

Advisory Committee Briefing Document

Ezogabine for Partial Seizures in Epilepsy (NDA - 022345)

Peripheral and Central Nervous System Drugs Advisory Committee

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ABBREVIATIONS

ADD	Anticonvulsant Drug Development
ADR	Adverse drug reaction
AE	Adverse event
AED	Antiepileptic drug
ALT	Alanine aminotransferase
ANCOVA	Analysis of covariance
AST	Aspartate aminotransferase
AUA	American Urological Association
AUA SI	American Urological Association Symptom Index
AUC	Area under the plasma concentration-time curve
AUC(0- τ)	Area under the plasma concentration-time curve over the dosing interval
AUC(0- ∞)	Area under the plasma concentration-time curve from zero up to infinity
BFNC	Benign Familial Neonatal Convulsions
BID	Twice daily
C-CASA	Columbia Classification Algorithm of Suicide Assessment
CHMP	Committee for Medicinal Products for Human Use
CI	Confidence interval
C _{max}	Maximum concentration
CNS	Central nervous system
ECG	Electrocardiogram
EFD	Embryofetal development studies
EU	European Union
EURAP	European and International Registry of Anti-Epileptic Drugs in Pregnancy
EZG	Ezogabine
FDA	Food and Drug Administration
GABA	Gamma-aminobutyric acid
ICH	International Conference of Harmonization
ILAE	International League Against Epilepsy
INN	International Non-proprietary Names
IR	Immediate release
ITT	Intent-to-treat
IVH	Intraventricular hemorrhages
MedDRA	Medical Dictionary for Regulatory Activities
MTD	Maximum tolerated doses
n/a	not applicable
NAAED	North American Anti-Epileptic Drug
NAMR	N-acetyl metabolite
NMDA	N-methyl-D-aspartate
NDA	New Drug Application
P&CNS	Peripheral and Central Nervous System Drugs Advisory Committee
PBO	Placebo
PCC	Potential clinical concern
PCT	Pivotal Controlled Trials
PD	Pharmacodynamic

PDA	Patent ductus arteriosus
PHN	Post-herpetic neuralgia
PK	Pharmacokinetic
PPN	Pre and post-natal study
PTZ	Pentylentetrazole
PVR	Post void residual
QID	Four times a day
QTc	QT interval corrected
QTcB	QT interval corrected with Bazett's formula
QTcF	QT interval corrected with Fridericia's formula
QTcI	QT interval
RDS	Respiratory distress syndrome
ROP	retinopathy of prematurity
RTG	Retigabine
SAE	Serious adverse event
SD	Standard deviation
SOC	System organ class
SPA	Special Protocol Assessment
SUDEP	Sudden unexplained death in epilepsy
t _{1/2}	Elimination half-life
TEAE	Treatment-emergent adverse events
TESAE	Treatment-emergent serious adverse events
TID	Three times daily
T _{max}	Time to maximum concentration / reach C _{max}
UK	United Kingdom
ULN	Upper limit of normal
US	United States
USAN	United States Adopted Names
UTI	Urinary tract infection
VNS	Vagus nerve stimulation

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Ativan	Norvasc
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Dilantin	Tegretol
Keflex	Topamax
Keppra	Toradol
Neupro	Voltaren

1. EXECUTIVE SUMMARY

This document is prepared for members of the Food and Drug Administration (FDA) Peripheral and Central Nervous System Drugs Advisory Committee (P&CNS) for the purpose of describing information pertinent to an assessment of the benefit and risks for ezogabine (also known by the International Non-proprietary (INN) name retigabine), the first neuronal potassium channel opener developed for the treatment of epilepsy.

- Ezogabine demonstrates statistically significant and clinically relevant efficacy in patients with partial seizures still uncontrolled despite treatment with 1 to 3 other concurrent antiepileptic drugs (AEDs).
- The most commonly reported adverse events (AEs) with ezogabine are CNS related. In addition, consistent with ezogabine's effect on bladder smooth muscle, adverse events related to voiding dysfunction and urinary retention have been reported.
- A risk mitigation plan is proposed that will ensure the safe and effective use of ezogabine in epilepsy patients.
- Ezogabine offers an effective new treatment option for the adjunctive treatment of uncontrolled partial seizures.

1.1. Epilepsy Background

Epilepsy is one of the most common chronic neurological disorders. It is commonly diagnosed after 2 or more unprovoked seizures separated by at least 1 day, affecting approximately 50 million people worldwide and with an estimated 1-year prevalence of 0.7% in the United States [Hirtz, 2007].

Partial-onset seizures are the most common type of seizure in adult patients. For partial seizures, there is a focal epileptic zone (site of seizure onset), and seizure activity is initially limited to one hemisphere. Partial seizures can be further sub-divided into simple partial (without impairment of consciousness), complex partial (with impairment of consciousness with or following a simple partial onset) and secondarily generalized (i.e., partial seizures, either simple or complex, which evolve to generalized tonic-clonic seizures). Simple partial seizures, depending on the anatomical site of origin of the seizure, may have motor, somatosensory or special sensory, autonomic or psychic signs or symptoms.

1.2. Unmet Medical Need for New Treatment Options

Epilepsy is a serious and potentially life threatening disease and patients with epilepsy have significantly increased morbidity, including closed head injury, fractures, burns, dental injury and soft tissue injury [Spitz, 1998; Wirrell, 2006]. Decline in or worsening of memory, cognition, depression and sexual function and other lifestyle limitations occur frequently in patients with epilepsy. Patients with epilepsy also have an increased risk of mortality compared to the general population.

Despite the fact that there are already many approved pharmacologic agents to treat epilepsy, many patients are not adequately treated with currently available options. It is estimated that nearly a third of patients with epilepsy have either intractable or uncontrolled seizures or have significant adverse side effects secondary to medication limiting their ability to appropriately control their epilepsy with medication [Kwan, 2000; Stephen, 2001; Semah, 1998].

Individualization of AED therapy on the basis of efficacy and tolerability remains the hallmark of current disease management. Clinicians who treat people with epilepsy must select the appropriate drug or drugs that best control seizures in the individual patient with an acceptable level of untoward side-effects. Individual differences in efficacy and tolerability between patients require a treatment regimen that is adjusted to the individual patient's need. The high empiric failure rate with existing drugs due to lack of efficacy, adverse events (AEs), and drug interactions supports the need for new treatment options for patients with epilepsy.

1.3. Scientific Rationale for Ezogabine in Epilepsy

The pharmacological profile of ezogabine is different from currently approved AEDs. The primary mode of action of ezogabine is at KCNQ (Kv7) ion channels. Current agents have minimal to no effects on neuronal potassium gated channels, although it is known that these channels play a major role in the control of neuronal excitability. Ezogabine is the first neuronal potassium channel opener developed for the treatment of epilepsy. The drug stabilizes neuronal KCNQ channels in the open position, increasing the stabilizing membrane current and preventing bursts of action potentials during the sustained depolarizations associated with seizures. While the primary pharmacology of ezogabine is mediated by activation of KCNQ (Kv7) channels, a further reported pharmacological activity of ezogabine is the augmentation of gamma-aminobutyric acid (GABA) mediated neurotransmission, a mechanism of action thought to contribute to the efficacy of a number of other AEDs. However, the relevance of these GABA effects to the observed anticonvulsant efficacy of ezogabine *in vivo* has not been established.

Human genetic mutations in KCNQ potassium channels underlie several inheritable disorders, including Benign Familial Neonatal Convulsions (BFNC) (KCNQ2 and KCNQ3), dominant deafness (KCNQ4), and long QT syndrome (KCNQ1)) and demonstrating their fundamental importance in the control of cellular or neuronal excitability in humans. In the case of KCNQ2 and 3, the loss of function associated with the identified mutations suggests a clear strategy to increase KCNQ2/3 activity as a targeted means to restore the control of neuronal excitability in patients with epilepsy. KCNQ 2/3 channels are highly expressed in the central nervous system (CNS), the peripheral nervous system and in the smooth muscle of hollow organs such as the urinary bladder.

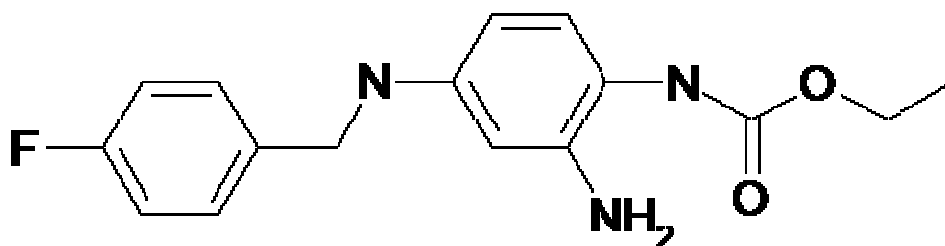
Ezogabine demonstrates selectivity of action for KCNQ channels comprising KCNQ2 and KCNQ3 (EC₅₀s 0.6-2.5 μ M) over those composed of KCNQ4 (EC₅₀ = 5.2 μ M) and KCNQ5 (EC₅₀ = 6.4 μ M) and is devoid of opener activity at the cardiac channel KCNQ1, only showing inhibitory effects at high concentrations (IC₅₀~100 μ M; see Section 2.4). These findings are consistent with the results of structure-function and

modeling studies that confirm the localization of the ezogabine binding site to a region near the KCNQ activation gate that is conserved in KCNQ2-5 channels but absent in KCNQ1 [Wuttke, 2005]. Furthermore, ezogabine has been shown to be effective in a wide range of preclinical models designed to measure anticonvulsant activity, and in the maximal electroshock tests, where these effects were blocked by a KCNQ inhibitor.

1.4. Physicochemical Properties

Pharmaceutical Information

The chemical name of ezogabine is N-[2-amino-4-(4-fluorobenzylamino)-phenyl] carbamic acid ethyl ester, and it has the following structure:



The empirical formula is C₁₆H₁₈FN₃O₂, representing a molecular weight of 303.3.

The physicochemical properties of ezogabine are similar photometrically to bilirubin and can result in a false positive serum analysis for bilirubin. During the clinical development program, crystals with a bilirubin-like appearance were detected in the urine of patients taking ezogabine. Investigations indicate these crystals are not bilirubin, but their composition remains undetermined. Thus, crystalluria was reviewed and discussed (Section 6.6.1.3). A further consequence of the refractive properties of ezogabine results in the potential for chromaturia and a false positive result on assays for proteinuria on dipsticks.

1.5. Nonclinical Information

The toxicological effects of ezogabine were generally consistent across multiple nonclinical species, with the majority of findings believed to be directly or indirectly the result of the actions of ezogabine on its primary therapeutic target (KCNQ2-5 family of K⁺ ion channels) and seen at exposures similar to or less than those achieved in man at a dose of 1200 mg/day. These findings are believed to be relevant to CNS effects and to reduction in smooth muscle contractility.

1.6. Development Program

There has been a comprehensive clinical development program evaluating the efficacy and safety of ezogabine as adjunctive therapy in the treatment of patients with uncontrolled partial seizures with or without secondary generalization. The evidentiary requirements for efficacy and safety are supported principally by results from three adequate and well-controlled studies:

- Phase IIb Study 3065A1-205-AU/EU/US [205]
- Phase III Studies VRX-RET-E22-301 [301] and VRX-RET-E22-302 [302])

The Phase III program for ezogabine has involved 845 patients, enrolled by approximately 120 sites in 17 countries worldwide.

Long term efficacy and safety data are provided principally by three open-label extension studies: Study 3065A1-212 (Study 212), extension to Study 205; Study VRX-RET-E22-303 (Study 303), extension to Study 301 and Study VRX-RET-E22-304 (Study 304), extension to Study 302.

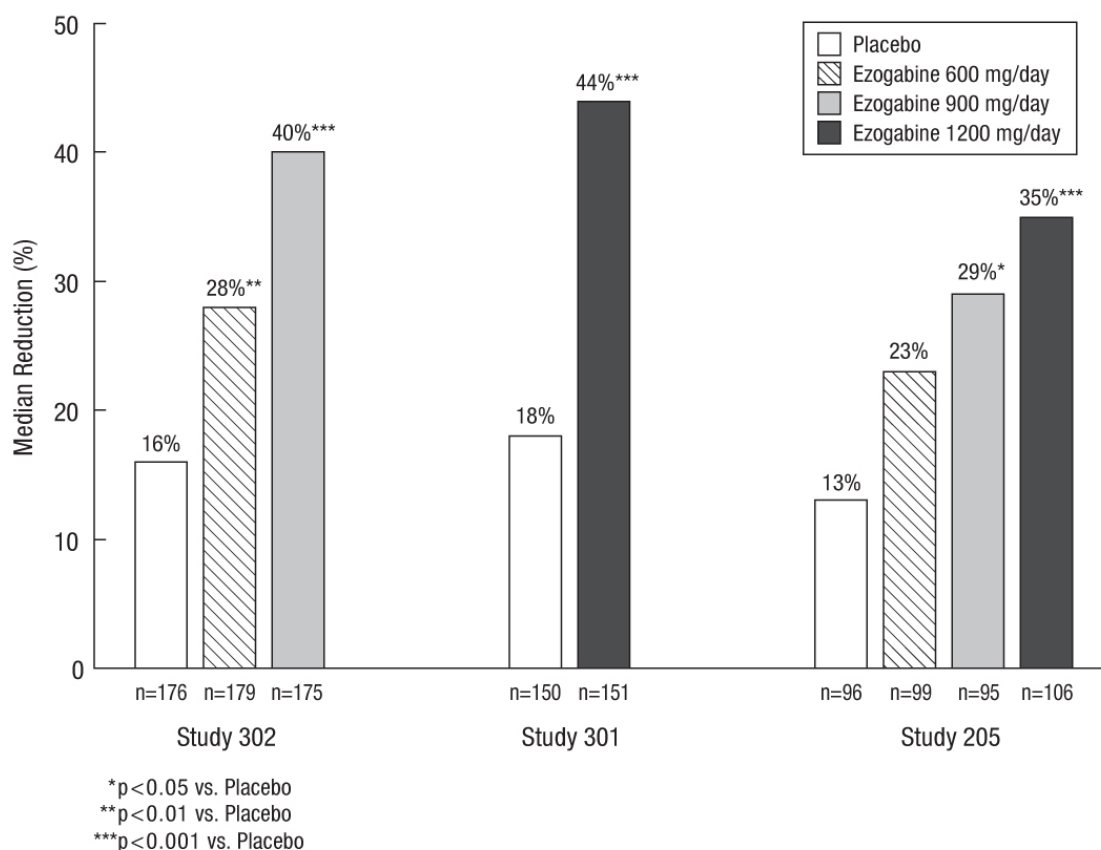
1.7. Summary of Major Efficacy Findings

Results from the three adequate and well-controlled fixed dose studies in patients with uncontrolled epilepsy taking 1 to 3 other AEDs provide substantial evidence of effectiveness for ezogabine across the dose range of 600 to 1200 mg/day.

Previous AEDs have been approved by the FDA based on the percent change in the 28-day total partial seizure frequency occurring between baseline and the double-blind phase (titration and maintenance phases combined). This was also the primary endpoint in the ezogabine trials ([Figure 1](#)).

- A statistically significant linear dose-response for ezogabine across the range of 600 to 1200 mg/day was established in Study 205.
- Statistical superiority for 600 mg/day, 900 mg/day and 1200 mg/day doses compared to placebo were independently substantiated in two Phase III, randomized, controlled trials (Studies 301 and 302).
 - Study 302 provided evidence of efficacy compared with placebo at 600 and 900 mg/day ($p < 0.007$ and $p < 0.001$ respectively).
 - Study 301 provided evidence of efficacy compared with placebo at 1200 mg/day ($p < 0.001$).

Figure 1 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



Note: numbers rounded for clarity of display

The efficacy demonstrated for the primary endpoint was replicated across other relevant endpoints. The percent change from baseline in 28-day total partial seizure frequency in the entire treatment period ranged from 23.4% to 44.3% across the dose range of 600 to 1200 mg/day ezogabine (Section 5.6.3.1). Across the dose range, 23.2% to 44.4% of patients had at least a 50% reduction in monthly seizure frequency during the entire treatment period (Section 5.6.4.1). These studies confirm a dose-related increase in efficacy across the dose range of 600 to 1200 mg/day, whether defined in terms of the percent change from baseline in seizure frequency or responder rate. Ezogabine demonstrated efficacy irrespective of the number or type of AED to which it was added. In addition, long-term maintenance of efficacy of ezogabine has been demonstrated in 3 open-label extension trials.

1.8. Summary of Major Safety Findings

As of 2 October 2009, there have been 2247 total subjects exposed to ezogabine. This includes 747 subjects from clinical pharmacology studies and 1365 unique subjects exposed to at least one dose of ezogabine in either Phase II or III epilepsy studies; with

approximately 453 patients being exposed to at least 600 mg/day ezogabine for at least 12 months and 765 being exposed for at least 6 months. The ezogabine dose range with the greatest exposure to drug was 900 mg/day to 1200 mg/day (612.31 total patient-years) (Section 6.2).

Thirteen Phase II/III studies were conducted with retigabine in patients with partial epilepsy. These included 4 Phase IIa studies (200/201, 202, 209, and 214); 3 randomized, double-blind, placebo controlled Phase IIb/III studies (205, 301, and 302); and 6 open label extension studies (extensions from Phase IIa: 8017, 208, and 216; extensions from Phase IIb/III: 212, 303, and 304). The two safety populations assessed for patients with epilepsy are referred to as *the pivotal controlled trials* (PCTs); i.e. Studies 205, 301 and 302, and the *all Phase II/III studies combined*.

The safety profile seen in the PCTs in uncontrolled partial epilepsy is consistent with pre-clinical and clinical pharmacology findings. The most commonly reported AEs are CNS related. In addition, adverse events of urinary retention and bladder voiding dysfunction have been reported. The bladder AEs are likely due to the effect of ezogabine on KCNQ3 channels in bladder smooth muscle. Potential safety issues that may be related to the pharmacology of ezogabine have been specifically evaluated in the clinical development program for ezogabine and are described below:

- **Urinary retention** (Section 6.6.1.2):

Consistent with the effect of ezogabine on smooth muscle, adverse events related to urine voiding dysfunction and urinary retention (e.g., dysuria, urinary hesitation, urinary retention) were reported for 5% of the ezogabine-treated patients across all doses (Total EZG group) compared to 3% on placebo in the PCTs. Urinary hesitation, residual urine volume and urinary retention were reported by 2%, 1%, and 1% of the Total EZG group compared to 1%, 0.2%, and 0.5% placebo with no clear dose response relationship across ezogabine dose groups. Overall, 4/1365 patients from the Phase II/III studies required catheterization for urinary retention. In the open-label extension Study 303, there was 1 patient who experienced persistent urinary retention requiring intermittent self-catheterization as a result of prolonged acute urinary retention.

Despite the adverse events of urinary retention that were reported, no association with UTI was observed. UTI was reported by 20/427 (5%) of patients in the placebo group and 35/813 (4%) of patients in the Total EZG group. In the PCTs, of the 35 events of UTI in the Total EZG group, none was preceded by an AE of urinary retention. In the All Phase II/III Combined group, 1 out of 105 UTI events were preceded by an AE of urinary retention.

- **Adverse events associated with crystalluria** (Section 6.6.1.3):

In the PCTs AEs possibly related to urinary crystals (i.e., nephrolithiasis, renal colic, crystalluria and urine analysis abnormal) were reported more often in the Total EZG group than in placebo (9 [1%] versus 2 [0.5%]). There were 4 cases of nephrolithiasis in the Total EZG group (all occurred in the 1200 mg/day group of Study 301), and none in the placebo group.

- **QT interval effects** (Section 6.6.5):

Any potential effect on QT prolongation would not be predicted from the pharmacology of ezogabine at the hERG and KCNQ1 channels. The Thorough QT Study in healthy volunteers demonstrated a slight (7 msec) and transient (1, 2 and 3 hours post-dose) prolongation of cardiac repolarization. AE and electrocardiogram (ECG) data (HR and QTc intervals) from the Integrated Clinical Pharmacology and Phase II/III clinical trial databases and studies does not indicate major effects of ezogabine on cardiac rhythm/conduction. However, a clinically relevant effect of ezogabine on cardiac repolarization in some patients cannot be excluded completely based on the results of the Thorough QT Study (Section 6.6.5.1).

- **Neuropsychiatric events** (Section 6.6.2):

Hallucinations and psychotic disorders have been reported in clinical trials with other AEDs. In the ezogabine PCTs, events related to hallucination or psychosis were reported in 32/813 (4%) patients in the Total EZG group and 3/427 (<1%) in the placebo group. The frequency of events appeared dose-related (2%, 3%, and 7% of patients in the 600 mg/day, 900 mg/day, and 1200 mg/day groups, respectively), but the actual dose at the time of reporting indicates that most events occurred during the titration phase before patients achieved their target dose of up to 1200 mg/day.

- **Hepatic effects** (Section 6.6.6):

Abnormal elevations of liver function tests were reported in 1% of patients in the placebo group compared with 3% of patients in the Total EZG group (Table 51). In the ezogabine groups, there was a slight dose-related effect for hepatic enzyme increases (2%, 3%, and 4% of the 600, 900 and 1200 mg/day groups, respectively).

Among ezogabine-treated patients, the most common liver enzyme abnormalities reported as AEs were increased gamma-glutamyl transferase (GGT) (2% of the 900 mg/day group) and increased alanine aminotransferase (ALT) (1% of the 1200 mg/day group). All other liver enzyme abnormalities reported as AEs were <1% of patients in any ezogabine dose group. Few (<1%) were considered serious adverse events (SAEs) or led to withdrawal.

Most frequently reported treatment emergent adverse events (Section 6.7.1):

Dizziness and somnolence were the most frequent TEAEs (23% and 22%, respectively). Headache and fatigue were the other AEs reported by >10% of the Total EZG group (15% each). Among these 4 TEAEs, a greater proportion of patients in the Total EZG 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 EZG and placebo groups (15% and 16%, respectively).

In the PCTs TEAEs leading to discontinuation were reported for a greater proportion of ezogabine patients than for placebo patients (11% placebo versus 25% Total EZG). It should be noted that the PCTs employed forced titration to a fixed dose rather than the flexible dosing paradigm employed in treating epilepsy in clinical practice.

Death and SUDEP (Section 6.3):

During the PCTs, the rate of death was 24.0 per 1000 patient-years on placebo versus 9.5 per 1000 patient-years on ezogabine. In the entire ezogabine epilepsy clinical development program, there were 12 treatment emergent deaths (including deaths reported as of 2 October 2009 and in the compassionate use program) in patients treated with ezogabine in 1556 patient-years of exposure, i.e., a rate of 7.7 per 1000 patient-years.

The most common cause of death in the program was sudden unexpected death in epilepsy (SUDEP). In the PCTs, the rate of SUDEP was 8.0 per 1000 patient-years in placebo versus 4.7 per 1000 patient-years in ezogabine with an overall SUDEP rate of 4.5 per 1000 patient-years on ezogabine across the entire ezogabine epilepsy program (as of 2 October 2009).

1.9. Summary of Post-Marketing Risk Mitigation Plan

Given the potential safety issues outlined above, the Sponsor has proposed post-marketing risk mitigation activities. These will include initiatives to help educate health care providers and patients about the potential risks of ezogabine, including urinary retention, to help ensure that these events will be recognized and treated promptly.

The post-marketing risk mitigation plan for healthcare practitioners will include an introductory letter to healthcare practitioners, a website which will include information on the potential risks associated with ezogabine, a toll free call customer response center to answer questions from practitioners, and peer-to-peer education by other healthcare practitioners.

A medication guide will be provided that informs patients of important potential risks, how to prevent or identify those risks and what to do with the event occurs. A patient website for ezogabine will be established that will include information that is consistent with the medication guide. A customer response center, staffed by trained employees will be available to answer patient questions and provide a copy of the medication guide.

In addition, prospective risk assessment activities will be initiated which will incorporate a post-marketing observational study intended to quantify the risk of the urinary adverse events within a real world context (See Section 8.3).

1.10. Benefit:Risk Conclusion

Epilepsy is a serious disease associated with significant morbidity and mortality. Despite the fact that there are numerous available AEDs, nearly a third of patients are not adequately controlled with current therapies. Ezogabine has demonstrated convincing efficacy in such patients with uncontrolled partial seizures with an acceptable safety profile. A risk mitigation plan is proposed that will ensure the safe and effective use of ezogabine. In the context of the serious nature of epilepsy, current standard of care and available treatments, the benefit:risk profile is favorable and supports the use of ezogabine 600 to 1200 mg/day for the adjunctive treatment of partial onset seizures.

2. INTRODUCTION AND BACKGROUND

2.1. Introduction

Valeant Pharmaceuticals North America is seeking marketing approval of ezogabine (POTIGA™), for the *adjunctive treatment for patients 18 years of age and older with partial onset seizures with or without secondary generalization*. A New Drug Application (NDA 22-345) was filed with the US Food and Drug Administration (FDA) in October 2009 and a 120-Day Safety Update was submitted in February 2010. A Proposed Pediatric Study Request (PPSR) has been submitted to FDA addressing the pediatric studies necessary to use ezogabine appropriately in pediatric populations. This briefing document provides an overview of data contained in the New Drug Application (NDA) pertinent to an assessment of the benefits and risks of ezogabine in adult patients with partial epilepsy.

The proposed product labeling recommends that the initial dose of ezogabine should be 100 mg 3 times daily (300 mg/day) and 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 1,200 mg/day based on individual patient response.

Ezogabine (pronounced: ez oh'ga been) is the United States Adopted Name (USAN) and proposed established name. The drug is more commonly known by the International Non-proprietary (INN) name retigabine. The USAN was changed from retigabine to ezogabine earlier this year, as the result of FDA concern that retigabine is orthographically and phonetically similar to rotigotine, the established name for a drug that is approved but presently not marketed in the United States (trade name: Neupro). Although the USAN has changed, the INN remains retigabine. Throughout this briefing document, the preferred reference to the drug will be ezogabine. However, since all of the studies described in the NDA predate the recent change in USAN, some reference to the drug as retigabine is unavoidable. Accordingly, it is emphasized to the reviewer that ezogabine and retigabine refer to the same drug.

2.2. Epilepsy

Epilepsy is one of the most common chronic neurological disorders in children and adults. An epileptic seizure consists of repetitive, synchronous discharges of a population of neurons in the brain which may have associated motor, sensory or autonomic clinical correlates. Epilepsy is commonly diagnosed after 2 or more unprovoked seizures separated by at least 1 day. Provoked seizures are those which occur in the setting of an acute neurological insult or systemic disorder, such as head trauma, brain tumor, cerebrovascular malformation, central nervous system infection or toxic/metabolic conditions. Recurrent seizures caused by a known lesion or abnormality of the brain are called symptomatic epilepsy. Although the diagnosis of epilepsy is based on clinical features, ancillary testing including electroencephalography and neuroimaging of the brain (cranial computed tomography, magnetic resonance imaging) often provide supportive or confirmatory data.

Under the International Classification of Epileptic Seizures [[Commission](#), 1981], seizures are further classified as either partial (focal, localization related) or generalized. Partial seizures arise from one area of the brain, and they are further subdivided into simple, in which awareness and memory are preserved (also called an aura) or complex, where there is transient alteration of awareness and memory. The clinical behavior that is associated with a partial seizure is dependent upon the area of the brain where the seizure began as well as the propagation of the ictal discharge to other areas of the brain. Partial seizures that spread to involve both cerebral hemispheres and have associated clonic motor activity are called secondarily generalized seizures. Conversely, generalized seizures arise from both cerebral hemispheres simultaneously, and they have no lateralizing or focal clinical manifestations. Generalized seizures are further subdivided based on ictal semiology into absence, myoclonic, clonic, tonic, tonic-clonic and atonic. Typically, partial or generalized seizures last 5 minutes or less. However, prolonged seizures of either type may occur, and seizures that last 30 minutes or longer are called status epilepticus [[Working Group on Status Epilepticus](#), 1993].

Generalized seizures comprise 50% of all seizures in children, but in adults, partial seizures occur more commonly, estimated at 70% of all seizures [[Hauser](#), 1992]. Status epilepticus is the presenting seizure in as many as 5% of patients with epilepsy, and up to 16% of all patients with epilepsy will have at least one episode of status epilepticus during their life [[Hauser](#), 1990]. Patients that have a history of a prolonged seizure or status epilepticus are more likely to have recurrence of a prolonged seizure or status epilepticus [[Shinnar](#), 2001].

Multiple factors are posited to be required to result in the pathogenesis of the hyperexcitable state that culminates in an epileptic seizure. Three key elements have been hypothesized: the capability of cellular membranes of pacemaker neurons to develop intrinsic bursts discharges, a reduction in gamma-aminobutyric acid (GABA) inhibition and enhancement of excitation through neuronal circuits [[Prince](#), 1986]. However, the actual pathogenic mechanisms of epileptogenesis and the clinical condition of epilepsy are varied and the details are not completely known. Most antiepileptic drugs (AEDs) have one or more documented mechanisms of action which might control or reduce seizure frequency and severity.

2.3. Unmet Medical Need and Current Therapy

2.3.1. Unmet Medical Need

Epilepsy is among the most common neurological disorders, affecting approximately 50 million people worldwide and with an estimated 1-year prevalence of 0.7% in the United States [Hirtz, 2007]. Partial-onset seizures are the most common type of seizures in adult patients.

Epilepsy is a serious and potentially life-threatening disease, and despite the fact that there are many approved pharmacologic agents, many patients are not adequately treated with currently available options. It is estimated that nearly a third of patients with epilepsy have either intractable or uncontrolled seizures or have significant adverse side effects secondary to medication limiting their ability to appropriately control their epilepsy with medication [Kwan, 2000; Stephen, 2001; Semah, 1998].

Patients can be considered drug resistant when they have failed to have seizure control after adequate trials with 2 or more AEDs when used appropriately and tolerated by the patient [Kwan, 2010]. These individuals may then be candidates for alternative treatments, including epilepsy surgery, vagal nerve stimulation or direct brain stimulation. However, the majority of these patients continue to have seizures, with only epilepsy surgery for temporal lobe epilepsy having been demonstrated to be superior to maximal medical therapy [Wiebe, 2001]. Patients who participate in clinical trials of investigational AEDs generally have had epilepsy for more than 10 years, have failed multiple AED therapies, and are considered unlikely to become seizure free with currently available AED therapy.

Patients with epilepsy have significantly increased morbidity, including closed head injury, fractures, burns, dental injury and soft tissue injury [Spitz, 1998; Wirrell, 2006]. Decline in or worsening of memory, cognition, depression and sexual function and other lifestyle limitations occur frequently in patients with epilepsy. Patients with epilepsy also have an increased mortality risk compared to the general population. Overall, it is believed that this risk is due primarily to the underlying causes of epilepsy [Forsgren, 2005]. However, in patients with uncontrolled epilepsy, the greatest seizure related risk of mortality is due to sudden unexpected death in epilepsy (SUDEP) [Tomson, 2004; Hitiris, 2007]. The most common direct seizure related cause of death in adolescents and young adults is sudden unexpected death, which is 24 times more common than in the general population [Forsgren, 2005]. In adult patients presenting with status epilepticus, the risk of death has been reported as high as 19% [DeLorenzo, 1999].

The introduction of new AEDs during the last two decades has increased therapeutic choices but there remains a significant unmet medical need for additional treatment options.

2.3.2. Current Treatment

Selection of AED treatment is based on empirical assessment of the probability of achieving seizure freedom and associated side-effect profiles, rather than on the rational application of a treatment that correlates with a specific functional or biochemical

abnormality [Perucca, 2000; Perucca, 2002]. Individualization of AED therapy on the basis of efficacy and tolerability remains the hallmark of current disease management. Clinicians who treat people with epilepsy must select the appropriate drug or drugs that best control seizures in the individual patient with acceptable tolerability. Individual differences in efficacy and tolerability between patients require a treatment regimen that is adjusted to the individual patient.

Pharmacological therapy is the initial option for treatment of patients with newly diagnosed epilepsy. The treatment of an individual patient with partial seizures is focused on reduction of seizure frequency, with seizure freedom the ultimate goal. Usually, treatment consists of daily anticonvulsant medication. Antiepileptic drugs exert their therapeutic effect in the central nervous system (CNS), and generally share common CNS side effects such as sedation, somnolence, lethargy and ataxia. The exact correlation between pharmacology and antiepileptic action is not known for currently approved AEDs. Potential mechanisms of action include modulation of voltage-gated sodium ion channels (sodium and calcium), enhancement of inhibitory neurotransmission (GABA) or attenuation of excitatory neurotransmission (glutamate) [Rogawski, 2004]. Many AEDs may have multiple potential mechanisms of action, while some have mechanisms which remain unclear.

The goal of medical therapy is to have complete seizure control without side effects. Monotherapy is preferable to polytherapy, since this limits drug-drug interactions and reduces side effects [Karceski, 2005]. However, epilepsy patients must often take more than one AED in order to achieve therapeutic success. For many epilepsy patients, adequate seizure control is still not achieved despite treatment with multiple AEDs. There continues to be approximately 30% of epilepsy patients for whom current treatment options do not provide adequate seizure control with acceptable tolerability [Elger, 2008].

Eleven AEDs (felbamate, gabapentin, lamotrigine, topiramate, tiagabine, levetiracetam, oxcarbazepine, zonisamide, pregabalin, lacosamide, and vigabatrin) have been approved in the US since 1993. For all AEDs in current use, dosing is individualized based on clinical response and for each of these AEDs, a range of doses are associated with efficacy and tolerability; none are devoid of the potential for serious untoward events.

2.4. Scientific Rationale for Ezogabine in the Treatment of Epilepsy

The pharmacological profile of ezogabine is different from currently approved AEDs. Ezogabine's primary mode of action is at KCNQ (Kv7) ion channels. Current agents have minimal to no effects on neuronal potassium gated channels although these channels have a major role in the control of neuronal excitability. Ezogabine is the first neuronal potassium channel opener developed for the treatment of epilepsy. KCNQ channels regulate neuronal responsiveness to excitatory input and are a powerful inhibitory force in the brain. Ezogabine stabilizes neuronal KCNQ channels in the open position, increasing the stabilizing membrane current and preventing bursts of action potentials during the sustained depolarizations associated with seizures.

Human genetic mutations in KCNQ potassium channels underlie several inheritable disorders, including a form of epilepsy, demonstrating their fundamental importance for the control of cellular or neuronal excitability in humans. These inheritable disorders include long QT syndrome (KCNQ1), Benign Familial Neonatal Convulsions (BFNC) (KCNQ2 and KCNQ3), and dominant deafness (KCNQ4) [Shieh, 2000, Jentsch, 2000]. Characterization of the functional effects of the mutations in KCNQ2 and KCNQ3 demonstrated a direct causal link between reduced KCNQ activity in the brain and a loss of control of neuronal excitability resulting in seizures. This finding is in concordance with preclinical data in which transgenic KCNQ2 +/- mice, deficient in one copy of the KCNQ2 gene, show increased sensitivity to the chemo-convulsive agent pentylenetetrazole (PTZ). Consequently, it has been widely suggested that strategies to increase KCNQ2/3 activity represent a novel targeted means to restore the control of neuronal excitability in patients with epilepsy [Maljevic, 2008].

In vitro pharmacology studies demonstrate that ezogabine acts as a selective positive allosteric modulator (opener) of neuronal KCNQ2-5 (Kv7.2-5) potassium channels, in particular KCNQ2/3 and KCNQ3/5 (Table 1) over those composed of KCNQ4 and KCNQ5, and is devoid of opener activity at the cardiac channel KCNQ1, only showing inhibitory effects at high concentrations (IC50~100 uM) [Main, 2000; Tatulian, 2003; Wickenden, 2000, Rundfeldt, 2000]. These findings are consistent with the results of structure-function and modeling studies that confirm the ezogabine binding site to a region near the KCNQ activation gate that is conserved in KCNQ2-5 channels but absent in KCNQ1 [Wuttke, 2005].

Table 1 Pharmacological Action of Ezogabine at KCNQ Channels

Assay	Effect	EC50 or IC50
KCNQ2/3	Positive allosteric modulator	EC50 = 1.6 uM
KCNQ3/5	Positive allosteric modulator	EC50 = 1.4 uM
KCNQ2	Positive allosteric modulator	EC50 = 2.5 uM
KCNQ3	Positive allosteric modulator	EC50 = 0.6 uM
KCNQ4	Positive allosteric modulator	EC50 = 5.2 uM
KCNQ5	Positive allosteric modulator	EC50 = 6.4 uM
KCNQ1	Not a positive allosteric modulator Weak inhibitor	IC50 ~ 100 uM

References: [Tatulian, 2001; Yeung, 2008; Wickenden, 2000; Wickenden, 2001; Rundfeldt, 2000]

The heteromeric KCNQ2/3 and KCNQ3/5 channels are highly expressed in the CNS and are now known to be the molecular correlates of the native M-current (a potassium current negatively regulated by muscarinic receptor activation), characterized in neurons, that contributes a continual hyperpolarizing influence to the cell resting membrane potential (Table 2). These KCNQ channels therefore serve to stabilize the resting membrane potential and control the sub-threshold electrical excitability of neurons. Ezogabine's action to enhance and prolong the opening of these channels can therefore result in further stabilization of the cell membrane potential leading to increased control

of the hyperexcitability that can occur during the initiation and propagation of seizure activity in the brain [Maljevic, 2008]. KCNQ2/3 and KCNQ3/5 channels are also expressed more widely throughout the peripheral nervous system and in the smooth muscle of hollow organs such as the urinary bladder and uterus. KCNQ1 and KCNQ4 channels are predominantly expressed in the heart and inner ear, respectively, but also occur in other tissues (Table 2) suggesting potential for pharmacological benefit in the selective targeting of neuronal KCNQ2/3 and KCNQ3/5 channels and also identifying appropriate target tissues for the evaluation of any on target side effects and toxicities.

Table 2 Summary of the Distribution and Expression of KCNQ Channels

Subunit	Major Expression	Other expression	Predominant Function
KCNQ1	Heart, cardiac myocytes, Cochlea	Bladder, aortic baroreceptors, vasculature, intestine, kidney, uterus	Forms IKs channel responsible for cardiac action potential repolarization. Potassium transport.
KCNQ2	Brain, spinal cord, peripheral nervous system including ganglia	Aortic baroreceptors	Heteromerises with KCNQ3 or KCNQ5 to form native 'M-current'. Also exists as KCNQ2 homomers. Controls excitability.
KCNQ3	Brain, spinal cord, peripheral nervous system including ganglia	Bladder	Heteromerises with KCNQ2 or KCNQ5 to form 'M-current'. Controls excitability.
KCNQ4	Cochlea, vestibular hair cells	Brain, heart, vasculature, uterus	Potassium transport
KCNQ5	Brain, spinal cord, peripheral nervous system including ganglia	Bladder, aortic baroreceptors, vasculature, skeletal muscle, uterus	Heteromerises with KCNQ5 to form 'M-current'. Also exists as KCNQ5 homomers. Controls excitability.

References: [Jentsch, 2000; Brown, 2009; Lerche, 2000; Schroeder, 2000; Kharkovets, 2000; Yeung, 2007; Wladyka, 2008; Passmore, 2003; McCallum, 2009].

A further reported pharmacological contribution to the activity of ezogabine may be through augmentation of GABA-mediated neurotransmission, a mechanism of action thought to contribute to the efficacy of a number of other AEDs; however, in the majority of studies ezogabine concentrations of ≥ 10 μ M are required for effect (Table 3). Consequently, the relevance of this pharmacology to the observed anticonvulsant efficacy of the drug *in vivo* has yet to be established. Overall the pharmacological data considered in the context of the concentrations associated with human efficacy support the conclusion that the primary mechanism of action of ezogabine is through its activity at KCNQ channels (Table 3).

Table 3 Pharmacological Action of Ezogabine: Activity at KCNQ vs other Targets

Pharmacological Mode of action	Effect	Level of activity or EC50 or IC50 where determined	Ratio of activity to Cmax achieved at 1200 mg in clinic ^a
KCNQ	Positive allosteric modulator	EC50 = 1.6 μ M at KCNQ2/3	~ 1
GABA	Positive allosteric modulator at GABAA receptors (non-benzodiazepine site)	Significant effects at > 10 μ M in the majority of studies	> 10 fold
	Effects on GABA metabolism	Significant effects at 20 μ M	20 fold
Calcium channels	Weak inhibitor	IC50 > 100 μ M at neuronal Cav channels (29% inhibition at 100 μ M)	> 100 fold
Sodium channels	Weak inhibitor	IC50 > 100 μ M at neuronal Nav channels (25% at 100 μ M)	> 100 fold
Glutamate receptors	No effect at NMDA, AMPA or Kainate receptors	No effect up to 10 μ M	> 10 fold
Other: Broad Selectivity Profile	No additional activities detected	No significant interactions in 62 assays of ion channels, transporters, enzymes and 2 nd messenger systems at 10 μ M	> 10 fold

a. estimated as 1.0 μ M based on Cmax at 1200 mg = 1520 ng/mL. PPB = 80% and MW Ezogabine = 303.3
References: [Tatulian, 2001; Otto, 2002; Rundfeldt, 2000, van Rijn, 2003, van Rijn, 2004; Kapetanovic, 1995].

Preclinical efficacy studies, including those conducted by the NIH novel Anticonvulsant Drug Development (ADD) program, have demonstrated the broad spectrum antiepileptic potential of ezogabine [Rostock, 1996]. Ezogabine increased the threshold for seizure induction produced by maximal electroshock, pentylenetetrazol, picrotoxin, and N methyl-D-aspartate (NMDA) demonstrating anticonvulsant efficacy versus generalized seizures. Ezogabine also displayed inhibitory properties in multiple electrical kindling models (including those incorporating repetitive amygdala, corneal and hippocampal stimulation), both during kindling development and in the fully kindled state, suggesting particular benefit for the treatment of partial onset seizures. Further studies have also demonstrated the efficacy of ezogabine in models of refractory partial epilepsy including the 6Hz psychomotor seizure test and in rats that are resistant to lamotrigine following

kindling in the presence of this drug. Ezogabine was also effective in preventing status epilepticus seizures in rodents with cobalt induced epileptogenic lesions and inhibited tonic extensor seizures in a number of distinct genetically seizure-prone mice. The relevance of these models to human epilepsy, however, is not known. In further studies, the KCNQ inhibitor XE-991 was able to fully inhibit the effects of ezogabine in the maximal electroshock test demonstrating that the KCNQ opener activity of ezogabine mediates its anticonvulsant efficacy in this model.

