entries for SAEs of diarrhea. One of the diarrhea events occurs on the same date as hypokalemia, the second is recorded 4 weeks preceding the hypokalemia event. It is possible that diarrhea resulted in the electrolyte disturbance. The second patient with a possibly related AE has an entry for second degree AV block. This event occurs 3 months prior to the event of hyperkalemia. This same patient also has two entries for 1st degree AV block pre-study. In this case the hyperkalemia is not related to the cardiac rhythm disturbance.

Reviewer comment: Examination of subject with PCC values for K+ in the high or low range reveals no trend of increase values associated with dose, however there are a majority of PCC events at week 6 or later. 2 of 19 events are low PCC values for K+ while the remainders are high PCC values. Analysis for related AEs reveal only one related adverse event in a case of hypokalemia. This occurred in a patient with a concurrent listing for diarrhea which is a confounding factor for potassium loss. There are a greater number of unique patients with PCC range hyperkalemia in the ezogabine treatment than the placebo group and a tendency toward more cases as exposure increases. In the analysis of central tendency there is no trend of change in mean value of potassium. The shift analysis reveals a notable increase in shift to abnormal in the 900mg group over placebo (4.6%). **This trend although not conclusive of causality should be noted in labeling in "Clinical Trials Experience" section at the Common Adverse Reaction In All Controlled Clinical Studies section, following the table of "at least 2%" , in the paragraph where sentence 1 reads "Other adverse reactions reported in these 3 studies in <2% of patients treated with POTIGA and numerically greater than placebo".**

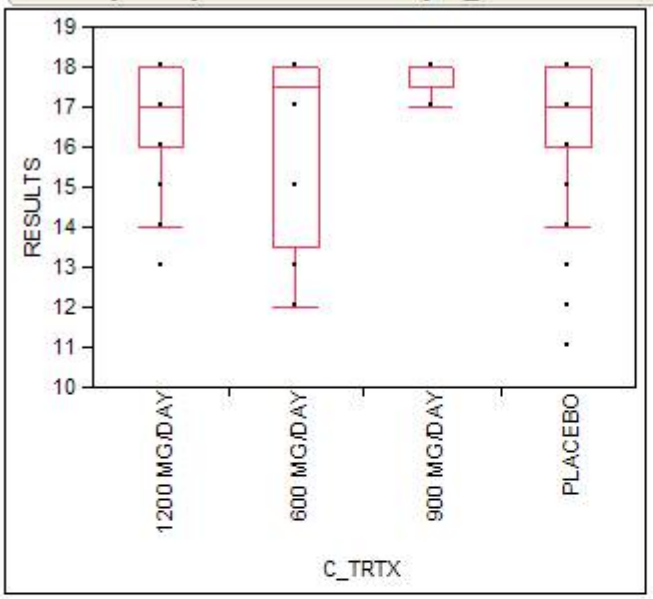
Bicarbonate (HCO_3)

The chemistry dataset is searched for bicarbonate values in the PCC range. There are 64 events with values in the PCC range, 62 are in the low range (see table 86 for outlier criteria), and 2 in the high range. These 64 events are generated by 38 unique patients. There are 72 PCC values in the placebo treatment group. Among ezogabine treatment patients with low PCC values there are 12 in the 600mg group, 9 in the 900mg group and 41 in the 1200mg group. The median value in the placebo, 600mg, 900mg and 1200mg groups are 17,18, 17.5, and 17meq/l respectively. The mean values for each group are 16.6, 16.2, 17.8 and 17meq/l respectively, figure 12.

The 38 unique patient identification numbers are used to search the adverse event database (AE) to determine if adverse event preferred or verbatim terms are medically related to the abnormal bicarbonate value. These 38 unique patient IDs yield 300 adverse events. Fifteen of these adverse events are SAEs, generated by 8 unique patients. Among the preferred and verbatim terms associated with the low bicarbonate

values there are 5 that may cause low bicarbonate, convulsion (term occurrence x 3), vomiting (term occurrence x 2), diarrhea and prolonged diarrhea. The remainder are of uncertain relationship, table 97.

Figure 12 HCO_3 values in range of PCC, compare Placebo, 600mg, 900mg, 1200mg, medians and means.



Quantiles

Level	Minimum	10%	25%	Median	75%	90%	Maximum
1200 MG/DAY	13	14.2	16	17	18	18	18
600 MG/DAY	12	12	13.5	17.5	18	18	18
900 MG/DAY	17	17	17.5	18	18	18	18
PLACEBO	11	14	16	17	18	18	18

Means and Std Deviations

Level	Number	Mean	Std Dev	Std Err Mean	Lower 95%	Upper 95%
1200 MG/DAY	41	16.9268	1.38546	0.21637	16.490	17.364
600 MG/DAY	12	16.1667	2.48022	0.71598	14.591	17.743
900 MG/DAY	9	17.7778	0.44096	0.14699	17.439	18.117
PLACEBO	72	16.5833	1.65086	0.19456	16.195	16.971

Table 97 event terms associated with 15 SAEs identified from AE database occurring in 8 patients with low PCC bicarbonate (HCO3) values.

PTNAME (Preferred term)	AETERM (verbatim term)
CONVULSION	INCREASED SEIZURE FREQUENCY
CONVULSION	INCREASED RATE OF SEIZURES
CONVULSION	INCREASED SEIZURE RATE
COORDINATION ABNORMAL	ATAXIA
DEHYDRATION	DEHYDRATION

DEVICE MALFUNCTION	VNS MALFUNCTION
DIARRHOEA	DIARRHEA
DIARRHOEA	PROLONGUED DIARRHOEA
DIZZINESS	DIZZINESS
EPILEPSY	WORSENING OF EPILEPSY
HYPOKALAEMIA	HYPOKALEMIA
NAUSEA	TO RULE OUT NAUSEA
SEPSIS	SEPSIS
SYNCOPE	TO RULE OUT VOMITTING
VOMITING	SYNCOPAL EPISODE

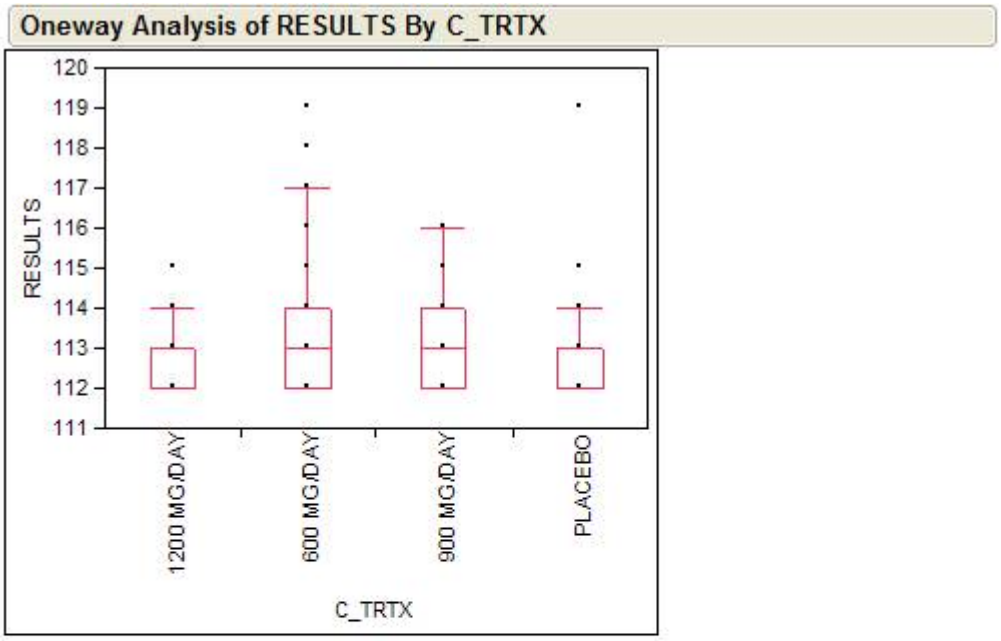
Reviewer Comment: There are no meaningful differences between the number of values of bicarbonate values of potential clinical concern in the placebo and the ezogabine treatment groups. There is some evidence of dose response in the ezogabine treatment group based on the observation of 41 events in the 1200mg group with only 9 in the 900mg and 12 in the 600mg group. This is overshadowed by the overall comparison of placebo and total ezogabine treatment groups where the placebo group had 72 low bicarbonate events and the ezogabine treatment group had a total of 62 low bicarbonate events. There is no signal for ezogabine related decline in bicarbonate and only 2 high bicarbonate events.

Chloride (Cl)

The frequency of occurrence of values in the high range of potential clinical concern (PCC) in addition to the median and mean group values for the placebo, 600mg, 900mg and 1200mg groups are compared, figure 13. Twenty seven events occurred in the placebo group with a median value of 112meq/l and a mean of 113meq/l. The 600mg group had 57 occurrences in the high PCC range with a median value of 113meq/l and a mean of 113.4meq/l. the 900mg group had 44 occurrences with a median value of 113meq/l and a mean of 113meq/l. The 1200mg group had 29 occurrences with a median of 112meq/l and a mean of 112.5meq/l. The maximum PCC value in the placebo group was 119meq/l with no higher maximum among the ezogabine treatment groups.

The frequency of occurrence of values in the low range of potential clinical concern (PCC) in addition to the median and mean group values for the placebo, 600mg, 900mg and 1200mg groups are compared, figure 14. Forty one events occurred in the placebo group with a median value of 91meq/l and a mean of 90meq/l. The 600mg group had 55 occurrences with a median of 90meq/l and a mean of 89meq/l. The 900mg group had 35 occurrences with a median of 91meq/l and a mean of 91meq/l. The 1200mg group had 27 occurrences with a median of 91meq/l and a mean of 91meq/l.

Figure 13 CI- High values of PCC, Placebo, 600mg, 900mg, 1200mg, medians, means, number of events each group.



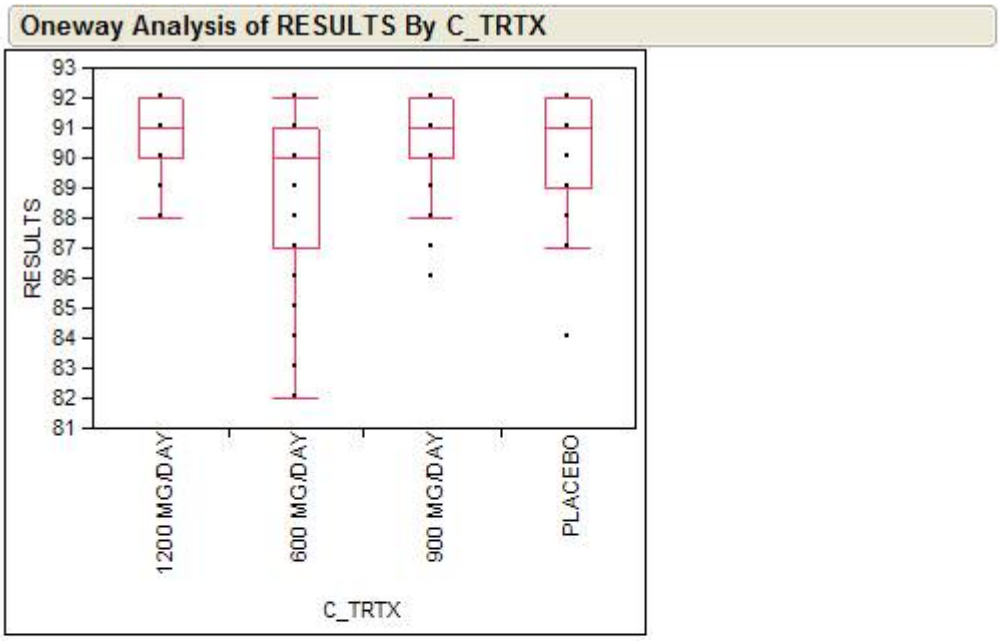
Quantiles

Level	Minimum	10%	25%	Median	75%	90%	Maximum
1200 MG/DAY	112	112	112	112	113	114	115
600 MG/DAY	112	112	112	113	114	116.2	119
900 MG/DAY	112	112	112	113	114	114	116
PLACEBO	112	112	112	112	113	115	119

Means and Std Deviations

Level	Number	Mean	Std Dev	Std Err Mean	Lower 95%	Upper 95%
1200 MG/DAY	29	112.552	0.90972	0.16893	112.21	112.90
600 MG/DAY	57	113.474	1.88135	0.24919	112.97	113.97
900 MG/DAY	44	112.955	1.09872	0.16564	112.62	113.29
PLACEBO	27	113.000	1.56893	0.30194	112.38	113.62

Figure 14 Cl- Low values of PCC, Placebo, 600mg, 900mg, 1200mg, medians, means, number of events each group.



Quantiles

Level	Minimum	10%	25%	Median	75%	90%	Maximum
1200 MG/DAY	88	89	90	91	92	92	92
600 MG/DAY	82	84.6	87	90	91	92	92
900 MG/DAY	86	87.6	90	91	92	92	92
PLACEBO	84	87	89	91	92	92	92

Means and Std Deviations

Level	Number	Mean	Std Dev	Std Err Mean	Lower 95%	Upper 95%
1200 MG/DAY	27	90.8889	1.15470	0.22222	90.432	91.346
600 MG/DAY	55	88.8545	2.85072	0.38439	88.084	89.625
900 MG/DAY	35	90.6571	1.66173	0.28088	90.086	91.228
PLACEBO	41	90.1463	1.98193	0.30953	89.521	90.772

Reviewer Comment: There is no noteworthy clinical difference in the frequency of high or low outlier values (PCC) between the placebo and ezogabine treatment groups based on the frequency of occurrence as well as the outlier group median and mean values of chloride. In addition there are similar numbers of outliers in the high PCC and low PCC groups.

Renal Function

The sponsor table of high and low PCC values of placebo, 600mg, 900mg and 1200mg at baseline and post baseline is examined. There was no meaningful difference between placebo- and ezogabine-treated groups regarding the incidence of high values of PCC for creatinine, urea or uric acid post baseline and no evidence of a dose relationship, table 98. The value for creatinine PCC high values post baseline for combined ezogabine treatment groups based on the CHEM.xpt dataset is examined for

congruency with the sponsor table 142, p251 ISS. The sponsor table indicates 4/781 cases had values of PCC for high creatinine. The reviewer exam of the CHEM dataset results in the same finding, 4/781 have value of PCC for high creatinine.

Table 98 Outlier table of Creatinine value for RCT (pivotal controlled trials)
Key: B= Baseline, P-B = post baseline

Creatinine					
PCC high B	0	<1.0 (2/279)	0	0	<1.0 (2/807)
P-B	<1.0 (1/413)	<1.0 (2/271)	<1.0 (2/260)	0.0	<1.0 (4/781)

The single renal failure case is examined:

Patient 3065 A1-205~000032~000448, Renal Failure: The patients first adverse symptoms began approximately 3 weeks after starting ezogabine, see timeline of events appendix 9.11. The patient suffered sweats , myalgia, fatigue, cough and polydipsia. The patient was subsequently found to have creatinine approximately 4x ULN and was hospitalized, upon hospitalization The patient was catheterized and immediately delivered 1500 ml of cloudy urine (positive for protein but not for blood or glucose). Diagnosis was acute renal failure secondary to urinary retention. Case narrative indicates patient improved but follow up creatinine not noted in case report.

All patients with creatinine above reference range but below PCC were captured from the CHEM.xpt database. This capture resulted in 24 unique patients. These patient USUBJID's were then matched to the AE.xpt database. This resulted in identification of 166 adverse events associated with the 24 patients. The PTNAME (preferred term for the adverse event) is examined for terms related to urinary tract disorder. 22 of the 166 adverse events are related to urinary tract. The 22 adverse events occur in 9 patients, none are listed as SAEs, however patient 090509 also has an SAE of sepsis which occurred approximately 2 weeks after the event of nephritis. It is unclear if the two events were related. Patient 001141 had 11 of the adverse events. This patient experienced two instances of "blood in urine", 2 instances of "hematuria", and 7 instances of "urinary tract infection". Patient 002513 had 3 adverse events including 2 instances of "protein urine present" and one instance of "bacteria urine identified". The remaining patients each had one instance of a term related to urinary tract function. These can be seen in figure 15.

Figure 15 22 AEs associated with urinary tract dysfunction which occurred in patients with creatinine above reference range but below PCC value.

3065 A1-205~000077~001141			VRX-RET-E22-301~000025~002513	
PTNAME			PTNAME	
BLOOD URINE PRESENT	HAEMATURIA	URINARY TRACT INFECTION	BACTERIA URINE IDENTIFIED	PROTEIN URINE PRESENT
2	2	7	1	2

VRX-RET-E22-301~000152~015201	VRX-RET-E22-301~000201~020109	VRX-RET-E22-301~000202~020221	VRX-RET-E22-302~000451~045109
PTNAME	PTNAME	PTNAME	PTNAME
URINARY TRACT INFECTION	CHROMATURIA	NEPHROLITHIASIS	CHROMATURIA
1	1	1	1

VRX-RET-E22-302~000605~060507	VRX-RET-E22-302~000854~085403	VRX-RET-E22-302~000905~090509	
PTNAME	PTNAME	PTNAME	
URINE OUTPUT INCREASED	DYSURIA	NEPHRITIS	URINARY TRACT INFECTION
1	1	1	1

Reviewed Comment: four patients had post baseline creatinine in the PCC range. One of these four patients developed renal failure, apparently due to urinary tract obstruction and withdrew from the study. The remaining three had no SAE report and in all cases the creatinine returned to normal. Those patients with creatinine above reference range but below range of PCC were evaluated for occurrence of adverse urinary tract events. Events identified were hematuria, bacturia, proteinuria, chromaturia, urinary tract infection, dysuria, nephritis and urine output decreases. The event of renal failure due to urinary tract obstruction (case 3065A1-205-032-0448) is the most serious and **should be in the "additional adverse reactions observed during all phase 2/3 clinical studies" section of labeling.**

Metabolism Indices

Overall, there were a very low proportion of patients with values of PCC in glucose or calcium, with no meaningful differences between placebo- and ezogabine-treated groups. There was an increase in the incidence of low glucose values of PCC post baseline when compared with baseline, but there was no meaningful difference between the placebo- and ezogabine-treated groups. The noteworthy metabolic parameter was cholesterol. There was and increase in all ezogabine groups compared to placebo post baseline without a dose response effect. The frequency of values in the range of clinical concern was high at baseline in both the placebo and ezogabine treatment groups. This high frequency of cholesterol in the PCC range is consisted with variability of the cholesterol values in the study population and dilutes the likelihood that the post baseline trend in higher cholesterol values represents a safety signal.

Liver Function

Transaminase values are examined; baseline is compared to post baseline and placebo compared to each of the ezogabine treatment groups.

ALT elevation in the 600mg and 900mg ezogabine in the ≥3 x ULN range are observed for 1.5% and 3.1% of patients respectively compared with 1.0% in the placebo group. In the ≥5 x ULN range for ALT there is a <1% occurrence in the placebo group, and in the 600mg, 900mg and 1200mg there is a <1% (1/272), 1.1% and <1%(2/250) occurrence respectively. In both ≥3 x ULN and ≥5 x ULN groups, the frequency of occurrence was greatest in the 900mg group, table 99.

In the RCT, double blind chemistry dataset there are 22 instances of ALT values in the PCC range occurring in 14 unique patients. These unique patient IDs are used to search the AE database for events related to hepatic dysfunction. 22 events related to hepatic or GI function are identified among these 14 patients, 5 of these events in 3 patients are noted to be SAEs. The preferred terms for these SAEs in subject 3065 A1-205~000032~000448 and patient VRX-RET-E22-301~000105~010511 are transaminases increased. In patient VRX-RET-E22-302~000252~025213 the preferred term is liver function test abnormal.

Case Reports:

3065 A1-205~000032~000448: a 53 yo female simultaneously had elevated transaminases, elevated bilirubin, urinary retention with obstructive uropathy and symptoms of myalgia, fatigue, cough, and sweats. C reactive protein value found to be 328mg/l (normal <12). Ezogabine was discontinued with improvement of this syndrome and no sequelae reported. ALT decreased from 193 to 60 u/l in two weeks.

VRX-RET-E22-301~000105~010511: a 52yo Hispanic female developed increased transaminases on day 42 of ezogabine therapy while taking 350mg TID. AST = 147u/l, ALT= 132u/l. Patient withdrawn from study, also complained of concurrent dizziness, language disturbance and somnolence. Last dose of study drug on (b) (6), ALT normalized on (b) (6). Maximum bilirubin occurred on 8/21/07 and maintained through the interval (b) (6) was within normal range at 8.55umol/l. This case of elevated transaminases with normal bilirubin does not fulfill conditions of Hy's Law.

VRX-RET-E22-302~000252~025213: a 49 yo female was found to have abnormal liver function tests on (b) (6), when the patient should have reached a dose of 900mg/day, although the AE database indicates a dose of 533mg on 12/9/07 and a dose of 900mg on (b) (6). On (b) (6) ALT = 188 IU/l and AST 102 IU/L. Ezogabine was discontinued o (b) (6). ALT returned to a normal level of 22 IU/l on (b) (6). Total bilirubin did not exceed reference range, maximum value noted at week 6, (b) (6)7 was 8.55umol/l. The interval of elevated transaminases was also associated with nausea and vomiting, the patient was hospitalized for constipation of (b) (6) and a CT of the abdomen and pelvis revealed renal calculi.

AST values are evaluated and reveal the placebo rate of ≥3 x ULN to be 1.0%, and <1.0% (1/413), 1.1% and 1.2% in the 600mg, 900mg and 1200mg groups respectively. In the ≥5 x ULN range the placebo rate is 0 while the 600mg, 900mg and 1200mg rates are 0, <1% (1/262) and <1% (2/251) respectively, table 99.

Direct examination of the RCT, double blind dataset reveals 9 instances of values in the range ≥ 3x ULN in 7 patients. Five instances in 5 patients are ≥ 3x ULN while 4 instances in 3 patient are ≥ 5x ULN, one patient has an occurrence at two points in time, week numbers 2 and 12. Subject ID of the 7 patients with AST in the range of ≥ 3x ULN or greater are compared with those patients with elevations of ALT in the range of ≥ 3x ULN. Those with matching IDs are removed from the AST group. Each patient in the ALT abnormal group has been evaluated for AE and SAE in the adverse events database thus the ID number is removed to avoid double searching. The remaining three patient ID of the AST abnormal group are searched in the AE database for hepatic related events.

Search of the AE database for events matching the three previously non examined patient IDs reveals only one patient with AE database entries. This patient is VRX-RET-E22-302~000602~060214 with 6 adverse event entries. None of the events is an SAE. Two of the events, transaminases increased are related to hepatic function. These events occur on (b) (6) at doses of 600mg and 900mg of ezogabine respectively also representing study weeks 2 and 8. Review of the chemistry database for this patient reveals the maximum elevations of AST occurred at study weeks 2 and 12, with AST values of 231IU/L and 300IU/L respectively. AST values at weeks 2 through 12 inclusive were elevated above reference range, although only two were in PCC range ≥ 3x ULN. This patient was withdrawn on adverse event date (b) (6).

Case Report

VRX-RET-E22-302~000602~060214: a 33 yo male who developed elevated transaminases with a maximum on day 86. The highest levels measured were on (b) (6)), when ALT was 102 mg/dL (>2X the upper level normal of 48 mg/dL) and AST was 300 mg/dL (6.7X the upper level normal of 45 mg/dL). Alkaline phosphatase remained within the normal range. The patient also experience mild urinary retention and had mild prostatitis. Total bilirubin values (obtained for this subject ID from CHEM database) do not exceed upper limit of reference range, 20.52umol/l. The maximum value is 18.81umol/l.

Total bilirubin values are evaluated and reveal the placebo occurrence of elevation in the PCC range is <1% (2/243) while the 600mg, 900mg and 1200mg ezogabine treatment rates are 0, <1% (1/261), and 0 respectively. The single total bilirubin elevated to the PCC range, found in patient USUBJID 3065 A1-205~000019~000248, does not have an adverse event related to hepatic dysfunction, there are 32 AEs identified with this patient all under the preferred term ”diplopia”. The elevated bilirubin of this patient occurs in week 4 and normalizes thereafter while continuing treatment table 99.

Table 99 Liver Function Indices of Potential Clinical Concern (Safety Population: RCT, Studies 205, 301, and 302) Key: B= Baseline, P-B = post baseline

		RTG	**RTG**	**RTG**	**RTG**

		Placebo	600 mg/day	900 mg/day	1200 mg/day	Total
		(N=427)	(N=281)	(n=273)	(N=259)	(N=813)
AST						
PCC high	B	<1.0 (2/426)	0	0	0	0
(≥3 x ULN)	P-B	1.0 (4/413)	<1.0 (1/272)	1.1 (3/261)	1.2 (3/251)	<1.0 (7/784)
(≥5 x ULN)	P-B	0	0	<1.0 (1/261)	<1.0 (2/251)	<1.0 (3/784)
(≥10 x ULN)	P-B	0	0	0	0	0
ALT						
PCC high	B	0	0	0	0	0
(≥3 x ULN)	P-B	1.0 (4/413)	1.5 (4/272)	3.1 (8/261)	<1.0 (2/250)	1.8 (14/783)
(≥5 x ULN)	P-B	<1.0 (1/413)	<1.0 (1/272)	1.1 (3/261)	<1.0 (2/250)	<1.0 (6/783)
(≥10 x ULN)	P-B	0	0	0	0	0
Alkaline phosphatase						
PCC high	B	<1.0 (1/426)	0	0	0	0
(≥3 x ULN)	P-B	<1.0 (2/413)	<1.0 (1/271)	0	0	<1.0 (1/782)
Total bilirubin						
PCC high	B	0	0	<1.0 (1/273)	0	<1.0 (1/810)
	P-B	<1.0 (2/413)	0	<1.0 (1/261)	0	<1.0 (1/783)

Hy's Law screen: A screen of the clinical chemistry database for elevated ALT, or Bilirubin values and matched values of elevated ALT with corresponding bilirubin values to determine if a Hy's law threshold is reached.

Match subjects with Total Bilirubin ≥30umol/L to all ALT

A screening of the chemistry database of total Bilirubin values is performed to capture all bilirubin values greater than or equal to 30umol/l (1.46 ULN). These USUBJID are then matched against the CHEM database subset of all ALT values to capture the ALT values of each USUBJID (subject ID fielt) with Total Bilirubin greater than 30umol/l. This yields 242 entries of ALT values. 4 of these entries are ≥1.9 ULN for ALT generated by two subjects. 3 entries are generated by subject **3065 A1-208~020879~000014**, representing the following values of ALT: 71 IU/L, 86 IU/L and 101 IU/L (2.1ULN). Although only one of the values for ULN is > 1.9, the three highest ALT values are provided in the chart below to provide evidence that no trend of increasing ALT with concurrently increasing total bilirubin. The single elevation of total bilirubin to greater than 1.46 ULN which triggered the capture of subject 000014 in the analyis is not present on the chart because there was no elevated ALT corresponding to the elevated bilirubin. Subject 3065 **A1-205~000032~000448** has the highest value entry of 193 IU/L (5.2 ULN) on visit date 5/2/2000.

Subject ID	ALT IU/L	Total bilirubin umol/L	Alkaline Phosphatase IU/L	Visit date	Study phase/ day
3065 A1-208~020879~000014	**71** (ULN=48) 1.5 ULN	**22.23** (ULN= 20.5) 1.08 ULN	**72** (ULN=145)	07/11/2001	OL, >week 80
3065 A1-208~020879~000014	**88** (ULN=48) 1.8 ULN	**15.4** (ULN= 20.5) .75 ULN	**92** (ULN=145)	9/24/01	OL, >week 80
3065 A1-208~020879~000014	**101** (ULN=48) 2.1 ULN	**10.26** (ULN= 20.5) .50 ULN	**115** (ULN=145)	10/3/01	OL, >week 80
A1-205~000032~000448	**193** (ULN=37) 5.2 ULN	**34** (ULN= 20.5) 1.66 ULN	**383** (ULN=100)	5/2/2000	DB week 4

Match subjects with ALT >3 ULN to all Total Bilirubin

75 instances of ALT > 3 ULN are identified in the CHEM dataset. These are generated by 49 unique subjects. These 49 subject IDs are match to the total bilirubin subset of the CHEM dataset to yield 396 total bilirubin entries. The bilirubin results are sorted to reveal total bilirubin values greater than the upper limit of normal. 4 instances of total bilirubin generated by 4 unique subjects are identified. The maximum bilirubin value found is 34umol/L equal to 1.65 ULN.

Subject ID	ALT IU/L	Total bilirubin umol/L	Alkaline Phosphatase IU/L	Visit date	Study phase/ day
3065 A1-205~000024~000349	**186** (ULN=37) 5.2 ULN	**25** (ULN=20.5) 1.22 ULN	**154** (ULN=100) 1.5 ULN	8/25/2000	DB week 6
VRX-RET-E22-304~000853~085314	**282** (ULN=48) 5.9 ULN	**23.94** (ULN=20.5) 1.2 ULN	**84** (ULN=145)	7/23/07	OL, 7.5 months
3065 A1-205~000052~000650	**165** (ULN=37) 4.6 ULN	**21** (ULN=20.5) 1.02 ULN	**49** (ULN=100)	8/1/2000	DB week 12
A1-205~000032~000448	**193** (ULN=37) 5.2 ULN	**34** (ULN=20.5) 1.66 ULN	**383** (ULN=100) 3.8 ULN	5/2/2000	DB week 4

Reviewer Comment: screening of the CHEM.xpt dataset containing the pooled entries of 34 studies did not reveal any entries for ALT and Total Bilirubin values which reached Hy's Law threshold. Patient 000448 exceeded the threshold value for ALT at 5.2 x ULN but the concurrent Total bilirubin was 1.66 x ULN. In addition this patient had an elevated alkaline phosphatase which was at a level of 3.8 x ULN raising the prospect of a contributing obstructive process.

Outlier Analysis (All Phase II/III combined)

Hematology

Red blood cells: Overall, there were a low proportion of patients with values meeting PCC criteria in red cell indices.

White Blood Cells: 1.4% of subjects had low total WBC count at baseline which increased to 3.6% post baseline this is similar in magnitude to the baseline and post-baseline frequency of occurrence of low PCC values in the RCT group. There was no overall change in frequency of corresponding observations for neutrophils (absolute) in the all phase II/III combined observation pool compared to the RCT pool. In the all phase II/III combined pool there were 11.5% with low PCC values at baseline and 19.2% post baseline, table 100, whereas in the RCT pool (table 92) there were 8.6% with low PCC values at baseline in the total ezogabine group and 17.1% with low PCC values post baseline in the total ezogabine group. In the RCT group the frequency of low PCC values at baseline in the ezogabine 1200mg group was 14% and 22.4% post baseline. Therefore overall there is no meaningful change in the profile of occurrence of low PCC values in the all phase II/III combined pool compared with the RCT only pool. The incidence of PCC values of high eosinophils was lower than in the Pivotal Controlled Trials. There is no noteworthy difference in the frequency of low or high PCC values for platelets compared to the observations in the RCT pool of observations.

Table 100 Hematology Values of Potential Clinical Concern (Safety Population: All Phase II/III Combined) Key: B= Baseline, P-B = post baseline

		Percentage of Patients (n/N)
		RTG
		(N=1365)
Hemoglobin		
PCC low	B	<1.0 (8/1340)
	P-B	1.2 (15/1301)
Hematocrit		
PCC low	B	<1.0 (11/1329)
	P-B	1.2 (15/1300)
White Blood Cells		
PCC low	B	1.4 (19/1340)
	P-B	3.6 (47/1301)
PCC high	B	<1.0 (2/1340)
	P-B	<1.0 (10/1301)
Neutrophils (absolute)		
PCC low	B	11.5 (152/1317)
	P-B	19.2 (245/1277)
Eosinophils (absolute)		
PCC high	B	1.1 (14/1290)
	P-B	1.4 (18/1255)
Platelets		
PCC low	B	<1.0 (10/1333)
	P-B	1.2 (16/1300)
PCC high	B	<1.0 (4/1333)
	P-B	1.1 (14/1300)

Reviewer Comment: there is no noteworthy divergence between the observations of hematologic values in the RCT compared to the "all phase II/III combined" pool. Those trends of higher frequency PCC low values in WBC and neutrophil counts are maintained at approximately the same magnitude as the RCT pool.

Clinical Chemistry

Electrolytes- As in the Pivotal Controlled Trials group, a small proportion of patients had values of PCC for sodium (high and low), and potassium (high) post baseline (Table 101). The incidences of sodium and potassium values of PCC appeared to be similar to the Pivotal Controlled Trials group. As in the Pivotal Controlled Trials group, post baseline PCC values (high or low) were common for chloride; 10% of patients had PCC high values of chloride post baseline. More patients in the All Phase II/III Combined group had PCC low values of bicarbonate compared to the Total RTG group in the Pivotal Controlled Trials (13% vs. 9%).

Table 101 Electrolyte values of Potential Clinical Concern (All Phase II/III combined)

Key: B= Baseline, P-B = post baseline		Percentage of Patients (n/N)
		RTG
		(N=1365)
Sodium		
PCC low	B P-B	2.2 (30/1336) 4.1 (53/1302)
PCC high	B P-B	<1.0 (2/1336) <1.0 (10/1302)
Potassium		
PCC low	B P-B	<1.0 (1/1333) <1.0 (4/1299)
PCC high	B P-B	<1.0 (7/1333) 2.3 (30/1299)
Chloride		
PCC low	B P-B	4.1 (54/1305) 6.7 (85/1270)
PCC high	B P-B	4.8 (62/1305) 9.8 (125/1270)
Bicarbonate		
PCC low	B P-B	7.9 (61/777) 12.6 (95/755)
PCC high	B P-B	<1.0 (5/777) <1.0 (4/755)

Renal Function: The incidences of creatinine, urea or uric acid values meeting high PCC criteria were very low (<1%) however the was an increase in the absolute occurrences of high PCC values for creatinine compared to the corresponding placebo

value in the RCT pool. This increase remains less than 1% and while noteworthy is of uncertain clinical significance, table 102.

Table 102 Renal Function Values of Potential Clinical Concern (Safety Population: All Phase II/III Combined) Key: B= Baseline, P-B = post baseline

	Percentage of Patients (n/N)
	EZO (N=1365)
Urea	
PCC high	
B	<1.0 (2/1331)
P-B	<1.0 (5/1297)
Creatinine	
PCC high	
B	<1.0 (4/1332)
P-B	<1.0 (9/1300)
Uric acid	
PCC high	
B	<1.0 (1/1327)
P-B	0

Metabolic Indices

Glucose: there were 1.5% greater occurrences of glucose in the PCC low range post baseline with little difference in the occurrence of PCC high values

Calcium: there were 0.9% greater occurrences of calcium in the PCC low range post baseline with little difference in the PCC high values from baseline to post baseline.

Cholesterol: there were 7.2% greater occurrences of cholesterol in the PCC high range post baseline similar to the RCT pool.

Reviewer Comment: overall observations of change in frequency of PCC values between baseline and post baseline in the “all phase II/III combined” group is similar to those seen in the RCT observation pool.

7.4.3 Vital Signs

Table 103 Vital Sign Reference Range and Outlier Criteria

Vital Sign (unit)	Reference Range	Change Values of PCC
Systolic Blood Pressure (mmHg)	90-160	≥20
Diastolic Blood Pressure (mmHg)	50-105	≥15
Heart Rate (bpm)	50-100	≥15
Temperature (C)	<38.5	NA
Orthostatic Hypotension - SBP	NA	≥20 decrease on standing
Orthostatic Hypotension - DBP	NA	≥10 decrease on standing

Body Temperature, RCT, Double blind phase

Body temperature is examined; no subject has a temperature exceeding 37.8 degrees C. All subjects at all visits are then examined for any temperature after baseline that exceeds 38^0 C (100.4^0 F). Eight cases are found, 5 in the placebo group, 3 in ezogabine treated patients.

The three patients who developed fever in the DB RCT group are displayed in table 104. All recovered, the maximum temperature noted is 39^0 C (102.2^0 F).

Table 104 subjects and events capture in search for post baseline body temperature > 38^0 C

USUBJID	AE	Temperature	AEDATE	VDATE	Status
VRX-RET-E22-302~000556~055601	Bronchitis	39^0 C	11/22/06	11/20/06	Recovered
VRX-RET-E22-302~000606~060604	Respiratory tract infection	38.4^0 C	7/30/06	8/1/06	recovered
VRX-RET-E22-302~000902~090212	Body Tinea	38^0 C	11/15/07	11/20/07	recovered

Body Temperature all studies.

All studies are examined for temperature > 38^0 C at baseline. No subject/patient has temperature greater than 38^0 C at baseline. Subsequent search of all studies for temperature that exceeds 38^0 C following baseline, only the same 3 patients returned on the search of the RCT, DB phase are identified.

Reviewer Comment: there is no evidence that ezogabine treatment is associated with elevation in body temperature. No patients had temperature elevated beyond 38^0 C at baseline. Following baseline 1.2% of placebo patients in RCT trials developed temperature greater than 38^0 C and 0.4% of ezogabine treated patients developed temperature greater than 38^0 C.

RCT Outlier Analysis, Blood Pressure / Pulse

Five parameters of blood pressure outliers are evaluated, Standing systolic blood pressure, orthostatic blood pressure-systolic, orthostatic blood pressure- diastolic, diastolic blood pressure standing, pulse standing. Orthostatic blood pressure is the difference between supine and standing blood pressure. This offers a view in a single reading of the response to postural challenge. This parameter is available in studies 301 and 302 only. Standing systolic and diastolic blood pressures are available in all three RCT trials and this is reflected in the larger number of patients in each dose group. Pulse standing is also evaluated because this is informative if there is an increase in

heart rate to compensate for a decrease in systemic vascular resistance or intravascular volume.

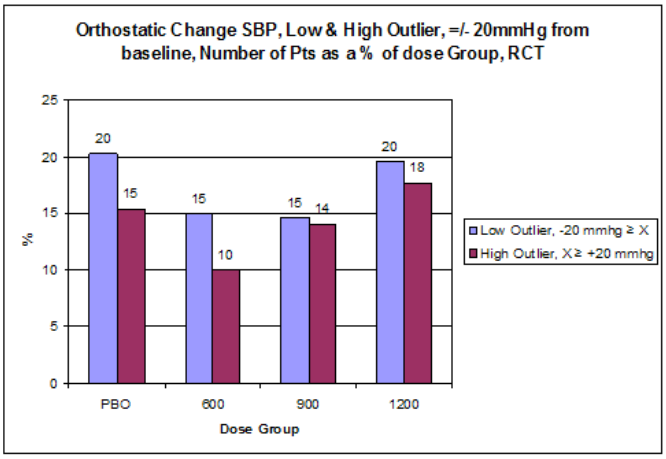
Low outlier values are captured from the vital sign dataset by setting the threshold of interest for blood pressure values at less than or equal to -20mmHg from baseline. All values from any study visit which meet this threshold are captured. Duplicate subject ID's are then eliminated to obtain the number of unique patients who have a low threshold value at any study visit. Those subject IDs are then sorted by dose group. This same process is repeated for high outlier values except the threshold is set to greater then or equal to +20mmhg change from the baseline blood pressure value. This process is repeated for each blood pressure parameter of interest noted in the previous paragraph. The value of interest for the blood pressure parameters is a decline in the values compared to placebo. The concern for pulse is an increase in heart rate compared to placebo. The high outliers are examined in the analysis to act as an index of the variability of blood pressure in the sample group. To normalize the number of unique patients found in placebo and each ezogabine dose group, a percent of patients with the outlier value is computed by dividing the number of affected patients by the number in the respective dose or placebo group. These results are shown in table 105 and displayed visually in the subsequent graphics.

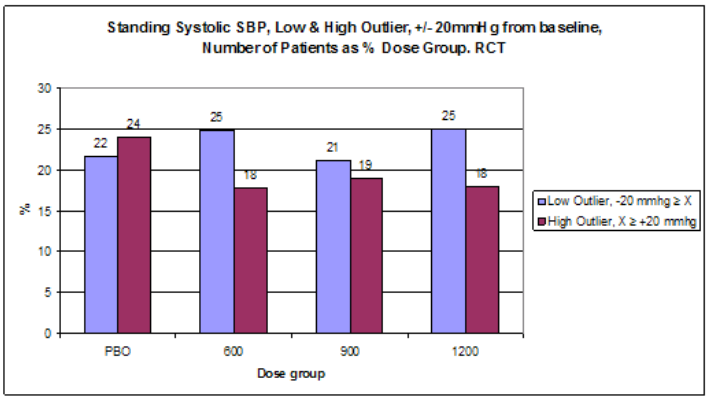
The largest spread between placebo and treatment blood pressure in any of the parameters is 3%. This occurs in standing systolic blood pressure at the 600mg and 900mg dose. There are a greater number of low outlier patients than high outlier patients in all dose groups of standing systolic blood pressure except placebo. In the systolic component of the orthostatic blood pressure gradient the number of low outlier patients is less then or equal to placebo at each dose group. There are larger numbers of low value than high value oulier patients at each dose group, however there are a larger number of placebo low outlier value patients than high outlier value patients. In the diastolic component of the orthostatic blood pressure gradient parameter the maximum there are 3 percent more low value outliers in the 600mg group than placebo, however there are only 1% greater low value outliers than placebo in the 900mg and 1200mg groups. There are greater number of high value outlier patients then low value patients in the 900 mg and 1200mg dose groups. The standing diastolic blood pressure reveals 2% greater numbers of low outlier value patients in the placebo group than in the ezogabine treatment group at the 600mg and 900mg dose groups. There is a 1% greater number of low value outliers in the 1200mg ezogabine treatment group than placebo. The percent of low value outlier patients is greater then high value outlier patients in each dose group.

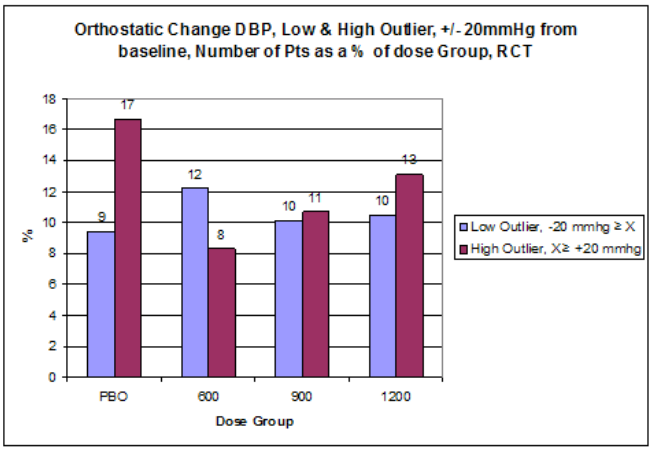
Evaluation of standing pulse reveals that the percent of patients in each ezogabine treatment group do not exceed the percent of low outlier patients in the placebo group. There are greater numbers of high then low outlier patients at all ezogabine doses and placebo. The excess of high outlier value patients is greater in placebo than any of the ezogabine dose groups.

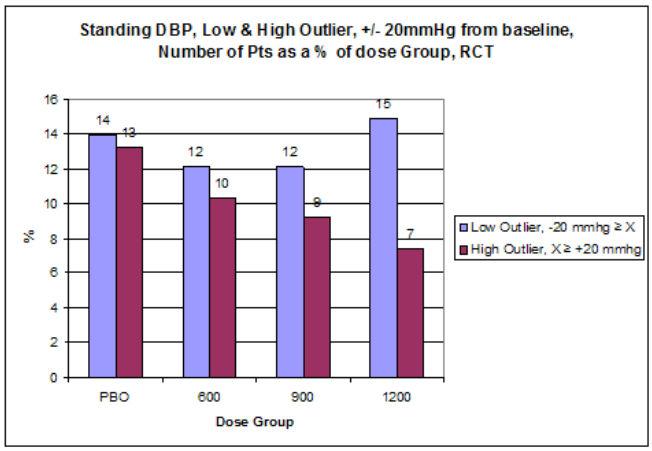
Table 105 Frequency of Outliers in 4 Blood pressure and one pulse parameter, ezogabine compared to placebo and low value outlier frequency compared to high value frequency

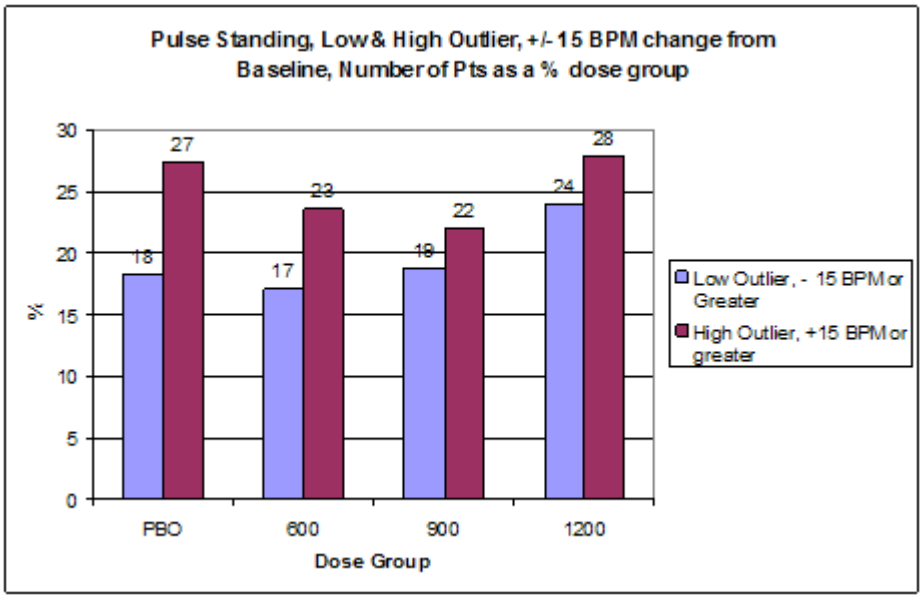
	Pt number / dose Group	Low PCC unique Patients	% Low Outlier, -20 mmhg ≥ X	High PCC Unique Patients	% High Outlier, X ≥ +20 mmhg	Δ% Low, Rx - PBO	Δ% Low-High
Standing Systolic Blood Pressure							
PBO	424	92	22	102	24		-2
600	281	70	25	50	18	3	7
900	273	58	21	52	19	0	2
1200	255	64	25	46	18	3	7
OH Systolic							
PBO	331	67	20	51	15		5
600	181	27	15	18	10	-5	5
900	178	26	15	25	14	-6	1
1200	153	30	20	27	18	-1	2
OH Diastolic							
PBO	331	31	9	55	17		-7
600	181	22	12	15	8	3	4
900	178	18	10	19	11	1	-1
1200	153	16	10	20	13	1	-3
Diastolic BP Standing							
PBO	424	59	14	56	13		1
600	281	34	12	29	10	-2	2
900	273	33	12	25	9	-2	3
1200	255	38	15	19	7	1	7
Pulse Standing			Low Outlier, -15 BPM or Less		High Outlier, +15 BPM or Less	**Δ% High, Rx - PBO**	
PBO	424	77	18	116	27		-9
600	281	48	17	66	23	-4	-6
900	273	51	19	60	22	-5	-3
1200	255	61	24	71	28	0	-4











A search of the case history narratives (deaths, SAEs, discontinuations) was performed. This revealed 1 case with hypotension as one of the adverse event terms. This case

3065A1-102-80034 occurred in a phase 1 clinical pharmacology study assigned to receive 300mg of ezogabine a day. The patient reported dizziness and lightheadedness on the first day of dosing ezogabine and withdrew from the study. The narrative does not report the blood pressure values. Two additional cases were identified with hypotension appearing in the narrative but not as an adverse event term. **Case 301-15304** had the term hypotension present in an adverse event entry for dizziness, Dysarthria, nightmare and dry skin. On the date of the hypotension, day 29 of treatment with 900mg, the patient had a supine blood pressure of 102/60mmHg which declined on standing to 80/40. Standing pulse was 87, pulse supine 75. The patient had a 17mmHg decline in systolic orthostatic blood pressure difference from baseline. The patient continued in the study for an additional 14 days before discontinuation due to dizziness. The second case identified with hypotension in the narrative but not as an adverse event term was a patient in the compassionate use program who suffered hypotension in the course of sepsis on day 1300 of treatment.

Case 301-15304, AE Term Dizziness found to have hypotension in vital signs dataset							
	Event Terms (PT)	BP	Date	Supine	standing	Supine	standing
301-15304	Dizziness, nightmares, Dysarthria		4/20/07	115/80	110/80	70	71
			5/7/07	130/80	105/65	75	84
			5/18/07	102/60	80/40	75	87
			1/6/07	110/80	80/60	74	88
			6/20/07	90/60	80/50	80	88
			7/19/07	95/60	89/50	60	70

Reviewer Comment: The most notable result in outlier analysis of blood pressure is in the standing systolic blood pressure parameter. This trend is not strong, with a maximum 3% separation at the 600mg and 900mg dose and is not reproduced in the three additional parameters which were examined. There is no difference between placebo and ezogabine treatment in the standing pulse parameter. This supports the conclusion that there is not a strong signal for drop in blood pressure due to ezogabine. Analysis 3 of appendix 9.12 (dizziness) examines postural blood pressure change in the double blind phase of the RCTs. No signal for orthostatic blood pressure instability was identified. Single cases; however are identified where hypotension does develop related to ezogabine treatment. There is one case (**3065A1-102-80034)** in a phase 1 study where there is a report (blood pressure value not provided) of hypotension on day 1 of dosing, leading to withdrawal and one case (**301-15304**) where hypotension in the narrative of an AE for dizziness reveals the patient developed a decline in blood pressure during ezogabine treatment. In addition, the evaluation of cases of syncope (discussion to follow) there are 3 cases in the "All Phase II/III combined" group where there is a finding of a reduced systolic blood pressure parameter at every post baseline visit. This combination of findings rises to a threshold of evidence needed to place **"hypotension seen in clinical trials" in the "additional adverse reactions**

Observed during All Phase 2 and 3 Clinical trials" under heading "Cardiovascular disorders, general".

Syncope

The reports of syncope as an SAE were examined in RCT and "All Phase II/III Combined" groups to determine if these events would identify an additional line of evidence that there was a significant signal for hypotension with ezogabine use.

The primary cause of syncope is due to loss of adequate cerebral perfusion to maintain consciousness. This cause of the hemodynamic alteration may occur due to transient alterations in cardiac output caused by cardiac rhythm disturbance or a loss of blood pressure support due to change in intravascular volume or vasomotor instability. Cardiac dysrhythmia or alteration of vasomotor stability or is most relevant for examination of possible drug effect. Based on the foregoing concepts the salient analysis of syncope which has occurred in ezogabine clinical trials will be directed at cardiac adverse events, ECG analysis and blood pressure analysis.

RCT

	Seizures and Related Events (Safety Population: RCT, Studies 205, 301, and 302)				
	Number (%) of patients				
	Placebo N=427	**Ezogabine**			
Preferred term		**600 mg/day N=281**	**900 mg/day N=273**	**1200 mg/day N=259**	**Total N=813**
Syncope	1 (0.2)	0	3 (1.1)	2 (0.8)	5 (0.6)

In controlled trials there were 2 ((0.2%) cases of syncope in the placebo group and 5 (0.6%) cases in ezogabine treatment with no dose response. Within this group there was one withdrawal from ezogabine treatment and this case was also entered as an SAE (case 03101). The features of the event are most consistent with a seizure.

All Phase II/III Combined Group

In the "All Phase II/III Combined Group" there were a total of 12 cases of syncope. There was one additional study withdrawal, (case 25214). The patient had a fainting episode after 54 days of treatment with 1200mg ezogabine a day.

Integrated Clinical Pharmacology Analysis Set

There was one case of syncope in a healthy volunteer participant in study E22-106. This was a study of ezogabine and oral contraceptive. The patient was treated with ezogabine for 30 days and had achieved and sustained a dose of 600mg a day for two days when the fainting episode occurred.

Blood Pressure

The blood pressure trends for the 12 patients with adverse events of syncope in the "All Phase II/III Combined Group" is examined at all study visits. In 5 of the 12 cases there was no change from baseline blood pressure or the blood pressure increased over the baseline reading. In the remaining 7 of these 12 cases there are blood pressure values with a decline from baseline captured at some of the post baseline visits while in 3 of these there is a decline in blood pressure noted at all post baseline study visits. In 5 of the 7 cases there was a recorded decline from baseline blood pressure within 14 days of the event.

Dizziness was a common adverse event in ezogabine clinical trials. Dizziness may be caused by a disturbance of central or peripheral vestibular function or alteration of blood pressure stability. The more common and threatening etiology in the case of a new anticonvulsant drug is an alteration in hemodynamic stability. An extensive analysis of the relationship of hypotension as a possible cause of dizziness did not reveal hypotension to be a cause of dizziness, appendix 9.12. However analysis of blood pressure outlier data did reveal a separation from placebo in sitting systolic blood pressure, and in supine to standing systolic blood pressure table 105.

Cardiac

Overall examination of section 7.3.5 "Cardiac Rhythm / Conduction abnormalities", did not reveal a compelling cardiac safety signal within the "All Phase II/III Combined Group" of studies. Examination of ECGs reveals a small effect of QT prolongation; the IRT QT team did not feel this trend would have clinical significance. There was no notable occurrence of abnormalities in non-QT ECG parameters. The abuse potential study did have two noteworthy cardiac AEs that are relevant to the syncope discussed fully in "Significant Adverse Events" section 7.3.4, "Cardiac". There was one case of a spontaneously resolving cardiac asystole, which occurred on a background of baseline bradycardia but was otherwise unexplained and a case of asymptomatic ventricular tachycardia.

All 12 syncope AEs from within the "All Phase II/III Combined Group" were examined for their association with cardiac adverse events. When the subject ID's of these 12 patients were linked with all AEs from the AE dataset there were 256 adverse events captured. None of these was contained within the SOC- "Cardiac Disorders" and examination of each term did not reveal a cardiac association.

Reviewer Comment: the controlled trials reveal only a small separation between placebo and ezogabine treatment for syncope (0.4%), placebo 0.2% vs 0.6% ezogabine treatment. Examination of all syncope cases in the All Phase II/III Combined Group reveals there is a weak trend toward hypotensive effect with cases divided 58% - 42% between those patients with syncope who had decline in a systolic blood pressure parameter from baseline and those who did not. There is no significant signal for a cardiac cause to underlie occurrence of syncope. There are two cases of concern, one,

the case of 25 second asystole (and syncope) in the abuse potential study (case 108-9077), second the case in a healthy volunteer (E22-106-00004) in the clinical pharmacology study of ezogabine and oral contraceptive. The case of cardiac asystole points to follow up need for postmarketing pharmacovigilance for cardiac arrhythmia, which has been proposed in risk management by the sponsor. The case in the healthy volunteer is without further explanation, but is insufficient to counter the small separation between placebo and ezogabine treatment in controlled clinical trials. The overall analysis does not identify a signal which dictates a need for syncope in labeling.

Weight: Weight analysis provided in Section 7.5.3, Drug – Demographic Interactions

7.4.4 Electrocardiograms (ECGs)

There was variation between studies in the collection and interpretation of ECGs in the RCTs (studies 205, 301 and 302). Study 205 was the earliest study. In this study a 12 lead ECG was obtained at screening and study treatment days 1, 56, and 112. In this study only a holter monitor was obtained at screening. The source of interpretation for the study 205 ECGs is not provided. In study 301 there was a 12 lead ECG obtained at weeks 2,4, 6, 7, 8, 18, 20, 22, and 24. The baseline ECG was repeated 3 times with tracings 3 min apart. All ECGs were obtained on standardized equipment and transmitted to a central laboratory electronically. In Study 302 a 12 lead ECG was obtained at weeks 2,4,6,16,18 and 20. At baseline the ECG was repeated 3 times with tracings scheduled 3 min apart. All were obtained on standardized equipment and transmitted electronically to a central laboratory for interpretation. All open label and extension studies had 12 lead ECG performed at the beginning of the open label section. Tracings were also captured at subsequent time points that varied from study to study but which, overall provided a profile of ECG features with continued use of ezogabine.

Central Tendency and Change from Baseline (RCT)

Sponsor summary statistic and change from baseline tables for heart rate, RR interval, PR interval, QRS interval, uncorrected QT interval, QTc interval with Bazett's and Fridericia's correction (QTcB and QTcF, respectively) are reviewed. There were no clinically noteworthy changes in PR interval, RR interval and QRS interval compared to placebo group during the course of weeks 2 to 18.

Mean change from baseline between weeks 2 and 18 using Bazzett's criteria reveal the first QTcB gradient from placebo >5% in weeks 12 , 16 and 18, table 106. Notable increase is seen in week 12 in the 900mg and 1200mg dose groups at 16.7msec and 14.2 msec respectively with placebo at week 12 equal to -0.1msec. Week 12 is not a representative sample point due to the small sample size at this sampling interval, only 27 ezogabine treated patients are captured at this time point. The trend of notable increase in change from baseline is continued, although not increasing in magnitude, at week 16 with mean change from baseline for placebo, 600mg, 900mg, and 1200mg equal to 4.3msec, 2.9msec, 7.1msec and 9.5msec respectively. At week 16 there are

423 ezogabine treated patient ECGs captured. The mean change from baseline at week 18 again is not progressively increasing in magnitude or in a dose responsive manner but are notably larger than placebo in the 600mg and 900mg dose group. The values at week 18 for placebo, 600mg, 900mg, and 1200mg dose groups are 2.2msec, 14.6msec, 10.5msec, and 4.2msec respectively.

Examination of the mean change from baseline by week using Bazzett's criteria reveals the largest gradient from placebo occurs in week 12 at the 600mg and 900mg dose, equal to 16.8msec (placebo = -0.1msec) and 14.3msec (placebo = -0.1msec) respectively. In order of decreasing magnitude the remaining changes from baseline >5msec over placebo are 12.8msec 8.7msec and 5.2msec occurring in weeks 18 at 600mg, 900mg, and week 16 at 1200mg respectively.

Mean change from baseline between weeks 2 and 18 using Fridericia's criteria reveal the first QTcF gradient from placebo >5% in weeks 12, 16 and 18, table 106. Notable increase is seen in week 12 at the 900mg and 1200mg dose, again there is a small sample size at this time point, 27 ezogabine treated patients. At week 16, where 421 ezogabine treated patients are captured, reveals change from baseline values for placebo, 600mg, 900mg, and 1200mg equal to 4.3msec, 3.6msec, 8.0msec and 4.2msec respectively. At week 18, where 98 ezogabine treated patients are captured reveals change from baseline values for placebo, 600mg, 900mg and 1200mg equal to 3.6msec, 11.3msec, 10.6msec, and 3.3msec respectively.

Examination of the mean change from baseline by week using Fridericia's criteria reveals the largest gradient from placebo occurs in week 12 at the 900mg and 1200mg dose equal to 15.3msec (placebo= 1.4msec) and 13.4msec (placebo= 1.4msec) respectively. In order of decreasing magnitude the remaining changes from baseline >5msec over placebo are 6.7msec and 7.0msec occurring in week 18 at the 600mg and 900mg dose respectively.

Reviewer Comment: there is a consistent observation of increase magnitude of QTcB and QTcF at week 12, 16 and 18 of the pivotal controlled trials. There were 5 values QTcB values which were 5msec greater than the placebo value and 4 observations more than 5msec greater than placebo using QTcF. In both QTcB and QTcB the 2 largest changes from baseline occurred at week 12 ECGs where the sample group was very small. All of the noteworthy values identified in the preceding discussion are in the range of 5 to 20msec, where the determination of risk is inconclusive in the "E14 Clinical Evaluation of QT/QTc Interval Prolongation", Guidance for Industry. These value represent descriptive observations rather than statistics designed for hypothesis testing and are therefore of uncertain significance but indicate a need to be alert for a QT safety signal in the categorical analysis of QT recordings as well as in the thorough QT study,.

Table 106 Baseline Bazzett's QTc and Friderica's QTc and Change in Bazzett's QTc and Friderica's QTc from Baseline (Safety Population: RCT, Studies 205, 301, and 302)

	Number of Patients PR Interval (MSEC)				
	Placebo N=427	**RTG 600 mg/day N=281**	**RTG 900 mg/day N=273**	**RTG 1200 mg/day N=259**	**RTG Total N=813**
	Bazzett's QTc (MSEC)				
Baseline mean(±SD)	**398.3 (23.82)**	**395.9 (24.80)**	**394.1 (24.88)**	**393.3 (26.33)**	**394.5 (25.31)**
Change from Baseline, mean(±SD)					
Week 2	-0.9 (16.23)	1.8 (16.75)	-0.0 (14.01)	0.8 (15.89)	0.9 (15.60)
Week 4	0.6 (16.77)	-0.7 (16.47)	0.1 (16.29)	3.3 (16.25)	0.8 (16.39)
Week 6	-0.5 (17.86)	1.0 (15.65)	2.3 (15.97)	2.1 (15.28)	1.8 (15.62)
Week 8	0.8 (17.90)	1.9 (22.21)	2.4 (22.01)	2.5 (18.66)	2.3 (20.53)
Week 12	-0.1 (13.76)	0.9 (26.79)	16.7 (22.80)	14.2 (26.98)	8.7 (26.22)
Week 16	4.3 (19.27)	2.9 (18.12)	7.1 (16.51)	9.5 (19.39)	5.5 (17.79)
Week 18	2.2 (16.86)	14.6 (16.27)	10.5 (18.03)	3.1 (17.39)	4.2 (17.48)
	Fridericia's QTc (MSEC)				
Baseline mean(±SD)	**389.1 (21.36)**	**387.1 (21.68)**	**384.8 (23.67)**	**386.0 (24.48)**	**386.0 (23.26)**
Change from Baseline, mean(±SD)					
Week 2	-0.6 (13.53)	1.1 (14.30)	-0.0 (13.49)	0.1 (13.00)	0.4 (13.63)
Week 4	0.4 (13.72)	0.6 (14.62)	1.3 (14.52)	2.0 (15.62)	1.3 (14.88)
Week 6	-0.6 (15.22)	1.5 (13.51)	3.0 (13.59)	2.0 (15.29)	2.1 (14.08)
Week 8	1.5 (16.00)	2.9 (19.13)	5.1 (19.05)	2.8 (16.57)	3.4 (17.95)
Week 12	1.4 (17.18)	2.1 (22.87)	16.7 (16.75)	14.8 (20.20)	9.5 (21.26)
Week 16	4.3 (16.11)	3.6 (16.12)	8.0 (15.22)	9.1 (17.21)	6.2 (16.04)
Week 18	3.6 (14.28)	11.3 (12.03)	10.6 (10.73)	3.3 (16.36)	4.2 (15.95)

Outliers

RCT

Table 107 provides a categorical overview of outliers identified using both Bazett's and Fridericia' criteria, placebo and all dose groups are compared.

Examination of QTc using Bazett's criteria reveals that patients with increase greater than 30msec over baseline occur in greater frequency than placebo for all dose groups, although there is not a clear dose response there is an increase in frequency of occurrence between the 600mg and 900mg group. There are very few patients with an increase greater than 60msec over baseline. The group with change from baseline >60msec is examined to determine the range of baseline values and if the resulting values exceeded 450msec.

The examination of the patients with increase from baseline greater than 60msec (table 67) reveals 7 instances of change from baseline >60msec. these seven instances were generated by 5 unique patients. The mean baseline QTcB of these five patients is

348.5msec with a range of 337msec to 361msec with a maximum resulting QTcB of 424msec, therefore none of the 5 unique subjects had a resulting QTcB in an abnormal range. There was a trend in the >60msec change from baseline values to occur in the later portion of the double blind trial. 4 of seven instances occurred at week 16, one of 7 at week 12, one at week 6 and one at week. 2. The median of occurrences was in week 16.

The frequency of QTcB with post baseline values ≥450msec in the placebo, 600mg, 900mg and 1200mg groups was 4.7%, 1.9%, 3.9% and 5.2% respectively. There was a dose response between 600mg and 1200mg, however only the 1200mg group exceeded placebo by a margin of 0.5%. There was only one occurrence of QTcB with a post baseline value greater than 480msec, Table 107.

Examination of QTcF reveals the frequency of values which exceeded baseline by > 30msec was greater than placebo in all dose groups with a dose response. The values for Δ over baseline greater than 30msec for placebo, 600mg, 900mg, and 1200mg were 7.9%, 9.8%, 11.8%, and 12.1% respectively. There was 1 subject each in the placebo group 2 subjects in the 900mg and 1 in the 1200mg group with a Δ from baseline greater than 60msec.

Examination of the patients using QTcF found to have an increase from baseline greater than 60msec (table 109), reveals 4 instances of change from baseline >60msec generated by 3 unique subjects. The mean baseline value of these 3 patients was 354msec with a range of 344 to 377msec with a maximum resulting QTcF of 440msec, therefore none of the 3 unique subjects had a resulting QTcF in an abnormal range.

The frequency of values for QTcF which were ≥450msec in the placebo, 600mg, 900mg and 1200mg dose groups was 1.0%, <1%, 1.2%, and 1.3% respectively. This reveals a dose response but with only a small margin of occurrence over placebo of 0.2% and 0.3% in the 900mg ad 1200mg groups respectively. There was only one subject found by QTcF to have a post baseline value ≥480msec. This event occurred on an already abnormal baseline value of 461 msec with a resultant QTcF of 490msec due to a change from baseline of 28msec.

Table 107 Findings for QTc of Potential Clinical Concern (Safety Population: RCT, Studies 205, 301, and 302) Categorical analysis

	Number of Patients2/Number of Patients Evaluable (%)				
	Placebo (N=427)	**RTG 600 mg/day (N=281)**	**RTG 900 mg/day (N=273)**	**RTG 1200 mg/day (N=259)**	**RTG Total (N=813)**
QTc Bazett's					
Increase >30 msec from baseline	47/403 (11.7)	41/266 (15.4)	36/255 (14.1)	42/232 (18.1)	119/753 (15.8)
Increase >30 msec and ≤60 msec from baseline	47/403 (11.7)	39/266 (14.7)	35/255 (13.7)	42/232 (18.1)	116/753 (15.4)
Increase >60 msec from baseline	2/403 (<1)	2/266 (<1)	1/255 (<1)	2/232 (<1)	5/753 (<1)
Post-baseline ≥450	19/403	5/266	10/255	12/232	27/753

msec[1]	(4.7)	(1.9)	(3.9)	(5.2)	(3.6)
Post-baseline ≥480 msec[1]	0	1/266 (<1)	0	0	1/753 (<1)
Post-baseline ≥500 msec1	0	0	0	0	0
QTc Fridericia's					
Increase >30 msec from baseline	32/403 (7.9)	26/266 (9.8)	30/255 (11.8)	28/232 (12.1)	84/753 (11.2)
Increase >30 msec and ≤60 msec from baseline	32/403 (7.9)	26/266 (9.8)	28/255 (11.0)	28/232 (12.1)	82/753 (10.9)
Increase >60 msec from baseline	1/403 (<1)	0	2/255 (<1)	1/232 (<1)	3/753 (<1)
Post-baseline ≥450 msec1	4/403 (1.0)	2/266 (<1)	3/255 (1.2)	3/232 (1.3)	8/753 (1.1)
Post-baseline ≥480 msec1	0	1/266 (<1)	0	0	1/753 (<1)
Post-baseline ≥500 msec1	0	0	0	0	0
1. baseline value greater than this value of missing included					

Table 108 Patients identified with change from baseline QTc Bazett's >60msec

USUBJID	Treatment	Δ Baseline	Baseline	RESULT	WEEK
3065 A1-205~000078~001159	PLACEBO	67.6665689	329.354925	397.021494	8
VRX-RET-E22-301~000105~010506	PLACEBO	90.5209827	341.656758	432.177741	4
VRX-RET-E22-301~000105~010506	PLACEBO	64.3432415	341.656758	406	8
3065 A1-205~000085~001237	600 MG/DAY	61.3219895	351.350964	412.672954	2
3065 A1-205~000097~001402	600 MG/DAY	64.0154169	355.5462	419.561616	16
VRX-RET-E22-302~000351~035102	900 MG/DAY	62.4457249	361.116313	423.562038	6
VRX-RET-E22-302~000351~035102	900 MG/DAY	62.3104024	361.116313	423.426715	16
3065 A1-205~000044~000887	1200 MG/DAY	69.7554179	337.166032	406.92145	12
3065 A1-205~000044~000887	1200 MG/DAY	61.8298741	337.166032	398.995906	16
3065 A1-205~000077~001133	1200 MG/DAY	66.4897807	337.364318	403.854099	16

Table 109 Patients identified with change from baseline QTc Fridericia's >60msec

USUBJID	Treatment	Δ Baseline	Baseline	Result	WEEK
VRX-RET-E22-301~000105~010506	PLACEBO	69.8697925	345.612008	415.4818	4
VRX-RET-E22-301~000105~010506	PLACEBO	60.387992	345.612008	406	8
3065 A1-205~000023~000331	900 MG/DAY	61.762955	343.886853	405.649808	8
3065 A1-205~000024~000349	900 MG/DAY	62.4454134	377.604576	440.04999	8
3065 A1-205~000044~000887	1200 MG/DAY	61.5024712	341.065417	402.567888	12
3065 A1-205~000044~000887	1200 MG/DAY	62.5449476	341.065417	403.610365	16

Other ECG Parameters (heart rate, PR and QRS intervals)

- Heart rate decreases meeting PCC criteria (<50 bpm and decrease from baseline ≥15 bpm) were recorded at least once in 5/403 (1.2%), 0, 2/255 (<1.0%), and 1/233 (<1.0%) patients in the placebo, 600, 900, and 1200 mg/day dose groups, respectively.

- Heart rate increases meeting PCC criteria (>100 bpm and increase from baseline ≥15 bpm) were recorded at least once in 9/403 (2.2%), 3/266 (1.1%), 3/255 (1.2%), and 2/233 (<1.0%) patients in the placebo, 600, 900, and 1200 mg/day dose groups, respectively.

- PR interval changes meeting PCC criteria (≥210 msec and increased from baseline) were recorded at least once in 17/403 (4.2%), 11/266 (4.1%), 10/255 (3.9%), and 9/233 (3.9%) patients in the placebo, 600, 900, and 1200 mg/day dose groups, respectively.

- Lastly, QRS interval changes meeting PCC criteria (≥120 msec and increased from baseline) were recorded at least once in 7/403 (1.7%), 2/266 (<1.0%), 6/255 (2.3%), and 1/233 (<1.0%) patients in the placebo, 600, 900, and 1200 mg/day dose groups, respectively.

All Phase II/III Combined

Categorical Analysis

Examination of ECGs from the "All Phase II/III Combined" group using Bazett's and Fridericia's criteria is compared to the total ezogabine results of the "pivotal clinical trials" group. This comparison strategy is selected because the numerical values for each category in table 110 represent the pooled frequency of occurrences for all ezogabine dose groups in each category. The comparison reveals larger numbers in the category of "Increase >30 msec from baseline", "Increase >30 msec and ≤60 msec from baseline" and "Increase >60 msec from baseline " in the "All Phase II/III Combined" group for both QTcB and QTcF. There is also an increase in the categories of the number of post baseline select value of 450, 480 and 500msec but these percent increases have a maximum of 1%.

Table 110 QTc Findings of Potential Clinical Concern in Categories of increase compared to baseline and specified post baseline values (All Phase II/III combined) compared to the same findings in RCT group.

	Number of Patients[2]/Number of Patients Evaluable (%)	Values in each category for "ezogabine total" from RCTs only (see table 110,	Δ "All Phase II/III Combined" -RCTs table percent only

		n/N (%)	
	EZO	**EZO**	
	(N=1365)	**(N= 813)**	
QTc Bazett's			
Increase >30 msec from baseline	253/1213 (20.9)	119/753 (15.8)	**5.1**
Increase >30 msec and ≤60 msec from baseline	246/1213 (20.3)	116/753 (15.4)	**4.9**
Increase >60 msec from baseline	22/1213 (1.8)	5/753 (<1)	1.14
Post-baseline ≥450 msec1	56/1213 (4.6)	27/753 (3.6)	1.0
Post-baseline ≥480 msec1	6/1213 (<1.0)[3]	1/753 (<1)	0.36
Post-baseline ≥500 msec1	1/1213 (<0.1)[4]	0	.08
QTc Fridericia's			
Increase >30 msec from baseline	198/1213 (16.3)	84/753 (11.2)	**5.1**
Increase >30 msec and ≤60 msec from baseline	196/1213 (16.2)	82/753 (10.9)	**5.3**
Increase >60 msec from baseline	12/1213 (1.0)	3/753 (<1)	0.6
Post-baseline ≥450 msec1	18/1213 (1.5)	8/753 (1.1)	0.4
Post-baseline ≥480 msec1	3/1213 (<1.0)[5]	1/753 (<1)	0.11
Post-baseline ≥500 msec1	0	0	

Reviewer Comment: Categorical examination of the RCT group outliers first by those with > 30msec increase in QT compared to baseline reveals using both Bazett's and Fridericia's QT correction all dose groups have an increase number of patients compared to placebo who have increased their QT greater than 30msec. In the QTcB group there is not a does response, rather the 600mg and 1200mg dose groups have the largest number of outliers in the >30msec range at 15.4% and 18.1% respectively compared to placebo with 11.7%. In the QTcF group there is a dose response of 9.8% 11.8% and 12.1% in the 600mg, 900mg and 1200mg groups respectively compared to placebo at 7.9%.

Examination of Bazett's correction reveal that of those 5 patients with 7 instances of change from baseline greater than 60msec none was shifted to an abnormal QT duration although there was a trend for +60msec change to occur later in the study. When examining post baseline QT intervals there is a dose response noted. In those occurrences of QT ≥450msec post baseline, however only the 1200mg ezogabine dose exceeds placebo by a margin of 0.5%. Examination of the RCT group outliers using Friderica's method reveal 3 patients with a change from baseline ≥60msec. none of these was shifted to an abnormal QT duration. Examination of the occurrence of post baseline QTcF values ≥450msec reveal greater frequency in ezogabine treatment groups than placebo; however the margin of increase in excess of placebo is small, not exceeding 0.3% (1200mg group). Categorical examination of the "All Phase II/III Combined" group reveals an approximately 5% increase in frequency of change from baseline greater than 30msec indicating a possible relationship between QT lengthening and duration of exposure. In the examination of measures of central tendency in RCTs, QT was found to be longer at weeks 12,16 and 18 (longer duration) and at higher doses is congruent with the subtle but consistent trend of increase in QTcF and QTcB outliers with dose and duration. These ECG findings are also consistent with the conclusion of the IRT QT review which indicated "the potential effect

of ezogabine on QT prolongation is likely to be small and should not have important clinical significance except perhaps in those subjects who are at the highest risk"[11].

Non QT ECG parameters did not reveal notable differences in frequency of outliers (values in range of PCC –potential clinical concern) greater than placebo.

7.4.5 Special Safety Studies/Clinical Trials

The sponsor performed a Thorough QT study: VRX-RET-E22-103: A Double-Blind Randomized Parallel-group Trial to Define the ECG Effects of Ezogabine Using a Maximum Tolerated Dose Compared with Placebo and Moxifloxacin (a Positive Control) in Healthy Men and Women: A Thorough ECG Trial

The analysis provided by the FDA Interdisciplinary Review Team for QT Studies will be presented in this section.

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

Overall Summary of Findings:

The sponsor used QTcI as their primary correction method. Based on our evaluation for different correction methods, we believe QTcF corrects RR more sufficiently than QTcI in this study; therefore, FDA analysis results based on QTcF are suggested for the labeling.

In this randomized, double-blinded (except for the use of moxifloxacin), active and placebo controlled, 3-arm parallel study, 120 healthy subjects received ezogabine, placebo, or moxifloxacin. Overall summary of findings is presented in table 111. The largest upper bounds of the 2-sided 90% CI for the mean difference between ezogabine 400 mg and placebo was above 10 ms.

Table 111 The Point Estimates and the 90% CIs Corresponding to the Largest Upper Bounds for Ezogabine (400 mg) and the Largest Lower Bound for Moxifloxacin (FDA Analysis)

Treatment	Time (hrs)	ΔΔQTcF (ms)	90% CI (ms)
Ezogabine (400 mg)	3	7.7	(3.5, 11.9)
Moxifloxacin 400 mg	1	13.1	(8.5, 17.8)

The relationship between ΔΔQTcF and ezogabine concentrations is visualized in figure 16 . The slope of the exposure-response relationship is slightly but significantly greater

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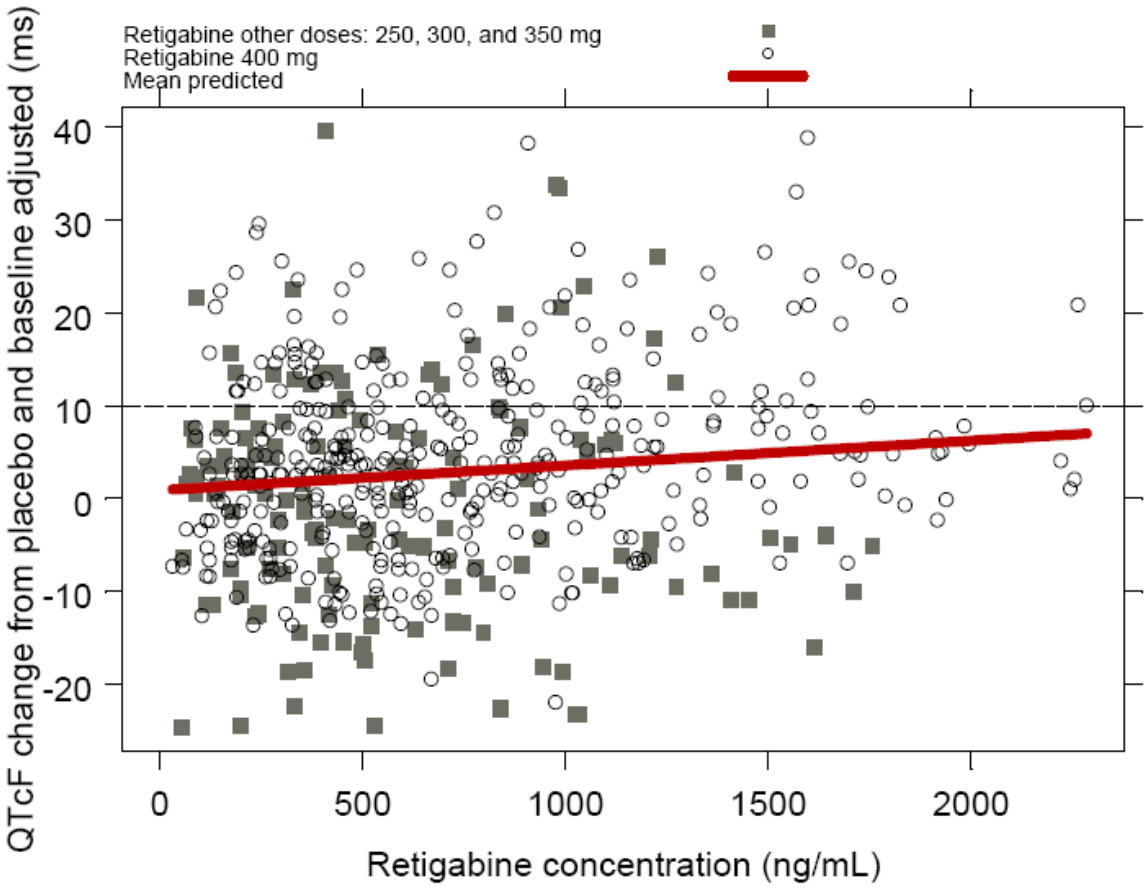
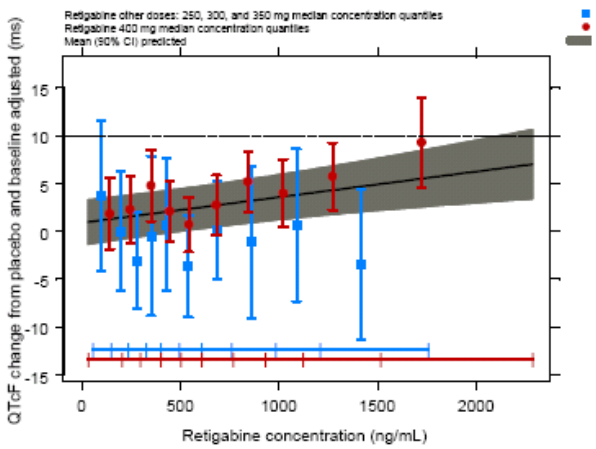
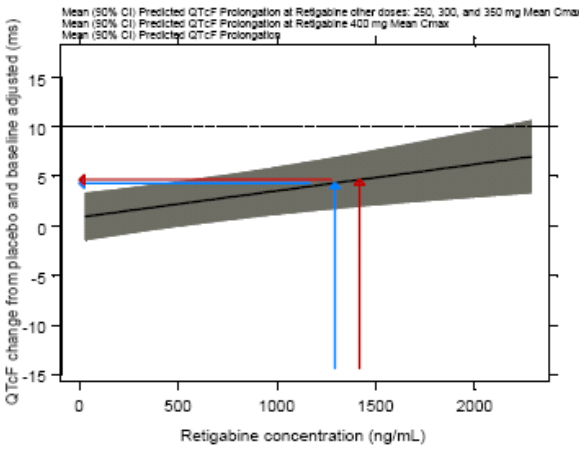
than 0 (slope: 0.00227 with p-value: 0.0081). The upper 90% confidence boundary of the median concentration for the 10th-quantiles of the 1200 mg/day dose excesses the clinical threshold per ICH E-14, 10 ms, bottom left panel figure 16 . Also in the quantile plot, the ΔΔQTcF in the 1200- mg/day dose group is consistently higher than in the sub-dose group. Therefore, the potential effect of ezogabine on QT prolongation exists. However, the upper 90% confidence boundary of the median concentration for the 10th-quantiles for the 1200- mg/day dose is below 15 ms and the mean values of Cmax for both the highest tolerated dose and sub-dose are all below 5 ms. Hence, the potential effect of ezogabine on QT prolongation is likely to be small and should not have important clinical significance except perhaps in those subjects who are at the highest risk.

Figure 16 ΔΔQTcF vs. ezogabine concentration. Observed data (Top), Concentration Quantile plot (Bottom Left), and Predicted ΔΔ QTcF at mean Cmax (Bottom Right).







The QTc prolongation risk of ezogabine was evaluated under the highest titratable dose for healthy subjects (aimed 400 mg TID) over a 21-day period in the TQT study. Supratherapeutic dose is not included in this study due to tolerability issues. The exposures in the TQT study is lower than those that will occur in a clinical setting due to intrinsic factors (e.g., renal and hepatic impairment could cause 27-43% increase in C_{max} and about 100% increase in AUC) influencing ezogabine exposure.

QT-IRT Comments
The moxifloxacin profile is not what we expected. The rising phase is missing.
The maximum moxifloxacin induced ΔΔQTcF effect reaches peak almost at the first available time point, which is 1 hr after dose. We want to understand what happened before 1 hour. Please extract data for moxifloxacin, placebo at 15 minute, 30 minute post-dose and the corresponding baseline for us to evaluate.

Reviewer Comment: The results of the IRT-QT analysis are consistent with analysis of the controlled trial (RCT 205, 301, 302) ECG –QT data, there is a small but consistent increase in QT length related to the ezogabine treatment and proportional to concentration. The potential effect on QT prolongation should not have important clinical significance in the uncomplicated patient on therapeutic dosage. A QT prolonging effects is present which intrinsically is a source of small risk in the mainstream treatment population, however a subpopulation at higher risk are those with congenital long QT syndrome, Heart failure, ventricular hypertrophy, hypokalemia, hypomagnesemia or in patients taking concomitant medications known to increase the QT interval. This risk will need to be present in labeling. The IRT-QT team has provided preliminary editorial change to the label in their consult[12], table 112.

Table 112 IRT-QT Consult, Preliminary Label Revision

Label Section	Label Text
[redacted]	[redacted]

(b) (4)

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(b) (4)

We have used red-strike out for suggested text to be deleted and blue font for text to be included. Our recommendations are suggestions only. We defer final decisions regarding labeling to the review division

7.4.6 Immunogenicity

Ezogabine is a small molecule agent, less likely than a therapeutic protein to elicit an antibody response. No signal has emerged for a multiorgan hypersensitivity response although patient 0448 had a cluster of features that raised suspicion. This individual had laboratory evidence of hepatic dysfunction (increased transaminases and bilirubin), with an extremely elevate c-reactive protein and concurrent renal failure. No eosinophilia was reported. There was coexisting severe urinary retention (PVR 1500ml) The patient also had symptoms of myalgia and fatigue. Subsequently renal failure was found to be due to obstructive uropathy. The elevated c-reactive protein may have been caused by the renal failure, with no fever, skin reaction or eosinophilia there are inadequate core features to consider multiple organ hypersensitivity syndrome. Ezogabine has not presented sufficient evidence of a signal for eosinophilia. Only in the shift analysis did the absolute eosinophil count show a weak dose response noted with 1.1% greater than placebo at 600mg/day, 1.2% greater than placebo at 900mg/day and 3% greater than placebo at 1200mg/day.

Reviewers note concerning patient 0448, although ALT and bilirubin were elevated (2x ULN and 1.7 ULN respectively) the magnitude of elevation did not reach the threshold necessary to fulfill Hy's Law (ALT 3x ULN and bilirubin 2x ULN).

7.5 Other Safety Explorations

7.5.1 Dose Dependency for Adverse Events

In patients treated with ezogabine, the overall incidence of TEAEs increased with increasing dose category, ranging from 32% with the lowest dose of ezogabine (>0 mg to <300 mg) to 69% with the highest dose (1200 mg or more), table 113. Adverse events are included in table 113 if there is a dose response in a minimum of 3 consecutive dose groups. These AEs are according to actual dose regardless of study phase.

Pharmacokinetic-pharmacodynamic (PK-PD) analyses were conducted to evaluate the relationship between predicted ezogabine steady-state systemic exposure (area under the curve over the dosing interval (AUC(0-τ)) and key efficacy / safety endpoints using data pooled from Studies 301 and 302.

PK/PD analyses were conducted to investigate the relationship between AUC(0-τ) and the probability of efficacy (≥50% reduction from baseline in total partial seizure frequency) and the probability of occurrence of adverse events. This analysis showed

that over the entire AUC(0-τ) range observed in Studies 301 and 302, the probability of ≥50% decrease from baseline in seizure frequency was higher than the probability of any of the AE occurring. The slope of the exposure-response relationship for probability of efficacy was similar to that for dizziness and coordination abnormal whereas the slope of the exposure response relationship for dysarthria, somnolence, tremor and vision blurred were less steep; indicating that these latter AEs were less sensitive to changes in exposure, figure 17.

A summary of the predicted response by dose level from the PK/PD analyses for efficacy and safety endpoints from Studies 301 and 302 is shown in table 114.

Table 113 Most Common TEAEs[1] in the Total RTG Group by Dose, where dose response is present in minimum of 3 consecutive dose groups (RCT, Studies 205, 301, and 302)

	Number (%) of Patients					
	Dose					
Preferred Term	**0 mg (N=17)**	**>0 mg to <300 mg (N=187)**	**300 mg to <600 mg (N=796)**	**600 mg to <900 mg (N=747)**	**900 mg to <1200 mg (N=449)**	**1200 mg or more (N=178)**
Any Event	**2 (11.8)**	**60 (32.1)**	**387 (48.6)**	**383 (51.3)**	**277 (61.7)**	**123 (69.1)**
Dizziness	0	6 (3.2)	79 (9.9)	77 (10.3)	57 (12.7)	22 (12.4)
Somnolence	0	11 (5.9)	68 (8.5)	68 (9.1)	47 (10.5)	8 (4.5)
Headache	1 (5.9)	5 (2.7)	45 (5.7)	51 (6.8)	31 (6.9)	13 (7.3)
Confusional state	0	4 (2.1)	19 (2.4)	31 (4.1)	22 (4.9)	6 (3.4)
Vertigo	0	4 (2.1)	23 (2.9)	24 (3.2)	13 (2.9)	7 (3.9)
Tremor	0	1 (<1.0)	13 (1.6)	22 (2.9)	21 (4.7)	12 (6.7)
Coordination abnormal	0	2 (1.1)	18 (2.3)	23 (3.1)	13 (2.9)	8 (4.5)
Diplopia	0	2 (1.1)	24 (3.0)	27 (3.6)	10 (2.2)	5 (2.8)
Vision blurred	0	0	11 (1.4)	21 (2.8)	14 (3.1)	3 (1.7)
Asthenia	0	1 (<1.0)	16 (2.0)	19 (2.5)	10 (2.2)	2 (1.1)
Speech disorder	0	2 (1.1)	7 (<1.0)	15 (2.0)	12 (2.7)	8 (4.5)
Urinary tract infection	0	0	8 (1.0)	10 (1.3)	14 (3.1)	8 (4.5)
Gait disturbance	0	2 (1.1)	10 (1.3)	12 (1.6)	8 (1.8)	3 (1.7)
Convulsion	0	4 (2.1)	7 (<1.0)	9 (1.2)	7 (1.6)	6 (3.4)
Aphasia	0	2 (1.1)	8 (1.0)	5 (<1.0)	10 (2.2)	5 (2.8)
Balance disorder	0	0	9 (1.1)	11(1.5)	9 (2.0)	3 (1.7)

1. Defined as events that were reported in at least 5% of patients in any treatment group.
Note: Events are reported in this table by actual dose regardless of study phase (titration, maintenance, taper).

Figure 17 Probability of Efficacy (≥50% reduction in seizure frequency) and Adverse Events versus Ezogabine AUC(0-τ)

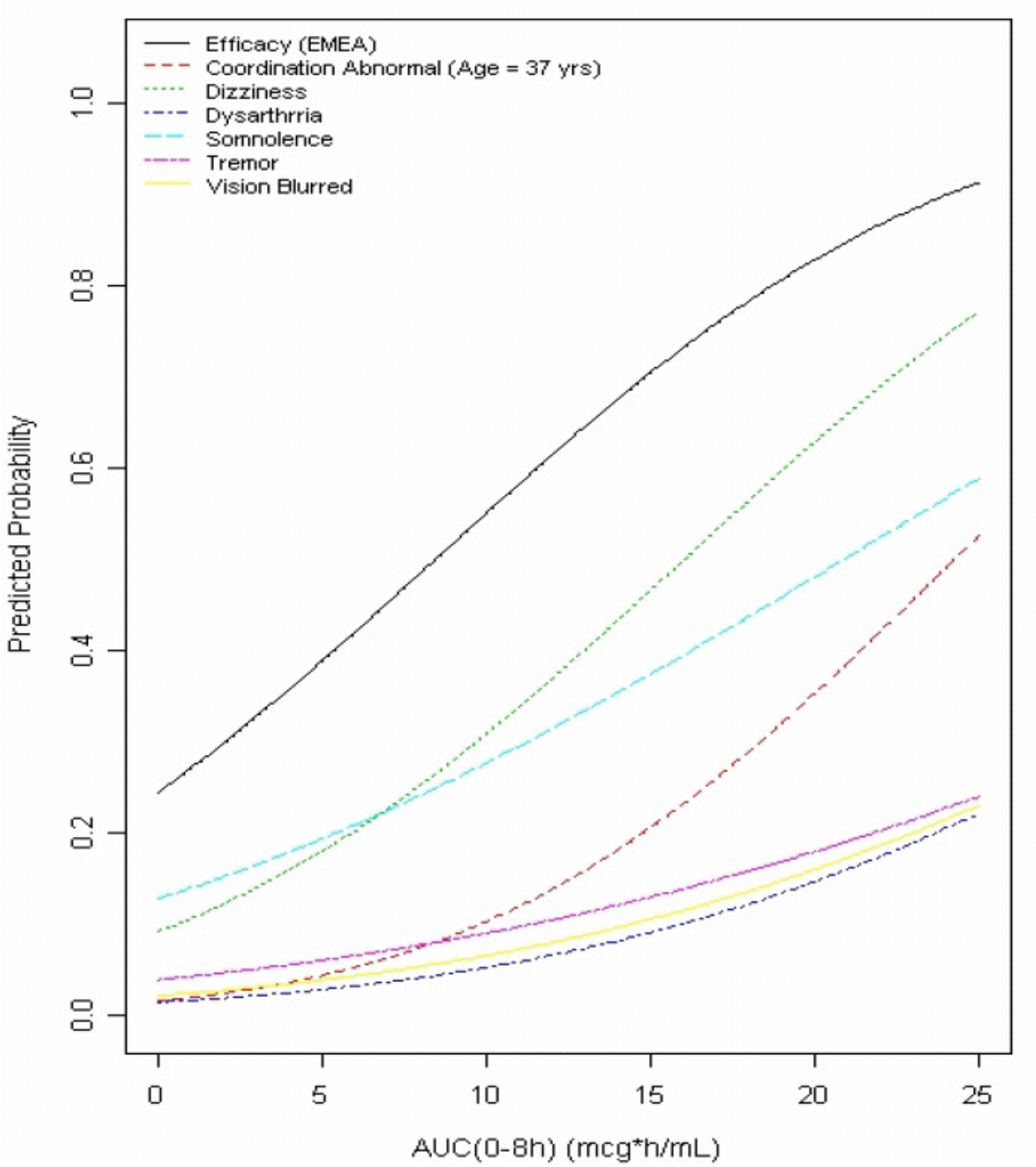


Table 114 Summary of Predicted Responses by Dose based on PK/PD Analyses for Efficacy and Safety Endpoints from Studies 301 and 302

Dose	Placebo	600 mg/day	900 mg/day	1200 mg/day

Dose	Placebo	600 mg/day	900 mg/day	1200 mg/day
Median AUC(0-τ) (ug.h/mL)	0	4.35	6.78	9.67
Predicted % change in seizure frequency	-18.9	-40.9	-51.8	-55.9
Probability of >50% reduction in seizure frequency	0.24	0.37	0.44	0.54
Probability of Dizziness	0.09	0.17	0.22	0.30
Probability of Somnolence	0.13	0.18	0.22	0.27
Probability of Coordination Abnormal	0.02	0.04	0.06	0.10
Probability of Dysarthria	0.01	0.03	0.04	0.05
Probability of Tremor	0.04	0.06	0.07	0.09
Probability of Vision Blurred	0.02	0.04	0.05	0.06

7.5.2 Time Dependency for Adverse Events

RCT (pivotal controlled trials)

The pattern of distribution for the overall incidence of TEAEs by time to first occurrence was similar among treatment groups and AEs were generally reported within the first 8 weeks table 115,

Table 115 Overall Incidence of TEAEs by Time to First Occurrence (Safety Population: RCT, Studies 205, 301, and 302)

Time to First Occurrence	n/N (%) of Patients				
		RTG	RTG	RTG	RTG
(Days/Weeks)	Placebo	600 mg/day	900 mg/day	1200 mg/day	Total
1 to < 8 (up to Wk 1)	109/427 (25.5)	93/281 (33.1)	89/273 (32.6)	85/259 (32.8)	267/813 (32.8)
8 to < 14 (Wks 1 to <2)	40/418 (9.6)	32/274 (11.7)	25/265 (9.4)	32/254 (12.6)	89/793 (11.2)
14 to < 28 (Wks 2 to <4)	67/411 (16.3)	40/270 (14.8)	54/262 (20.6)	45/249 (18.1)	139/781 (17.8)
28 to < 56 (Wks 4 to <8)	56/406 (13.8)	25/263 (9.5)	39/246 (15.9)	54/237 (22.8)	118/746 (15.8)
56 to <84 (Wks 8 to <12)	29/384 (7.6)	7/237 (3.0)	11/218 (5.0)	8/194 (4.1)	26/649 (4.0)
84 to < 182 (Wks 12 to <26)	17/366 (4.6)	10/266 (4.4)	5/205 (2.4)	3/172 (1.7)	18/603 (3.0)
182 to < 273 (Wks 26 to <39)	0/14 (0)	0/2 (0)	0	0/10 (0)	0/12 (0)
273 to < 366 (Wks 39 to <52)	0	0	0	0	0
366 (Wk 52) or later	0	0	0	0	0

The sponsor provides a table of AEs occurring in >10% of patients presented by time of occurrence and dose. The AEs that are captured by this category are: dizziness,

somnolence, headache, fatigue, confusional state, tremor, coordination abnormal and vision blurred. The trend in the 600mg and 900mg dose groups is that these adverse events rise in frequency during the first 2 weeks, reach a maximum at 4 weeks then decline in frequency. This pattern is shifted to reach a maximum in the 4 to 8 week interval in the 1200mg dose group.

7.5.3 Drug-Demographic Interactions

Race: other than Caucasian, there were no race categories comprising ≥5% of the Safety Population; therefore, analyses by race were not conducted.