2.5. Overview of the Clinical Development Program

2.5.1. Development History

The safety and tolerability profile of ezogabine for the treatment of adults with partial onset seizures has been evaluated in a comprehensive clinical development program comprising 45 clinical studies including:

- 29 Phase I studies
- 4 completed Phase IIa studies
- 3 placebo controlled safety/efficacy studies (1 Phase IIb and 2 Phase III studies)
- 6 open-label extension studies (of which, 2 remain ongoing)
- 1 compassionate use program
- 2 Phase II studies that were conducted in other indications (bipolar disorder; post-herpetic neuralgia [PHN])

Upon transfer of ownership from Wyeth to Asta-Medica in 2001, some of the open-label extensions to Phase II studies were terminated. Patients who were judged by the investigator to have received benefit from ezogabine and not adequately treated with available options alone, were allowed to roll over into a new compassionate use protocol, which has made ongoing access to ezogabine possible for a limited number of patients (5 currently).

The Phase IIa epilepsy program comprised four uncontrolled studies, including three open-label studies (Studies 3065A1-200/201, 3065A1-202, and 3065A1-209) and one randomized, double-blind, study evaluating different titration schemes (Study 3065A1-214). Three of the Phase II studies evaluated ezogabine as add-on therapy (Studies 200/201, 202, and 214) and contribute supportive efficacy and safety data in the intended use population. In these studies, patients were treated for between 7 and 24 weeks with doses of ezogabine of up to 2400 mg daily, administered via twice daily (BID) or three times daily (TID) dosing schemes. In Study 202, background AEDs could be tapered down after achieving the maintenance phase and ezogabine could be administered for up to two weeks as a monotherapy for partial onset seizures. These three Phase II studies each had open-label extension protocols (Studies D23129/8017, 3065A1-208 and 3065A1-216 were the extensions to Studies 200/201, 202, and 214 respectively). A fourth study (Study 209) was conducted in patients with epilepsy undergoing pre-surgical assessment, to whom ezogabine (up to 2400 mg/day, 4 times daily scheme) was administered as monotherapy following discontinuation of background AEDs. Treatment

with ezogabine lasted for four days. Based on the results of an early Phase II study (Study 202) ezogabine started at either 100 mg/day or 200 mg/day and titrated to 1200 mg/day (administered either as a BID or TID regimen) was associated with reduction in total seizures relative to baseline. The tolerability findings from this study were significant in determining the maximum daily dose (1200 mg/day), the preferred dose administration schedule (TID) and speed of titration to be used during the rest of the development program.

The evidentiary requirements for efficacy and safety are supported principally by results from three adequate and well-controlled studies:

- Study 3065A1-205-AU/EU/US [205] – Phase IIb study conducted by Wyeth
- Studies VRX-RET-E22-301 [301] and VRX-RET-E22-302 [302]) – Phase III studies conducted by Valeant

The Phase III program for ezogabine has involved 845 patients, enrolled by approximately 120 sites in 17 countries worldwide.

Long term efficacy and safety data are provided by three open-label extension studies: Study 3065A1-212 (Study 212), extension to Study 205; Study VRX-RET-E22-303 (Study 303), extension to Study 301 and Study VRX-RET-E22-304 (Study 304), extension to Study 302.

2.5.2. Regulatory History

Key regulatory interactions included:

- End of Phase II Meeting: FDA provided input on the design features of the Phase III studies (VRX-RET-E22-301 [301] and VRX-RET-E22-302[302] and the Sponsor's proposal for assessment of drug-drug interactions via population pharmacokinetic (PK) modelling.
- Special Protocol Assessment (SPA) Review of Phase III Studies: FDA agreement on the design of study protocols (301 and 302) occurred in accordance with the Agency's SPA mechanism.
- Pre-NDA Communications: Formal Pre-NDA communications were held. FDA affirmed input provided at the EoP2 meeting, including categorization of Studies 205, 301 and 302 as the pivotal trials that will contribute to the final decision on approval.
- At the EoP2 meeting, the Agency agreed with the Sponsor's proposal to defer submission of pediatric data. As part of pre-NDA communications, the Agency reconfirmed its agreement in this regard.
- Design Features of the Thorough QT Study reflected FDA input and review suggestions.
- The NDA was submitted to FDA October 2009; the 120 day safety update February 2010.

3. NONCLINICAL

The pharmacology, pharmacokinetics and toxicology of ezogabine have been investigated in a comprehensive nonclinical development program which comprises >350 nonclinical studies including: safety pharmacology, repeat dose toxicity (up to 13 weeks in mice, 26 weeks in rats, 52 weeks in dogs and 10 days in monkeys), genotoxicity studies, carcinogenicity (rats and neonatal mice), reproductive toxicity and mechanistic studies. The major human metabolite (N-acetyl metabolite, NAMR) is not formed in the dog and was evaluated in additional 13 week studies in the rat and dog.

The toxicological effects of ezogabine were generally consistent across multiple nonclinical species, with the majority of findings interpreted to be directly or indirectly the result of ezogabine's actions on its primary therapeutic target (KCNQ2-5 family of K⁺ ion channels) and were seen at exposures similar to or less than those achieved in man at a dose of 1200 mg/day. Clinical and hematological changes were observed in the dog NAMR studies and although these findings are considered to be species-specific, neutropenia and infection have been noted as adverse events of special interest in the clinical program. The principal nonclinical findings relevant to human are summarized below.

3.1. CNS Effects

CNS findings included hypo- and hyperactivity, ataxia, tremors, and, at the highest exposures, convulsions. Although CNS findings were seen at exposures similar to those achieved in humans at 1200 mg, they represent a ~10-fold margin over the efficacious dose (i.e., ED₅₀) for generalized seizure model in rats. The CNS signs were dose-dependent and dose-limiting in multiple species, but were reversible and some studies suggested that animals could acclimate to the CNS clinical signs. Similar effects of extended CNS pharmacology at toxic doses are reported for a variety of other AEDs.

3.2. Smooth Muscle Effects

Ezogabine's effects on KCNQ channels in the smooth muscle of the urinary bladder and gall bladder would be expected to result in reduced contractility of one or the other organ in some species.

Inhibition of micturation showed species sensitivity following the order: mouse > rat > dog > monkey. Rodent species are particularly sensitive to inhibition of micturition due to inability to exert control over bladder musculature. Bladder distension due to the inability to actively urinate was most severe in mice, where the increased urine pressure led to hydronephrosis. Renal pathology was not seen in species (dog, monkey) able to actively urinate. Patients are expected to be significantly less sensitive than the animal models to bladder and secondary renal toxicity due to the ability of humans to exert active control of bladder smooth muscle contractions. Results from early clinical studies suggested that ezogabine can exhibit some pharmacologic effect on human bladder function as evidenced by reports of mild urinary retention or hesitancy (see Section 6.6.1).

In dogs, ezogabine was found to cause a recurrent pattern of highly specific focal hepatocellular changes in the liver tissue layer directly overlying the gall bladder. Mechanistic studies demonstrated that these localized lesions developed as a result of mechanical compression secondary to gall bladder enlargement that occurred as a result of ezogabine/KCNQ mediated relaxation of the gall bladder smooth muscle. To date, this finding has not been observed clinically (see Section 6.6.9).

3.3. Effects on Cardiovascular System

The pattern of expression of the KCNQ channels in the vascular (arterial) smooth muscle suggests that ezogabine administration could result in hypotension due to the inhibition of vascular smooth muscle contraction. Ezogabine produces electrophysiologic responses in arterial smooth muscle consistent with activation of KCNQ channels in the arterial myocytes. Cardiovascular studies in dogs and pigs indicate that ezogabine can relax vascular smooth muscle and has the potential to reduce blood pressure. However, ezogabine was not consistently associated with blood pressure decreases when administered by routes other than the intravenous route (suggesting that the blood pressure effect was C_{max} associated). There is no evidence from the clinical studies that ezogabine is associated with clinically significant changes in blood pressure in humans (see Section 6.6.5).

Ezogabine minimally inhibited hERG-mediated inward tail currents with an IC₅₀ of 59 to ~100 μ M which represents >50-fold the expected peak free drug plasma C_{max} concentration at 1200 mg/day. Ezogabine had no effect on ECG parameters (including corrected QT interval) monitored continuously by telemetry in conscious, unrestrained beagle dogs at clinically equivalent exposures for 7 days.

3.4. Reproductive Effects

Ezogabine had no effect on fertility, general reproductive performance, or early embryonic development when administered to rats. The teratogenic potential of ezogabine was evaluated in rats and rabbits in embryofetal development studies (EFD). The overall nonclinical reproductive and developmental toxicity profile for ezogabine suggests that ezogabine is not teratogenic. However, exposures achieved in reproductive and developmental toxicity studies provide no safety margin for human exposure at therapeutic doses and the lack of risk to human fetuses has not yet been fully established. Dosing with ezogabine did result in increased post-implantation loss and decreased fetal survival in the rat pre and post-natal study (PPN); however, the doses used in the PPN and rat EFD were similar and there were no malformations associated with these doses. The decreased fetal viability in the PPN is consistent with the maternal toxicity observed in the study and there is a correlation between the severity of maternal signs and the degree of fetal impairment. Additionally, ezogabine and/or its metabolites have been shown to cross the placenta in rats as well as to be excreted in the breast milk of rats. Therefore, ezogabine should be used during pregnancy only if the potential benefit justifies the potential risk to the fetus. It is not known if ezogabine is excreted in human milk; however, because of the potential for serious adverse reactions in nursing infants from ezogabine, a decision should be made whether to discontinue nursing or to discontinue the drug, taking into account the importance of the drug to the mother.

3.5. Mutagenicity and Carcinogenicity

Ezogabine, the circulating human metabolite NAMR, and minor impurities in ezogabine present no genotoxic risk as assessed in a standard battery of *in vitro* and *in vivo* genotoxicity studies. Ezogabine has also shown no carcinogenic potential in two contemporary carcinogenicity studies (neonatal mouse model and standard 2-year rat study).

3.6. Potential for Drug Interactions

Ezogabine showed little or no potential to inhibit or induce the major cytochrome P450 isoenzymes and is primarily metabolized through glucuronication (see Section 4). Therefore ezogabine has little potential for pharmacokinetic interaction with most concomitant drugs. Ezogabine increased the thiopental sodium induced sleep time in rats, but no or weak interactions were observed with the other tested anesthetic agents (propofol, halothane or methohexital sodium). Although no human data exist, ezogabine may increase the duration of anesthesia induced by some anesthetics (e.g., thiopental).

3.7. Physicochemical Properties

The physicochemical properties of ezogabine are similar photometrically to bilirubin and can result in a false positive serum analysis for bilirubin as has been observed during the clinical program where crystals with a bilirubin-like appearance were detected in the urine of patients taking ezogabine; although subsequent investigation indicated these crystals are not bilirubin, their composition currently remains undetermined. Ezogabine is poorly water soluble with a bluish color when dissolved and a further consequence of its physicochemical and refractive properties is the potential for chromaturia as well as a false positive result on assays for proteinuria on dipsticks.

3.8. Conclusions

Overall, the majority of nonclinical safety findings are believed to be directly or indirectly the result of ezogabine's actions on its primary therapeutic target (KCNQ2-5 family of K⁺ ion channels) resulting in CNS effects and reduction in smooth muscle contractility. It should also be noted that the human metabolite NAMR has lower potency or no anticonvulsant activity in *in vivo* anticonvulsant models.

4. CLINICAL PHARMACOLOGY

The human pharmacokinetic profile of ezogabine has been derived from *in vitro* studies, Phase I volunteer studies, and population modeling and exposure assessments from Phase I-III studies.

4.1. Bioequivalence of Market Image Tablets and Product used in Pivotal Studies

There were two immediate release (IR) presentations, capsule and tablet, used during ezogabine development. Bioequivalence has been established between the capsule formulation used in the Phase II efficacy study (Study 205) and the IR tablet and between

the IR tablets used in the Phase III efficacy studies (Studies 301 and 302) and the market image tablet. Therefore an equivalent safety and efficacy profile between the pivotal studies and the marketed product is expected.

4.2. Pharmacokinetics

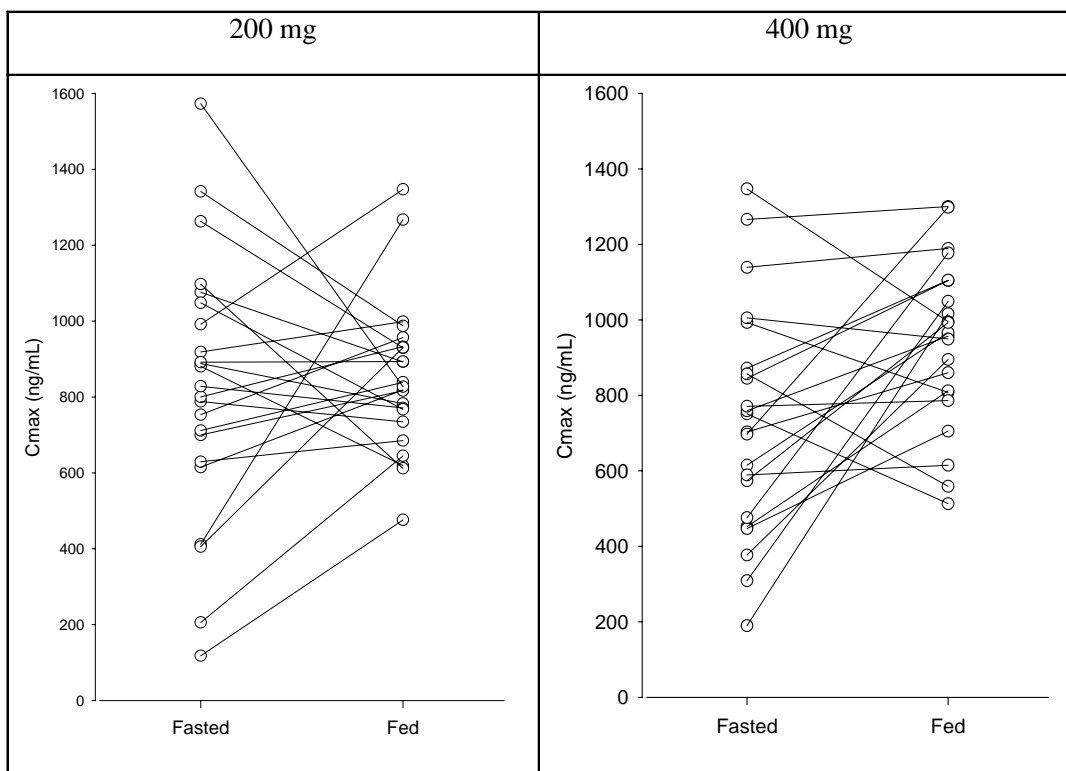
4.2.1. Absorption

After both single and multiple oral doses, ezogabine is rapidly absorbed with median Tmax values generally between 0.5 and 2 hours. The absolute oral bioavailability of ezogabine is approximately 60%.

Ezogabine is highly permeable *in vitro* and readily soluble under gastric conditions. However, its solubility is significantly lower in more alkaline and neutral pH conditions; thus, peak exposure in the fasted state may be more variable depending on when gastric emptying occurred.

Administration of ezogabine with a high-fat meal resulted in no change in overall extent of ezogabine absorption (AUC). The 14% and 38% increase in Cmax values observed with a high-fat meal from the 200 mg and 400 mg dose strengths, respectively, does not appear to be due to a systematic increase in Cmax across each individual subject ([Figure 2](#)). In the majority of subjects there was no impact of a high fat meal on Cmax values; with some subjects demonstrating lower Cmax in the fed state. The difference in mean peak exposure was driven by select individuals having low peak exposure in their fasted state when compared to their fed state. Thus, the fed state appears to reduce variability observed in ezogabine rate of absorption in the fasted state.

Figure 2 Individual Cmax Values Observed in the Fasted and Fed State for IR Tablets of Ezogabine



Therefore, the proposed dosing recommendation to take ezogabine without regard to food, as employed in the Phase II and Phase III clinical trials, is not likely to result in any safety or efficacy concern.

4.2.2. Distribution

Ezogabine is about 80% bound to plasma protein over the concentration range of 0.1 to 2 mcg/mL. It is widely distributed within the body with a steady-state volume of distribution of 2 to 3 L/kg following intravenous dosing.

4.2.3. Metabolism

Ezogabine is exclusively metabolized in humans via metabolic pathways other than cytochrome P450. The major metabolic pathways of ezogabine in humans are N-glucuronidation and N-acetylation. The primary metabolites of ezogabine were the N2- and N4-glucuronides of ezogabine, the N-acetyl metabolite of ezogabine (NAMR) and the N2- and N4-glucuronides of NAMR.

The overall systemic exposure to NAMR was similar to that of ezogabine, with the systemic exposure to both ezogabine and NAMR accounting together for approximately

10% of the circulating drug related material. The N-glucuronide metabolites of ezogabine and of NAMR are the predominant circulating metabolites.

NAMR is less potent than ezogabine in animal seizure models. In rodent models of electroshock protection NAMR has 1/3rd to 1/5th of the activity of ezogabine and has less than 1/10th of the activity of ezogabine in rodent models of partial seizure protection. NAMR was well tolerated in Irwin and Rotarod side effect profiling studies in rodents demonstrating a lack of apparent neurotoxicity or motor side effects at doses more than 10-fold greater than ED50 (or more than 5-fold greater than those demonstrating impairment with ezogabine). Therefore NAMR is not expected to have any impact on the overall pharmacological activity / safety of administered ezogabine.

The *in-vitro* activity of the N-glucuronide metabolites of ezogabine and NAMR has not been tested. However, considering the generally-recognized low pharmacologic activity of glucuronide conjugates the N-glucuronides are considered unlikely to contribute to the overall pharmacological activity/safety profile of ezogabine.

4.2.4. Elimination

Excretion is predominantly by the renal route. Although the measured absolute bioavailability of ezogabine is 60%, a total of approximately 84% of a radiolabeled dose is recovered in the urine, likely as a result of first pass hepatic metabolism of ezogabine followed by metabolite renal elimination. Unchanged ezogabine accounts for 36% of the administered dose, the N-acetyl metabolite 18%, and the N-glucuronides of ezogabine and its N-acetyl metabolite 24% in urine. Only 14% of ezogabine is excreted in the feces.

Ezogabine has an elimination half-life ($t_{1/2}$) of approximately 6 to 10 hours. The total clearance of ezogabine from plasma following intravenous dosing is 0.4 to 0.6 L/hr/kg for patients with normal renal and hepatic function.

4.2.5. Linearity

Pharmacokinetics of ezogabine are linear following single oral administration over the dose range of 25 mg to 600 mg and over the steady-state therapeutic dose range of 200 mg to 400 mg three times daily.

4.3. Drug Interactions

In vitro studies have demonstrated that the drug-drug interaction potential for ezogabine is low.

In vitro studies using human liver microsomes showed little or no potential for ezogabine to inhibit the major cytochrome P450 isoenzymes (including CYP1A2, CYP2A6, CYP2C8, CYP2C9, CYP2C19, CYP2D6, CYP2E1, and CYP3A4/5). In addition, ezogabine and NAMR did not induce the highly inducible CYP1A2 or CYP3A4/5 enzymes in human primary hepatocytes. Therefore, the pharmacokinetics of drugs that are substrates for the cytochrome P450s will not be affected when coadministered with ezogabine.

Since the route of metabolism for ezogabine is not cytochrome P450 mediated, drugs that are inducers, inhibitors or substrates of P450 enzymes would not be expected to impact the pharmacokinetics of ezogabine.

Ezogabine is neither a substrate nor an inhibitor of the P-glycoprotein transporter and would not be expected to interact with drugs which are either P-glycoprotein inhibitors or substrates. However, an *in vitro* study showed that P-glycoprotein mediated drug transport may be inhibited by NAMR at free drug concentrations of $\geq 10 \mu\text{M}$. As this metabolite only circulates systemically and is not present in the GI tract, an interaction with the oral absorption of other drugs that are P-glycoprotein substrates with ezogabine coadministration would not be anticipated. In addition, the N-acetyl metabolite's protein binding level coupled with its low activity at P-glycoprotein suggest low/no interaction with concomitant medications at the blood : brain barrier. However, NAMR may inhibit the renal tubular secretion of digoxin, resulting in increased serum levels.

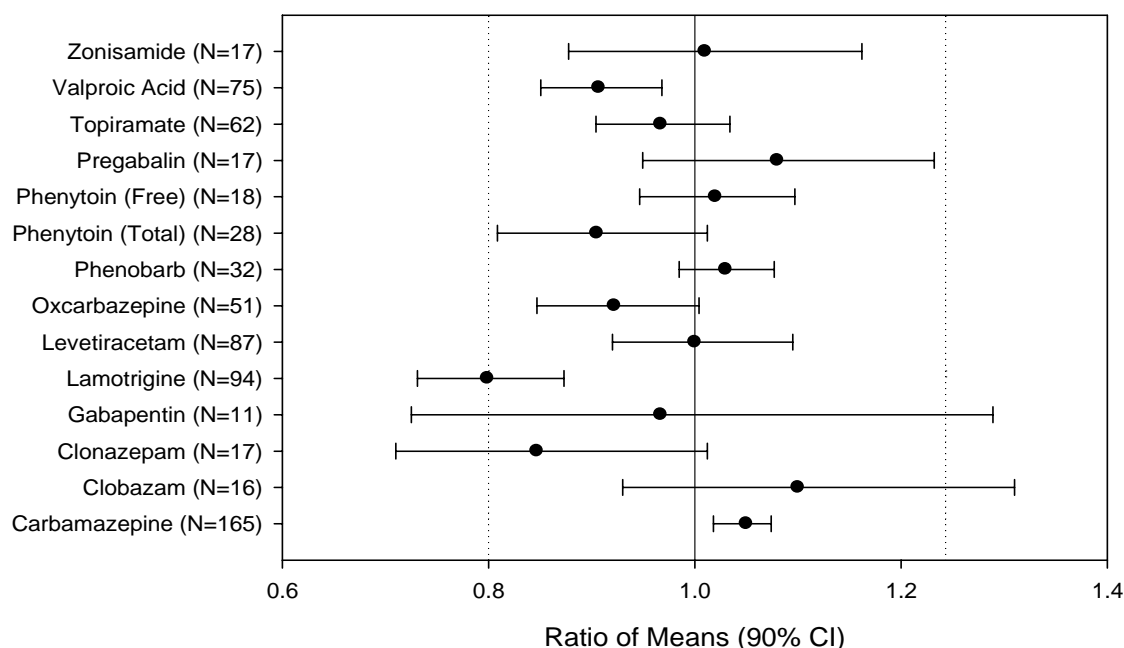
4.3.1. Phase III Studies Concomitant AED Population Exposure Assessment

The impact (drug-drug interaction) of the addition of ezogabine to existing AEDs was investigated in two Phase III clinical studies (301 and 302) by examining the trough concentrations of AEDs. A confidence interval approach was taken by examining the trough AED concentrations prior to and after steady state dosing for ezogabine.

Overall, ezogabine at doses of 600, 900 and 1200 mg/day had little or no effect on the trough plasma concentrations of the following AEDs: carbamazepine, gabapentin, levetiracetam, oxcarbazepine, phenobarbital, phenytoin, pregabalin, topiramate, and zonisamide. For most AEDs, the 90% confidence intervals of their geometric mean ratios with and without concomitant ezogabine fell entirely within the 80% to 125% bioequivalence limits ([Figure 3](#)).

The three AEDs which showed a small reduction in trough concentrations (clonazepam, lamotrigine and valproate) are all primarily cleared by glucuronidation whereas the other AEDs which did not show a reduction in trough concentration are not primarily cleared by glucuronidation. This may indicate some induction of glucuronidation but the effect on trough concentration was small (10-20%) compared to other enzyme inducing AEDs such as carbamazepine, phenytoin and phenobarbital (50-75% reduction in exposure on AEDs cleared by glucuronidation) and thus administration of ezogabine as add-on therapy does not warrant clinical dose adjustment of these co-administered AEDs.

Figure 3 Effects of Ezogabine on Trough AED Concentrations in Epileptic Subjects



N = number of subjects on concomitant AED (an individual subject could be on more than one AED)

4.3.2. Impact of AEDs on Ezogabine Exposure

A population pharmacokinetic modeling and analysis of the Phase 1-3 pharmacokinetic data showed that there were no clinically significant effects of the following AEDs on ezogabine pharmacokinetics: carbamazepine, lamotrigine, levetiracetam, oxcarbazepine, phenobarbital, phenytoin, topiramate, and valproate.

Data in a small number of patients in a Phase II study exposed to 300 to 1200 mg/day ezogabine showed ezogabine clearance and total exposure were not altered by topiramate (N=5) or valproate (N=4). However, upon discontinuation of the background AEDs carbamazepine (N=8) and phenytoin (N=9), ezogabine clearance decreased by approximately 30%.

Overall drug-drug investigations indicate that no dose adjustments of ezogabine are required when concomitantly administered with other AEDs or when other AEDs are withdrawn.

4.3.3. Lamotrigine

In a study with 29 healthy subjects, 200 mg lamotrigine coadministered with 600 mg/day ezogabine resulted in a clinically nonsignificant 15% increase in ezogabine concentrations, and ezogabine resulted in a clinically nonsignificant 18% reduction in lamotrigine concentrations.

4.3.4. Phenobarbital

In a study with 15 healthy subjects in which 90 mg of phenobarbital was coadministered with 600 mg/day of ezogabine, there was no evidence for induction of ezogabine metabolism with repeated once-daily dosing of 90 mg phenobarbital. Also, there was no effect of ezogabine on phenobarbital pharmacokinetics.

4.3.5. Oral Contraceptives

In a study that evaluated ezogabine at 750 mg/day (250 mg TID), coadministration of the oral contraceptive (1 mg norethindrone/0.035 mg ethinyl estradiol) with ezogabine to 25 female subjects did not induce the metabolism of norethindrone. Ethinyl estradiol exposure was considered bioequivalent with and without co-administered ezogabine, while C_{max} was lower with concomitant ezogabine (79%, 72-87 CI). Therefore, ezogabine is not thought to have a clinical impact on dosing or oral contraceptive use.

4.3.6. Special Populations

A population pharmacokinetic analysis was performed using sparse blood sampling from the pivotal phase II and III clinical studies (205, 301 and 303) combined with pharmacokinetic data from 20 clinical Phase 1-3 studies. The analysis was conducted to evaluate intrinsic or extrinsic factors (covariates) that contribute to the pharmacokinetic variability of ezogabine across the subject/patient groups. The final mean (95% CI) parameter estimates for clearance (L/hr) and central volume of distribution (L) were 34.4 (34.1-34.8) and 256 (246-265), respectively. Of the intrinsic covariates tested, the following factors impacted the systemic clearance of ezogabine: creatinine clearance and body surface area, coadministration of lamotrigine.

4.3.6.1. Race

A population PK analysis that tested the effects of a number of covariates on ezogabine pharmacokinetics based on pooled PK data from 1220 subjects within 22 Phase 1, 2 and 3 clinical studies available at the time of analysis, concluded that there were no statistically significant or clinically meaningful differences between Caucasians and non-Caucasians in steady state ezogabine exposure. The data set was developed for this dichotomous analysis (Caucasians versus non-Caucasians) since a large portion of the population for pharmacokinetic modeling was Caucasian (83.4%) and there were not enough subjects within the other races for accurate analysis.

In addition a *post-hoc* meta-analysis across 6 healthy subject studies demonstrated a 19% reduction in ezogabine clearance in healthy black subjects relative to healthy Caucasian subjects.

It is considered that dosage adjustment of ezogabine is not recommended on the basis of race.

4.3.6.2. Gender

No effect of gender on the pharmacokinetics of ezogabine was observed during the population pharmacokinetic analysis.

The results of a single-dose study showed that in young adult subjects ezogabine C_{max} was approximately 50% higher in females than in males, and in elderly subjects (66 to 82 years of age) ezogabine C_{max} was approximately 100% higher in females compared with males. The ezogabine AUC was approximately 20% to 30% higher in females than in males. However, there was no gender difference in weight-normalized clearance, which is consistent with the significant relationship between ezogabine clearance and body surface area observed in the population pharmacokinetic analysis. Of note, there is no statistically significant evidence of a difference in seizure response between males and females. Thus no adjustment of the ezogabine dose specific to gender is recommended.

4.4. Pediatric Patients

The pharmacokinetics of ezogabine in pediatric patients has not been investigated.

4.5. Geriatric Patients

In a single-dose, open-label study, ezogabine was eliminated more slowly by elderly volunteers (aged 66 to 82 years, n=24) relative to healthy young adult volunteers (n=24), resulting in higher AUC (approximately 40% to 50%) and longer terminal half-life (30%). In addition, a significant relationship between ezogabine clearance and creatinine clearance observed in the population pharmacokinetic analysis is consistent with the observed effect of renal impairment on ezogabine pharmacokinetics and may be a contributing factor in the reduced ezogabine clearance observed in elderly subjects. There were insufficient numbers of elderly patients enrolled in clinical trials to establish the efficacy and safety of ezogabine in this population.

4.6. Renally Impaired Patients

In a single-dose study, the ezogabine AUC was increased by approximately 30% in patients with mild renal impairment (creatinine clearance 50 to 80 mL/min) and by approximately 100% in patients with moderate impairment to end-stage renal disease (creatinine clearance <50 mL/min) relative to healthy subjects. The effect of hemodialysis on ezogabine clearance has not been adequately established. It is anticipated that in patients with moderate to severe renal impairment that the initial and maintenance doses should be halved.

4.7. Hepatically Impaired Patients

Ezogabine AUC is not affected by mild hepatic impairment (Child-Pugh score 5 to 6), but is increased by approximately 50% in subjects with moderate hepatic impairment (Child-Pugh score 7 to 9) and by approximately 100% in subjects with severe hepatic impairment (Child-Pugh score >9) relative to healthy subjects. It is anticipated that in patients with moderate and severe hepatic impairment that the initial and maintenance doses should be halved.

5. CLINICAL EFFICACY

Dose selection and titration schemes for the pivotal studies were derived from three open-label Phase II studies (Study 3065A1-200/201 [Study 200/201], Study 3065A1-202 [Study 202] and Study 3065A1-214 [Study 214]) conducted early in the clinical program.

The results from three adequate and well-controlled studies (Study 205, Study 301 and Study 302) provide substantial evidence of effectiveness for ezogabine across a dose range of 600 to 1200 mg/day as the first of a new class of drug for adjunctive treatment of partial onset seizures in adults, with or without secondary generalization.

Evidence suggestive of persistent efficacy during long term treatment with ezogabine is provided by three open-label extension studies: Study 3065A1-212 (Study 212), extension to Study 205; Study VRX-RET-E22-303 (Study 303), extension to Study 301 and Study VRX-RET-E22-304 (Study 304), extension to Study 302.

A summary of studies supporting clinical efficacy of ezogabine in the adjunctive treatment of adults with partial onset seizures is provided in [Table 4](#).

Table 4 Summary of Efficacy Studies Supporting Clinical Efficacy of Ezogabine in the Adjunctive Treatment of Adults with Partial Onset Seizures

Study Number	Phase	Design and Control	Primary Objectives	Duration ^a (titration and maintenance only)	Regimens	Number of Patients ^c
Pivotal Efficacy Studies						
205	2b	Double-blind, randomized, placebo-controlled, parallel group	Efficacy & safety	16 weeks (8 week titration phase and 8 week maintenance phase)	200 mg TID	101
					300 mg TID	95
					400 mg TID	106
					Placebo	97
301	3	Double-blind, randomized, placebo-controlled, parallel group	Efficacy & safety	18 weeks (6 week titration phase and 12 week maintenance phase)	400 mg TID	154
					Placebo	152
302	3	Double-blind, randomized, placebo-controlled, parallel group	Efficacy & safety	16 weeks (4 week titration phase and 12 week maintenance phase)	200 mg TID	181
					300 mg TID	179
					Placebo	179
Supportive Phase IIa Efficacy Studies						
200/201	2a	Open-label, uncontrolled, randomized, parallel group	Safety, tolerability, PK and preliminary efficacy	24 weeks	EZG BID regimen: slow titration rate (25 mg/day) up to 400 mg/day	5
					EZG BID regimen: medium titration rate (100 mg/day) up to 1200 mg/day	23
					EZG BID regimen: fast titration (200 mg/day) up to 2400 mg/day	18
202	2a	Open-label, uncontrolled, randomized, parallel group	Safety, tolerability, PK and preliminary efficacy	15 weeks	EZG (BID or TID regimen) + AED monotherapy (valproic acid) up to 1600 mg/day ^b	8
					EZG (BID or TID regimen)+ AED monotherapy (carbamazepine) up to 1600 mg/day ^b	22
					EZG (BID or TID regimen)+ AED monotherapy (phenytoin) up to 1600 mg/day ^b	19
					EZG (BID or TID regimen)+ AED monotherapy (topiramate) up to 1600 mg/day ^b	11

Study Number	Phase	Design and Control	Primary Objectives	Duration ^a (titration and maintenance only)	Regimens	Number of Patients ^c
Supportive Phase IIa Efficacy Studies (Continued)						
214	2a	Double-blind, randomized, parallel group	Safety, tolerability, PK and preliminary efficacy	7 weeks	EZG (TID regimen) titration rate : 150 mg/2 days up to 1200 mg/day	24
					EZG (TID regimen) titration rate: 150 mg/4 days up to 1200 mg/day	25
					EZG (TID regimen) titration rate: 150 mg/7 days up to 1200 mg/day	24
Open-Label Extension Studies that Support long-Term Efficacy						
212	2b	Open-label, long term extension study to Study 205	Safety, tolerability, long term efficacy	540 Days (1.5 years)	EZG 900 mg/day (followed by flexible titration up to 1200 mg/day)	222
303	3	Open-label, long term extension study to Study 301	Safety, tolerability, long term efficacy	ongoing	EZG 1200 mg/day (followed by flexible titration 600 to 1200 mg/day)	181
304	3	Open-label, long term extension study to Study 302	Safety, tolerability, long term efficacy	ongoing	EZG 900 mg/day (followed by flexible titration 600 to 1200 mg/day)	375

- a. Weeks for evaluation of efficacy
b. Amended final maximum dose
c. Number enrolled

5.1. Rationale for Dose Selection in the Phase II and Phase III Program

The collective data from the early Phase IIa studies (200/201 and 202) as well as data from Study 205 and Study 214 were critical in supporting the rationale for the ezogabine dosing regimen in terms of identifying: i) the starting dose (300 mg/day), ii) dose range to be tested (600 to 1200 mg/day), iii) TID dosing regimen and iv) speed of titration (150 mg/week) that were adopted in the Phase III pivotal efficacy studies. Full details of the study designs and a summary of results for the supportive efficacy studies (Study 200/201, Study 202 and Study 214) are provided in Appendix 11.2.

In a series of preliminary Phase IIa 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 IIa 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. The proposed product labeling recommends that the initial dose of ezogabine should be 100 mg 3 times daily (300 mg/day) and 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 1200 mg/day based on individual patient clinical response.

The Phase IIb dose ranging study (Study 205) in patients with partial epilepsy included investigation of three targeted doses of ezogabine: 600 mg, 900 mg and 1200 mg/day administered as a TID regimen (200 mg TID, 300 mg TID and 400 mg TID respectively).

The titration scheme including the starting dose (300 mg/day) and dose escalation regimen (150 mg/week) was based on an evaluation of the overall safety, tolerability and preliminary efficacy data obtained from Studies 200/201 and 202. The selected targeted dose range that included ezogabine 1200 mg/day and the minimum daily dose judged to be effective (400 to 600 mg/day) in the majority of patients included in the early Phase IIa studies.

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 were 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. Evidence for clinical effectiveness was further corroborated by a change in Clinical Global Impression of Improvement (CGIC) scores across all doses tested compared with placebo. The results of Study 205 provided the basis for further confirming efficacy for ezogabine 600 to 1200 mg/day in patients with partial epilepsy as add-on therapy.

Study 214 assessed the optimal speed of dose escalation for ezogabine starting at 300 mg/day and dose escalated using three different schemes that extended to 6 weeks titration in order to achieve a maximum tolerated dose of 1200 mg/week. The results of this study were to inform the titration schedule for inclusion in the Phase III studies. A dose escalation by 150 mg every 7 days was determined as being better tolerated than similar dose titration regimens administered less than every 7 days.

5.2. Pivotal Efficacy Study Designs

All three pivotal efficacy studies were international, multicenter, parallel-group randomized, double-blind, placebo-controlled, fixed dose studies. The study designs were contemporaneously consistent with clinical trial methodology employed for other AEDs used as adjunctive treatment for partial seizure epilepsy.

Study 205 was designed to assess the efficacy and safety of ezogabine 600 mg/day (200 mg three times daily [TID]), 900 mg/day (300 mg TID), and 1200 mg/day (400 mg TID). This study also provides the primary dose-response data in the clinical development program (Section 5.1). Independent substantiation of efficacy across the dose range of 600 mg/day to 1200 mg/day was obtained from Studies 301 and 302 which investigated doses of 1200 mg/day (Study 301) and 600 and 900 mg/day (Study 302).

Table 5 shows the major features of Studies 205, 301 and 302. In all three studies ezogabine was administered according to a TID regimen and was to be taken without regard to food intake. Study 205 used a capsule formulation of ezogabine in strengths of 50 mg, 100 mg and 200 mg. Studies 301 and 302 used a tablet formulation in strengths of 50 mg, 100 mg and 300 mg (Study 301 only) (See Section 4.1). It should be noted that Studies 301 and 302 may have recruited patients with more difficult to control seizures as a result of the higher number of background AEDs that were allowed. In addition, Studies 301 and 302 stipulated that patients were to have a diagnosis of epilepsy for ≥ 2 years (Section 5.3).

Consistent with the 2000 EU CHMP Note for Guidance on the Clinical Investigation of Medicinal Products in the Treatment of Epilepsy Disorders, Studies 301 and 302 were

designed with a 12-week maintenance period. Study 205, designed before the CHMP Note for Guidance, had an 8-week maintenance period.

Both Studies 301 and 302 had a forced titration scheme but Study 301 allowed a single dose reduction to 1050 mg/day at the start of the maintenance period (end of Week 7) for patients who did not tolerate 1200 mg/day at the end of the forced titration scheme. Study 205 allowed down titration in decrements of 100 mg/day for up to two occasions during the titration period.

Table 5 Major Features of Pivotal Efficacy Studies 205, 301 and 302

	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
Dosage Forms Used	50 mg, 100 mg or 200 mg IR capsules (note: 600 mg dose = 2X100 mg capsule TID; 900 mg dose = 3X100 mg capsule TID; 1200 mg dose = 1X 200 mg and 2X 100 mg capsule TID)	50 mg, 100 mg, 300 mg IR tablets (note: 1200 mg dose = 1X 300 mg tablet and 2X 50 mg tablets TID)	50 mg and 100 mg IR tablets (note: 300 mg dose = 3X 100 mg tablets TID)
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
Countries	Australia, Belgium, Croatia, Czech Republic, Finland, France, Germany, Israel, Italy, Netherlands, New Zealand, Norway, Poland, Portugal, Slovakia, Spain, Sweden, UK, and US	Argentina, Brazil, Canada, Mexico, and US	Australia, Belgium, France, Germany, Hungary, Israel, Poland, Russia, S Africa, Spain, UK, Ukraine, and US
Number of Background AEDs	≤2	≤3	≤3
Minimal duration of prior epilepsy diagnosis	Not specified ^a	≥2 years	≥2 years

a. Documented seizure frequency of ≥4 partial seizures on average per month during the previous 2 months before the baseline evaluations. Patients were not to be seizure free for >30 consecutive days

Further details on the study designs are provided in Section 5.2.1 for Study 205 and Section 5.2.2 for Studies 301 and 302.

5.2.1. Study 205

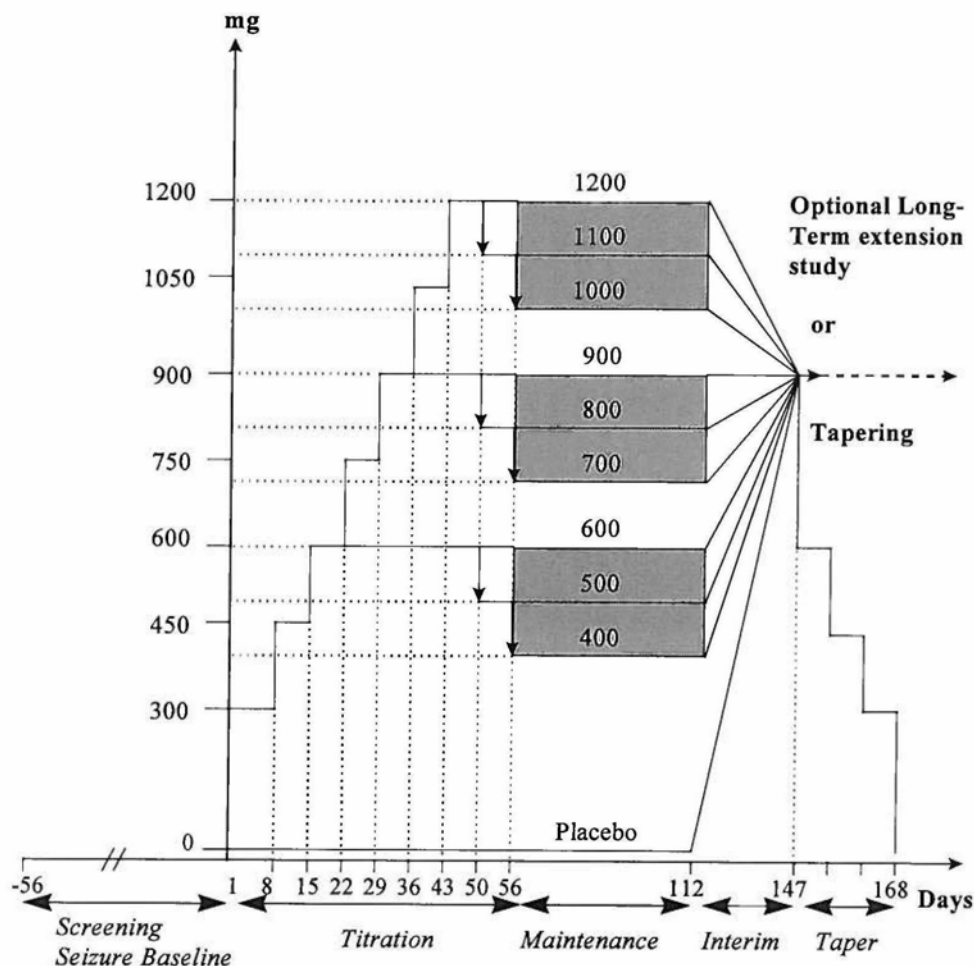
Study 205 was a randomized, double-blind, placebo-controlled, multi-center, dose-ranging study of ezogabine (600, 900 and 1200 mg/day) in patients (age 16 to 70 years) with partial-onset seizures. The objectives of this study were to evaluate the efficacy and safety of ezogabine 200 mg TID, 300 mg TID and 400 mg TID compared with placebo,

when administered as add-on therapy in patients with partial epilepsy receiving one or two pre-specified AEDs.