Age: Less than 5% of patients were either <18 or ≥65 years of age which reduces the applicability of AEs between age groups. Adverse events reported by patients ≥65 years of age were generally consistent with the most common AEs.

> SAEs by age: Two patients ≥65 years of age reported SAEs, Patient 050705, a 69 year old female in Study 302, reported somnolence, dizziness and gait disturbance as SAEs. All events resolved and the patient continued in the study. Patient 002111, a 71 year old male in Study 301, reported confusional state and psychotic disorder as SAEs. The patient was withdrawn from the study due to the events. The events resolved and were considered by the investigator to be drug-related.

Gender: There was no evidence of gender specific TEAEs related to treatment with ezogabine. Generally females reported a higher incidence of TEAEs for each adverse event regardless of treatment group. Divergent from this trend, tremor was more commonly reported among males at the 1200mg dose (16% males, 9% females). The other most common TEAEs were reported in slightly larger proportions of females than males taking ezogabine. With this in mind, most of the common TEAEs other than headache and fatigue were generally dose proportional within either gender.

Of the most common TEAEs, individual TEAEs that were reported disproportionally in females (different by more than 1.5-fold) compared with males taking ezogabine (Total RTG group), were memory impairment (8% of females versus 4% of males), and disturbance in attention (7% versus 5%). All were in the nervous system disorders SOC. No other single preferred term reported for ≥5% of either gender in the Total RTG group was different by more than 1.5-fold when comparing the genders.

Weight Integrated analysis and by sex:

RCT

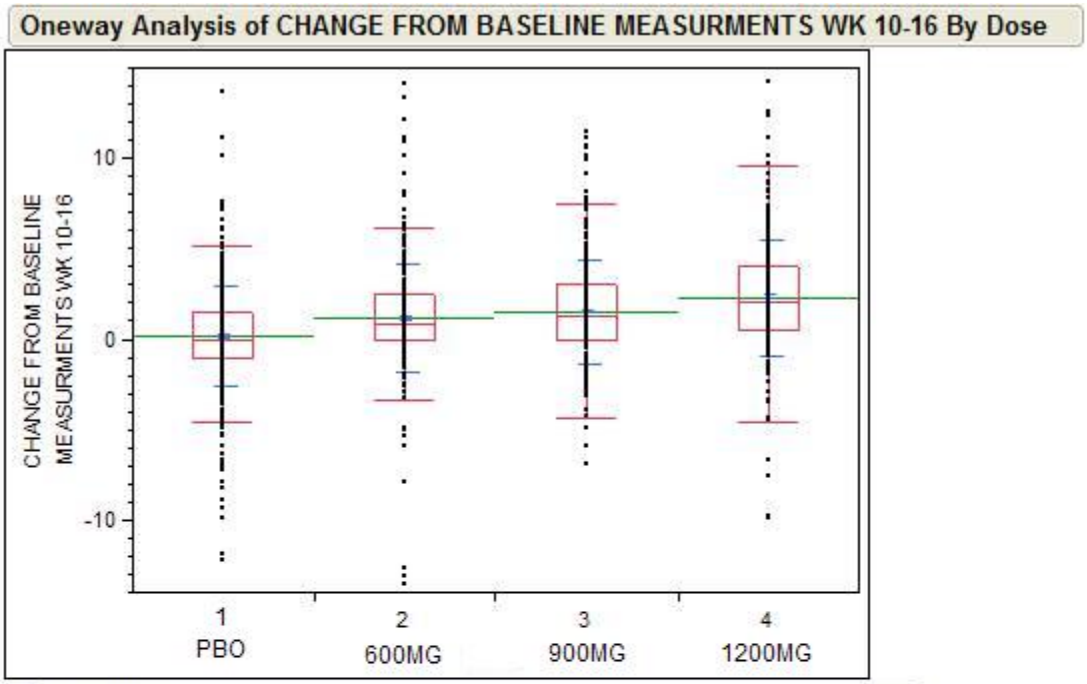
Change in weight from baseline in the week 10 to 16 interval is evaluated for placebo, 600mg, 900mg and 1200mg. The week 10 to 16 interval is chosen to allow time for an effect to be seen. The interval of examination is ended at week 16 to keep

measurements from all studies within the double blind control period. 2 outliers are excluded from the analysis of means and medians in the RCTs and an additional 2 from the analysis of values in the range of PCC (potential clinical concern). Those excluded are the following subject IDs: 090218, 001416, 000119, and 000117. These subjects are excluded due to an occurrence in each of a very large change in weight recorded at one visit bracketed by weight measurements which deviate little from value preceding the change. It is not physiologically plausible for such a large weight change to occur in 4 weeks time (the interval between the visits). These outlier values are provided in the table below. In case 119 there are two recordings on week 8 but 5 days apart, in this 5 day interval there is a -45.8 kg decline in weight.

ID	WEEK	VISDT	RESULTO	CHGBASE	change Kg
90218	8	1/16/2008	49.7	2.7	
	12	2/14/2008	93.0	46.0	43.3
	16	3/12/2008	48.5	1.5	
1416	10	7/25/2007	113.4	0.5	
	14	8/27/2007	68.9	-44.0	-44.5
	18	9/24/2007	112.9	0.0	
119	6	11/27/2006	166.0	2.7	
	8	12/6/2006	120.2	-43.1	-45.8
	8	12/11/2006	164.2	0.9	
117	6	11/6/2006	118.4	-11.3	
	4	10/16/2006	94.3	-35.4	24.1
	2	10/2/2006	116.6	-13.2	

Examination of weight change from baseline at all visits from week 10 to 16 for placebo and all ezogabine doses reveal a trend of weight increase over baseline. The median weight change from baseline for placebo is 0 with a mean of 0.17kg. The 600mg dose group has a median increase from baseline of 0.8kg with a mean of 1.1kg. The 900mg dose group has a median increase from baseline of 1.25kg with a mean of 1.5kg and the 1200mg dose group has a median increase of 2kg with a mean of 2.3kg, figure 18.

Figure 18 Mean and median weight change from baseline, pooled weigh measurements from all RCT study visits in the 10 to 16 week interval by EZO dose



Quantiles

Level	Minimum	10%	25%	Median	75%	90%	Maximum
1	-12.3	-2.6	-1	0	1.5	3.175147	13.60777
2	-13.7	-1.6	0	0.8	2.496069	4.5	14
3	-7	-2	0	1.25	3	4.8	11.33981
4	-10	-1.36078	0.453592	2	4.082331	6	14.06136

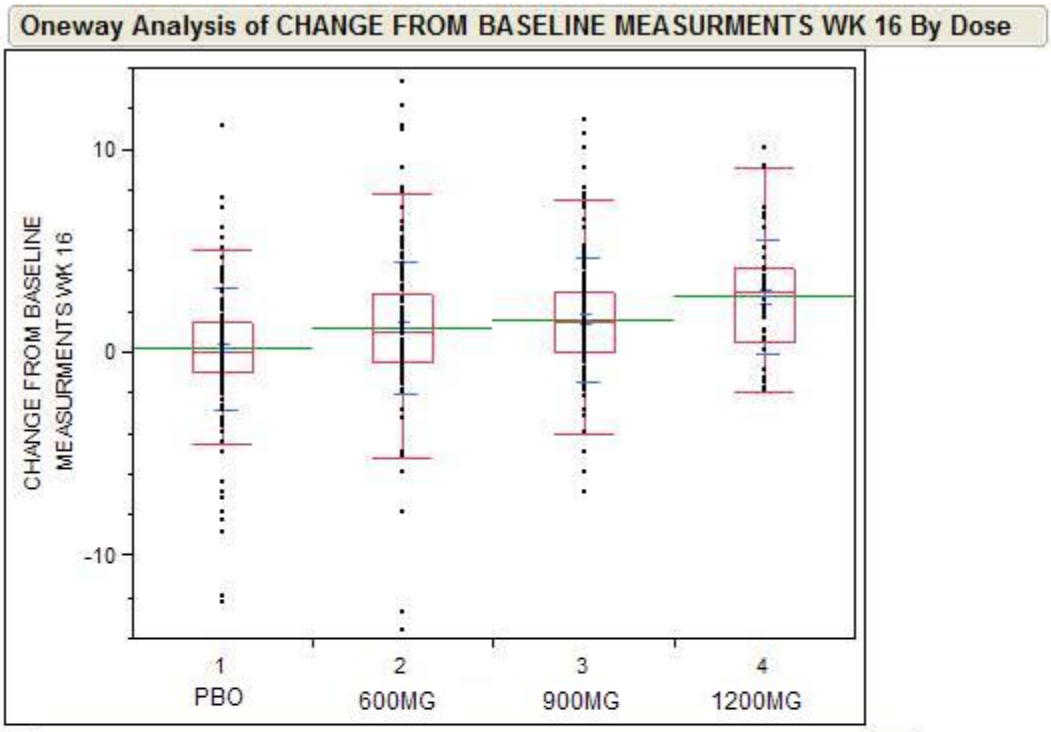
Means and Std Deviations

Level	Number	Mean	Std Dev	Std Err Mean	Lower 95%	Upper 95%
1	739	0.16522	2.71764	0.09997	-0.031	0.3615
2	450	1.14830	2.99800	0.14133	0.871	1.4260
3	402	1.46856	2.88056	0.14367	1.186	1.7510
4	359	2.26824	3.24025	0.17101	1.932	2.6046

Derived from pooled weight measurements from all RCT study visits in the week 10 to 16 interval

The same analysis of medians and means for all patients on placebo and all ezogabine doses is performed for weight values obtained at week 16. The median weight change from baseline for the placebo group is 0 with a mean of 0.16kg. The 600mg dose group has a median increase from baseline of 1kg with a mean of 1.2kg. The 900mg dose group has a median increase from baseline of 1.5kg with a mean of 1.6kg and the 1200mg dose group has a median increase from baseline of 3kg with a mean of 2.7kg. This analysis again reveals an increase in weight over baseline with a dose response and a more prominent increase than the pooled 10 to 16 week interval figure 19.

Figure 19 Mean and median weight change from baseline, weigh measurements from RCT study visits week 16 by EZO dose



Quantiles

Level	Minimum	10%	25%	Median	75%	90%	Maximum
1	-12.3	-3	-1	0	1.5	3.56	11
2	-13.7	-2	-0.45	1	2.9	4.85	13.2
3	-7	-1.98	0	1.5	3	4.8	11.33981
4	-2	-1.28	0.5	3	4.186748	6.57	10

Means and Std Deviations

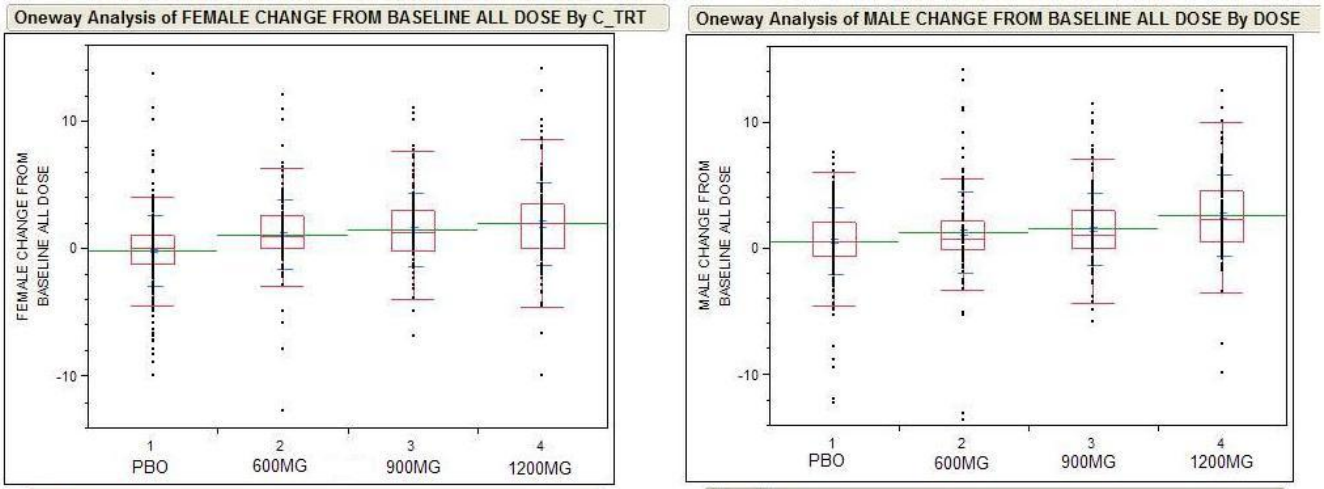
Level	Number	Mean	Std Dev	Std Err Mean	Lower 95%	Upper 95%
1	223	0.16265	2.98933	0.20018	-0.232	0.5571
2	204	1.21141	3.25763	0.22808	0.762	1.6611
3	181	1.61123	3.05142	0.22681	1.164	2.0588
4	62	2.72375	2.79932	0.35551	2.013	3.4346

Derived from weight measurments at RCT study visit week 16

The pooled values for change from baseline weight derived from all weigh measurements in the interval from week 10 to week 16 are examined for males and females independently. The males have weight increase over baseline similar to females with median values for the placebo, 600mg, 900mg and 1200mg groups of 0, 1, 1.3 and 2 kg respectively compared to 0.5, 0.7, 1.0 and 2.2 in females, figure 20. Medians and means of pooled values for change from baseline weight at all visits in the interval week 10 to 16 are compared for all ezogabine doses combined (600mg, 900mg and 1200mg). This analysis reveals a median change from baseline of 1.2kg for both males and females with a mean for males of 1.7kg and females 1.5kg. These values

demonstrate no meaningful difference in the positive weight effect of ezogabine between males and females, figure 21.

Figure 20 Mean and median weight change from baseline by sex, pooled weigh measurements from all RCT study visits in the 10 to 16 week interval by EZO dose



Quantiles

Level	Minimum	10%	25%	Median	75%	90%	Maximum
1	-10	-3	-1.19484	0	1.066466	2.247573	13.60777
2	-12.8	-1.88	0	1	2.6	4.1	12
3	-7	-2	-0.15	1.3	3	4.8	11
4	-10	-1.66	0	2	3.55	5.579186	14.06136

Means and Std Deviations

Level	Number	Mean	Std Dev	Std Err Mean	Lower 95%	Upper 95%
1	372	-0.1765	2.75179	0.14267	-0.457	0.1041
2	233	1.0940	2.76972	0.18145	0.737	1.4515
3	181	1.4578	2.88037	0.21410	1.035	1.8803
4	173	1.9423	3.22355	0.24508	1.459	2.4261

Quantiles

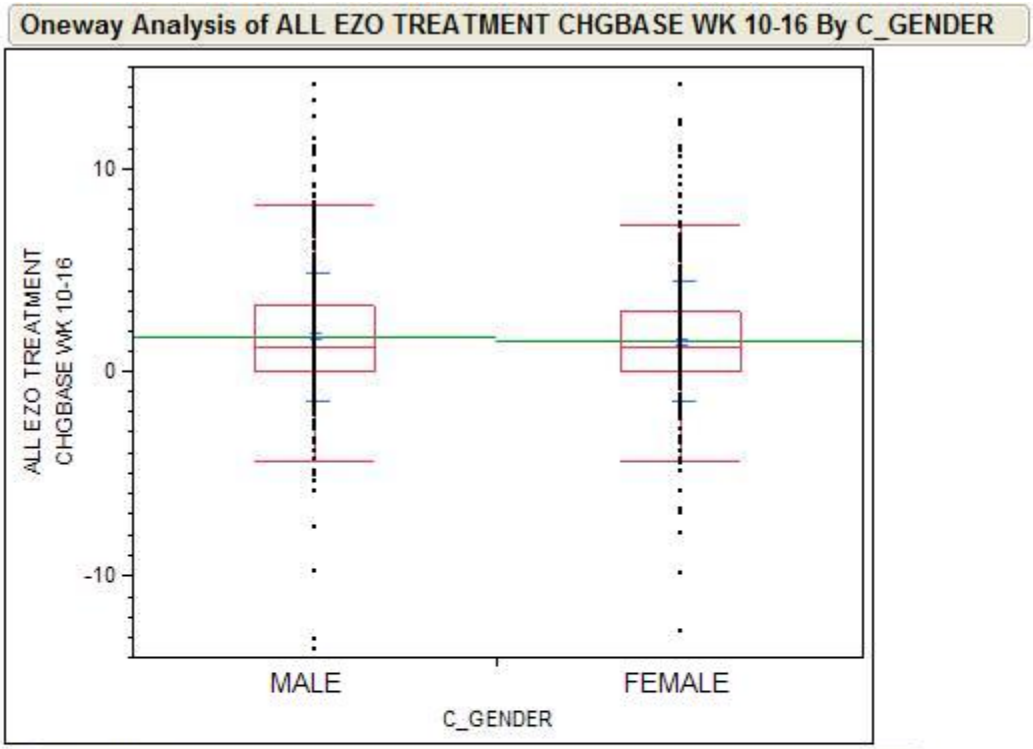
Level	Minimum	10%	25%	Median	75%	90%	Maximum
1	-12.3	-2	-0.70799	0.5	2	3.605748	7.5
2	-13.7	-1.5	-0.1	0.7	2.183981	5	14
3	-6	-1.88	0	1	2.95	4.8	11.33981
4	-9.9	-0.83	0.5	2.222603	4.551943	6.63	12.4

Means and Std Deviations

Level	Number	Mean	Std Dev	Std Err Mean	Lower 95%	Upper 95%
1	367	0.51157	2.64148	0.13788	0.2404	0.7827
2	217	1.20656	3.23068	0.21931	0.7743	1.6388
3	221	1.47733	2.88722	0.19422	1.0946	1.8601
4	186	2.57139	3.23489	0.23719	2.1034	3.0393

Derived from weight obtained at all study visits in the week 10 to 16 interval

Figure 21 Change from baseline weight by sex from pooled weight measurements in the RCT study interval weeks 10 to 16, all ezogabine treatment groups combined.



Quantiles

Level	Minimum	10%	25%	Median	75%	90%	Maximum
1	-13.7	-1.2	0	1.2	3.268787	5.443108	14
2	-12.8	-1.84	0	1.2	3	4.837903	14.06136

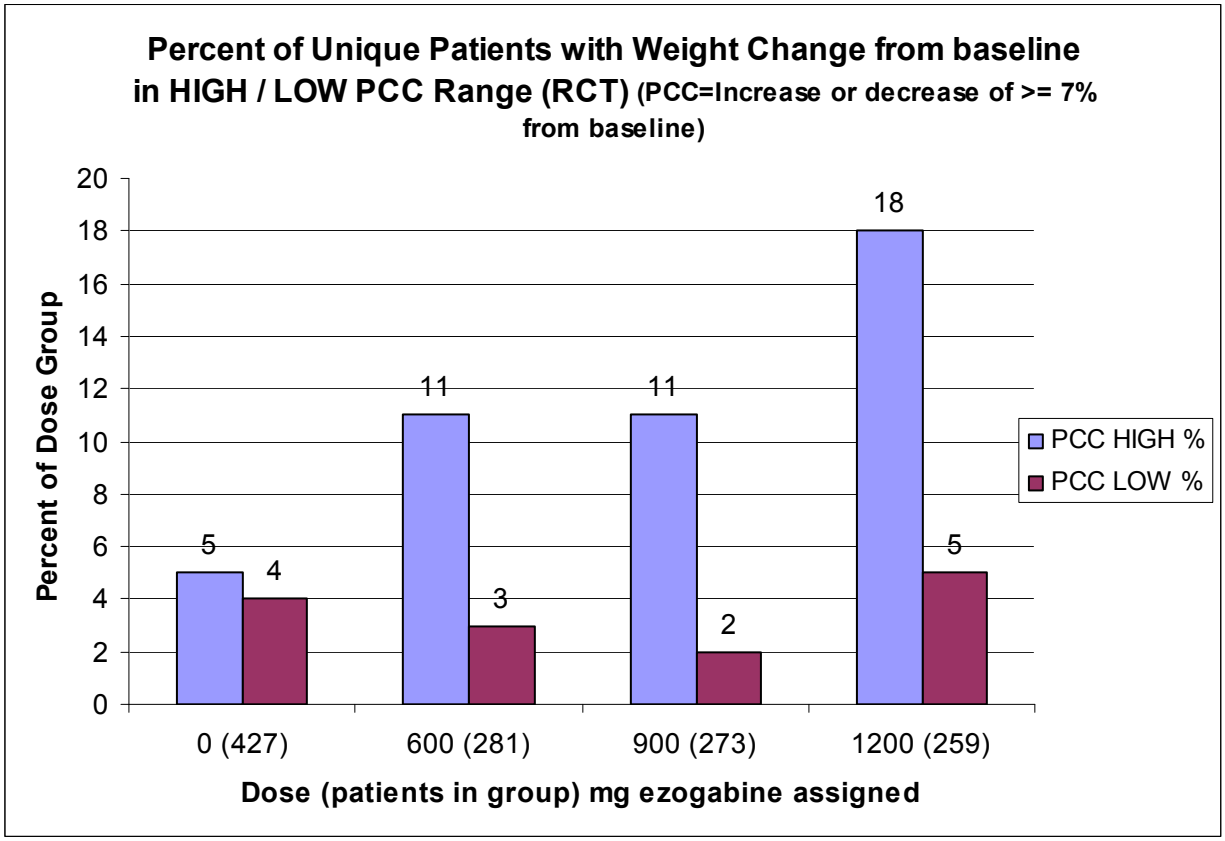
Means and Std Deviations

Level	Number	Mean	Std Dev	Std Err Mean	Lower 95%	Upper 95%
1	624	1.70928	3.16210	0.12659	1.4607	1.9579
2	587	1.45622	2.95930	0.12214	1.2163	1.6961

Derived from weight obtained from study patients at all visits in the week 10 to week 16 interval

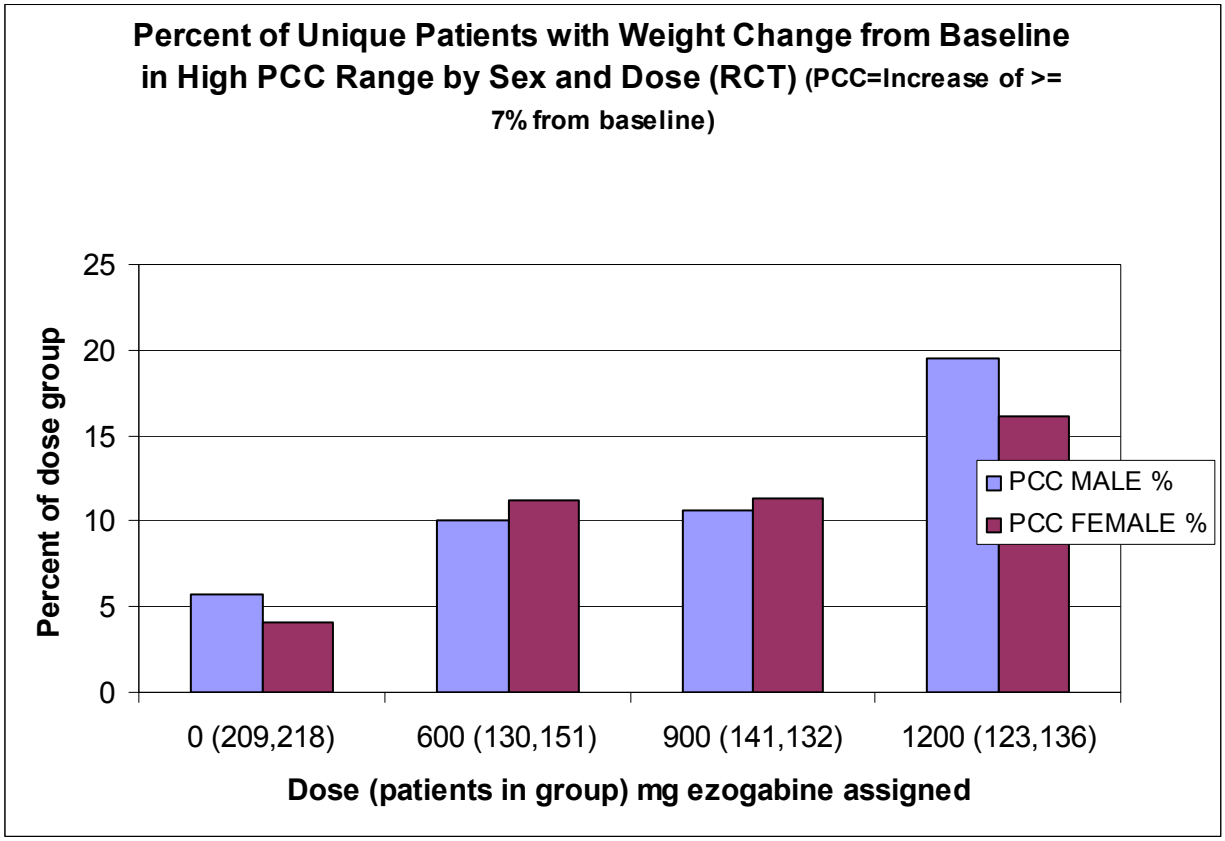
The frequency of values in both the high and low PCC (potential clinical concern) range are examined by ezogabine dose. This analysis reveals an increase in the percent of patients with PCC high values as the ezogabine dose increases. There is no meaningful difference in the percent of patients with a PCC value in the low range as the ezogabine dose increases. High range PCC values occur in 5%, 11%, 11% and 18% of the placebo, 600mg, 900mg and 1200mg dose groups respectively. Low range PCC values occur in 4%, 3%, 2% and 5% of the placebo, 600mg, 900mg and 1200mg dose groups respectively. There is no trend of dose related increase in PCC low values whereas the high PCC values have a notable increase over placebo in the ezogabine treatment groups with the largest separation (13%) occurring in the 1200mg dose group, figure 22.

Figure 22 Percent of Unique Patients (RCT) with Weight Change from baseline in HIGH / LOW PCC Range



The frequency of values in the high PCC range occurring in each dose group are compared by sex. This reveal that the frequency of high PCC values is greater in ezogabine treatment than in placebo but there is little difference between males and females. Males have 6%, 10% , 11% and 20% occurrence of high PCC values in the placebo, 600mg, 900mg and 1200mg groups respectively. Females have 4%, 11%, 11% and 16% occurrence of high PCC values in the placebo, 600mg, 900mg and 1200mg groups respectively, figure 23.

Figure 23 Percent of Unique Patients (RCT) with Weight Change from Baseline in High PCC Range by Sex and Ezogabine Dose



Reviewer Comment: Evaluation of the median and mean change from baseline weight in the pooled measurements from patient visits in the 10 to 16 week study interval and at a single visit at week 16 is performed. The analysis reveals an increase in weight compared to placebo at all ezogabine treatment doses and a dose response effect. The evaluation of outliers (weight values in the range of potential clinical concern) reveals a notable increase in percent of patients affected in the ezogabine treatment group compared to placebo with the largest percentage of affected patients in the 1200mg dose group. The medians and means of change from baseline weight in the week 10 to week 16 interval reveal a dose response of weight increase as dose of ezogabine increases, however there is no meaningful difference between the male and female profile of weight gain. A comparison between the change in baseline weight between males and females treated with ezogabine at all doses, using the pooled weight measurements for the 10 to 16 week study interval reveals the median weight gain for both groups equal at 1.2kg and the means similar at 1.7kg for male and 1.5kg for females.

These evaluations indicate that ezogabine is associated with weight gain, there is greater gain in weight as dose increases, but there is no difference in the weight positive effect between males and females.

In current labeling there is no reference to weight gain, only an indication that appetite increase and decrease is seen. The large percent of patients who have a PCC value for weight change from baseline as well as the + difference in medians and means between ezogabine and placebo treatment marks a **need for weight gain to be present in labeling**. This may be stated following the paragraph "Other adverse reactions…" in section 6.1 Clinical trial experience as; although no adverse event of "abnormal weight gain" was recorded in the RCTs, a dose related weight gain has occurred in clinical trials.

7.5.4 Drug-Disease Interactions

Renal Insufficiency

Study VRX-RET-E22-101 "Single-dose pharmacokinetics of ezogabine in healthy subjects and patients with various degrees of renal insufficiency" examined the pharmacokinetics of ezogabine in a small sample of subjects with renal insufficiency. Five strata were created ranging from healthy subjects to patients requiring dialysis, table 116.

Table 116 AUC0-t, AUC0-inf, and Cmax determination for plasma ezogabine and the N-acetyl metabolite of ezogabine for each renal-impaired group and the normal renal function group

Mean +/_ SD					
Pharmacokinetic Parameters	**Group 1 N = 6**	**Group 2 N = 5**	**Group 3 N = 5**	**Group 4 N = 4**	**Group 5 N = 6**
Ezogabine					
AUC0-t (ng*hr/mL)	1578 ± 516.7	2049 ± 457.6	2980 ± 625.5	3417 ± 1145	3304 ± 428.4
AUC0-inf (ng*hr/mL)	1700 ± 513.5	2160 ± 469.6	3172 ± 640.4	3657 ± 1203	3557 ± 477.5
Cmax (ng/mL)	269 ± 106	277 ± 158	339 ± 207	283 ± 130	127 ± 63.0
N-Acetyl Metabolite					
AUC0-t (ng*hr/mL)	1529 ± 407.0	2315 ± 556.3	3377 ± 912.1	4021 ± 1172	5730 ± 1099
AUC0-inf (ng*hr/mL)	1792 ± 393.8	2761 ± 692.5	4164 ± 1662	4372 ± 1440	6774 ± 1653
Cmax (ng/mL)	137 ± 29.1	157 ± 19.8	215 ± 66.9	192 ± 43.8	142 ± 41.6

SD = standard deviation.
Group 1: Creatinine clearance >80 mL/min (healthy subjects with normal renal function)
Group 2: Creatinine clearance ≥50 to ≤80 mL/min (mild renal impairment)
Group 3: Creatinine clearance ≥30 to <50 mL/min (moderate renal impairment)
Group 4: Creatinine clearance <30 mL/min (severe renal impairment)
Group 5: Requiring dialysis (patients with ESRD, end-stage renal disease)

The study identified a clear relationship between the extent of renal impairment and the PK of ezogabine. As the severity of the renal impairment increased in patients

relative to healthy subjects (Group 1), ezogabine exposure parameters AUC0-t and AUC0-inf increased exposure was 30% higher for patients with mild renal impairment (Group 2) and approximately 100 -120% higher for patients with moderate impairment (Group 3) to ESRD (Group 5).

Hepatic insufficiency

Study VRX-RET-E22-102: "Single-dose pharmacokinetics study of ezogabine in patients with various degrees of hepatic impairment" examined the pharmacokinetics and safety of ezogabine in healthy adult volunteers and in patients with varying degrees of hepatic impairment following a single oral dose of ezogabine 100mg. Four groups were created, one healthy and 3 with progressively more advance hepatic dysfunction. Ratios of
least-squares means (LSM) for each hepatic group (Groups 2, 3, and 4) and the healthy subjects group (Group 1) were calculated using the exponentiation of the difference between group LSM from the analyses on log -transformed Cmax, AUC0-t, and AUC0-inf. The ratios were expressed as percentages relative to the healthy subjects (Group 1), table 117

Table 117 Geometric means of AUC_{0-t}, AUC_{0-inf}, and C_{max} were for ezogabine and the N-acetyl metabolite of ezogabine; comparisons of these values for each hepatically impaired group to the normal liver function group

% MR (90% CI)			
Pharmacokinetic Parameters	Group 2 vs Group 1	Group 3 vs Group 1	Group 4 vs Group 1
ezogabine			
AUC0-t (ng*hr/mL)	90.75 (61.31, 134.33)	157.23 (106.22, 232.73)	214.32 (144.79, 317.24)
AUC0-inf (ng*hr/mL)	90.79 (61.73, 133.53)	151.86 (103.25, 223.35)	209.04 (142.13, 307.46)
Cmax (ng/mL)	72.50 (47.18, 111.39)	131.02 (85.27, 201.31)	127.27 (82.83, 195.54)
N-Acetyl Metabolite			
AUC0-t (ng*hr/mL)	74.17 (57.57, 95.57)	122.12 (94.77, 157.35)	124.07 (96.29, 159.87)
AUC0-inf (ng*hr/mL)	77.31 (58.88, 101.52)	126.74 (96.52, 166.42)	134.77 (102.63, 176.97)
Cmax (ng/mL)	83.11 (63.07, 109.52)	112.97 (85.73, 148.87)	80.29 (60.93, 105.80)

MR = mean ratio, CI = confidence interval
Group 1: Normal liver function (healthy volunteers)
Group 2: Mild impairment (Child-Pugh scores of 5 to 6)
Group 3: Moderate impairment (Child-Pugh scores of 7 to 9)
Group 4: Severe impairment (Child-Pugh scores >9)

There was a clear relationship between the extent of hepatic impairment and the pharmacokinetics of ezogabine. Ezogabine AUC parameters in subjects with mild hepatic impairment were similar to those in healthy subjects; however, subjects with moderate hepatic impairment had AUC parameter values approximately 50% higher than those in healthy subjects, and subjects with severe hepatic impairment had ezogabine AUC parameters approximately twice those of healthy subjects.

Reviewer Comment: AUC_{0-t} of ezogabine is seen to increase by 100 to 120% in moderate or greater renal failure. The recommendation in proposed labeling for dose adjustment for patients with moderate or greater renal insufficiency is appropriate for this observation. The increase AUC_{0-t} seen in patients with hepatic insufficiency is not as steep as that seen in renal failure. The recommendation in proposed labeling for dose reduction only in severe hepatic impairment is an appropriate response.

7.5.5 Drug-Drug Interactions

Absorption, Distribution, Metabolism and Elimination of ezogabine

A brief review of the ADME of ezogabine is relevant to understanding the mechanism of potential drug- drug interactions.

Ezogabine is generally rapidly absorbed after single or multiple dosing, with time to maximum concentration (tmax) values typically ranging from about 0.5 to 2.0 hours. The absolute bioavailability of ezogabine immediate release formulations is approximately 60%.

Ezogabine is not a substrate of the P-glycoprotein transport system and does not significantly inhibit the P-gp mediated transport.

In-vitro data indicate that the plasma protein binding of ezogabine is moderate (approximately 80%) and protein binding displacement interactions with ezogabine administration would not be expected.

Metabolism is extensively through formation of the N-acetyl metabolite of ezogabine (NAMR) and through N-glucuronidation of both ezogabine and NAMR. There is no evidence for oxidative metabolism via P450 enzymes. In human plasma, the N2-glucuronide of ezogabine is the predominant metabolite.

Ezogabine is mainly eliminated through the renal route, as evidenced by 84% of total radioactivity recovered in the urine, with unchanged parent compound in urine accounting for 36% of the administered dose. Approximately 14% of an orally administered dose is eliminated in the feces with unchanged drug accounting for 3% of the administered dose.

Drug Interactions with ezogabine

Impact of Co-administration of Ezogabine on Exposure of AEDs

The effect of ezogabine on clearance of other AEDs was assessed by examining the trough AED concentrations prior to and during ezogabine administration. Overall, ezogabine had little or no effect on the trough concentrations of a wide range of concomitant AEDs (carbamazepine, clobazam, clonazepam, gabapentin, levetiracetam, oxcarbazepine, phenobarbital, phenytoin, pregabalin, topiramate, valproic acid and

zonisamide). However, ezogabine co-administration was associated with a 20% decrease in lamotrigine concentrations. In a separate study in healthy subjects ezogabine administered as 300 mg BID resulted in an 18% decrease in exposure of lamotrigine (3065A1-109).

Impact of co-administration of Antiepileptic Drugs on the Pharmacokinetics of Ezogabine

Inducers of Glucuronidation

In a population pharmacokinetic analysis which included pharmacokinetic data from the 2 Phase III primary efficacy studies (Studies 301 and 302), the impact of coadministration of individual enzyme inducing AEDs (EIAEDs) was evaluated as part of the covariate analysis. There was no evidence that subjects already taking the enzyme inducing AEDs carbamazepine, phenytoin or phenobarbital had any impact on the CL of ezogabine compared to subjects not taking the respective EIAED.

In a drug-drug interaction study conducted in healthy volunteers (n=15) (Study 3065A1-113), co-administration of phenobarbital (90 mg once daily) with ezogabine (200mg TID) for 21 days had no effect on the pharmacokinetics of ezogabine.

Inhibitors of Glucuronidation

A preliminary assessment of the impact of co-administration of the enzyme inhibitor, valproate, on the pharmacokinetics of ezogabine was conducted. In the small number of subjects analyses (n=4), there was no evidence that co-administration of valproate (750 – 2250 mg/day) had any impact on the pharmacokinetics of ezogabine. In the population PK analysis there was no significant effects of valproate (n=252) on the pharmacokinetics of ezogabine.

Drug Interactions with Oral Contraceptives

At ezogabine doses of up to 750 mg/day, there was no impact on the pharmacokinetics of the estrogen or progestogen components of oral contraceptive steroids (3065A1-112 and VRX-RET-E22-106). In addition, no effect of oral contraceptive steroids on ezogabine PK was observed.

Drug interactions with Ethanol

The AUC and Cmax of ezogabine are increased by 36% and 23%, respectively, after coadministration with a 1 g/kg dose of ethanol (VRX-RET-E22-107). Ezogabine did not affect the PK of ethanol. With the exception of a modest increase in visual blurring, ezogabine administered alone or in combination with a large ethanol dose did not have any meaningful effect on any of the subjective effects parameters or on the balance, cognitive or psychomotor endpoints.

Adverse Events by Concomitant AED

The proportions of patients reporting at least 1 TEAE appeared to increase with increasing ezogabine dose based on the number of concomitant AEDs they were taking (1, 2, or >2), table 119. Among placebo-treated patients and patients in the 900 and 1200 mg/day ezogabine groups, patients on ≥2 concomitant AEDs had the highest frequency of reporting at least 1 TEAE. The same dose-related increase in TEAE reporting observed in the overall population was also generally observed within each concomitant AED subgroup, with the exception of the subgroup taking >2 AEDs, which had a higher rate in the placebo group (79%) than in both the 600 or 900 mg/day groups (69 to 72%).

Table 118 Concomitant Antiepilepsy Drug Usage (RCT)

	Number (%) of Patients				
		RTG	RTG	RTG	RTG
	Placebo (N=427)	600 mg/day (N=281)	900 mg/day (N=273)	1200 mg/day (N=259)	Total (N=813)
Number of Concomitant AEDs					
1 AED	93 (21.8)	76 (27.0)	62 (22.7)	60 (23.2)	198 (24.3)
2 AEDs	221 (51.8)	144 (51.2)	164 (60.1)	154 (59.5)	462 (56.8)
>2 AEDs	113 (26.5)	61 (21.7)	47 (17.2)	45 (18.1)	153 (18.8)

Table 119 Summary of TEAEs According to Number of Concomitant Antiepilepsy Drug Used. (RCT)

	Number of Patients with 1 or more AEs/Number of Patients in Subpopulation (%)				
		RTG	RTG	RTG	RTG
	Placebo (N=427)	600 mg/day (N=281)	900 mg/day (N=273)	1200 mg/day (N=259)	Total (N=813)
Any Event	**318 (74.5)**	**207 (73.7)**	**223 (81.7)**	**227 (87.6)**	**657 (80.8)**
Number of Concomitant AEDs					
1 AED	69/93 (74.2)	54/76 (71.1)	50/62 (80.6)	53/60 (88.3)	157/198 (79.3)
2 AEDs	160/221 (72.4)	111/144 (77.1)	139/164 (84.8)	131/154 (85.1)	381/462 (82.5)
>2 AEDs	89/113 (78.8)	42/61 (68.9)	34/47 (72.3)	43/45 (95.6)	119/153 (77.8)

TEAEs By Concomitant AED Used in >15% of the Population

RCT

Use of AED was evenly distributed across the treatment groups with the exception of carbamazepine. Of the placebo patients, 47% used concomitant carbamazepine while across the ezogabine groups 50% to 59% of patients used concomitant carbamazepine, table 120.

Table 120 Concomitant Antiepilepsy Drug Usage for AEDs Taken by Greater than or equal to 15% of Patients (RCT)

	Number (%) of Patients

		RTG	RTG	RTG	RTG
	Placebo	**600 mg/day**	**900 mg/day**	**1200 mg/day**	**Total**
	(N=427)	**(N=281)**	**(N=273)**	**(N=259)**	**(N=813)**
Carbamazepine	201 (47.1)	146 (52.0)	161 (59.0)	130 (50.2)	437 (53.8)
Lamotrigine	125 (29.3)	62 (22.1)	70 (25.6)	78 (30.1)	210 (25.8)
Valproic acid	113 (26.5)	74 (26.3)	64 (23.4)	47 (18.1)	185 (22.8)
Topiramate	75 (17.6)	55 (19.6)	45 (16.5)	38 (14.7)	138 (17.0)
Levetiracetam	68 (15.9)	46 (16.4)	42 (15.4)	31 (12.0)	119 (14.6)

The differences in proportions of patients reporting any TEAE among the subgroups defined by particular AED usage were small (up to 15% for patients taking placebo and up to 10% for the Total RTG group), table 121. Among patients in the placebo group, the proportion of patients reporting TEAEs was highest for those taking topiramate and levetiracetam (81% each). Patients taking ezogabine were more likely to report AEs when taking levetiracetam (88% in the Total RTG group). The small number of patients who received some AEDs makes drawing conclusions based on these data difficult.

Table 121 Summary of TEAEs According to Concomitant Antiepilepsy Drugs Taken by Greater than or equal to 15% of Patients

	Number of Patients with 1 or more AEs/Number of Patients in Subpopulation (%)				
		RTG	**RTG**	**RTG**	**RTG**
	Placebo (N=427)	**600 mg/day (N=281)**	**900 mg/day (N=273)**	**1200 mg/day (N=259)**	**Total (N=813)**
Any Event	**318/427 (74.5)**	**207/281 (73.7)**	**223/273 (81.7)**	**227/259 (87.6)**	**657/813 (80.8)**
Carbamazepine	144/201 (71.6)	102/146 (69.9)	127/161 (78.9)	112/130 (86.2)	341/437 (78.0)
Lamotrigine	92/125 (73.6)	50/62 (80.6)	57/70 (81.4)	73/78 (93.6)	180/210 (85.7)
Valproic acid	75/113 (66.4)	57/74 (77.0)	49/64 (76.6)	40/47 (85.1)	146/185 (78.9)
Topiramate	61/75 (81.3)	43/55 (78.2)	34/45 (75.6)	34/38 (89.5)	111/138 (80.4)
Levetiracetam	55/68 (80.9)	36/46 (78.3)	38/42 (90.5)	31/31 (100.0)	105/119 (88.2)

Examination of the frequency of an adverse event in the total ezogabine group reveals dizziness was more frequent in patients taking levetiracetam (33%) or lamotrigine (31%) than any combination (23%). The incidence of somnolence was higher with valproic acid (27%) and carbamazepine (24%) but lowest for patients taking levetiracetam (11%) compared with the overall incidence of 22%. Of the patients taking valproic acid with 1200 mg/day ezogabine, 38% reported somnolence. Differences in the rate of reporting of each common TEAE among patients taking ezogabine and any AED(s) versus patients taking ezogabine in combination with a given AED were generally small. Elevations in adverse event rate for a concomitant AED which occur more than 5% in frequency over the value in the any AED category for that AE are highlighted in yellow, table 122. The most noteworthy among these observations is the relation between dizziness and levetiracetam where the occurrence over any AED and over placebo is greater in all dose groups. There is also an observation of frequent occurrence of fatigue and concomitant levetiracetam at 600mg and 900mg. The only remaining observation of an AED with an adverse effect association in more than one dose group is for the AE “aphasia” where levetiracetam has an occurrence >5% more than “any AED” row in the 900mg and 1200mg dose group.