The study consisted of four phases: an 8-week prospective Baseline Phase during which patients were evaluated for seizure frequency, an 8-week Titration Phase to the final targeted randomized dose and an 8-week Maintenance Phase during which patients received a fixed dose regimen (Figure 4).

After completing the double-blind phase, patients could enroll in a long term, open-label, extension study (Study 3065 A1-212 [Study 212]), after a 5-week interim phase of dose adjustment. Patients who completed the double-blind study and who opted not to continue into the open-label extension study were discontinued from treatment by gradual down titration of study medication, over a 3-week period.

Figure 4 Study Design – Study 205



During Week 1 of the titration phase, patients in the ezogabine arms received ezogabine 300 mg/day (100 mg TID). At weekly intervals thereafter, the dose was increased by

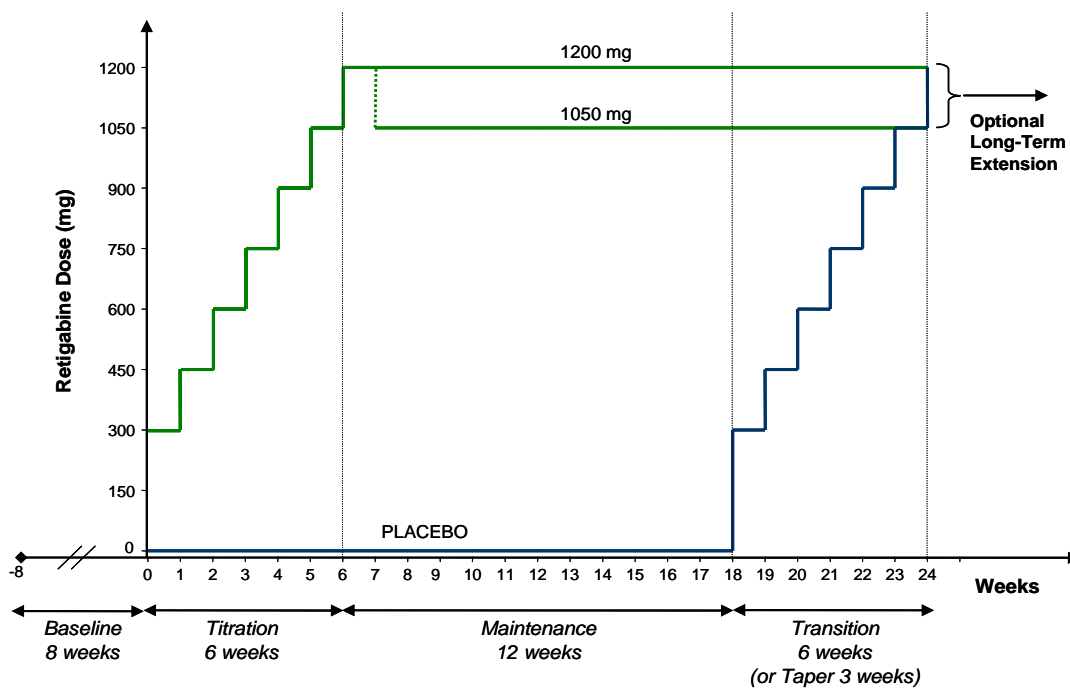
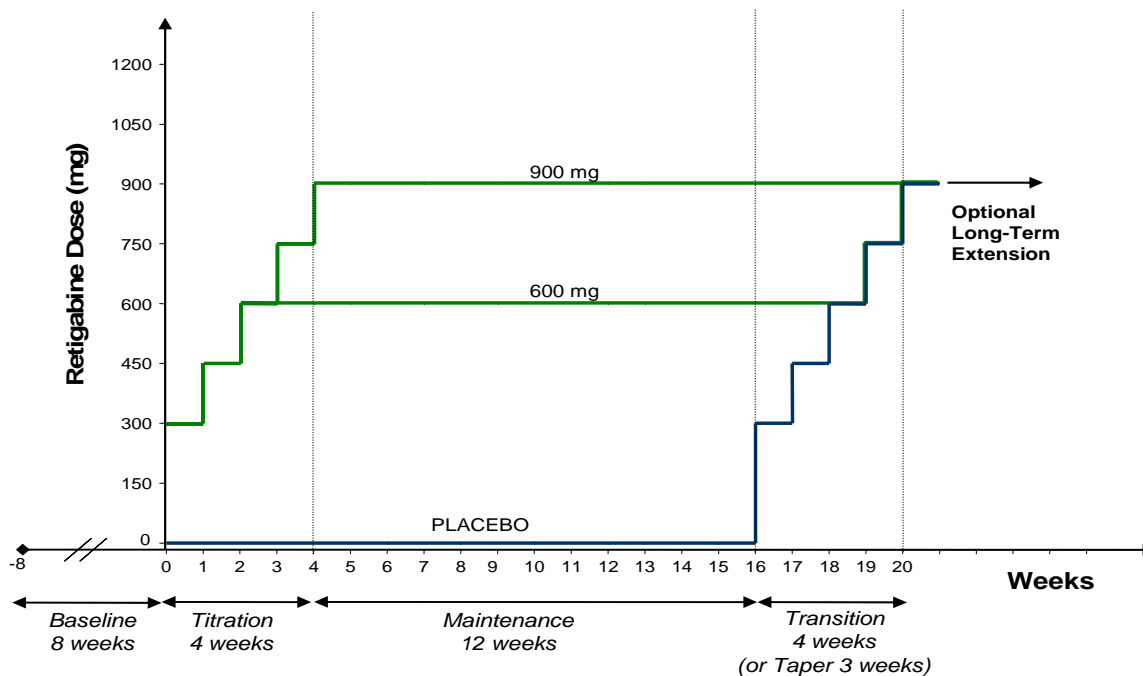
150 mg/day (50 mg TID) such that the patients in the 600 mg/day arm attained their target dose by Day 15, the 900 mg/day arm by Day 29, and the 1200 mg/day arm by Day 43. From Day 43 to the end of the 8-week forced-titration phase (Day 56), the dose could be reduced on up to two occasions by 100 mg/day at weekly intervals if required due to lack of tolerability. Thus the final targeted dose could be 400, 500 or 600 mg/day in the 600 mg/dose group, 700, 800 or 900 mg/day in the 900 mg/dose group or 1000, 1100 or 1200 mg/day in the 1200 mg/dose group. No further changes in dose (either target or reduced dose) were allowed during the 8-week maintenance phase. After completing the double-blind phase, patients could enroll in a long term, open-label, extension study (Study 3065A1-212) after a 5-week interim phase of dose adjustment. Patients completing the double-blind study and who opted not to continue into the open-label extension study were discontinued from treatment by gradual down titration of study medication over a 3-week period.

5.2.2. Studies 301 and 302

Studies 301 and 302 were similarly designed Phase III studies for assessing the efficacy and safety of ezogabine (tablets) in patients (aged 18 to 75 years) with refractory partial epilepsy. Both were randomized, double-blind, placebo-controlled, multi-center, parallel-group studies with similar inclusion and exclusion criteria.

Study 301 included assessment of ezogabine (1200 mg/day; 400 mg TID) compared with placebo. Study 302 included assessment of ezogabine 900 mg/day (300 mg TID) and ezogabine 600 mg/day (200 mg TID) compared with placebo.

Both studies included an 8-week prospective Baseline Phase during which patients were evaluated for seizure frequency, followed by a Titration Phase during which the ezogabine dose was increased by 150 mg/week (50 mg TID) [up to 4 weeks in Study 302 and 6 weeks in Study 301]. At the end of the titration period, patients were maintained on a fixed dose for a 12-week Maintenance Period ([Figure 5](#) and [Figure 6](#)).

Figure 5 Study Design- Study 301**Figure 6 Study Design- Study 302**

The only exception was that in Study 301 patients had a single opportunity to down titrate to 1050 mg/day at the end of Week 7, if they were unable to tolerate the targeted

ezogabine dose (1200 mg/day). Patients who down-titrated were then to continue at 1050 mg/day for the remainder of the maintenance period.

After completing the double-blind phase, patients could enroll in a long term, open-label, extension study (Study VRX-RET-E22-303 for Study 301 and Study VRX-RET-E22-304 for Study 302) after a transition phase of dose adjustment. In Study 301, this was a 6-week double-blind transition phase during which patients already randomized to ezogabine 1200 mg/day were maintained on this dose level and patients previously on placebo during the double-blind phase, were dose escalated to ezogabine 1200 mg/day in a double-blind, double-dummy manner. In Study 302, this was a 4-week double-blind transition phase during which patients already randomized to ezogabine 900 mg/day were maintained on this dose level and patients previously on placebo or ezogabine 600 mg/day during the double-blind phase, were dose escalated to ezogabine 900 mg/day in a double-blind, double-dummy manner. Thereafter, patients received open-label treatment with ezogabine that could be titrated between 600 to 1200 mg/day to achieve the most effective and tolerated dose. In both Studies 301 and 302 patients could be down-titrated off blinded treatment over 3 weeks, either if they chose not to continue into the open-label extension study, or if they were unable to complete the transition phase.

5.3. Selection of Patient Population in Pivotal Efficacy Studies

The pivotal efficacy studies (Studies 205, 301 and 302) recruited patients with partial onset seizures (simple partial seizures and/or complex partial seizures with or without secondary generalization) in accordance with the International League Against Epilepsy (ILAE) classification criteria [Commission, 1981]. Patients with simple partial seizures as their only qualifying seizure type were only eligible for study participation if there was a motor component to their seizures. The patient population for each of the three studies was classified according to clinical criteria widely accepted and consistent with that used in other clinical trials.

In Studies 301 and 302 patients were eligible if they had a diagnosis of epilepsy for ≥ 2 years and had received treatment previously with at least two AEDs concurrently or sequentially, without significant clinical benefit in the opinion of the investigator. In addition, such patients could be receiving up to three AEDs at stable doses (with or without VNS) for at least 1 month prior to screening and throughout the study treatment period. The patients in Studies 301 and 302 must have had at least 4 seizures per 28 days during the 8-week prospective baseline period and could not be seizure-free for more than 21 days during the baseline period. The use of vigabatrin and felbamate was prohibited in Studies 301 and 302 in order to avoid the potential for development of retinopathy and hepatic failure associated with each of these respective agents.

In contrast, patients recruited into Study 205 were only eligible if receiving up to two AEDs (vagal nerve stimulation was included as an AED therapy) at stable doses for at least 1 month prior to screening and throughout the study treatment period. The patients must have had at least 4 seizures per 28 days during the 8-week prospective baseline period and could not be seizure-free for more than 30 days during the baseline period. Vigabatrin, felbamate and tiagabine were not considered established AEDs at the time Study 205 was conducted and thus were excluded.

Supplemental use of vagal nerve stimulation was allowed in all studies if the regimen had been initiated at least 6 months previous to study enrolment and was maintained constant for at least 1 month prior to screening and for the duration of the study. Pre-specified restricted use of benzodiazepines to control seizure flurries (i.e., continuous seizure activity such that individual seizures cannot be distinguished within an episode) was allowed in Studies 301 and 302; use of benzodiazepines as background AEDs was permitted in Study 205 as long as the dose was kept constant for at least 1 month before screening and for the duration of treatment. Use of benzodiazepines as rescue or as last resort to control seizure flurries was also permitted according to pre-defined criteria in this study. Across all three studies, agents known to lower seizure threshold, for example, neuroleptics, were prohibited. However, antidepressants at low doses including monoamine oxidase inhibitors were permitted in the Studies 301 and 302 provided the dose and regimen was kept constant throughout the study.

Enrolment criteria excluded patients with significant medical conditions including those that would confound assessment of efficacy. Patients were excluded from study participation if they had a history of status epilepticus, seizure clusters or seizure flurries within the 12 months prior to study entry (6 months for Study 205), pseudo seizures, non-epileptic events or any type of psychogenic seizures. Evidence of progressive CNS disease (e.g., CNS lupus, tumors, multiple sclerosis, Alzheimer's disease), lesion or encephalopathy also precluded eligibility for study entry.

5.4. Efficacy Measures

5.4.1. Primary Efficacy Measures

The primary efficacy measure in Study 205 was the percentage change in total partial seizure frequency per 28 days from baseline to the double-blind (titration + maintenance) phase (Section 5.5).

In agreement with the FDA for US registration, the primary efficacy endpoint in Studies 301 and 302 was the percent change from baseline to the double-blind period in total partial seizure frequency per 28 days.

5.4.2. Secondary Efficacy Measures

A list of select secondary endpoints in Studies 205, 301 and 302 is provided below:

- Responder rate in the double-blind phase (defined as those experiencing a $\geq 50\%$ reduction in 28-day total partial seizure frequency from baseline to the double-blind phase).
- Responder rate in the maintenance phase (defined as those experiencing a $\geq 50\%$ reduction in 28-day total partial seizure frequency from baseline to the maintenance phase).
- Percent change from baseline to the maintenance phase in total partial seizure frequency per 28 days.

- Percent of patients experiencing a reduction from baseline in 28-day total partial seizure frequency in categories of 75 to 100%, 50 to <75%, 25 to <50%, >0 to <25% in addition to a category for those with no change/increase in seizures
- Percent of patients who were seizure free (all seizure types) during the double-blind phase and maintenance phase. This was a *post-hoc* analysis in Study 205.
- Percent of seizure-free days (all seizure types) (Studies 301 and 302 only) during the double-blind phase and maintenance phase. This was a *post-hoc* analysis in Study 205.

5.5. Efficacy Analyses and Statistical Considerations in the Phase IIb/III Studies

At screening, a seizure history was documented. Throughout the study, patients were asked to record any seizure activity in a seizure diary. The diary data were then transferred to the CRF by the investigator or a designated and trained individual. Seizure information was collected on the CRF for each seizure type noted below.

All seizure types collected: Simple partial seizures with motor signs, Simple partial seizures without motor signs, Complex partial seizures, Flurries, Partial seizures evolving to secondarily generalized, Partial status epilepticus, Convulsive status epilepticus, Absence seizures, Myoclonic seizures, Tonic-clonic seizures, Tonic seizures, Atonic seizures, Unclassified seizures.

The primary seizure category is defined as total partial seizures (with status epilepticus and with flurries) and will be referred to in this document as **total partial seizures**.

Total partial seizures was calculated as: simple partial seizures with motor signs + simple partial seizures without motor signs + complex partial seizures + partial seizures evolving to secondarily generalized + partial status epilepticus + convulsive status epilepticus + (10 if flurries='YES').

The primary endpoint is the percentage change in monthly total partial seizure rate from baseline to the double-blind phase (titration + maintenance phase). The baseline phase monthly total partial seizure rate was defined as:

$$\frac{\text{Total partial seizures reported during the baseline phase}}{\text{Number of days in the baseline phase}} \times 28$$

The monthly total partial seizure rate during the double-blind phase was similarly calculated.

The percentage change was calculated as follows:

$$\frac{\text{Monthly partial seizure rate (double-blind phase) - baseline phase}}{\text{Monthly partial seizure rate (baseline phase)}} \times 100$$

A reduction in seizure rate was indicated by a percentage change of less than zero.

A responder was defined as a patient who had at least a 50% reduction in the monthly rate of seizures.

The number of seizure free days per 28 days was calculated as follows:

$$\frac{\text{Total number of days without seizures}}{\text{Number of days in phase}} \times 28$$

It is well documented that the primary efficacy variable is not normally distributed [Pierce, 1993; Johnson, 1993]. Consequently, for all 3 pivotal controlled studies the primary analysis methods of the primary endpoint are based on ranks. Median values are primarily used to describe the data.

In Study 205, a rank analysis of covariance (ANCOVA) was pre-specified and used to analyze the primary endpoint data, percentage change in monthly total partial seizure rate from baseline to the double-blind phase, with the rank of the baseline monthly seizure rate as a covariate and treatment and center as factors in the model.

Dose response was investigated by using a closed test procedure for a monotonic trend [Rom, 1994] utilizing a family of two-sided hypotheses sequentially tested at the 5% level.

As part of this procedure 300 mg/day TID and 200 mg/day TID vs. placebo were tested. A *post-hoc* analysis was added to test 400 mg/day TID and placebo.

Responder rate (50% reduction from baseline in partial onset seizure frequency) was analyzed using logistic regression with center and treatment as effects in the model.

In Studies 301 and 302, the primary efficacy variable was analyzed using a non-parametric rank analysis of covariance stratified by geographic region and 28-day baseline seizure category based on standardized ranks of percent change for all patients as response within each stratum.

In Study 302, the comparison of 900 mg/day ezogabine vs. placebo was considered the primary comparison and was assessed at the 5% level. If this was significant then the assessment of 600 mg/day ezogabine vs. placebo was conducted to further understand the dose response relationship.

Responder rates were analyzed utilizing Fisher's exact test.

Across the three pivotal studies the patient populations upon which the double-blind efficacy analyses were based, were defined as follows:

- In Study 205, the Intent-to-treat (ITT) population was defined as all randomized patients who received at least one dose of study drug, had a baseline seizure evaluation and at least one seizure evaluation on-therapy.
- In Studies 301 and 302, the ITT population defining efficacy included all randomized patients who received at least one dose of study drug.

Assumptions underlying the determination of study sample size requirements, varied across the three pivotal trials:

- All 3 studies included an equal ratio randomization schedule.
- In Study 205, 82 patients per group were assumed, 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 5%.
- In Studies 301 and 302, the sample size was based on the percentage of responders observed in Study 205.
In Study 301, a sample size of 125 per treatment arm, was required in order to detect a 17% difference in responder rates between ezogabine 1200 mg/day and placebo (33% in active group vs 16% placebo group) with 85% power and a two-sided significance level of 5%.
In Study 302, a sample size of 151 per treatment arm, was required in order to detect a 16% difference in responder rates between ezogabine 900 mg/day and placebo (32% in active group vs 16% placebo group) with 85% power and a two-sided significance level of 5%.

Efficacy data were analyzed according to the assigned randomized treatment arm.

5.5.1. Integrated Efficacy Analyses

Efficacy data were integrated across the three pivotal studies to provide additional evidence of the efficacy of ezogabine for the primary and key secondary endpoints as well as for specific subgroups in the NDA. Within this briefing document, the integrated subgroup analyses of Studies 205, 301 and 302 with respect to the primary endpoint that are discussed include : i) gender, ii) age, iii) race, iv) number of background AEDs at baseline, v) seizure subtype (simple partial, complex partial, secondarily generalized) and vi) geographic region (US and non-US).

For the integrated summaries of the pivotal trials (205, 301 and 302) the primary ITT analysis population defined for the double-blind phase analyses was defined as for Studies 301 and 302 and consisted of all randomized patients who received at least one dose of study drug.

The percent change in 28-day total partial seizure frequency was analyzed using non-parametric Rank ANCOVA as defined for the pivotal Studies 301 and 302 with adjustment for study.

Because the integrated analyses were performed after all studies were unblinded, no multiplicity adjustment was considered for multiple comparisons.

To ensure appropriate comparisons between groups, patients combined across ezogabine treatment groups were compared only to the placebo subjects from those studies which included the specific treatment groups. For example, the combined set of ezogabine 900 mg/day patients (Studies 205 and 302) were compared only to the combined set of placebo patients from Studies 205 and 302.

In Safety Section 6.6.4, integrated efficacy data across the three pivotal studies are provided for the percent of patients experiencing a reduction from baseline in 28 day total partial seizure frequency in categories of 75 to 100%, 50 to <75%, 25 to <50%, >0 to <25% in addition to a category for those with no change/increase in seizures.

In a separate analysis, efficacy data were also integrated across the respective open-label extension studies (212, 303 and 304) to the 3 pivotal studies (205, 301 and 302) to provide supportive evidence of long term maintenance of effect with ezogabine.

For the integrated summaries of the open-label extension studies, efficacy was assessed on the 'safety population' defined as all patients who successfully completed the transition phase of the respective double-blind parent study and received at least one dose of ezogabine in the open-label extension study.

All endpoints were summarized by the treatment groups to which subjects were randomized in the prior double-blind studies. Since all subjects in Studies 212, 303 and 304 received ezogabine, there were no inferential treatment comparisons performed for the integrated open-label studies.

5.6. Efficacy Results

5.6.1. Patient Disposition

In each of the three randomized, controlled trials, the percentages of patients who withdrew from the study for any reason were reported, as were the percentages of patients who withdrew due to adverse events (Table 6).

Withdrawals for any reason were reported for 15% to 22% in the placebo groups, 25% to 28% in the ezogabine 600 mg/day groups, 32% to 34% in the 900 mg/day groups, and 37% to 43% in the 1200 mg/day groups.

The most common reason for discontinuation was adverse event. Withdrawals due to adverse events were reported for 8% to 13% of the placebo groups, 14% to 21% of the ezogabine 600 mg/day groups, 22% to 26% of the 900 mg/day groups, and 27% to 31% of the 1200 mg/day groups. Withdrawal due to lack of efficacy was not common ($\leq 4\%$ of patients in any treatment group), and there was no clear dose relationship.

Table 6 Summary of Patient Disposition during the Double-Blind Phase in Randomized, Controlled Trials (Studies 205, 301 and 302)

	Number (%) of Patients								
	Study 205				Study 302			Study 301	
	Placebo	EZG 600 mg/day	EZG 900 mg/day	EZG 1200 mg/day	Placebo	EZG 600 mg/day	EZG 900 mg/day	Placebo	EZG 1200 mg/day
Population									
Randomized	97	101	95	106	179	181	179 ^a	152	154 ^a
Safety	96	100	95	106	179	181	178	152	153
ITT ^a	96	99	95	106	-	-	-	-	-
ITT Double-Blind ^b	-	-	-	-	179	181	178	152	153
Patient Disposition (Safety Population)									
N	96	100	95	106	179	181	178	152	153
Discontinued	21 (21.9)	28 (28.0)	32 (33.7)	45 (42.5)	27 (15.1)	46 (25.4)	56 (31.5)	26 (17.1)	56 (36.6)
Reason for Discontinuation									
Adverse Event	12 (12.5)	21 (21.0)	21 (22.1)	33 (31.1)	14 (7.8)	26 (14.4)	46 (25.8)	13 (8.6)	41 (26.8)
Unsatisfactory response- efficacy	4 (4.2)	1 (1.0)	4 (4.2)	1 (0.9)	5 (2.8)	0	0	2 (1.3)	4 (2.6)
Lost to follow-up (failed to return)	0	0	1 (1.1)	0	2 (1.1)	4 (2.2)	1 (0.6)	2 (1.3)	1 (0.7)
Protocol violation	3 (3.1)	3 (3.0)	0	4 (3.9)	2 (1.1)	6 (3.3)	3 (1.7)	4 (2.6)	4 (2.6)
Patient request unrelated to study	1 (1.0)	2 (2.0)	4 (4.2)	4 (3.9)	1 (0.6)	5 (2.8)	3 (1.7)	1 (0.7)	0
Other event	1 (1.0)	1 (1.0)	2 (2.1)	3 (2.8)	3 (1.7)	5 (2.8)	3 (1.7)	4 (2.6)	6 (3.9)

a. One patient was randomized, but never received study drug

b. For Study 205, the primary efficacy population was the Intent to Treat (ITT) population including all randomized patients who took at least one dose of study drug and had a baseline seizure evaluation and a post baseline seizure evaluation in the treatment period. For Studies 301 and 302, the primary efficacy population was the ITT double-blind population which was defined as all randomized patients who received at least one dose of study drug.

5.6.2. Patient Demographic and Baseline Characteristics

Patient demographics in the three pivotal trials were similar across the studies and male and female patients were divided approximately equally across the studies and treatment groups (Table 7). The mean age range across the three studies was 35 to 38 years, and elderly (≥ 65 years) patients ($n=10$) accounted for $<1\%$ of the total population studied. The majority of patients across all three studies were White/Caucasian. Study 301 included a greater percentage of Hispanic, Black and Other race patients than Studies 205 and 302. The majority of patients (1062/1240) were from non-US geographical regions. The contribution of data from US patients was mainly from Study 301 (148/178 US patients).

Across the three pivotal studies the median baseline seizure frequency ranged from 8 to 12 seizures per month. Studies 301 and 302 could be considered as recruiting more refractory patient groups compared to Study 205, based upon inclusion criteria with respect to concomitant AED use i.e., patients were allowed up to three AEDs compared to only two AEDs in Study 205. The majority of patients in Study 301 and Study 302 received ≥ 2 AEDs. In Study 205, the majority of patients received 2 AEDs. The most commonly used AEDs at baseline included carbamazepine, lamotrigine, valproic acid, levetiracetam and topiramate.

Table 7 Summary of Demographic and Baseline Characteristics – Randomized, Controlled Trials (Safety Population: Studies 205, 301 and 302)

	Study 205				Study 302			Study 301	
	Placebo N=96	EZG 600 mg/day N=100	EZG 900 mg/day N=95	EZG 1200 mg/day N=106	Placebo N=179	EZG 600 mg/day N=181	EZG 900 mg/day N=178	Placebo N=152	EZG 1200 mg/day N=153
Age, years									
mean \pm SD	34.5 \pm 10.3	36.8 \pm 10.9	37.0 \pm 10.1	38.3 \pm 11.9	37.7 \pm 11.75	37.5 \pm 12.02	37.7 \pm 12.77	36.7 \pm 11.63	37.7 \pm 12.55
Sex, n (%)									
Female	48 (50)	46 (46)	47 (49)	51 (48)	90 (50.3)	105 (58.0)	85 (47.8)	80 (52.6)	85 (55.6)
Male	48 (50)	54 (54)	48 (51)	55 (52)	89 (49.7)	76 (42.0)	93 (52.2)	72 (47.4)	68 (44.4)
Race, n (%)									
White/Caucasian	89 (93)	98 (98)	92 (97)	103 (97)	169 (94.4)	173 (95.6)	170 (95.5)	78 (51.3)	90 (58.8)
Black	2 (2)	1 (1)	1 (1)	0	2 (1.1)	2 (1.1)	1 (0.6)	15 (9.9)	15 (9.8)
Hispanic	0	0	0	0	0	0	0	47 (30.9)	39 (25.5)
Asian	1 (1)	0	1 (1)	1 (<1)	3 (1.7)	0	2 (1.1)	1 (0.7)	1 (0.7)
Other	4 (4)	1 (1)	1 (1)	2 (2)	5 (2.8)	6 (3.3)	5 (2.8)	11 (7.2)	8 (5.2)
Monthly Baseline Seizure Frequency									
Median (range)	8.5 (3, 869)	8.5 (1, 271)	7.9 (4, 230)	10.4 (2, 220)	9.3 (3, 485)	9.5 (3, 858)	10.3 (3, 343)	11.3 (4, 885)	12.1 (4, 2166)
Number of AEDs, n (%)									
1	33 (34)	26 (26)	26 (27)	31 (29)	40 (22.3)	49 (27.1)	35 (19.7)	21 (13.8)	32 (20.9)
2	62 (65)	72 (72)	69 (73)	74 (70)	87 (48.6)	76 (42.0)	99 (55.6)	70 (46.1)	79 (51.6)
3	1 (1)	2 (2)	0	1 (<1)	52 (29.1)	56 (30.9)	44 (24.7)	61 (40.1)	42 (27.5)
Vagal nerve stimulator used?^a									
Yes	n/a	n/a	n/a	n/a	6 (3.4)	4 (2.2)	4 (2.2)	17 (11.2)	12 (7.8)
No	n/a	n/a	n/a	n/a	173 (96.6)	177 (97.8)	174 (97.8)	135 (88.8)	141 (92.2)
Duration of Illness, years									
mean \pm SD	20.7 \pm 11.0	20.7 \pm 11.8	19.6 \pm 12.0	20.2 \pm 11.3	22.8 \pm 11.84	22.5 \pm 13.02	22.5 \pm 12.71	23.1 \pm 12.77	23.7 \pm 13.00
Geographic region (US and Non-US), n (%)									
US	7 (7.3)	8 (8.0)	7 (7.4)	5 (4.7)	0	3 (1.7)	0	71 (46.7)	77 (50.3)
Non-US	89 (92.7)	92 (92.0)	88 (92.6)	101 (95.3)	179 (100)	178 (98.3)	178 (100)	81 (53.3)	76 (49.7)

n/a=not applicable

- a. In Study 205, 2 patients had received vagal nerve stimulation besides regular AED treatment at some time before entering the study (1 patient in the ezogabine 600 mg/day group and 1 patient in the ezogabine 900 mg/day group).

5.6.3. Primary Efficacy Results (Studies 205, 301 and 302)

5.6.3.1. Percent Change from Baseline in 28-Day Total Partial Seizure Frequency – ITT Double-Blind Population

Ezogabine was superior to placebo in the primary efficacy analysis in all three pivotal efficacy studies. In Study 205 a linear dose response relationship was established for ezogabine (600 to 1200 mg/day) ([Table 8](#)).

The 900 and 1200 mg/day doses of ezogabine were statistically superior to placebo in both studies (Study 205 and 302) in which they were tested ($p \leq 0.05$ for all comparisons). The 600 mg/day dose was statistically superior to placebo in one of two studies in which it was tested (Study 302; $p=0.007$). There was numerical improvement in the 600 mg/day dose group over placebo in Study 205 (-23% versus -13% respectively; $p=0.199$) ([Table 8](#)). Study 205 had a smaller sample size than the Studies 301 and 302 and this may have, in part, contributed to the ezogabine 600 mg dose failing to statistically differentiate from placebo.

Table 8 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

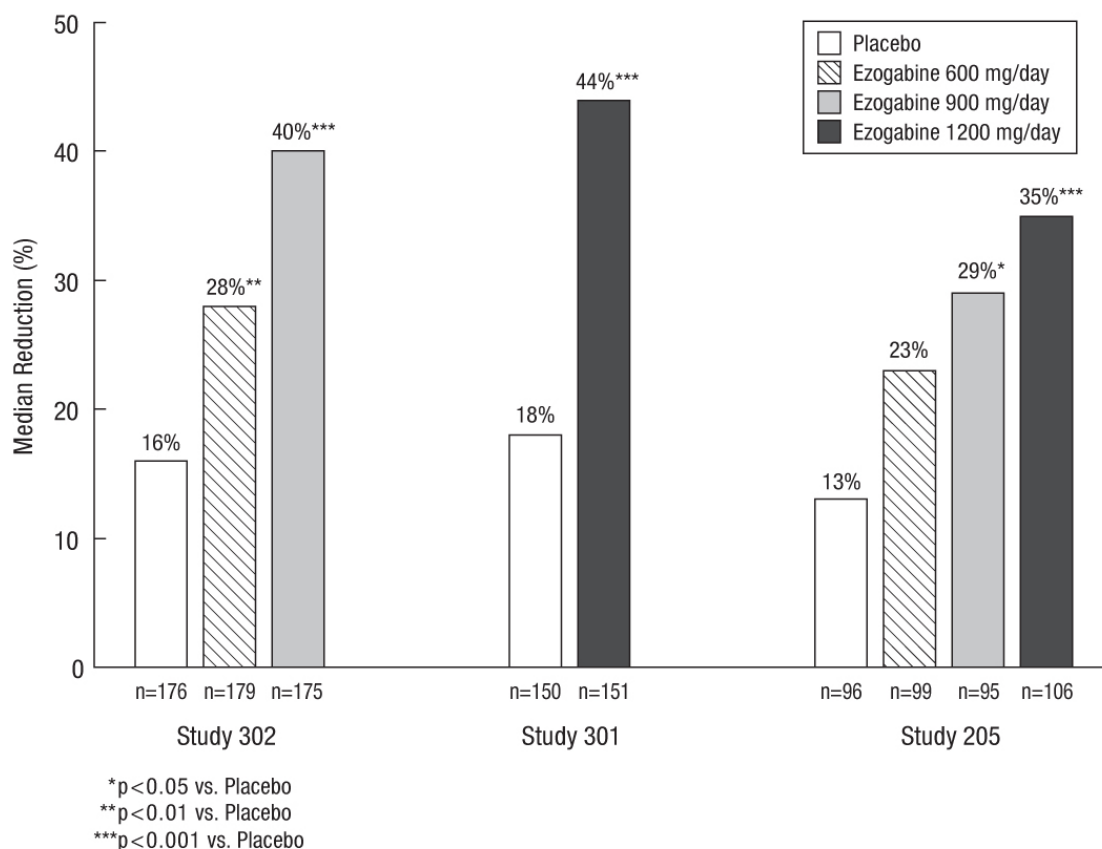
	Placebo	EZG 600 mg/day	EZG 900 mg/day	EZG 1200 mg/day
Study 205				
N	96	99	95	106
n	96	99	95	106
Baseline Frequency				
Mean ± SD	25.3 ± 91.82	18.1 ± 32.31	16.7 ± 28.65	18.9 ± 27.58
Median (Range)	8.5 (3, 868)	8.5 (1, 271)	7.9 (4, 230)	10.4 (2, 220)
Post-baseline Frequency				
Mean ± SD	17.3 ± 34.08	22.8 ± 75.96	15.2 ± 27.54	14.8 ± 24.12
Median (Range)	7.2 (0, 196)	6.3 (0, 692)	6.0 (0, 168)	6.8 (0, 152)
Percent Change from Baseline				
Mean ± SD	-3.3 ± 75.03	8.5 ± 190.94	-14.1 ± 70.35	-23.5 ± 64.87
Median (Range)	-13.1 (-100, 533)	-23.4 (-100, 1703)	-29.3 (-100, 298)	-35.2 (-100, 375)
P-value ^a	-	0.199	0.043	<0.001
Study 302				
N	179	181	178	n/a
n	176	179	175	n/a
Baseline Frequency				
Mean ± SD	30.3 ± 68.96	25.2 ± 67.30	24.2 ± 39.44	n/a
Median (Range)	9.3 (3, 485)	9.5 (3, 858)	10.3 (3, 343)	n/a
Post-baseline Frequency				
Mean ± SD	29.1 ± 68.23	19.9 ± 40.03	17.7 ± 31.30	n/a
Median (Range)	8.2 (0, 450)	7.4 (0, 393)	6.7 (0, 214)	n/a
Percent Change from Baseline				
Mean ± SD	-1.1 ± 138.37	-20.4 ± 51.02	-27.8 ± 56.12	n/a
Median (Range)	-15.9 (-100, 1712)	-27.9 (-94, 250)	-39.9 (-100, 226)	n/a
P-value ^b	-	0.007	<0.001	n/a
Study 301				
N	152	n/a	n/a	153
n	150	n/a	n/a	151
Baseline Frequency				
Mean ± SD	35.3 ± 87.03	n/a	n/a	46.1 ± 184.81
Median (Range)	11.3 (4, 885)	n/a	n/a	12.1 (4, 2166)
Post-baseline Frequency				
Mean ± SD	29.9 ± 54.80	n/a	n/a	36.1 ± 151.79
Median (Range)	9.5 (1, 420)	n/a	n/a	7.4 (0, 1736)
Percent Change from Baseline				
Mean ± SD	1.6 ± 95.09	n/a	n/a	-25.1 ± 64.75
Median (Range)	-17.5 (-90, 628)	n/a	n/a	-44.3 (-100, 302)
P-value ^b	-	n/a	n/a	<0.001

n/a=not applicable (dose group not included in this study)

N=Number of patients in the population; n=number of patients with post-baseline data

- The p-values presented are from the original closed test using rank ANCOVA under the assumption of monotonicity.
- In Studies 301 and 302, the p-values are for the treatment comparison versus placebo using non-parametric rank ANCOVA

Figure 7 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



Note: numbers rounded for clarity of display

Studies 301 and 302 were substantially similar in design (Section 5.2) and conducted at the same time, albeit in different geographic regions. Additionally the placebo response was similar in the two studies (Table 8). The data from Study 302 (ezogabine 600 mg/day and 900 mg/day) showed a dose-related treatment difference for median percent reduction in seizure frequency from baseline to the double-blind phase (-15.9% placebo versus -27.9% at 600 mg/day and -39.9% at 900 mg/day [Study 302]). Data from Study 301 provided further evidence in support of increasing response with increasing dose of ezogabine (-17.5% placebo versus -44.3% at 1200 mg/day [Study 301]) albeit from independent trials completed under varying conditions and across time. The results support the linear dose response relationship established in Study 205 (Figure 7).

5.6.4. Secondary Efficacy Endpoints

5.6.4.1. Responder Rate in the ITT Double-Blind Population

Responder rates with ezogabine at 900 mg/day and 1200 mg/day were significantly higher than placebo in both studies where those doses were tested and at 600 mg/day in Study 302 ($p \leq 0.008$ for all comparisons). The responder rate for the 600 mg/day dose in Study 205 was numerically higher than placebo (23.2% versus 15.6%), but the difference was not statistically significant ($p=0.189$).

Table 9 Responder Rates (Double-Blind Phase) – ITT Double-Blind Population: Studies 205, 301 and 302

	Number (%) of Patients			
	Placebo	EZG 600 mg/day	EZG 900 mg/day	EZG 1200 mg/day
Study 205				
N	96	99	95	106
n	96	99	95	106
Responders	15 (15.6)	23 (23.2)	30 (31.6)	35 (33.0)
Non-Responders	81 (84.4)	76 (76.7)	65 (68.4)	71 (77.0)
P-value ^a	-	0.189	0.008	0.001
Study 302				
N	179	181	178	n/a
n	179	181	178	n/a
Responders	31 (17.3)	57 (31.5)	70 (39.3)	n/a
Non-Responders	148 (82.7)	124 (68.5)	108 (60.7)	n/a
P-value ^b	-	0.002	<0.001	n/a
Study 301				
N	152	n/a	n/a	153
n	152	n/a	n/a	153
Responders	27 (17.8)	n/a	n/a	68 (44.4)
Non-Responders	125 (82.2)	n/a	n/a	85 (55.6)
P-value ^b	-	n/a	n/a	<0.001

n/a=not applicable (dose not included in this study)

Responders were defined as patients with $\geq 50\%$ reduction in 28-day total partial seizure frequency

Patients without post baseline seizure data were assumed non-responders.

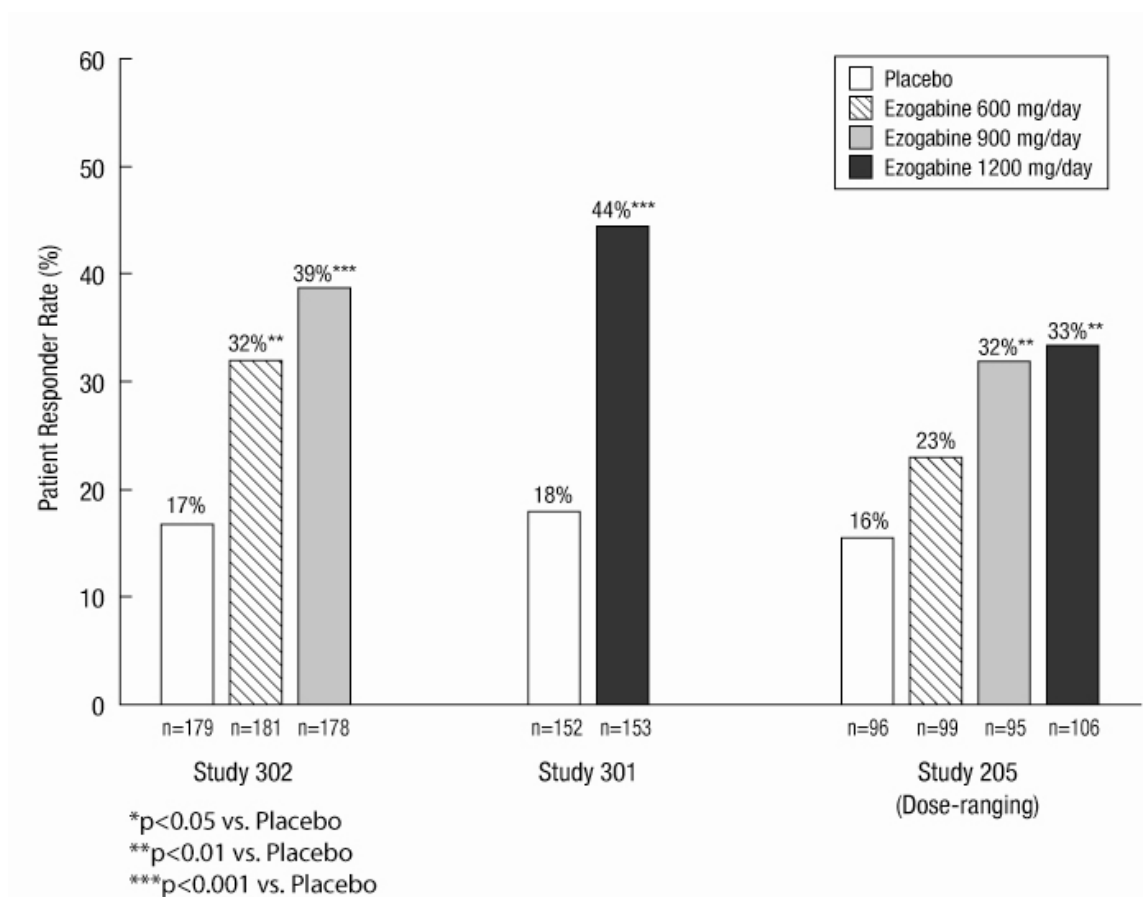
a. The p-values presented are from the original pre-planned analysis using logistic regression

b. P-value from Fisher's Exact test

The placebo responder rate was similar across both Studies 301 and 302 (Table 9). The data from Study 302 (ezogabine 600 mg/day and 900 mg/day) showed a dose-related treatment difference for the responder analysis in the double-blind phase. Data from Study 301 provides further evidence of increasing response with increased dose of ezogabine 1200 mg/day (Table 9).

When all three studies are considered together the results for the double-blind phase responder rate endpoint support the dose response noted in the percent change analysis presented in Section 5.6.3.

Figure 8 Responder Rates (Double-Blind Phase) – ITT Double-Blind Population: Studies 205, 301 and 302



Note: numbers rounded for clarity of display

5.6.4.2. Responder Rate in the ITT Maintenance Population

Ezogabine was superior to placebo on the responder rate in all three pivotal efficacy studies (Table 10). When considering the responder analysis in the maintenance phase for Study 205, the data overall for ezogabine 1200 mg/day supports evidence for efficacy with a strong trend to support ezogabine 900 mg/day.

Table 10 Responder Rates (Maintenance Phase) – ITT Maintenance Population: Studies 205, 301 and 302

	Number (%) of Patients			
	Placebo	EZG 600 mg/day	EZG 900 mg/day	EZG 1200 mg/day
Study 205				
N	78	83	74	68
Responders	20 (25.6)	23 (27.7)	30 (40.5)	28 (41.2)
Non-responders	58 (74.4)	60 (72.3)	44 (59.5)	40 (58.8)
P-value ^a	-	0.845	0.057	0.010
Study 302				
N	164	158	149	n/a
Responders	31 (18.9)	61 (38.6)	70 (47.0)	n/a
Non-responders	133 (81.1)	97 (61.4)	79 (53.0)	n/a
P-value ^b	-	<0.001	<0.001	n/a
Study 301				
N	137	n/a	n/a	119
Responders	31 (22.6)	n/a	n/a	66 (55.5)
Non-responders	106 (77.4)	n/a	n/a	53 (44.5)
P-value ^b	-	n/a	n/a	<0.001

n/a=not applicable (dose not included in this study)

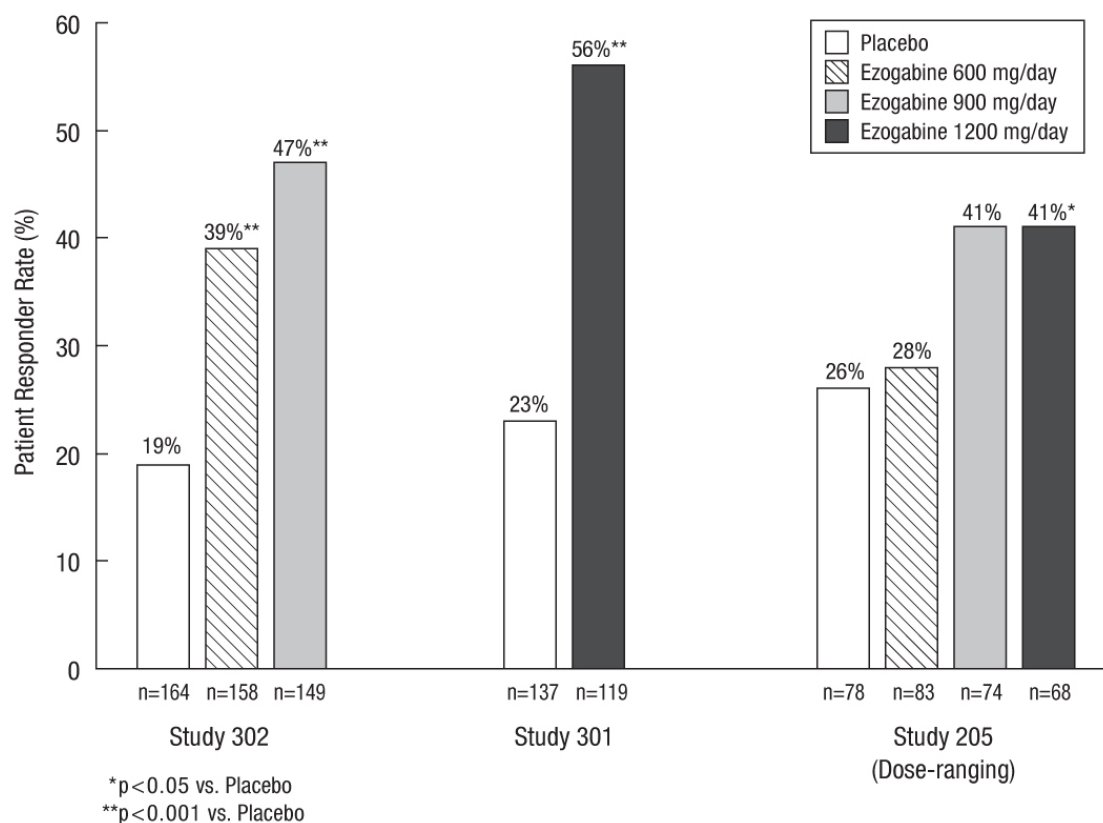
Responders were defined as patients with $\geq 50\%$ reduction in 28-day total partial seizure frequency

- The p-values presented are from the original closed test using logistic regression under the assumption of monotonicity
- P-value from Fisher's Exact test

The data from Study 302 (ezogabine 600 mg/day and 900 mg/day) showed a statistically and clinically relevant dose-related treatment difference for the responder analysis in the maintenance phase (18.9% placebo versus 38.6%, $p < 0.001$ at 600 mg/day and 47%, $p < 0.001$ at 900 mg/day). Data from Study 301 provided further evidence in support of increasing response with increasing dose of ezogabine (22.6% placebo versus 55.5%, $p < 0.001$, at 1200 mg/day).

The responder rates for ezogabine at 900 mg/day and 1200 mg/day ranged from 40 to 56% across the three studies (Figure 9). The placebo response rates for Study 205 were slightly higher (~26%) compared to that seen in the later Phase III studies (~23%, Study 301; ~19%, Study 302).

Figure 9 Responder Rate (Maintenance Phase) – ITT Maintenance Population: Studies 205, 301 and 302



Note: numbers rounded for clarity of display

5.6.4.3. Percent Change from Baseline in 28-Day Total Partial Seizure Frequency in the ITT Maintenance Population

The median percent reduction from baseline in the 28-day total partial seizure frequency in the ITT maintenance population across the three studies comparisons increased with increasing ezogabine dose (Table 11).

Dose effects were statistically significant at 1200 mg/day in Studies 205 and 301, and at 600 mg/day and 900 mg/day in Study 302. In Study 205, there were numerically larger improvements observed in median percent change in seizure frequency at 600 mg and 900 mg, but the results were not statistically significant.

Table 11 Percent Change from Baseline in Total Partial Seizure Frequency (Maintenance Phase) – ITT Maintenance Population: Studies 205, 301 and 302

	Placebo	EZG 600 mg/day	EZG 900 mg/day	EZG 1200 mg/day
Study 205				
N	78	83	74	68
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
Study 302				
N	164	158	149	n/a
n	164	158	149	n/a
Mean ± SD	-5.1 ± 133.27	-25.0 ± 55.96	-30.9 ± 80.49	n/a
Median	-17.4	-35.3	-44.3	n/a
Range	-100, 1589	-100, 253	-100, 714	n/a
P-value ^b	-	0.002	<0.001	n/a
Study 301				
N	137	n/a	n/a	119
n	137	n/a	n/a	119
Mean ± SD	-3.1 ± 135.74	n/a	n/a	-32.0 ± 91.86
Median	-18.9	n/a	n/a	-54.5
Range	-100, 1382	n/a	n/a	-100, 660
P-value ^b	-	n/a	n/a	<0.001

n/a=not applicable (dose group not included in this study)

- The p-values presented are from the original closed test using rank ANCOVA under the assumption of monotonicity.
- P-value for treatment comparison versus placebo using non-parametric rank ANCOVA.

5.6.4.4. Other Secondary Efficacy Endpoints

The significant results in primary efficacy analyses were further supported by other secondary endpoints (see Appendix 11.1, Table A 1):

- Distribution of the seizure frequency profiles by pre-defined percentage categories (Studies 301 and 302, $p \leq 0.022$). Ezogabine treatment resulted in greater proportion of patients having $\geq 50\%$ and $\geq 75\%$ reductions in seizure frequency compared to placebo. Based upon the distribution profiles by pre-defined percentage categories there was no evidence for worsening of seizures (no change or increase in seizure frequency from baseline) with ezogabine treatment.

In the *post-hoc* analyses for Study 205 that pre-defined percentage categories including no change/increase, with the exception of the 600 mg/day group, there was a significant difference between treatment groups with respect to the distribution categories in the ITT double-blind population. A statistically significant difference

was only observed for ezogabine 1200 mg/day in the maintenance phase analysis. Similar to the pre-defined percentage categories analyses in Studies 301 and 302, there was no evidence for worsening of seizures (no change or increase in seizure frequency from baseline) with ezogabine treatment.

- Number of seizure-free patients. The number of seizure free patients was statistically significant from placebo for ezogabine 1200 mg/day in the maintenance phase analysis of Study 301 ($p=0.027$).
- Percentage of seizure-free days. In Studies 301 and 302, there were statistically significant effects at all tested doses in both the double-blind and maintenance phase analyses ($p \leq 0.021$ at all tested doses and phase). In Study 205, statistically significant treatment effects were observed at ezogabine 1200 mg/day in the percentage of seizure-free days in the double-blind phase.

5.6.5. Subgroup Analyses

The results of integrated subgroup analyses that included intrinsic factors (age, gender, race) and extrinsic factors (number of background AEDs at baseline, US versus non-US patients, seizure subtypes) indicated there was no evidence to support a need for dose adjustment of ezogabine by subgroup. A summary of subgroup analyses is provided below.

5.6.5.1. Analysis by Age

There were too few elderly patients ($n=10$) to support a meaningful analysis of this subgroup separately. Across the pivotal trials eligible patients for inclusion were 16 to 75 years. The majority of patients fell within the age groups 18 to 64 years as is typical for these types of studies. Because there were too few patients ≥ 65 years, a subgroup analysis of the elderly patients was not possible. A dichotomized subgroup analysis by 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 performed to assess the rigour of efficacy by these age groups (Table 12). Overall, the response to treatment with ezogabine was not affected by age as defined in this analysis.

Table 12 **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	EZG 600 mg/day	EZG 900 mg/day	Placebo ^b	EZG 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.

Treatment by age interaction comparison vs placebo: ezogabine 600 mg/day vs placebo (p=0.343), ezogabine 900 mg/day vs placebo (p=0.187), ezogabine 1200 mg/day vs placebo (p=0.348).

- Consists of the placebo patients corresponding to the comparison with ezogabine 600 mg and 900 mg (Studies 205 and 302).
- Consists of the placebo patients corresponding to the comparison with ezogabine 1200 mg (Studies 205 and 301).
- Comparison vs placebo based on Rank Transformation Residual ANCOVA.

5.6.5.2. Analysis by Gender

In the integrated analysis there was a statistically significant reduction from baseline in 28-day total partial seizure rate at all doses of ezogabine compared with placebo in female patients (Table 13). The magnitude of effect increased with increasing doses of ezogabine.

There was a smaller numerical improvement in seizure reduction in the pooled analysis for males compared to females treated with ezogabine. However there was no evidence of a statistically significant difference in the overall response to treatment with ezogabine according to gender.

Table 13 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	EZG 600 mg/day	EZG 900 mg/day	Placebo ^b	EZG 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.

Treatment by gender interaction comparison vs placebo: ezogabine 600 mg/day vs placebo (p=0.186), ezogabine 900 mg/day vs placebo (p=0.089), ezogabine 1200 mg/day vs placebo (p=0.125).

- 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.

5.6.5.3. Analysis by Race

The integrated analysis by race was limited by the large proportion of Whites/Caucasians included across the three pivotal efficacy studies (approximately 86%). A meaningful evaluation of the effects of racial subgroups was confined to a comparison of Whites versus all other racial groups combined (non-Whites) specifically in the treatment cohort with the largest samples for racial subgroup comparison. The analysis was focused primarily to Study 301 which included a significant minority of non-White patients i.e., mainly Hispanics recruited on the basis of the regional stratification criteria in this study. This study only evaluated efficacy of ezogabine 1200 mg/day. This analysis was not performed for the ezogabine 600 mg/day and 900 mg/day dose groups because the proportion of Non-Whites patients is small in both treatment groups (EZG 600 mg/day: N=10; EZG 900 mg/day: N=11). The overall response to treatment with ezogabine was not significantly different in the racial groups studied i.e., Whites versus non-Whites (Table 14).

Table 14 **Percent Change from Baseline in 28-Day Total Partial Seizure Frequency by Race (Double-Blind Phase) – ITT Double-Blind Population (Studies 205 and 301 Integrated)**

	Placebo ^a	EZG 1200 mg/day
White/Caucasian	N=167	N=193
n	166	192
Mean ± SD	-9.9 ± 48.90	-22.6 ± 64.91
Median	-15.1	-35.2
Range	-100, 203	-100, 375
P-value ^b	-	<0.001
Non-White	N=81	N=66
n	80	65
Mean ± SD	19.6 ± 135.10	-29.9 ± 64.18
Median	-10.9	-47.6
Range	-89, 628	-100, 216
P-value ^b	-	<0.001

Only patients with baseline and post-baseline seizures were included in the analysis.

Treatment by race interaction comparison vs placebo: ezogabine 1200 mg/day vs placebo (p=0.276); overall ezogabine vs placebo (0.167).

- Consists of the placebo patients corresponding to the comparison with ezogabine 1200 mg (Studies 205 and 301).
- Comparison vs placebo based on Rank Transformation Residual ANCOVA

5.6.5.4. Number of Background AEDs at Baseline

In an integrated analysis by number of background AEDs received at baseline, the greatest proportion of patients fell into the category of receiving ≥2 background AEDs at baseline.

There was some evidence of variability in the magnitude of response to treatment by number of background AEDs at baseline and ezogabine dose ([Table 15](#)). However, the overall response to treatment with ezogabine was not statistically significantly different by number of background AEDs received at baseline. The specific AEDs contributing to the number of background AEDs at baseline was not considered in the interpretation of this analysis.

Table 15 Percent Change from Baseline in 28-Day Total Partial Seizure Frequency by Number of Background AEDs (Double-Blind Phase) – ITT Double-Blind Population (Studies 205, 301 and 302 Integrated)

	Placebo ^a	EZG 600 mg/day	EZG 900 mg/day	Placebo ^b	EZG 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	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.

Treatment by number of background AEDs at baseline interaction comparison vs placebo: ezogabine 600 mg/day vs placebo (p=0.674), ezogabine 900 mg/day vs placebo (p=0.277), ezogabine 1200 mg/day vs placebo (p=0.762).

- Consists of the placebo patients corresponding to the comparison with ezogabine 600 mg and 900 mg (Studies 205 and 302).
- Consists of the placebo patients corresponding to the comparison with ezogabine 1200 mg (Studies 205 and 301).
- Comparison vs placebo based on Rank Transformation Residual ANCOVA

5.6.5.5. Analysis by Seizure Sub-Type at Baseline

An integrated analysis to assess efficacy by baseline seizure subtype indicated that overall, the response to treatment at all doses of ezogabine was not significantly different between patients with and without simple partial seizures, or patients with or without complex partial seizures. The types of seizures occurring during the 8-week screening period and recorded at baseline were: complex partial seizures (86%); simple partial seizures (33%); and secondarily generalized seizure types (35%). The data for patients with secondarily generalized seizure subtype indicated numerical evidence for a reduction in total partial seizure rate across the ezogabine 600 mg/day and 900 mg/day dose groups. The response to treatment for the percent change in total 28-day total partial seizures at 1200 mg/day was significantly different in patients with secondarily generalized seizures compared with patients without secondarily generalized seizures (p<0.001). This treatment interaction for the 1200 mg/day group was also significant for

the percent change in 28-day total partial seizures in the maintenance phase ($p=0.015$) and in the responder rate for the double-blind phase ($p=0.021$), but not for the responder rate in the maintenance phase ($p=0.055$) (See Appendix 11.3).

Table 16 Percent Change from Baseline in 28-Day Total Partial Seizure Frequency by Seizure Type (Double-Blind Phase) – ITT Double-Blind Population (Studies 205, 301 and 302 Integrated)

	Placebo ^a	EZG 600 mg/day	EZG 900 mg/day	Placebo ^b	EZG 1200 mg/day
Simple partial seizures^d					
Patients with simple partial seizures	N=77	N=100	N=81	N=81	N=82
n	74	100	81	81	80
Mean \pm SD	18.4 \pm 205.55	-12.6 \pm 76.37	-12.1 \pm 70.83	6.5 \pm 100.43	-27.6 \pm 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 \pm SD	-9.5 \pm 62.08	-8.6 \pm 140.85	-27.6 \pm 56.95	-3.6 \pm 80.82	-23.0 \pm 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^e					
Patients with complex partial seizures	N=238	N=229	N=231	N=213	N=233
n	237	226	230	211	232
Mean \pm SD	-9.1 \pm 59.64	-9.1 \pm 128.41	-26.8 \pm 58.24	-1.8 \pm 92.76	-27.4 \pm 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 \pm SD	47.0 \pm 294.56	-14.1 \pm 86.18	-1.1 \pm 76.02	8.5 \pm 46.53	3.1 \pm 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

	Placebo ^a	EZG 600 mg/day	EZG 900 mg/day	Placebo ^b	EZG 1200 mg/day
Secondarily generalized seizures^f					
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.

- Consists of the placebo patients corresponding to the comparison with ezogabine 600 mg and 900 mg (Studies 205 and 302).
- Consists of the placebo patients corresponding to the comparison with ezogabine 1200 mg (Studies 205 and 301).
- Comparison vs placebo based on Rank Transformation Residual ANCOVA.
- Treatment by seizure subtype interaction (with or without simple partial seizures) comparison vs placebo: ezogabine 600 mg/day vs placebo (p=0.378), ezogabine 900 mg/day vs placebo (p=0.935), ezogabine 1200 mg/day vs placebo (p=0.277).
- Treatment by seizure subtype interaction (with or without complex partial seizures) comparison vs placebo: ezogabine 600 mg/day vs placebo (p=0.300), ezogabine 900 mg/day vs placebo (p=0.326), ezogabine 1200 mg/day vs placebo (p=0.575).
- Treatment by seizure subtype interaction (with or without secondarily generalized seizures) comparison vs placebo: ezogabine 600 mg/day vs placebo (p=0.458), ezogabine 900 mg/day vs placebo (p=0.167), ezogabine 1200 mg/day vs placebo (p<0.001).

5.6.5.6. Analysis by Region

Across the three pivotal trials, the majority (approximately 86%) of patients were from non-US regions. The majority of US sites came from Study 301 which only evaluated efficacy of ezogabine 1200 mg/day. Therefore the integrated analysis was restricted to the highest studied dose. The results indicated no statistically significant regional differences between US and non-US treated patients in their response to treatment with ezogabine (Table 17).

Table 17 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	EZG 1200 mg/day	Overall Placebo	Overall EZG
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.

Treatment by region (US or Non-US) interaction comparison vs placebo: ezogabine 1200 mg/day vs placebo (p=0.303); overall ezogabine vs placebo (p=0.466).

- Consists of the placebo patients corresponding to the comparison with ezogabine 1200 mg (Studies 205 and 301).
- Comparison vs placebo based on Rank Transformation Residual ANCOVA

5.6.6. Long Term Open-label Extensions to the Pivotal Studies (Studies 212, 303 and 304)

Long term efficacy included evaluation of the percent change in total partial seizure frequency and responder rate in extension studies (Studies 212, 303 and 304) of the three pivotal efficacy studies (Studies 205, 301 and 302 respectively). A total of 222/279 (79.5%) patients in Study 205, 181/224 (81%) patients in Study 301 and 375/409 (92%) patients in Study 302 completed the double-blind phase and enrolled into the open-label extension Studies 212, 303 and 304, respectively. A total of 603 (77.5%) patients were exposed to ≥6 months of ezogabine, 365 (46.9%) patients were exposed to ≥12 months of ezogabine at the time of data cut-off for the interim reports for Studies 303 and 304 (30 June 2008).

Patients received open-label treatment with ezogabine that could be titrated between 600 to 1200 mg/day to achieve the most effective and tolerated dose. Background AEDs could be dose adjusted in combination with appropriate dose adjustments to ezogabine. The influence of any changes in the usage of concomitant AEDs on the long term efficacy evaluation for ezogabine was not assessed in these studies.

In Study 212, the average dose received across the entire open-label phase was not assessed. However the majority of patients received either 900 mg/day (105/222, 47.3%) or 1200 mg/day (52/222, 23.4%) as their maximum dosage. Only approximately 10% of patients had their maximum daily dose spanning the dose range 450 to 800 mg/day. High

ezogabine maintenance doses were also achieved in Study 303 (mean dose 1052.3 \pm 274.43 mg/day; median dose was 1063.3) and Study 304 (mean dose 860.9 \pm 239.57; median dose was 875.5 mg/day).

The median percent reduction in seizures across the entire open-label treatment phase was 52.0%, and the overall responder rate was 52.5%. A similar magnitude of effect for each efficacy measure was observed within each study. Therapeutic efficacy was retained in patients who remained on treatment. The magnitude of response tended to increase over time. The median percent reduction in seizures in the three open-label extension studies ranged from 49.3 to 55.7% at 3 months, 50.4 to 59.3% at 6 months and 49.3 to 63.4% at 12 months.

5.7. Efficacy Conclusions

The results from three adequate and well-controlled studies (Studies 205, 301 and 302) provide substantial evidence of effectiveness for ezogabine as the first of a new class of drug for adjunctive treatment of partial onset seizures in adults, with or without secondary generalization. These studies confirm a dose-related increase in efficacy, whether defined in terms of the percent change from baseline or responder rate. The magnitude of the treatment effect over the 600 to 1200 mg/day range was clinically relevant for this patient population and similar to the efficacy reported for a number of approved AEDs [Brodie, 2004, Abou-Khalil, 2005; Cross, 2009; Halasz, 2009; Ben-Menachem, 2007; Elger, 2009, Shorvon, 2000].

In a meta-analysis that described efficacy data on 14 approved AEDs in over 11,000 patients with refractory epilepsy, the pooled weighted risk difference between active treatment and placebo in achieving a 50% reduction in seizure frequency was estimated at 21% (95% CI 19-24, $p < 0.001$) [Beyenburg, 2010]. The treatment effects for ezogabine in the double-blind phase, particularly across the dose groups of 900 mg/day (Study 205: 16.0%; Study 302: 22.0%) and 1200 mg/day (Study 205: 17.4%; Study 301: 26.6%), fell within the range described in this analysis.

Ezogabine has a low potential for drug-drug interaction including co-administered enzyme inducing and inhibiting AEDs. The studies used ezogabine in combination with many commonly used AEDs including carbamazepine, lamotrigine, valproic acid, levetiracetam and topiramate.

The subgroup analyses by race, age, gender US/non-US patients, background AEDs, and seizure type, did not indicate a need for dose adjustments by subgroup. Of note, however, the majority of patients in the trials were <65 years of age and predominantly White/Caucasian.

The efficacy demonstrated in the three pivotal studies, supported by data from long-term open-label studies provide substantial evidence of efficacy of ezogabine for adjunctive therapy in the treatment of partial onset seizures in adults, with or without secondary generalization.

6. CLINICAL SAFETY

The safety profile of ezogabine is based on a safety database derived from a total of 45 clinical studies, including:

- 29 completed Phase I studies
- Five completed Phase II studies; 2 completed Phase III studies 301 and 302; and 6 long-term, open-label extension studies (2 of which are ongoing; Study 303 and Study 304 which are the uncontrolled extensions of 301 and 302, respectively) investigating ezogabine as an adjunctive treatment of adults with partial onset seizures;
- an ongoing compassionate use program; and
- 2 studies in other indications, comprising a completed study in post-herpetic neuralgia (PHN) and a completed study in bipolar disorder (VRX-RET-E22-NP201 and D-23129/8040, respectively).

This data set comprises complete safety data on 1365 epilepsy patients exposed to ezogabine with more than 1400 patient-years of exposure and complete information from 747 volunteers who participated in single-dose and repeat dose clinical pharmacology studies.

The profile seen in the Phase IIb-III epilepsy studies is consistent with pre-clinical and clinical pharmacology findings demonstrating that the safety findings are consistent with the predicted pharmacology of ezogabine and not unexpected when the pharmacological profile is taken into account. Consistent with other AEDs, the most commonly reported AEs involved the CNS. Within this section are described specific areas of interest related to ezogabine's pharmacological effect on smooth muscle, particularly the urinary bladder. Other key safety information includes potential cardiac effects, neuropsychiatric effects, and potential hepatic effects.

Safety data from the PHN study and the clinical pharmacology studies are not systematically summarized in this overview. However, where this information impacts or informs the understanding of the safety profile in epilepsy, appropriate cross-reference is made.

6.1. Study Groupings and Statistical Considerations

Safety data were summarized for all patients who were randomized and received at least one dose of study drug.

Adverse events (AEs) were recorded throughout the study. For Study 205 these AEs were coded using the COSTART dictionary. For Studies 301 and 302 AEs were coded using Medical Dictionary for Regulatory Activities (MedDRA).

A treatment emergent AE was defined as an AE which was not present prior administration of the test drug or additionally for Study 205 if present at the start of the study but severity increased while on treatment.

Adverse events were summarized by body system and preferred terms. In any given category patients were counted only once even if they had multiple occurrences of a single preferred term. For summaries of severity and relationship to study drug the worst case was taken.

In Study 205 AEs were compared across treatment groups using fishers exact test only for events with an incidence of $\geq 5\%$ across all treatment groups.

Differences in mean laboratory, vital signs and ECG parameters were assessed using paired t-tests. At each visit treatments were compared using one way ANCOVA with baseline value as a covariate. Differences in the percentage of subjects with values of potential clinical importance were compared using fisher's exact test.

American Urological Association (AUA) Symptom Index scores were compared using one way ANCOVA with treatment and center as factors and baseline value as a covariate. Dose response on symptom severity was analyzed at visit 9 using a Cochran-Mantel-Haenszel test.

No adjustments for multiple comparisons were applied to any safety data analyses.

Safety data were summarized according to the assigned randomized treatment arm.

6.1.1. Integrated Safety Analyses

For the reporting of integrated safety data key groupings were defined.

Pivotal Controlled Trials (PCT): this was the principal data set that provided the primary information concerning the clinical safety of ezogabine. It comprised 3 randomized, double-blind, placebo-controlled trials with similar durations, populations, and primary outcome measures (Studies 3065 A1-205 [Study 205], VRX-RET-E22-301 [Study 301] and VRX-RET-E22-302 [Study 302]). Data presented for the PCT group reflect safety information presented in the original NDA submission.

All Phase II/III Combined: Long-term safety with ezogabine was evaluated using an All Phase II/III Combined grouping. A total of 5 completed Phase II studies (Studies 200/201, 202, 205, 209, 214); 2 completed Phase III studies (Studies 301 and 302); and 6 long-term, open-label extension studies (Studies 208, 212, 216, 8017 and ongoing studies, VRX-RET-E22-303 [Study 303] and VRX-RET-E22-304 [Study 304]) make up the Phase II/III Combined grouping. Study 303 and Study 304 were long-term extension studies of Study 301 and Study 302, respectively. Each unique epilepsy patient receiving ezogabine is included in this grouping. Patients who took placebo in a double-blind study and then did not enter an open-label extension were not included. Patients who took placebo in a double-blind study and then entered an open-label extension were included from the time the patient started ezogabine dosing. Patients who enrolled into extension studies after completing their parent study were only counted once within this analysis set. Data presented for the All Phase II/III Combined group reflect safety data presented in the 2 October 2009 120 Day Safety Update.

Consistent with the definition used in Studies 301 and 302, treatment emergent AEs are defined as any AE reported after the first dose of study treatment was received. For AEs reported in the extension studies where the patient took placebo in the parent study, an AE was treatment emergent in the All Phase II/III Combined datasets if the start date was after the first dose of ezogabine treatment.

Adverse events that were reported more than 30 days after the end of treatment were not included within any summaries although these were listed. For all other data, assessments taken more than 7 days past the last day on study drug were not included in any analyses.

All continuous laboratory assessments were converted to SI units where applicable using SI normal ranges. Standardized normal ranges based on the normal ranges used by the central lab for the largest studies (301/302/303/304) were used in preference to the individual laboratory supplied normal ranges. Standard criteria for defining markedly abnormal values were applied.

In order to standardize the reporting of ECG data, specific definitions of values of potential clinical concern were used.

In patients who received ezogabine in the parent study and continued into the extension study or chose not to continue into the extension study, baseline was defined as per the parent study. For subjects who were received placebo in the parent study and continued into the extension study, baseline was defined as the final assessment collected within the parent study.

Subgroup analyses were conducted on the PCT and the All Phase II/III combined groupings. These subgroup analyses included evaluation of AEs by gender and age.

Safety topics of special interest are defined: are defined in Section 6.6.

A comprehensive search strategy was utilized to capture these AEs of special interests across all Phase II and III studies using MedDRA preferred terms, verbatim terms and text strings relating to the AEs of special interest.

For each of these topics of special interest data were summarized and relative risk ratios with 95% confidence intervals were constructed.

Selected safety data from 2 additional sources are also provided:

Integrated Clinical Pharmacology Studies: healthy subjects who received at least 1 dose of the 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. Safety data from this grouping are presented in Section 6.6.2 (Hallucinations and Psychosis) and Section 6.6.5 (Effects on Cardiac Conduction).

Study VRX-RET-E22-NP201: was a Phase IIa proof-of-concept study to evaluate the efficacy and safety of maximum tolerated doses (MTDs) of ezogabine up to 900 mg/day

versus placebo in patients with PHN. Patients were randomized 2:1 to ezogabine or placebo and stratified based on whether or not the patients were using medications to treat PHN at baseline. The study consisted of a 3-week 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. Doses of study drug were escalated by 150 mg/day once per week until MTD was reached (150 mg/day to 900 mg/day). Safety data from this study are presented in Section 6.7.4.1 (Population Subgroup-Age), Section 6.6.1 (Renal/Urinary Events), Section 6.6.5 (Effects on Cardiac Conduction), and Section 6.6.6 (Hepatic Effects). All adverse events from studies included in the integrated safety summaries were recoded to MedDRA.

6.2. Clinical Exposure

To date, there have been a total of 2247 exposures to ezogabine in the clinical development program (Table 18). This includes 747 volunteers in short-term and repeat dosing studies, 10 patients in completed bipolar disorder Study D-23129-8040 and 125 patients in completed PHN Study VRX-RET-E22-NP201.

In the PCTs (Studies 205, 301, and 302) a total of 813 patients received ezogabine, and the extent of exposure to ezogabine was approximately 211 patient-years. The mean duration of exposure was 106.5 days in the placebo group and 94.6 days in the Total EZG group, with ranges of 1 to 161 days and 1 to 196 days, respectively. In the ezogabine groups, mean total exposure was slightly higher in the 600 mg group (97.6 days) than in the 900 mg/day (92.5 days) and 1200 mg/day (93.5 days) groups.

Across the Phase II/III clinical trials in epilepsy, 1365 unique subjects were exposed to at least one dose of ezogabine (Table 18). As of 2 October 2009, total exposure to ezogabine was approximately 1420 patient-years while the median total exposure was 261 days (range 1 to 1736 days). Estimated exposure for the ongoing compassionate use program was approximately 136 patient-years. Most patients were exposed to ezogabine at doses of 900 mg/day to <1200 mg/day; with 612 total patient-years exposure (Table 19). As of 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.

Demographic characteristics of patients in the Pivotal Controlled Trials were comparable across ezogabine dose groups and similar to patients in the placebo groups. Most patients in the Total EZG group (802/813, 99%) were between the ages of 18 and 64 (median age 37 years) and were equally divided by gender. Less than 1% (3) of patients were <18 years old and less than 1% (8) of patients were ≥65 years old. At least 89% of patients were Caucasian. Similar demographic characteristics were seen across the all Phase II/III Combined Studies grouping.

Table 18 Enumeration of Unique Patients Exposed to Study Medication

	Number of Patients	
	Placebo	EZG
Total Unique Exposures in Clinical Pharmacology Studies	70 ¹	747 ^{2,3}
Phase II and Phase III Study Groupings		
PCT (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	2112
Other EZG Studies		
Study VRX-RET-E22-NP201, PHN ³	62	125
Study D-23129/8040, Bipolar Disorder	0	10
Total Unique Exposures to EZG	559	2247

1. Includes unique placebo exposure in parallel group studies (3065A1-101, 3065A1-102, 3065A1-107, and VRX-RET-E22-103)
2. Includes unique EZG exposure numbers, regardless of formulation; patients may have also received control drug.
3. As of the original NDA submission there were 669 unique patient exposures in the Clinical Pharmacology studies, there were an additional 78 patient exposures subsequent to the submission thus 669+78=747 unique patients.

Table 19 Summary of Total Exposure to Ezogabine by Dose Range (Safety Population: All Phase II/III Combined)

Total time on drug, n	EZG Dose (mg/day)					
	>0 to <300	300 to <600	600 to <900	900 to <1200	≥1200	Unknown
≤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

6.3. Deaths

As of 2 October 2009, there were a total of 19 deaths reported in the ezogabine clinical development program:

- 15 treatment-emergent deaths (including the Compassionate Use Program).

- 3 of the 15 received placebo (3/427, 0.7%). All 3 occurred in the titration phase.
- 12 of the 15 received ezogabine (12/1365, 0.9%). Two occurred in the titration phase and 10 occurred during the maintenance phase.
- 4 pre- or post-treatment deaths (non-treatment-emergent).

Treatment-emergent deaths are summarized in [Table 20](#), while non-treatment-emergent deaths are summarized in [Table 21](#).

During the PCTs the rate of death was 24.0 per 1000 patient-years on placebo versus 9.5 per 1000 patient-years on ezogabine. In the entire ezogabine epilepsy clinical development program (including deaths reported as of 2 October 2009 and in the compassionate use program), there were 12 treatment emergent deaths in patients treated with ezogabine in 1556 patient-years of exposure (1420 patient-years in the epilepsy clinical development program plus 136 patient-years in the compassionate use program), i.e., a rate of 7.7 per 1000 patient-years.

The most common cause of death in the program was sudden unexpected death in epilepsy (SUDEP), which is discussed below. Non-SUDEP causes of death included assault, and injuries sustained during a seizure in one patient each in the placebo group. In ezogabine-treated patients the most common non-SUDEP cause of death was neoplastic (metastatic neoplasm, multiple myeloma); there were single reports of cardiopulmonary failure, diabetic ketoacidosis, and subdural hematoma.

All treatment-emergent deaths were evaluated against established criteria for sudden unexpected death in epilepsy (SUDEP) using the following criteria:

- The victim suffers from epilepsy, defined as recurrent unprovoked seizures.
- The victim died unexpectedly while in a reasonable state of health.
- The death occurred “suddenly” (in minutes), when known.
- The death occurred during normal activities and benign circumstances.
- An obvious medical cause for death was not found.
- The death was not directly caused by a seizure or status epilepticus [[Annegers](#), 1997].

Each event was classified into “definite”, “probable”, or “possible SUDEP” depending on the evidence available. An event was considered a definite SUDEP when all the above criteria are met and no alternative etiology other than SUDEP was identified post-mortem. . A death was considered probable SUDEP when a fatal event met all criteria but lacked post-mortem data, and possible SUDEP when SUDEP could not be ruled out but there was insufficient evidence regarding the circumstances of the death [[Tomson](#), 2005].

Within the PCT grouping, possible, probable or definite SUDEP occurred in 1 out of 427 patients on placebo (0.7%) and 1/813 (0.2%) in the EZG group (600 mg).

- This represents a rate of SUDEP of 8.0 per 1000 patient-years in placebo versus 4.7 per 1000 patient-years in ezogabine

Overall in the Phase II/III Combined studies, 7 of the 12 deaths on ezogabine met the conservative criteria for possible, probable, or definite SUDEP. This represents an overall rate for SUDEP of 4.5 per 1000 patient-years on ezogabine across the entire ezogabine epilepsy program.

- Hence, there is no evidence of any worsening of the death or SUDEP rate in patients treated with ezogabine compared with those treated with placebo, and there is no evidence of worsening death rates over time with long-term ezogabine treatment.

The overall number of deaths and SUDEP in the ezogabine program was consistent with what has been reported in the literature and in other AED development programs. The incidence of SUDEP in various studies in the literature has been reported to be between 1.2 and 9.3 per 1000 person-years [Tomson, 2005; Lathers, 2002] with a tighter estimate of 2.0 to 6.0 per 1000 person-years in chronic refractory epilepsy similar to the patient population enrolled in ezogabine clinical studies [Tomson, 2005]. As noted previously, young adults with severe or intractable epilepsy are considered a subgroup of epileptics who are at particularly high risk for SUDEP [Lathers, 2002]. With a median age of 37.2 years, a median duration of 17 years for epilepsy, and over 71% of the patient population requiring at least 2 background AEDs, these data demonstrate the refractory nature of the epilepsy being treated in the ezogabine program. These data indicate the potentially greater baseline risk for SUDEP in the ezogabine program as compared to the general epilepsy population. Thus, the rate of SUDEP in the ezogabine program is similar to the expected rates based on the epilepsy literature.

Table 20 SUDEP Classification of All Treatment-Emergent Deaths in the Overall Ezogabine Program

Treatment Group/Dose	Study ID	Patient ID	Demographics (Age, Race, Sex)	Adverse Event (Preferred Term)	SUDEP classification	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
EZG (mg/day)						
600	302	55408	55/C/M	SUDEP	Probable SUDEP	Found dead in bed; no autopsy
600	CU	015349	27/C/F	SUDEP	Probable SUDEP	Found dead in bed; no autopsy
600	CU	033-100	58/O/F	Subdural hematoma	Not SUDEP	Reported after 2 October 09
675	208	00004	60/C/F	Metastatic neoplasm	Not SUDEP	Multiple tumors in liver/lung
800 ¹	208	00013	39/C/F	Death	Probable SUDEP	Found dead on kitchen floor; no autopsy
900	304	55305	46/C/F	Sudden death	Possible SUDEP	Autopsy: likely died during seizure
900 ¹	304	85111	42/C/M	Asphyxia	Possible SUDEP	Reported to have experienced asphyxia during seizure; no autopsy
950	304	055601	53/C/F	Multiple myeloma	Not SUDEP	None
1050	214	00059	34/C/F	Cardiopulmonary failure; arteriosclerosis	Not SUDEP	Autopsy: morbid obesity; advanced cardiovascular disease
1200	301	02513	57/B/M	Diabetic ketoacidosis; bacteria urine identified	Not SUDEP	Glucose: 582; Autopsy: DKA (acetone, marked hyperglycemia); cardiovascular disease
1200 ¹	304	25210	25/C/F	SUDEP	Probable SUDEP	Found dead by family in morning; no autopsy.
1200	CU	046126	24/C/M	SUDEP	Probable SUDEP	Found dead in bed; no autopsy

Patients highlighted in grey are from the PCTs

1. Dosing records indicate last known dose of ezogabine was >30 days before event. Subjects 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, NA=Not Applicable, O=Other

Table 21 Non-Treatment-Emergent Deaths

Study	Patient ID	Demographics (Age, Race, Sex)	Adverse Event (Preferred Term)	Study Day
Prior to dosing				
301	05309	36/C/M	Drowning	Prior to dosing
302	70303	35/C/M	Death	Prior to dosing
More than 30 days after last dose				
202	00009	41/C/M	Completed suicide	35 days after last dose
301	02703	27/B/F	Death	102 days after last dose ¹

1. Date of death is approximate. Patient was found dead 102 days after her last known dose of study drug. The patient was reported as missing 2 days earlier.

6.4. Serious Adverse Events (SAEs)

In the integrated safety database, 6% of placebo-treated patients and 9% of ezogabine-treated patients reported a TESA in the PCTs. TESAEs were reported for 8%, 7%, and 11% of the 600, 900, and 1200 mg/day groups, respectively.

In the PCT group ([Table 22](#)):

- The most frequently reported TESAE was convulsions followed by psychotic disorder. The incidence of convulsion was similar between the placebo and Total EZG groups (1.2% and 1.5%, respectively) and there was no clear indication of any ezogabine dose relationship. See Sections 6.6.4 and 6.6.2 for a full discussion of seizure worsening, and hallucinations and psychosis, respectively.
- Psychotic disorder was reported in few patients (0 in placebo and 6 (<1%) of the Total EZG group).
- Other TESAEs were reported in a low proportion of patients (<1% of patients in any treatment group). Nausea, encephalopathy, confusional state and suicidal ideation were reported only in the ezogabine 1200 mg/day group.
- There was no notable difference in the reporting incidence of TESAE by phase despite there being a higher number of events reported in the 1200 mg/day ezogabine group (16/427 [3.7%] placebo group and 43/813 [5.3%] total EZG group in the titration phase compared to 11/383 [2.9%] placebo group and 28/658 [4.4%] total EZG group in the maintenance phase). An examination of the dose at time of occurrence of the AE suggests that many of these events occurred at lower doses during the course of the first 8 weeks of treatment (titration period).

Table 22 **TESAEs Reported by Greater than or equal to 2 Patients in Any Treatment Group by Preferred Term (Safety Population: PCT, Studies 205, 301, and 302)**

Preferred Term	Number (%) of Patients				
	Placebo (N=427)	EZG 600 mg/day (N=281)	EZG 900 mg/day (N=273)	EZG 1200 mg/day (N=259)	EZG 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)
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

Across the All Phase II/III study grouping, at least one TESAE was reported by 17% of patients who received ezogabine (Table 23). The types and incidences of TESAEs were similar to those reported in the PCT grouping. The most common TESAEs were seizure-related events including convulsion, complex partial seizures, epilepsy, grand mal convulsion with a combined incidence of 4%, followed by psychotic disorder at <1%. Seizure related events are discussed in Section 6.6.4, while psychosis and related events are discussed in Section 6.6.2.