Table 122 Most Commonly Reported (in at least 5%of patients in Total RTG Group Taking Any Combination of Concomitant AEDs) Adverse Events by Concomitant Antiepilepsy Drug. (RCT)

		Number (%) of Patients				
Preferred Term	**AED**	**Placebo N = 427**	**RTG 600 mg/day N = 281**	**RTG 900 mg/day N = 273**	**RTG 1200 mg/day N = 259**	**RTG Total N = 813**
Dizziness	Any AED(s)	38 (8.9)	41 (14.6)	64 (23.4)	84 (32.4)	189 (23.2)
	Carbamazepine	16 (8.0)	16 (11.0)	34 (21.1)	41 (31.5)	91 (20.8)
	Lamotrigine	10 (8.0)	13 (21.0)	21 (30.0)	30 (38.5)	64 (30.5)
	Valproic acid	4 (3.5)	12 (16.2)	14 (21.9)	16 (34.0)	42 (22.7)
	Topiramate	5 (6.7)	7 (12.7)	8 (17.8)	10 (26.3)	25 (18.1)
	Levetiracetam	8 (11.8)	13 (28.3)	14 (33.3)	12 (38.7)	39 (32.8)
Somnolence	Any AED(s)	51 (11.9)	43 (15.3)	67 (24.5)	69 (26.6)	179 (22.0)
	Carbamazepine	22 (10.9)	24 (16.4)	45 (28.0)	36 (27.7)	105 (24.0)
	Lamotrigine	9 (7.2)	11 (17.7)	14 (20.0)	17 (21.8)	42 (20.0)
	Valproic acid	17 (15.0)	15 (20.3)	16 (25.0)	18 (38.3)	49 (26.5)
	Topiramate	11 (14.7)	8 (14.5)	8 (17.8)	11 (28.9)	27 (19.6)
	Levetiracetam	10 (14.7)	1 (2.2)	6 (14.3)	6 (19.4)	13 (10.9)
Headache	Any AED(s)	68 (15.9)	34 (12.1)	47 (17.2)	39 (15.1)	120 (14.8)
	Carbamazepine	33 (16.4)	19 (13.0)	23 (14.3)	26 (20.0)	68 (15.6)
	Lamotrigine	18 (14.4)	7 (11.3)	17 (24.3)	11 (14.1)	35 (16.7)
	Valproic acid	13 (11.5)	6 (8.1)	8 (12.5)	9 (19.1)	23 (12.4)
	Topiramate	11 (14.7)	6 (10.9)	6 (13.3)	4 (10.5)	16 (11.6)
	Levetiracetam	11 (16.2)	6 (13.0)	6 (14.3)	1 (3.2)	13 (10.9)
Fatigue	Any AED(s)	25 (5.9)	45 (16.0)	40 (14.7)	34 (13.1)	119 (14.6)
	Carbamazepine	14 (7.0)	18 (12.3)	23 (14.3)	13 (10.0)	54 (12.4)
	Lamotrigine	6 (4.8)	17 (27.4)	10 (14.3)	14 (17.9)	41 (19.5)
	Valproic acid	3 (2.7)	6 (8.1)	6 (9.4)	7 (14.9)	19 (10.3)
	Topiramate	2 (2.7)	11 (20.0)	7 (15.6)	5 (13.2)	23 (16.7)
	Levetiracetam	6 (8.8)	15 (32.6)	14 (33.3)	2 (6.5)	31 (26.1)
Confusional state	Any AED(s)	11 (2.6)	12 (4.3)	21 (7.7)	42 (16.2)	75 (9.2)
	Carbamazepine	4 (2.0)	4 (2.7)	13 (8.1)	17 (13.1)	34 (7.8)
	Lamotrigine	2 (1.6)	4 (6.5)	4 (5.7)	17 (21.8)	25 (11.9)
	Valproic acid	1 (0.9)	7 (9.5)	6 (9.4)	6 (12.8)	19 (10.3)
	Topiramate	3 (4.0)	2 (3.6)	4 (8.9)	6 (15.8)	12 (8.7)
	Levetiracetam	0	0	3 (7.1)	2 (6.5)	5 (4.2)
Tremor	Any AED(s)	12 (2.8)	7 (2.5)	26 (9.5)	32 (12.4)	65 (8.0)
	Carbamazepine	3 (1.5)	3 (2.1)	12 (7.5)	15 (11.5)	30 (6.9)
	Lamotrigine	4 (3.2)	2 (3.2)	11 (15.7)	8 (10.3)	21 (10.0)
	Valproic acid	3 (2.7)	2 (2.7)	8 (12.5)	6 (12.8)	16 (8.6)
	Topiramate	2 (2.7)	1 (1.8)	2 (4.4)	4 (10.5)	7 (5.1)
	Levetiracetam	3 (4.4)	3 (6.5)	5 (11.9)	3 (9.7)	11 (9.2)
Coordination abnormal	Any AED(s)	12 (2.8)	14 (5.0)	14 (5.1)	30 (11.6)	58 (7.1)
	Carbamazepine	4 (2.0)	4 (2.7)	4 (2.5)	12 (9.2)	20 (4.6)
	Lamotrigine	3 (2.4)	1 (1.6)	7 (10.0)	13 (16.7)	21 (10.0)
	Valproic acid	4 (3.5)	6 (8.1)	6 (9.4)	3 (6.4)	15 (8.1)
	Topiramate	1 (1.3)	3 (5.5)	2 (4.4)	3 (7.9)	8 (5.8)
	Levetiracetam	2 (2.9)	3 (6.5)	3 (7.1)	8 (25.8)	14 (11.8)
Disturbance in attention	Any AED(s)	4 (<1.0)	17 (6.0)	15 (5.5)	17 (6.6)	49 (6.0)
	Carbamazepine	2 (1.0)	6 (4.1)	11 (6.8)	7 (5.4)	24 (5.5)
	Lamotrigine	1 (0.8)	4 (6.5)	3 (4.3)	6 (7.7)	13 (6.2)
	Valproic acid	0	6 (8.1)	3 (4.7)	0	9 (4.9)
	Topiramate	1 (1.3)	4 (7.3)	2 (4.4)	2 (5.3)	8 (5.8)
	Levetiracetam	2 (2.9)	7 (15.2)	4 (9.5)	4 (12.9)	15 (12.6)

Preferred Term	AED	Number (%) of Patients				
		Placebo N = 427	RTG 600 mg/day N = 281	RTG 900 mg/day N = 273	RTG 1200 mg/day N = 259	RTG Total N = 813
Memory impairment	Any AED(s)	11 (2.6)	7 (2.5)	15 (5.5)	24 (9.3)	46 (5.7)
	Carbamazepine	5 (2.5)	2 (1.4)	8 (5.0)	11 (8.5)	21 (4.8)
	Lamotrigine	3 (2.4)	3 (4.8)	8 (11.4)	11 (14.1)	22 (10.5)
	Valproic acid	3 (2.7)	2 (2.7)	2 (3.1)	6 (12.8)	10 (5.4)
	Topiramate	3 (4.0)	4 (7.3)	1 (2.2)	3 (7.9)	8 (5.8)
	Levetiracetam	1 (1.5)	0	4 (9.5)	1 (3.2)	5 (4.2)
Vision blurred	Any AED(s)	9 (2.1)	5 (1.8)	12 (4.4)	27 (10.4)	44 (5.4)
	Carbamazepine	4 (2.0)	4 (2.7)	7 (4.3)	12 (9.2)	23 (5.3)
	Lamotrigine	1 (0.8)	2 (3.2)	3 (4.3)	13 (16.7)	18 (8.6)
	Valproic acid	3 (2.7)	0	1 (1.6)	3 (6.4)	4 (2.2)
	Topiramate	2 (2.7)	1 (1.8)	0	3 (7.9)	4 (2.9)
	Levetiracetam	1 (1.5)	1 (2.2)	3 (7.1)	5 (16.1)	9 (7.6)
Asthenia	Any AED(s)	8 (1.9)	12 (4.3)	15 (5.5)	11 (4.2)	38 (4.7)
	Carbamazepine	3 (1.5)	5 (3.4)	11 (6.8)	8 (6.2)	24 (5.5)
	Lamotrigine	0	2 (3.2)	4 (5.7)	1 (1.3)	7 (3.3)
	Valproic acid	0	5 (6.8)	1 (1.6)	2 (4.3)	8 (4.3)
	Topiramate	0	1 (1.8)	2 (4.4)	2 (5.3)	5 (3.6)
	Levetiracetam	1 (1.5)	0	1 (2.4)	1 (3.2)	2 (1.7)
Speech disorder	Any AED(s)	4 (<1.0)	5 (1.8)	14 (5.1)	18 (6.9)	37 (4.6)
	Carbamazepine	0	2 (1.4)	7 (4.3)	11 (8.5)	20 (4.6)
	Lamotrigine	1 (0.8)	1 (1.6)	6 (8.6)	5 (6.4)	12 (5.7)
	Valproic acid	3 (2.7)	3 (4.1)	3 (4.7)	7 (14.9)	13 (7.0)
	Topiramate	1 (1.3)	1 (1.8)	1 (2.2)	1 (2.6)	3 (2.2)
	Levetiracetam	1 (1.5	0	1 (2.4)	2 (6.5)	3 (2.5)
Convulsion	Any AED(s)	19 (4.4)	6 (2.1)	10 (3.7)	16 (6.2)	31 (3.8)
	Carbamazepine	8 (4.0)	2 (1.4)	1 (0.6)	9 (6.9)	12 (2.7)
	Lamotrigine	5 (4.0)	3 (4.8)	7 (10.0)	7 (9.0)	17 (8.1)
	Valproic acid	4 (3.5)	2 (2.7)	3 (4.7)	4 (8.5	9 (4.9)
	Topiramate	2 (2.7)	3 (5.5)	0	1 (2.6)	4 (2.9)
	Levetiracetam	4 (5.9)	0	4 (9.5)	0	4 (3.4)
Aphasia	Any AED(s)	4 (<1.0)	3 (1.1)	9 (3.3)	17 (6.6)	29 (3.6)
	Carbamazepine	1 (0.5)	1 (0.7)	3 (1.9)	4 (3.1)	8 (1.8)
	Lamotrigine	0	0	2 (2.9)	10 (12.8)	12 (5.7)
	Valproic acid	0	1 (1.4)	1 (1.6)	4 (8.5)	6 (3.2)
	Topiramate	1 (1.3)	2 (3.6)	1 (2.2)	2 (5.3)	5 (3.6)
	Levetiracetam	3 (4.4)	0	4 (9.5)	4 (12.9)	8 (6.7)
Balance disorder	Any AED(s)	3 (<1.0)	8 (2.8)	8 (2.9)	13 (5.0)	29 (3.6)
	Carbamazepine	1 (0.5)	3 (2.1)	6 (3.7)	3 (2.3)	12 (2.7)
	Lamotrigine	1 (0.8)	2 (3.2)	3 (4.3)	7 (9.0)	12 (5.7)
	Valproic acid	0	3 (4.1)	1 (1.6)	1 (2.1)	5 (2.7)
	Topiramate	0	2 (3.6)	0	3 (7.9)	5 (3.6)
	Levetiracetam	0	0	2 (4.8)	4 (12.9)	6 (5.0)
Constipation	Any AED(s)	6 (1.4)	4 (1.4)	11 (4.0)	13 (5.0)	28 (3.4)
	Carbamazepine	2 (1.0)	0	6 (3.7)	7 (5.4)	13 (3.0)
	Lamotrigine	2 (1.6)	2 (3.2)	3 (4.3)	5 (6.4)	10 (4.8)
	Valproic acid	1 (0.9)	1 (1.4)	1 (1.6)	2 (4.3)	4 (2.2)
	Topiramate	2 (2.7)	3 (5.5)	2 (4.4)	4 (10.5)	9 (6.5)
	Levetiracetam	1 (1.5)	0	3 (7.1)	0	3 (2.5)
Paraesthesia	Any AED(s)	9 (2.1)	7 (2.5)	4 (1.5)	14 (5.4)	25 (3.1)
	Carbamazepine	2 (1.0)	4 (2.7)	1 (0.6)	9 (6.9)	14 (3.2)
	Lamotrigine	1 (0.8)	1 (1.6)	2 (2.9)	4 (5.1)	7 (3.3)
	Valproic acid	1 (0.9)	2 (2.7)	2 (3.1)	2 (4.3)	6 (3.2)
	Topiramate	2 (2.7)	3 (5.5)	0	4 (10.5)	7 (5.1)

Preferred Term	AED	Number (%) of Patients				
		Placebo N = 427	RTG 600 mg/day N = 281	RTG 900 mg/day N = 273	RTG 1200 mg/day N = 259	RTG Total N = 813
	Levetiracetam	3 (4.4)	3 (6.5)	1 (2.4)	1 (3.2)	5 (4.2)
Adverse events where there is no occurrence more than 5% over the any AED row have been removed						

Treatment Emergent Serious Adverse Events

RCT

Examination of the active dose groups indicated that the TESAE incidence among patients taking ezogabine in combination with the most commonly reported background AEDs was greater than placebo, with the exception of patients taking ezogabine and carbamazepine. When looking at the frequency of any SAE by concomitant AED for the Total RTG group, the highest incidence was reported in patients taking ezogabine and levetiracetam (15.1%), while the lowest incidence was reported in patients taking ezogabine and valproic acid. In addition, there appeared to be a relationship to the frequency of TESAEs and dose only for patients receiving ezogabine and levetiracetam, table 123.

Table 123 Serious Adverse Events by Concomitant AEDs Taken by Greater than or equal to 15% of Patients. RCT

	Number of Patients with ≥1 SAEs/Number of Patients in Subpopulation (%)				
		RTG	RTG	RTG	RTG
	Placebo (N=427)	600 mg/day (N=281)	900 mg/day (N=273)	1200 mg/day (N=259)	Total (N=813)
Any SAE	**25/427 (5.9)**	**23/281 (8.2)**	**18/273 (6.6)**	**29/259 (11.2)**	**70/813 (8.6)**
Carbamazepine	16/201 (8.0)	12/146 (8.2)	8/161 (5.0)	12/130 (9.2)	32/437 (7.3)
Lamotrigine	6/125 (4.8)	8/62 (12.9)	5/70 (7.1)	10/78 (12.8)	23/210 (11.0)
Valproic acid	4/113 (3.5)	4/74 (5.4)	2/64 (3.1)	6/47 (12.8)	12/185 (6.5)
Topiramate	2/75 (2.7)	5/55 (9.1)	2/45 (4.4)	4/38 (10.5)	11/138 (8.0)
Levetiracetam	2/68 (2.9)	3/46 (6.5)	7/42 (16.7)	8/31 (25.8)	18/119 (15.1)

For those on carbamazepine, lamotrigine, valproic acid, topiramate or levetiracetam almost all TESAEs were reported by a single patient in any ezogabine dose group. TESAEs reported by more than a single patient in any ezogabine dose group are presented in tabular form in table 124.

Table 124 SAE reports in more than a single patient presented by concomitant AED.

			RTG	RTG	RTG
Concomitant AED	**SAE**	**Placebo**	**600 mg/day**	**900 mg/day**	**1200 mg/day**
Carbamazepine	Convulsion	2/201 (1.0)	2/146 (1)	0	4/130 (3)
	Psychotic disorder	0	0	1/161 (<1%)	2/130 (2%)
Lamotrigine	Convulsion	3/125 (2%)	2/62 (3%)	2/70 (3%)	3/78 (4%)
Valproic acid	Psychotic	0	0	0	2/47 (4%)

	disorder				
Topiramate	Convulsion	0	3/55 (6%)	0	0
	Confusional state	0	0	0	2/38 (5%)
Levetiracetam	encephalopathy	0	0	0	2/31 (7%)
	Convulsion	1/68 (2%)	0	2/42 (5%)	0

All Phase II/III Combined

As would be expected with longer exposure times, a greater percentage of patients reported SAEs during the Phase II/III Combined studies compared to the Pivotal Controlled Trials. While there was an increase in the percentage of reports of SAEs for each concomitant AED, the trend was similar to that in the Pivotal Controlled Trials. The incidence of SAEs for individual concomitant AEDs was similar to the overall incidence of SAEs with the exception of levetiracetam which was higher than the overall percentage of SAEs.

Reviewer Comment: In the category of most common adverse events in AEDs taken by greater than or equal to 15% (most commonly used AEDs) of patients the most prominent association is between levetiracetam and dizziness. Levetiracetam and fatigue and levetiracetam and aphasia. There were 15 additional observations of AE associated with an AED with a frequency greater than 5% over any AED, however these were single occurrences for a given AED and are not reinforced by recurrence at additional dose groups. All of these instances cited, occurred in greater frequency than placebo.

In the category of serious adverse events in association with AEDs taken by greater than ore equal to 15% of patients, lamotrigine, valproic acid, topiramate and levetiracetam when taken with ezogabine were associated with higher frequency of AEs than when taken with placebo for all dose groups and total ezogabine with the exception of valproic acid at the 900mg group which had 0.4% less events than placebo. Among the commonly used concomitant AEDs carbamazepine with ezogabine had a higher rate of AE than placebo only at the 600mg and 1200mg dose group but not at 900mg or total ezogabine.

Overall the adverse event rate is higher with ezogabine and one concomitant AED than the commonly used concomitant AEDs and placebo. This trend increases with a second concomitant AED. Associations of specific commonly used concomitant AED and specific adverse events were noteworthy for levetiracetam and dizziness, fatigue and aphasia. There were no other prominent relationships between common AEs and concomitant AEDs. Although there was a prominent relationship between levetiracetam and dizziness, fatigue and aphasia, dizziness and fatigue are the most common background AEs rendering the observed occurrence with levetiracetam of uncertain significance.

The observation of SAEs with concomitant AEDs in two or more patients reveals convulsion to occur more than placebo in three of the commonly used AEDs which were carbamazepine, topiramate and levetiracetam. This is unlikely to represent a safety

signal for these AEDs, rather is more likely represents the high frequency of use of these agent in the refractory epilepsy population (76% of ezogabine patients) and the addition of concomitant AED points to the refractory nature of the underlying epilepsy in these patients.

7.6 Additional Safety Evaluations

7.6.1 Human Carcinogenicity

Carcinogenic impurities that originate from intermediate steps in synthesis. These are currently under review.

7.6.2 Human Reproduction and Pregnancy Data

Non-Clinical Information

The teratogenic potential of ezogabine has been evaluated in preclinical studies involving rats and rabbits. The overall nonclinical reproductive and developmental toxicity profile for ezogabine suggests that ezogabine is not teratogenic and has a low potential for fetal risk. However, exposures were generally less than those expected at therapeutic doses and the lack of risk to human fetuses has not yet been fully established.

As of the 31 December 2008 submission cut-off date, a total of 11 pregnancies have been reported (Table 184). Eight pregnancies were reported in female patients exposed to ezogabine while 3 pregnancies occurred in the female partners of male patients exposed to ezogabine. Of the 8 female patients who reported pregnancies, 5 patients electively terminated their pregnancies, and 3 patients carried their babies to term. Of the 3 patients who delivered, 2 delivered full-term, healthy infants. The remaining patient, who had a very short exposure to ezogabine (8 doses over 3 days), delivered a premature male infant with a patent ductus arteriosus and polydactyly at approximately 28-weeks gestation.

All three pregnancies that occurred in the female partners of male patients resulted in normal births. Narratives for all pregnancies are presented in m5.3.5.3, Narratives.

As of the 31 December 2008 submission cut-off, no pregnancies have been reported in Clinical Pharmacology study, ongoing Studies 3227-CU (compassionate use in epilepsy), VRX-RET-E22-NP201 (PHN), and VRX-RET-E22-MR103 (MR and IR formulation comparison). There were no pregnancies reported in Studies 303 or 304 between the integrated ISS database cut-off (30 June 2008) and the submission data cut-off date (31 December 2008).

Pregnancies in Female Patients Who Carried to Term

Three female patients exposed to ezogabine carried their pregnancies to delivery. All 3 pregnancies resulted in live births with 2 having normal births without complications and 1 delivering a very premature male infant with a patent ductus arteriosus and polydactyly.

Patient 00185, Study 205 (1200 mg/day, pregnancy), was a 25-year-old female who became pregnant after her the last dose of ezogabine. The patient reported using the concomitant medication valproic acid. The patient was reported to have had a normal delivery with no abnormalities approximately 13 months after withdrawing from the study.

Patient 20207, Study 301 (1200 mg/day, pregnancy), a 21-year-old African-American female, was withdrawn from the study due to pregnancy on Day 3. The patient had a pregnancy test during the baseline visit on Day 0 and began taking study medication on Day 1. On Day 2, the pregnancy test came back positive, and the patient was withdrawn from the study on Day 3. The patient received a total of 8 doses of ezogabine 100 mg tablets before stopping, but she continued her multiple concomitant AEDs for the duration of her gestational period. Concomitant medications included carbamazepine, clonazepam, valproic acid, and acetylsalicylic acid. The patient experienced premature labor, amniorrhexis, a prolapsed cord, and delivered a live 1205-gram male via emergency Cesarean section at 27 5/7-weeks gestational age (150 days after her last dose of ezogabine). The neonate required cardiopulmonary resuscitation with orotracheal intubation, cardiac massage, and adrenaline upon birth. The patient did well, and she was discharged from the hospital after 9 days. However the infant's perinatal course was complicated by anoxia, respiratory distress syndrome (RDS), patent ductus arteriosus (PDA), intraventricular hemorrhages (IVH), septicemia, retinopathy of prematurity (ROP), bilateral inguinal hernias, and bilateral hand polydactyly. The infant was eventually discharged from the hospital (245 days after last dose of study drug) after receiving treatment and recovering from these events. The infant weighted 3650 grams and was involved in infant stimulation programs including physical, occupational, and phono-audiology therapies (255 days after last dose of study drug). The infant's ophthalmologist reported that he was doing well.

Patient 10502, Study 303 (open-label ezogabine, pregnancy), was a 26-year-old Hispanic female who became pregnant on approximately Day 200. Concomitant medications included carbamazepine and lamotrigine. Last menstrual period (LMP) was Day 198. The patient was reportedly compliant with a double barrier contraceptive method until November of 2006 (approximately 1 month prior to estimated conception). The patient completed dosing on Day 268 and subsequently gave birth 191 days after her last dose to a normal male at 38 weeks gestational age weighing 2586 grams with APGAR scores of 8 and 9.

Reviewer Comment: The nonclinical profile is inconclusive due to dosage that was generally lower than those expected at therapeutic doses and the relation of ezogabine to the gestational difficulties and fetal malformation experienced by patient 20207 are of uncertain relation to ezogabine the reviewer concludes that ezogabine should be considered pregnancy category C.

7.6.3 Pediatrics and Assessment of Effects on Growth

Only 5 patients under age 18 participated in the pivotal clinical trials, 4 were 17 years of age and one was 14. Study 205 enrolled patients as young as age 16, Study 301 and 302 enrolled only age 18 and older. There are insufficient pediatric age patients to evaluate effects of ezogabine on growth.

7.6.4 Overdose, Drug Abuse Potential, Withdrawal and Rebound

Dependence Labeling Analysis

Analysis of Withdrawal Effects

The sponsor ISS (Integrated Summary of Safety) section on withdrawal effects divides events into those which were reported for ***abrupt discontinuation***, defined as a taper phase of ≤7 days, or no taper and ***non-abrupt discontinuation*** (withdrew from the study with a taper of >7days) and had an AE during the study medication taper. The reviewer feels that the most informative interval is the abrupt discontinuation category which may include those with no medication taper at all or a short taper. This very reduced taper is likely to induce the most physiologically threatening effect due to sudden cessation. The longer, greater than 7 day, taper interval may reveal adverse effects induced by a relative withdrawal in the early phase of the withdrawal interval.

The adverse effects reported by the sponsor in both the abrupt and greater than 7 day taper are examined. In the abrupt discontinuation group there are two adverse event terms which contained a patient cohort which was fully known to the reviewer from analysis of the special section, “Psychosis and Hallucinations”. These terms are “psychotic disorder” and “hallucination visual”. The sponsor indicates that there were three events of psychotic disorder attributed to abrupt withdrawal and 2 events of “hallucination, visual” due to abrupt withdrawal.

Non-confirmation of 4 cases of “psychotic disorder” subsequent to study drug discontinuation

There were 7 adverse event of “psychotic disorder” in the RCT trials. Six of these cases of adverse event term “psychotic disorder” in the RCT trials resulted in study withdrawal or SAE. The case narratives of these six cases reveals that 5 of the “psychotic disorder” events occurred while the patients were receiving their full assigned dose of ezogabine before initiation of any drug taper. This examination reveals that a maximum of two cases could have occurred following study drug taper or discontinuation which is divergent from the sponsor report indicating 4 cases of psychotic disorder occurred subsequent to study drug taper or discontinuation.

Non-confirmation of 2 cases of “hallucination, visual” subsequent to study drug discontinuation

The sponsor table indicates 2 ezogabine patients experienced “hallucination, visual” upon discontinuation of ezogabine. Examination of the AE dataset reveals 37 unique patients with an adverse event of “hallucination, visual”. Within these 37 patients 3 are identified with an affirmative entry in the ABDIS (Patient abruptly discontinued study) field. One of these 3 patients is found to have an imputed adverse event start date that is subsequent to the last dose of ezogabine date, indicated by the AESTDT1 (imputed AE date) AND LDOSEDT (Last dose date) fields respectively. Review of these 3 case narrative reports reveals that the adverse event of “hallucination, visual” preceded the study drug discontinuation rather than occurring subsequent to the study drug discontinuation as a withdrawal effect. This analysis indicates that the adverse events of “hallucination, visual” attributed to abrupt discontinuation, actually began before cessation of study drug.

In light of the divergence between the case narratives and the sponsor report of the timeline of the two adverse events, (“psychotic disorder” and “hallucination, visual”) the remaining adverse events attributed to abrupt discontinuation are called into question. An information request was sent to the sponsor to determine if the occurrence of adverse events can be more accurately partitioned between those occurring before and after ezogabine discontinuation.

In response to this information request the sponsor provides improved partition between events which occur during study drug taper and those occurring strictly following cessation of ezogabine. All the cases identified as occurring during abrupt discontinuations strictly following cessation of ezogabine are evaluated. In those instances where case narratives are available, these are reviewed to determine accuracy of the category (abrupt, strictly after drug cessation) designations.

The sponsor indicates two events of “psychotic disorder” occur in the category “abrupt, strictly after drug cessation”. The two case narratives are available for review, case 302-85416 and 301-20309. Examination of the case reports reveals that all elements of the adverse event “psychotic disorder” were present while on full assigned dose of ezogabine, prior to intervention of drug taper. In a case of tremor, listed as category “abrupt, strictly after drug cessation” 205-1191, the event is found to occur before drug cessation. These inaccuracies cast doubt on the reliability of the category assignments of all ezogabine withdrawal associated adverse events.

Because of the uncertainty in category assignment of the withdrawal adverse events a further examination is performed to determine the ability of the adverse event reporting mechanism to accurately assign adverse events on a timeline relative to ezogabine discontinuation. The sample case report forms of studies 201, 301 and 302 are examined and do not have a method of entry dedicated to the timeline of withdrawal events relative to ezogabine cessation. Subsequently the 204, 301 and 302 study protocols are examined for wording which would define a mechanism to create an accurate timeline of pre and post ezogabine discontinuation withdrawal adverse events. No such definition or mechanism is identified in these protocols.

Although the assignment validity of adverse events to specific discontinuation or taper intervals is clouded, the terms are examined to identify potential signals for a withdrawal phenomena or syndrome. Among those events in the abrupt discontinuation category, definitively placed in the post drug cessation interval, the following terms are found: “coordination abnormal”, “aphasia”, “tremor”, “psychotic disorder”, and “myalgia”. The maximum separation from placebo among these terms are “myalgia” at 5% and “Tremor” at 4%. There were no study withdrawals or SAE due to myalgia thus no available narrative to examine the timeline of events more closely. There were 8 adverse events of myalgia in the titration and maintenance, double blind study interval. Two (25%) of these occurred in the abrupt discontinuation interval, after cessation of ezogabine. These two events represent 5% of all discontinuation events in the abrupt category for the ezogabine 600mg / day group. This represents the second largest separation from placebo of all adverse events in all discontinuation categories. The high proportion of events in discontinuation and the large separation from placebo lend some weight to causality. However, the possibility that examination of the 21 adverse event terms present in the discontinuation intervals will yield a term with 5% separation from placebo by chance is present. As noted in the previous discussion, “tremor” is invalid due to the indication in a case report of one of the two cases that the tremor began at least 4 months prior to ezogabine discontinuation or taper. There were also 64 patients with an adverse event report of tremor within the titration and maintenance study interval and only 2 occurred in the abrupt discontinuation interval. This disproportion of occurrence, with only 3.1% of adverse events in the post discontinuation interval does not support a causal relationship to this interval.

Two additional terms are identified with a large separation from placebo; these are confusional state and headache. The term confusional state had a maximum 4% separation from placebo with a dose response and occurred in the abrupt discontinuation category (≤7days) where the event occurred prior to last medication dose. Headache occurred in the category of non-abrupt discontinuation (>7days) with a maximum separation from placebo of 7% and a dose response. Both of these adverse events were very common throughout the study, lessening the likelihood of specificity for withdrawal phase events.

Reviewer Comment:
The objective in the analysis of adverse events associated with ezogabine withdrawal is to identify signs or symptoms which are coupled clearly enough with drug withdrawal to indicate evidence of physical dependence. The initial analysis of the sponsor in the ISS and the request for information to clarify the ISS reveals a cluster of adverse events associated with abrupt withdrawal or graduated taper greater than 7 days. Among each of the adverse events in this cluster the absolute numbers and percentage (of all withdrawn patients) are small. Among all discontinuation categories, the adverse event “headache” and “confusional state” have a the largest separation from placebo with a dose response, maximum 7% and 4% respectively. These adverse events “headache” and “confusional state” are common throughout the study and therefore lack specificity for the withdrawal interval. Myalgia has a 5% separation from placebo at the 600mg/day ezogabine dose only. This single occurrence of a 5% separation, among 21 adverse event terms, at only the lowest ezogabine dose does not provide adequate level of

evidence for causality. The protocols do not designate that these adverse events are captured in a manner to accurately differentiate whether the event caused the withdrawal or resulted from the withdrawal. The method of adverse event collection is only competent to capture events from a time interval nearby the ezogabine stop date without a clear before or after differentiation. Based on the aforementioned analysis the adverse events captured in association with ezogabine withdrawal cannot be claimed as events related physiologically to the cessation or reduction of ezogabine treatment.

Drug Abuse Potential

See Appendix for Evaluation of overdose cases and analysis of euphoria related terms,

Reviewer Comment: In their 8 factor analysis of potential need for scheduling the sponsor provides a robust argument that ezogabine be approved for marketing without CSA scheduling. This argument is supported by the mechanism of action which is to open neuronal KCNQ potassium channels. Potassium channel action is not a recognized ligand for abuse related agents, however the sponsor also notes that in vitro preclinical studies indicate that ezogabine has the potential to modulate gamma-aminobutyric acid (GABA) mediated neurotransmission although at concentrations greater than those required for the target potassium channel actions. The sponsor also emphasizes subjective effects similar to levetiracetam but also notes in the human abuse potential study, the incidence of euphoric mood was similar to alprazolam but lower then levetiracetam. The incidence of euphoric mood similar to alprazolam points to some possibility to act as a drug with abuse potential and the prospective of action on GABA neurotransmission offers a mechanism for this behavior.

Review of euphoria related terms in the pivotal clinical trials (RCTs) identifies 20 ezogabine treated patients and one placebo patient who has an AE congruent with one of the euphoria related terms panel. This represents 2.5% of the ezogabine treated cohort and 0.2% of the placebo population. If only those euphoria related terms with the least ambiguity are retained, euphoric mood and feeling drunk, the percentage of ezogabine treated patients' declines to 11/813 or 1.4%. I have a concern about the validity of two of the events in ezogabine patients where the verbatim terms "euphonia" are mapped to the PT "euphoria". It is unclear if euphonia is a misspelling for euphoria or is completely mismatched to the PT. Removal of these two questionable euphoria terms then further reduces the occurrence in the ezogabine treatment patients to 1.1%. The euphoria cases are strengthened somewhat by the two inappropriate affect preferred terms, these are mapped to the verbatim terms laughter. This increases the unambiguous euphoria related AEs in the ezogabine population to 1.4% vs 0.2% in placebo.

Titration Rate and Euphoric Mood:
Review of the integrated pharmacology studies identifies 234 occurrences of terms contained in the euphoria panel (of terms provided by CSS). These occur in 61 patients. The most common term is "euphoric mood" which occurs in 149 instances followed by

"feeling drunk" in 47 instances. The data also reveal that 171 of the 234 events are produced by only 2 of the 21 pharmacology studies. The two studies are VRX-RET-E22-103 and VRX-RET-E22-106, subsequently to be identified as study 103 and 106. These 171 events represent 73% of all reported euphoria related events in the pharmacology studies and are reported by 38 subjects. These 38 subjects represent 62% of the 61 subjects who reported euphoria related adverse events in any of the integrated pharmacology studies. These 61 subjects who reported euphoria related AEs represent 13% of the 475 total population who received ezogabine in the pharmacology studies. This 2 study spike in the reporting of euphoria related events stands out with even greater contrast when seen on the background of 21 pharmacology studies with a total of 475 subjects participating. The integrated pharmacology studies also have a noticeable higher occurrence of euphoria related AEs compared to the pivotal controlled trials, 13% vs 2.5%. This difference is likely due to titration rate. These studies had rapid titration rates compared to the pivotal controlled trials, double (2x) the rate in study 103 and almost four times (4x) the rate in study 106. The predominant euphoria related AE in study 103 was "feeling drunk" (74%) and the predominant euphoria related AE in study 106 was euphoric mood, 81%. The reason for the strong divergence between the choices of euphoria related terms between the studies is unclear.

In conclusion: there are a small number of unambiguous euphoria associated adverse events in the ezogabine treated cohort of the double blind trials, although small, this is contrasted with no unambiguous euphoria related terms in the placebo group. One patient in the placebo group had an AE from the euphoria panel of terms that is mapped to a verbatim report of "hallucination at night during sleep" which is unlikely to be a true mood elevating or reinforcing experience. Overall, though numerically small, there is a sharp contrast between 1.4% occurrence of euphoria terms in the ezogabine treatment group and none in placebo.

The integrated pharmacology studies, although uncontrolled, revealed a strong trend of euphoria related adverse events occurring in healthy volunteers in the two studies where there was a rapid titration of ezogabine. The observations from the double blind treatment group and the pharmacology studies raise the possibility that there is an effect of mood elevation in some individuals especially with rapid dose escalation. It is uncertain if this will translate into a reinforcing experience that will result in abuse.

Human Abuse Potential Study (VRX-RET-E22-108) See Appendix for body of study

Title: A Randomized, Double-Blind, Placebo- and Active-Controlled Crossover Study to Evaluate the Abuse Potential of Ezogabine in Recreational Polydrug Users.

Reviewer Comment: Similar to the examination of abuse related terms in the phase I and pivotal controlled trials where euphoria related terms were given the greatest weight, the reviewer places greatest weight on the positive subjective effects in the abuse potential study. The sedative effects are less specific because of their commonality in anticonvulsant agents' thus more difficult terms from which to extract a signal. The negative subjective effects are informative by the inconsistent ezogabine

differentiation from the positive control, alprazolam and also from levetiracetam. This implies that in the event there is a signal for abuse potential negative subjective effects would not neutralized abuse potential.

Table 26 –measures of balance of effects- reveals that ezogabine 600mg is found more favorable than placebo on all measures which favor taking the drug. It is noteworthy that levetiracetam 4000mg reveals similar findings compared to placebo. In the direct comparison between ezogabine 600mg and levetiracetam 4000mg there was no separation between the two drugs. In the analysis of positive subjective effects, table 27 (summary of pairwise comparisons for positive subjective effects) ezogabine 600mg is significantly favored over placebo in all measures and ezogabine 300mg is significantly separated from placebo in 4 of 7 measures. When ezogabine 300mg and 600mg are compared to alprazolam 1.5mg and 3mg alprazolam is significantly favored over ezogabine on only 7 of 28 measures. In this series of comparisons alprazolam is favored over ezogabine at all doses for the measure of “high”. When ezogabine was compared directly to levetiracetam, the latter was favored significantly over ezogabine 300mg on measures of “good effects” and “high”. There was no difference between ezogabine 600mg and levetiracetam 4000mg on any measures of positive subjective effects.

Examination of negative subjective effects reveals placebo superior to ezogabine 300mg on the ARCI LSD question group. Ezogabine 600mg is found unfavorable compared to placebo on the experience of “bad drug effects”, the ARCI, LSD questions, and “pleasant physical state”.

In conclusion the occurrence of euphoria related adverse effects exclusively in the ezogabine treatment cohort of the pivotal controlled trials, in addition to a spike of euphoria related adverse effects in those phase I trials with the most rapid titration rate in healthy subjects and the findings of “drug liking” and positive subjective effects in excess over placebo indicate a signal for abuse potential. More refined quantification of the signal and determination if this signal rises to the threshold necessary for ezogabine to be prescribed on a scheduled basis will await **evaluation by the CSS**.

9 Appendices

9.1 Literature Review/References

See Footnotes

9.2 Labeling Recommendations

1. Dose: Because of the escalation in adverse effects in the interval between the 900mg and 1200mg dose a target dose of 900mg should be recommended with further dose escalation to 1200mg only if directed by clinical response. See Slope

2. Voiding dysfunction; the clinical reviewer agrees with the labeling recommendations pertinent to urinary retention and the related information for patients. The labeling modifications are provided with the track changes by DRUP (Division of Reproductive and Urologic Products**)**. The track changes represent modifications of the original label made by DRUP.

WARNINGS AND PRECAUTIONS
5.1 Urinary Retention

(b) (4)

17 PATIENT COUNSELING INFORMATION
17.1 Urinary Retention

(b) (4)

3. QT prolongation: the IRT-QT Studies Consultation provides the following recommendations for label modification. The clinical reviewer agrees with these modifications provided in a tabular format below.

Label Section	Label Text
5.2 QT Interval Effect	(b) (4)
12.2 Pharmacodynamics	
17.2 QT Interval Effect	
We have used red-strike out for suggested text to be deleted and blue font for text to be included. Our recommendations are suggestions only. We defer final decisions regarding labeling to the review division	

4. Psychiatric Disorders: In proposed labeling (b) (4) however the conditions of high dose and rapid titration which are more commonly associated with the emergence of hallucinations and

psychosis are not presented. In addition the foregoing analysis indicates that when ezogabine is administered to patients with history of psychiatric disorder there should be increase vigilance for adverse psychiatric and behavioral symptoms. These conditions should be added to section 5.5 of warnings and precautions. See Adverse Psychiatric Reactions.

5. Hyperkalemia should be noted in labeling in "Clinical Trials Experience" section at the Common Adverse Reaction In All Controlled Clinical Studies section, following the table of "at least 2%" , in the paragraph where sentence 1 reads "Other adverse reactions reported in these 3 studies in <2% of patients treated with POTIGA and numerically greater than placebo". See Potassium Outliers.

6. Hypotension should be noted in labeling in "Clinical Trials Experience" section at the Common Adverse Reaction In All Controlled Clinical Studies section, following the table of "at least 2%" , in the paragraph where sentence 1 reads "Other adverse reactions reported in these 3 studies in <2% of patients treated with POTIGA and numerically greater than placebo". This position in labeling is recommended although there are parameters of hypotension exceeding 2%, the most compelling is "orthostatic hypotension-systolic" with a value 1.4% in excess of placebo. See Blood Pressure Outliers.

7. Weight gain: In current labeling there is no reference to weight gain, only an indication that appetite increase and decrease is seen. The large percent of patients who have a PCC value for weight change from baseline as well as the + difference in medians and means between ezogabine and placebo treatment marks a need for weight gain to be present in labeling. This may be stated following the paragraph "Other adverse reactions…" in section 6.1 Clinical trial experience as; although no adverse event of "abnormal weight gain" was recorded in the RCTs, a dose related weight gain has occurred in clinical trials. See Weight.

9.3 Advisory Committee Meeting

Advisory Committee meeting was scheduled and took place on August 11, 2010. The quick minutes are provided below:

Questions to the Committee:

1. Substantial evidence of effectiveness consists of data from adequate and well-controlled clinical trials ("trials" usually interpreted as more than one). Has the sponsor provided substantial evidence of the effectiveness for ezogabine as adjunctive treatment in partial onset seizures? YES/NO/ABSTAIN

   YES: 13 NO: 0 ABSTAIN: 0

Committee Discussion: *The committee members unanimously agreed that the sponsor has provided substantial evidence of the effectiveness for ezogabine as adjunctive treatment in partial onset seizures.*

2. Urinary retention appears to be a significant safety issue for ezogabine. Do you believe that urinary retention can be mitigated by patient monitoring? YES/NO/ABSTAIN

YES: 11 NO: 0 ABSTAIN: 2

Committee Discussion: *The majority of the committee agreed that adequate patient monitoring can mitigate the risk of urinary retention. One panel member abstained due to lack of clinical expertise while another panel member abstained because of the lack of clearly defined patient monitoring methods. A panel Urologist indicated that while it is a reasonable expectation that patient monitoring will mitigate the adverse effect of urinary retention, understanding the mechanism of ezogabine mediated voiding dysfunction is needed to allow the desired precision needed for prediction of an adverse effect. This panel member recommended a phase IV urodynamic study.*

3. If the answer to question #2 is YES, what is the best approach to monitoring patients?

Committee Discussion: *The committee agreed that with the current state of knowledge symptomatic monitoring is the best approach for Neurologists treating patients with this drug. The neurologists on the panel questioned the utility of the AUA symptom index; however, the urologists supported the AUA symptom index as the most appropriate approach to screen patients for symptoms of voiding dysfunction. The urologists on the panel acknowledged that although the AUA symptom index did not have predictive value for voiding dysfunction in the controlled trials, the symptom profile is the best developed instrument for capturing symptoms of voiding dysfunction. Any change in voiding pattern should be a trigger for further inquiry when following patients.*

The neurologists were also concerned about how to monitor patients who are cognitively impaired (i.e., Alzheimer's, TBI, etc) where symptom monitoring will not be possible. For this subpopulation, one urologist recommended monitoring spot residuals with ultrasound and urologic referral for further guidance if necessary. The committee agreed that an intensive educational campaign for providers as well as patients will help mitigate the risk.

4. Should monitoring also be instituted for infection and urolithiasis? YES/NO/ABSTAIN

YES: 0 NO: 13 ABSTAIN: 0

Committee Discussion: *The committee members unanimously agreed that monitoring should not be instituted for infection and urolithiasis. It was noted that monitoring may be helpful in patients with a history of kidney stones.*

5. If the answer to question #4 is YES, what would be the best approach to monitoring patients?

Committee Discussion: *There was no discussion as everyone voted "NO" to question #4.*

6. Are there specific patient populations who may be at increased risk for urinary retention, infection or stones, e.g. elderly males, patients with other risks of urinary dysfunction, cognitively impaired patients (dementia or acute change in the level of alertness), children, patients on other medications that may affect voiding (e.g. anticholinergic medication)?

Committee Discussion: *The committee agreed that there are specific patient populations who may be at increased risk for urinary retention, infection, and stones. These patients may include males over age 65, individuals whom there is a concern regarding the ability to communicate in an effective and timely fashion about new urinary symptoms, and patients with urinary comorbidities . The panel does not recommend use of ezogabine in children less than 12 years old until after an urodynamic study in adults is conducted first.*

7. Are there other serious safety issues associated with the use of ezogabine that would preclude its approval?

Committee Discussion: *The committee members unanimously agreed that there are no other serious safety issues that they are aware of that would preclude the Agency's approval of ezogabine. A few committee members recommended that the drug product be studied in subpopulations such as the elderly, spinal cord injury patients, and Alzheimer's patients. A panel neurologist indicated there would be value in further exploration of KCNQ channel genetic polymorphisms and the occurrence of atrial fibrillation in ezogabine treated patients. Additionally, the committee suggested additional studies on dosing to better determine if the risk for certain adverse events are increased with increased doses.*

9.4 Evaluation of overdose cases and analysis of euphoria related terms

Overdose Cases

There are 9 cases of reported overdose in the safety database. Seven of these events are reported as accidental overdose and 2 were clearly intentional overdose. Of the seven accidental overdose events one is such a large quantity that accident is unlikely, raising the total to three intentional.

Accidental overdose		
Case #	Dose	Effect
00078	Increased from 100mg to 200mg tablet	No effect, dose subsequently increased to 600mg/day
00126	Entire day 300mg TID taken as single 900mg dose	Non-specific, " did not feel good at all"
00613	Dose accidently escalated from 300mg to 400mg TID	Nausea, vomiting, diplopia, hand tremor and dizziness. Dose reduced to 200mg TID
25108	Reported near overdose, no quantification	Panic attack
25104	On 300mg TID , took two doses at once.	Non-specific report of effect, states only mild ezogabine intoxication

90203	900mg single dose	Confusion disorientation

Intentional Overdose		
Case #	Dose	Effect
000167	2500 to 3000mg single dose.	Confused agitated, EEG slowing, somnolence, seizure the following day, required mechanical ventilation following the seizure.
65404	Dose uncertain	Sudden change in mental status to coma, then uncharacteristic seizure, 4 day recovery
20214	Ingested 10.1 grams over three days, reported as confusion about medication instructions	Somnolence, confusion, ataxia, Dysarthria, dizziness. Discharged same day from hospital.

Reviewer Comment: none of the narrative reports indicate overdose based on seeking positive psychological experience although this cannot be completely excluded. In those cases where a single extra dose or a whole day dose at a single time was ingested are unlikely to be abuse associated.

Euphoria Related terms in controlled trials

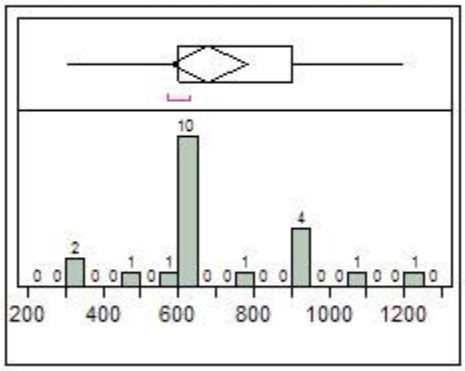
The PTNAME field in the adverse event database is searched for euphoria related terms provided by CSS (controlled substances staff). These terms include the following: “Euphoric mood”, “Elevated mood”, “Feeling abnormal”, “Feeling drunk, “Feeling of relaxation”, “Thinking abnormal”, “Hallucination”, and “Inappropriate affect”. The PT name column is searched in a subset of the AE database selected for RCT (pivotal controlled trials) in double blind phase by capturing patients in titration or maintenance interval of the studies 205, 301 or 302. There are 24 instances of a euphoria term identified, these instances contain the following six preferred terms (PT): euphoric mood, feeling abnormal, feeling drunk, hallucination, inappropriate affect and thinking abnormal, figure 24. These preferred terms are mapped from 15 verbatim terms shown in table 128, and figure 25. Twenty three (23) of these events occur in ezogabine treated patients compared to only one occurrence in placebo. The 23 events in ezogabine treatment occur in 20 unique patients. In two patients no dose is recorded at the time of the adverse event. The distribution of ezogabine dose at time of adverse event has a median of 600mg, with a mean of 680mg.

Table 125 Map of verbatim terms to preferred terms in patients with euphoria related adverse events, 23 ezogabine and 1 placebo event

Map of verbatim terms to preferred terms in patients with euphoria related adverse events, 23 ezogabine and 1 placebo event	
AETERM (verbatim term)	PTNAME (preferred term)
LAUGHTER	INAPPROPRIATE AFFECT
LAUGHTER	INAPPROPRIATE AFFECT
LAUGHTER	INAPPROPRIATE AFFECT

Map of verbatim terms to preferred terms in patients with euphoria related adverse events, 23 ezogabine and 1 placebo event	
HALLUCINATIONS	HALLUCINATION
HALLUCINATIONS	HALLUCINATION
DRUGED FEELING(NO DRUGS OR ALCOHOL TAKEN)	FEELING DRUNK
SENSATION OF DRUNKNESS	FEELING DRUNK
INTERMITTENT FEELING OF INTOXICATION	FEELING DRUNK
DRUNKENESS SENSATION	FEELING DRUNK
HALLUCINATIONS	HALLUCINATION
DRUNK FEELING STATE	FEELING DRUNK
EUPHORIA	EUPHORIC MOOD
HALLUCINATIONS	HALLUCINATION
HALLUCINATION	HALLUCINATION
FLOATING FEELING AFTER STUDY DRUG INTAKE	FEELING ABNORMAL
EUPHORY	EUPHORIC MOOD
HALLUCINATIONS	HALLUCINATION
ABNORMAL THINKING	THINKING ABNORMAL
MODIFICATION OF COUNCIOUNESS(FEELING DRUNK AFTER TAKING IP LASTING FOR 15-30MIN)	FEELING DRUNK
LAUGHTER FOR NO REASON	INAPPROPRIATE AFFECT
DRUNKEN FEELING-30 MINUTES AFTER STUDY DRUG BEEN TAKEN	FEELING DRUNK
EUPHONIA	EUPHORIC MOOD
EUPHONIA	EUPHORIC MOOD
HALLUCINATIONS AT NIGHT DURING SLEEP (placebo)	HALLUCINATION (placebo)

Figure 24 EZO dose in RCT patients with euphoria related AE



Distributions

EZO dose at time of adverse event

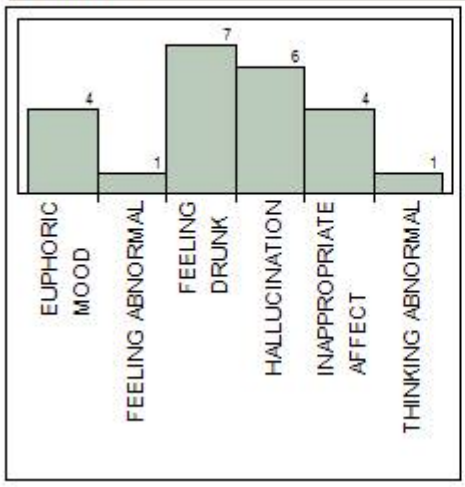
Quantiles

100.0%	maximum	1200.0
99.5%		1200.0
97.5%		1200.0
90.0%		1028.6
75.0%	quartile	900.0
50.0%	median	600.0
25.0%	quartile	600.0
10.0%		330.0
2.5%		300.0
0.5%		300.0
0.0%	minimum	300.0

Moments

Mean	680.61429
Std Dev	228.06188
Std Err Mean	49.767182
upper 95% Mean	784.42681
lower 95% Mean	576.80176
N	21

Figure 25 Distribution of PTs among 23 Euphoria related AEs in 20 EZO treated patients



Distributions

PTNAME

Frequencies

Level	Count	Prob
EUPHORIC MOOD	4	0.17391
FEELING ABNORMAL	1	0.04348
FEELING DRUNK	7	0.30435
HALLUCINATION	6	0.26087
INAPPROPRIATE AFFECT	4	0.17391
THINKING ABNORMAL	1	0.04348
Total	23	1.00000

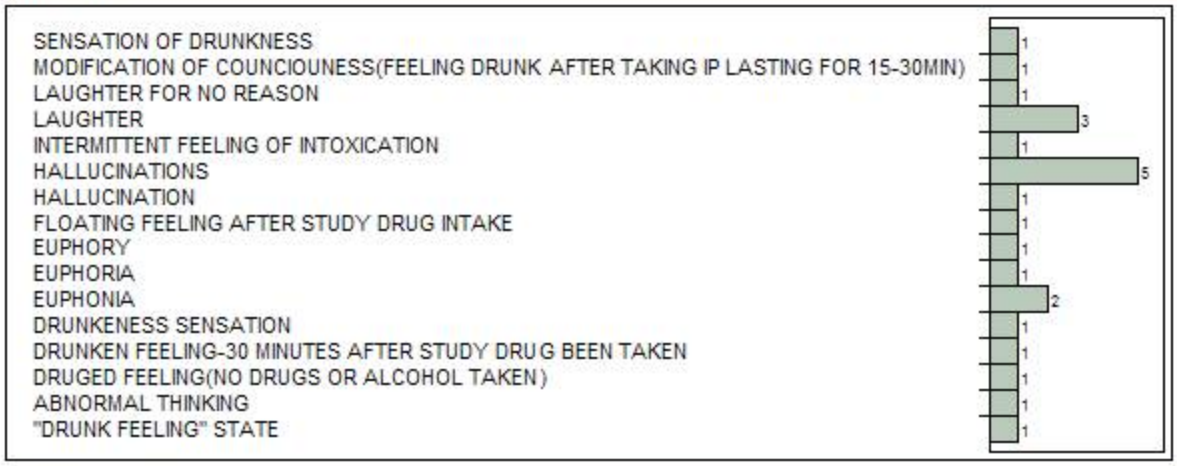
N Missing 0

6 Levels

Figure 26 Distribution of verbatim terms among 23 Euphoria related AEs in 20 EZO treated patients

Distributions

AETERM



Frequencies

Level	Count	Prob
"DRUNK FEELING" STATE	1	0.04348
ABNORMAL THINKING	1	0.04348
DRUGED FEELING(NO DRUGS OR ALCOHOL TAKEN)	1	0.04348
DRUNKEN FEELING-30 MINUTES AFTER STUDY DRUG BEEN TAKEN	1	0.04348
DRUNKENESS SENSATION	1	0.04348
EUPHONIA	2	0.08696
EUPHORIA	1	0.04348
EUPHORY	1	0.04348
FLOATING FEELING AFTER STUDY DRUG INTAKE	1	0.04348
HALLUCINATION	1	0.04348
HALLUCINATIONS	5	0.21739
INTERMITTENT FEELING OF INTOXICATION	1	0.04348
LAUGHTER	3	0.13043
LAUGHTER FOR NO REASON	1	0.04348
MODIFICATION OF COUNCIOUNESS(FEELING DRUNK AFTER TAKING IP LASTING FOR 15-30MIN)	1	0.04348
SENSATION OF DRUNKNESS	1	0.04348
Total	23	1.00000

N Missing 0
16 Levels

Dizziness is included in the list of euphoria related terms from CSS, however this is also an AE seen commonly in AED treatment and has been commonly reported in ezogabine use. This term was analyzed independently then evaluated for overlap with the 23 non-dizziness AEs. In the RCT studies there were 363 dizziness events in the ezogabine treatment patients during the titration and maintenance phase of the study and 52 events in the placebo treatment patients. Sixteen of the 20 unique ezogabine treated subjects with a euphoria related adverse event also had an AE of dizziness. The single placebo patient with a euphoria related adverse event did not have an additional AE of dizziness. In addition to the 16 patients with an AE of euphoria and dizziness there were 172 unique subjects in the ezogabine treated cohort who experienced dizziness without euphoria related event. Unless it is expected that dizziness would

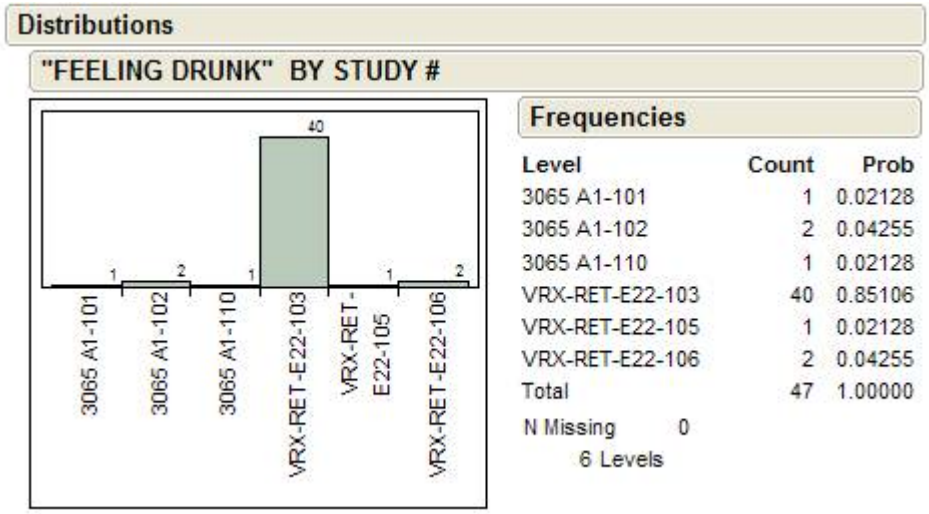
occur as an isolated euphoria related event, it is more likely that dizziness is a stand alone adverse effect and does not appear to be a trigger for concurrent euphoria related adverse event terms.

Integrated Pharmacology Studies

Euphoria related terms provided by the CSS are evaluated for occurrences as preferred terms (PT) in the adverse event database of the Integrated Pharmacology Studies (IPS). These terms include the following: “Euphoric mood”, “Elevated mood”, “Feeling abnormal”, “Feeling drunk, “Feeling of relaxation”, “Thinking abnormal”, “Hallucination”, and “Inappropriate affect”.

Feeling drunk: there were 47 events in 25 unique subjects. 40 of these events in 20 patients occurred in study VRX-RET-E22-103 and 5 additional subjects each in a different study, figure 27. Study 103 is a thorough QT study with a rapid titration to 1200mg/day. The 20 subjects with an AE of feeling drunk represent 50% of the ezogabine treatment group in study E22-103. This is likely related to the rate of titration which is more than double the titration rate recommended in proposed labeling. This study accounted for the overwhelming majority of “feeling drunk” adverse events.

Figure 27 AE "feeling drunk" distribution by study



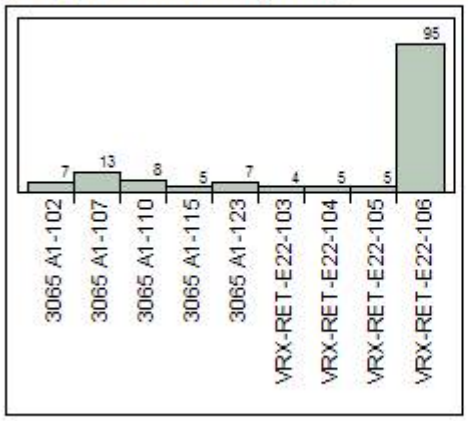
Euphoric mood: There were 149 events of the AE “euphoric mood” in 33 unique subjects. 95 (64%) of these events, occurred in study VRX-RET-E22-106, and 13 (8.7%) occurred in study 3065 A1-107, F28. The 95 events in study 106 were reported by 16 subjects. Study VRX-RET-E22-106 was a PK interaction study evaluating the effect of repeated ezogabine dosing on the PK of oral contraceptives in healthy adult female volunteers. This study had a very rapid ezogabine titration rate, proceeding from 0 on day 22 of study to 900mg by day 35, a span of only 13 days, representing a rate almost 4 times faster than proposed labeling. In the ezogabine dose group (≥600mg/day) 14 (47%) subjects reported an AE of “euphoric mood”. The median ezogabine dose associated with the AE “euphoric mood” in study E22-106 was 750mg,

with a mean of 877mg, a minimum of 300mg and a maximum of 1650mg, figure 29. The high frequency of adverse effects that developed during the rapid titration resulted in an attenuation of the day 35 target dose to 250mg TID rather than 300mg TID.

Study 3065 A1-107 entitled “A 30 day Safety and Tolerability Study of Various Titration Regimens of Ezogabine (GKE-841) in Healthy Male Subjects” was also a titration study; however the rate of dose escalation was only modestly more rapid than the rate in proposed labeling. There were multiple adverse effects and all 9 subjects were withdrawn from the study. The sponsor stopped the study due to non-serious AEs, although a 34 year old male patient had a 3 beat run of non-sustained ventricular tachycardia. Compared to the proposed labeling the titration rate was not excessive, it is unclear why AEs reached a magnitude which resulted in termination of the study.

In study VRZ-RET-E22-103, the QT study with a high titration rate and a high frequency of the AE (PT) term “Feeling Drunk”, there was one subject who reported 4 instances of euphoric mood. This subject reported a euphoric mood AE at the following dose intervals, 450mg, 600mg, 750mg and 900mg.

Figure 28 “euphoric mood” distribution by study

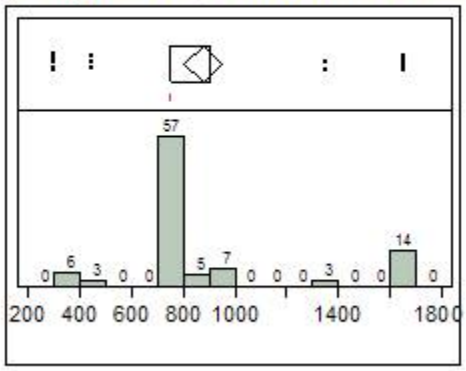


Frequencies

Level	Count	Prob
3065 A1-102	7	0.04698
3065 A1-107	13	0.08725
3065 A1-110	8	0.05369
3065 A1-115	5	0.03356
3065 A1-123	7	0.04698
VRX-RET-E22-103	4	0.02685
VRX-RET-E22-104	5	0.03356
VRX-RET-E22-105	5	0.03356
VRX-RET-E22-106	95	0.63758
Total	149	1.00000

N Missing 0
9 Levels

Figure 29 Study E22-106 EZO dose distribution at time of AE- Euphoric mood



Distributions

Study E22-106, EZO dose distribution at time of AE Euphoric mood.

Quantiles

100.0%	maximum	1650.0
99.5%		1650.0
97.5%		1650.0
90.0%		1650.0
75.0%	quartile	900.0
50.0%	median	750.0
25.0%	quartile	750.0
10.0%		630.0
2.5%		300.0
0.5%		300.0
0.0%	minimum	300.0

Moments

Mean	877.36842
Std Dev	365.15578
Std Err Mean	37.464193
upper 95% Mean	951.75445
lower 95% Mean	802.98239
N	95

Feeling abnormal: there were 12 adverse event of feeling abnormal found in three of the clinical pharmacology studies. the majority, 9 of 12 were in study VRX-RET-E22-103.

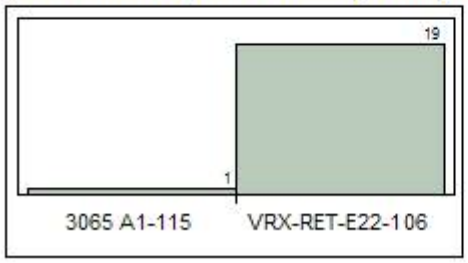
Within study E22-103 the 9 “feeling abnormal” adverse events were reported by 4 (10%) of subjects. The median dose at time of adverse events was 600mg with a mean of 678mg, a maximum of 1000mg and a minimum of 450mg. The verbatim term for all 9 reports was “floating sensation”

Feeling of Relaxation: there were 4 adverse events of “feeling of relaxation”, one event occurring in each of 4 studies, 3065A1- 103, 3065A1- 110, 3065A1- 123, VRX-RET-E22-103.

Thinking abnormal: there was one instance of “thinking abnormal” in study E22-106. The corresponding verbatim term was abnormal thoughts. The dose of ezogabine at the time of the event was 900mg/day.

Hallucination: there were 20 instances of “hallucination” in the integrated clinical pharmacology studies, 19 of these occurred in study VRX-RET-E22-106, and 1 in study 3065A1-115, figure 30. The 19 AEs of hallucination in study 106 were reported by 6 patients. 6 of the 19 verbatim terms were “saw images while eyes closed”, 1 was “saw images while half asleep” and the remaining 12 verbatim terms were “hallucination”. These 6 patients represent 15% of the ezogabine treated group. The median dose at AE onset was 750mg, with a mean of 721mg, a maximum dose of 1650mg and a minimum of 300mg. The dose distribution is seen in figure 31.

Figure 30 Hallucination, distribution by study



Distributions

Hallucinaton, distribution by study

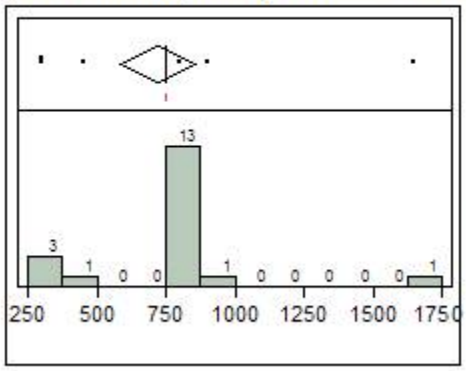
Frequencies

Level	Count	Prob
3065 A1-115	1	0.05000
VRX-RET-E22-106	19	0.95000
Total	20	1.00000

N Missing 0

2 Levels

Figure 31 EZO dose distribution for AE "hallucination" in study E22-106



Distributions

Hallucination, Study 106 dose distribution

Quantiles

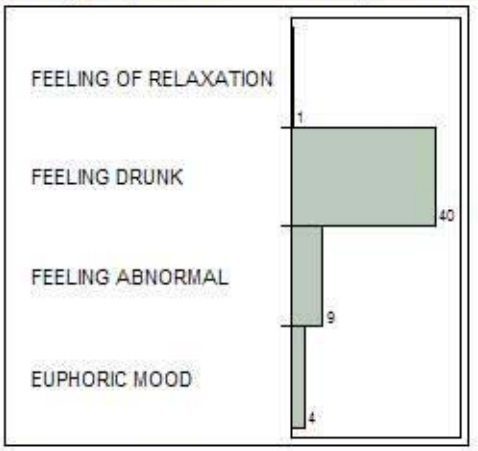
100.0%	maximum	1650.0
99.5%		1650.0
97.5%		1650.0
90.0%		900.0
75.0%	quartile	750.0
50.0%	median	750.0
25.0%	quartile	750.0
10.0%		300.0
2.5%		300.0
0.5%		300.0
0.0%	minimum	300.0

Moments

Mean	721.05263
Std Dev	290.26606
Std Err Mean	66.591601
upper 95% Mean	860.95639
lower 95% Mean	581.14887
N	19

<u>Inappropriate affect:</u> there was no result in the integrated pharmacology studies when seeking the AE, preferred term "inappropriate affect"

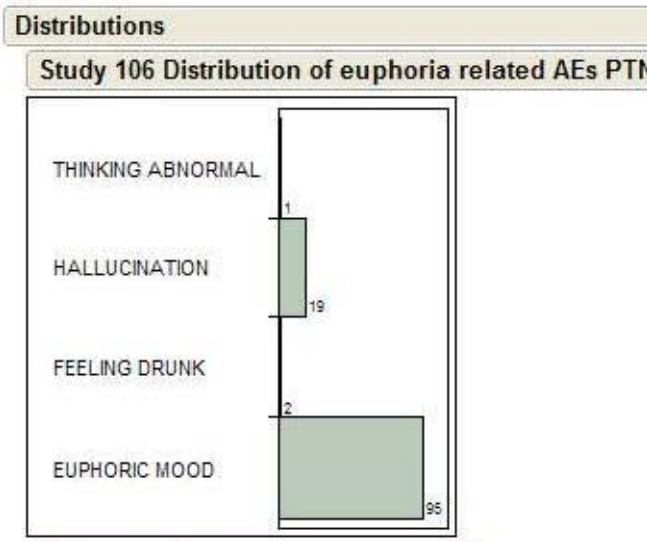
Figure 32 Distribution of euphoria related terms (PTs) in studies 103 & 106



Frequencies

Level	Count	Prob
EUPHORIC MOOD	4	0.07407
FEELING ABNORMAL	9	0.16667
FEELING DRUNK	40	0.74074
FEELING OF RELAXATION	1	0.01852
Total	54	1.00000

N Missing 0
4 Levels

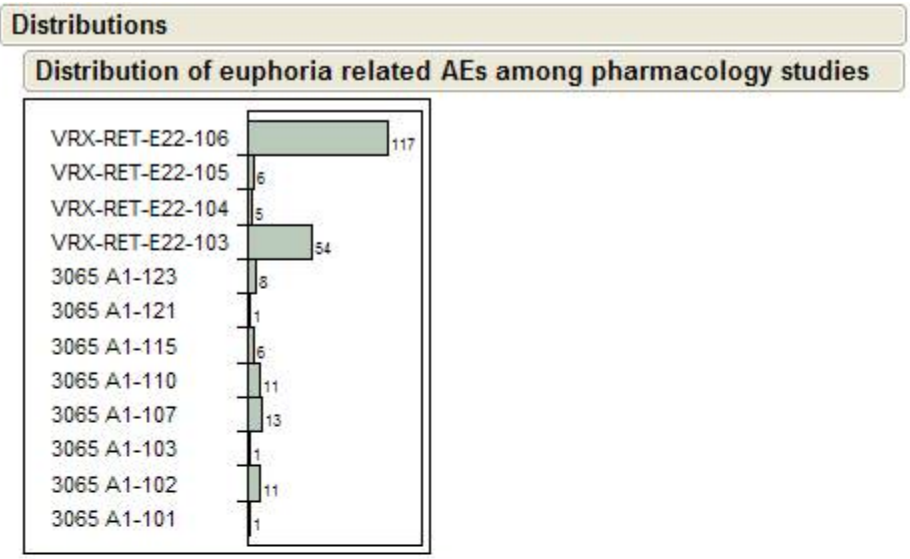


Frequencies

Level	Count	Prob
EUPHORIC MOOD	95	0.81197
FEELING DRUNK	2	0.01709
HALLUCINATION	19	0.16239
THINKING ABNORMAL	1	0.00855
Total	117	1.00000

N Missing 0
4 Levels

Figure 33 Distribution of euphoria related AEs in pharmacology studies



Frequencies

Level	Count	Prob
3065 A1-101	1	0.00427
3065 A1-102	11	0.04701
3065 A1-103	1	0.00427
3065 A1-107	13	0.05556
3065 A1-110	11	0.04701
3065 A1-115	6	0.02564
3065 A1-121	1	0.00427
3065 A1-123	8	0.03419
VRX-RET-E22-103	54	0.23077
VRX-RET-E22-104	5	0.02137
VRX-RET-E22-105	6	0.02564
VRX-RET-E22-106	117	0.50000
Total	234	1.00000

N Missing 0
12 Levels

Reviewer Comment: In their 8 factor analysis of potential need for scheduling the sponsor provides a robust argument that ezogabine be approved for marketing without CSA scheduling. This argument is supported by the mechanism of action which is to open neuronal KCNQ potassium channels. Potassium channel action is not a recognized ligand for abuse related agents, however the sponsor also notes that in vitro preclinical studies indicate that ezogabine has the potential to modulate gamma-aminobutyric acid (GABA) mediated neurotransmission although at concentrations greater than those required for the target potassium channel actions. The sponsor also emphasizes subjective effects similar to levetiracetam but also notes in the human abuse potential study, the incidence of euphoric mood was similar to alprazolam but lower then levetiracetam. The incidence of euphoric mood similar to alprazolam points to some possibility to act as a drug with abuse potential and the prospective of action on GABA neurotransmission offers a mechanism for this behavior.

Review of euphoria related terms in the pivotal clinical trials (RCTs) identifies 20 ezogabine treated patients and one placebo patient who has an AE congruent with one of the euphoria related terms panel. This represents 2.5% of the ezogabine treated cohort and 0.2% of the placebo population. If only those euphoria related terms with the least ambiguity are retained, euphoric mood and feeling drunk, the percentage of ezogabine treated patients' declines to 11/813 or 1.4%. I have a concern about the validity of two of the events in ezogabine patients where the verbatim terms "euphonia" are mapped to the PT "euphoria". It is unclear if euphonia is a misspelling for euphoria or is completely mismatched to the PT. Removal of these two questionable euphoria terms then further reduces the occurrence in the ezogabine treatment patients to 1.1%. The euphoria cases are strengthened somewhat by the two inappropriate affect preferred terms, these are mapped to the verbatim terms laughter. This increases the unambiguous euphoria related AEs in the ezogabine population to 1.4% vs 0.2% in placebo.

Review of the integrated pharmacology studies identifies 234 occurrences of terms contained in the euphoria panel (of terms provided by CSS). These occur in 61 patients. The most common term is "euphoric mood" which occurs in 149 instances followed by "feeling drunk" in 47 instances. The data also reveal that 171 of the 234 events are produced by only 2 of the 21 pharmacology studies, figure 33. The two studies are VRX-RET-E22-103 and VRX-RET-E22-106, subsequently to be identified as study 103 and 106. These 171 events represent 73% of all reported euphoria related events in the pharmacology studies and are reported by 38 subjects. These 38 subjects represent 62% of the 61 subjects who reported euphoria related adverse events in any of the integrated pharmacology studies. These 61 subjects who reported euphoria related AEs represent 13% of the 475 total population of subjects who received ezogabine in the pharmacology studies. This 2 study spike in the reporting of euphoria related events stands out with even greater contrast when seen on the background of 21 pharmacology studies with a total of 475 subjects participating. The integrated pharmacology studies also have a noticeable higher occurrence of euphoria related AEs compared to the pivotal controlled trials, 13% vs 2.5%. This difference is likely due to titration rate. These studies had rapid titration rates compared to the pivotal controlled trials, double (2x) the rate in study 103 and almost four times (4x) the rate in study 106. The predominant euphoria related AE in study 103 was "feeling drunk" (74%) and the predominant euphoria related AE in study 106 was euphoric mood, 81%, figure 32 above. The reason for the strong divergence between the choices of euphoria related terms between the studies is unclear.

9.5 Human Abuse Potential Study (VRX-RET-E22-108)

Title: A Randomized, Double-Blind, Placebo- and Active-Controlled Crossover Study to Evaluate the Abuse Potential of Ezogabine in Recreational Polydrug Users.

This was a randomized, double-blind, placebo- and active comparator-controlled single dose crossover study. Subjects received single doses of placebo and alprazolam 2 mg

on 2 consecutive days during an initial Qualification Phase. Subjects able to sufficiently distinguish placebo from alprazolam during the Qualification Phase, were randomized to the Treatment Phase to receive single oral doses of the following 7 treatments: Ezogabine 300 mg, Ezogabine 600 mg, Ezogabine 900 mg or placebo, Alprazolam 1.5mg, Alprazolam 3 mg, Levetiracetam 4000 mg, and Placebo. The treatments were separated by a washout interval of 7 days.

Subjects were healthy male and females between 18 and 55 years of age who were recreational polydrug users with a history of CNS depressant use. CNS depressant use was defined as a minimum of 10 lifetime recreational experiences with CNS depressants (e.g., benzodiazepines, barbiturates, flunitrazepam, zopiclone, zolpidem, cannabis, gammahydroxy butyric acid [GHB]). Thirty-five subjects were planned to be enrolled in this study with the intent to have 28 completers.

The primary pharmacodynamic variables were: Visual Analog Scales (VASs): Drug Liking ("at this moment"), Overall Drug Liking, and Take Drug Again and Addiction Research Center Inventory (ARCI): Morphine Benzedrine Group (MBG)

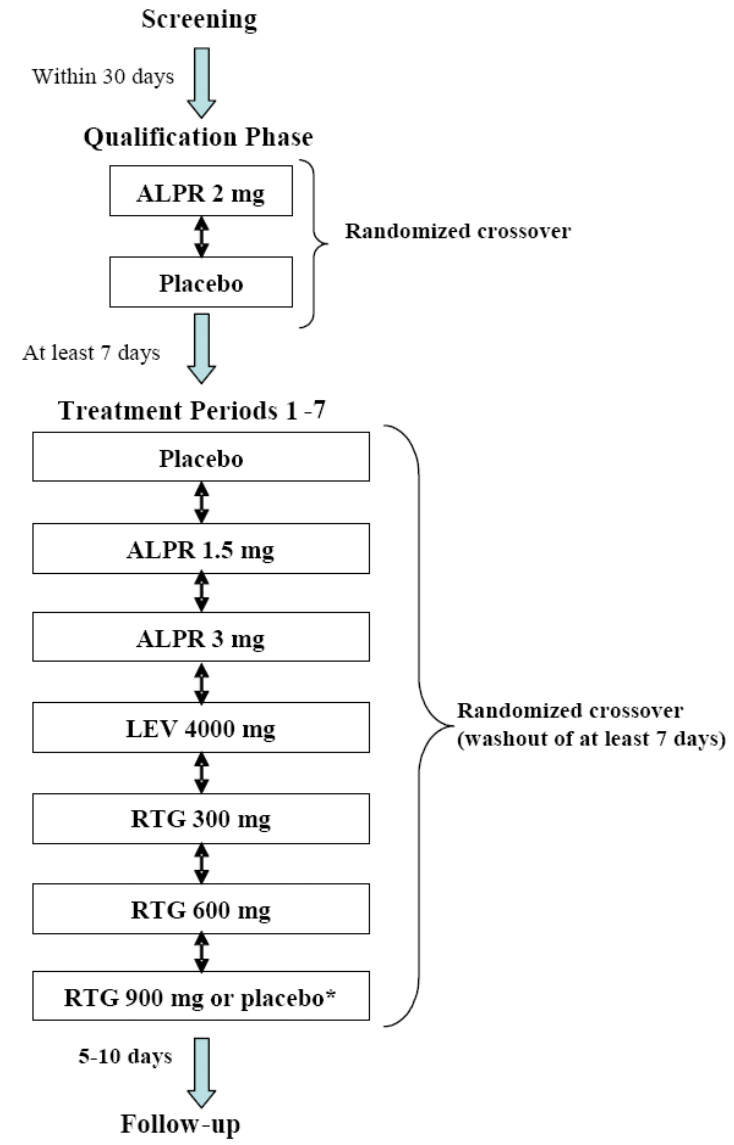
Secondary pharmacodynamic variables were: Subjective Drug Value (SDV), visual analog scales rating (VAS) "high", "good drug effect", "any drug effect", " bad drug effect", "alertness/drowsiness", "dizziness", "floating", "pleasant mental/Physical state", "color brighter", "sounds louder", and "drug similarity" also ARCI for pentobarbital cholopromazine alcohol group (PCAG), lysergic acid diethylamide (LSD) and amphetamine, benzedrine group (BG).

Neurocognitive measures were also performed including: choice reaction time, motor reaction time, recognition reaction time, total reaction time, and percent correct responses. A divided attention test was performed including mean response hit latency, mean % over road, mean greatest distance from center of road, mean root mean square distance and % target hits.

In addition to standard descriptive statistics and graphical presentations, the mean maximum effect (Emax), mean minimum effect (Emin), and time-weighted means (TWmean) of all variables were analyzed using a standard mixed-effect model for a crossover study. The following contrasts were tested:

- Each dose of alprazolam compared to placebo
- Each dose of ezogabine compared to placebo
- Levetiracetam 4000 mg compared to placebo
- Each dose of ezogabine compared to each dose of alprazolam
- Each dose of ezogabine compared to levetiracetam 4000 mg

Figure 34 Schematic of Human Abuse Potential Study Design (VRX-RET-E22-108)



* 900 mg always given after 600 mg; placebo if 600 mg not tolerated
ALP=alprazolam; LEV=levetiracetam; RTG=retigabine

Disposition and Demographics

Thirty-six qualified healthy recreational drug using subjects were randomized to the Treatment Phase and received at least one dose of study drug. Twenty-six (72.2%) subjects completed the study, had no major protocol violations, and were included in the pharmacodynamic analysis population. Based on an unexpected serious adverse event (SAE) experienced by one subject administered 900 mg ezogabine (Subject 9077; nonfatal, spontaneously resolving asystole reported as a cardiac arrest), it was concluded that all subsequent subjects should receive placebo instead of 900 mg

ezogabine, independent of the individual subject's tolerability of ezogabine 600 mg. Therefore, only 6 subjects received the 900 mg ezogabine dose, of whom 3 (8.3%) completed the study and were included in the pharmacodynamic analysis population.

Recreational Polydrug Use Inclusion Criteria

Polydrug use with a history of CNS depressant use, defined as 10 lifetime occasions of non-medical use of drugs with depressant/sedative properties (e.g., benzodiazepines, barbiturates, gamma hydroxybutyrate (GHB), flunitrazepam, zopiclone, zolpidem, cannabis, etc.) and at least one non-medical use in the past year. Polydrug use was defined as non-medical use of more than one class of drug in the past year (i.e., in addition to depressant use, use on at least one occasion in the past year of another class of recreational drug, such as opioids, hallucinogens, dissociatives, or stimulants).

Selection and Timing of Dose for Each Subject

In the Qualification Phase, subjects randomly received 2 mg alprazolam (4 × 0.5 mg) and placebo to match alprazolam orally, each separated by 24 hours between dosing. In the Treatment Phase, subjects were randomized to a treatment sequence in which they received one of the following treatments per treatment period in double-blinded fashion: placebo, alprazolam 1.5 mg, alprazolam 3 mg, levetiracetam 4000 mg, ezogabine 300 mg, ezogabine 600 mg, and ezogabine 900 mg or placebo. The treatment sequences were partially fixed such that no subject would receive the 900 mg dose of ezogabine prior to having received and tolerated the 600 mg dose. To maintain blinding, the number of tablets and capsules administered at each treatment period was identical (i.e., 23 tablets and capsules total).

Qualification phase of Abuse Potential Study 108

Dosing Sequence	**Qualification Day 1**	**Qualification Day 2**
A	Alprazolam 2 mg (4 × 0.5 mg tablets)	Placebo (4 tablets)
B	Placebo (4 tablets)	Alprazolam 2 mg (4 × 0.5 mg tablets)

Table 126 Treatment Sequence for Qualifying Period

Unblinding and data review occurred after each qualification cohort. For a subject to be eligible for the Treatment Phase, they must have shown the following:

1. A peak score in response to alprazolam at least 10% greater than that of placebo on the Drug Liking Visual Analogue Scale (VAS), Overall Drug Liking VAS, Take Drug Again VAS, and the Addiction Research Center Inventory (ARCI) Morphine Benzedrine Group (MBG).
2. Responses consistent with the known pharmacologic effects of alprazolam and placebo on the 6 measures listed in 1, as judged by the investigator or designee.

3. The ability to tolerate alprazolam 2 mg, as judged by the investigator or designated physician based on available safety data.
4. General behavior suggestive that they could successfully complete the study, as judged by the clinic staff.

If eligible, subjects proceeded to the Treatment Phase following an interval of at least 7 days before dosing (i.e., at least 7 days between Day 2 dosing in the Qualification Phase and Day 1 of the first treatment period).

Treatment Phase of Study

Treatment A:	Placebo
Treatment B:	Alprazolam 1.5 mg
Treatment C:	Alprazolam 3 mg
Treatment D:	Levetiracetam 4000 mg
Treatment E:	Ezogabine 300 mg
Treatment F:	Ezogabine 600 mg
Treatment G:	Ezogabine 900 mg or placebo

Table 127 Drug administration steps in treatment phase

The 7 treatment periods were separated by a minimum of 7 days between dosing. The assessments described in this section were performed during each treatment period.

Subjects reported to the clinic on the afternoon prior to dosing (Day –1) at each treatment period. On admission to the clinic, subjects underwent the following assessments: review of changes in their medical history and concomitant medications; review of their ongoing eligibility criteria; symptom-directed brief physical exam, if necessary (according to the judgment of the investigator or designee); 12-lead ECG; vital signs measurements (heart rate, blood pressure, oral temperature, and respiratory rate); clinical laboratory tests (hematology, chemistry, urinalysis); urine drug screen; breath alcohol test; serum pregnancy test (female subjects only); pharmacodynamic practice session; review of any AEs; and a pharmacodynamic practice session.

Subjects received one of the treatments specified in table 127 at each of the 7 treatment periods (one per period). The following assessments were conducted during each treatment period, figure 35.

Assessment/Procedure	Time Points
Randomization	Treatment period 1 only; predose on Day –1 or Day 1, depending on the availability of eligibility results
Pharmacodynamic refresher	Approximately 1 hour predose (prior to the baseline assessments)
Study Drug Administration	Day 1 with 250 mL of non-carbonated water, plus additional increments of 50 mL each, as needed
Vital signs	Predose and 0.5, 1, 2, 3, 4, 6, 8, 12, and 24 hours postdose. Oral temperature was assessed at predose only.
VASs[a]	Predose and 0.5, 1, 2, 3, 4, 6, 8, 12, and 24 hours postdose
ARCI	Predose and 0.5, 1, 2, 3, 4, 6, 8, 12, and 24 hours postdose
CRT and DA	Predose and 1, 3, 6, 12, and 24 hours postdose
Overall Drug Liking, Take Drug Again VAS and SDV	6, 12, and 24 hours postdose
Drug Similarity VASs	12 and 24 hours postdose
Pharmacokinetic Sampling	Predose and 1.5, 3.5, 6.5, 11.5, and 23.5 hours postdose
12-lead ECG	2.5 and 6.5 hours postdose
Continuous cardiac telemetry	Predose to at least 8 hours postdose (longer if clinically indicated)
AEs	Collected and recorded throughout the study; however, AEs were also elicited using a non-leading question at predose and 2, 4, 8, 12, and 24 hours postdose

AE = Adverse event; ARCI = Addiction Research Center Inventory; CRT = Choice Reaction Time; DA = Divided Attention test; ECG = Electrocardiogram; SDV = Subjective Drug Value; VAS = Visual analogue scale
a VASs that refer specifically to the study drug, such as Drug Liking, Good Drug Effects, etc., were not administered at predose

Figure 35 Timing and sequence of treatment period assessments; see Appendix 9.6 for assessment tools

Findings; Study (VRX-RET-E22-108)

Positive subjective effects and balance measures

A summary of pairwise comparisons on measures of the balance of effects (Drug Liking VAS [at this moment], Overall Drug Liking VAS, and Take Drug Again VAS) are summarized in table 128 - (measures of balance of effects). Analysis results on positive effects measures (ARCI MBG, SDV, High VAS, and Good Drug Effects VAS) are summarized in table 129 (Summary of Pairwise Comparisons for Positive Subjective Effects). These results demonstrated that:

- Compared with placebo both doses of alprazolam were associated with significant and persistent effects on all primary measures (ARCI MBG, and Drug Liking, Overall Drug Liking, and Take Drug Again VASs).

- Levetiracetam 4000 mg also showed significantly greater effects compared to placebo on most of these primary and secondary measures, other than SDV Emax.

- Ezogabine 300 mg Emax values were significantly greater than placebo on 3 of 4 primary measures (ARCI MBG, Drug Liking, and Take Drug Again VASs but not Overall Drug Liking VAS Emax). Consistent with the relatively short duration of effects, ezogabine 300 mg was not significantly different from placebo on TWmean for Good Drug Effects VAS, High VAS and SDV. Ezogabine 600 mg was associated with significantly greater effects compared to placebo on both Emax and TWmean values for these variables.

- On most of these measures, ezogabine was not significantly different from either alprazolam or levetiracetam.

Table 128 Summary of Pairwise Comparisons for Measures of Balance of Effects

Contrast	Drug Liking VAS Emax		Overall Drug Liking VAS Emax		Take Drug Again VAS Emax		Take Drug Again VAS TWmean	
	Δ	P	Δ	P	Δ	P	Δ	P
Alprazolam vs. Placebo								
ALP 1.5 – PBO	20.5	<.001*	14.4	0.005*	30.3	<.001*	32.1	<.001*
ALP 3 – PBO	25.3	<.001*	18.8	<.001*	32.0	<.001*	35.8	<.001*
Levetiracetam vs. Placebo								
LTC 4000 – PBO	21.0	<.001*	12.4	0.043	25.9	0.005*	28.5	0.001*
Retigabine vs. Placebo								
RTG 300 – PBO	17.0	0.001*	9.9	0.112	21.1	0.023	24.7	0.006*
RTG 600 – PBO	22.9	<.001*	17.5	0.002*	33.2	<.001*	37.7	<.001*
Retigabine vs. Alprazolam								
RTG 300 – ALP 1.5	-3.4	0.473	-4.5	0.436	-9.2	0.288	-7.5	0.369
RTG 300 – ALP 3	-8.2	0.055	-8.9	0.087	-10.9	0.159	-11.1	0.137
RTG 600 – ALP 1.5	2.5	0.574	3.0	0.572	2.9	0.718	5.6	0.471
RTG 600 – ALP 3	-2.3	0.569	-1.4	0.784	1.1	0.881	1.9	0.792
Retigabine vs. Levetiracetam								
RTG 300 – LTC 4000	-4.0	0.338	-2.5	0.622	-4.8	0.524	-3.9	0.592
RTG 600 – LTC 4000	1.9	0.644	5.1	0.319	7.3	0.336	9.2	0.211

Δ = Least square mean of difference; ALP 1.5 = Alprazolam 1.5 mg; ALP 3 = Alprazolam 3 mg; Emax = mean maximum effect; LTC 4000 = Levetiracetam 4000 mg; P = p-value; PBO = Placebo; RTG 300 = Retigabine 300 mg; RTG 600 = Retigabine 600 mg; TWmean = Time-weighted mean (over 24 hours); VAS = Visual analogue scale.

* Significant difference (p<0.05)

Table Notes: There were no significant overall treatment effects for: Drug Liking VAS Emin and TWmean, Overall Drug Liking Emin and TWmean and therefore the data are not presented in this table.

There were no significant differences for alprazolam vs. placebo for: Pleasant Mental or Physical State Emax or TWmean values and therefore the data are not presented in this table as the endpoints could not be validated.

Pleasant Mental and Physical State VASs are shown in the negative effects table since the direction of the effect was towards less pleasant state, or more "unpleasant" state (i.e., lower Emin = greater feeling "unpleasant"; higher Emin = less feeling "unpleasant")

Least squares mean differences (Δ) were estimated from a linear mixed-effect ANCOVA with treatment sequence, period and treatment as fixed effects, baseline (predose) value as a covariate, and subject within treatment sequence as a random effect.

Table 129 Summary of Pairwise Comparisons for Positive Subjective Effects

Contrast	ARCI MBG Emax		SDV Emax		SDV TWmean		Good Effects VAS Emax		Good Effects VAS TWmean		High VAS Emax		High VAS TWmean	
	Δ	P	Δ	P	Δ	P	Δ	P	Δ	P	Δ	P	Δ	P
Alprazolam vs. Placebo														
ALP 1.5 – PBO	4.5	<.001*	12.1	<.001*	10.17	0.002*	44.1	<.001*	10.0	0.009*	55.8	<.001*	13.0	<.001*
ALP 3 – PBO	5.3	<.001*	15.5	<.001*	10.18	0.004*	50.9	<.001*	21.1	<.001*	66.8	<.001*	23.6	<.001*
Levetiracetam vs. Placebo														
LTC 4000 – PBO	3.6	0.002*	8.0	0.059	6.25	0.107	44.9	<.001*	13.9	0.002*	56.1	<.001*	11.8	<.001*
Retigabine vs. Placebo														
RTG 300 – PBO	3.5	0.004*	9.3	0.032*	7.25	0.068	39.0	<.001*	4.5	0.329	45.6	<.001*	5.7	0.079
RTG 600 – PBO	4.8	<.001*	10.1	0.009*	9.11	0.011*	50.4	<.001*	10.5	0.011*	60.8	<.001*	6.8	0.019*
Retigabine vs. Alprazolam														
RTG 300 – ALP 1.5	-1.0	0.352	-2.9	0.476	-2.92	0.430	-5.1	0.463	-5.5	0.205	-10.2	0.170	-7.3	0.017*
RTG 300 – ALP 3	-1.8	0.069	-6.2	0.087	-2.93	0.377	-11.8	0.059	-16.6	<.001*	-21.2	0.002*	-18.0	<.001*
RTG 600 – ALP 1.5	0.3	0.790	-2.1	0.579	-1.06	0.757	6.3	0.331	0.6	0.887	5.0	0.463	-6.2	0.027*
RTG 600 – ALP 3	-0.5	0.582	-5.4	0.122	-1.07	0.738	-0.5	0.938	-10.6	0.006*	-6.0	0.349	-16.9	<.001*
Retigabine vs. Levetiracetam														
RTG 300 – LTC 4000	-0.1	0.937	1.3	0.702	1.00	0.754	-5.9	0.327	-9.4	0.012*	-10.5	0.104	-6.1	0.020*
RTG 600 – LTC 4000	1.2	0.206	2.1	0.545	2.86	0.378	5.5	0.373	-3.4	0.369	4.7	0.463	-5.0	0.059

Δ = Least squares mean of difference; ALP 1.5 = Alprazolam 1.5 mg; ALP 3 = Alprazolam 3 mg; ARCI = Addiction Research Center Inventory; Emax = mean maximum effect; LTC 4000 = Levetiracetam 4000 mg; MBG = Morphine Benzedrine Group; P = p-value; PBO = Placebo; RTG 300 = Retigabine 300 mg; RTG 600 = Retigabine 600 mg; SDV = Subjective Drug Value; TWmean = Time-weighted mean (over 24 hours); VAS = Visual analogue scale.
* Significant difference (p<0.05)
Table Notes: There were no significant overall treatment effects for: ARCI MBG TWmean and therefore the data are not shown in this table.
Least squares mean differences (Δ) were estimated from a linear mixed-effect ANCOVA with treatment sequence, period and treatment as fixed effects, baseline (pre-dose) value as a covariate, and subject within treatment sequence as a random effect.

Negative subjective Effects

A summary of pairwise comparisons for ezogabine negative effects (Bad Effects VAS, Pleasant Mental/Physical State VASs [Emin], ARCI LSD [dysphoria]) is shown in table 130 (Summary of Pairwise Comparisons for Negative Subjective Effects). These results demonstrated that:

- Alprazolam 3 mg was associated with the greatest negative effects; these were significantly greater than placebo on Bad Drug Effects (Emax only), and ARCI LSD. In addition, Emin values for Pleasant Mental and Physical State VASs showed significant negative effects of alprazolam 3 mg (i.e., lower Emin values or greater “unpleasant” state).

- Levetiracetam 4000 mg showed significantly higher Bad Drug Effects VAS Emax and lower Pleasant Mental/Physical State VAS Emin values versus placebo.

- Ezogabine 300 mg showed significantly greater negative effects compared to placebo on ARCI LSD Emax, while ezogabine 600 mg also showed significantly greater effects on Bad Drug Effects VAS Emax and Pleasant Physical State Emin.

- Ezogabine showed no significant differences in negative effects compared to alprazolam 1.5 mg. Ezogabine was associated with significantly fewer negative

effects compared to alprazolam 3 mg on most measures although ezogabine 600 mg was not different from alprazolam 3 mg on ARCI LSD Emax or TWmean. ARCI LSD Emax was significantly greater for ezogabine 600 mg compared to levetiracetam 4000 mg.

Table 130 Summary of Pairwise Comparisons for Negative Subjective Effects

Contrast	Bad Drug Effects Emax		ARCI LSD Emax		ARCI LSD TWmean		Pleasant Mental State VAS Emin[a]		Pleasant Physical State VAS Emin[a]	
	Δ	P	Δ	P	Δ	P	Δ	P	Δ	P
Alprazolam vs. Placebo										
ALP 1.5 – PBO	21.4	0.004*	2.3	<.001*	0.22	0.119	-13.1	0.005*	-14.1	0.002*
ALP 3 – PBO	46.0	<.001*	3.0	<.001*	0.51	0.001*	-14.4	0.004*	-19.8	<.001*
Levetiracetam vs. Placebo										
LTC 4000 – PBO	24.1	0.006*	1.3	0.055	0.24	0.145	-11.2	0.040*	-12.7	0.020*
Retigabine vs. Placebo										
RTG 300 – PBO	17.4	0.051	1.5	0.032*	0.09	0.602	-4.3	0.441	-8.5	0.126
RTG 600 – PBO	31.0	<.001*	2.8	<.001*	0.25	0.093	-5.3	0.288	-9.8	0.049*
Retigabine vs. Alprazolam										
RTG 300 – ALP 1.5	-3.9	0.636	-0.7	0.255	-0.13	0.416	8.8	0.092	5.6	0.281
RTG 300 – ALP 3	-28.6	<.001*	-1.4	0.015*	-0.42	0.004*	10.1	0.031*	11.3	0.016*
RTG 600 – ALP 1.5	9.6	0.211	0.5	0.396	0.04	0.799	7.8	0.106	4.3	0.371
RTG 600 – ALP 3	-15.0	0.038*	-0.2	0.746	-0.26	0.067	9.1	0.044*	10.0	0.026*
Retigabine vs. Levetiracetam										
RTG 300 – LTC 4000	-6.6	0.357	0.2	0.729	-0.15	0.265	6.9	0.124	4.2	0.344
RTG 600 – LTC 4000	6.9	0.343	1.5	0.012*	0.01	0.923	5.9	0.193	2.9	0.519

Δ = Least squares mean of difference; ALP 1.5 = Alprazolam 1.5 mg; ALP 3 = Alprazolam 3 mg; ARCI = Addiction Research Center Inventory; Emax = mean maximum effect; LTC 4000 = Levetiracetam 4000 mg; MBG = Morphine Benzedrine Group; P = p-value; PBO = Placebo; RTG 300 = Retigabine 300 mg; RTG 600 = Retigabine 600 mg; TWmean = Time-weighted mean (over 24 hours); VAS = Visual analogue scale.
* Significant difference (p<0.05)
[a] Although statistical differences were observed the size of the differences was small and probably not clinically relevant.
Table Notes: For Pleasant Mental and Physical State VASs, lower Emin = greater feeling "unpleasant"; higher Emin = less feeling "unpleasant".
There were no significant overall treatment effects (or no significant effect of the positive control) for: Bad Effects TWmean.
Least squares mean differences (Δ) were estimated from a linear mixed-effect ANCOVA with treatment sequence, period and treatment as fixed effects, baseline (pre-dose) value as a covariate, and subject within treatment sequence as a random effect.

Reviewer Comment: Similar to the examination of abuse related terms in the phase I and pivotal controlled trials where euphoria related terms were given the greatest weight, the reviewer places greatest weight on the positive subjective effects in the abuse potential study. The sedative effects are less specific because of their commonality in anticonvulsant agents thus more difficult terms from which to extract a signal. The negative subjective effects are informative by the inconsistent ezogabine differentiation from the positive control, alprazolam and also from levetiracetam. This implies that in the event there is a signal for abuse potential negative subjective effects would not neutralized abuse potential.

Table 128–measures of balance of effects- reveals that ezogabine 600mg is found more favorable than placebo on all measures which favor taking the drug. It is noteworthy that levetiracetam 4000mg reveals similar findings compared to placebo. In the direct comparison between ezogabine 600mg and levetiracetam 4000mg there was no separation between the two drugs. In the analysis of positive subjective effects, table 129 (summary of pairwise comparisons for positive subjective effects) ezogabine

600mg is significantly favored over placebo in all measures and ezogabine 300mg is significantly separated from placebo in 4 of 7 measures. When ezogabine 300mg and 600mg are compared to alprazolam 1.5mg and 3mg alprazolam is significantly favored over ezogabine on only 7 of 28 measures. In this series of comparisons alprazolam is favored over ezogabine at all doses for the measure of “high”. When ezogabine was compared directly to levetiracetam, the latter was favored significantly over ezogabine 300mg on measures of “good effects” and “high”. There was no difference between ezogabine 600mg and levetiracetam 4000mg on any measures of positive subjective effects.

Examination of negative subjective effects reveals placebo superior to ezogabine 300mg on the ARCI LSD question group. Ezogabine 600mg is found unfavorable compared to placebo on the experience of “bad drug effects”, the ARCI, LSD questions, and “pleasant physical state”.

In conclusion the occurrence of euphoria related adverse effects exclusively in the ezogabine treatment cohort of the pivotal controlled trials, in addition to a spike of euphoria related adverse effects in those phase I trials with the most rapid titration rate in healthy subjects and the findings of “drug liking” and positive subjective effects in excess over placebo indicate a signal for abuse potential. More refined quantification of the signal and determination if this signal rises to the threshold necessary for ezogabine to be prescribed on a scheduled basis will await evaluation by the CSS.