Table 23 **TESAEs Reported by Greater than or equal to 3 Patients by Preferred Term (Safety Population: All Phase II/III Combined)**

Preferred Term	Number (%) of Patients
	EZG (N=1365)
Any SAE	230 (16.8)
Convulsion	35 (2.6)
Psychotic disorder	9 (0.7)
Confusional state	7 (0.5)
Status epilepticus	8 (0.6)
Complex partial seizures	7 (0.5)
Epilepsy (increased seizure frequency)	7 (0.5)
Grand mal convulsion	6 (0.4)
Dizziness	5 (0.4)
Chest pain	5 (0.4)
Pneumonia	5 (0.4)
Hyponatraemia	5 (0.4) ^a
Somnolence	4 (0.3)
Headache	4 (0.3)
Conversion disorder	4 (0.3)
Urinary retention	4 (0.3)
Pregnancy	4 (0.3)
Coma	3 (0.2)
Mental status changes	3 (0.2)
Drug toxicity	3 (0.2)
Overdose	3 (0.2)
Abdominal pain	3 (0.2)
Diarrhoea	3 (0.2)
Nausea	3 (0.2)
Vomiting	3 (0.2)
Fatigue	3 (0.2)
Urinary tract infection	3 (0.2)
Renal colic	3 (0.2)
Cholelithiasis	3 (0.2)
Transaminases increased	3 (0.2)
Vertigo	3 (0.2)
Head Injury	3 (0.2)

a. In the PCTs, there were 0 reports of hyponatraemia in the placebo group and 1 (0.1%) in the 1200mg EZG group.

6.5. Adverse Events Leading to Withdrawal

In the PCTs, TEAEs leading to discontinuation were reported for greater proportions of ezogabine patients than for placebo patients (11% placebo versus 25% Total EZG). The majority of AEs leading to withdrawal were reported in the titration phase (30/427 [7.9%] placebo group and 151/813 [18.6%] total EZG group) compared to the maintenance phase (15/383 [3.9%] placebo group and 53/658 [8.1%] total EZG group).

The most common (>2% in Total EZG group) TEAEs leading to discontinuation were dizziness (6%), confusional state (4%), fatigue (3%), and somnolence (3%) (Table 24). Among the ezogabine dose groups, TEAEs leading to discontinuation were reported for

17%, 25%, and 31% of the 600, 900, and 1200 mg/day groups, respectively. There was a dose relationship for ezogabine discontinuations due to dizziness (1%, 3%, 6%, and 8% of the placebo, 600 mg/day, 900 mg/day, and 1200 mg/day groups) and confusional state (<1%, 1%, 3%, and 8%, respectively).

Table 24 TEAEs Leading to Discontinuation Reported by >2% of Patients in Any Treatment Group by Preferred Term (Safety Population: PCT, Studies 205, 301, and 302)

Preferred Term	Number (%) of Patients				
	Placebo (N=427)	EZG 600 mg/day (N=281)	EZG 900 mg/day (N=273)	EZG 1200 mg/day (N=259)	EZG 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)

Across the Combined Phase II/III Studies, TEAEs leading to discontinuation were reported by 437 of 1365 (32%) ezogabine-treated patients. The nature and frequency of events leading to withdrawal were similar to those reported in the PCT grouping. The most common events leading to withdrawal were dizziness (74/1365, 5%), somnolence (60/1365, 4%), confusional state (49/1365, 4%), fatigue (45/1365, 3%) coordination abnormal (27/1365, 2%) and disturbance of attention (26/1365, 2%). All other TEAEs leading to discontinuation were reported in less than 2% of patients.

6.6. Safety Topics of Special Interest

Safety topics of special interest that will be discussed in this section will include:

- Renal/Urinary Disorders
- Cardiac Rhythm/Conduction Abnormalities
- Hallucinations and Psychosis
- Suicidal Behavior and Ideation
- Seizure Worsening, Status Epilepticus and Seizure-Related AEs
- Hepatic Effects
- Speech and Cognitive Effects
- Neutropenia or Infections

- Gall Bladder Effects

6.6.1. Effects of Ezogabine on the Urinary Tract and Kidneys

The pharmacological action of ezogabine as a potassium channel opener has the potential to effect contraction of the bladder smooth muscle. These effects were initially observed in the pre-clinical studies where mice developed urinary retention. In clinical trials, some patients have also been observed to develop urinary retention. Thus, extensive review of urinary retention during the clinical program has been performed and is discussed in this section.

During the clinical program, crystals with a bilirubin-like appearance were detected in the urine of patients taking ezogabine. Investigations indicate these crystals are not bilirubin, but their composition remains undetermined. Thus, crystalluria throughout the urinary tract was reviewed and is discussed in this section. A further consequence of the refractive properties of ezogabine results in the potential for chromaturia and a false positive result on assays for proteinuria on dipsticks.

Because of the potential for urinary retention, an additional potential complication is the development of urinary tract infections, and this is also discussed in this section.

In order to provide a comprehensive discussion of this topic, overall summaries of adverse events related to Renal/Urinary Disorders are provided in Appendix 11.7 and Appendix 11.8.

6.6.1.1. Overall Incidence of Urinary Tract and Renal Adverse Events

In the PCTs, AEs related to renal and urinary disorders were reported for greater proportions of patients in the Total EZG group than the placebo group (17% versus 13%) (Table 25). The relative risk of any such event was greatest for the ezogabine 1200 mg/day dose group (1.9; 95% CI 1.409, 2.695). The majority of the events potentially relating to voiding dysfunction including urinary tract infection, dysuria, urinary hesitation, and urinary retention were reported during the first 8 weeks of treatment (Table 26).

Table 25 Adverse Events of Renal/Urinary Disorders Reported by 2 or More Patients in Any Treatment Group (Safety Population: PCT)

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 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) ^a
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)
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)

**Table 26 Select Urinary Tract and Renal AEs by Time to First Occurrence
(Safety Population: PCT, Studies 205, 301, and 302)**

Treatment Group/Preferred Term	Number (%) of Patients					
	Days					
	1 to <8	8 to <14	14 to <28	28 to <56	56 to <84	84 to <182
Placebo, N=427						
N ¹	427	418	411	406	384	366
UTI	1 (0.5)	0	2 (0.5)	8 (2.0)	8 (2.1)	1 (0.3)
Dysuria	1 (0.2)	1 (0.2)	0	1 (0.2)	0	0
Urinary hesitation	1 (0.2)	0	1 (0.2)	2 (0.5)	0	0
Urinary retention	0	0	1 (0.2)	1 (0.2)	0	0
EZG 600 mg/day, N=281						
N ¹	281	274	270	263	237	226
UTI	0	0	1 (0.4)	2 (0.8)	0	2 (0.9)
Dysuria	2 (0.7)	0	1 (0.4)	1 (0.4)	0	0
Urinary hesitation	0	0	4 (1.5)	1 (0.4)	1 (0.4)	0
Urinary retention	0	0	0	1 (0.4)	0	0
EZG 900 mg/day, N=273						
N ¹	273	265	262	246	218	205
UTI	0	2 (0.8)	1 (0.4)	3 (1.2)	1 (0.5)	2 (1.0)
Dysuria	0	0	1 (0.4)	1 (0.4)	1 (0.5)	2 (1.0)
Urinary hesitation	0	0	2 (0.8)	1 (0.4)	0	0
Urinary retention	0	0	2 (0.8)	1 (0.4)	1 (0.5)	0
EZG 1200 mg/day, N=259						
N ¹	259	254	249	237	194	172
UTI	1 (0.4)	1 (0.4)	6 (2.4)	6 (2.5)	5 (2.6)	2 (1.2)
Dysuria	2 (0.8)	0	1 (0.4)	4 (1.7)	1 (0.5)	2 (1.2)
Urinary hesitation	1 (0.4)	2 (0.8)	0	3 (1.3)	1 (0.5)	2 (1.2)
Urinary retention	1 (0.4)	0	0	1 (0.4)	0	0
EZG Total, N=813						
N ¹	813	793	781	746	649	603
UTI	1 (0.1)	3 (0.4)	8 (1.0)	11 (1.5)	6 (0.9)	6 (1.0)
Dysuria	4 (0.5)	0	3 (0.4)	6 (0.8)	2 (0.3)	4 (0.7)
Urinary hesitation	1 (0.1)	2 (0.3)	6 (0.8)	5 (0.7)	2 (0.3)	2 (0.3)
Urinary retention	1 (0.1)	0	2 (0.3)	3 (0.4)	1 (0.2)	0

Note: Gray shading indicates events reported in the first 8 weeks (56 days) of treatment.

1. The denominator (N) for the AE is the number of patients in the Safety Population in the study during the time category.

There were 5 SAEs relating to renal/urinary disorders in 4 (<1%) patients in the Total EZG group compared to 1 (0.2%) SAE on placebo (Table 27). No SAEs were reported in the 1200 mg/day group. All patients were reported to have recovered. Brief narratives for these 5 patients are presented below.

Table 27 Serious Adverse Events Due to Renal/Urinary Disorders (Safety Population: PCT)

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
Placebo							
301	005203	55/C/M	Placebo	Urinary retention	25	Y spontaneously	N
Ezogabine							
205	000448	53/C/F	600 (600)	Renal failure	20	Y spontaneously post EZG w/d	Y
302	025108	31/C/F	900 (600)	Urinary retention	19	Y spontaneously	N
205	000125	39/C/M	900 (900)	Renal colic	43, 49	Y w/ lithotripsy	N
302	025405	34/C/F	900 (600)	Atonic urinary bladder	21	Y spontaneously post EZG w/d	Y
			900 (unk)	Urinary incontinence	63	Y spontaneously Pre EZG w/d	

C= Caucasian, H = Hispanic, A = Asian, M = Male, F = Female, UNK= Unknown

Ezogabine-treated Patients:

Patient 3065A1-205-010-000125 was a 39-year-old Caucasian male who was receiving ezogabine 900 mg when he was hospitalized 05 - 07 Jan 2000 (Days 43-45) for severe calculus renal (Calculus Ureteric). The patient was treated with extracorporeal shock wave lithotripsy and pain management. On 12-14 Jan 2000 (Days 48-50), the patient was re-hospitalized, however, re-lithiasis could not be demonstrated. The patient's concomitant AEDs were carbamazepine and lamotrigine. The events resolved and the patient continued in the study with no actions taken with ezogabine.

Patient 205-000448 was a 53-year-old Australian female who was receiving 200 mg TID of ezogabine as an add on therapy for the treatment of temporal lobe epilepsy. Therapy with ezogabine began on 05 April 2000 and the patient received ezogabine for just over one month when she was admitted to the hospital after a history of 11 days of symptoms of myalgia, fatigue, cough, sweats and polydipsia and laboratory findings of elevated liver function tests and renal failure with BUN of 12.3 (normal <9), and creatinine of 190 (normal <124). On the day of admission (06 May 2000) the patient felt unwell and had symptoms of abdominal pain and orthopnea with pulmonary edema, and findings of nystagmus and urinary retention on examination. On 06 May 2000, a catheter was used to evacuate 1.5 L of urine from the bladder. Ezogabine was discontinued. Urinalysis showed many leukocytes but no growth was seen on urine cultures. On an unknown date an ultrasound scan revealed some dilatation of the upper urinary tract (ureters and kidneys). The investigator and medical monitor considered the urinary retention and renal failure to be serious and possibly related to ezogabine.

Patient 302-25108 is a 31 year old Caucasian female receiving 600 mg ezogabine who reported mild urinary retention on 29 Jan 2007 manifesting as an occasional inability to empty her bladder. She was randomized to the ezogabine 900 mg group. A urine culture performed on 21 Feb 2007 (Day 42) was negative for bacteria. On 06 Mar 2007, a post void residual (PVR) bladder ultrasound was normal and on 08 Mar 2007 the urinary retention resolved. The patient continued on treatment, increased her ezogabine dose to 1200 mg and continued into the open-label extension study; she continued to experience intermittent symptoms of urinary retention.

Patient 302-25405 is a 34 year old Caucasian female receiving 600 mg ezogabine who experienced decreased bladder sensation on 02 Nov 2006 (Day 21). She continued in the study and increased her dose to 900 mg. Postvoid residual volumes between 30 Nov 2006 and 14 Dec 2006 (Day 63) ranged between 70 and 159 mL. The patient discontinued from the study and took the last dose of study drug on 05 Jan 2007; postvoid residual volume on 08 Jan 2007 was 70mL and returned to normal on 25 Jan 2007, 20 days after the last dose of ezogabine. Bladder sensation returned to normal on 21 Feb 2007. During subsequent follow-up postvoid residual volumes ranged between 20 and 130 mL.

Placebo:

Patient 301-005203 was a 55-year-old Canadian male. He was receiving study medication of placebo when he was hospitalized for increased seizures on 11 September 2006, approximately four weeks after initiating study medication. He developed urinary retention the day after admission on 12 September 2006, and had his hospitalization extended by one day. The urinary retention resolved with one time bladder catheterization on 12 September 2006. Urine culture from the day of urinary retention showed no growth. The patient had no urinary retention when he first entered the clinical study. This patient continued on study medication and completed the 301 study. He has rolled over into the 303 open label extension trial. The investigator considered the urinary retention to be serious because of prolonged hospitalization and unrelated to study medication. An alternative basis for the urinary retention was not provided.

Nine patients discontinued due to renal/urinary events ([Table 28](#)). Of these, 3 (0.7%) patients were in the placebo treatment group and 6 (0.7%) were receiving ezogabine. There was no clear pattern to onset of event leading to discontinuation, and most cases for patients receiving ezogabine were reported at 600 mg/day.

Table 28 Discontinuations Due to Renal/Urinary Disorders (Safety Population: PCT)

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)
Placebo							
301	020217	34/C/F	Placebo	Polyuria, Urinary retention	43, 44	N	Y spontaneously post EZG w/d
205	000647	22/C/F	Placebo	Renal colic	10	N	Y spontaneously w/ pain meds
302	040121	46/C/F	Placebo	Polyuria	47	N	Y spontaneously post EZG w/d
Ezogabine							
302	070101	22/C/F	600 (600)	Urinary tract infection	77	N	Y With medication during EZG w/d
205	000448	53/C/F	600 (600)	Renal failure	20	Y	Y spontaneously post EZG w/d
302	090509	49/C/M	600 (377.8)	Nephritis	81	N	Y with medication pre EZG w/d
301	001303	26/C/M	1200 (1050)	Hematuria	42	N	Y spontaneously during EZG w/d
302	025405	34/C/F	900 (600)	Atonic urinary bladder	21	Y	Y spontaneously post EZG w/d
302	030301	48/C/F	900 (900)	Urinary retention	29	N	Y spontaneously during EZG w/d

C= Caucasian, H = Hispanic, A = Asian, M = Male, F = Female.

In the All Phase II/III Combined group, 26% of patients treated with ezogabine reported renal and urinary disorder AEs. There was a similar incidence of SAEs reported in this population vs the Pivotal Controlled Trials group (1% vs <1%), with the most common SAE being urinary retention. Few patients discontinued (1.2%).

6.6.1.2. Voiding Dysfunction and Urinary Retention

Beginning with the Phase III program, in addition to routine adverse event reporting patients were monitored for potential urinary retention by:

- American Urological Association (AUA) Symptom Index score, a 7-item Likert-scored scale describing urinary bladder function, was to be completed by the investigator at Visit 3 of the baseline phase, at Visit 6 (end of titration phase), at Visit 9 (during maintenance phase), at Visit 11 (completion of maintenance phase), and at the final study visit to assess the patient's bladder function.
- Post-void Residual Bladder Ultrasound to investigate the possible effects of ezogabine on bladder function, all patients underwent a single baseline post-void residual (PVR) bladder ultrasound between Weeks -3 and 0 (prior to Visit 3) during the baseline phase, at Visits 9 and 11 during the maintenance phase, and at Visit 16 (final study visit). The PVR bladder ultrasound was performed by a urologist, a qualified ultrasound technician or by a qualified study nurse who was certified to do PVR bladder ultrasound, based on training and documentation.

6.6.1.2.1. Voiding Dysfunction and Urinary Retention Adverse Events

Adverse events related to voiding dysfunction and urinary retention (e.g., dysuria, urinary hesitation, urinary retention) were reported for 5% of the Total EZG-treated group compared to 3% on placebo in the PCTs. Urinary hesitation, residual urine volume and urinary retention were reported by 2%, 1%, and 1% of the Total EZG group compared to 1%, 0.2%, and 0.5% placebo with no clear dose response relationship across ezogabine dose groups. One of these events ([Patient 205-000448](#)) required patient withdrawal.

Table 29 Adverse Events of Voiding Dysfunction and Urinary Retention (Safety Population: PCT)

Preferred Term	Number (%) of Patients				
	Placebo N=427	Ezogabine			
		600mg/day (N=281)	900mg/day (N=273)	1200mg/day (N=259)	Total (N=813)
Any event	11 (2.6)	12 (4.3)	13 (4.8)	18 (6.9)	43 (5.3)
Urinary hesitation	4 (0.9)	6 (2.1)	3 (1.1)	9 (3.5)	18 (2.2)
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)
Bladder disorder	1 (0.2)	1 (0.4)	0	1 (0.4)	2 (0.2)
Hypertonic bladder	0	1 (0.4)	0	1 (0.4)	2 (0.2)
Micturition frequency decreased	0	2 (0.7)	0	0	2 (0.2)
Urine flow decreased	2 (0.5)	1 (0.4)	0	1 (0.4)	2 (0.2)
Micturition urgency	3 (0.7)	0	0	1 (0.4)	1 (0.1)
Atonic urinary bladder	0	0	1 (0.4)	0	1 (0.1)
Bladder diverticulum	0	0	1 (0.4)	0	1 (0.1)
Bladder pain	0	0	0	1 (0.4)	1 (0.1)
Bladder spasm	0	0	0	1 (0.4)	1 (0.1)
Dysuria	0	0	1 (0.4)	0	1 (0.1) ^a
Micturition disorder	0	1 (0.4)	0	0	1 (0.1)
Oliguria	0	0	0	1 (0.4)	1 (0.1)
Urinary incontinence	0	0	1 (0.4)	0	1 (0.1)
Urinary tract disorder	1 (0.2)	0	0	0	0

a. Only specific raw AE terms were mapped to AEs of interest based on medical review. For that reason, not all AEs in a given preferred term are included in the "voiding and urinary retention" category above (e.g. 1 of 19 patients with a dysuria AE appear in this table).

Across the Phase II/III program the profile and time of first occurrence of AEs related to renal/urinary events was similar to the PCTs with slightly more males than females reporting AEs of urinary hesitation (25, 4% versus 17, 2%).

Serious cases of urinary retention requiring catheterization were reported in 5 patients (2 placebo and 3 on ezogabine) across the Phase II/III program. This was reversible in all but 1 patient ([Patient 303-03505](#)), who experienced persistent urinary retention requiring intermittent self-catheterization, potentially as a result of a delay in diagnosis and obtaining appropriate therapy. Generally, urinary retention of any severity occurred during the first 8 weeks of treatment. Brief narratives are provided below and full narratives are provided in Appendix [11.9](#).

[Patient 205-000448](#) was a 53-year-old Australian female who was receiving 200 mg TID of ezogabine as an add on therapy for the treatment of temporal lobe epilepsy. Therapy with ezogabine began on 05 April 2000 and the patient received ezogabine for just over one month when she was admitted to the hospital after a history of 11 days of symptoms of myalgia, fatigue, cough, sweats and polydipsia and laboratory findings of elevated liver function tests and renal failure with BUN of 12.3 (normal <9), and creatinine of 190 (normal <124). On the day of admission (06-May-2000) the patient felt unwell and had symptoms of abdominal pain and orthopnea with pulmonary edema, and findings of nystagmus and urinary retention on examination. On 06-May-2000, a catheter was used to evacuate 1.5 L of urine from the bladder. Ezogabine was discontinued. Urinalysis showed many leukocytes but no growth was seen on urine cultures. On an unknown date an ultrasound scan revealed some dilatation of the upper urinary tract (ureters and kidneys). The investigator and medical monitor considered the urinary retention and renal failure to be serious and possibly related to ezogabine.

[Patient 301-005203](#) was a 55-year-old Canadian male. He was receiving study medication of placebo when he was hospitalized for increased seizures on 11 September 2006, approximately four weeks after initiating study medication. He developed urinary retention the day after admission on 12 September 2006, and had his hospitalization extended by one day. The urinary retention resolved with one time bladder catheterization on 12 September 2006. Urine culture from the day of urinary retention showed no growth. The patient had no urinary retention when he first entered the clinical study. This patient continued on study medication and completed the 301 study. He has rolled over into the 303 open label extension trial. The investigator considered the urinary retention to be serious because of prolonged hospitalization and unrelated to study medication. An alternative basis for the urinary retention was not provided.

[Patient 303-03505](#) was a 31 year old Caucasian male previously randomized to placebo in Study 301 who experienced psychomotor agitation and urinary retention after 82 days on ezogabine (overall Day 211 of study). The patient presented to the ER after approximately 18 hours of urinary retention. A PVR ultrasound in the ER showed 900 mL of urine. The patient was described as uncooperative and in distress in the ER. After some difficulties, eventual insertion of a Foley catheter revealed approximately 1200 mL of urine. Past medical history included a traumatic brain injury, rattlesnake bite with antivenom treatment, hypertension, sleep apnea, gastroesophageal reflux disease, and a VNS implant. Concomitant medications included carbamazepine, pregabalin,

lamotrigine, and pantoprazole. The study medication was withdrawn immediately and the patient was taught self catheterizations on 19 Feb 2008. Urodynamic studies on 24 Mar 2008 indicated normal bladder compliance, a sensation of fullness upon filling, no leak with valsalva maneuvers, but an inability to void during the exam. No EMG activity was noted. PVR volume was 882 mL. The patient continued intermittent self catheterizations. A follow-up PVR in a urology office on 5 May 2008 was 91 mL. Additional follow-up information on 9 July 2008 revealed some interval improvement. The patient was voiding spontaneously on a regular basis, but continued to require intermittent catheterizations, although less frequently than before. The event is considered ongoing and still followed at this time.

Patient 303-00902 was a 39 year old Caucasian male who experienced post-ictal psychosis and urinary retention after 691 days on ezogabine. Past medical history included decreased cognition and auditory hallucinations. Concomitant medications included oxcarbazepine, pregabalin, levetiracetam, sertraline, multivitamins, coenzyme, and glucosamine. Urologic consultation in the hospital revealed an enlarged prostate and a PVR volume of 700 mL. The patient was discharged with a Foley catheter and recovered from the event after 8 days. The patient remained in the study. Additional PVR volumes from the database at baseline, Day 68, Day 126, Day 196, Day 252, and Day 532 were normal at 37, 37, 17, 10, 40 and 17 mL, respectively.

Patient 304-50102 was a 46 year old Caucasian female who was randomized to ezogabine 900 mg/day during the double blind phase of Study 302 and reported urinary retention after 57 days on study medication. Past medical history included a traumatic brain injury. Concomitant medications included carbamazepine and clobazam. Because the patient reported an excellent therapeutic response, she decided to remain in the study and began self-catheterization on 6 May 2007. During Study 304, PVR volume was elevated during Month 1 and Month 12 at 200 mL and 150 mL, respectively. The patient eventually withdrew from the study on 8 Nov 2007 due to increased seizures. During the patient's follow-up visit on 28 Nov 2007, the patient reported she no longer required self-catheterizations and had no more voiding problems. Overall, PVR volumes from the clinical database at baseline, Day 57, Day 112, Day 168, Day 231, and Day 505 were 7, 60, 180, 200, 95, and 150 mL, respectively.

6.6.1.2.2. American Urological Association Symptom Index and Post-void Residual Volume

American Urological Association Symptom Index (AUA SI)

In the Pivotal Controlled Trial grouping, results indicate that mean AUA SI Total scores for both the placebo and Total EZG groups remained relatively stable throughout the study ([Table 30](#)), although there was considerable variability. The majority of scores were in the "mild" range for both placebo and Total EZG groups throughout the study.

Table 30 Change from Baseline in American Urological Association Symptom Index Total Scores (Safety Population: PCT, Studies 205, 301, and 302)

Statistic	Placebo (N=427)	EZG 600 mg/day (N=281)	EZG 900 mg/day (N=273)	EZG 1200 mg/day (N=259)	EZG Total (N=813)
Baseline phase Mean (SD)	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)
Change from Baseline to:					
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)
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)

Note: Study 205 initiated the AUA Questionnaire as a protocol amendment approximately 1yr after initiation of the study. The AUA Questionnaire was administered at Baseline, Wk 6, 10, 18 and end of study for Study 301 and Baseline, Wk 4, 8, 16, and end of study for Study 302.

Post-void Residual Volume (PVR)

In the Pivotal Controlled Trials grouping, mean PVR bladder volumes were similar at baseline between placebo and all ezogabine dose groups (Table 31). Mean change from baseline in PVR bladder volume increased in the Total EZG group compared with a decrease in the placebo group, however no consistent effect was seen over time.

Table 31 Baseline and Change from Baseline in Post-Void Residual Bladder Urine Volume (Safety Population: Studies 301 and 302)

Statistic	Placebo (N=427)	EZG 600 mg/day (N=281)	EZG 900 mg/day (N=273)	EZG 1200 mg/day (N=259)	EZG Total (N=813)
Baseline phase Mean (SD)	n=313 19.7 (48.8)	n=178 17.4 (30.6)	n=168 21.5 (40.6)	n=143 30.1 (74.3)	n=489 22.5 (50.3)
Change from Baseline to:					
Week 8 Mean (SD)	n=146 -0.5 (24.9)	n=130 10.2 (69.6)	n=115 4.6 (47.3)	n=5 14.6 (39.8)	n=250 7.7 (59.7)
Week 10 Mean (SD)	n=110 -4.9 (47.1)	n=2 -34.0 (48.1)	n=3 -39.7 (65.3)	n=85 22.3 (90.6)	n=90 19.0 (89.7)
Week 16 Mean (SD)	n=136 -3.1 (29.1)	n=117 12.9 (82.8)	n=97 -1.0 (49.4)	n=2 -23.5 (3.5)	n=216 6.3 (69.6)
Week 18 Mean (SD)	n=92 -9.7 (43.4)	n=4 -8.5 (20.2)	n=1 0	n=63 9.4 (56.6)	n=68 8.2 (54.8)

Note: PVR was not performed in Study 205. The PVR was performed at Baseline, Wk 10, 18 and end of study for Study 301 and Baseline, Wk 8, 16, and end of study for Study 302.

PVRs greater than 150 mL were measured at any time post baseline in 3/295 (1.0%), 12/155 (7.7%), 10/136 (7.4%), 11/109 (10.1%) patients in the placebo, 600, 900, and 1200 mg/day groups, respectively.

Independent Summary

Because of the potential association of ezogabine with urinary retention and its potential clinical significance an independent summary report of renal and urinary events associated with ezogabine (up to 31 December 2007) was conducted by Claus G. Roerhrborn M.D., F.A.C.S., Professor and Chairman, Department of Urology, UT Southwestern Medical Center, Dallas Texas (Report). A copy of this report is provided in Appendix 11.10. Professor Roerhrborn noted:

- There are virtually no group changes noticed in the AUA Symptom Index and only few individual patients experience temporary increases in AUA Symptom Index, not necessarily correlating to relevant AE reporting.
- There are no group changes in the amount of PVR. While some patients experience (mostly temporary) increases in PVR, these are NOT correlated to AE reporting, AUA Symptom Index increases or any other measurable outcomes. Furthermore, such increases in PVR even in at risk men with BPH have not been found to be reliable predictor of serious outcomes.
- A careful and detailed review of the 9 cases (5 on ezogabine in PCT, 1 on placebo in PCT and 3 in open labeled trials) of SAEs related to urinary retention do not reveal a particular pattern that would lend itself to restrictions, contraindication or other monitoring recommendations. Furthermore, the overall rates of *serious* adverse events of urinary retention are similar in placebo (1 per 100 patient years) and active drug (7 per >900 patient years) when calculated based on total exposure in all studies.

- It is both impractical and not indicated based on the data from Studies 301 [303] and 302 [304] to recommend routine measurement of PVR or AUA Symptom Index in women or men about to be treated with ezogabine.
- It might be reasonable to suggest non-invasive measurement of PVR or referral to a urologist for such measurement in those patients who spontaneously report urinary hesitancy during the course of treatment with ezogabine.

The independent report supports the overall conclusion that the clinical studies seem to indicate that ezogabine can exhibit a pharmacological effect on human bladder function as evidenced by a higher frequency of renal and urinary adverse events and a mild, but reversible increase in PVR volumes at certain doses when compared to placebo.

However, these do not appear to be associated with an increase in urinary tract infections or renal failure.

6.6.1.2.3. Urinary Adverse Events in Study NP201

Study NP201 was a study in post-herpetic neuralgia in which patients were randomized to receive ezogabine 150-900 mg/day in a 2:1 ratio. The mean age of patients was 65.3. The study provides additional data for ezogabine in an older population relative to epilepsy. Patients with symptomatic bladder outflow obstruction were excluded from Study NP201, however it is likely that some patients with asymptomatic benign prostatic hyperplasia (BPH) were included. Overall, urinary events were slightly more common in the ezogabine-treated group with 19 (15.2%) patients reporting an event compared to 8 (12.9%) patients in the placebo group. The most common events were urinary retention (4 patients in the EZG group and 1 patient in the placebo group), micturition frequency decreased (3 patients in the EZG group and 0 in the placebo group) with all other events being reported by 2 or fewer patients. Of the 4 patients who reported urinary retention in the ezogabine group, 3 were over the age of 65 years (range 69-76 years) and 3 were male. EZG dose at time of onset ranged from 450-600mg/day and onset of symptoms ranged from 14-36 days after initiation of treatment. None of these events were reported as SAEs.

Of the 19 ezogabine-treated patients who reported urinary AEs, the majority of these continued treatment. A total of 3 (2.4%) patients discontinued ezogabine due urinary events of bladder pain, dysuria and urinary retention, compared to none with placebo.

Brief narratives of the 3 patients who discontinued due to urinary events are presented below:

- Patient 020-004 was a 59 year old male with a history of BPH, who discontinued due to dysuria in the absence of other symptoms.
- Patient 020-007 was a 65 year old female who reported multiple AEs that led to discontinuation. She experienced eustachian tube dysfunction, toothache, muscle twitching and bladder pain.
- Patient 025-003 was a 76 year old female, who reported multiple AEs that led to discontinuation. She experienced balance disorder, disturbance in attention and urinary retention. Concomitant medication at study entry included oxybutynin and

amitriptyline (and both were continued throughout the study). She presented with a high post void residual volume at baseline, which increased while on ezogabine.

All 3 cases resolved without sequelae.

6.6.1.2.4. UTIs and Related Signs and Symptoms

During ezogabine trials, UTIs were diagnosed based on the patient's signs and symptoms or, in some cases, based on dipstick urinalysis results only. UTIs were not routinely confirmed by urine cultures (not required by protocol).

The incidence of AEs of UTIs and related symptoms and signs (a possible complication of renal/urinary events) were not notably higher for ezogabine compared to placebo in the PCTs (8% placebo versus 9% Total EZG), with UTI-related events only more common than placebo in the 1200 mg/day group (Table 32). In the PCT group, of the 35 events of UTI in the Total EZG group none were preceded by an AE of urinary retention. In the All Phase II/III Combined group, 1 out of 105 UTI events were preceded by an AE of urinary retention. There were no reports of SAEs due to UTIs in the PCTs.

Table 32 Adverse Events of Urinary Tract Infections and Related Signs and Symptoms in Any Treatment Group (Safety Population: PCT)

Preferred Term	Number (%) of Patients				
	Placebo N=427	Ezogabine			
		600mg/day (N=281)	900mg/day (N=273)	1200mg/day (N=259)	Total (N=813)
Any event	33 (7.7)	18 (6.4)	16 (5.9)	38 (14.7)	72 (8.9)
Urinary tract infection	20 (4.7)	5 (1.8)	9 (3.3)	21 (8.1)	35 (4.3) ^a
Dysuria	3 (0.7)	4 (1.4)	3 (1.1)	10 (3.9)	17 (2.1) ^b
Urine analysis abnormal	4 (0.9)	2 (0.7)	3 (1.1)	8 (3.1)	13 (1.6)
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)
Cystitis	1 (0.2)	1 (0.4)	0	1 (0.4)	2 (0.2)
Pyuria	0	0	1 (0.4)	0	1 (0.1)
Urethral pain	1 (0.2)	1 (0.4)	0	0	1 (0.1)
Bacteria urine	0	0	1 (0.4)	0	1 (0.1)
White blood cells urine	0	1 (0.4)	0	0	1 (0.1)
Urine odor abnormal	0	0	0	1 (0.4)	1 (0.1)
White blood cells urine positive	1 (0.2)	0	0	0	0

a. Of the 35 events of UTI in the Total EZG group none were preceded by an AE of urinary retention.

b. Only specific raw AE terms were mapped to AEs of interest based on medical review. For that reason, not all AEs in a given preferred term are included in the "voiding and urinary retention" category above (e.g. 17 of 35 patients with a dysuria AE appear in this table).

6.6.1.3. Urinary Crystals

As discussed in Section 6.6.1, urinary crystals having the microscopic appearance of bilirubin were observed in urine samples collected during the Phase III trials (Studies 301, 302, 303 and 304). These crystals were observed in the urine of 15% of patients (127 out of 843) in the Phase III program only, and only occurred in patients who received active drug. There have been no reports in any of the other Phase I or Phase II

ezogabine studies. The crystals were not reported in association with nephrolithiasis nor were there any observed effects on relevant laboratory data or post-void residual urine volume (PVR) in these patients. In addition, a chemical analysis of urine samples containing crystals determined that the crystals were not bilirubin.

6.6.1.3.1. Adverse Events Related to Urinary Crystals

In the PCTs AEs possibly related to urinary crystals were reported more often in the Total EZG group than in placebo (9 [1%] versus 2 [0.5%]) and there were 4 cases of nephrolithiasis in the Total EZG group (all occurred in the 1200 mg/day group of Study 301), and none in the placebo group (Table 33). One of the patients (301-00901) had a prior history of nephrolithiasis at least 4 years prior to the clinical trial. Another patient (301-20210) reported concomitant use of topiramate, an AED associated with nephrolithiasis. The other 2 patients (301-000302 and 301-020221) had no known predisposing factors for nephrolithiasis. None of the patients with nephrolithiasis had any laboratory reports of bilirubin-like crystals. The stone for only 1 patient was analyzed and found to be calcium oxalate.

Table 33 Adverse Events of Urinary Crystals Reported in Any Treatment Group (Safety Population: PCT)

Preferred Term	Number (%) of Patients				
	Placebo N=427	Ezogabine			
		600mg/day (N=281)	900mg/day (N=273)	1200mg/day (N=259)	Total (N=813)
Any event	2 (0.5)	1 (0.4)	2 (0.7)	6 (2.3)	9 (1.1)
Nephrolithiasis	0	0	0	4 (1.5)	4 (0.5)
Renal colic	1 (0.2)	0	2 (0.7)	1 (0.4)	3 (0.4)
Crystalluria	0	1 (0.4)	0	0	1 (0.1)
Urine analysis abnormal	1 (0.2)	0	0	1 (0.4)	1 (0.1)

Renal colic was also reported in 3 (0.4%) patients receiving ezogabine; 1 patient (205-000125) reported renal colic as an SAE (Table 33).

In the All Phase II/III Combined group nephrolithiasis (10/1365), renal colic (7/1365) and calculus ureteric (1/1365) were uncommon and occurred at a combined incidence of 1% (17/1365) in ezogabine (1 patient had both an AE of nephrolithiasis and renal colic). Brief narratives for these subjects are provided below.

Ezogabine-treated Patients:

Patient 3065A1-205-042-000848/212-042-000482 (nephrolithiasis) was a 33-year-old Caucasian male who was randomized to treatment with 900 mg of ezogabine along with carbamazepine (Hermolepsin) when he had a kidney stone of moderate severity on 19 Dec 2000 (Day 138). The event was reported as resolved on the same day, but was later updated to 'persisted' on Day 278. He continued in the study and was referred to a urology consult. However, no treatment information was provided.

Patient 3065A1-20212-00014/20879-00013 (nephrolithiasis) was a 39-year-old female with a history of nephrolithiasis, renal colic, pyelonephritis, and S/P surgery for kidney stones, who was taking ezogabine 400 mg/day along with phenytoin when she began experiencing mild pain at the both renal angles, left more than right, on 25 Feb 1999 (Day 96). Beginning on 15 Mar 1999 (Day 114), the patient developed severe left renal pain, reported to be from a kidney stone, along with nausea and vomiting. It is unknown if she passed a stone. The patient continued in the study and was taking 700 mg of ezogabine monotherapy when she had 2 consecutive hospitalizations, on 03 Jun 2000 (Day 560) and 10 Jun 2000 (Day 567), due to recurrent left flank pain. There was hematuria associated with the first event, but a cystoscopy with retrograde pyelogram was negative for renal stones. There was no hematuria present during the second event. The patient continued on 600 mg of ezogabine when she was re-admitted on 02 Oct 2000 (Day 681) with right renal colic and gross hematuria. She did not pass a stone and a number of diagnostic tests (cystoscopy, renal angiogram, biopsy, and post-biopsy CAT scan of the left kidney) did not reveal any etiology of the hematuria. The patient was discharged from the hospital as hematuria had subsided and continued in the study.

Patient 214-012-000116/216-012-000093 (nephrolithiasis) was a 32-year-old Caucasian male with a history of kidney stone in 1997 who was taking ezogabine 800 mg/day in combination with Dilantin and Keppra when he had a mild kidney stone on 09 Oct 2001 (Day 109). The event was reported as resolved on the same day, but no other information, including treatment details, was provided. The patient continued in the study.

Patient 301-20221 (nephrolithiasis) was a 36- year-old Caucasian male who was taking ezogabine 1200 mg/day in combination with topiramate, lamotrigine and clobazam when he had a mild nephric lithiasis on 20 Aug 2007 (Day 70). A urinalysis collected on the same day had results within normal ranges. The event was reported as resolved without sequelae on 15 Oct 2007 (Day 126), but no additional details, including the treatment information, were provided. The patient continued in the study without interruption.

Patient 301-00302 (nephrolithiasis) was a 32- year-old Caucasian male who was taking 950 mg of ezogabine daily in combination with Depakote and Tegretol XR in the maintenance phase of the double-blinded study when he passed a kidney stone on 06 Sep 2006 (Day 96). He recovered on the same day and continued in the study.

Patient 301-00901 (nephrolithiasis) was a 38- year-old Caucasian male, with a history of kidney stones in 2001 and 2002, who was taking 1050 mg of ezogabine daily in combination with levetiracetam when he reported back discomfort beginning on 25 Feb 2006 (Day 52) followed by hematuria and penile pain on 28 Feb 2006 (Day 55). He was diagnosed with a kidney stone on 01 Mar 2006 (Day 56) via X-rays and abdominal/pelvic CT scans. He took a prophylactic treatment with Keflex 2000 mg for 7 days following a cystoscopy on 14 Mar 2006. Additional information on treatment of the event was not available. The subject recovered without sequelae on 12 Apr 2006 (Day 98) and continued in the study without interruption.

Patient 301-20210 (nephrolithiasis) was a 37- year-old Caucasian female had mild renal lithiasis on 19 Jan 2007 (Day 49), 7 days after she had permanently stopped taking 1050 mg of ezogabine per day, without tapering, during the maintenance phase of the study.

Concomitant antiepileptics included lamotrigine and clobazam. At the time of the final study visit, the event was ongoing. No further details, including treatment of the event, were provided.

Patient 303-20413 (nephrolithiasis) was a 34-year-old African-American female who was taking ezogabine 1200 mg/day (had received placebo in the double-blind phase) in combination with phenytoin and clonazepam when she had renal calculus of moderate severity on 05 Oct 2007 (Day 263). She was treated with Etoricoxib and Hioscine until the event resolved without sequelae on 09 Oct 2007 (Day 267).

Patient 304-70204 (nephrolithiasis) was a 35-year-old Caucasian male who was receiving ezogabine, at a dose of 1200 mg/day, along with pregabalin and carbamazepine, when he experienced 2 episodes of mild renal microlithiasis, on 28 Feb 2008 (Day 564) and 04 Mar 2008 (Day 569), each resolving on the same day. No additional information, including treatment details, was provided. The patient continued in the study with no actions taken with ezogabine.

Patient 303-02511 (nephrolithiasis) was a 21-year-old Caucasian female who was taking ezogabine 1000 mg daily (had received ezogabine 1200 mg in the double-blinded study) in combination with topiramate and clonazepam when she developed a kidney stone on 26 Jun 2009 (Day 995), managed with Toradol 30 mg for 1 day. The event was reported as resolved without sequelae on 01 Jul 2009 (Day 1000), however it was not specified if the patient passed the stone. She continued in the study with no changes to ezogabine.

Patient 3065A1-205-094-001358 (renal colic) was a 26-year-old Caucasian female receiving ezogabine 750 mg at the time of the event who was treated for mild renal colic (Renal Colic) from 13-15 Mar 2001 (Day 126-128). The subject had been randomized to the 200 mg TID group. The patient was treated with tramadol, algin, and hyoscini butylbromidum. The patient's concomitant AEDs were valproic acid and topiramate. The event resolved and the patient completed the study with no actions taken with ezogabine.

Patient 3065A1-205-074-001092 (renal colic) was a 27-year-old Caucasian female who was receiving ezogabine 800 mg when she was treated for moderate nephritic colic (Renal Colic) on 02 - 09 Dec 2000 (Day 85 - 92, recorded as multiple events) and 28 Dec 2000 (Day 111). The subject had been randomized to 400 mg TID group. The patient was treated with metoclopramide, diclofenac, scopolamine, and paraffin oil, during the first period and metamizol during the later event. The patient's concomitant AED was carbamazepine. The patient had previously been treated with topiramate from Feb 1999 to Oct 1999. All of the events resolved and the patient continued in the study with no actions taken with ezogabine.

Patient 3065A1-205-010-000125 (renal colic) was a 39-year-old Caucasian male who was receiving ezogabine 900 mg when he was hospitalized 05 - 07 Jan 2000 (Days 43-45) for severe calculus renal (Calculus Ureteric). The patient was treated with extracorporeal shock wave lithotripsy and pain management. On 12-14 Jan 2000 (Days 48-50), the patient was re-hospitalized, however, re-lithiasis could not be demonstrated.

The patient's concomitant AEDs were carbamazepine and lamotrigine. The events resolved and the patient continued in the study with no actions taken with ezogabine.

Patient 3065A1-212-078-000547 (calculus ureteric) was a 35-year-old Caucasian female receiving ezogabine 900 mg who began to experience problems with urinating on 11 Oct 2001 (Day 413) and underwent an ureterolithotripsy performed on 15 Dec 2001, in an outpatient setting. The patient's concomitant AEDs included carbamazepine and topiramate. The patient was previously treated with Sabril (vigabatrin) (Sep 1995), Topamax (topiramate) (27 May 1999), and Tegretol (carbamazepine) (1981). The event resolved following the ureterolithotripsy and the patient completed Study 212 with no actions taken with ezogabine.