9.6 Abuse Potential Study (VRX-RET-E22-108) Assessment Scales

Figure 36 Individual Visual Analogue Scales in Abuse potential study

Scale	Excluded predose	Bipolar*	Domain	Question text	Response anchors
Subjective Effects					
Good Drug Effects	Yes		Positive	I can feel good drug effects	0: Definitely not 100: Definitely so
High			Positive	I am feeling high	
Bad Drug Effects	Yes		Negative	I can feel bad drug effects	
Any Drug Effects	Yes		Other effects	I can feel any drug effect	
Dizziness			Other effects	I am feeling dizzy	
Alertness/Drowsiness		Yes	Sedative/ Stimulant	My mental state is	0: Very drowsy 100: Very alert
Pleasant Mental State		Yes	Positive/ Negative	The feeling in my mind is…	0: Very unpleasant 100: Very pleasant
Pleasant Physical State		Yes	Positive/ Negative	The feeling in my body is…	
Drug Liking, Overall Drug Liking and Take Drug Again					
Drug Liking	Yes	Yes	Balance	At this moment, my liking for this drug is	0: Strong disliking 100: Strong liking
Overall Drug Liking	Yes	Yes	Balance	Overall, my liking for this drug is	0: Strong disliking 100: Strong liking
Take Drug Again	Yes		Balance	I would take this drug again	0: Definitely not 100: Definitely so
Perceptual/Dissociative Effects					
Floating			Other effects	I feel as if I am floating	0: Not at all 100: Very much
Colours brighter		Yes	Other effects	Colours around me seem…	0: Duller than usual 100: Brighter than usual
Sounds louder		Yes	Other effects	Sounds around me seem…	0: Quieter than usual 100: Louder than usual

* There was no response anchor marking '50' but on a bipolar scale this represented a neutral value

Figure 37 Visual Analogue Scale Representative Images

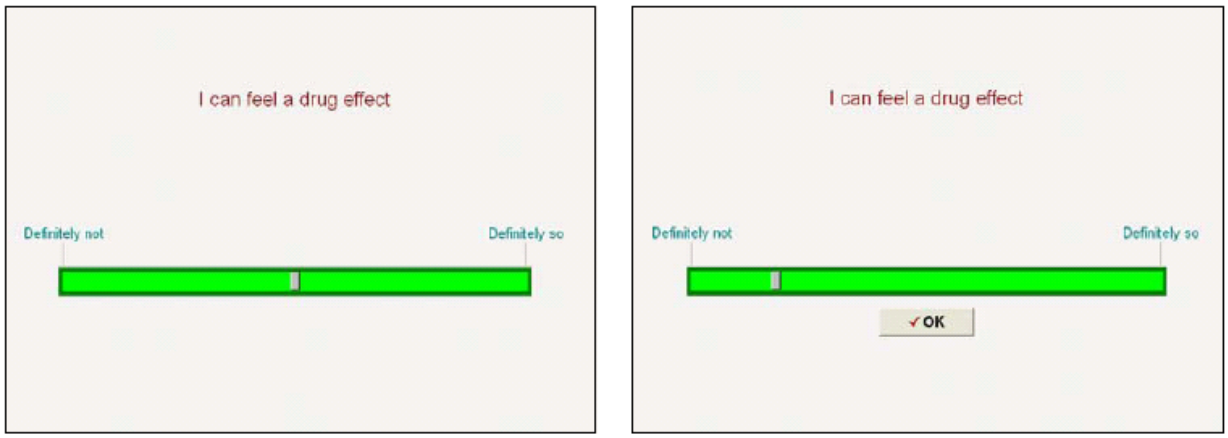


Figure 38 Drug Similarity Visual Analogue Scales

Question text	Response anchors
"How familiar was the effect of the drug you most recently received?"	0: Very unfamiliar 100: Very familiar
"How similar is the drug you most recently received to [drug name]?"*: • Phencyclidine (PCP) • Caffeine • Cocaine (including crack) • Codeine or morphine • Ecstasy (MDMA) • Heroin • Lysergic acid diethylamide (LSD) • Methadone • Nicotine • Placebo • D-amphetamine ("Speed") or methamphetamine • Pseudoephedrine (Sudafed) • THC (marijuana, cannabis, hash) • Halcion, Xanax™, or Valium™ • Ketamine ("Special K")	0: Not at all similar 100: Very similar

* Note that this list is not inclusive and was customized based on each subject's personal experience, reported at his or her Screening assessment (Appendix 16.2.4.4). The question was repeated for each of the drug names in the subject's list.

Figure 39 Subjective Drug Value Representative Images

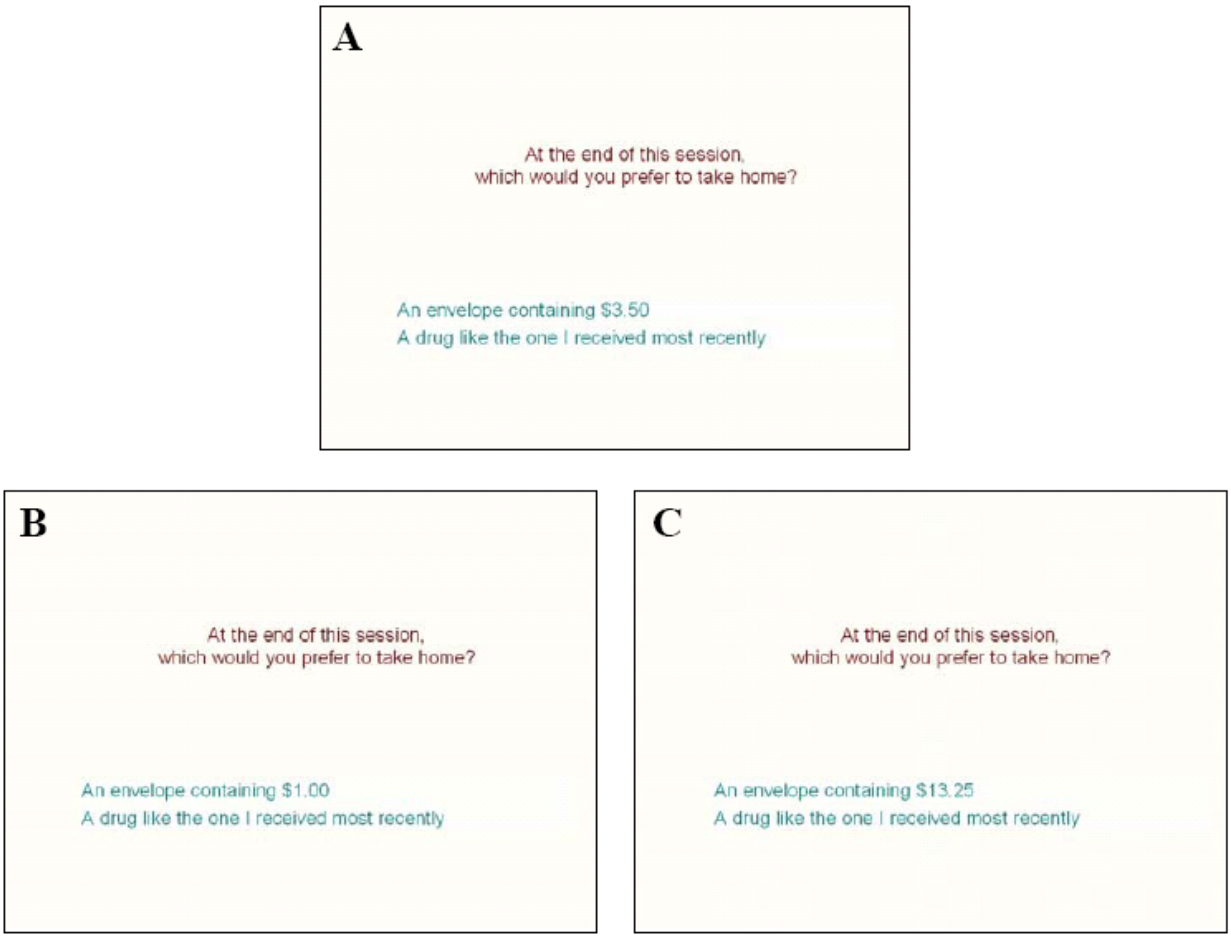


Figure 40 Questions Contributing to 5 ARCI Scales

Questions Contributing to 5 ARCI Scales	Scale				
	A	PCAG	MBG	BG	LSD
My speech is slurred		T			
I am not as active as usual		T			
I have a feeling of just dragging along rather than coasting		T			
I feel sluggish		T			
My head feels heavy		T			
I feel like avoiding people, although I usually do not feel this way		T			
I feel dizzy		T			
It seems harder than usual to move around		T			
I am moody		T			
People might say that I am a little dull today		T		F	
I feel drowsy		T			F
I am full of energy		F			
Today I say things in the easiest possible way			T		
Things around me seem more pleasing than usual			T		
I have a pleasant feeling in my stomach			T		
I feel I will lose the contentment that I have now			T		
I feel in complete harmony with the world and those about me			T		
I can completely appreciate what others are saying when I am in this mood			T		
I would be happy all the time if I felt as I feel now			T		
I feel so good that I know other people can tell it			T		
I feel as if something pleasant had just happened to me			T		
I would be happy all the time if I felt as I do now			T		F
I feel more clear headed than dreamy		F	T	T	
I feel as if I would be more popular with people today	T		T		
I feel a very pleasant emptiness	T		T		
My thoughts come more easily than usual	T		T	T	
I feel less discouraged than usual	T		T		
I am in the mood to talk about the feelings I have			T	T	
I feel more excited than dreamy	T	F			
Answering these questions is very easy today	T			T	
My memory seems sharper to me than usual	T			T	
I feel as if I could do these tests for hours*	T			T	
I feel very patient	T				F
Some parts of my body are tingling	T			T	T
I have a weird feeling	T				T
My movements seem faster than usual				T	
I have better control over myself than usual				T	
My movements seem slower than usual				F	
I find it hard to keep my mind on a task or job				F	
I don't feel like reading anything right now				F	
It seems I'm spending longer than I should on each of these questions					T
My hand feels clumsy					T
I notice my hand shakes when I do these tests*					T
I have a disturbance in my stomach					T
I have an increasing awareness of bodily sensations					T
I feel anxious and upset					T
I have unusual weakness of my muscles					T
A thrill has gone through me one or more times since I started this test		F			T
My movements are free, relaxed, and pleasurable					F

T = True item
F = False item
* - *item wording slightly modified for computer assessment*

Figure 41 Choice Reaction time Task

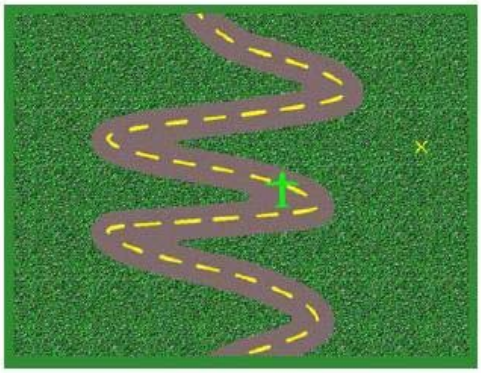
Choice Reaction Time (CRT) is a classic test of reaction time that was used to measure psychomotor performance. Subjects were instructed quickly to press buttons on a numeric keypad that corresponded spatially to the keys displayed on a screen image of that keypad.

The middle square was the "home" position (Figure 9-4A); using the index finger of the dominant hand, the subject was required to hold the central start button, until one of the outer boxes was illuminated (Figure 9-4B). The subject was to depress the corresponding response key as quickly as possible, at which time the illumination was terminated as feedback. After a response was made, the subject was required to return his or her finger to the home position and repress the central key. The test took approximately 2 to 3 minutes to complete.

The number and positions of the illuminated outer squares changed periodically throughout the test. The number of alternative choices increased over blocks of responses in each test cycle (from 4 to 8 choices).

The main outcome measures were the mean reaction times for the 50 stimuli: the Recognition Reaction Time (RRT, i.e., the time between stimulus onset and lifting of the finger from the start button) and the Motor Reaction Time (MRT, i.e., the time between lifting and depressing the response button). The Total Reaction Time (TRT) was the sum of the RRT and MRT. The accuracy of responses was also measured as percentage correct responses.

Figure 42 Divided Attention Task



The DA consisted of a manual tracking task with a visual target detection task. During testing, the subject was presented with the image of an airplane and a randomly curving road. As the road moved down the screen, the subject was to try to position the image of the airplane over the center of the road using a joystick. At random times during this process, a visual target briefly presented itself at random positions on the screen and immediately disappeared. The subject was to respond to the visual target as fast as possible by pressing a button on the joystick. A representative image of the airplane and screen is displayed in the figure above.

9.7 IND Safety report text, patient 03505 Persistent urinary retention.

Ezogabine Clinical Study Report

VRX-RET-E22-303: "A Multicenter, Open-Label, Long-Term, Safety, Tolerability and Efficacy of Ezogabine in Adult Epilepsy Patients With Partial-Onset Seizures (Extension of Study VRX-RET-E22-301)", (Valeant sponsored study, USA)

(b) (6): A report was received describing a 31- year-old Caucasian male (035-05 (b) (6)), enrolled in the above-referenced clinical trial, who experienced the medically-significant events of PSYCHOMOTOR AGITATION and URINARY RETENTION approximately 1 month after starting the open-label extension study. The patient was previously hospitalized on (b) (6) for psychomotor agitation, but this earlier event was considered resolved on (b) (6). The patient had an ultrasound in the emergency department which revealed 900 cc of urine retained in the bladder. Previously the patient had post-void residual of 120 cc but this was considered not clinically significant as no urinary symptoms were reported at most recent visit on (b) (6) The medical monitor instructed the patient to be emergently catheterized. The patient will be withdrawn from the study.

Medical history included hypertension, sleep apnea, vagal nerve stimulator implantation, gastroesophageal reflux disease and psychomotor agitation. Concomitant medications included carbamazepine, lamotrigine, pregabalin and pantoprazole.

(b) (6): Additional information received revealed the event of Psychomotor Agitation resolved on (b) (6). The patient completed tapering the study drug on (b) (6).

(b) (6): Additional information received revealed that the patient was evaluated by a urologist on (b) (6). A post void residual ultrasound performed noted that after instillation of 250 cc normal saline into the bladder the patient voided less than 50 cc. The patient was taught intermittent self catheterizations. The patient was seen again for follow-up on (b) (6) where a diagnosis of urinary retention of uncertain etiology was made. Urodynamic studies to assess the exact etiology have been planned.

(b) (6) through (b) (6): Additional information received revealed the patient had experienced approximately 18 hours of progressive urinary retention before seeking treatment in the emergency department of a community hospital. At the time the patient was agitated and in acute distress. After some difficulty, a Foley catheter was inserted and approximately 1200 cc of urine was evacuated from the bladder. The patient followed up with another urologist for urodynamic studies performed on (b) (6). The patient informed the urologist that four or five times a day, he would experience a "strong urge" to void but had difficulty
urinating. His urine stream would "end prematurely" and "sputter". The urodynamic study demonstrated normal bladder compliance, but no EMG activity during filling of the bladder. The patient experienced a sensation of fullness upon filling and no leak was present during cough or valsalva maneuvers. However, the patient was unable to void (voided volume was O ml, PVR was 882 ml. Detrusor contraction was not sustained. The findings were reported to be consistent with a neurogenic bladder. Subsequent plan included intermittent self catheterization, a trial of Flomax (tamsulosin), maintenance of a bladder log and follow-up in 6 weeks for a repeat PVR. On (b) (6), a CT scan of

the lumbar spine and pelvis with and without contrast revealed mild degenerative disc changes with mild dural sac indentation. No root sleeve involvement and no compression or mass was seen along the superior lumbar plexus and the superior aspect of the sacral plexus.

(b) (6): Additional information received revealed an unremarkable CT scan of the abdomen and pelvis performed on (b) (6). Specifically, the kidneys were without hydronephrosis, the ureters were not dilated, and the bladder was unremarkable. There was no evidence for renal stones.

(b) (6): Additional information received revealed the patient returned to the urology clinic for a follow up and was seen by a nurse practitioner. The patient continues on Flomax (tamsulosin) for treatment, which has helped, and has been keeping a bladder log. According to clinic notes, the patient "pushes and strains" to empty his bladder, voiding anywhere from 0 to 600 cc and catheterizing an average of 300 to 400 cc at a time. The patient reported self catheterizations up to four times daily. A post void residual in the office revealed 91 cc of residual urine.

(b) (6): A brief telephone conversation with the investigator on (b) (6) revealed that the patient reported improved symptoms in a conversation earlier that day. The patient reported the ability to spontaneously void and was self catheterizing less frequently than before. A voiding diary was thus requested from the patient on 3-Jun-2008, A voiding diary was received from the patient on (b) (6) covering a period from (b) (6). During the first week of the voiding diary, the patient documented spontaneous voids each time, but self catheterized 3 -4 times a day. The patient spontaneously voided an average of 313 cc (range: 100 to 500 ml while catheterizing an average of 344 cc (range: 100 to 650 ml per episode during this period. By the last week of the diary, the patient indicated 1-3 self catheterizations per day and averaged 340 cc (range: 100 to 700 ml per void versus 280 cc (range: 100 to 600 ml per catheterizations.

The investigator assessed the events as serious and probably related to the study medication. The sponsor assessed the event of psychomotor agitation as serious, unexpected and possibly related to the study medication and assessed the event of urinary retention as serious, expected and possibly related.

(b) (6): Additional information received from the site confirmed the patient began early tapering of study medication on (b) (6) and completed the tapering process on (b) (6). The patient's final study visit occurred on (b) (6) The Primary Investigator confirmed the patient was seen in the emergency department for the event of bladder retention, but was not admitted.

(b) (6) Additional information received from the Principal Investigator confirmed the site has been regularly contacting the patient to follow-up on the status of urinary retention. The site confirmed the event as ongoing.

(b) (6): Additional information received from the PI provided the diagnoses based on a Urodynamic Study, performed on (b) (6), as incomplete emptying of bladder and neurogenic bladder, with a marked decrease in sensation, increased capacity, and no contact ions of the study. The patient was prescribed Flomax (tamsulosin hydrochloride) and advised to continue keeping a bladder log. The patient was asked to follow-up in six weeks to recheck the PVR and review the bladder log. The PI confirmed the patient has been performing self catheterization multiple times daily.

The assessments of the PI and the Sponsor remained unchanged.

(b) (6): Additional information received from the PI confirmed the event of urinary retention is ongoing. The assessments of the PI and the Sponsor remained unchanged.

(b) (6): Additional information received from the PI confirmed the patient was stable, with continuing urinary retention, as of 14-0ct-2009. The PI assessed the event as recovered with sequelae.

The assessments of the PI and the Sponsor remained unchanged.

(b) (6): Additional information received from the PI confirmed the patient is stable with sequelae of self – catheterization

The assessments of the PI and the Sponsor remained unchanged.

B6. Relevant Tests/Laboratory Data – Continued

aspect of the sacral plexus.
(b) (6): CT of Abdomen/Pelvis was unremarkable without evidence for renal stones.
(b) (6) PVR revealed 91 cc of residual urine.

(b) (6): Urodynamic testing:
#1: Urethral cath inserted size 14FR: Post void residual volume: 400 mls
#2: Urethral cath inserted size 8FR: Post void residual volume: 900 mls; pressure flow study performed: unable to void mls

Rectal cath inserted
Filling phase fill rate: medium First urge at: 524 ml Capacity at: 882 ml
Compliance: Normal
EMG activity during filling phase: Silent

Abdominal leak point pressures (standing): at 250 ml
cough pabd: 104 cm H20 129 cm H20 203 cm H20 Result: Leak absent
Valsalva pabd: 107 cm H20 Result: Leak absent

Voiding Phase Study: Could not void for the study
Detrusor contraction: Not sustained

Voided volume: 0ml PVR: 882 ml
Voiding technique: Detrusor contraction
EMG activity during filling phase: Silent

Post void residuals:
(b) (6): 121 ml
0 ml
: 24 ml
0 ml

9.8 STUDY 3065A1-205: Summary of GCP Issues At Site Number 021 Sponsor Report

During the ezogabine clinical development program several changes in corporate sponsors have taken place for study 3065A1-205, which was completed in 2001. This study was originally sponsored and conducted by Wyeth. The rights to ezogabine were acquired by Valeant in 2005. Valeant subsequently obtained the Wyeth study records for the trial (including case report forms and electronic datasets).

In preparation for the marketing applications for ezogabine, contact with the Study 205 investigators was made to notify them of the planned submissions and to confirm the availability of source documentation. In addition, site visits were initiated at selected centers in order to verify appropriate record keeping and access to the study files. During the course of document review at one site (Site 021 where 20 patients were enrolled), multiple Good Clinical Practice (GCP) non-compliance issues were identified, relating to Principal Investigator oversight, informed consent procedures and study documentation. These issues had not been adequately corrected during the course of the study.
The site was subsequently revisited to conduct a more thorough quality control check and source data verification for the 20 patients enrolled. The following types of GCP issues were noted:

- deficient Informed Consent process i.e.:
    - evidence that the Informed Consent date for four subjects was changed to one day earlier than the date recorded in source documents in order to match the date of the first non-invasive screening study assessments (e.g., echocardiograms and electrocardiograms)
    - screening assessments (e.g., echocardiograms and electrocardiograms) conducted one day prior to obtaining Informed Consent for five subjects (in addition to the four above)
    - Informed Consent for two subjects not signed or dated

- date discrepancies between source documents, CRFs and vendor reports
- missing assessments including electrocardiograms, echocardiograms, Holter monitoring and laboratory assessments
- incomplete source documents including those for unscheduled visits and background
- AEDs
- random and minimal transcription errors for seizure diary data

9.9 AUA Symptom Index

The AUA SI consists of 7 questions, each rated on a scale of 0 to 5, for a total score range from 0 to 35. The AUA SI assesses symptoms of urinary frequency, urgency, and related effects. By convention, a score of 0 to 7 indicates mild symptoms (usually implying no need for any treatment), a score of 8 to 18 indicates moderate symptoms, and a score of 19 to 35 indicates severe symptoms[13].

13 Barry MJ, et al. (1992). The American Urological Association symptom index for benign prostatic hyperplasia. Journal of Urology, 148: 1549–1557.

AUA Symptom Index							
		Not at all	Less than 1 time in 5	Less than half the time	About half the time	More than half the time	Almost always
1.	During the last month or so, how often have you had a sensation of not emptying your bladder completely after you finished urinating?	0	1	2	3	4	5
2.	During the last month or so, how often have you had to urinate again less than 2 hours after you finished urinating?	0	1	2	3	4	5
3.	During the last month or so, how often have you found you stopped and started again several times when you urinated?	0	1	2	3	4	5
4.	During the last month or so, how often have you found it difficult to postpone urination?	0	1	2	3	4	5
5.	During the past month or so, how often have you had a weak urinary stream?	0	1	2	3	4	5
6.	During the last month or so, how often have you had to push or strain to begin urination?	0	1	2	3	4	5
		None	1 Time	2 Times	3 Times	4 Times	5 Times or More
7.	During the last month, how many times did you most typically get up to urinate from the time you went to bed at night until the time you got up in the morning?	0	1	2	3	4	5

9.11 Case 00448, Study 205 Timeline of Laboratory and Clinical Events

		Day 1	Day 19	Day 23	Day 27	Day 31	Day 35	Day 38	41
Date									(b) (6)
	Study drug status/ intervention	First EZO		600mg EZO		Last EZO Hospitalized (amp & gent rx)		D/C hospital	
	Symptoms		Myalgia, fatigue, cough, sweats (fever?)	Aches, lethargy, sweats, urinary frequency. No temp in dataset					
	Findings					1500cc cloudy urine, bilateral Swollen kidneys	Urine culture clear, Antibiotics discontinued		
	Baseline Lab values								
ALT U/L	12			60	193	61	82		60

		Day 1	Day 19	Day 23	Day 27	Day 31	Day 35	Day 38	41
Date									(b) (6)
				(1.2 ULN)	(5.2 ULN)	(1.5 ULN)	(2 ULN)		(1.6)
AST U/L	14			29 (.58 ULN)	93 (2.6 ULN)	40 (1.3 ULN)	57 (1.9 ULN)		47 (1.3)
Bilirubin umol/L	6			23 (1.15 ULN)	34 (1.7 ULN)	34 (1.7 ULN)	18 (.9 ULN)		11
Alk Phos U/L	40			152 (1.2ULN)	383 (3.8 ULN)	125 (1.1 ULN)	115 (1 ULN)		124 (1.2)
Creatinine mmol/L				.38 (3.8 ULN)	.19 (1.8)	.40 (4 ULN)	.16 (1.6 ULN)		.056
BUN mmol/L	5			22.9 (2.7ULN)	12.3	24.8 (3.75ULN)	10.2 (1.5ULN)		6.2
Bladder volume						1500ml			
Na+ mmol/L	133			130	127	129	142		
K+ mmol/L	3.8			5.3	4.3	4.7	3.2		
CRP mg/L				328 (27.3 ULN)					
Hb G/L	140.99				120.4				
WBC GI/L	5				9.8				
Neutrophils GI/L	2.85				7.84				
Neutrophils %	57				80				
Bands GI/L	0				0				
Lymphocytes GI/L	1.65				1.07				
Lymphocytes %	33				11				

9.12 Analysis of Dizziness / Blood pressure relationship

Dizziness

Analysis 1: SAE Dizziness

Examination of the AE.xpt database reveals 6 SAE (serious adverse events) captured under the PTNAME dizziness. One subject is on placebo. The remaining five subjects are presented in table 131.

Table 131 Blood pressure changes in subjects with SAE with PT name - dizziness

Table	Blood pressure changes in subjects with SAE with PT name -dizziness					
Study	SITEID-SUBJID	History	Date Event	Date Orthostatic BP (Δ baseline)	Systolic BP sitting/standing (Δ baseline) date	comment
205	00085-001240	Subject on placebo				

Table	Blood pressure changes in subjects with SAE with PT name -dizziness					
Study	SITEID-SUBJID	History	Date Event	Date Orthostatic BP (Δ baseline)	Systolic BP sitting/standing (Δ baseline) date	comment
208	020879-000001	36 yo M in long term 1⁰ safety & tolerability study hospitalized on (b) (6) for dizziness, lethargy and fatigue. RTG discontinued on 1/7/99.	(b) (6)		10/28/98 110/108 (-10/0) Pulse 72/70 11/25/98 120/120 (0/12) Pulse 74/76	No significant orthostatic change detected. -10 change from baseline. Unlikely cause of dizziness.
212	000090-000613	30 yo M in OL 1⁰ safety & tolerability study. Vomiting diplopia, tremor and dizziness after accidently advancing dose from 900mg/day to 1200mg/day. Resolved after dose reduction to 600mg/day	2/28/01		No postural measurement in this study. 3/2/01 BP= 120/80, p66 4/3/01 BP= 130/80,p72 Max systolic Δ from baseline -10mmHg.	No values for month of hospitalization. No sitting hypotension after dose adjustment. Uncertain if event related to medication.
302	000401-040119	57 yo F. hospitalized for dizziness, ataxia, and SVT. Concomitant AEDs CBZ, topiramate, Keppra.	(b) (6)	1/16/07 systolic -10, (-30) 2/1/07 Systolic 0 (-20) 2/14/07 Systolic -30 (-50)		Patient continued in study, no further dizziness AE reported. Dizziness event likely related to blood pressure
302	000507-050705	69 yo F, had somnolence day 1. Dizziness and gait disturbance. Discontinued due to gait on 3/24/07. RTG started on 2/13/07.	3/19/07	2/27/07 Systolic +5 (+6) 3/14/07 Systolic +12 (+13) 3/26/07 Systolic +7 (+8).		RTG discontinued on 3/24. no orthostatic hypotension present. No negative change from baseline in BP detected. No + orthostatic pulse gradient. Dizziness unrelated to BP change.
304	000905-090503	32 yo M. hospitalized for slow speech, bradykinesia on (b) (6). dizziness on (b) (6), ataxia-dizziness on (b) (6) RTG last dose (b) (6)	(b) (6)	4/1/08 Systolic -11 (0) 6/2/08 Systolic -15 (-4) 9/2/08 Systolic -22 (-11)		Subject had orthostatic gradient on placebo (study 302) of -19 systolic. Only minimal worsening on RTG treatment. Relationship to study drug uncertain.

Analysis 2: interaction of incidents of ≥-20mmHg change from baseline in postural blood pressure with the AE (adverse event) dataset of cases with preferred term of "dizziness". Studies 301 and 302.

Review strategy: all dizziness events in the AE.xpt file under the column PTNAME are captured. From the vit.xpt file all entries for orthostatic hypotension-SBP (systolic blood pressure) which reveal a change from baseline greater than -20 mmHg are captured for studies 301 and 302. The events occurring in placebo treatment are separated from those receiving ezogabine. The events of orthostatic systolic blood pressure value ≤-20 mmhg from each study are then matched to the subset of the AE dataset containing the preferred term "dizziness" for the titration and maintenance phase (combined) of studies

301 and 302. This match identifies subjects who have an orthostatic drop in systolic blood pressure more negative than or equal to -20mmhg and an adverse event of dizziness. This match does not confirm the events are related; however the events are examined to determine if there is a temporal relationship and the magnitude of the orthostatic change is also considered. Orthostatic events and dizziness adverse events separated by greater than 30 days are considered too distant to have a temporal relationship. The results for studies 301 and 302 are seen in tables 132 and 133.

Table 132 Study 301: Result of subject ID with orthostatic systolic BP ≤-20mmhg matched to AE dataset, PTNAME "dizziness"

SUBJID	AE Start Date (AE dataset)	Visit Date (from Vital Signs dataset)	Change from baseline value at visit date
Placebo (152 patients total**): 5 instances, 4 patients**			
002512	12/21/06	11/28/06	-21
003005	2/22/07	3/8/07	-23
010211	4/15/07		
020212	2/6/07	2/2/07	-34
020212	4/1/07		
1200mg (153 patients total**): 24 instances, 13 patients**			
205	6/8/2006	6-14-06	-20
302	6/6/2006		
302	6/29/2006		
1410	5/18/2007	05/01/2007	-22
1501	6/6/2006	6/6/06	-22
3402	9/5/2006	9/6/06	-42
3402	9/5/2006	9/21/06	-47
10206	7/27/2006	8/7/06	-24
10206	8/4/2006		
10701	12/14/2006		
10701	12/15/2006		
10701	12/27/2006	1/10/07	-28
10701	1/12/2007		
10701	1/14/2007		
10701	1/31/2007		
10712	7/17/2007		
15304	4/30/2007	5/7/07	-20
20106	4/12/2007		
20106	4/26/2007	4/26/07	-20
20109	.		
20110	6/7/2007		
20221	7/30/2007		
20221	8/10/2007		
20221	9/22/2007		
Visit date and corresponding change from baseline value from the vital signs dataset are only provided if within 30 days of AE date			

Table 133 Study 302: Result of subject ID with orthostatic systolic BP ≤-20mmhg matched to AE dataset, PTNAME "dizziness"

SUBJID	AE Start Date (AE dataset)	Visit Date (from Vital Signs dataset)	Change from baseline value at visit date
PLACEBO (179 patients total)- 1 instance , 1 patient			
080108	6/9/07		
600mg (181 patients total) - 8 instances, 6 patients			
40125	4/9/2007	3/21/07	-40
40125	5/27/2007	5/30/07	-35
40141	9/20/2007		
40143	.		
50304	11/20/2006		
80204	4/18/2007	4/23/07	-27
80204	7/12/2007	7/17/07	-29
90514	11/28/2007		
900mg (178 patients total) - 12 instances, 6 patients			
40119	.		
40119	1/11/2007	1/3/07	-20
40119	1/22/2007	1/16/07	-30
45104	8/29/2006	7/10/06	-30
45108	8/14/2006	9/4/06	-25
50706	4/10/2007		
50706	4/20/2007	5/2/07	-21
50706	6/25/2007		
70603	7/20/2007	7/20/07	-30
80102	11/29/2006	11/21/06	-52
80102	11/30/2006	12/4/06	-30
80102	11/30/2006	12/09/06	-70
Visit date and corresponding change from baseline value from the vital signs dataset are only provided if within 30 days of AE date			

Reviewer Comment: In both studies 301 and 302 there is an increase in the number of instances of threshold orthostatic hypotension (≤-20mmhg) events associated with a dizziness adverse event in the ezogabine treatment patients compared to the placebo treatment groups. These findings suggest a relation between decline in orthostatic systolic blood pressure value and some of the instances of the adverse event "dizziness". In study 301 there are 5 instances and 4 patients in the placebo group compared to 24 instances and 13 patients in the 1200mg ezogabine treatment group. In the placebo group there were 3 events where the temporal proximity of the orthostatic event and the dizziness event were within 30 days while in the ezogabine 1200mg group there were 8 such associations. Overall in the titration and maintenance intervals of study 301 there were 112 instances of the AE "dizziness" occurring in 61 patients.

In study 302 there was only one instance of match between “dizziness” and an orthostatic systolic blood pressure drop ≥-20mmhg. In the 600mg treatment group there 8 instances in 6 patients where there was a match between orthostatic drop and the AD “dizziness”. The 900mg group had 12 instances in 6 patients of such a match. In the 600mg group 4 of the instances of orthostatic systolic blood pressure drop and “dizziness” occurred inside of a 30 day interval. The 900mg had 9 such occurrence within a 30 day interval. Overall in the titration and maintenance intervals of study 302 there were 134 instances of the AE “dizziness” occurring in 79 patients.

Analysis 3: Evaluation of Postural Blood Pressure Change ≥-20mmHg from baseline in the titration – maintenance phase of studies 205, 301 and 302.

Study 205

Examination of standing systolic blood pressure values is performed. The vital sign dataset for study 205, double blind treatment interval (titration-maintenance) for placebo and individual dose groups is examined for the occurrence of any change from baseline measurement ≤ -20mmHg from the baseline measurement. The median and mean of these measurements, which may occur at any visit during weeks 2 to 16 is generated for comparison to placebo and between dose groups, table 134.

Placebo: The placebo group had 43 measurements occurring in 18 patients of standing systolic blood pressure which had a decrease from baseline greater than -20mmHg. These had a median value of -30mmHg with a mean of -31mmHg. None of the incident of standing systolic blood pressure greater than -20mmhg resulted in a blood pressure value in the range of potential clinical concern. The 18 patients represent 19% of the total placebo group.

600mg: the 600mg group had 41 measurements occurring in 15 patients of standing systolic blood pressure which had a decrease from baseline greater than -20mmhg. These had a median value of -30mmhg with a mean of -32mmhg. None of the incidents of standing systolic blood pressure greater than -20mmhg resulted in a blood pressure value in the range of potential clinical concern. These 15 patients represent 15% of the 600mg treatment group.

900mg: the 900mg group had 56 measurements occurring in 25 patients of standing systolic blood pressure which had a decrease from baseline greater than -20mmhg. These had a median value of -20mmhg with a mean of -25mmhg. Two of the incidents of standing systolic blood pressure greater than -20mmhg resulted in a blood pressure value in the range of potential clinical concern but neither of these was associated with a reported adverse effect. These 25 patients represent 26% of the 900mg treatment group.

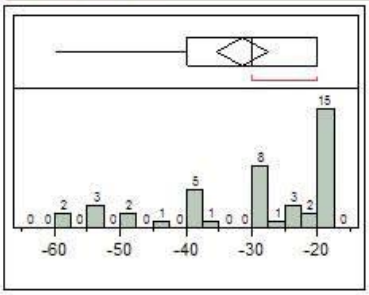
1200mg: the 1200mg group had 58 measurements occurring in 28 patients of standing systolic blood pressure which had a decrease from baseline greater than -20mmhg.

These had a median value of -20mmhg with a mean of -24mmhg. One of the incidents of standing systolic blood pressure greater then -20mmhg resulted in a blood pressure value in the range of potential clinical concern but this was not associated with a reported adverse effect. These 28 patients represent 26% of the 1200mg treatment group.

Table 134 Study 205, distribution of incidents of standing systolic blood pressure which are ≤ -20mmHg from the baseline measurement. Placebo and all dose

Distributions

CHGBASE PBO

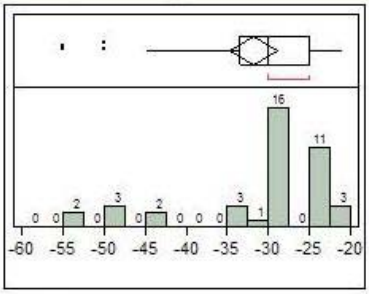


Quantiles		
100.0%	maximum	-20.00
99.5%		-20.00
97.5%		-20.00
90.0%		-20.00
75.0%	quartile	-20.00
50.0%	median	-30.00
25.0%	quartile	-40.00
10.0%		-55.00
2.5%		-60.00
0.5%		-60.00
0.0%	minimum	-60.00

Moments	
Mean	-31.46512
Std Dev	12.788292
Std Err Mean	1.9501963
upper 95% Mean	-27.52946
lower 95% Mean	-35.40077
N	43

Distributions

CHGBASE 600mg

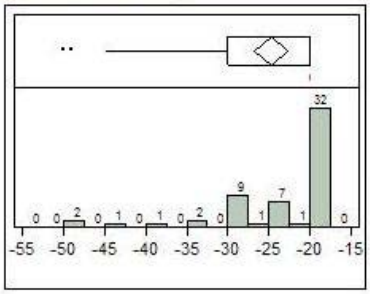


Quantiles		
100.0%	maximum	-21.00
99.5%		-21.00
97.5%		-21.05
90.0%		-23.40
75.0%	quartile	-25.00
50.0%	median	-30.00
25.0%	quartile	-33.50
10.0%		-50.00
2.5%		-55.00
0.5%		-55.00
0.0%	minimum	-55.00

Moments	
Mean	-31.70732
Std Dev	9.187611
Std Err Mean	1.4348638
upper 95% Mean	-28.80735
lower 95% Mean	-34.60728
N	41

Distributions

CHGBASE 900mg

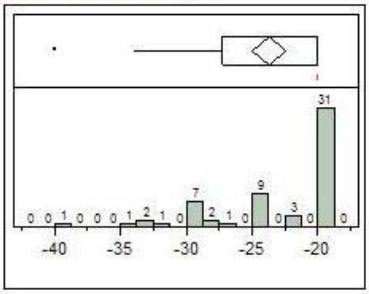


Quantiles		
100.0%	maximum	-20.00
99.5%		-20.00
97.5%		-20.00
90.0%		-20.00
75.0%	quartile	-20.00
50.0%	median	-20.00
25.0%	quartile	-30.00
10.0%		-33.60
2.5%		-49.58
0.5%		-50.00
0.0%	minimum	-50.00

Moments	
Mean	-24.71429
Std Dev	7.4118193
Std Err Mean	0.990446
upper 95% Mean	-22.72939
lower 95% Mean	-26.69918
N	56

Distributions

CHGBASE 1200mg



Quantiles		
100.0%	maximum	-20.00
99.5%		-20.00
97.5%		-20.00
90.0%		-20.00
75.0%	quartile	-20.00
50.0%	median	-20.00
25.0%	quartile	-27.25
10.0%		-30.20
2.5%		-37.15
0.5%		-40.00
0.0%	minimum	-40.00

Moments	
Mean	-23.7069
Std Dev	4.931135
Std Err Mean	0.6474897
upper 95% Mean	-22.41032
lower 95% Mean	-25.00347
N	58

Overall study 205 results: A larger number of patients in the 900mg and 1200mg treatment group had a decrease in standing systolic blood pressure ≥ -20mmhg than in placebo but among the ezogabine treatment groups only the 600mg dose group had a median equal to placebo while the ≥ -20mmhg subset of the 900mg and 1200mg groups had a smaller median decline in the standing systolic pressure compared to baseline than placebo. Both the 900mg and 1200mg groups had a median standing systolic blood pressure change from baseline of -20mmhg compared to the placebo value of -30mmhg. Only the 600mg dose group had a larger mean value of decline from baseline than placebo, -32mmhg while in the 900mg and 1200mg groups the mean decline from baseline were -25mmhg and -24mmhg respectively compared to a placebo value of -31mmhg.

Study 301

Study 301 dataset included an entry for orthostatic systolic and diastolic blood pressure measurement. This represents the change in diastolic or systolic blood pressure between the supine and standing position. The value for orthostatic change of the systolic blood pressure measurement was examined to determine the occurrences of change from baseline orthostatic value ≥ -20mmhg. The number of occurrences was determined in the double blind treatment interval (weeks 2 to 18), and the values could occur at any visit. There may be multiple incidents for a single patient. This analysis examines only the overall incidents of orthostatic systolic pressure decrease from baseline value greater than -20mmhg for both placebo and the 1200mg treatment group in the 2 to 18 week (titration-maintenance) interval, table 135.

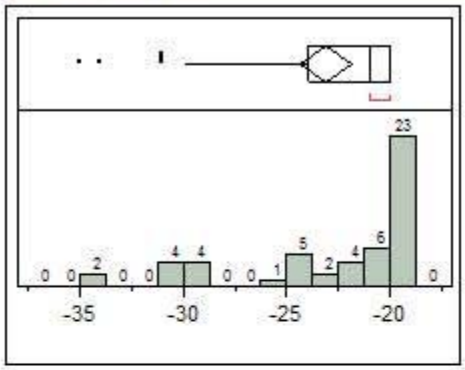
The placebo group had 51 measurements, occurring in 33 patients, of systolic orthostatic blood pressure measurement with decrease from the baseline value ≥ -20mmhg. These measurements had a median value of -21mmhg (only 1mmhg less than the capture threshold) with a mean of -23mmhg. These 33 patients represent 22% of the placebo treatment group.

The 1200mg ezogabine treatment group had 64 measurements, occurring in 29 patients, of systolic orthostatic blood pressure measurement with a decrease from the baseline value ≥ -20mmhg. These measurements had a median of -22mmhg (2 mmhg less than the capture threshold) with a mean of -26 mmhg. These 29 patient represent 19% of the 1200mg treatment group.

Table 135 Study 301, distribution of incidents of systolic orthostatic blood pressure measurement which are ≤ -20mmHg from the baseline measurement. Placebo and 1200mg dose.

Distributions

CHGBASE PBO

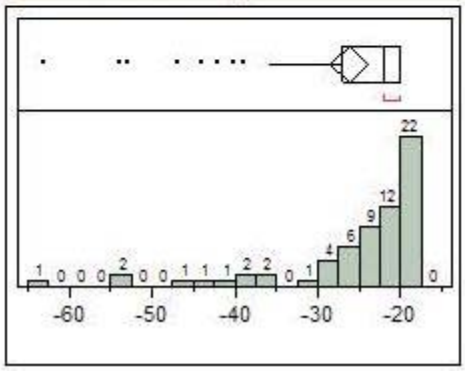


Quantiles		
100.0%	maximum	-20.00
99.5%		-20.00
97.5%		-20.00
90.0%		-20.00
75.0%	quartile	-20.00
50.0%	median	-21.00
25.0%	quartile	-24.00
10.0%		-31.00
2.5%		-34.70
0.5%		-35.00
0.0%	minimum	-35.00

Moments	
Mean	-23.11765
Std Dev	4.3710276
Std Err Mean	0.6120663
upper 95% Mean	-21.88828
lower 95% Mean	-24.34702
N	51

Distributions

CHGBASE 1200mg



Quantiles		
100.0%	maximum	-20.00
99.5%		-20.00
97.5%		-20.00
90.0%		-20.00
75.0%	quartile	-20.00
50.0%	median	-22.00
25.0%	quartile	-27.00
10.0%		-41.00
2.5%		-57.38
0.5%		-63.00
0.0%	minimum	-63.00

Moments	
Mean	-26.1875
Std Dev	9.4177728
Std Err Mean	1.1772216
upper 95% Mean	-23.83501
lower 95% Mean	-28.53999
N	64

Study 302

Study 302 dataset included an entry for orthostatic systolic and diastolic blood pressure measurement. This represents the change in diastolic or systolic blood pressure between the supine and standing position. The value for orthostatic change of the systolic blood pressure measurement was examined to determine the occurrences of change from baseline orthostatic value ≥ -20mmhg. The number of occurrences was determined in the double blind treatment interval (weeks 2 to 18), and the values could occur at any visit. There may be multiple incidents for a single patient. This analysis examines only the overall incidents of orthostatic systolic pressure decrease from baseline value greater than -20mmhg for the placebo, 600mg and 900mg groups in the 2 to 16 week (titration-maintenance) interval, table 136.

Placebo: the placebo group had 67 measurements, occurring in 34 patients, of systolic orthostatic blood pressure measurement with a decrease from the baseline value ≥ -

20mmhg. These measurements had a median value of -22mmhg (2 mmhg less than the capture threshold) with a mean of -28mmhg. These 34 patients represent 19% of the placebo group.

600mg: the 600mg group had 51 measurements, occurring in 27 patients, of systolic orthostatic blood pressure measurement with a decrease from the baseline value ≥ -20mmhg. These measurements had a median of -25mmhg (-5mm below the capture threshold) with a mean of -27mmhg. These 27 patients represent 15% of the 600mg treatment group.

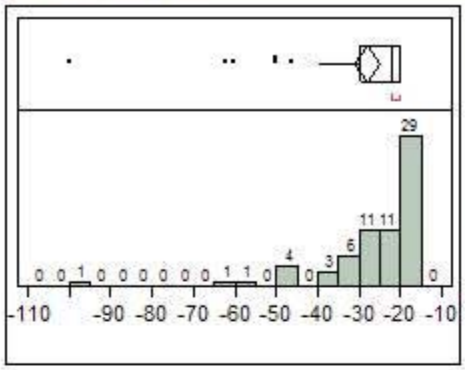
900mg: the 900mg group had 51 measurements, occurring in 26 patients, of systolic orthostatic blood pressure measurement with a decrease from the baseline value ≥ -20mmhg. These measurements had a median of -25mmhg ((-5mm below the capture threshold) with a mean of -29mmhg. These 26 patients represent 15% of the 900mg treatment group.

Reviewer Comment: Based on examination of standing systolic blood pressure change from baseline in study 205 and orthostatic systolic blood pressure change in studies 301 and 302 there is no signal for the development of orthostatic blood pressure instability due to ezogabine treatment. In study 205 the highest dose ezogabine groups had smaller deviations of median and mean from the baseline values. In study 301 the percent of patients with instances of ≥-20mmhg decline from baseline was smaller in the 1200mg ezogabine group than in placebo although the number of instances was greater and the range was noticeably greater due to several outliers (maximum -63mmhg). The difference in medians and means in placebo compared to ezogabine was small. In study 302 the percent of patients with decline ≥-20mmhg decline from baseline was smaller in the ezogabine 600mg and 900mg group compared to placebo, there were also fewer instances of this degree of decline in ezogabine treatment compared to placebo. There was a small increase in the medians (both -25 mmhg compared to placebo -22mmhg) of ezogabine treatment compared to placebo but the mean of the 600mg group was smaller than placebo.

Table 136 Study 302, distribution of incidents of systolic orthostatic blood pressure measurement which are ≤ -20mmHg from the baseline measurement. Placebo and 600mg and 900mg dose.

Distributions

CHGBASE PBO

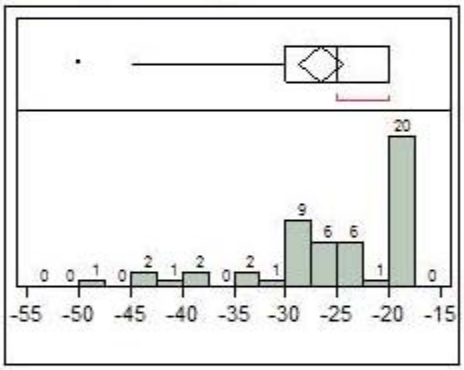


Quantiles		
100.0%	maximum	-20.0
99.5%		-20.0
97.5%		-20.0
90.0%		-20.0
75.0%	quartile	-20.0
50.0%	median	-22.0
25.0%	quartile	-30.0
10.0%		-46.0
2.5%		-73.4
0.5%		-100.0
0.0%	minimum	-100.0

Moments	
Mean	-28.02985
Std Dev	13.323447
Std Err Mean	1.6277181
upper 95% Mean	-24.78001
lower 95% Mean	-31.27969
N	67

Distributions

CHGBASE 600mg

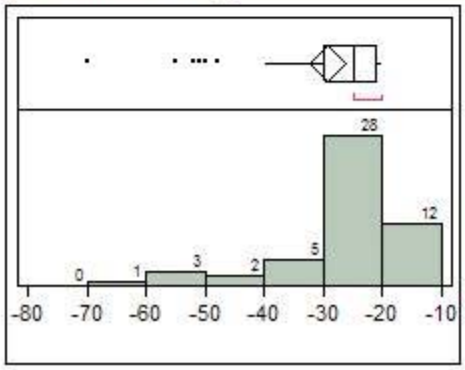


Quantiles		
100.0%	maximum	-20.00
99.5%		-20.00
97.5%		-20.00
90.0%		-20.00
75.0%	quartile	-20.00
50.0%	median	-25.00
25.0%	quartile	-30.00
10.0%		-40.00
2.5%		-48.50
0.5%		-50.00
0.0%	minimum	-50.00

Moments	
Mean	-26.60784
Std Dev	7.6917577
Std Err Mean	1.0770615
upper 95% Mean	-24.4445
lower 95% Mean	-28.77118
N	51

Distributions

CHGBASE 900mg



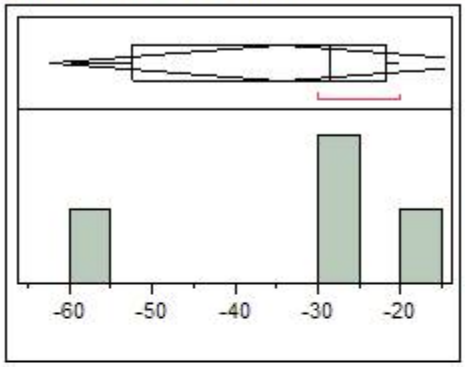
Quantiles		
100.0%	maximum	-20.00
99.5%		-20.00
97.5%		-20.00
90.0%		-20.00
75.0%	quartile	-21.00
50.0%	median	-25.00
25.0%	quartile	-30.00
10.0%		-49.60
2.5%		-65.50
0.5%		-70.00
0.0%	minimum	-70.00

Moments	
Mean	-29.19608
Std Dev	10.923405
Std Err Mean	1.5295827
upper 95% Mean	-26.12382
lower 95% Mean	-32.26834
N	51

Analysis 4: Examination of Blood Pressure Change related to postural challenge at mid titration phase; Study 205 (visit #4), 301 (visit #5), and 302 (visit #4).