Patient 3065A1-212-054-177 (renal colic) was a 28-year-old Caucasian female receiving ezogabine 900 mg/day when she reported experiencing nephritic colic (Renal Colic) on 28 Oct 2000 (Day 27). The subject had received placebo in study 205. Concomitant AEDs included carbamazepine and clobazam. The subject's prior AEDs included topiramate (29 Jun 1998 to 26 Dec 1999). The event was treated with diclofenac and metamizol and resolved on the same day. The subject continued in the study, taking 1050 mg of ezogabine daily, when she reported two more episodes of nephritic colic on 28 Nov 2000 (Day 58) and 05 Mar 2001 (Day 155). Similar to the initial event, these episodes were treated with drug therapy (diclofenac and metamizol for the earlier episode and diclofenac only during the latter one) with resolution of the symptoms within one day. The subject continued in the study and had no further reports of renal colic until his withdrawal from the study on 04 Mar 2002 due to lack of efficacy.

Patient 3065A1-212-023-000184 (renal colic) was a 33-year-old Caucasian male receiving ezogabine 1150 mg/day when he was hospitalized for left renal colic (Renal Colic) from 04 Dec 2000 (Day 266) to 14 Dec 2000 (Day 276). The subject had been randomized to 400 mg TID group in study 205. Concomitant AEDs included carbamazepine and lamotrigine. Abdominal ultrasound and intravenous pyelogram were both negative, but information on the treatment details was not provided. The subject continued in the study, without recurrence of colic, until he withdrew on 12 Mar 2001 due to lack of efficacy.

Patient 3065A1-205-075-001103 (renal colic) was a 41-year-old Caucasian female with a history of urinary tract infection treated with amoxicillin/clavulanic acid and nitrofurantoin prior to randomization (23 May to 18 Jul 2000) who was receiving ezogabine 900 mg in the titration phase of study. She experienced mild renal colic (Renal Colic) on 27-28 Aug 2000 (Day 40) which was treated with drotaverine and furazidin. The patient's concomitant AED was carbamazepine. The event resolved and the patient completed the study with no actions taken with ezogabine.

Placebo:

Patient 3065A1-205-052-000647 (renal colic) was a 22-year-old Caucasian female who was receiving placebo when she experienced moderate nephritic colic on 30 Mar 2000 (Day 10). The patient withdrew from study on 25 Apr 2000 due to the AE.

Two subjects experienced nephrolithiasis or renal colic during the pretreatment phase of the study:

Patient 3065A1-205-039-787 (renal colic) was a 36-year-old Caucasian male who was hospitalized from 10 Aug 2000 to 14 Aug 2000, during the screening phase of the study, with nephrolithiasis (Kidney Calculus). Urine microscopy and a urography were performed, revealing blood and a renal stone on the left side. The subject's pain was successfully treated with pethidin, ketobemidone, and indomethacin. A follow up urography on 13 Sep 2000 did not show any renal stones. Concomitant AEDs included lamotrigine and valproic acid. The subject had previously been treated with Topamax from 22 May 1997 to Aug 1997. The subject completed the screening phase of the study and was randomized to the placebo treatment group. There were no further reports of a renal stone and the subject completed the study.

Patient 3065A1-205- 010-0130 (renal colic) was a 49-year-old male who reported kidney colic (Kidney Pain) on 22 Apr 2000 in the pre-treatment phase of the study. Concomitant AEDs included carbamazepine and topiramate. The event lasted one day and was treated with Buscopan, Voltaren, and Tarivid. The subject was subsequently randomized to the placebo group and completed the study without experiencing any re-occurrence of this event.

6.6.1.3.2. Chromaturia

Chromaturia was identified in the PCTs and was reported at a higher rate with ezogabine-treated patients compared with those treated with placebo (13/813, 2% versus 1/427, <1%). There appeared to be a dose effect, with 2 (0.7%), 4 (2%) and 7 (3%) patients in the 600 mg/day, 900 mg/day and 1200 mg/day groups, respectively. There were no clinical sequelae to this observation. There were no gender differences in reporting.

In the study of ezogabine for the treatment of postherpetic neuralgia or PHN, Study NP201, urine samples of patients treated with ezogabine were frequently reported to be cloudy and abnormally colored. Protein readings of $\geq 1+$ were also reported and strongly associated with these color changes that occurred more often than in the placebo group. Urine samples were collected at the clinical center and then transported and analyzed by Covance Central Laboratories, whereas the urine samples in the pivotal Phase III studies were processed by Quintiles Laboratories. At specific study time points, up to one third of the patients treated with ezogabine at doses between 150-900mg/day had positive protein dipstick readings as assessed by an automated urine chemistry analyzer. This unexpected finding was also associated with reports of urinary cloudiness in up to 90% of ezogabine -treated patients and abnormal orange or brown coloration in up to 50% of ezogabine -treated patients. All of these changes completely resolved by the end of the 3-week treatment withdrawal phase and there were no significant changes in renal function.

A similar incidence of urinalysis findings has not been observed in the ezogabine development program for epilepsy that encompasses a total of 1365 patients exposed to ezogabine in short- and long-term Phase II and Phase III studies at doses of up to 1200mg/day. This includes the Phase III studies where the urinalysis was performed by Quintiles Laboratories. These findings have also not been observed in non-clinical or Phase 1 studies.

Furthermore, *in vitro* investigations conducted by Valeant have demonstrated that ezogabine, in the presence of water and oxygen, degrades over time producing dark colored solutions. While the exact nature of this degradation is not yet fully characterized, the pronounced color changes observed provide a possible explanation for the discoloration seen in the urine samples of PHN patients between collection and automated analysis up to 72 hours later.

It is hypothesized that the findings in the Study NP201 are likely to be the result of the *ex vivo* degradation of ezogabine or ezogabine metabolites excreted in the urine to produce the abnormal coloration that interferes, either directly or indirectly with the Covance protein dipstick assays performed by the iQ200 automated urinalysis system.

6.6.1.4. Urinalysis

6.6.1.4.1. Pivotal Controlled Trials (Studies 205, 301 and 302)

Integrated urinalysis data for the PCT grouping (Studies 205, 301, and 302) are summarized in [Table 34](#).

There was no indication that ezogabine had any adverse effect on urinalysis results.

Table 34 Summary of Urinalysis Evaluations at Any Post-Baseline Visit (Safety Population: PCT, Studies 205, 301, and 302)

	Percentage of Patients (n/N)				
	Placebo (N=427)	EZG 600 mg/day (N=281)	EZG 900 mg/day (N=273)	EZG 1200 mg/day (N=259)	EZG Total (N=813)
Blood present	97/412 (23.5)	57/269 (21.2)	46/260 (17.7)	48/247 (19.4)	151/776 (19.5)
Amorphous crystals present	62/412 (15.0)	99/269 (36.8)	89/260 (34.2)	12/247 (4.9)	200/776 (25.8)
Amorphous phosphate crystals present	19/412 (4.6)	2/269 (0.7)	5/260 (1.9)	9/247 (3.6)	16/776 (2.1)
Amorphous urate crystals present	55/412 (13.3)	25/269 (9.3)	27/260 (10.4)	56/247 (22.7)	108/776 (13.9)
Uric acid crystals present	32/412 (7.8)	29/269 (10.8)	33/260 (12.7)	35/247 (14.2)	97/776 (12.5)
Calcium oxalate crystals present	113/412 (27.4)	69/269 (25.7)	65/260 (25.0)	60/247 (24.3)	194/776 (25.0)
Glucose present	6/412 (1.5)	1/269 (0.4)	1/260 (0.4)	2/247 (0.8)	4/776 (0.5)
Hyaline casts present	57/412 (13.8)	24/269 (8.9)	25/260 (9.6)	13/247 (5.3)	62/776 (8.0)
Ketones present	14/412 (3.4)	3/269 (1.1)	6/260 (2.3)	7/247 (2.8)	16/776 (2.1)
Protein present	100/412 (24.3)	51/269 (19.0)	51/260 (19.6)	63/247 (25.5)	165/776 (21.3)
RBCs present	305/412 (74.0)	179/269 (66.5)	176/260 (67.7)	153/247 (61.9)	508/776 (65.5)
WBCs present	321/412 (77.9)	167/269 (62.1)	159/260 (61.2)	168/247 (68.0)	494/776 (63.7)

6.6.1.4.2. Study NP201

Positive urine dipstick protein readings for 1+ were reported in up to one-third of ezogabine-treated PHN patients enrolled in Study NP201 when assessed up to 96 hours after sample collection by a fully automated urine chemistry analyzer. In comparison,

protein was detected in the urine specimens of no more than 10% of placebo patients. These findings were not observed in the epilepsy studies, which used a different analyzer. Concurrently, urine turbidity was reported for nearly all (96%) ezogabine-treated patients compared with approximately one-third of placebo patients, and abnormal orange/brown discolouration of urine was reported in nearly half of ezogabine-treated patients, but in only 3% of placebo patients. No clinically meaningful changes in renal function were detected on other laboratory assessments, and no AEs were associated with the unexpected urinalysis findings which completely resolved with gradual ezogabine withdrawal over 3 weeks.

It was hypothesized that these findings were the result of *in vitro* degradation of renally-excreted ezogabine and ezogabine metabolites to produce urine discoloration and turbidity during the transport and storage of samples prior to analysis. The close association between the color and clarity changes and the positive protein readings suggested interference either directly or indirectly with the semi-quantitative analyses performed by the specific central laboratory facility utilized in the study.

Further discussion of the tests conducted to support this hypothesis is provided in Appendix [11.8, Section 3.4](#).

6.6.1.5. Renal Dysfunction

During the pivotal controlled trials, events possibly related to renal dysfunction and/or renal failure were reported only in patients receiving ezogabine (4, <1% vs 0). Most events (3, 1%) were reported in the 600 mg/day group. There were no events in the 1200 mg/day ezogabine group. There was 1 SAE of renal failure ([Patient 205-000448](#)); this patient was withdrawn from the study. A brief narrative was presented in Section [6.6.1.2](#).

With respect to urea and creatinine, there were no clinically abnormal trends. Although at certain time points urea levels demonstrated slight increases, all mean urea values remained well within normal ranges for all treatment groups at all time points. Clinically significant findings of urea and creatinine for all populations were uncommon and do not indicate any harmful effects of the drug on the renal and urinary system. Thus, there was no evidence that ezogabine treatment is associated with renal dysfunction (renal failure) based on review of AEs and laboratory data.

6.6.1.6. Summary of the Effects of Ezogabine on the Urinary Tract and Kidneys

Ezogabine affects the urinary bladder in rodent models inhibiting micturition and has the potential to cause such effects in humans. However, in clinical studies, the effects were limited in frequency and severity and were reversible following withdrawal of therapy, apart from 1 patient from an open-label extension study who continues to self-catheterize intermittently.

In double-blind studies more adverse events related to renal and urinary symptoms were reported for ezogabine than placebo (17 % vs 12.9%). There was no dose effect in terms of severity or seriousness. There were few SAEs (<1%) and few discontinuations (3 [0.7%] placebo vs 6 [0.7%] ezogabine). All patients in the PCTs who reported clinically

significant AEs or SAEs leading to discontinuation recovered while either remaining in the study or after discontinuation.

In the PCT group, results indicate that mean AUA SI scores for both the placebo and Total EZG groups remained relatively stable throughout the study, although there was considerable variability. The majority of scores were in the “mild” range for both placebo and Total EZG groups throughout the study. Mean change from baseline in PVR bladder volume increased in the Total EZG group compared with a decrease in the placebo group, however, no consistent effect was seen over time. AUA SI and PVR mean scores in the All Phase II/III Combined group remained low with long term exposure, suggesting no worsening of effects with long term treatment. The severity of clinical symptoms (urinary retention, hesitation, bladder pain) rather than PVR volumes or AUA SI scores alone should dictate the management of urinary tract disorders as high PVR volumes and AUA SI scores alone tended not to be predictive of serious adverse events.

Urinary tract infection-related AEs were reported by 9% of ezogabine-treated patients in the PCTs compared with 8% of placebo patients. Most UTIs were mild (16/20 [80%] in the placebo group and 27/35 [77%] in the Total EZG group) and resolved with treatment. As expected, UTIs were reported more commonly in females than in males. Ezogabine treatment does not seem to be associated with UTIs, despite there being an apparent increase in incidence at the 1200 mg/day group. UTIs were not routinely confirmed by urine cultures (not required by protocol).

Voiding dysfunction and urinary retention occurred at a higher frequency in patients receiving ezogabine than in patients receiving placebo. The most commonly reported event related to voiding dysfunction was urinary hesitation. Most of the events were mild in intensity and patients were able to continue in the study. Where events necessitated withdrawal of patients from the study, their symptoms generally returned to normal suggesting reversibility consistent with a pharmacological effect. Only one patient had any residual effects after discontinuation of study drug (See narrative for [Patient 303-03505](#) in Section 6.6.1.2.1). This patient had a complicated course following severe urinary retention including a concurrent SAE of psychomotor agitation and resultant delay in seeking medical treatment, demonstrated improvement by regaining spontaneous urination but continued to require intermittent self-catheterization.

During the pivotal controlled trials, events possibly related to renal dysfunction (renal failure) were reported only in patients receiving ezogabine (4, <1% vs 0). Most events (3, 1%) were reported in the 600 mg/day group. There were no events in the 1200 mg/day group. There was 1 SAE of renal failure; this patient was withdrawn from the study.

Urinary crystals having the microscopic appearance of bilirubin have been described intermittently in urine samples during the Phase III trials. These urinary crystals only occurred in patients who received active drug. No unusual trends in symptoms, AEs, laboratory findings, or PVR volumes were seen in these patients and analysis has confirmed that the crystals are not composed of bilirubin. In the All Phase II/III Combined group nephrolithiasis (10/1365), renal colic (7/1365) and calculus ureteric

(1/1365) were uncommon and occurred at a combined incidence of 1% (17/1365) in ezogabine (1 patient had both an AE of nephrolithiasis and renal colic).

It has been observed that because the refractive properties of ezogabine are similar to those of bilirubin, in routine serum analysis it is possible for ezogabine to cause a falsely elevated serum direct bilirubin reading. Investigators have been informed of this potential finding, and there have been no instances of jaundice or seeming confounding of clinical situations because of this potential laboratory interaction.

6.6.2. Hallucinations and Psychosis

Psychiatric AEs such as psychosis have been associated with some of the new antiepileptic drugs [Besag, 2001] and were seen during the clinical development program for ezogabine. Thus, an analysis of these events was conducted for the PCT trials and the Phase II/III combined Studies grouping. Events from PHN Study NP201 and Study RTG114137 are also presented. Preferred terms included in the search for possible events of hallucinations and psychosis were acute psychosis, agitation, déjà vu, delirium, delusion, delusional disorder (persecutory type), depersonalization, elevated mood, epileptic psychosis, euphoric mood, hallucination, hallucination auditory, hallucination visual, hallucinations mixed, hypomania, illusion, mood altered, paranoia, psychotic disorder and schizoaffective.

In the PCTs, events related to hallucination or psychosis were reported in 32/813 (4%) of patients in the Total EZG group and 3/427 (<1%) in the placebo group (Table 35). The frequency of events appeared dose-related (2%, 3%, and 7% of patients in the 600 mg/day, 900 mg/day, and 1200 mg/day groups, respectively), but the actual dose at the time of reporting indicates that most events occurred at less than 1200 mg/day.

Visual hallucination was the most frequent event in the category of hallucinations and psychosis with 8 (1%) events reported in the Total EZG group. Psychotic disorder was the second most frequent event with 7 (<1%) events reported in the Total EZG group; no visual hallucinations or psychotic disorder AEs were reported for the placebo group.

When all the hallucination terms (hallucination, hallucination visual and hallucination auditory) were combined, 2 (<1%) patients reported hallucinations in the placebo group, 4 (1.4%) patients in both the ezogabine 600 mg/day and 900 mg/day groups and 7 (3%) patients in the 1200 mg/day group.

When the two psychotic disorder terms were combined (psychotic disorder and acute psychosis), 1 (<1%) patient each in the 600 mg/day and 900 mg/day groups, and 6 (2.3%) patients in the 1200 mg/day group reported events, whereas none were reported by placebo patients.

Hallucinations and psychosis-related AEs appeared within the first 8 weeks of treatment in all dose-groups, with most events reported within 4 to 8 weeks. When examined by study phase, over half the events were reported during titration (19/32).

In the PCTs, 8 (1%) patients who received ezogabine reported SAEs related to psychosis and hallucinations, and 15 (2%) patients, all receiving ezogabine, discontinued treatment

due to psychosis and hallucinations (Table 35). A review of the SAEs identified that 6 of the 8 events were reported in the setting of increased seizures and/or were post-ictal psychotic events. Other events often were reported within the setting of intercurrent illness or in patients with well-documented histories of psychiatric illness.

Fifteen (2%) patients, all receiving ezogabine, discontinued during the PCTs due to psychosis and hallucination events. Most common were psychotic disorder and hallucination visual (5 patients each). The remaining events (deja vu, hallucination, illusion, acute psychosis, mood altered) each led to discontinuation in 1 patient.

Table 35 Adverse Events of Psychosis and Hallucinations (Safety Population: PCT)

Preferred Term	Number (%) of Subjects				
	Placebo N=427	Ezogabine			
		600mg/day (N=281)	900mg/day (N=273)	1200mg/day (N=259)	Total (N=813)
Any event	3 (0.7)	6 (2.1)	9 (3.3)	17 (6.6)	32 (3.9)
Hallucination, visual	0	2 (0.7)	2 (0.7)	4 (1.5)	8 (1.0)
Psychotic disorder	0	0	1 (<1.0)	6 (2.3)	7 (<1.0)
Hallucination	1 (<1.0)	1 (<1.0)	2 (<1.0)	2 (<1.0)	5 (<1.0)
Euphoric mood	0	1 (<1.0)	2 (<0.1)	1 (<1.0)	4 (<1.0)
Hallucination, auditory	1 (<1.0)	1 (<1.0)	0	1 (<1.0)	2 (<1.0)
Mood altered	0	0	0	2 (<1.0)	2 (<1.0)
Illusion	0	0	1 (<1.0)	0	1 (<1.0)
Acute psychosis	0	1 (<1.0)	0	0	1 (<1.0)
Agitation	1 (<1.0)	0	0	1 (<1.0)	1 (<1.0)
Déjà vu	0	1 (<1.0)	0	0	1 (<1.0)
Depersonalization	0	0	1 (<1.0)	0	1 (<1.0)
Paranoia	0	0	0	1 (<1.0)	1 (<1.0)

Across the All Phase II/III Studies, psychosis and hallucination AEs were reported by 6% of ezogabine patients. Hallucination, psychotic disorder, and hallucination, visual, were each reported by approximately 1% of patients. All other psychosis and hallucination AEs were reported by <1% of patients.

A total of 19 patients (including the 8 patients from the PCT trials) experienced SAEs related to psychosis and hallucinations (Table 36).

**Table 36 Serious Adverse Events Due to Psychosis and Hallucinations
(Safety Population: All Phase II/III Combined)**

Study	Patient ID	Age/Race/ Gender	Dose at time of AE (mg/day)	Preferred Term	Day of Onset	Resolved Y/N Y With medication during EZG w/d	Withdrawn Y/N
205	001109	46/C/F	400	Psychotic disorder	44	Y With medication during EZG w/d	Y
205	001141	46/C/M	1200	Psychotic disorder/ Transient post-ictal psychotic disorder	44	Y With medication pre EZG w/d	Y
301	002111	71/C/M	1000	Psychotic disorder	46	Y With medication post EZG w/d	Y
301	010201	32/H/F	700	Psychotic disorder	30	N/A	Y
301	020309	58/C/F	780	Psychotic disorder/ Exacerbation of chronic interictal psychosis	33	Y With medication post EZG w/d	Y
302	025411	46/C/F	600	Deja vu	57	Y With medication pre EZG w/d	Y
302	050206	46/C/F	600	Acute psychosis	49	Y With medication event started 5 days post EZG w/d	Y
302	085416	26/C/M	900	Psychotic disorder	9	Y spontaneously post EZG w/d	Y
202	100015	47/C/M	400	Delusion/ Paranoid Delusion	98	Y With medication	N
208	000012	51/C/F	500	Schizoaffective disorder	584	Y spontaneously	Y
205 ^a	000675	42/C/F	900	Delirium/Delirious psychotic disorder	123	Y With medication pre EZG w/d	Y
205 ^a	001115	53/C/M	900	Hallucination	114	Y With medication pre EZG w/d	Y
212	000628	39/C/F	900	Hypomania	143	N With medication post EZG w/d	Y
216	000044	41/C/M	1200	Psychotic disorder/ postictal psychosis	233	Y With medication pre EZG w/d	N
303	000902	39/C/M	900	Epileptic psychosis/ postictal psychosis	698	Y With medication	N
304	040101	46/C/M	900	Hallucination	446	Y With medication	N

Study	Patient ID	Age/Race/ Gender	Dose at time of AE (mg/day)	Preferred Term	Day of Onset	Resolved Y/N	Withdrawn Y/N
302 ^a	040118	30/C/M	N/A	Psychotic disorder/ Postictal disorder	24	Y With medication event started 2 days post EZG w/d	Y
304	055606	41/C/F	900	Psychotic disorder	264	Y With psychotherapy post EZG w/d	Y
304	090203	47/X/M	1050	Agitation	204	Y With medication pre EZG w/d	N

C = Caucasian, H = Hispanic, A = Asian, M = Male, F = Female, X=Other.

a. Reported in the transition phase of the parent study, i.e., during transition to the open-label extension

Patients highlighted in grey are also included in SAEs for PCTs

N/A=Not available, patient was lost to follow-up.

A total of 34/1365 (2%) patients withdrew due to AEs of psychosis and hallucination. The most common event leading to discontinuation was psychotic disorder (<1%) followed by hallucination and hallucination visual (<1%), and delusional disorder persecutory type (<1%). Of particular note, 5/27 patients from Study 209 discontinued due to psychosis-related AEs. This study explored a rapid dose escalation regimen using a four times a day (QID) regimen to target doses. Dose escalation was poorly tolerated at the higher target doses.

In summary, events of psychosis and hallucinations were reported more frequently for ezogabine-treated patients than for patients receiving placebo during the PCTs. Despite there being a higher number of events reported in the ezogabine 1200 mg/day group, an examination of the dose at time of occurrence of the AE suggests that many of these events were reported at lower doses.

In Study NP201, (a study of ezogabine in the treatment of post herpetic neuralgia in which patients were randomized 2:1 ezogabine:placebo) no psychosis-related TEAEs were reported for any patient in this study (including the preferred terms acute psychosis, psychotic disorder, fear, abnormal behavior, agitation, or aggression).

Hallucination was reported by 3 (2%) patients in the ezogabine 150-900 mg group and 0 in the placebo group. Mood altered was reported by 2 (2%) patients in the ezogabine 150-900 mg group and 0 in the placebo group. None of these events were reported as an SAE and none led to discontinuation.

Study RTG114137 is an open-label, randomized, single centre, repeat dose, up- titration Phase I study designed to assess the impact of urine sample handling procedures (interval between collection and analysis; role of specimen stabilizers) on urinalysis outcomes in healthy males and females aged 40 to 65 years receiving ezogabine doses of 300mg/day to 900mg/day for 4 weeks. This study was initiated after the 120-day Safety Cut-off date. One subject (Subject 32) reported a serious acute psychotic episode approximately 3 weeks after beginning ezogabine. The subject recovered approximately

10 minutes after onset of the event, but was withdrawn from the study. Due to this and similar but less severe reports of hallucination, ataxia, and confusional state, the investigator terminated the study; at the time of study termination 32 patients had received treatment.

A brief narrative of this case is provided below.

Subject 32 - A 42 year old male with a history of drug and alcohol abuse, along with an episode of impulsive suicidal behaviour that was not disclosed prior to study entry was enrolled in Study 137.

On 24 May 2010, 23 days after the start of ezogabine and approximately 40 minutes after the second dose of Day 24 ezogabine (900mg/d), the subject developed a severe psychotic episode that was clinically significant and experienced a severe incident of hallucination. The subject became agitated and referred to wanting to commit suicide. After approximately 10 minutes of being restrained the subject was able to calm down. Laboratory assessments on 24 May 2010 shortly after the SAE occurred were within normal limits. Treatment with ezogabine was discontinued and the subject was withdrawn from the study. The event was reported as resolved on 24 May 2010. The investigator considered that there was a reasonable possibility that the psychotic episode may have been caused by ezogabine and that the event was possibly due to study participation. He also commented that the subject's medical history, drug and alcohol abuse was not disclosed to the investigator at enrolment.

6.6.3. Suicidality

Class labelling for marketed AEDs and suicidality was adopted by FDA in April 2009 based on a meta-analysis conducted by the FDA for suicidality in placebo controlled trials from 11 marketed AEDs which demonstrated an increase in the risk of suicidal thoughts or behavior in patients taking these drugs for any indication (0.43% risk in patients taking AED versus 0.22% in patients taking placebo).

Valeant conducted an independent adjudication of all SAEs according to the Columbia Classification Algorithm of Suicide Assessment (C-CASA) procedure; adjudication was managed by Dr. Kelly Posner, Columbia University. No completed suicides were reported ([Table 37](#)). However, Patient 301-00123 in the 1200 mg/day treatment group made a suicide attempt. There were 3 events of suicidal ideation; 2 on placebo (<1%; Patients 301-10216 and 301-55509) and 1 in the 1200 mg/day ezogabine group (<1%; Patient 205-00457).

There were no episodes of self-injurious behavior with unknown intent or without suicidal intent, and none of death without enough information for adjudication. Overall, there were no completed suicides in placebo or ezogabine-treated patients and rates of suicidality in the ezogabine and placebo groups were similar.

Table 37 Suicidality Assessment: Completed Suicide, Suicidality, and Self-Injurious Behavior (Safety Population: PCT)

Preferred Term	Number (%) of Subjects				
	Placebo N=427	Ezogabine			
		600mg/day N=281	900mg/day N=273	1200mg/day N=259	Total N=813
Any event	2 (<1%)	0	0	2 (<1%)	2 (<1%)
Completed suicide	0	0	0	0	0
Suicide attempt	0	0	0	1 (<1%)	1 (<1%)
Preparatory actions towards imminent suicidal behavior	0	0	0	0	0
Suicidal ideation	2 (<1%)	0	0	1 (<1%)	1 (<1%)
Self-injurious behavior intent unknown	0	0	0	0	0
Not enough information: death	0	0	0	0	0
Self-injurious behavior without suicidal intent.	0	0	0	0	0

Data cut-off date was 31st Dec 2007

Overall, there was no evidence that adding ezogabine to an existing regimen of AEDs results in any increase in events of suicide, suicidality, or self-injurious behavior. Nonetheless, class labeling related to suicidality will be adopted for ezogabine.

6.6.4. Seizure Worsening, Status Epilepticus and Seizure Related Adverse Events

Worsening of seizures was assessed by the following: an increase in seizure frequency, seizure severity as reflected by occurrence of status epilepticus, the appearance of new seizure types occurring after baseline and, in particular, seizure-related AEs.

In the pivotal efficacy studies (Study 205, 301 and 302) based upon the distribution profiles by pre-defined percentage categories, there was no evidence for worsening of total partial seizures (no change or increase in seizure frequency from baseline) with ezogabine treatment ([Table A 1](#)). Similarly, the integrated analysis of total partial seizure frequency indicated there was no evidence for worsening of seizures, as evidenced by similar proportions of patients with no change or increases in total partial seizure frequency across the treatment groups ([Table 38](#)).

Table 38 Percent Reduction in 28-Day Total Partial Seizure Frequency by Reduction Category (Double-Blind Phase) – ITT Double-Blind Population: Studies 205, 301 and 302

	Number (%) of Patients				
	Placebo ^a N=275	EZG 600 mg/day N=281	EZG 900 mg/day N=273	Placebo ^b N=248	EZG 1200 mg/day N=259
Studies 205, 301 and 302 Integrated					
Percent Reduction					
n	275	281	273	248	259
75 to 100%	20 (7)	25 (9)	37 (14)	14 (6)	41 (16)
50 to <75%	26 (9)	55 (20)	63 (23)	28 (11)	62 (24)
25 to <50%	57 (21)	63 (22)	63 (23)	55 (22)	49 (19)
>0 to <25%	77 (28)	61 (22)	39 (14)	67 (27)	43 (17)
No change or increase	95 (35)	77 (27)	71 (26)	84 (34)	64 (25)
P-value ^c		0.002	<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. P-value from CMH test.

Status epilepticus was rarely seen in the PCTs, with single cases reported in the 900 mg/day and 1200 mg/day ezogabine treatment arms. Neither patient had a history of status epilepticus and both events occurred during titration. A total of 8/1365 (<1%) cases of status epilepticus were reported in All Phase II/III studies. The data are considered to reflect the low frequency of events of status epilepticus and the greater number of patients randomized to the ezogabine group (N=813) compared to the placebo group (N=427). Brief narratives for the patients with status epilepticus are provided below:

- VRX-RET-E22-301-001-09 was a 47-year-old Caucasian female, randomized to 400 mg TID treatment group, who was receiving 950 mg of ezogabine in the transition phase of the study when she was hospitalized with partial status epilepticus (Status Epilepticus) on 20 Dec 2006 (Day 164). A continuous video EEG showed recurrent electrographic and clinical seizures. Concomitant AEDs included levetiracetam and lamotrigine. Laboratory results on admission revealed a levetiracetam level of 70 mcg/mL (5-40 mcg/mL) and lamotrigine level of 39.7 mcg/mL (3- 14), which the investigator considered was likely a lab error. A repeat lamotrigine level on 27 Dec 2006 was 6.8 mcg/mL. The patient was treated with two 2-mg doses of Ativan and slowly returned to baseline by the following morning. The patient continued in the study on 300 mg TID daily dose of ezogabine.
- VRX-RET-E22-301-013-08 was a 44 year-old Caucasian female, randomized to 400 mg TID treatment group, was receiving 900 mg of ezogabine in the titration phase of the study when she was hospitalized with status epilepticus (Status Epilepticus) on 13 May 2007 (Day 31). The seizures stopped following administration of 10-mg diazepam en route to the hospital. Concomitant AEDs included phenytoin and

levetiracetam. Laboratory results on admission were significant for sub-therapeutic levels of phenytoin at 5.5 and 5.8 mcg/mL (10-20) and the patient was treated with a 400 mg bolus of phenytoin, increasing the serum level to 10.4 mcg/mL. The patient was discharged from the hospital on 14 May 2007 and withdrawn from the study on 24 May 2007.

Summary data from the PCTs on the proportion of patients that reported new seizure types indicated that there was no difference between the placebo and ezogabine treatment groups in the occurrence of new seizure types (Appendix 11.1, Table A 2).

In the PCTs, seizure-related AEs (any event) were reported in both the Total EZG group (7%) and placebo group (6%) (Table 39). The relative risk of experiencing seizure related AEs in all patients who received ezogabine compared to placebo in the randomized controlled trials was 1.19, ranging from 0.76 to 1.86. The 95% CIs spanned 1.0 at each dose group (600 mg/day, 900 mg/day and 1200 mg/day).

The most common seizure-related AE was convulsion (MedDRA coded convulsion), which was reported in 4%, 2%, 3%, and 6% of patients in the placebo, 600 mg/day, 900 mg/day, and 1200 mg/day groups, respectively. AEs coded as 'convulsion' included generalized seizures as well as increased seizure frequency or severity or in some cases injuries associated with seizures from which a convulsion was presumed to have occurred. A total of 2% (7/427 patients) in the placebo group and 1% (9/813 patients) in the Total EZG group withdrew from the study because of convulsions.

Table 39 Seizures and Related Adverse Events (Safety Population: PCT)

Preferred term	Number (%) of patients				
	Placebo N=427	Ezogabine			
		600mg/day N=281	900mg/day N=273	1200mg/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)

Overall, the rate of seizure-related events reported as SAEs was similar between the placebo and ezogabine groups. Convulsion and myoclonus were the only seizure-related

SAEs reported by more than two patients in any treatment group. SAEs of all events were reported for 2% (7/427) of patients in the placebo group and 2% of patients (19/813) in the Total EZG group. SAEs of convulsion were reported for 1% (7/427) of patients in the placebo group and 2% of patients (12/813) in the Total EZG group. SAEs of myoclonus were reported in 2 patients (1%) in the 600 mg/day group, and none on placebo.

In the preclinical studies of ezogabine, proconvulsant activity was observed in the ezogabine repeat dose toxicity studies at dose/exposure levels that were approximately 10-fold greater than those associated with anti-epileptic activity in the non-clinical rodent efficacy studies; proconvulsant activity was not seen in non-clinical efficacy studies with ezogabine at doses in the rodent therapeutic range. The proconvulsant activity of ezogabine occurs at supratherapeutic (toxic) doses (≥ 61.9 mg/kg) in standard laboratory animals rather than in epileptic animals.

Overall, efficacy and safety data from the PCTs indicate that the use of ezogabine does not lead to an increase in seizure frequency, new types of seizures, seizure-related SAEs, or seizures leading to discontinuation. Overall, these data do not support that ezogabine worsens seizures and suggest that ezogabine is not epileptogenic or proconvulsant at clinically relevant doses.

6.6.5. Effects on Cardiac Conduction

Ezogabine demonstrates selectivity of action for the neuronal/smooth muscle potassium channels KCNQ2 and KCNQ3 (EC₅₀s 0.6 – 2.5 μ M) over KCNQ4 and KCNQ5 (EC₅₀s 5.2 – 6.4 μ M) and is devoid of channel opener activity at the cardiac channel KCNQ1. Only inhibitory effects were observed on KCNQ1 and only at high concentrations (IC₅₀ 50 - 100 μ M). Ezogabine minimally inhibited hERG-mediated inward tail currents in the same concentration range. Data on additional cardiac ion channels (Nav1.5, Kv1.5, Cav1.2, KCNQ1/minK) showed inhibition with IC₅₀s from ≥ 20 – 60 μ M. Because of its effects on the potassium channels the myocardial safety profile of ezogabine is a topic of special interest and has been evaluated carefully in clinical studies and pre-clinical animal models both *in vivo* and *in vitro*.

6.6.5.1. Thorough QT Evaluation (VRX-RET-E22-103)

This was a double-blind, randomized, parallel-group study to determine the potential for ezogabine to have a threshold pharmacologic effect on cardiac repolarization, as detected by QT/QTc prolongation. One hundred and twenty (120) healthy male and female subjects were enrolled and randomly assigned to the following treatment groups

One hundred and twenty (120) healthy male and female subjects were enrolled and randomly assigned to the following treatment groups:

Group 1: Ezogabine treatment group: 40 subjects received ezogabine tablets starting at 100 mg TID on Days 1 to 3, titrating up at the rate of 50 mg/dose every 3 days to 400 mg TID on Days 19 to 21. An additional single 400-mg dose was administered in the morning on Day 22.

- Group 2:** Placebo treatment group: 40 subjects received placebo tablets following the identical TID dosing schedule to ezogabine-treated subjects. A placebo tablet was administered in the morning on Day 22.
- Group 3:** Positive control (moxifloxacin) group: 40 subjects received moxifloxacin tablets following the identical TID schedule to ezogabine-treated subjects. A single 400-mg dose of moxifloxacin was administered in the morning on Day 22.

The three groups of subjects were balanced evenly by gender. Of the enrolled subjects, 115 subjects were included in the electrocardiogram (ECG) evaluation and 38 ezogabine-treated subjects were included in the PK/pharmacodynamic (PD) evaluation.

The ICH E14 guidelines generally suggest studying a drug in “substantial multiples” of the intended therapeutic dose. Since anticonvulsants have a narrow therapeutic window, “substantial multiples” may not be possible in healthy subjects. This issue was acknowledged by FDA during communications leading to finalization of the protocol. Accordingly, the Agency recommended that the study include a dose that is considered the highest tolerable dose. The 400 mg dose was selected for this study since it had been determined in Phase I trials to be the maximum tolerated dose in healthy volunteers and represents the maximum single dose recommended for treatment of epilepsy patients (400 mg TID is highest recommended dose).

Five 12-lead ECGs were downloaded from a digital continuous 12-lead ECG recording device at Hour 0 and at 1, 2, 3, 4, 5, 6, 8, 10, 12, 14, 16, 18, 23.5 hours for time course in absence of ezogabine (baseline) and on Day 22 or on the day of early withdrawal. Blood samples were collected at the time points matching those for ECG measurements. ECG analyses were performed centrally and all ECGs for a given subject were analyzed by the same reader. The primary time-matched analysis was performed on placebo-corrected change in QTc interval from baseline at each time point. The ECGs at each timepoint for baseline and Day 22 were initially averaged and the on-treatment time point value was then subtracted from the baseline value to produce the change from baseline value. The Intersection Union Test was used to generate a 90% confidence interval for the QTc delta at each time point. Genotyping for UDP glucuronosyltransferase and N-acetyltransferase was determined at baseline.

Approximately 1/3 of subjects were able to achieve the target top dose of 1200 mg/day due to limited tolerability of the ezogabine accelerated titration scheme (increase of 50 mg TID every 3 days) in a healthy volunteer population. Therefore ECG (and PK) results were examined for 2 populations;

1. ITT-ECG population: all subjects with available ECG and PK at baseline and after dose (N=38)
2. Completers: subject that completed the study and titrated to 1200mg/day as per protocol (N=26)

In the ITT-ECG population, the point estimate and the upper boundary of the two-sided 90% or one-sided 95% confidence interval at each time point from the time-matched analyses are presented in [Table 40](#). For the ezogabine treatment group, all the upper

bound of two-sided 90% or one-sided 95% confidence intervals were less than 10 msec, except for that at 3 hours post-dose which was 10.3 msec. In contrast, the upper bound of two-sided 90% or one-sided 95% confidence intervals in the moxifloxacin treatment group were all greater than 10 msec (except at 14 hours post-dose, which was 9.6 msec), demonstrating sensitivity of the analysis.

Table 40 Time-Matched Difference from Placebo of Individual Corrected QT Interval (QTcI) in Subjects receiving Ezogabine 400 mg TID (N=38) or Single Moxifloxacin Dosing (n=38) (ITT-ECG Population)

Time (h)	EZG Treatment		Moxifloxacin Treatment	
	Estimate (msec)	Upper Bound (msec)	Estimate (msec)	Upper Bound (msec)
1	2.6	8.1	11	16.5
2	4.3	9.9	9.4	14.9
3	5.0	10.3	9.3	14.6
4	2.5	8.0	10.7	16.2
5	0.2	5.4	7.2	12.4
6	1.2	6.7	8.0	13.5
8	-2.6	2.7	6.0	11.3
10	-0.5	4.8	6.6	11.9
12	1.5	6.9	5.0	10.4
14	1.6	6.8	4.5	9.6
16	2.6	8.2	6.4	11.9
18	1.3	6.7	5.2	10.5
23.5	4.4	9.1	6.2	11.0

For the “Completer” group the time matched placebo and baseline corrected QTcI showed that all means values were less than or equal to 5 msec except at 2 h (6.4 msec) and 3 h (6.7 msec). All upper CIs were less than 10 msec except at 1 h, 2 h and 3 h post dose where the upper CI were 10.4 msec, 12.5 msec and 12.6 msec respectively.

Table 41 Time-Matched Difference from Placebo of Individual Corrected QT Interval (QTcI) in Subjects Receiving ezogabine 400 mg TID (N=26) or Single Moxifloxacin Dosing (N=37) (Completer Population)

Time (h)	EZG Treatment		Moxifloxacin Treatment	
	Estimate (msec)	Upper Bound (msec)	Estimate (msec)	Upper Bound (msec)
1	4.2	10.4	11.4	17.0
2	6.4	12.5	9.8	15.4
3	6.7	12.6	9.7	15.0
4	2.9	9.03	11	16.6
5	2.1	7.96	7.7	13.0
6	3.3	9.36	8.5	14.0
8	-1.1	4.85	6.7	12.1
10	0.4	6.35	7.1	12.5
12	3.9	9.99	5.5	10.9
14	3.4	9.05	5.0	10.1
16	2.7	8.97	6.8	12.4
18	1.0	7.10	5.6	11.1
23.5	4.6	9.98	6.5	11.4

No gender effect was identified and there were no clinically-significant morphologic changes identified. In addition, no ezogabine effects on heart rate, or PR or QRS intervals were noted.

Ezogabine PK parameters for the overall ezogabine treatment group and the subset of subjects who completed the study at the intended 400 mg TID dose regimen are summarized in [Table 42](#). Using concentration data from all ezogabine-treated subjects, the change from baseline (not placebo-corrected) of QTcI and QTcF were analyzed by repeated measure linear mixed models with ezogabine concentration as a fixed effect and subject as a random effect. The slopes were weakly, but statistically-significantly positive and estimated to be 0.0017 msec/(ng/mL) for the concentration–QTcI relationship and 0.0018 msec/(ng/mL) for QTcF relationship. The regression analysis resulted in predicted mean changes in QTcI at the ezogabine mean C_{max} (1501 ng/mL) at 400 mg TID of 2.55 msec for ezogabine.