Study 205: a value for systolic orthostatic blood pressure change (gradient of systolic blood pressure between supine and standing) was not obtained in study 205. To investigate the effect of ezogabine on orthostatic blood pressure the standing systolic blood pressure was examined at visit number 4. The change from baseline measurement ≥-20mmHg was chosen as the cutoff to be significant orthostatic change (as in study 301 & 302). The placebo group at visit number 4 had 4 events with a median change in standing systolic blood pressure from baseline of -28.5mmHg and a mean of -34mmHg with a range of -60mmHg to -20mmHg. The ezogabine treatment group had 22 events with a median change in standing systolic blood pressure from baseline of -20mmHg and a mean of -25mmHg with a range of -55mmHg to -20mmHg. The events in the placebo group are small in number with one outlier at -60mmHg change from baseline which clouds a robust comparison. Overall there was not a clear difference in standing blood pressure maintenance between the placebo and ezogabine treated patients at visit number 4, figure 43.

Figure 43 Study 205, distribution of standing systolic blood pressure Δ from baseline ≥-20 in placebo and ezogabine treatment at visit # 4



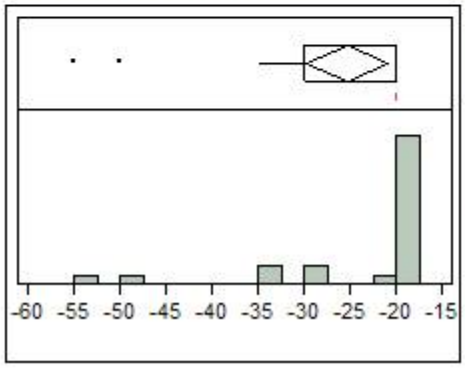
Distributions

205 V4 PBO CHGBASE

Quantiles		
100.0%	maximum	-20.00
99.5%		-20.00
97.5%		-20.00
90.0%		-20.00
75.0%	quartile	-21.75
50.0%	median	-28.50
25.0%	quartile	-52.50
10.0%		-60.00
2.5%		-60.00
0.5%		-60.00
0.0%	minimum	-60.00

Moments	
Mean	-34.25
Std Dev	17.670597
Std Err Mean	8.8352985
upper 95% Mean	-6.132137
lower 95% Mean	-62.36786
N	4

205 V4 RTG CHGBASE

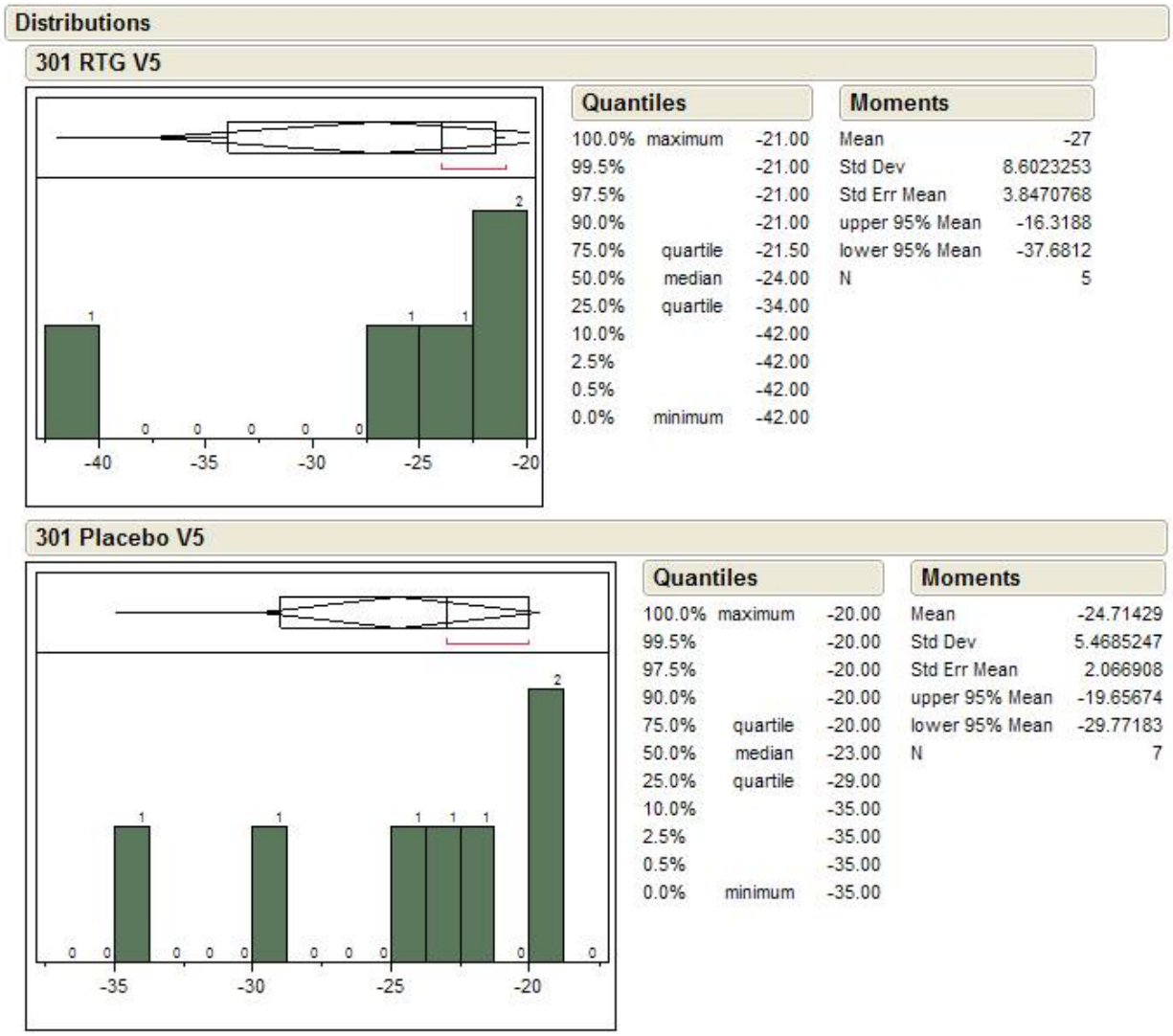


Quantiles		
100.0%	maximum	-20.00
99.5%		-20.00
97.5%		-20.00
90.0%		-20.00
75.0%	quartile	-20.00
50.0%	median	-20.00
25.0%	quartile	-30.00
10.0%		-45.50
2.5%		-55.00
0.5%		-55.00
0.0%	minimum	-55.00

Moments	
Mean	-25.27273
Std Dev	10.090929
Std Err Mean	2.1513932
upper 95% Mean	-20.79866
lower 95% Mean	-29.74679
N	22

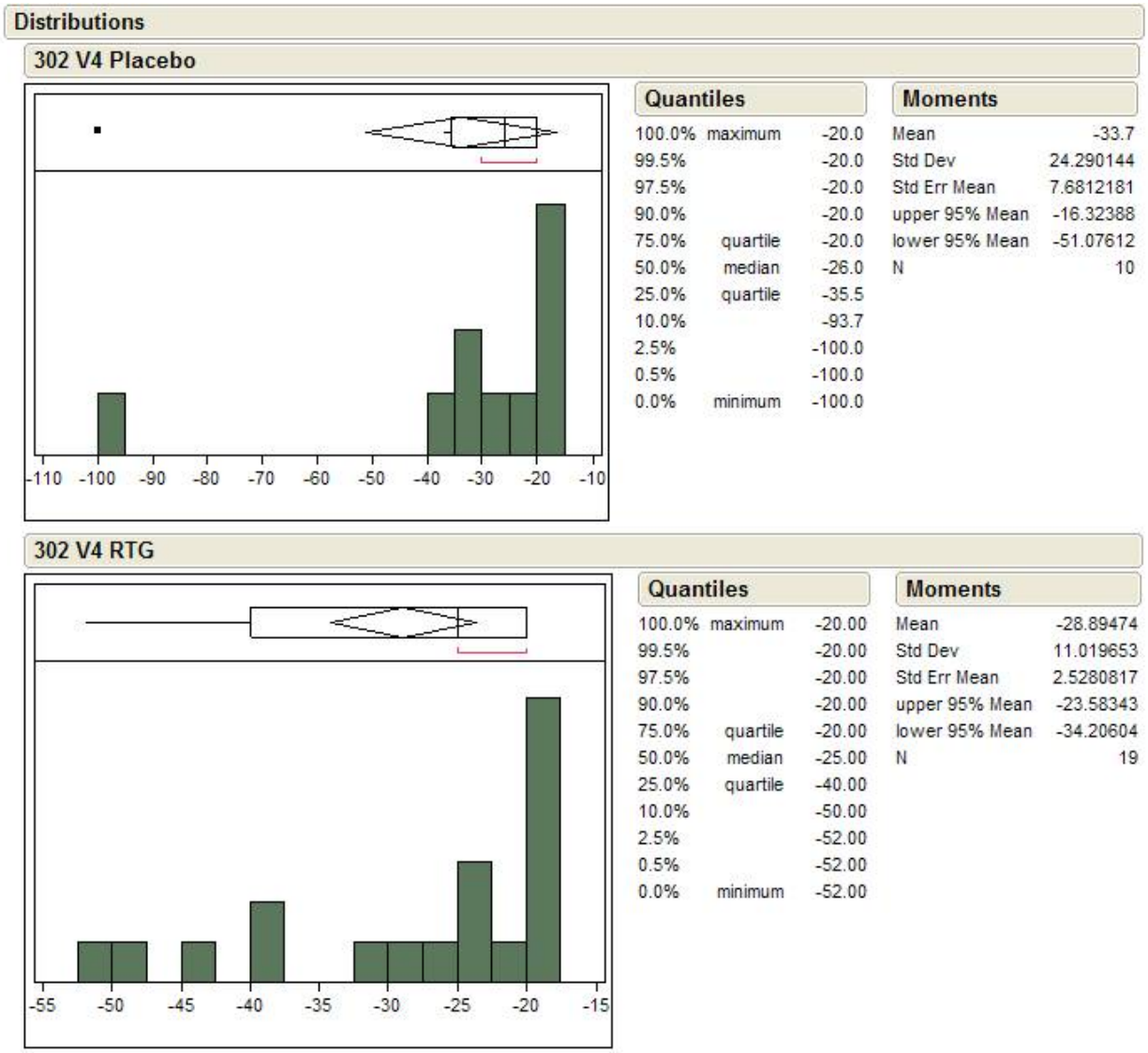
Study 301: Change from baseline of the systolic, orthostatic blood pressure measurement was compared between placebo and ezogabine treated groups at mid-titration interval, visit number 5. A change from baseline measurement of ≥-20mmHg was chosen as the cutoff to be significant. There were few events overall. The placebo group had 7 events with a median change of -23mmHg and a mean of -24.7 mmHg and a range of -35mmHg to -20mmHg. The ezogabine treated group had 5 events with a median change of -24mmHg and a mean of -27mmHg with a range of -42 mmHg to -20mmHg. Overall there was not a clear difference in orthostatic systolic blood pressure maintenance between the placebo and ezogabine treated patients at visit number 5, figure 44..

Figure 44 Study 301, distribution of orthostatic systolic BP Δ from baseline ≥-20 in placebo and ezogabine treatment at visit # 5



Study 302: Change from baseline of the systolic, orthostatic blood pressure measurement was compared between placebo and ezogabine treated groups at mid-titration interval, visit number 4. A change from baseline measurement of ≥-20mmHg was chosen as the cutoff to be significant. In the placebo group there were 10 events with a median change of -26mmHg and a mean of 33.7mmHg with a range of -100mmHg to -20mmHg. The ezogabine treatment group had 19 events with a median change of -25mmHg a mean of -28.9mmHg and a range of -52mmHg to -20mmHg. There was an outlier in the placebo group with a value of -100mmHg otherwise the remaining 9 changes from baseline were between -40mmHg and -20mmHg. If this value is deleted the median change is -22mmHg with a mean of -26.3 and a range of -37mmHg to -20mmHg. Overall there was not a clear difference in orthostatic systolic blood pressure maintenance between the placebo and ezogabine treated patients at visit number 5, figure 45.

Figure 45 Study 302, distribution of orthostatic systolic BP Δ from baseline ≥-20 in placebo and ezogabine treatment at visit # 4



Reviewer Comment: The evaluation of the difference in response to postural blood pressure challenge in the pivotal controlled trials at mid titration interval did not reveal a clinically notable difference between the placebo and ezogabine treated patients.

Reviewer Comment (analysis 1-4): Overall the data do not support a signal for destabilization of blood pressure upon postural challenge as a clinically meaningful cause of the AE "dizziness", although analysis 2 (interaction of low BP events and dizziness-AE dataset) reveal more frequent interactions in ezogabine treatment groups than placebo. There is a single causal case of dizziness related to orthostatic hypotension due to ezogabine identified. This finding indicates that in rare cases or due to idiosyncratic cause, ezogabine may induce significant orthostatic hypotension.

9.13 Laboratory Findings

9.13.1 Central Tendency Analysis

9.13.1.1 Hematology

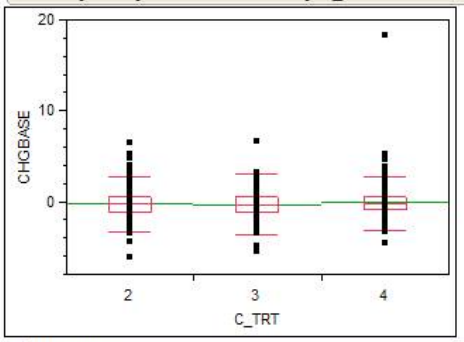
RBC (red blood cells): Red blood cells reveal a negative change from mean in at each measurement (weeks 2 to 18) in both placebo and ezogabine treatment. The decrease is greater in the ezogabine treatment group with a maximum in the 1200mg/day group at week 6, however this negative change is small, 2.0%, and 1.79% more than placebo.

WBC (white blood cells); At baseline, there was no meaningful difference between the placebo group and ezogabine groups for mean white blood cells. Mean white blood cells showed a slight decrease from baseline in the ezogabine-treated groups that was apparent from Week 2 but did not appear to decrease further over time, and there was no evidence of a dose relationship.

Examination of WBC change from baseline in ezogabine treated patients across all dose groups at 8 weeks reveals no significant trend of dose response. A graphic displaying the distribution of change from baseline at 600mg (x axis = 2), 900mg (x axis = 3) and 1200mg (x axis =4) with accompanying tables of medians and means at each dose are provided in figure 46A. This analysis reveals a small negative median and mean change in the difference from baseline with little variation among dose groups. Examination of the median and mean change from baseline of the 1200mg dose group in ezogabine treated patients from weeks 2 to 18 reveals a maximum median change of -0.4GI/L at week 14. There is a maximum mean change from baseline of -.37GI/L at week 14. A table of median and mean values for weeks 2 to 18 with a graphic display of this analysis is presented in figure 46B. The change from baseline WBC count of the placebo group is examined for comparison to the treatment group changes discussed above. In the placebo group at week 8 the median change from baseline is -0.1GI/L and the mean change from baseline is -0.11GI/L figure 47.The sponsor examination of individual mean change from baseline of all ezogabine dose groups at weeks 2 to 18 reveals small declines from baseline that are greater than placebo. The maximum two declines greater than placebo are .40GI/L (6.62%) at week 18 in the 600mg dose group and .39GI/L (6.4%) in the 900mg dose group at week 16.

Figure 46 Examination of WBC change from baseline at week 8 across all dose groups (A)- (600mg=2, 900mg=3, 1200mg=4) / Examination of WBC change from baseline weeks 2 -18 at 1200mg Dose (B)

Oneway Analysis of CHGBASE By C_TRT



Quantiles

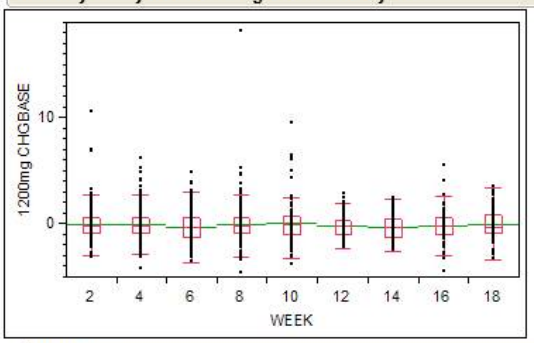
Level	Minimum	10%	25%	Median	75%	90%	Maximum
2	-6.3	-1.9	-1.1	-0.2	0.5	1.21	6.3
3	-5.7	-1.98	-1.2	-0.3	0.5	1.36	6.5
4	-4.7	-1.7	-0.9	-0.2	0.6	1.5	18.1

Means and Std Deviations

Level	Number	Mean	Std Dev	Std Err Mean	Lower 95%	Upper 95%
2	228	-0.22368	1.51685	0.10046	-0.4216	-0.0257
3	211	-0.33744	1.48781	0.10243	-0.5394	-0.1355
4	224	-0.06563	1.85217	0.12375	-0.3095	0.1782

A

Oneway Analysis of 1200mg CHGBASE By WEEK



Quantiles

Level	Minimum	10%	25%	Median	75%	90%	Maximum
2	-3.3	-1.6	-0.9	-0.15	0.6	1.41	10.4
4	-4.4	-1.66	-0.8	-0.2	0.6	2	6.1
6	-3.7	-1.8	-1.2	-0.3	0.6	1.2	4.7
8	-4.7	-1.7	-0.9	-0.2	0.6	1.5	18.1
10	-3.9	-1.8	-1	-0.1	0.7	1.8	9.4
12	-2.3	-1.67	-0.95	-0.2	0.3	1.17	2.7
14	-2.6	-2	-1.2	-0.4	0.5	1	2.4
16	-4.6	-2.2	-1	-0.2	0.6	1.25	5.4
18	-3.4	-1.72	-0.875	-0.3	0.875	1.51	3.4

Means and Std Deviations

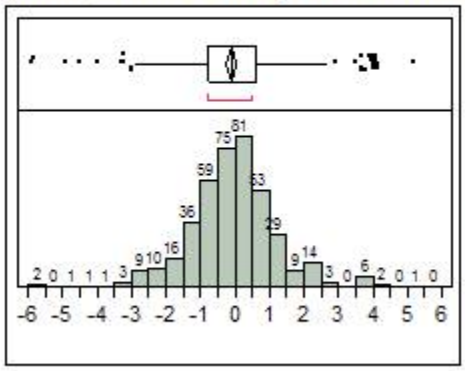
Level	Number	Mean	Std Dev	Std Err Mean	Lower 95%	Upper 95%
2	248	-0.05645	1.43384	0.09105	-0.2358	0.1229
4	233	-0.03605	1.46399	0.09591	-0.2250	0.1529
6	283	-0.29894	1.28762	0.07654	-0.4496	-0.1483
8	224	-0.06563	1.85217	0.12375	-0.3095	0.1782
10	110	0.12091	2.00124	0.19081	-0.2573	0.4991
12	72	-0.20694	1.03724	0.12224	-0.4507	0.0368
14	95	-0.36737	1.14292	0.11726	-0.6002	-0.1345
16	64	-0.18594	1.56457	0.19557	-0.5768	0.2049
18	88	-0.09545	1.37028	0.14607	-0.3858	0.1949

B

Figure 47 WBC Placebo Group Change from Baseline at Week 8

Distributions

WBC, Placebo Change from baseline, WK 8



Quantiles

100.0%	maximum	5.200
99.5%		4.094
97.5%		2.840
90.0%		1.380
75.0%	quartile	0.600
50.0%	median	-0.100
25.0%	quartile	-0.800
10.0%		-1.600
2.5%		-2.970
0.5%		-5.746
0.0%	minimum	-5.900

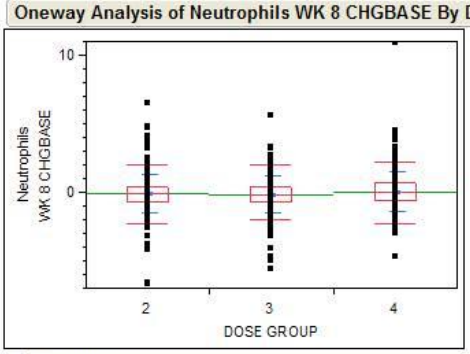
Moments

Mean	-0.112409
Std Dev	1.3661471
Std Err Mean	0.0673871
upper 95% Mean	0.0200585
lower 95% Mean	-0.244876
N	411

Neutrophils; Mean neutrophil values were generally stable across all treatment groups with no clinically significant changes over time. Examination of neutrophil change from baseline in ezogabine treated patients across all dose groups at 8 weeks reveals no significant trend of dose response. A graphic displaying the distribution of change from baseline at 600mg (x axis = 2), 900mg (x axis = 3) and 1200mg (x axis =4) with accompanying tables of medians and means at each dose are provided in figure 48A. . This analysis reveals a small negative median and mean change in the difference from baseline with little variation among dose groups. Examination of the median and mean change from baseline of the 1200mg dose group in ezogabine treated patients from weeks 2 to 18 reveals a maximum median change of -0.3GI/L at week 14. There is a maximum mean change from baseline of -0.21GI/L at week 14. A table of median and mean values for weeks 2 to 18 with a graphic display of this analysis is presented in figure 48B. Examination of the distribution of change from baseline in absolute neutrophil count at week 12 for all dose groups accompanied by median and mean values of the change is presented in figure 49. The sponsor examination of individual mean change from baseline of all ezogabine dose groups at weeks 2 to 18 reveals small declines from baseline that are greater than placebo.

Figure 48 Examination of Neutrophil change from baseline at week 8 across all dose groups (A)- (600mg=2, 900mg=3, 1200mg=4) / Examination of Neutrophil change from baseline weeks 2 -18 at 1200mg Dose (B)

Oneway Analysis of Neutrophils WK 8 CHGBASE By DOSE GROUP



Quantiles

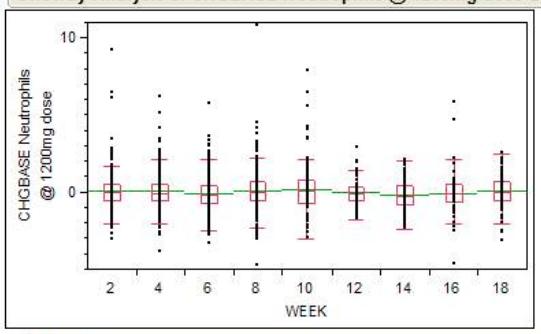
Level	Minimum	10%	25%	Median	75%	90%	Maximum
2	-6.7	-1.512	-0.68	-0.0854	0.42	1.102	6.3532
3	-5.69	-1.4537	-0.70515	-0.205	0.39005	1.3537	5.51
4	-4.8185	-1.61806	-0.5825	-0.03	0.66	1.601	10.77

Means and Std Deviations

Level	Number	Mean	Std Dev	Std Err Mean	Lower 95%	Upper 95%
2	227	-0.11691	1.40226	0.09307	-0.3003	0.06649
3	210	-0.17291	1.34305	0.09268	-0.3556	0.00980
4	222	0.04434	1.46234	0.09815	-0.1491	0.23776

A

Oneway Analysis of CHGBASE Neutrophils @ 1200mg dose By WEEK



Quantiles

Level	Minimum	10%	25%	Median	75%	90%	Maximum
2	-3.11	-1.37268	-0.545	-0.0443	0.49095	1.212	9.11
4	-3.8938	-1.35896	-0.58	-0.09	0.53	1.59834	6.13
6	-3.3879	-1.418	-0.7513	-0.17	0.45185	1.3	5.68
8	-4.8185	-1.61806	-0.5825	-0.03	0.66	1.601	10.77
10	-3.01	-1.83	-0.7675	0.095	0.748425	1.846	7.8
12	-1.7875	-1.21385	-0.52805	-0.0966	0.3177	1.17447	2.8326
14	-2.42	-1.475	-0.78	-0.3	0.43	1.06	2.05
16	-4.6923	-1.6	-0.61043	-0.11185	0.509175	1.02155	5.764
18	-3.19	-1.34	-0.53	-0.05	0.72	1.48	2.43

Means and Std Deviations

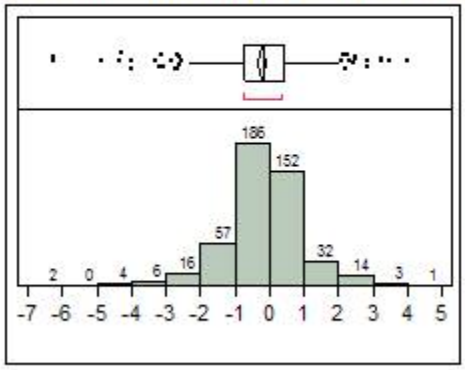
Level	Number	Mean	Std Dev	Std Err Mean	Lower 95%	Upper 95%
2	245	0.03999	1.28738	0.08225	-0.1220	0.2020
4	231	0.04147	1.28589	0.08461	-0.1252	0.2082
6	281	-0.10638	1.14961	0.06858	-0.2414	0.0286
8	222	0.04434	1.46234	0.09815	-0.1491	0.2378
10	110	0.18513	1.68749	0.16090	-0.1338	0.5040
12	72	-0.06235	0.87981	0.10369	-0.2691	0.1444
14	94	-0.21270	0.98351	0.10144	-0.4141	-0.0113
16	64	-0.07031	1.45642	0.18205	-0.4341	0.2935
18	87	0.02510	1.09449	0.11734	-0.2082	0.2584

B

Figure 49 Distribution of neutrophil counts change from baseline, all dose groups combined at week 12.

Distributions

CHGBASE ABS NEUTROPHIL COUNT WK 12, ALL DOSES



Quantiles

100.0%	maximum	4.007
99.5%		3.418
97.5%		2.222
90.0%		1.052
75.0%	quartile	0.408
50.0%	median	-0.158
25.0%	quartile	-0.726
10.0%		-1.550
2.5%		-3.067
0.5%		-5.722
0.0%	minimum	-6.253

Moments

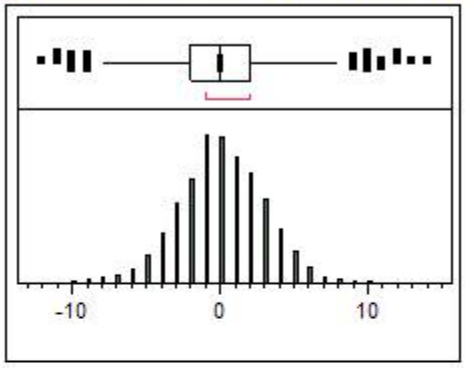
Mean	-0.194275
Std Dev	1.2281605
Std Err Mean	0.0564709
upper 95% Mean	-0.08331
lower 95% Mean	-0.30524
N	473

9.13.1.2 Electrolytes: median, mean and outlier analysis. (All electrolyte analysis are performed on the RCT group weeks 2-18)

Sodium (Na+)

Examination of the change from baseline of all changes from baseline at all doses weeks 2-18 reveal a near normal distribution in both groups with a very small shift to higher values of the median and mean in the ezogabine treatment group with a small increase in the range of the positive and negative maximum values in ezogabine treatment group, figure 50

Figure 50 Distribution of changes from baseline values in placebo treatment group compared to ezogabine treatment at all doses weeks 2-18 RCT

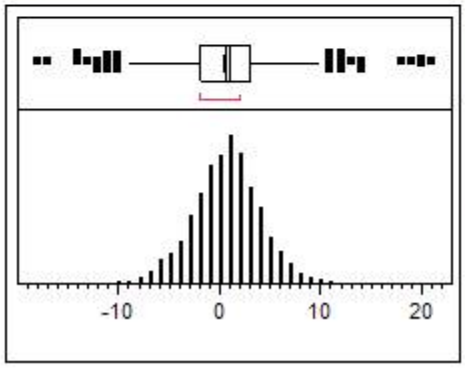


Distributions

PLACEBO TREATMENT CHGBASE Na+

Quantiles		
100.0%	maximum	14.00
99.5%		10.00
97.5%		6.00
90.0%		4.00
75.0%	quartile	2.00
50.0%	median	0.00
25.0%	quartile	-2.00
10.0%		-4.00
2.5%		-6.00
0.5%		-9.00
0.0%	minimum	-12.00

Moments	
Mean	0.0409127
Std Dev	3.164812
Std Err Mean	0.0627712
upper 95% Mean	0.1640005
lower 95% Mean	-0.082175
N	2542



EZO TREATMENT CHGBASE Na+

Quantiles		
100.0%	maximum	21.00
99.5%		11.00
97.5%		8.00
90.0%		5.00
75.0%	quartile	3.00
50.0%	median	1.00
25.0%	quartile	-2.00
10.0%		-4.00
2.5%		-7.00
0.5%		-10.00
0.0%	minimum	-18.00

Moments	
Mean	0.5733967
Std Dev	3.6284697
Std Err Mean	0.055922
upper 95% Mean	0.6830332
lower 95% Mean	0.4637601
N	4210

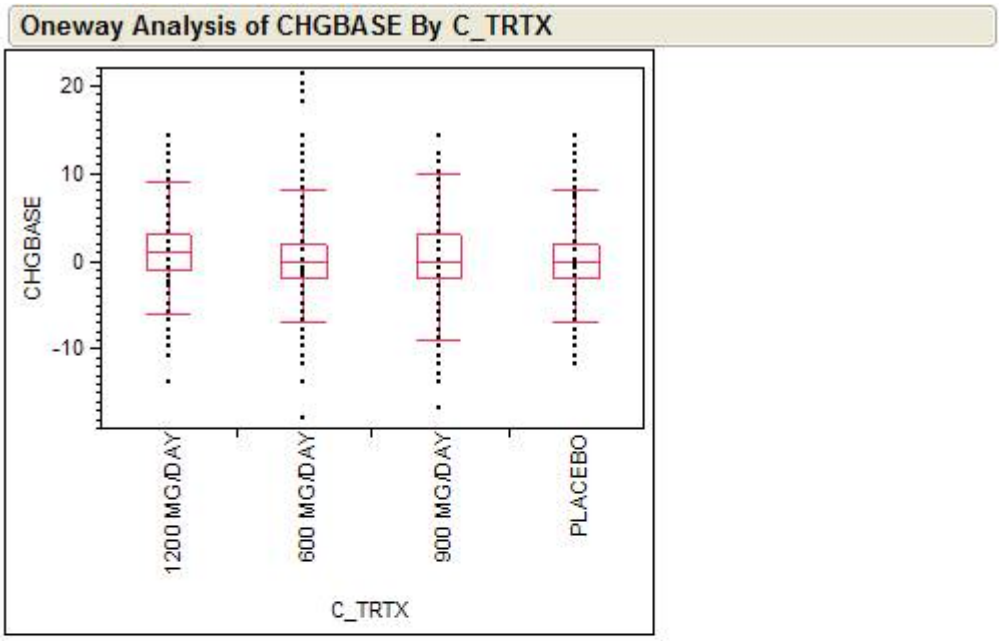
Serum sodium is first examined by the following column selection from the chem..xpt dataset, 120 day safety update; laborder 18, week 2-18, c_trt ≥2 to capture the treatment group and c_trt=1 for placebo group.

The distribution of all changes from baseline is examined for the three doses at all weeks 2 to 18. The mean change from baseline is 1mmol/l with a maximum of 21mmol/l

and minimum of -18 mmol/l. Changes which are greater than 2 SD (standard deviations) from the mean (7.77mmol/l, rounded to 8) or less than 2 SD (standard deviations) from the mean (-7.77mmol/l, rounded to -8) are examined to determine if they are associated with result values for sodium in the range of PCC (potential clinical concern). This is expanded upon further in the outlier analysis section.

Sponsor ISS tables: the sponsor ISS tables are examined for change in serum Na+ at each week of the RCT across each dose groups separately, compared to placebo at the same week of the study. There only small changes noted without notable differences between placebo and all dose groups. The 1200mg dose group tends to have a larger positive change from baseline than the placebo group or the 600mg and 900mg dose group. This is examined by comparing the change from baseline in placebo and all dose groups during weeks 2 to 18 in the pivotal clinical trials (RCTs) as seen in figure 51. The median change from baseline of the placebo, 600mg and 900mg groups are all 0 while the median of the 1200mg group is 1mmol/l. The mean change from baseline of the placebo, 600mg and 900mg groups are all contained between .4mmol/l and .18mmol/l while the 1200mg group has a mean of 1.2mmol/l. This suggests a small dose related change toward a higher Na+ value in the 1200mg group.

Figure 51 Change from baseline serum Na+ during weeks 2 – 18 RCT placebo and each dose group compared



Missing Rows 10

Quantiles

Level	Minimum	10%	25%	Median	75%	90%	Maximum
1200 MG/DAY	-14	-3	-1	1	3	5	14
600 MG/DAY	-18	-4	-2	0	2	4	21
900 MG/DAY	-17	-4	-2	0	3	5	14
PLACEBO	-12	-4	-2	0	2	4	14

Means and Std Deviations

Level	Number	Mean	Std Dev	Std Err Mean	Lower 95%	Upper 95%
1200 MG/DAY	1434	1.18550	3.31380	0.08751	1.014	1.3572
600 MG/DAY	1435	0.18188	3.78032	0.09979	-0.014	0.3776
900 MG/DAY	1341	0.33781	3.70095	0.10106	0.140	0.5361
PLACEBO	2542	0.04091	3.16481	0.06277	-0.082	0.1640

The increase in the 1200mg group seen in figure 51 prompts an examination of the frequency of outliers in placebo and each of the dose groups to determine if the small increase in change in Na+ from baseline is resulting in more serious increase in serum Na+ values in a subset of the high dose group outlier analysis section.

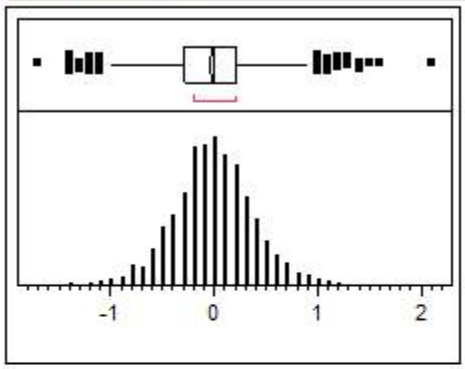
Potassium (K+)

Potassium level changes from baseline are examined by comparing median and means of placebo treatment and all dose groups combined then placebo and each dose group individually. Outliers are also examined by capturing patients with K+ values within the PCC range either high or low, examined in outlier analysis section.

Figure 52 K+ Change from baseline, placebo compared to ezogabine all doses, WK 2-18.

Distributions

PBO CHGBASE



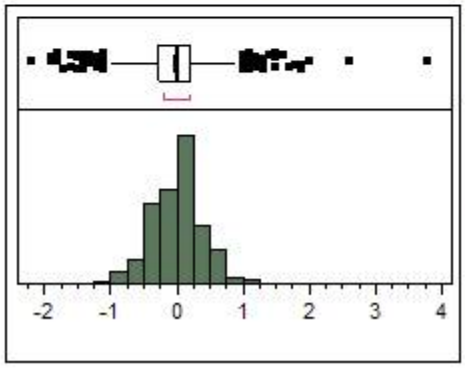
Quantiles

100.0%	maximum	2.100
99.5%		1.157
97.5%		0.800
90.0%		0.500
75.0%	quartile	0.200
50.0%	median	0.000
25.0%	quartile	-0.300
10.0%		-0.500
2.5%		-0.800
0.5%		-1.200
0.0%	minimum	-1.700

Moments

Mean	-0.016935
Std Dev	0.406245
Std Err Mean	0.0081477
upper 95% Mean	-0.000958
lower 95% Mean	-0.032912
N	2486

K+ 600 - 1200 CHGBASE



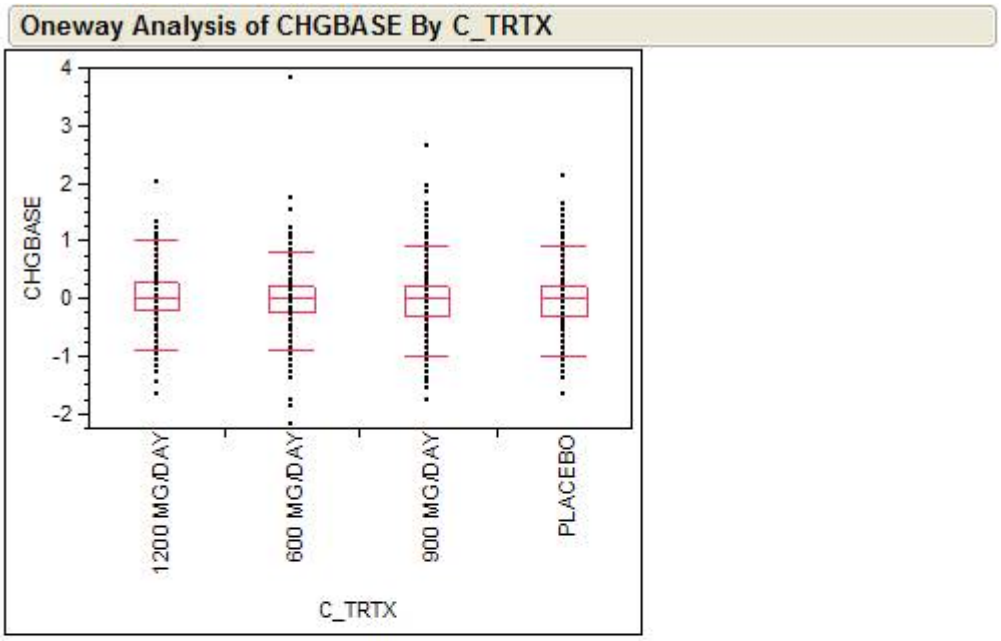
Quantiles

100.0%	maximum	3.800
99.5%		1.243
97.5%		0.800
90.0%		0.500
75.0%	quartile	0.200
50.0%	median	0.000
25.0%	quartile	-0.300
10.0%		-0.500
2.5%		-0.900
0.5%		-1.244
0.0%	minimum	-2.200

Moments

Mean	-0.019249
Std Dev	0.4166006
Std Err Mean	0.0064967
upper 95% Mean	-0.006511
lower 95% Mean	-0.031986
N	4112

Figure 53 K+ mean change from baseline placebo and all dose groups, WK 2-18, medians and means.



Missing Rows 34

Quantiles

Level	Minimum	10%	25%	Median	75%	90%	Maximum
1200 MG/DAY	-1.7	-0.5	-0.2	0	0.3	0.5	2
600 MG/DAY	-2.2	-0.5	-0.25	0	0.2	0.4	3.8
900 MG/DAY	-1.8	-0.6	-0.3	0	0.2	0.5	2.6
PLACEBO	-1.7	-0.5	-0.3	0	0.2	0.5	2.1

Means and Std Deviations

Level	Number	Mean	Std Dev	Std Err Mean	Lower 95%	Upper 95%
1200 MG/DAY	1415	0.00502	0.393233	0.01045	-0.0155	0.0255
600 MG/DAY	1394	-0.02414	0.404799	0.01084	-0.0454	-0.0029
900 MG/DAY	1303	-0.04037	0.451258	0.01250	-0.0649	-0.0158
PLACEBO	2486	-0.01693	0.406245	0.00815	-0.0329	-0.001

Bicarbonate (HCO_3)

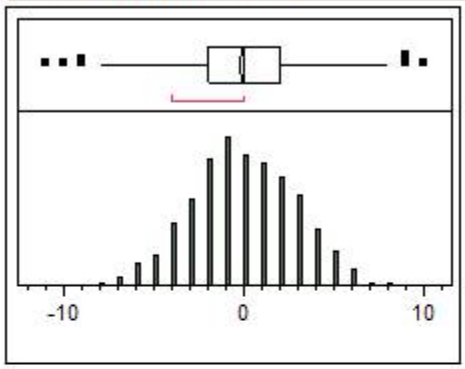
Examination of bicarbonate change from baseline of placebo compared to ezogabine treatment in all dose groups combined reveals medians are both equal to zero. The means are very close, -0.13 for the control group and -0.17 for the ezogabine treatment group. The treatment group has greater extreme values with maximum and minimum values of the placebo group 10 , -11meq/l respectively and 12, -16 for the ezogabine treatment group, figure 54 . Examination of the placebo and each dose group independently reveals medians all equal to zero and means closely spaced, figure 55.

Values of potential clinical concern are captured from the placebo and ezogabine treatment groups and discussed in electrolyte outliers.

Figure 54 HCO_3 Change from baseline, Placebo, All EZO treatment groups, medians, means.

Distributions

HCO3 PBO CHGBASE



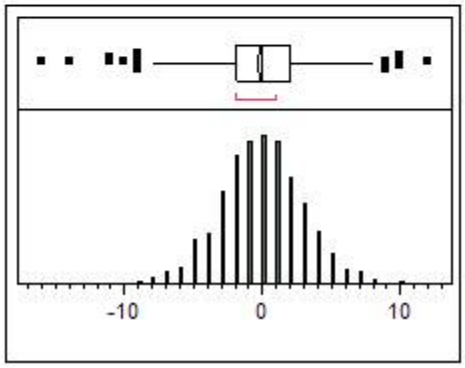
Quantiles

100.0%	maximum	10.00
99.5%		8.00
97.5%		5.15
90.0%		4.00
75.0%	quartile	2.00
50.0%	median	0.00
25.0%	quartile	-2.00
10.0%		-4.00
2.5%		-6.00
0.5%		-8.00
0.0%	minimum	-11.00

Moments

Mean	-0.130903
Std Dev	2.9548367
Std Err Mean	0.0722413
upper 95% Mean	0.0107903
lower 95% Mean	-0.272595
N	1673

HCO3 ALL EZO treatment CHGBASE



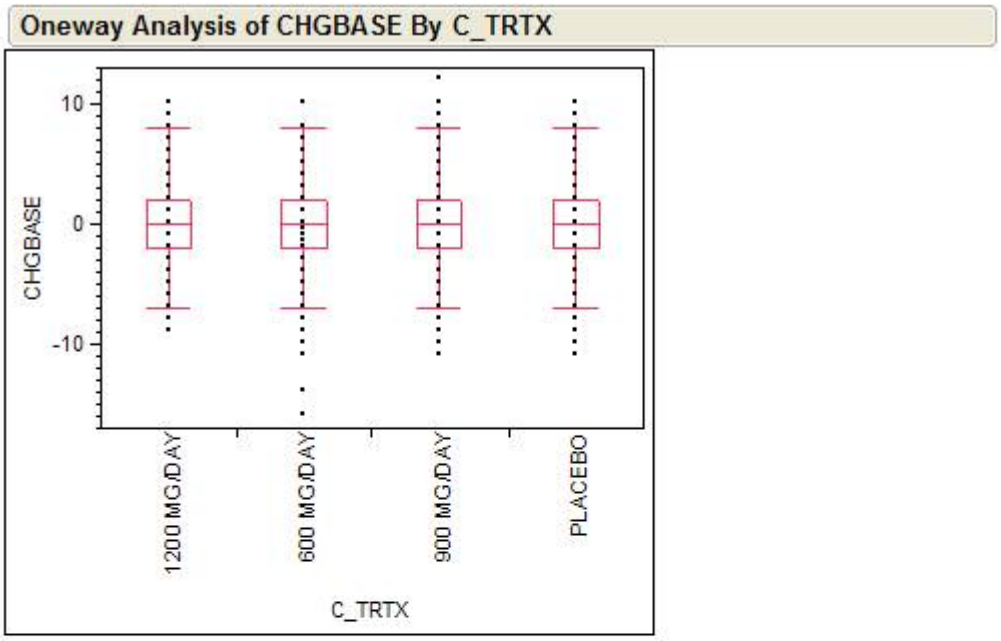
Quantiles

100.0%	maximum	12.00
99.5%		8.00
97.5%		6.00
90.0%		4.00
75.0%	quartile	2.00
50.0%	median	0.00
25.0%	quartile	-2.00
10.0%		-4.00
2.5%		-6.00
0.5%		-9.00
0.0%	minimum	-16.00

Moments

Mean	-0.169585
Std Dev	3.1185721
Std Err Mean	0.0669462
upper 95% Mean	-0.0383
lower 95% Mean	-0.300871
N	2170

Figure 55 HCO_3 mean change from baseline placebo and all dose groups, WK 2-18, medians and means.



Missing Rows 19

Quantiles

Level	Minimum	10%	25%	Median	75%	90%	Maximum
1200 MG/DAY	-9	-4	-2	0	2	4	10
600 MG/DAY	-16	-4	-2	0	2	3	10
900 MG/DAY	-11	-4	-2	0	2	4	12
PLACEBO	-11	-4	-2	0	2	4	10

Means and Std Deviations

Level	Number	Mean	Std Dev	Std Err Mean	Lower 95%	Upper 95%
1200 MG/DAY	797	-0.07905	3.10819	0.11010	-0.2952	0.1371
600 MG/DAY	717	-0.23849	3.02255	0.11288	-0.4601	-0.0169
900 MG/DAY	656	-0.20427	3.23451	0.12629	-0.4522	0.0437
PLACEBO	1673	-0.13090	2.95484	0.07224	-0.2726	0.0108

Chloride (Cl)

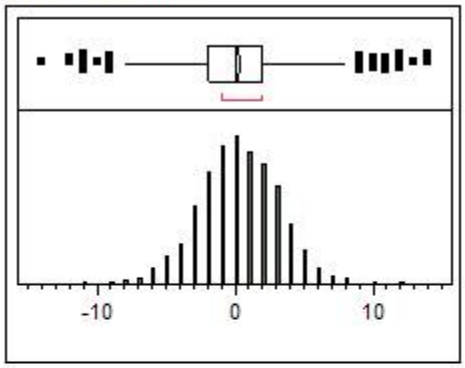
Change from baseline chloride levels for placebo and ezogabine treatment groups are compared. This comparison reveals a median change from baseline of 0 meq/l in the placebo group and 1 meq/l in the ezogabine treatment group. All events at weeks 2 – 18 are used in the analysis, figure 56. The mean change in baseline of the placebo group is .23meq/l, with a mean of .79meq/l in the ezogabine treatment group. The median and mean change from baseline for all events week 2- 18 of the placebo group, 600mg, 900mg, and 1200mg groups are compared, figure 57. The comparison reveals the placebo group has a median of 0meq/l and mean of .23meq/l change from baseline (as in the preceding analysis). The 600mg median change from baseline is 0meq/l, with a mean of .40meq/l. The 900mg group had a median change from baseline of 1meq/l with a mean of .58meq/l. The 1200mg group had a median change from baseline of 1meq/l

and a median of 1meq/l. The 600mg dose group had the largest maximum change from baseline value of 30meq/l, comparatively the 900mg, 1200mg and placebo group minimum and maximum values were similar in magnitude.

Figure 56 Cl- Change from baseline, Placebo compared to ezogabine all doses, weeks 2-18, all events.