Figure 10 Relationship between Ezogabine Plasma Concentration and change from baseline in QTcI for All Subjects

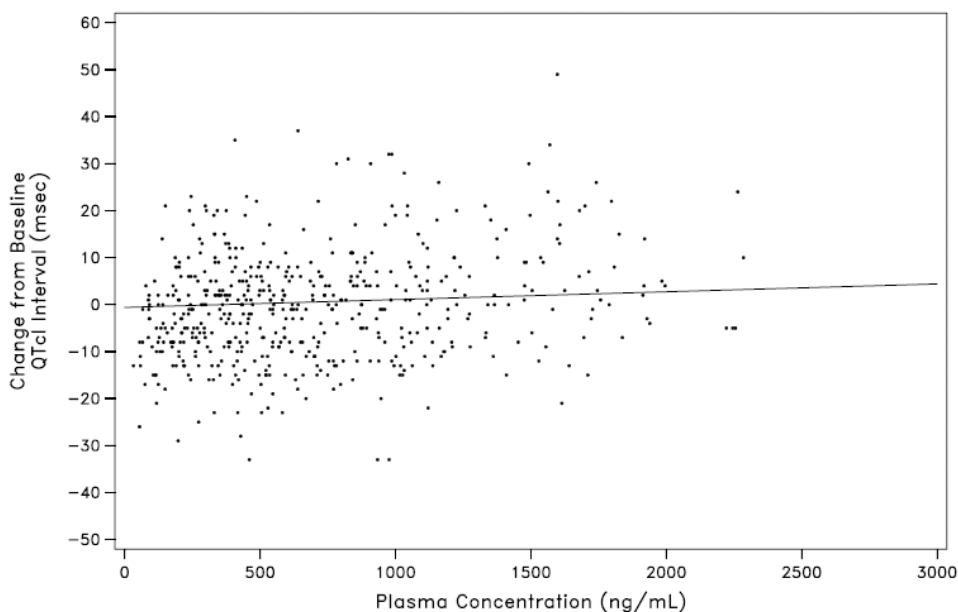


Table 42 Pharmacokinetic Parameters of Ezogabine Following Ezogabine 400 mg TID

Analyte / Parameter	Completer Subset		Overall Population	
	N	Mean (CV%)	N	Mean (CV%)
AUC _{0-8h} (ng•h/mL)	26	7993 (37)	38	7514 (37)
C _{max} (ng/mL)	26	1501.20 (32)	38	1446 (30)
t _{max} ^a (h)	26	1.00 (1.00, 4.00)	38	1.00 (1.00, 4.00)
t _{1/2} (h)	15	10.12 (28)	22	10.35 (27)

a. Median (minimum, maximum)

The assessment of the data from the overall ezogabine treatment group showed no apparent effect on cardiac repolarization; however, analysis of the completer population indicated a slight and transient QT-prolonging effect of ezogabine on cardiac repolarization in healthy volunteers titrated up to 1200 mg/day, occurring within 3 hours of dosing. The demonstrated effect was less than moxifloxacin at all time points and may only have important clinical significance in patients at increased risk for QT prolongation, such as patients with heart disease who take QT prolonging medications.

An AE of syncope vasovagal was reported by two subjects: one ezogabine-treated and one placebo-treated (1/40, 2.5% for each treatment group). Heart rate increased was reported for 1 placebo-treated subject (1/40, 2.5%). No AEs under the system organ class (SOC) of cardiac disorders were reported.

6.6.5.2. Analysis of ECGs in Pivotal Controlled Trials

Mean baseline QTcB was 393.3 to 398.3 msec across treatment groups, and mean baseline QTcF was 384.8 to 389.1 msec across treatment groups. There were no clinically relevant changes in mean QTcB or QTcF over the treatment period.

Changes from baseline for PR, Bazetts' QTc and Friderica's QTc intervals reflected this observation ([Table 43](#)). Mean baseline heart rate was 67.8 to 70.1 bpm across treatment groups and there were no clinically relevant changes in mean heart rate during the treatment period.

Table 43 Baseline PR Interval, Bazzett's QTc and Friderica's QTc and Change in PR Interval, Bazzett's QTc and Friderica's QTc from Baseline (Safety Population: PCT, Studies 205, 301, and 302)

	PR Interval (MSEC)				
	Placebo N=427	EZG 600 mg/day N=281	EZG 900 mg/day N=273	EZG 1200 mg/day N=259	EZG Total N=813
Total Population Baseline mean(\pm SD)	427 159.7 (22.42)	278 158.8 (22.19)	273 161.8 (26.01)	257 156.8 (22.10)	808 159.2 (23.58)
Change from Baseline, mean(\pm SD)					
Week 2	-1.2 (11.97)	-2.0 (11.40)	-1.0 (11.96)	-1.0 (13.03)	-1.3 (12.08)
Week 4	-0.5 (11.06)	-1.6 (10.88)	-1.6 (11.82)	-0.1 (12.10)	-1.2 (11.58)
Week 6	-0.6 (14.43)	-1.4 (13.09)	-0.8 (12.12)	0.6 (13.77)	-0.6 (13.00)
Week 8	0.4 (12.74)	1.0 (15.44)	2.3 (15.36)	1.0 (13.73)	1.3 (14.63)
Week 12	-1.8 (13.11)	-3.2 (8.98)	-6.3 (2.92)	-6.2 (9.63)	-4.9 (8.36)
Week 16	-1.2 (13.13)	0.1 (13.56)	1.4 (13.39)	1.2 (14.85)	0.8 (13.65)
Week 18	-0.7 (12.02)	-1.4 (10.65)	-1.3 (9.48)	1.2 (11.59)	0.9 (11.35)
Bazzett's QTc (MSEC)					
Baseline mean(\pm 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(\pm 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)
Friderica's QTc (MSEC)					
Baseline mean(\pm 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(\pm 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)

QTcB and QTcF, categorized according to standard intervals to aid determination of criteria for potential clinical concern (PCC), are summarized in [Table 44](#). Values of post-baseline QTcB or QTcF ≥ 480 msec, or increases of >60 msec from baseline were infrequent, occurring in $<1\%$ of patients across all treatment groups including placebo. The one patient (Patient 302-40141) who had a QTcB/QTcF ≥ 480 msec had a QTcB/QTcF ≥ 450 msec at baseline, and this was an isolated value at Week 8 of treatment in the 600 mg/day group. There was an indication of a higher proportion of patients with at least one report of an increase in QTcB or QTcF >30 msec at longer treatment

durations. There was no indication of a higher proportion of patients with at least one report of an increase in QTcB or QTcF >60 msec at longer treatment durations.

Table 44 Findings for QTc of Potential Clinical Concern (Safety Population: PCT, Studies 205, 301, and 302)

	Number of Patients ² /Number of Patients Evaluable (%)				
	Placebo (N=427)	EZG 600 mg/day (N=281)	EZG 900 mg/day (N=273)	EZG 1200 mg/day (N=259)	EZG 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 msec ¹	19/403 (4.7)	5/266 (1.9)	10/255 (3.9)	12/232 (5.2)	27/753 (3.6)
Post-baseline ≥480 msec ¹	0	1/266 (<1)	0	0	1/753 (<1)
Post-baseline ≥500 msec ¹	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 msec ¹	4/403 (1.0)	2/266 (<1)	3/255 (1.2)	3/232 (1.3)	8/753 (1.1)
Post-baseline ≥480 msec ¹	0	1/266 (<1)	0	0	1/753 (<1)
Post-baseline ≥500 msec ¹	0	0	0	0	0

1. And baseline < this value or missing.

2. A patient may be counted more than once, if they had ECG parameters that met different criteria across various timepoints.

Data are for any post-baseline finding.

Other ECG parameters assessed for outlier values of PCC (heart rate and PR and QRS intervals) were observed in both placebo and active dose groups at similar frequencies:

- 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.

ECG abnormalities reported as TEAEs are presented in Section 6.6.5.3

In summary, there was no indication of a clinically significant difference between the ezogabine and placebo groups in terms of the proportion of patients with increased QTcB or QTcF interval from baseline or other ECG parameters (heart rate and PR and QRS intervals).

6.6.5.3. Cardiac Rhythm/Conduction Abnormalities Reported as Adverse Events

6.6.5.3.1. Pivotal Control Trials

Overall, cardiac events were infrequent in the epilepsy population. Table 45 summarizes events which could be related to cardiac rhythm/conduction abnormalities, reported in 4% of placebo patients and 5% of ezogabine patients. No dose dependency was observed, with events reported by 5%, 6% and 3% of patients in the 600, 900 and 1200 mg/day groups, respectively (Table 45).

The relative risk of reporting any cardiac rhythm/conduction abnormality in the randomized controlled trials was 1.143 for the Total EZG group, with a 95% confidence interval between 0.65 and 2.01. Relative risk ratios for the 600, 900, and 1200 mg/day groups were 1.25, 1.38, and 0.78, respectively, with the lower bounds of the 95% confidence intervals falling below unity for all doses.

Table 45 Cardiac Rhythm/Conduction Abnormalities Reported in at Least 2 Patients in any Treatment Group (Safety Population: PCT)

	Number (%) of Patients				
Preferred Term	Placebo N=427	Ezogabine			
		600 mg/day N=281	900 mg/day N=273	1200 mg/day N=259	EZG 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

Events of cardiac rhythm/conduction abnormalities were reported sporadically with no clustering in any particular phase of treatment or specific length of exposure. During titration, 7 (2%) patients reported cardiac events in the placebo group versus 20 (3%)

patients in the Total EZG group. During maintenance, another 11 (3%) patients reported cardiac events in were reported in the placebo group versus 17 (3%) in the Total EZG group.

Syncope was reported in 5 patients in the Total EZG group compared with 1 patient in the placebo group. Four of the 5 reported events were reported at doses ranging from 600-900 mg/day. One patient (301-003101) reported syncope in the 1200 mg/day group; the event was reported on Day 34 of the titration phase while the patient was taking 900 mg ezogabine/day and was an SAE; this patient was withdrawn from the study.

An additional report of syncope was reported in a study evaluating the abuse liability of ezogabine in volunteers with a history of recreational drug use. The subject was a 34 year healthy female with a significant history of recreational drug use who became unresponsive approximately 2 hours following a single 900 mg dose of ezogabine; telemetry showed normal sinus rhythm followed by a 25 second period of asystole which resolved spontaneously via a junctional escape rhythm, with full recovery within 5 minutes. Subsequent review of the pharmacokinetic data revealed that the plasma ezogabine and N-acetyl ezogabine concentrations drawn approximately 15 minutes prior to the event were quite low (245 ng/mL and 226 ng/mL, respectively). Earlier in the study the subject had exhibited peak ezogabine and NAMR concentrations of 884 ng/mL and 665 ng/mL after a 600 mg dose without experiencing any similar events.

Serious Adverse Events

There were a total of 4 SAEs related to cardiac rhythm/conduction abnormalities:

- Subject 03003 (Study 301) was a 28 year old female receiving placebo who developed asymptomatic Mobitz 1 atrioventricular block on Day 42 which required placement of a pacemaker.
- Subject 01116 (Study 205) was a 41 year old Caucasian male receiving placebo who had a 7.4 sec ventricular asystole noted on Holter monitor during a complex partial epilepsy seizure. The subject completed the study.
- Subject 03101 (Study 301) was a 36 year old Caucasian female receiving ezogabine 1200 mg qD who experienced a 20-minute loss of consciousness on 02 Jun 2007 (Day 34) followed by confusion for 10 min that was not associated with seizure activity. Blood pressure after the event was 89/61 mm Hg and pulse 65 bpm. The patient experienced several small seizures after transport to the emergency room. CPK-MB was <1 ng/mL and Troponin I 0.01 ng/mL. The patient continued in the study with no actions taken with ezogabine until her withdrawal from the study on 02 Jul 2007 due to events of abnormal behavior and affect lability in addition to the syncope.
- Subject 90514 (Study 302) is a 37 year old Caucasian female receiving ezogabine 600 mg qD was hospitalized for chest pain on 24 Nov 2007 (Day 5) after T wave inversion was noted on her electrocardiogram. Cardiac enzymes were normal and review of previous electrocardiograms showed that the T wave inversion was unchanged since 2005. The patient recovered without treatment and completed the study.

Adverse Events Leading to Withdrawal

Nine patients were withdrawn due to cardiac rhythm/conduction abnormalities ([Table 46](#)). Seven of the nine patients were receiving ezogabine.

Table 46 All Patients Discontinuing Treatment due to Cardiac Rhythm/Conduction Abnormalities (Safety Population: PCT)

Study	Patient ID	Age/Race/Sex	Treatment Group (mg/day) (Actual dose at time of AE)	Preferred Term	Resolved Y/N
Placebo					
301	003003	28/H/F	Placebo	Atrioventricular block	Y With medication and pacemaker implant
302	050507	58/C/M	Placebo	ECG QT corrected interval prolonged	Y Spontaneously
Ezogabine					
302	040906	38/C/F	600 (600)	Palpitations	Y Spontaneously post EZG w/d
302	030102	45/C/M	900 (600)	Palpitations	Y Spontaneously post EZG w/d
205	000585	23/C/M	900 (600)	Tachycardia	Y Spontaneously during EZG w/d
205	001330	27/C/M	900 (600)	ECG ST Segment depression	Y With medication
302	055832	37/C/F	900 (750)	Heart rate irregular	Y Spontaneously post EZG w/d
301	004102	36/C/F	1200 (900)	Palpitations	Y Spontaneously post EZG w/d
301	003101	36/C/F	1200 (857.1)	Syncope	Y With medication prior to EZG w/d

Further details on specific cardiac events are provided below.

Arrhythmias

Eleven patients (1.4%) reported arrhythmia in the Total EZG group compared with 2 (0.4%) patients in the placebo group (Table 47). Sinus bradycardia and heart rate irregular were reported by 2 patients in the 600 and 900 mg/day ezogabine treatment groups; all other events were reported by only 1 patient. Of the 11 patients in the Total EZG group, 1 patient randomized to 600mg/day withdrew due to tachycardia and 1 patient randomized to 900mg/day withdrew due to an irregular heart rate; the patient in whom ventricular extrasystole was reported recovered without withdrawing from the study. Of the 2 patients on placebo who had an arrhythmia, 1 reported ventricular asystole (an SAE for Patient 205-001116) and 1 reported tachycardia.

Table 47 Arrhythmias Reported In At Least 1 Patient In Any Treatment Group (Safety Population: PCT)

Preferred Term	Number (%) of Subjects				
	Placebo N=427	Ezogabine			
		600mg/day N=281	900mg/day N=273	1200mg/day N=259	EZG Total N=813
Sinus Bradycardia	0	2 (0.7)	0	0	2 (0.2)
Heart Rate Irregular	0	0	2 (0.7)	0	2 (0.2)
Arrhythmia	0	1 (0.4)	0	0	1 (0.1)
Bradycardia	0	0	1 (0.4)	0	1 (0.1)
Sinus Tachycardia	0	0	1 (0.4)	0	1 (0.1)
Supraventricular Tachycardia	0	0	1 (0.4)	0	1 (0.1)
Tachycardia	1 (0.2)	0	1 (0.4)	0	1 (0.1)
Ventricular Asystole	1 (0.2)	0	0	0	0
Ventricular Extrasystoles	0	0	1 (0.4)	0	1 (0.1)
Heart Rate Increased	0	0	0	1 (0.4)	1 (0.1)

Conduction Abnormalities and QTc interval

Conduction abnormalities were reported more frequently with placebo (6 events, 1.4%) than in the Total EZG group (2 events, 0.2%) (Table 48). Both events were reported in the 600 mg/day group. Two patients on placebo withdrew from the studies (Patient 301-0030003, with an SAE of atrioventricular block and 302-050507 due to ECG QT corrected interval prolonged) (Table 46). There were no conduction abnormality-related SAEs in ezogabine patients.

Table 48 Conduction Abnormalities Reported In At Least 1 Patient In Any Treatment Group (Safety Population: PCT)

	Number (%) of Subjects				
Preferred Term	Placebo N=427	Ezogabine			
		600mg/day N=281	900mg/day N=273	1200mg/day N=259	EZG 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

6.6.5.3.2. Integrated Clinical Pharmacology Studies

Seven patients were withdrawn from treatment due to a cardiac rhythm/conduction abnormality in the Clinical Pharmacology Safety Population ([Table 49](#)). The events in Patients 107-050006, 108-09077 and 108-09008 were reported as SAEs. A brief narrative for Subject 108-09077 is provided below.

Subject 108-9077 was a 34 year healthy female with a significant history of recreational drug use who became unresponsive approximately 2 hours following a single 900 mg dose of ezogabine; telemetry showed normal sinus rhythm followed by a 25 second period of asystole which resolved spontaneously via a junctional escape rhythm, with full recovery within 5 minutes. Subsequent review of the pharmacokinetic data revealed that the plasma ezogabine and N-acetyl ezogabine concentrations drawn approximately 15 minutes prior to the event were quite low (245 ng/mL and 226 ng/mL, respectively). Earlier in the study the subject had exhibited peak ezogabine and NAMR concentrations of 884 ng/mL and 665 ng/mL after a 600 mg dose without experiencing any similar events.

Table 49 All Patients Discontinuing Treatment Due to Cardiac Rhythm Abnormalities (Clinical Pharmacology Studies)

Study	Patient ID	Age/Race/ Gender	EZG dose (day of treatment for repeat dose study)	Preferred Term	SAE Y/N	Onset from last EZG dose	Resolved (Y/N)
3065A1-100	000001	29/C/M	200 (single dose)	Ventricular extrasystoles	N	15 days	N/A
3065A1-102	080044	27/B/M	300 (Day 10)	Ventricular extrasystoles	N	11 hr	Y Spontaneously post w/d
VRX- RET- E22-106	000004 ¹	48/C/F	200 TID (day 30)	Syncope	N	≈ 17 min after 2 nd dose	Y Spontaneously prior to w/d
3065A1-107	050006	34/C/M	400 BID (day 16)	Chest Discomfort/ Ventricular extrasystoles/ Palpitations	Y	3:40 hours after evening dose	Y Spontaneously prior to w/d
3065A1-107	050008	34/C/M	400 BID (day 15)	Extrasystoles	N	Time N/A after the evening dose	Y Spontaneously prior to w/d
VRX- RET- E22-108	09077	34/C/F	900 (single dose)	Cardiac Arrest/asystole	Y	≈ 2 hr	Y Spontaneously prior to w/d
VRX- RET- E22-108	09008	41/C/M	900 (Single dose)	Ventricular tachycardia	Y	2.5 hr	Y Spontaneously prior to w/d

1. Not recorded by ECG

In patients treated with ezogabine in the Clinical Pharmacology Studies grouping, QTc prolongation was reported for 1 patient (<1%). This event was not serious, and did not result in discontinuation.

A further PK/PD analysis of the relationship between ezogabine concentrations and QTcF values in the healthy volunteer population and Phase II studies in a population of patients with epilepsy indicated there was only a weak positive relationship between ezogabine concentrations and QTcF values that was of similar magnitude to that observed in the Thorough QTc study

6.6.5.3.3. Study VRX-RET-E22-NP201 (Post-Herpetic Neuropathic Pain)

In the post-herpetic neuropathic pain study, in which patients were randomized 2:1 ezogabine: placebo and initiated at 150 mg/day and titrated to a maximally tolerated dose of 900 mg/day, the proportion of patients who reported cardiac disorder TEAEs was 6% in the ezogabine group and 2% in the placebo group (Table 50).

In the ezogabine group, a total of 12 cardiac events were reported in 8 (6%) patients. A total of 4 (3%) TEAEs of atrial fibrillation were reported in the ezogabine group and

none in the placebo group. Two of the atrial fibrillation events were considered TESAEs (Patient 016-002 and Patient 042-008) and one event led to withdrawal (Patient 016-002).

Of the 4 cases of atrial fibrillation reported in this study, 2 patients were male and 2 were female; age range was 73-84 years. One patient had a history of hypertension and another patient had a history of diabetes. One patient was subsequently diagnosed with *Clostridium difficile* colitis, while 2 patients were found to have coronary occlusion and/or left ventricular hypertrophy. The event was considered serious in 2 patients and led to withdrawal of ezogabine in 1 patient.

Table 50 Cardiac Disorder and Vascular Disorder Treatment-Emergent Adverse Events (Study NP201: Safety Population)

Preferred term	Number (%) of patients	
	Ezogabine 150-900 mg (N=125)	Placebo (N=62)
Any cardiac disorder TEAE	8 (6.4)	1 (1.6)
Atrial Fibrillation	4 (3.2)	0 (0.0)
Palpitations	4 (3.2)	1 (1.6)
Angina Pectoris	1 (0.8)	0 (0.0)
Cardiac Failure Acute	1 (0.8)	0 (0.0)
Cardiac Failure Congestive	1 (0.8)	0 (0.0)
Cardiomegaly	1 (0.8)	0 (0.0)

Note: Treatment-emergent adverse events presented in descending order of incidence in the ezogabine 150-900 mg group.

Note: a patient could have reported more than one event.

Brief narratives for the patients with atrial fibrillation are provided below:

- 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 7 November she was admitted with a diagnosis of fast atrial fibrillation. The patient commenced Norvasc (amlodipine) for hypertension approximately one week before presentation (30 October 2008). 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 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 9th October, 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 10 October 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 SAEs.

- **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 4 November, 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 26 November 2008 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.
- **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 16th October (Day 22), 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.

All of these cases occurred in subjects with significant comorbidities.

6.6.5.4. Summary

A review of AE and ECG data (HR and QTc intervals) from the Integrated Clinical Pharmacology and Phase II/III clinical trial databases and studies discussed above does not indicate ezogabine demonstrates major effects on cardiac rhythm/conduction. However, based on the findings from the Thorough QT study (VRX-RET-E22-103) caution should be exercised when ezogabine is prescribed with medicinal products known to increase QT interval and high risk patient groups such as those with congenital long QT syndrome, congestive heart failure, ventricular hypertrophy, hypokalemia or hypomagnesemia.

6.6.6. Hepatic Effects

It has been observed that because the refractive properties of ezogabine are similar to those of bilirubin, both ezogabine and the N-acetyl metabolite interfere with the standard diazo-method bilirubin assays used in routine clinical laboratory serum analysis. It is possible for ezogabine to cause a falsely elevated serum direct bilirubin reading. Investigators have been informed of this potential finding, and there have been no instances of jaundice or seeming confounding of clinical situations because of this potential laboratory interaction.

6.6.6.1. Pivotal Controlled Trials

In the PCTs, 1% of patients in the placebo group compared with 3% of patients in the Total EZG group reported AEs of abnormal hepatic enzymes ([Table 51](#)). In the ezogabine groups, there was a slight dose-related effect for the 'any hepatic enzyme event' term (2%, 3%, and 4% of the 600, 900 and 1200 mg/day groups, respectively).

Among ezogabine groups, the most common liver enzyme abnormality AEs were gamma-glutamyl transferase (GGT) increased (2% of the 900 mg/day group) and alanine aminotransferase (ALT) increased (1% of the 1200 mg/day group). All other liver enzyme abnormality AEs were reported for <1% of patients in any ezogabine dose group.

There did not be a pattern with respect to time of hepatic enzyme AE reporting and few (<1%) were considered SAEs or led to withdrawal.

Table 51 Hepatic Enzyme Adverse Events (Safety Population: PCT)

Preferred Term	Number (%) of Patients				
	Placebo N=427	Ezogabine			
		600mg/day N=281	900mg/day N=273	1200mg/day N=259	Total N=813
Any hepatic enzyme event ¹	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

1. Preferred terms were combined to give an overall incidence for hepatic enzyme events

Adverse events are presented in descending order of the proportion of patients for whom the event was reported in the Total EZG group.

Alk phos = alkaline phosphatase, ALT = alanine aminotransferase, AST = aspartate aminotransferase, GGT= gamma-glutamyl transferase

Clinical chemistry

There was a low incidence (<1% to 3% among ezogabine dose groups) of high values of PCC (>3 x upper limit of normal [ULN]) for aspartate aminotransferase (AST) or ALT, with no clear difference between placebo- and ezogabine-treated groups post-baseline; however, there appeared to be a slightly increased incidence of elevated ALT post-baseline in patients randomized to ezogabine 900 mg/day (Table 52).

When the criterion for PCC for AST and ALT was ≥ 5 x ULN, there was no evidence of a difference between placebo- and ezogabine-treated groups in the incidence of high AST or ALT, and no evidence of a dose relationship. There were no elevations of AST or ALT ≥ 10 x ULN in any group.

As summarized in Table 52, AST ≥ 5 x ULN post baseline was reported in 3 patients receiving ezogabine and none receiving placebo. ALT ≥ 5 x ULN post baseline was reported in 1 patient receiving placebo and in 6 patients receiving ezogabine. Five patients (1 placebo, 4 ezogabine) were withdrawn due to LFT AEs. Mini narratives for all cases of AST or ALT ≥ 5 x ULN are included below. Two patients (301-10511 and 205-0471) had both AST and ALT ≥ 5 x ULN.

In the placebo group:

- Patient 302-50207 was a 58-year-old Caucasian female, taking phenytoin and clonazepam as background AEDs, randomized to placebo. She had an elevated ALT on Day 7 of 321 IU/L (AST was 123 IU/L). The patient was withdrawn from the study due to the serious adverse event of liver function impairment. The patient's transaminases normalized by Day 19.

Among ezogabine-treated patients:

- Patient 301-10511 was a 52-year-old Hispanic female, taking valproic acid and topiramate as background AEDs, randomized to ezogabine 1200 mg/day. She had elevated ALT and AST on Day 49 of 220 IU/L and 180 IU/L, respectively. The patient was withdrawn from the study for the serious adverse event of increased transaminases. Her last dose of ezogabine was on Day 70, and transaminases normalized by Day 79.
- Patient 205-0471, a 54-year-old Caucasian female, taking lamotrigine and carbamazepine as background AEDs, randomized to ezogabine 1200 mg/day. She had elevated ALT of 367 IU/L and AST of 195 IU/L on Day 20 while taking 450 mg/day of ezogabine. A repeat assessment on Day 20 revealed an ALT of 21 IU/L and AST of 15 IU/L and no further follow-up was available. The patient was later withdrawn from the study due to hyperhidrosis and diplopia and her last dose of ezogabine was on Day 34.
- Patient 302-60214 was a 33-year-old Caucasian male, taking valproic acid as a background AED, randomized to ezogabine 900 mg/day. He had elevated AST of 231 IU/L, $\geq 5 \times$ ULN, on Day 14 while taking ezogabine 300 mg/day, which improved to 46 IU/L on Day 28, but then increased again to 300 IU/L on Day 86. The patient was withdrawn from the study due to the adverse event of increased liver enzymes and his last dose of ezogabine was on Day 99. The last available value for AST was 52 IU/L on Day 112.
- Patient 302-25213 was a 49-year-old Caucasian female, taking pregabalin, phenytoin, and clonazepam as background AEDs, randomized to ezogabine 900 mg/day. She had elevated ALT of 188 IU/L on Day 42. The patient was withdrawn from the study due to the adverse event of elevated liver function tests. ALT was 22 IU/L on Day 98.
- Patient 205-0349 was a 37-year-old Caucasian female, taking lamotrigine and carbamazepine as background AEDs, randomized to 900 mg/day ezogabine. She had an elevated ALT of 186 IU/L on Day 46. AST and GGT were also elevated on Day 46 (127 IU/L and 310 IU/L, respectively). The patient later discontinued from the study (and ezogabine) on Day 60 due to the adverse event of diarrhea. The ALT returned to within normal limits by Day 71.
- Patient 205-0448 was a 53-year-old Caucasian female, taking valproic acid and carbamazepine as background AEDs, randomized to 600 mg/day ezogabine. She had an elevated ALT of 193 IU/L on Day 28. The patient was withdrawn from the study due to the serious adverse events of abnormal liver function tests and

renal failure. Here last dose of ezogabine was on Day 32, and ALT decreased to 60 IU/L ten days later.

- Patient 205-1018 was a 40-year-old Caucasian male, taking carbamazepine as a background AED, randomized to 900 mg/day ezogabine. He had an elevated ALT of 185 IU/L on Day 14 and 203 IU/L on Day 43. The patient continued in the study and ALT returned to within normal limits by Day 57.

Total bilirubin values meeting the criterion for PCC post-baseline were observed in 2 placebo-treated and 1 ezogabine-treated patients ([Table 52](#)).

- Patient 205-0351 was a 24 year old Caucasian female, taking carbamazepine and clobazam as background AEDs, randomized to placebo. She had an elevated bilirubin of 45 IU/L on Day 29. The patient continued in the study and bilirubin returned to within normal limits.
- Patient 205-1482 was a 31 year old Caucasian male taking clonazepam and gabapentin as background AEDs, randomized to placebo. He had an elevated bilirubin of 38 IU/L on Day 112. The patient continued into the study 212 and bilirubin returned to within normal limits.
- Patient 205-0248 was a 23 year old Caucasian female, taking carbamazepine and lamotrigine as background AEDs, was randomized to ezogabine 900mg/day. She had an elevated bilirubin of 45 IU/L on Day 29. She continued in the study and bilirubin returned to within normal limits.

There were few alkaline phosphatase values meeting the criterion for high PCC, one in placebo and one the ezogabine 600mg/day group ([Table 52](#)).

It is notable that there were no reports of patients who met criteria for Hy's Law, (AST or ALT > 3 x ULN) AND (ALP < 2 x ULN) AND (Total Bilirubin \geq 2 x ULN).

For information regarding liver function test of PCC in the All Phase II/III grouping refer to Appendix [11.4](#).

Table 52 Liver Function Indices of Potential Clinical Concern (Safety Population: PCT, Studies 205, 301, and 302)

		Percentage of Patients (n/N)				
		Placebo (N=427)	EZG 600 mg/day (N=281)	EZG 900 mg/day (n=273)	EZG 1200 mg/day (N=259)	EZG Total (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)

B=baseline, P-B=post-baseline, ULN=upper limit of normal

6.6.6.2. Study VRX-RET-E22-NP201 (Post-Herpetic Neuropathic Pain)

Few patients met clinically significant criteria for laboratory test results. For ALT, 10 patients receiving ezogabine experienced a result ≥3x ULN compared with 2 patients receiving placebo (Table 53). For AST, 5 patients receiving ezogabine experienced a result ≥3x ULN compared with 1 patient receiving placebo. For total bilirubin, 1 patient receiving ezogabine and 1 patient receiving placebo experienced a result ≥34.2 umol/L.

Of the patients receiving ezogabine that experienced an ALT or AST result ≥3x ULN, no patient demonstrated any evidence of hepatocellular injury, determined by total bilirubin values ≥2x ULN (Hy's Law). The 1 patient in the ezogabine group with clinically significant total bilirubin levels had normal ALT and AST results at all measured timepoints. One placebo-treated patient experienced ALT and AST values ≥3x ULN in addition to elevated bilirubin levels ≥2x ULN at Maintenance Week 4; the patient experienced AEs of fatty liver alcoholic and hepatomegaly shortly after the clinically significant ALT, AST, and bilirubin findings.

Table 53 Summary of Patients with Clinically Significant Liver-related Laboratory Results

Patient No	Treatment	Age	Gender	Visit	Study Day	Value
Clinically Significant ALT ($\geq 3 \times$ ULN)						
007-010	Ezogabine	71 years	Male	Maintenance Week 2	57	129 U/L
016-002	Ezogabine	73 years	Female	Early Termination	23	144 U/L
017-006	Ezogabine	64 years	Male	Titration Week 6	43	131 U/L
021-003	Ezogabine	68 years	Female	Titration Week 6	50	115 U/L
				Maintenance Week 2	57	167 U/L
040-001	Ezogabine	81 years	Female	Maintenance Week 4	71	118 U/L
042-002	Ezogabine	65 years	Female	Titration Week 4	31	245 U/L
				Early Termination	35	349 U/L
				Retest	43	213 U/L
				Retest	51	106 U/L
042-005	Ezogabine	60 years	Male	Maintenance Week 2	44	480 U/L
				Early Termination	46	422 U/L
				Retest	52	278 U/L
				Retest	58	140 U/L
101-009	Ezogabine	48 years	Female	Titration Week 2	15	124 U/L
				Titration Week 4	30	195 U/L
				Retest	36	313 U/L
				Retest	43	207 U/L
				Maintenance Week 2	50	155 U/L
				Taper Week 3	85	139 U/L
103-014	Ezogabine	61 years	Male	Maintenance Week 2	57	187 U/L
105-016	Ezogabine	40 years	Male	Titration Week 6	40	172 U/L
				Maintenance Week 2	55	336 U/L
				Maintenance Week 4	71	280 U/L
				Maintenance Week 4	78	202 U/L
				Retest	84	129 U/L
050-006	Placebo	57 years	Male	Titration Week 6	41	158 U/L
102-011	Placebo	63 years	Male	Maintenance Week 4	71	233 U/L
Clinically Significant AST ($\geq 3 \times$ ULN)						
016-002	Ezogabine	73 years	Female	Early Termination	23	122 U/L
042-002	Ezogabine	65 years	Female	Titration Week 4	31	116 U/L
				Early Termination	35	130 U/L
042-005	Ezogabine	60 years	Male	Maintenance Week 2	44	429 U/L
				Early Termination	46	321 U/L
				Retest	52	201 U/L
				Retest	58	115 U/L
043-003	Ezogabine	52 years	Male	Titration Week 4	28	112 U/L
				Titration Week 4	38	116 U/L
				Titration Week 6	46	120 U/L
105-016	Ezogabine	40 years	Male	Titration Week 6	40	126 U/L
				Maintenance Week 2	55	187 U/L
				Maintenance Week 4	71	150 U/L
				Maintenance Week 4	78	132 U/L
102-011	Placebo	63 years	Male	Maintenance Week 4	71	317 U/L
Clinically Significant Bilirubin (≥ 34.2 umol/L)						
043-006	Ezogabine	50 years	Male	Titration Day 0	1	82 umol/L
				Retest	8	43 umol/L
				Titration Week 2	15	63 umol/L
102-011	Placebo	63 years	Male	Maintenance Week 4	71	86 umol/L

ALT = alanine aminotransferase, AST = aspartate aminotransferase, ULN = upper limit of normal

6.6.7. Speech and Cognitive/Memory Effects

Cognitive and memory preferred terms further categorized as events relating to confusion, memory or processing. The following preferred terms were grouped to assess cognitive and memory events:

- Confusion: Confusion / disorientation / incoherent / confusional state
- Memory: Disturbance in attention / memory impairment / amnesia, /cognitive disorder
- Processing: Bradyphrenia / psychomotor retardation / dyslexia /dyspraxia / dysgraphia

The following terms were grouped to assess speech events:

- Speech disorder / dysarthria / aphasia / dysphemia / dysphasia / dyslalia.

In the PCTs, cognitive events were reported by 22% of patients in the Total EZG group and 8% of patients in the placebo group (Table 54). Memory type cognitive events were the most common and were reported in 14% of patients in the Total EZG group and 5% patients in the placebo group. There was an apparent relationship between AE incidence and randomized ezogabine dose for overall cognitive events in addition to the confusion and memory type of events.

Speech events were reported by 14% of patients in the Total EZG group and 3% of patients in the placebo group. There was an apparent relationship between AE incidence and randomized ezogabine dose for speech events.

A total of 66 of the 180 patients who reported cognitive events in the Total EZG group also reported speech events. Furthermore, 66 of the 115 patients who reported speech events also reported cognitive events. There appeared to be a dose-related trend in the ezogabine groups for patients reporting both speech and cognition-related AEs.

Table 54 Adverse Events Relating to Speech and Cognitive/Memory Effects (Safety Population: PCT)

Preferred Term ^a	Number (%) of Patients				
	Placebo (N=427)	EZG 600mg/day (N=281)	EZG 900mg/day (N=273)	EZG 1200mg/day (N=259)	EZG 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	11 (2.6)	21 (7.5)	32 (11.7)	62 (23.9)	115 (14.1)

a. Preferred terms were combined to give an overall incidence for that grouping

In the PCTs, cognitive events leading to discontinuation were reported by 7% of patients in the Total EZG group and 2% of patients in the placebo group (Table 55). Speech

events leading to discontinuation were reported by 4% of patients in the Total EZG group and 1% of patients in the placebo group.

Table 55 Adverse Events Leading to Discontinuation Relating to Speech and Cognitive/Memory Effects

Preferred Term ^a	Number (%) of Patients				
	Placebo (N=427)	EZG 600mg/day (N=281)	EZG 900mg/day (N=273)	EZG 1200mg/day (N=259)	EZG Total (N=813)
Cognitive events	7 (1.6)	9 (3.2)	17 (6.2)	29 (11.2)	55 (6.8)
Confusion type	6 (1.4)	5 (1.8)	9 (3.3)	22 (8.5)	36 (4.4)
Memory type	1 (0.2)	6 (2.1)	11 (4.0)	11 (4.2)	28 (3.4)
Processing type	0	0	0	2 (0.8)	2 (0.2)
Speech	3 (0.7)	5 (1.8)	13 (4.8)	15 (5.8)	33 (4.1)

a. Preferred terms were combined to give an overall incidence for that grouping

6.6.8. Neutropenia and Severe Infections

A potential safety signal of neutropenia was identified in the toxicity study of dogs in which NAMR was administered. This finding prompted the evaluations of neutropenia and infections in the ezogabine program. Of note, NAMR is not a natural metabolite in this species and FDA had requested a further toxicology study be conducted in rats with NAMR. This study confirmed that hematological changes following NAMR dosing was a dog only finding.

6.6.8.1. Pivotal Controlled Trials

The overall incidence of neutropenia or infection-related AEs of any severity was similar between the placebo and ezogabine groups (both 7%) (Table 56). Although leukopenia was reported at a higher rate in the Total EZG group compared with placebo (1.2% versus 0.5%), there was no dose-relationship and events of neutropenia were more common on placebo than in the Total EZG group (1.2% versus <1%).

The relative risk ratio across all dose groups ranged from 0.7 to 1.5, and the 95% CI included 1 in all groups. No pattern of time to first occurrence was evident in any treatment group. For the ‘any event’ category related to neutropenia or infection there did not appear to be a consistent relationship to dose although there appeared to be a possible dose effect among the ezogabine groups for UTI (1.8% of the 600 mg/day group, 3.3% of the 900 mg/day group, and 8.1% of the 1200mg/day group). As discussed earlier, UTIs were diagnosed based on the patient’s signs and symptoms or, in some cases, on dipstick urinalysis results only.

Table 56 Neutropenia or Infection Related Adverse Events (Safety Population: PCT)

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 event	30 (7.0)	14 (5.0)	13 (4.8)	28 (10.8)	55 (6.8)
Infection events					
Urinary tract infection	20 (4.7)	5 (1.8)	9 (3.3)	21 (8.1)	35 (4.3)
Bacteriuria	1 (0.2)	2 (0.7)	1 (0.4)	0	3 (0.4)
Pneumonia	0	1 (0.4)	0	2 (0.8)	3 (0.4)
Cystitis	1 (0.2)	1 (0.4)	0	1 (0.4)	2 (0.2)
Bronchopneumonia	0	1 (0.4)	0	0	1 (0.1)
Lobar pneumonia	0	0	1 (0.4)	0	1 (0.1)
Sepsis	0	1 (0.4)	0	0	1 (0.1)
Blood and Lymphatic events					
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
Investigations					
Bacteria urine	0	0	1 (0.4)	0	1 (0.1)
Bacteria urine identified	1 (0.2)	0	0	1 (0.4)	1 (0.1)
Hematology test abnormal	0	0	0	1 (<1)	1 (0.1)
Laboratory test abnormal	0	0	1 (0.4)	0	1 (0.1)
White blood cell count increased	0	1 (0.4)	0	0	1 (0.1)

6.6.9. Gall Bladder Effects

Gall bladder effects were seen in dogs due to the pharmacological action of ezogabine. In the PCTs, similar numbers of patients reported abnormalities of gall bladder function in the Total EZG and placebo groups ([Table 57](#)). 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 had an SAE of biliary colic.

Table 57 Hepatobiliary Abnormalities Reported In Any Treatment Group (Safety Population: PCT)

Preferred Term	Number (%) of Patients				
	Placebo N=427	Ezogabine			
		600mg/day N=281	900mg/day N=273	1200mg/day N=259	EZG Total N=813
Cholecystectomy	1 (0.2)	0	0	0	0
Cholecystitis	3 (0.7)	1 (0.4)	0	0	1 (0.1)
Hyperbilirubinemia	0	0	0	1 (0.4)	1 (0.1)
Jaundice	0	0	0	1 (0.4)	1 (0.1)
Biliary colic	0	0	0	1 (0.4)	1 (0.1)
Hepatic function abnormal	1 (0.2)	1 (0.4)	0	0	1 (0.1)

Within the All Phase II/III Combined data set a similarly low number of events were identified ([Table 58](#)).

Table 58 Hepatobiliary Abnormalities Reported (Safety Population: All Phase II/III Combined)

Preferred Term	Number (%) of Patients	
	EZG (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)	

Seven subjects reported SAEs 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.

One SAE of biliary colic was reported after 30th June 2008 in a patient taking ezogabine 900 mg.

6.7. Common Adverse Events in Epilepsy Clinical Trials

6.7.1. Pivotal Controlled Trials

6.7.1.1. Overall Incidence of AEs by Randomized Dose

The safety profile of ezogabine was consistent with the pre-clinical pharmacology of the compound and did not differ significantly across the various studies in the clinical development program for epilepsy. The AEs seen with ezogabine during the PCTs are generally consistent with those reported for other drugs in the AED class.

[Table 59](#) presents the TEAEs from the PCTs reported by $\geq 5\%$ of patients in any randomized treatment group.

In the Total EZG 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 EZG group (15% each). Among these 4 TEAEs, a greater proportion of patients in the Total EZG 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 EZG and placebo groups (15% and 16%, respectively).

Among the most common events, there were 4 TEAEs with a treatment difference $\geq 5\%$ for patients in each of the 3 ezogabine dose groups compared with placebo: dizziness, fatigue, vertigo, and disturbance in attention.

A TEAE was considered to be dose-related if the incidence was greater in the Total EZG group than in the placebo group and the incidence increased with each increasing ezogabine randomized dose. Among all events in [Table 59](#), there was an apparent relationship between AE incidences and randomized ezogabine dose for the following: 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.

Table 59 Adverse Events Reported by Greater than or equal to 5% of Patients in Any Treatment Group by Preferred Term (Safety Population: PCT, Studies 205, 301, and 302)

Preferred Term	Number (%) of Patients				
	Placebo (N=427)	EZG 600 mg/day (N=281)	EZG 900 mg/day (N=273)	EZG 1200 mg/day (N=259)	EZG Total (N=813)
Any event	318 (74.5)	207 (73.7)	223 (81.7)	227 (87.6)	657 (80.8)
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 (22.0)
Headache	68 (15.9)	34 (12.1)	47 (17.2)	39 (15.1)	120 (14.8)
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)
Vision blurred	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)
Speech disorder	4 (<1.0)	5 (1.8)	14 (5.1)	18 (6.9)	37 (4.6)
Dysarthria	3 (<1.0)	10 (3.6)	5 (1.8)	21 (8.1)	36 (4.4)
Urinary tract infection	20 (4.7)	5 (1.8)	9 (3.3)	21 (8.1)	35 (4.3)
Gait disturbance	5 (1.2)	6 (2.1)	13 (4.8)	15 (5.8)	34 (4.2)
Convulsion	19 (4.4)	6 (2.1)	9 (3.3)	16 (6.2)	31 (3.8)
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)	25 (3.1)

Table 60 displays the TEAEs with an incidence $\geq 2\%$ in any of the 600, 900, or 1200 mg/day groups and numerically greater than placebo in the Pivotal Controlled Trials grouping that were selected as adverse drug reactions (ADRs). This table of ADRs has been incorporated into the proposed product labeling for ezogabine.