Distributions

PBO CHGBASE



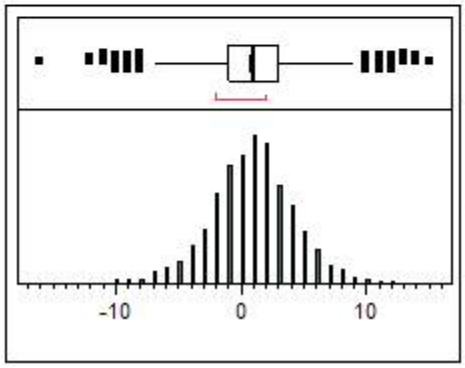
Quantiles

100.0%	maximum	14.00
99.5%		11.00
97.5%		6.00
90.0%		4.00
75.0%	quartile	2.00
50.0%	median	0.00
25.0%	quartile	-2.00
10.0%		-3.00
2.5%		-6.00
0.5%		-9.00
0.0%	minimum	-14.00

Moments

Mean	0.2281879
Std Dev	3.1834142
Std Err Mean	0.0632522
upper 95% Mean	0.3522192
lower 95% Mean	0.1041566
N	2533

EZO ALL DOSE CHGBASE



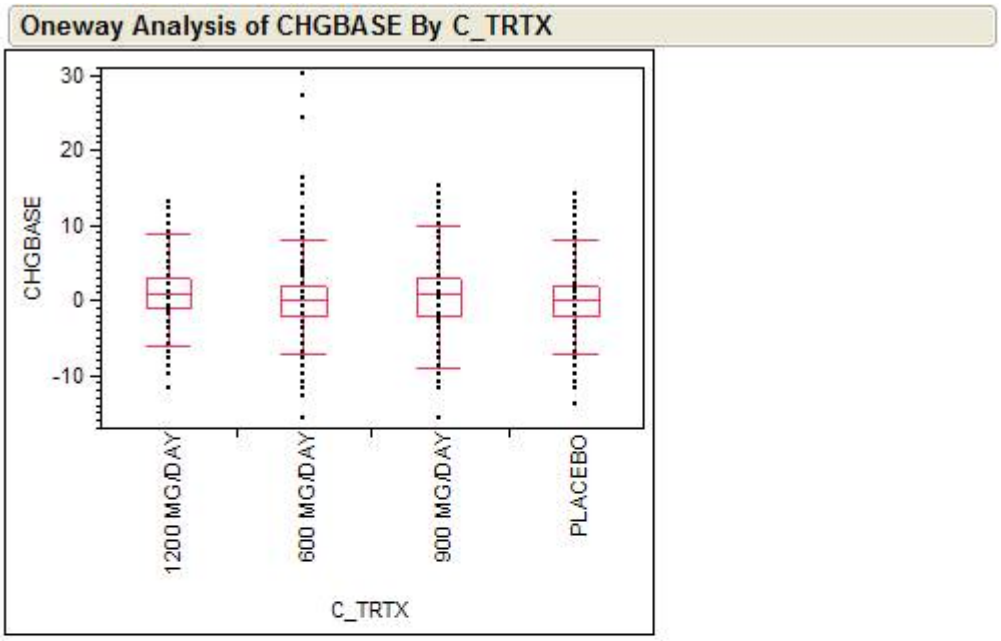
Quantiles

100.0%	maximum	15.00
99.5%		11.14
97.5%		8.00
90.0%		5.00
75.0%	quartile	3.00
50.0%	median	1.00
25.0%	quartile	-1.00
10.0%		-3.00
2.5%		-7.00
0.5%		-10.00
0.0%	minimum	-16.00

Moments

Mean	0.7902527
Std Dev	3.5230058
Std Err Mean	0.0669381
upper 95% Mean	0.9215064
lower 95% Mean	0.658999
N	2770

Figure 57 CI- Change from baseline, placebo, 600mg, 900mg, 1200mg, weeks 2-18, all events, medians, means.



Missing Rows 18

Quantiles

Level	Minimum	10%	25%	Median	75%	90%	Maximum
1200 MG/DAY	-12	-3	-1	1	3	5	13
600 MG/DAY	-16	-4	-2	0	2	4	30
900 MG/DAY	-16	-4	-2	1	3	5	15
PLACEBO	-14	-3	-2	0	2	4	14

Means and Std Deviations

Level	Number	Mean	Std Dev	Std Err Mean	Lower 95%	Upper 95%
1200 MG/DAY	1434	0.988842	3.36823	0.08895	0.81436	1.1633
600 MG/DAY	1430	0.404196	3.86021	0.10208	0.20395	0.6044
900 MG/DAY	1336	0.577096	3.67123	0.10044	0.38006	0.7741
PLACEBO	2533	0.228188	3.18341	0.06325	0.10416	0.3522

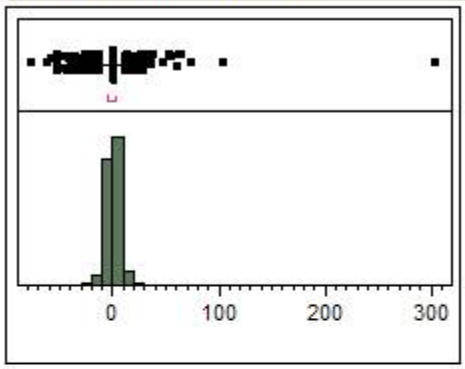
9.13.1.3 Liver Function

ALT

Figure 58 ALT placebo, all ezogabine treatment groups compare change from baseline, median, means.

Distributions

PBO CHGBASE WK 2-18



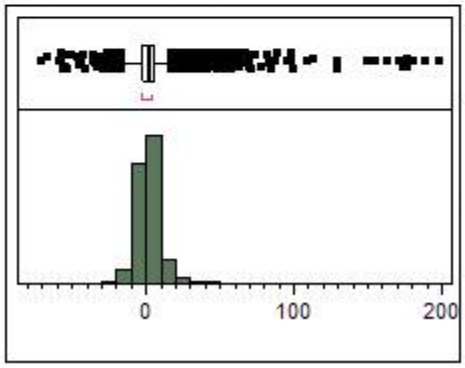
Quantiles

100.0%	maximum	305.0
99.5%		36.9
97.5%		16.0
90.0%		7.0
75.0%	quartile	3.0
50.0%	median	0.0
25.0%	quartile	-3.0
10.0%		-7.0
2.5%		-16.0
0.5%		-41.0
0.0%	minimum	-77.0

Moments

Mean	0.0934385
Std Dev	10.877332
Std Err Mean	0.2216635
upper 95% Mean	0.5281096
lower 95% Mean	-0.341232
N	2408

EZO CHGBASE WK 2-18



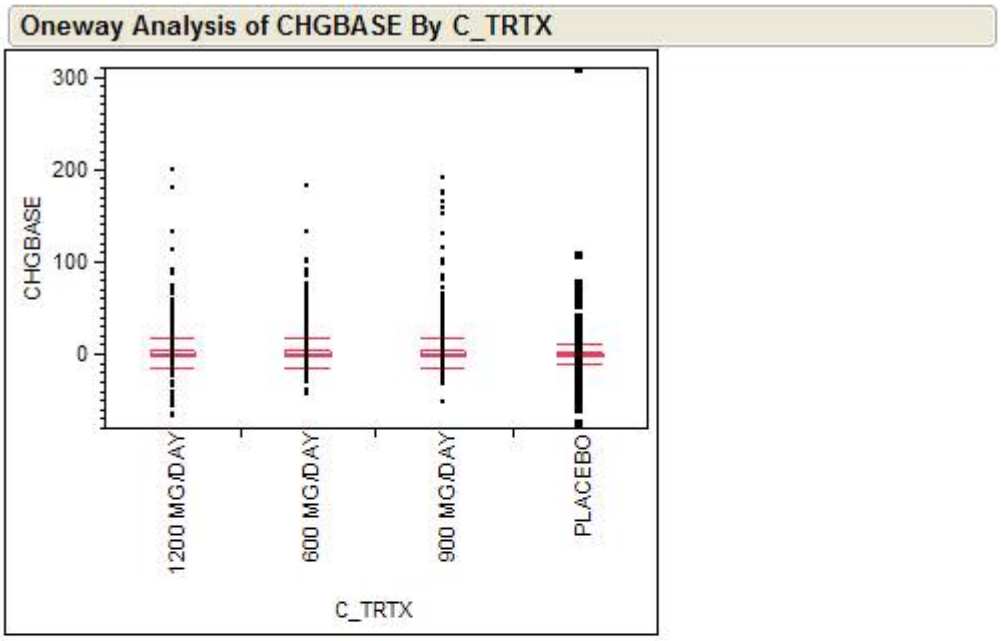
Quantiles

100.0%	maximum	198.0
99.5%		88.5
97.5%		38.0
90.0%		12.0
75.0%	quartile	5.0
50.0%	median	1.0
25.0%	quartile	-3.0
10.0%		-7.0
2.5%		-16.0
0.5%		-33.5
0.0%	minimum	-70.0

Moments

Mean	2.5467918
Std Dev	15.402162
Std Err Mean	0.2407764
upper 95% Mean	3.0188445
lower 95% Mean	2.0747391
N	4092

Figure 59 ALT change from baseline, compare placebo, 600mg, 900mg, 1200mg group medians and means.



Missing Rows 8

Quantiles

Level	Minimum	10%	25%	Median	75%	90%	Maximum
1200 MG/DAY	-70	-8	-3	1	5	12	198
600 MG/DAY	-46	-8	-3	1	5	12	181
900 MG/DAY	-54	-7	-3	0	5	13	189
PLACEBO	-77	-7	-3	0	3	7	305

Means and Std Deviations

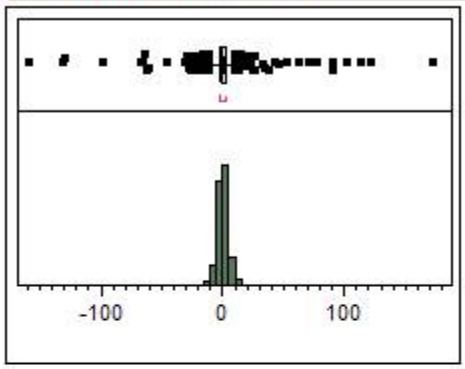
Level	Number	Mean	Std Dev	Std Err Mean	Lower 95%	Upper 95%
1200 MG/DAY	1343	2.39135	15.6885	0.42810	1.552	3.2312
600 MG/DAY	1420	2.40174	13.8928	0.36868	1.679	3.1250
900 MG/DAY	1329	2.85885	16.6039	0.45546	1.965	3.7523
PLACEBO	2408	0.09344	10.8773	0.22166	-0.341	0.5281

AST

Figure 60 AST change from baseline, placebo compared to all ezogabine dose groups combined, all weeks 2-18 combined, medians and means.

Distributions

AST PBO CHGBASE 2-18



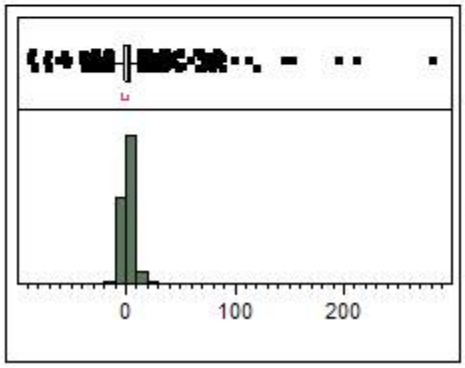
Quantiles

100.0%	maximum	173.0
99.5%		40.6
97.5%		11.0
90.0%		6.0
75.0%	quartile	3.0
50.0%	median	0.0
25.0%	quartile	-2.0
10.0%		-5.0
2.5%		-11.0
0.5%		-27.6
0.0%	minimum	-158.0

Moments

Mean	0.0634858
Std Dev	10.276959
Std Err Mean	0.2040751
upper 95% Mean	0.4636567
lower 95% Mean	-0.336685
N	2536

AST EZO CHGBASE WK 2-18



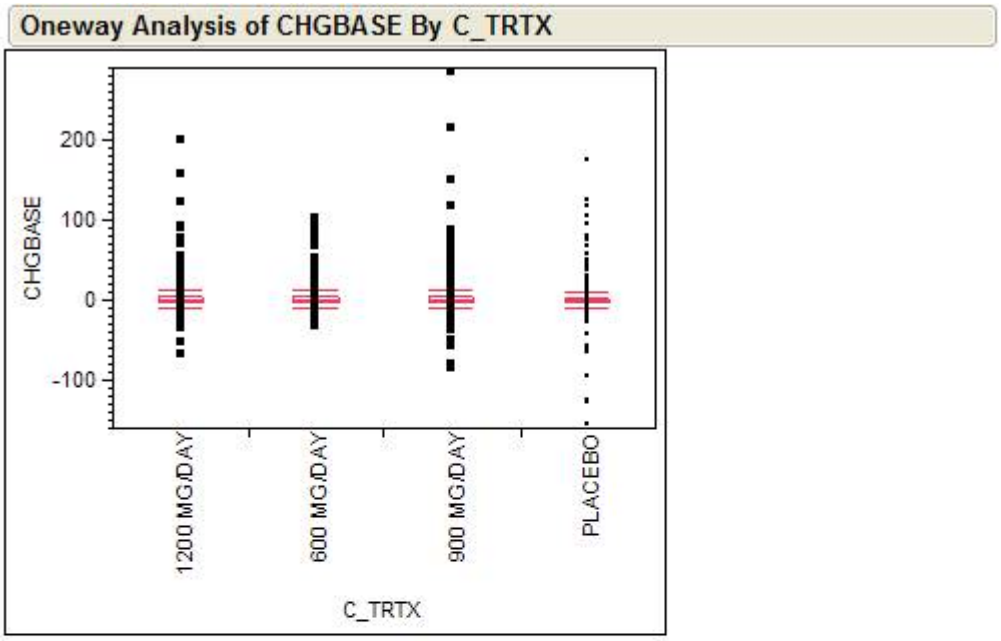
Quantiles

100.0%	maximum	282.0
99.5%		76.0
97.5%		21.0
90.0%		8.0
75.0%	quartile	4.0
50.0%	median	1.0
25.0%	quartile	-2.0
10.0%		-4.0
2.5%		-10.0
0.5%		-35.0
0.0%	minimum	-87.0

Moments

Mean	1.943302
Std Dev	12.498033
Std Err Mean	0.1928488
upper 95% Mean	2.3213877
lower 95% Mean	1.5652162
N	4200

Figure 61 AST change from baseline, placebo compared to 600mg, 900mg, 1200mg dose groups, all weeks 2-18 combined, medians and means.



Missing Rows 10

Quantiles

Level	Minimum	10%	25%	Median	75%	90%	Maximum
1200 MG/DAY	-71	-5	-2	1	4	8	197
600 MG/DAY	-34	-5	-2	1	4	8	100
900 MG/DAY	-87	-4	-2	1	4	8	282
PLACEBO	-158	-5	-2	0	3	6	173

Means and Std Deviations

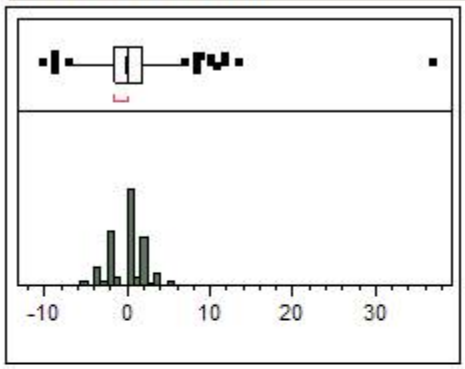
Level	Number	Mean	Std Dev	Std Err Mean	Lower 95%	Upper 95%
1200 MG/DAY	1435	1.90940	12.1306	0.32023	1.281	2.5376
600 MG/DAY	1428	1.84124	9.4385	0.24977	1.351	2.3312
900 MG/DAY	1337	2.08870	15.4208	0.42174	1.261	2.9160
PLACEBO	2536	0.06349	10.2770	0.20408	-0.337	0.4637

Total Bilirubin

Figure 62 Total Bilirubin change from baseline in placebo and ezogabine all dose groups combined, weeks 2-18, medians and means.

Distributions

TBILI PBO CHGBASE



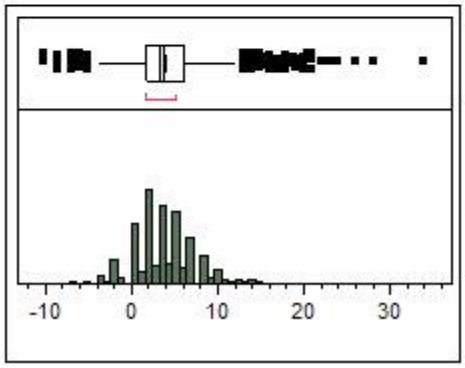
Quantiles

100.0%	maximum	37.00
99.5%		8.55
97.5%		5.13
90.0%		2.00
75.0%	quartile	1.71
50.0%	median	0.00
25.0%	quartile	-1.71
10.0%		-3.00
2.5%		-4.90
0.5%		-6.84
0.0%	minimum	-10.00

Moments

Mean	-0.027911
Std Dev	2.4043237
Std Err Mean	0.0478668
upper 95% Mean	0.065951
lower 95% Mean	-0.121773
N	2523

TBILI EZO CHGBASE



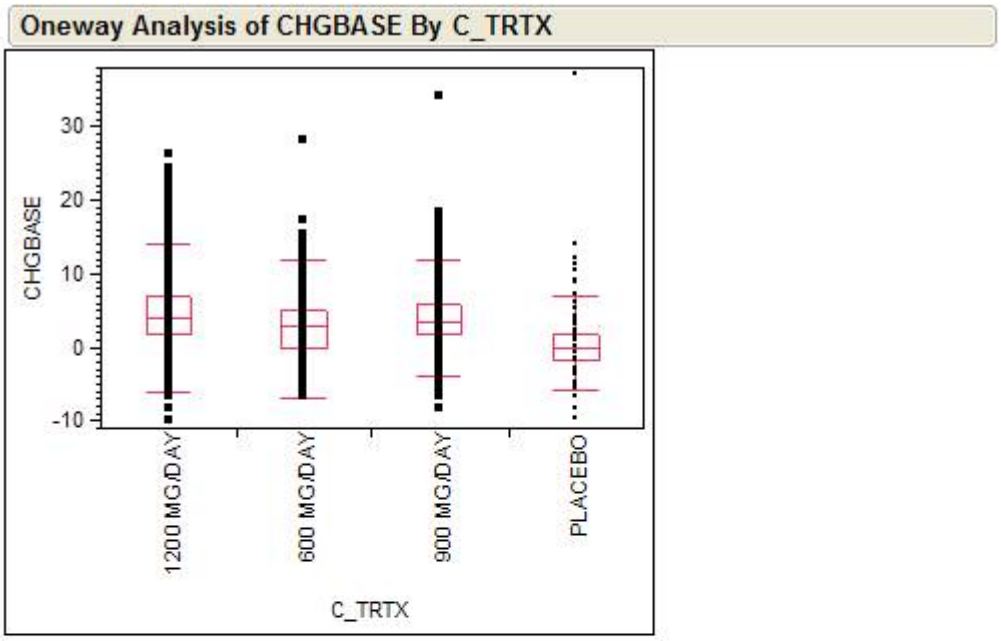
Quantiles

100.0%	maximum	34.00
99.5%		19.00
97.5%		13.68
90.0%		8.55
75.0%	quartile	6.00
50.0%	median	3.42
25.0%	quartile	1.71
10.0%		0.00
2.5%		-3.42
0.5%		-6.84
0.0%	minimum	-10.26

Moments

Mean	3.8619342
Std Dev	4.1203011
Std Err Mean	0.0638672
upper 95% Mean	3.987148
lower 95% Mean	3.7367203
N	4162

Figure 63 Total bilirubin change from baseline, placebo, 600mg, 900mg, 1200mg, weeks 2-28 combined, medians and means.



Missing Rows 11

Quantiles

Level	Minimum	10%	25%	Median	75%	90%	Maximum
1200 MG/DAY	-10.26	0	1.71	4	7	11	26
600 MG/DAY	-7	-1.71	0	3	5.13	6.84	28
900 MG/DAY	-8.55	0	1.71	3.42	6	8.55	34
PLACEBO	-10	-3	-1.71	0	1.71	2	37

Means and Std Deviations

Level	Number	Mean	Std Dev	Std Err Mean	Lower 95%	Upper 95%
1200 MG/DAY	1410	4.8917	4.88144	0.13000	4.637	5.1467
600 MG/DAY	1424	2.7859	3.38680	0.08975	2.610	2.9619
900 MG/DAY	1328	3.9224	3.64134	0.09992	3.726	4.1184
PLACEBO	2523	-0.0279	2.40432	0.04787	-0.122	0.0660

Group median and mean total bilirubin values are examined. Examination of all placebo compared to all ezogabine measurements weeks 2 to 18 reveal an increase in median and mean values from baseline compared to placebo, both in the combined ezogabine dose groups and placebo compared to the individual 600mg, 900mg and 1200mg dose groups, figures 62, 63. The median and mean change from baseline for placebo group is 0umol/L and -.03umol/L respectively. The median and mean change from baseline for ezogabine treatment group is 3.42umol/l and 3.9umol/l respectively. Examination of the individual ezogabine dose groups reveals means of 2.8, 3.9, and 4.9umol/l at the 600mmg, 900mg, and 1200mg dose respectively.

Analysis of change from baseline on a week by week basis for placebo and the individual 600mg, 900mg and 1200mg dose groups reveals an increase in mean values compared to placebo at all weeks at all doses. The increase in total bilirubin values

shows a trend of dose response beginning at week 4. there is no trend of increase in total bilirubin with increased duration of exposure, table 88.

9.13.1.4 Metabolic Indices

Median and mean change in blood glucose in studies 205, 301 and 302 comparing pooled treatment to pooled placebo are examined across the span of all visits weeks 2 to 18 in figure 64 and 65. In figure 28 the mean and median change in studies 205, 301 and 302 comparing dose groups to placebo are examined. In figures 66 and 67 week 4 alone is examined in the same fashion as figure 28.

Figure 64 Blood glucose change from baseline in placebo and ezogabine all dose groups combined, weeks 2-18, medians and means.

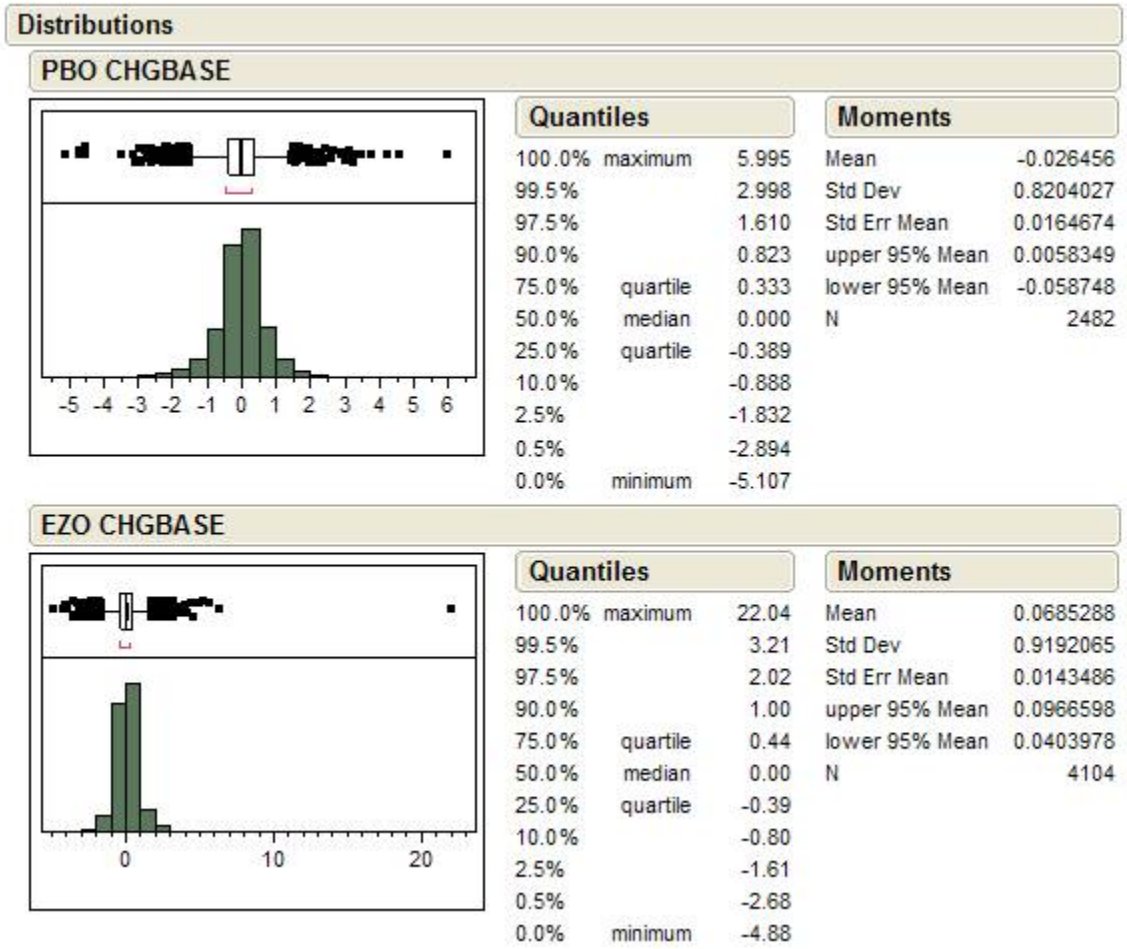
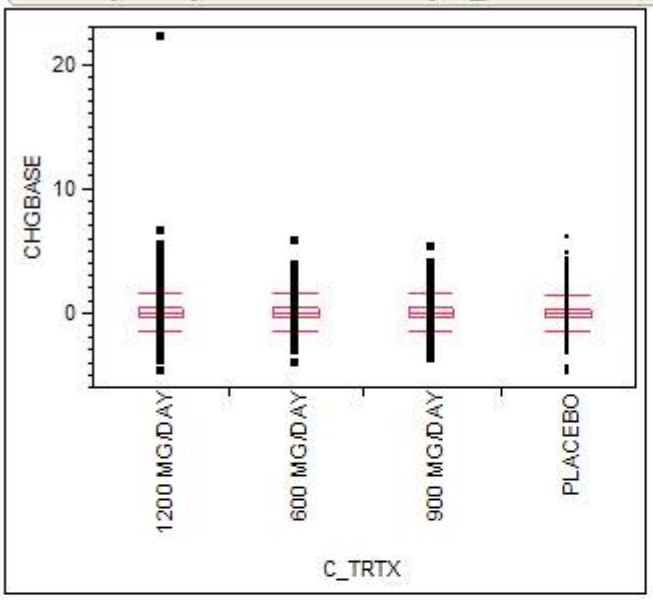


Figure 65 Blood glucose change from baseline, placebo, 600mg, 900mg, 1200mg, weeks 2-28 combined, medians and means.

Oneway Analysis of CHGBASE By C_TRTX



Missing Rows 38

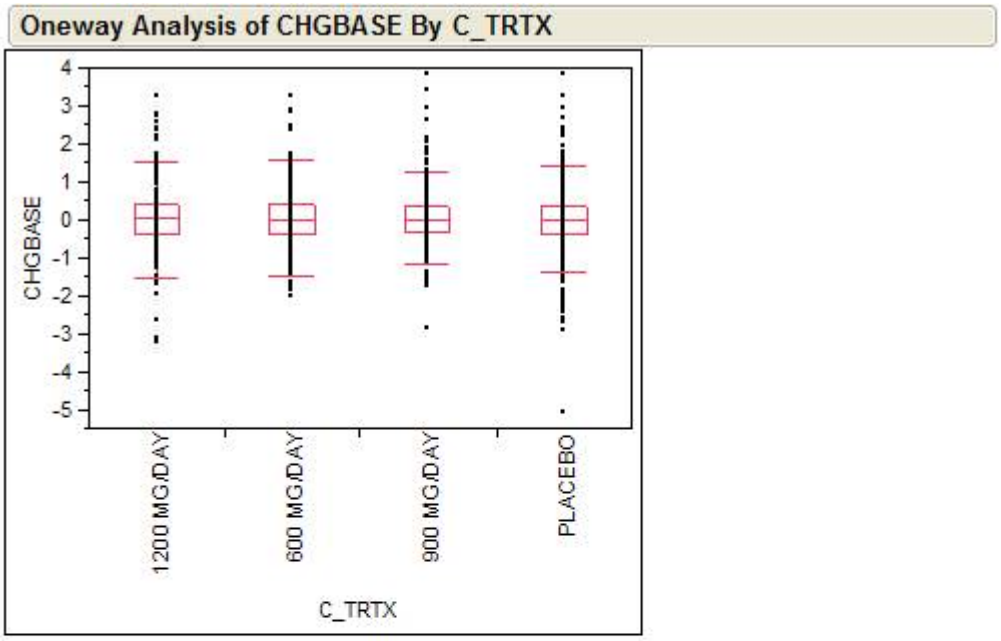
Quantiles

Level	Minimum	10%	25%	Median	75%	90%	Maximum
1200 MG/DAY	-4.88488	-0.8	-0.4	0	0.4	1	22.03747
600 MG/DAY	-4.16325	-0.72163	-0.33306	0	0.44408	0.99918	5.66202
900 MG/DAY	-3.8857	-0.88816	-0.38857	0	0.4	0.99918	5.05141
PLACEBO	-5.10692	-0.88816	-0.38857	0	0.33306	0.822855	5.99508

Means and Std Deviations

Level	Number	Mean	Std Dev	Std Err Mean	Lower 95%	Upper 95%
1200 MG/DAY	1412	0.06938	1.10100	0.02930	0.0119	0.12686
600 MG/DAY	1394	0.08949	0.80646	0.02160	0.0471	0.13186
900 MG/DAY	1298	0.04509	0.80911	0.02246	0.0010	0.08914
PLACEBO	2482	-0.02646	0.82040	0.01647	-0.0587	0.00583

Figure 66 Blood Glucose, change from baseline at week 4, placebo, 600mg, 900mg, 1200mg, medians and means.



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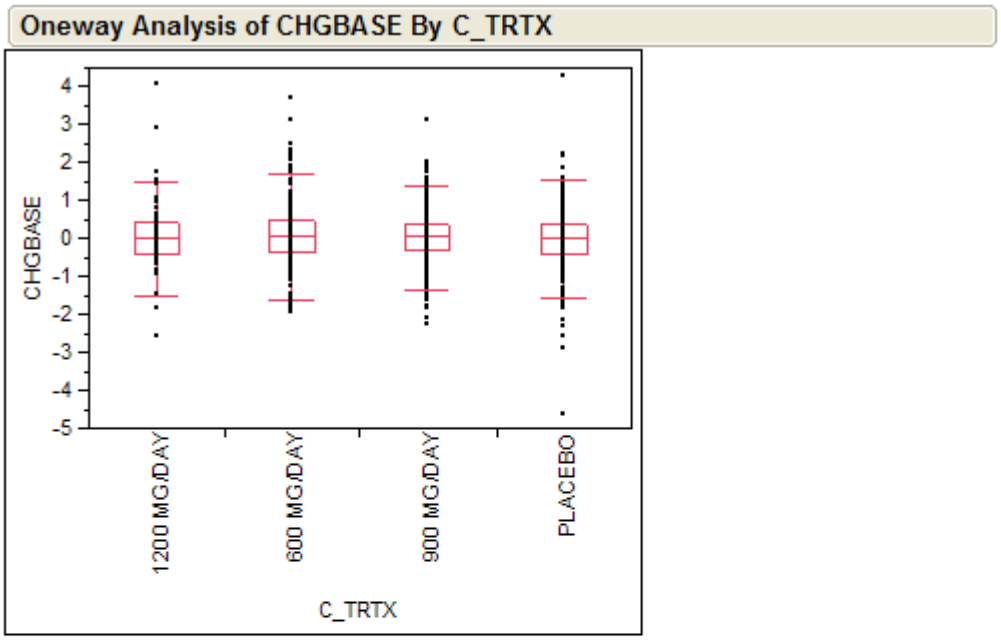
Quantiles

Level	Minimum	10%	25%	Median	75%	90%	Maximum
1200 MG/DAY	-3.27509	-0.77714	-0.4	0.05551	0.38857	0.99918	3.21958
600 MG/DAY	-2.05387	-0.87706	-0.38857	0	0.4	0.988078	3.191825
900 MG/DAY	-2.9	-0.72718	-0.33306	0	0.346938	0.889344	3.77468
PLACEBO	-5.10692	-0.98253	-0.38857	0	0.33306	0.982527	3.77468

Means and Std Deviations

Level	Number	Mean	Std Dev	Std Err Mean	Lower 95%	Upper 95%
1200 MG/DAY	229	0.04396	0.839150	0.05545	-0.0653	0.15323
600 MG/DAY	241	0.04387	0.803549	0.05176	-0.0581	0.14583
900 MG/DAY	238	0.04510	0.787413	0.05104	-0.0555	0.14565
PLACEBO	382	-0.01383	0.886169	0.04534	-0.1030	0.07532

Figure 67 Blood Glucose, change from baseline at week 12, placebo, 600mg, 900mg, 1200mg, medians and means.



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Quantiles

Level	Minimum	10%	25%	Median	75%	90%	Maximum
1200 MG/DAY	-2.6	-0.7	-0.4	0	0.424898	0.89408	4
600 MG/DAY	-2	-0.88261	-0.34694	0.077755	0.49959	0.99918	3.66366
900 MG/DAY	-2.3	-0.74383	-0.3	0.05551	0.394285	1.179426	3.05305
PLACEBO	-4.66284	-0.94367	-0.4	0	0.4	0.94367	4.21876

Means and Std Deviations

Level	Number	Mean	Std Dev	Std Err Mean	Lower 95%	Upper 95%
1200 MG/DAY	74	0.05596	0.893578	0.10388	-0.1511	0.26298
600 MG/DAY	210	0.08483	0.846527	0.05842	-0.0303	0.19999
900 MG/DAY	185	0.09122	0.775108	0.05699	-0.0212	0.20365
PLACEBO	219	-0.02590	0.911196	0.06157	-0.1473	0.09545

The median and mean change from baseline of the placebo group for weeks 2-18 combined is 0mmol/l and -.026mmol/l respectively. The median and mean changes from baseline for all ezogabine treatment groups combined for weeks 2-18 are 0mmol/l and .069mmol/l respectively, figure 64. The median change from baseline for individual ezogabine dose groups, weeks 2-18 combined for the 600mg, 900mg and 1200mg were all 0mmol/l. the mean change from baseline for individual ezogabine dose groups, weeks 2-18 combined for the 600mg, 900mg and 1200mg dose groups were .09mmol/l, 0.45mmol/l and 1.1mmol/l respectively, figure 65. The corresponding placebo median and mean values are noted above.

The mean and median change from baseline of the placebo, 600mg, 900mmg and 1200mg at weeks 4 (titration) and 12 (maintenance) are also examine to determine if

there is any notable change in glucose values during initial exposure compared to sustained exposure during maintenance. The analysis of glucose values at week 4 reveal the medians of placebo, 600mg, 900mg, and 1200mg are 0mmol/l, 0mmol/l, 0mmol/l, and .056mmol/l respectively. The means of the placebo and ezogabine dose groups, provided in the same order are -0.014mmol/l, 0.043mmol/l, 0.045mmol/l and 0.044mmol/l respectively, figure 66. The same analysis is carried out for placebo, 600mg, 900mg and 1200mg groups at 12 weeks. The medians for change in baseline at 12 weeks were 0mmol/l, 0.078mmol/l, 0.06mmol/l and 0mmol/l respectively, the means were -0.026mmol/l, 0.084mmol/l, 0.09mmol/l, 0.056mmol/l respectively, figure 67.

9.14 Severe Psychiatric Adverse Events, associated case summaries and search term tables

Case 10508 summary:

This 32-year-old Hispanic female, taking ezogabine in combination with valproic acid and topiramate for refractory complex partial seizures and with previous history of depression and suicidal ideas in Jan 2004, was hospitalized with major depression on (b) (6) that led to discontinuation of study drug treatment.

This patient took her first dose of blinded ezogabine on 17 Nov 2006 (Day 1) during titration phase of Study 301 and began open-label treatment on 04 May 2007 (Day 169) at a dose of 1050 mg/day. Weight loss was first reported beginning in Aug 2007 and was later attributed to a depressive state. Beginning (b) (6) she experienced mild bradykinesia and moderate tremor that continued. On (b) (6), she experienced Paraesthesia, facial edema, bradykinesia, and muteness. She presented at the emergency department in a catatonic state, crying, and moving her eyes only. After receiving midazolam, she stayed in the emergency department 1 hour for observation and was subsequently released home with a prescription for benzodiazepine and was scheduled for a psychiatry consult. On the following day, during a telephone follow-up, the patient reported improvement while experiencing a moderate somnolence.

At her psychiatry consult on (b) (6), the patient was incoherent and delusional and reported auditory and visual hallucinations as well as itching of the hands and face. She was admitted to the psychiatric unit of the hospital with severe depression and Paraesthesia of the hands and face. The patient was observed to have a pseudoseizure described as a fall “without disconnection” and erratic movements which lasted several minutes. The catatonic

episode was reported to be a conversion disorder motor episode associated with depression. The following day, she was reported to remain sad, but stable and without delusive ideas. Ezogabine was rapidly tapered from (b) (6) Fluoxetine, lorazepam, and sulprid were added to her treatment regimen. The patient demonstrated psychomotor delay and somnolence, but remained awake and maintained visual contact. Her speech had bradylalia but the thinking process was reported as coherent and she was able to understand and repeat phrases. Her memory was intact and, although she remained in a depressive mood, her hallucinations had disappeared and she denied delirious ideas. The patient was released from the hospital on (b) (6) and continued treatment with fluoxetine and lorazepam. Weight loss and slight bradykinesia continued and the depression was considered to be ongoing but controlled as of her last study visit on (b) (6)

The investigator assessed the event of major depression as serious and probably related to ezogabine. The sponsor assessed the event as serious, unexpected, and possibly related to ezogabine.

Medical history:
Status epilepticus, complex partial seizures, and partial seizures evolving to secondary generalization, all since 1976.

Skin hyperpigmentation on neck and arms (unknown date, continuing), typhoid fever (unknown dates).

Additional medical history received from the study site included cryptogenic epilepsy with personality changes (unknown dates) and emotional changes and suicidal ideations treated with fluoxetine (Jan 2004).

Concomitant medications other than AEDs:
trimethoprim (urinary tract infection)

END OF CASE REPORT

Case 00022 Summary

Study / Subject No.: **Age (yrs) / Sex / Race:**	VRX-RET-E22-106 / 22 52 / Female / Caucasian		
Event Terms (verbatim / preferred term):	Feeling of panic / panic reaction		
Ezogabine dose (Period) at onset: **Oral contraceptive co-administration** **Date of discontinuation (Study Day): Ezogabine dose (Period) at onset:**	Oral contraceptive + Ezogabine 300 mg TID 24 November 2007 (Day 22)–07 December 2007 (Day 35) Ortho® 1/35 07 December 2007 (Day 35)		
Adverse event as reported by investigator:	**Adverse event as coded:**	**SAE**	**DC'd due to AE:**
Feeling of panic	Panic reaction	No	Yes

Case summary: This 52-year-old Caucasian female experienced the severe AE of panic reaction that led to discontinuation of study drug. This subject had experienced at least one episode of dizziness per day from 26 November to 07 December 2007 of Periods 2 and 3 and had reported 3 incidences of visual disturbances while the dose of ezogabine was being titrated up. She experienced hallucinations on Days 27, 29, and 30 commencing within 20 to 60 minutes after the morning doses of ezogabine with oral contraceptive. The hallucinations lasted between 10 and 30 minutes. On 06 December 2007 (Day 34), ezogabine was increased to the maximum dose of 300 mg TID. The next day, she experienced severe panic reaction and visual hallucinations which occurred 9 minutes after the morning dose of study drug. Staff found her in her room "screaming and crying stating she had been split in half and was bleeding." She was administered 0.5 mg ativan to treat the panic reaction and was monitored closely by clinic staff. The visual hallucination resolved 10 minutes after onset and the panic reaction resolved 45 minutes after onset. The subject also experienced visual disturbances (blurred, seeing spots) 15 hours later which resolved after another 20 hours. Study drug was discontinued due to the panic reaction following the morning dose of 300 mg ezogabine and oral contraceptive on Day 35.

The investigator considered the panic reaction to be possibly related to study drugs.

Medical History: Non-smoker
Concomitant medication in addition to those mentioned above - None

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3. *Date of Event (mm/dd/yyyy)*
05/24/2010

5. *Describe Event or Problem*

This 42 -year-old male subject was enrolled in an open label, randomized, up-titration study to assess the effect of urine sample handling procedures on the safety results of urine obtained from healthy subjects receiving repeat doses of ezogabine/ezogabine. The subject was allocated to regimen B and received oral ezogabine/ezogabine three times per day (dosing schedule 8,8,8 hours) from 01 May 2010.

On 24 May 2010, 23 days after the start of ezogabine/ ezogabine and approximately 40 minutes after the second dose of Day 24 ezogabine/ezogabine, the subject developed a severe psychotic episode. The event was clinically significant (or requiring intervention). He also experienced severe incident of hallucination. At this point the subject was sitting at a table and began to get extremely agitated. He started throwing things, walking around and talking incoherently. He started attempting to break glass windows and a mirror and referred to wanting to commit suicide, at that point one of the study nurses attempted to calm the subject at which point he wrapped his arms around her and would

not release her until two other subjects restrained him in a recliner. After approximately 10 minutes of being restrained the subjects was able to calm down.

His neurological examination is unchanged from his admission and no new findings on the rest of physical examination. The subject was interviewed and examined the following day. He was calm, had little memory of the event, and had no sequelae. He did mention very little difficulties with the AM dosing throughout the study but the afternoon and evening doses he did mention the feeling of it coming on or a rush like he was doing drugs along with having a hand tremor, come in coordination and strange dreams that seem be more frequent and intense as the study went onward. He also described the feeling of having his heart racing but he would check his pulse with the clock and it was about 50 to 60 bpm.

Further history was obtained and the subject admitted to a history of substance abuse - 2-3 episode of LSD use in high school, which is over 25 years ago, no history of LSD flashbacks; stopped using because a friend had a bad trip. Has been in alcohol treatment back in 2003, and presently uses alcohol occasionally. No family history of substance abuse or suicide. Suicidality: the subject did recount an impulsive (no plan or forethought) suicide attempt/gesture back in 1996 during a fight with his girlfriend when he had been drinking and was fearful that he would have to go back to prison if she called the police on him. He then slashed his left wrist. He was then evaluated and there was some consideration of treating him for Bipolar disorder but on further questioning he does not relate a significant history of manic or depressive episodes.

Treatment with ezogabine/ezogabine was discontinued and the subject was withdrawn from the study. The event improved on an unspecified date.

The investigator considered that there was a reasonable possibility that the psychotic episode may have been caused by ezogabine/ezogabine and that the event was possibly due to study participation.

The sponsor assessed the event of psychotic episode as serious, expected and possibly related.

6. Relevant Tests/laboratory Data, Including Dates

24 May 2010 - hematology, clinical chemistry, urinalysis samples were all within normal limits. Results of a urine drug screen were pending at the time of reporting.

7. Other Relevant History, including Preexisting Medical Conditions (e.g. allergies, race, pregnancy, smoking and alcohol use, hepatic/renal dysfunction, etc.)

Substance abuse

Alcohol abuse

Attempted Suicide

Substance abuse history - 2-3 episode of LSD use in High School which is over 25 years ago, no history of and presently uses alcohol occasionally. No family history of substance abuse or suicide. Suicidality: subject did recount an impulsive (no plan or forethought) suicide attempt/gesture back in 1996 during a fight with his girlfriend when he had been drinking and was fearful that he would have to go back to prison if she called the police on him. He then slashed his left wrist. He was then evaluate~ and there was some consideration of treating him for Bipolar disorder but on further questioning he does not relate a significant history of manic or depressive episodes. This event could be related to alcohol use.

END CASE REPORT

Table A	
List of verbatim terms which represent psychotic symptoms	
"HEARING VOICES" INTERMITTENT	ORGANIC DELUSIONAL PSYCHOTIC DISORDER
CHG MENTAL STAT.-AGIT. IMP.CONCENTRATION PARANOIA	PARANOIA
DEPERSONALISATION EXPERIENCE	PARANOID DELUSIONS
DEPERSONALIZATION	PARANOID IDEATIONS
HEARS A VOICE	PARANOID PSYCHOSIS{WITH HALLUCINATIONS}
MILD HALLUCINATION	PARNOID DELUSION
THINKING ABNORMAL	PSYCHOSIS
TROUBLE THINKING STRAIGHT	PSYCHOSIS PARANOID
VISUAL ILLUSIONS	PSYCHOSIS (HALLUCINATION)
{PARANOID PSYCHOSIS WITH}HALLUCINATIONS	PSYCHOSIS TO OBSERVATION
{PARANOID}HALLUCINATORY{PSYCHOSIS}	PSYCHOTIC DISORDERS
ACUTE PSYCHOSIS	PSYCHOTIC EPISODES
AUDITORY HALLUCINATIONS	PSYCHOTIC REACTION
EXACERBATION OF CHRONIC INTERICTAL PSYCHOSIS	PSYCHOTIC SYMPTOMS
HALLUCINATION VISUAL	REDUCED RESPONSIVENESS -> PSYCHOSIS
HALLUCINATIONS	VISUAL AND AUDITIVE HALLUCINATIONS
INTERMITTENT VISUAL HALLUCINATIONS	VISUAL HALLUCINATIONS
OPTICAL HALLUZINATION	

Table B
List of Preferred Terms (PT) resulting from corresponding verbatim terms in the above Table A
ACUTE PSYCHOSIS
CONFUSIONAL STATE- *only cases mapped to AETERM "abnormal thinking" are retained in the analysis*
DELUSION
DELUSIONAL DISORDER, PERSECUTORY TYPE
DEPERSONALISATION

HALLUCINATION
HALLUCINATION, AUDITORY
HALLUCINATION, VISUAL
HALLUCINATIONS, MIXED
ILLUSION
PARANOIA
PSYCHOTIC DISORDER
THINKING ABNORMAL

Table C
List of additional select preferred terms representing psychotic symptoms associated with ≥ 2 case of withdrawal from study
AGITATED DEPRESSION
AGITATION
ANXIETY DISORDER
CATATONIA
CONVERSION DISORDER
DELIRIUM
EUPHORIC MOOD
HYPOMANIA
MAJOR DEPRESSION
PANIC ATTACK
ABNORMAL BEHAVIOUR
AFFECT LABILITY
AGGRESSION
ANXIETY
BRADYPHRENIA
DEPRESSION
DISORIENTATION
INSOMNIA
SUICIDAL IDEATION

Table D , combined search terms
ABNORMAL BEHAVIOUR
ACUTE PSYCHOSIS
AFFECT LABILITY
AGGRESSION
AGITATED DEPRESSION
AGITATION
ANXIETY
ANXIETY DISORDER
BRADYPHRENIA
CATATONIA
CONVERSION DISORDER
DELIRIUM
DELUSION
DELUSIONAL DISORDER, PERSECUTORY TYPE
DEPERSONALISATION

DEPRESSION
DISORIENTATION
EUPHORIC MOOD
HALLUCINATION
HALLUCINATION, AUDITORY
HALLUCINATION, VISUAL
HALLUCINATIONS, MIXED
HYPOMANIA
ILLUSION
MAJOR DEPRESSION
PANIC ATTACK
PARANOIA
PSYCHOTIC DISORDER
SUICIDAL IDEATION
THINKING ABNORMAL

Hallucination and Psychosis Subset, Clinical Features of Study Withdrawals

SUBID	STUDY	History / summary	AE	AGE	SEX	dose @ onset
10201	301	The patient began experiencing anxiety, nervousr	psychotic disorder	32	F	700
20309	301	The patient presented with a behavioral disturban	psychotic disorder	58	F	780
50206	302	history of schizophrenia, began to experience a s	acute psychosis	46	F	600
60507	302	He first reported experiencing mild visual hallucin	hallucination, visual	21	M	900
60509	302	visual hallucination beginning on day 30 near	hallucination, visual	42	F	800
85416	302	hx of "brain lobectomy" in 2000, on day 8 of ezog	psychotic disorder	28	M	300
125	301	progressive cognitive adverse efffects with emerge	hallucination, visual	55	F	857
3201	301	On 01 Sep 2006 (Day 45), she experienced sever	hallucination, visual	61	F	1050
5308	301	She experienced hallucinations from 01 Nov 2006	hallucination	37	F	750
15211	301	day 45 followed by mild confusional state, dysar	hallucination, visual	40	F	742.9
2111	301	patient's wife reported he became agitated,	psychotic disorder	71	M	1000
1141	205	post ictal pyschiatric symptoms- agression, agita	psychotic disorder	46	M	1200
Mean				44.8		806.7
SD						229.9

SUBID	Hospitalization	dechallange / recovery	SAE/ Withdrawal	TTO days	Case best approximates
10201	yes	unknown	yes / yes	30	drug effect
20309	yes	not provided	yes / yes	30	drug effect
50206	yes	not provided	yes / yes	49	drug effect
60507	no	yes, 9 day recovery	no / yes	42	drug effect
60509	no	yes	no / yes	30	drug effect
85416	yes	yes, 25 day to discharge	yes / yes	8	drug effect
125	no	yes, 1 day recovery	no / yes	34	drug intoxication with hallucination
3201	no	yes, 3 day recovery	no / yes	42	drug intoxication with hallucination
5308	no	yes, 3 day recovery	no / yes	30	drug intoxication with hallucination
15211	no	transient effects, resolved before ezogabine taper	no / yes	42	drug intoxication with hallucination
2111	yes	yes, 2 day recovery	yes / yes	42	drug related exacerbation of epilepsy with post
1141	yes	continued EZO	yes / no	42	post ictal psychosis
Mean	6 Y, 6 N			35.1	
SD				10.7	

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/s/

STEVEN T DINSMORE
11/29/2010

NORMAN HERSHKOWITZ
11/30/2010