Table 60 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: PCT, Studies 205, 301 and 302)

Preferred Term	Number (%) of Patients			
	Placebo (N=427)	EZG 600 mg/day (N=281)	EZG 900 mg/day (N=273)	EZG 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)

Medical judgment regarding possible pharmacologic association with ezogabine was applied.

6.7.2. Adverse Events by Study Phase

In the Pivotal Controlled Trials, the ezogabine dose was titrated, beginning with 300 mg/day and increasing weekly by 150 mg/day. Thus, patients reached a target dose of 600 mg/day after completing 2 weeks, a target dose of 900 mg/day after 4 weeks, and a target dose of 1200 mg/day after 6 weeks of titration. The titration phase of Study 302 was 4 weeks (placebo, 600 mg/day, and 900 mg/day groups); for Studies 205 and 301, it was 6 weeks (placebo and 1200 mg/day groups). The maintenance phase was 8 weeks for Study 205 and 12 weeks in Studies 301 and 302.

[Table 61](#) summarizes incidences of the most common TEAEs overall ($\geq 5\%$ in any treatment group) by study phase (titration or maintenance). In this analysis, only new events were counted for each phase. That is, if an event started during the titration phase and continued into the maintenance phase, it was only counted under titration; if an event started during the titration phase, resolved, and was reported again during the maintenance phase, it was counted under both phases.

During the titration phase of the Pivotal Controlled Trials, the incidence of any TEAE increased in a dose-related manner (58%, 62%, 70%, and 82% of the placebo, 600 mg/day, 900 mg/day, and 1200 mg/day groups, respectively) ([Table 61](#)). In contrast, during the maintenance phase, the incidence of TEAEs was comparable in the placebo and ezogabine 600 and 900 mg/day groups and higher only in the 1200 mg/day group: 58%, 55%, 56%, and 72%, respectively.

During the maintenance phase when patients had reached their randomized dose, an apparent dose relationship was observed for dizziness, confusional state, tremor, coordination abnormal, memory impairment, aphasia, and constipation, confirming results in the overall analysis. In addition, a dose-response relationship was observed for dysarthria during the maintenance phase of the study, although not in the overall analysis.

In both study phases, the most frequently reported TEAEs for the Total EZG group were dizziness, somnolence, headache, and fatigue, but the incidences were higher during the titration phase than during the maintenance phase for all treatment groups (placebo and all ezogabine doses).

For all of the most common TEAEs (reported in $\geq 5\%$ of patients in any treatment group), the incidences tended to be higher during the titration phase than in the maintenance phase in all treatment groups, including placebo.

The following TEAEs were observed at similar incidences in the titration and maintenance phases in the placebo group but at 2- to 3-fold greater incidences in the titration phase versus maintenance phase in the Total EZG group: dizziness (19.2% titration vs. 9.4% maintenance); vertigo (6.8% vs. 2.6%); coordination abnormal (5.5% vs. 2.6%); disturbance in attention (4.8% vs. 2.0%); asthenia (3.7% vs. 1.5%); speech disorder (3.8% vs. 1.4%); dysarthria (3.6% vs. 1.5%); and paraesthesia (2.3% vs. 0.9%).

Urinary tract infection was the only common TEAE observed at a greater incidence in the maintenance phase than in the titration phase in the Total EZG group; however, the incidence of urinary tract infection was also higher in the placebo group in the maintenance phase (3.1 vs 1.6%)

Table 61 Most Commonly Reported (Greater than or equal to 5% of Patients in any Treatment Group) TEAEs by Titration and Maintenance Phases (Safety Population: PCT, Studies 205, 301, and 302)

		Number (%) of Patients				
Preferred Term	Phase	Placebo T: N=427 M: N=383	EZG 600 mg/day T: N=281 M: N=243	EZG 900 mg/day T: N=273 M: 226	EZG 1200 mg/day T: N=259 M: N=189	EZG Total T: N=813 M: N=658
Any event	T	248 (58.1)	173 (61.6)	190 (69.6)	212 (81.9)	575 (70.7)
	M	222 (58.0)	134 (55.1)	127 (56.2)	136 (72.0)	397 (60.3)
Dizziness	T	23 (5.4)	33 (11.7)	52 (19.0)	71 (27.4)	156 (19.2)
	M	17 (4.4)	14 (5.8)	21 (9.3)	27 (14.3)	62 (9.4)
Somnolence	T	38 (8.9)	35 (12.5)	54 (19.8)	65 (25.1)	154 (18.9)
	M	17 (4.4)	11 (4.5)	18 (8.0)	11 (5.8)	40 (6.1)
Headache	T	45 (10.5)	28 (10.0)	30 (11.0)	31 (12.0)	89 (10.9)
	M	35 (9.1)	12 (4.9)	19 (8.4)	13 (6.9)	44 (6.7)
Fatigue	T	22 (5.2)	37 (13.2)	30 (11.0)	28 (10.8)	95 (11.7)
	M	5 (1.3)	13 (5.3)	11 (4.9)	7 (3.7)	31 (4.7)
Confusional state	T	9 (2.1)	9 (3.2)	17 (6.2)	37 (14.3)	63 (7.7)
	M	2 (<1.0)	4 (1.6)	5 (2.2)	7 (3.7)	16 (2.4)
Vertigo	T	5 (1.2)	17 (6.0)	17 (6.2)	21 (8.1)	55 (6.8)
	M	4 (1.0)	6 (2.5)	5 (2.2)	6 (3.2)	17 (2.6)
Tremor	T	6 (1.4)	6 (2.1)	17 (6.2)	20 (7.7)	43 (5.3)
	M	6 (1.6)	2 (<1.0)	11 (4.9)	12 (6.3)	25 (3.8)
Coordination abnormal	T	7 (1.6)	12 (4.3)	13 (4.8)	20 (7.7)	45 (5.5)
	M	5 (1.3)	4 (1.6)	3 (1.3)	10 (5.3)	17 (2.6)
Nausea	T	18 (4.2)	12 (4.3)	14 (5.1)	18 (6.9)	44 (5.4)
	M	6 (1.6)	6 (2.5)	4 (1.8)	3 (1.6)	13 (2.0)
Diplopia	T	3 (<1.0)	16 (5.7)	9 (3.3)	16 (6.2)	41 (5.0)
	M	5 (1.3)	12 (4.9)	8 (3.5)	4 (2.1)	24 (3.6)
Disturbance in attention	T	2 (<1.0)	12 (4.3)	11 (4.0)	16 (6.2)	39 (4.8)
	M	2 (<1.0)	7 (2.9)	4 (1.8)	2 (1.1)	13 (2.0)
Memory impairment	T	6 (1.4)	3 (1.1)	9 (3.3)	18 (6.9)	30 (3.7)
	M	6 (1.6)	3 (1.2)	7 (3.1)	8 (4.2)	18 (2.7)
Vision blurred	T	6 (1.4)	3 (1.1)	11 (4.0)	19 (7.3)	33 (4.1)
	M	4 (1.0)	3 (1.2)	1 (<1.0)	9 (4.8)	13 (2.0)
Asthenia	T	4 (<1.0)	7 (2.5)	13 (4.8)	10 (3.9)	30 (3.7)
	M	4 (1.0)	4 (1.6)	5 (2.2)	1 (<1.0)	10 (1.5)
Speech disorder	T	2 (<1.0)	3 (1.1)	13 (4.8)	15 (5.8)	31 (3.8)
	M	2 (<1.0)	2 (<1.0)	1 (<1.0)	6 (3.2)	9 (1.4)
Dysarthria	T	2 (<1.0)	9 (3.2)	4 (1.5)	16 (6.2)	29 (3.6)
	M	1 (<1.0)	1 (<1.0)	3 (1.3)	6 (3.2)	10 (1.5)
Urinary tract infection	T	7 (1.6)	2 (<1.0)	4 (1.5)	11 (4.2)	17 (2.1)
	M	12 (3.1)	2 (<1.0)	4 (1.8)	15 (7.9)	21 (3.2)
Gait disturbance	T	2 (<1.0)	5 (1.8)	7 (2.6)	11 (4.2)	23 (2.8)
	M	3 (<1.0)	2 (<1.0)	5 (2.2)	4 (2.1)	11 (1.7)
Convulsion	T	14 (3.3)	3 (1.1)	6 (2.2)	12 (4.6)	21 (2.6)
	M	6 (1.6)	3 (1.2)	3 (1.3)	4 (2.1)	10 (1.5)
Aphasia	T	4 (<1.0)	2 (<1.0)	5 (1.8)	14 (5.4)	21 (2.6)
	M	1 (<1.0)	1 (<1.0)	4 (1.8)	4 (2.1)	9 (1.4)
Balance disorder	T	2 (<1.0)	6 (2.1)	5 (1.8)	9 (3.5)	20 (2.5)
	M	1 (<1.0)	4 (1.6)	3 (1.3)	5 (2.6)	12 (1.8)
Constipation	T	3 (<1.0)	4 (1.4)	8 (2.9)	6 (2.3)	18 (2.2)
	M	3 (<1.0)	0	3 (1.3)	7 (3.7)	10 (1.5)

		Number (%) of Patients				
Preferred Term	Phase	Placebo T: N=427 M: N=383	EZG 600 mg/day T: N=281 M: N=243	EZG 900 mg/day T: N=273 M: 226	EZG 1200 mg/day T: N=259 M: N=189	EZG Total T: N=813 M: N=658
Paraesthesia	T	5 (1.2)	5 (1.8)	3 (1.1)	11 (4.2)	19 (2.3)
	M	6 (1.6)	3 (1.2)	1 (<1.0)	2 (1.1)	6 (<1.0)

M=maintenance phase; T=titration phase

Note: Common events were defined as events that were reported in at least 5% of patients in any treatment group.

The same patient could report more than one episode of the same adverse event and therefore potentially may be counted in both the titration and maintenance phases.

6.7.3. Adverse Events by Time to First Occurrence

The incidence of TEAEs by time to first occurrence was evaluated in the 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 62). A similar pattern was observed for the most common AEs (Table 63).

Table 62 Overall Incidence of TEAEs by Time to First Occurrence (Safety Population: PCT, Studies 205, 301, and 302)

Time to First Occurrence (Days/Weeks)	n/N (%) of Patients				
	Placebo	EZG 600 mg/day	EZG 900 mg/day	EZG 1200 mg/day	EZG 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

Note: The denominator (N) is the number of patients in the Safety Population in the study during the time category.

Table 63 Common Adverse Events (at Least 10% in any Treatment Group) by Time to First Occurrence (Safety Population: PCT, Studies 205, 301, and 302)

Treatment Group/Preferred Term	Number (%) of Patients					
	Days					
	1 to <8	8 to <14	14 to <28	28 to <56	56 to <84	84 to <182
Placebo, N=427						
N ¹	427	418	411	406	384	366
Dizziness	8 (1.9)	6 (1.4)	6 (1.5)	10 (2.5)	1 (<1.0)	7 (1.9)
Somnolence	18 (4.2)	6 (1.4)	9 (2.2)	9 (2.2)	6 (1.6)	3 (<1.0)
Headache	15 (3.5)	7 (1.7)	16 (3.9)	14 (3.4)	8 (2.1)	8 (2.2)
Fatigue	7 (1.6)	2 (<1.0)	7 (1.7)	7 (1.7)	0	2 (<1.0)
Confusional state	3 (<1.0)	0	2 (<1.0)	4 (1.0)	2 (<1.0)	0
Tremor	2 (<1.0)	0	3 (<1.0)	2 (<1.0)	2 (<1.0)	3 (<1.0)
Coordination abnormal	2 (<1.0)	2 (<1.0)	2 (<1.0)	4 (1.0)	0	2 (<1.0)
Vision blurred	3 (<1.0)	0	2 (<1.0)	1 (<1.0)	2 (<1.0)	1 (<1.0)
EZG 600 mg/day, N=281						
N ¹	281	274	270	263	237	226
Dizziness	13 (4.6)	3 (1.1)	16 (5.9)	4 (1.5)	1 (<1.0)	4 (1.8)
Somnolence	14 (5.0)	5 (1.8)	14 (5.2)	5 (1.9)	1 (<1.0)	4 (1.8)
Headache	8 (2.8)	6 (2.2)	11 (4.1)	5 (1.9)	1 (<1.0)	3 (1.3)
Fatigue	22 (7.8)	7 (2.6)	6 (2.2)	6 (2.3)	3 (1.3)	1 (<1.0)
Confusional state	3 (1.1)	1 (<1.0)	5 (1.9)	1 (<1.0)	1 (<1.0)	1 (<1.0)
Tremor	1 (<1.0)	1 (<1.0)	3 (1.1)	2 (<1.0)	0	0
Coordination abnormal	4 (1.4)	3 (1.1)	4 (1.5)	3 (1.1)	0	0
Vision blurred	0	1 (1.4)	1 (<1.0)	2 (<1.0)	1 (<1.0)	0
EZG 900 mg/day, N=273						
N ¹	273	265	262	246	218	205
Dizziness	15 (5.5)	9 (3.4)	22 (8.4)	14 (5.7)	2 (<1.0)	2 (1.0)
Somnolence	17 (6.2)	4 (1.5)	25 (9.5)	16 (6.5)	5 (2.3)	0
Headache	13 (4.8)	4 (1.5)	11 (4.2)	7 (2.8)	7 (3.2)	5 (2.4)
Fatigue	11 (4.0)	5 (1.9)	11 (4.2)	7 (2.8)	5 (2.3)	1 (<1.0)
Confusional state	2 (<1.0)	0	10 (3.8)	5 (2.0)	3 (1.4)	1 (<1.0)
Tremor	1 (<1.0)	2 (<1.0)	8 (3.1)	7 (2.8)	3 (1.4)	5 (2.4)
Coordination abnormal	2 (<1.0)	2 (<1.0)	6 (2.3)	4 (1.6)	0	0
Vision blurred	2 (<1.0)	0	6 (2.3)	4 (1.6)	0	0
EZG 1200 mg/day, N=259						
N ¹	259	254	249	237	194	172
Dizziness	13 (5.0)	9 (3.5)	25 (10.0)	31 (13.1)	4 (2.1)	2 (1.2)
Somnolence	15 (5.8)	6 (2.4)	21 (8.4)	24 (10.1)	3 (1.5)	0
Headache	5 (1.9)	3 (1.2)	12 (4.8)	12 (5.1)	6 (3.1)	1 (<1.0)
Fatigue	8 (3.1)	4 (1.6)	9 (3.6)	8 (3.4)	5 (2.6)	0
Confusional state	5 (1.9)	2 (<1.0)	13 (5.2)	20 (8.4)	0	2 (1.2)
Tremor	6 (2.3)	0	5 (2.0)	12 (5.1)	4 (2.1)	5 (2.9)
Coordination abnormal	4 (1.5)	1 (<1.0)	6 (2.4)	15 (6.3)	2 (1.0)	2 (1.2)
Vision blurred	3 (1.2)	1 (<1.0)	11 (4.4)	9 (3.8)	2 (1.0)	1 (<1.0)

Treatment Group/Preferred Term	Number (%) of Patients					
	Days					
	1 to <8	8 to <14	14 to <28	28 to <56	56 to <84	84 to <182
EZG Total, N=813						
N ¹	813	793	781	746	649	603
Dizziness	41 (5.0)	21 (2.6)	63 (8.1)	49 (6.6)	7 (1.1)	8 (1.3)
Somnolence	46 (5.7)	15 (1.9)	60 (7.7)	45 (6.0)	9 (1.4)	4 (<1.0)
Headache	26 (3.2)	13 (1.6)	34 (4.4)	24 (3.2)	14 (2.2)	9 (1.5)
Fatigue	41 (5.0)	16 (2.0)	26 (3.3)	21 (2.8)	13 (2.0)	2 (<1.0)
Confusional state	10 (1.2)	3 (<1.0)	28 (3.6)	26 (3.5)	4 (<1.0)	4 (<1.0)
Tremor	8 (1.0)	3 (<1.0)	16 (2.0)	21 (2.8)	7 (1.1)	10 (1.7)
Coordination abnormal	10 (1.2)	6 (<1.0)	16 (2.0)	22 (2.9)	2 (<1.0)	2 (<1.0)
Vision blurred	5 (<1.0)	2 (<1.0)	18 (2.3)	15 (2.0)	3 (<1.0)	1 (<1.0)

Note: Common events were defined as events that were reported in at least 10% of patients in any treatment group.

1. The denominator (N) for the AE is the number of patients in the Safety Population in the study during the time category.

6.7.4. Adverse Events in Population Subgroups

6.7.4.1. Age

Experience with ezogabine in elderly patients (≥ 65 years) with epilepsy was limited and included only 8 patients receiving ezogabine in the PCTs (2 additional patients received placebo). However, the mean age of patients in Study NP201 was higher (63 yrs of age) than that for the epilepsy trials (~ 37 yrs of age) and provides information regarding the safety of ezogabine in elderly patients, despite the different indication.

In Study NP201, TEAE data were analyzed according to the age groups ≥ 65 years (age range 65-84 years; median 73 years) and less than 65 years (age range 22-64; median 55 years). The data were reviewed with emphasis on the events of special interest that were identified in previous studies of ezogabine in epileptic patients in order to determine whether the TEAE rate from the study was disproportionately higher for older patients and, as such, might represent a need for additional caution in prescribing to this age group. Events related to an older population focused on common central nervous system-related events (particularly related to dizziness, cognitive function, and psychiatric), cardiac, and urinary disorders.

The data indicate that patients < 65 or ≥ 65 years of age reported a similar incidence of TEAEs with 91% and 89% of patients, respectively, reporting at least one TEAE (Table 64). Of the 5 most commonly reported AEs; dizziness, headache, nausea and fatigue were all more frequently reported by the younger than the older group. Psychiatric disorders, particularly confusional state, disorientation and hallucinations were also more commonly reported by patients < 65 years of age.

Events reported more frequently by patients ≥ 65 years of age, included somnolence, memory impairment, atrial fibrillation, amnesia, urinary retention, and speech disorder.

Of the 4 patients who reported urinary retention in the ezogabine group, 3 were over the age of 65 years (range 69-76 years) and 3 were male. EZG dose at time of onset ranged

from 450-600mg/day and onset of symptoms ranged from 14-36 days after initiation of treatment. None of the events met the definition of an SAE; one patient withdrew from the study due to urinary retention. The event resolved in all patients.

Table 64 AEs by Age (less than 65 years or at Least 65 years of age) for All Phases (Safety Population: Study NP201)

Adverse Event	Number (%) of Patients			
	Age <65		Age ≥65	
	Placebo N=34	EZG (N=64)	Placebo N=28	EZG (N=61)
Any event		58 (90.6)		54 (88.5)
Dizziness	6 (17.6)	26 (40.6)	2 (7.1)	19 (31.1)
Somnolence	4 (11.8)	18 (28.1)	3 (10.7)	23 (37.7)
Headache	2 (5.9)	13 (20.3)	6 (21.4)	10 (16.4)
Nausea	2 (5.9)	9 (14.1)	1 (3.6)	6 (9.8)
Fatigue	0	7 (10.9)	0	6 (9.8)
Memory Impairment	0	3 (4.7)	0	6 (9.8)
Confusional state	0	5 (7.8)	1 (3.6)	4 (6.6)
Atrial fibrillation	0	0	0	4 (6.6)
Amnesia	0	3 (4.7)	0	4 (6.6)
Disorientation	0	4 (6.3)	1 (3.6)	2 (3.3)
Tremor	1 (2.9)	0	0	3 (4.9)
Urinary Retention	0	1 (1.6)	1 (3.6)	3 (4.9)
Balance disorder	0	2 (3.1)	0	4 (6.6)
UTI	3 (8.8)	3 (4.7)	1 (3.6)	5 (8.2)
Palpitations	1 (2.9)	3 (4.7)	0	1 (1.6)
Hallucinations	0	3 (4.7)	0	0
Speech Disorder	0	0	0	2 (3.3)

The data from Study NP201 did not appear to demonstrate that elderly patients experience more CNS TEAEs during epileptic drug treatment than younger patients. Overall, the TEAE profile was similar between the age groups and do not indicate any specific concern about using ezogabine for elderly patients with epilepsy. However, due to age-related decreases in renal and cardiac function, as well as potential bladder outlet obstruction, patients over 65 years of age may be at increased risk for urinary and cardiac events reported with ezogabine, as noted by the greater incidence of urinary retention/urinary tract infections (UTIs) and atrial fibrillation noted in the subjects 65 years of age and older (see Section 6.6.1 for a discussion of urinary events and Section 6.6.5 for a discussion of cardiac events).

6.7.4.2. Gender

The overall adverse reaction profile of ezogabine was similar between females and males but AEs were more frequent in females. Across the PCT grouping, 77% of males (305 of 394) and 84% of females (352 of 419) reported AEs. However, tremor was more commonly reported by males at 1200 mg/day (16% of males, 9% of females). Most of the common TEAEs, other than headache and fatigue, were dose-proportional within either gender. There is a suggestion of a lower dose threshold in females for TEAEs of confusional state and vertigo, as the incidence of these events is higher for females than

males at 600mg/day (7% females vs <1% males for confusional state; 10% females vs 5% males for vertigo). However, the absolute numbers of patients reporting these TEAEs are small.

An approximately 1.5-fold or greater difference when comparing the most common TEAEs in the Total EZG group for females to males was reported for memory impairment (8% versus 4%, respectively), and disturbance in attention (7% versus 5%, respectively).

6.8. Pregnancies

To date, 13 pregnancies have been reported in the epilepsy program. Ten were in female patients exposed to ezogabine, and 3 in the female partners of male patients exposed to ezogabine. Of the 10 female patients, 5 elected to terminate their pregnancies, and 4 patients delivered healthy infants.

The remaining patient, a 21 year old African American female, delivered a premature male infant with a patent ductus arteriosus and polydactyly at approximately 28-weeks gestation. 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.

All 3 pregnancies in the female partners of male patients resulted in normal births.

There are no adequate and well-controlled studies with ezogabine in pregnant women and ezogabine should be used during pregnancy only if the potential benefit justifies the potential risk to the fetus. Based on this and the results of teratogenicity studies, it is proposed that ezogabine be classified as Pregnancy Category C.

6.9. Overdose

There is limited experience of overdose with ezogabine. Total daily doses of ezogabine over 2,500 mg were reported during clinical trials. In addition to adverse reactions seen at

therapeutic doses, symptoms reported with ezogabine overdose included agitation, aggressive behavior, and irritability. There were no reported sequelae. No deaths that resulted from an overdose with ezogabine were reported in the clinical trials. A total of 6/1365 (0.4%) patients were determined to have had an overdose of ezogabine. Coma was reported in a patient who ingested ezogabine as part of a multi-drug overdose. The multi-drug overdose included the AEDs valproic acid, topiramate and clozapine. The patient also tested positive for marijuana and tricyclics.

6.10. Post-Marketing Experience

Ezogabine is not marketed in any country in the world. All safety data included in this submission are from clinical studies conducted with ezogabine.

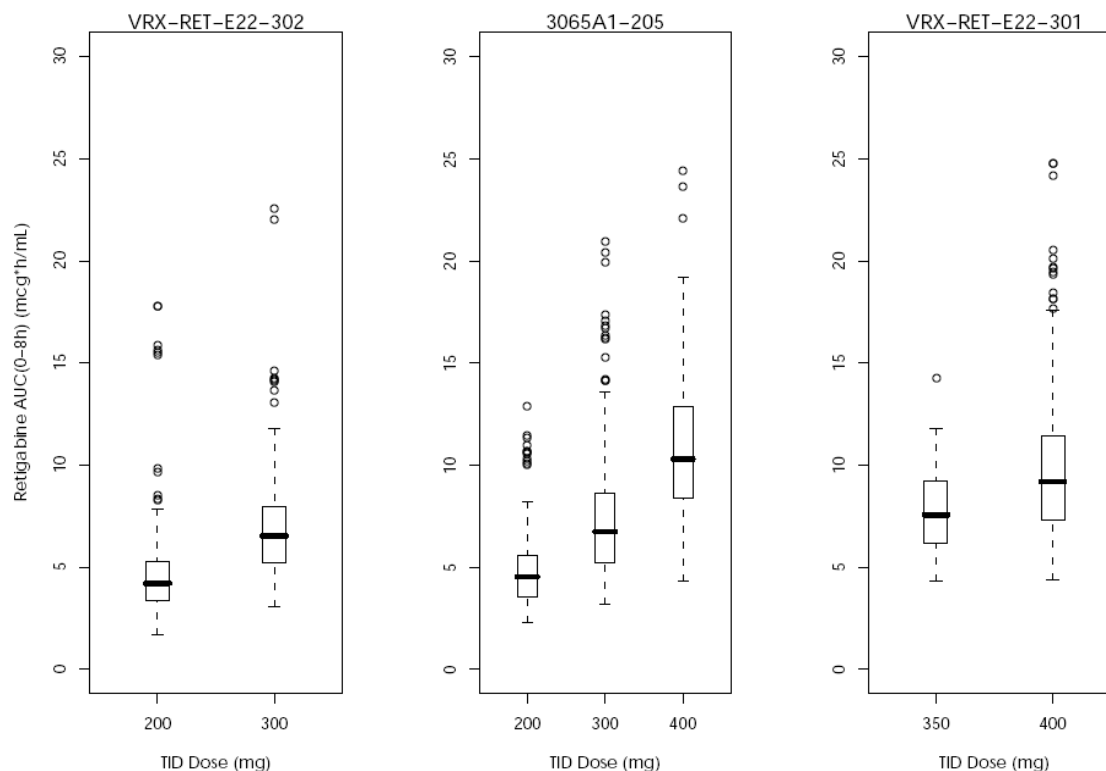
7. EPILEPSY PATIENT POPULATION EXPOSURE-RESPONSE RELATIONSHIP (EFFICACY AND SAFETY)

Epilepsy Patient Population Modeling of Efficacy and Adverse Events

Population exposure-response modeling was conducted from data collected in the epilepsy patients that participated in Studies 301 and 302 in order to evaluate the relationship between predicted ezogabine steady-state systemic exposure (area under the curve over the dosing interval (AUC(0-8h))) and key efficacy / safety endpoints. A total of 345 ezogabine-treated and 302 placebo-treated patients were included in the exposure-response analyses.

Exposure data from the three pivotal clinical studies demonstrate separation of the interquartile range between 200 mg, 300 mg and 400 mg TID doses and as expected, some overlap in the individual predicted AUC(0-8h) values between dose levels ([Figure 11](#)) whereby, for example, some patients receiving 900 mg/day had higher AUC(0-8h) values than other subjects receiving 1200 mg/day.

Figure 11 Whisker Plot of Predicted AUC(0-8h) Values for Ezogabine by Dose in Studies 205, 301 and 302



These exposure data (including placebo) when modeled with the efficacy and safety data showed that the percent reduction from baseline in total partial seizure frequency ranged from approximately 15 to 20% at zero AUC(0-8h) (i.e., placebo) to a maximum of 56% reduction from baseline in total partial seizure frequency at an AUC(0-8h) value which approximates to the median AUC(0-8h) associated with the 1200 mg/day dose. The AUC(0-8h) associated with 50% of the maximum response corresponds approximately to the median AUC(0-8h) observed for the dose of 900 mg/day.

Additional exposure-response analyses were conducted to investigate the relationship between AUC(0-8h) and the probability of efficacy ($\geq 50\%$ reduction from baseline in total partial seizure frequency) and the probability of occurrence of AEs.

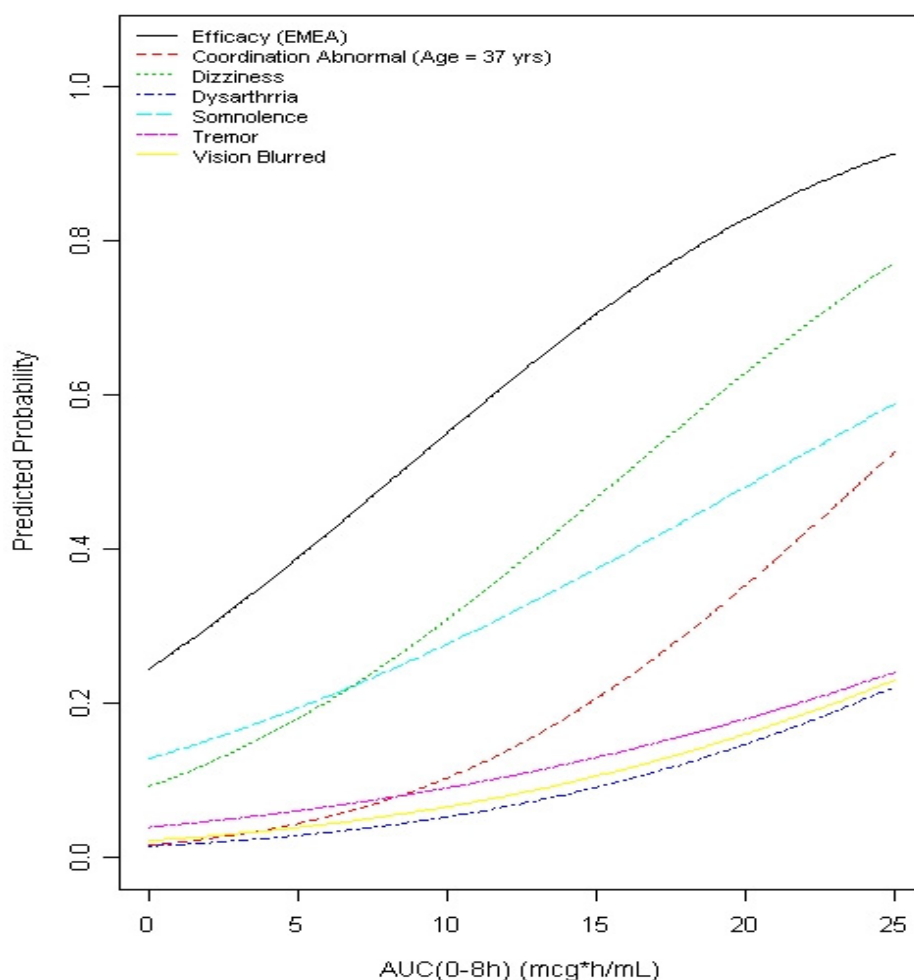
This analysis showed that over the entire AUC(0-8h) range observed in Studies 301 and 302, the probability of $>50\%$ decrease from baseline in seizure frequency was higher than the probability of any of the AE occurring. The slope of the exposure-response relationship for probability of efficacy was 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 12).

A summary of the predicted response by dose level from the analyses for efficacy and safety endpoints from Studies 301 and 302 is shown in Table 65.

Table 65 **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(0-8h) (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

Figure 12 **Probability of Efficacy ($\geq 50\%$ reduction in seizure frequency) and Adverse Events versus Ezogabine AUC(0-r)**



Overall the predictions from the analysis corroborates that efficacy increases with increasing dose over the dose range 600 to 1200 mg/day ([Table 65](#)). The results from the exposure-response analyses provide evidence for increasing efficacy through doses up to 1200 mg/day.

The moderate overlap, outside the interquartile range, in predicted exposure between doses of 600 mg/day to 1200 mg/day ([Figure 11](#)) highlight the need to dose titrate ezogabine based upon individual patient response for efficacy and tolerability/safety. Furthermore, although the probability of efficacy increases with increasing exposure, a clear threshold in ezogabine systemic exposure was not identified below which adverse events were predicted not to occur or above which efficacy was likely to occur. Dosing for a specific patient must be guided by their individual therapeutic response and individual tolerability.

8. POST-MARKETING RISK MANAGEMENT PLAN

8.1. Objectives for RMP

The goal of risk management for ezogabine is to minimize the occurrence and severity of identified adverse events, particularly those associated with urinary retention and to continue assessment of possible risks in the post marketing setting.

The table below summarizes the potential risks that have been identified during clinical and nonclinical studies and provides the focus for post marketing activities.

Table 66 Potential Risks of Interest

Risk	Assessed in clinical program	AEs Identified in clinical program	Planned Pharmacovigilance		Communication Plan	
			Routine ¹	Enhanced	Labelling	Enhanced
Suicidality	Yes	No	✓	✓	✓	✓
Urinary retention	Yes	Yes	✓	✓	✓	✓
QT effects	Yes	No	✓	✓	✓	✓
Neuropsychiatric effects	Yes	Yes	✓	✓	✓	✓
Raised liver function tests	Yes	Yes	✓	✓	✓	
Cardiac arrhythmias	Yes ²	Yes	✓	✓	✓	
Use in pregnancy	No	No	✓	✓	✓	
Gallbladder effects	No	No	✓	✓	✓	
Use in Elderly (>65 years)	No	Yes	✓	✓	✓	
Risk of medication errors	No	No	✓			

¹ Routine practice includes the standard signal detection and monitoring

² ECGs were assessed; 24 hour holter monitoring was not routinely included in the controlled studies

8.2. Post Marketing Risk Assessment

In addition to the regulatory requirements for reporting of individual and aggregate data, a robust and proactive signal management (signal detection and evaluation) process is in place for spontaneous adverse event data. In addition to the sponsor's standard pharmacovigilance procedures, enhanced pharmacovigilance activities are described below for the following potential risks:

8.2.1. Suicidality

In order to determine the potential risk for suicide or suicide related events with ezogabine, the following activities have been planned:

- Clinical studies will include the Columbia Classification Algorithm of Suicide Assessment.
- A customized case report form will be included in all clinical trials, which will collect important details on potentially suicide-related events including information relating to the nature, severity and outcome of these events, medical and psychiatric history, psychosocial stressors, and drug and alcohol use.

8.2.2. Urinary Retention

The following activities are planned to further characterize urinary retention associated with ezogabine (e.g. time to onset, background treatment, specific population effects and assessment of long-term safety):

- A targeted follow-up questionnaire for any AE reports relating to voiding dysfunction or urinary retention associated with ezogabine (reports originating via spontaneous post marketing reports and clinical studies). See Appendix 11.6 for targeted follow up questionnaire.
- A prospective epidemiological study of urinary retention following ezogabine exposure will be conducted with the objective of quantifying the possible risk of urinary retention associated with exposure to ezogabine in a real world setting (see Appendix 11.5). Other objectives are:
 - To determine the magnitude of the risk and time to onset of urinary retention (UR) associated with post marketing use of ezogabine.
 - To determine whether the risk and time to onset of UR varies according to age, concomitant antiepileptic drug use, and underlying co-morbidities.
 - To describe patients receiving ezogabine in terms of demographics, co-morbidities and concomitant anti-epileptic drug (AED) use.
 - To quantify the proportions of ezogabine users receiving concomitant medication potentially associated with UR and/or conditions pre-disposing to UR.

8.2.3. QT Effects

A clinically relevant effect of ezogabine on cardiac repolarization in patients at risk of QT prolongation cannot be excluded based on the results of the Thorough QT Study in healthy volunteers which demonstrated a slight (7 msec) and transient (1, 2 and 3 hours post-dose) effect of ezogabine on cardiac repolarization. The additional pharmacovigilance measures have been planned to further investigate the potential for QT effects with ezogabine:

- A targeted follow-up questionnaire will be completed for any AE reports potentially related to prolonged QT interval or Torsades de Pointes.
- Future clinical studies supporting the use of ezogabine for epilepsy will include formal ECG monitoring to provide population QTc interval data.

8.2.4. CNS and Neuropsychiatric Effects

Standard pharmacovigilance will focus on whether reports of accident and injury are associated with somnolence, dizziness and confusion and whether reports of psychosis and hallucinations are associated with any serious sequelae.

In addition, monitoring of discontinuation due to CNS AEs in future clinical studies will be assessed.

8.2.5. Raised Liver Function Tests

To further characterize the identified risks associated with elevated LFTs, additional pharmacovigilance measures are planned to determine whether they are associated with severe outcomes, for example hepatitis or hepatic failure and whether there is information that suggests the underlying etiology or independent risk factors for potential hepatic effects. The following activities are planned:

- Targeted follow-up questionnaire for AE reports relating to hepatobiliary events will be conducted.
- Liver function testing in clinical studies.
- The Sponsor's Safety database will be monitored routinely using specific Medical Dictionary for Regulatory Activities (MedDRA) preferred terms to identify reports of hepatobiliary events associated with ezogabine use. These data will be reviewed cumulatively approximately every six months.

8.2.6. Cardiac Arrhythmias

Targeted follow-up questionnaire for any AE reports potentially related to QT prolongation, including cardiac arrhythmias, e.g., Torsades des Pointes, will be conducted on an ongoing basis.

The Sponsor's Safety database will be monitored routinely using specific MedDRA preferred terms to identify reports of cardiac arrhythmias with ezogabine use. This data will be reviewed cumulatively approximately every six months.

8.2.7. Exposure during Pregnancy and Lactation

Pregnancies associated with ezogabine exposure will be monitored using the multi-AED pregnancy registries (North American Anti-Epileptic Drug (NAAED) and the European International Registry of Anti-Epileptics in Pregnancy (EURAP). These registries provide the Sponsor with semi-annual reports detailing the number of exposures to ezogabine in pregnancy and pregnancy outcomes (primary outcome of major congenital malformations) following *in utero* ezogabine exposure. Data will be reviewed by the Sponsor, and following consultation with registry scientific advisory committees, reported to regulators if a signal for a substantial increase in the risk of major congenital malformations is observed.

8.2.8. Gall Bladder Effects

There have been no data from clinical studies to suggest a risk to humans; however, there have been toxicology findings in dogs related to gall bladder enlargement. Spontaneous post marketing reports involving gall bladder events will be included in the cumulative review of the Sponsor's database.

8.2.9. Use in Patients Greater than or Equal to 65 years

In addition to the routine proactive pharmacovigilance activities that will specifically investigate events occurring in the elderly, the following additional measures are planned to characterize the benefit/risk of the urinary safety of ezogabine in the elderly population in particular:

- Participation of elderly patients in ezogabine epilepsy studies has been limited to date. The Sponsor will explore options to increase the participation of patients ≥ 65 years of age in planned efficacy and safety studies.
- Descriptive data from the planned epidemiology study to evaluate urinary symptoms in the elderly population (see Appendix 11.5) will be summarized on an interim basis prior to the final definitive analysis.

8.3. Post-Marketing Risk Minimization

8.3.1. Objective

The objective of the post marketing risk minimization plan will be to educate health care practitioners and patients about the potential risks of ezogabine. Specific activities are included to provide guidance on safe use and preventing avoidable injury. The risks of interest include the following:

Urinary retention:

- Urinary retention, dysuria and urinary hesitation were reported in controlled clinical studies in patients treated with ezogabine.
- Ezogabine must be used with caution in patients at risk of urinary retention.

QT interval effects:

- A slight and transient QT-prolonging effect was seen in healthy volunteers taking ezogabine.
- Caution is advised for patients taking medication known to increase the QT interval or with certain heart conditions.

CNS and neuropsychiatric events:

- Dizziness, somnolence, visual blurring, and psychiatric disorders (including confusional state, psychotic disorders, and hallucinations) have been reported with ezogabine.

- Patients should be informed of these effects. In addition patients should be advised not to drive, operate complex machinery, or engage in other hazardous activities as appropriate. Patients should be informed that ezogabine may cause psychiatric symptoms such as confusional state, disorientation, and hallucination. Patients and their caregivers should be instructed to notify their physicians if they experience psychotic symptoms.

Suicidality:

- Suicidal thoughts or behavior have been reported with AEDs, including ezogabine.
- Patients should be monitored for the emergence or worsening of depression, suicidal thoughts or behavior.

8.3.2. Communication Plan for Healthcare Practitioners

The post marketing risk minimization activities for ezogabine include a comprehensive communication plan to physicians to inform them on the potential safety information about the product. The content of the communication vehicles will be consistent with the product labeling and will focus on potential risks identified in the warning section of the label. After receiving FDA's agreement on the proposed physician directed materials, the sponsor will widely distribute them through a variety of vehicles to physicians who might prescribe ezogabine.

8.3.2.1. Introductory Letter for Healthcare Practitioners

An introductory letter for healthcare practitioners will be distributed via direct mail to potential prescribers of ezogabine. The letter will describe the indication of ezogabine, its appropriate dosing, and potential risks. The medication guide and product labeling will be attached to the mailing. The distribution list for this mailing will include epileptologists and neurologists who treat epilepsy identified through membership in national societies and prescription data.

Since the majority of epilepsy patients fill their prescriptions at retail and independent pharmacies, an announcement letter will be sent to pharmacists practicing in this setting. The letter will describe the indication of ezogabine, its appropriate dosing, and potential risks. The medication guide and product labeling will be attached to the mailing.

8.3.2.2. Website and Toll-free Call Center for Healthcare Practitioners

A website for healthcare practitioners will be created and will include information that informs on the potential risks associated with ezogabine. In addition, a customer response center will be staffed to answer questions customers may have about ezogabine.

8.3.2.3. Communication by Sales Representatives

Sales representatives will undergo comprehensive training on epilepsy and ezogabine prior to communicating with healthcare practitioners. They will be required to pass a test to include questions intended to demonstrate their understanding of safety information in the label. They will also be required to provide safety information on ezogabine during

sales calls with healthcare practitioners, both verbally and in writing, by providing a copy of the label.

8.3.2.4. Educating Healthcare Practitioners who will speak on behalf of Sponsor

Peer to peer presentations are an important forum for healthcare practitioners to learn about epilepsy and medications to treat epilepsy. The sponsor will train healthcare practitioners who present information on ezogabine on its behalf. These healthcare practitioners will be trained on the risks associated with ezogabine and the requirements for giving a fair and balanced presentation.

8.3.3. Communication Plan for Patients

8.3.3.1. Medication Guide

A Medication Guide will be provided that informs patients of important potential risks, how to prevent or identify those events, and what to do when an event occurs.

The Medication Guide will be attached to each unit of use bottle and to the samples distributed to physicians.

It is known that patients seek information from a variety of vehicles and media formats. So in addition to the packaging, the Medication Guide and/or the information in the Medication Guide will be made widely available via the web, printed materials, and the sponsor's call center.

8.3.4. Patient Website

A patient website for ezogabine will include information consistent with the Medication Guide for ezogabine and the Medication Guide itself.

8.3.5. Patient Education Brochure for Healthcare Practitioner Offices

A patient education brochure will be distributed to the offices of healthcare practitioners for dissemination to patients. The brochure will include information consistent with the Medication Guide for ezogabine and the Medication Guide itself.

8.3.6. Customer Response Center

A customer response center for patients will be staffed by trained employees who demonstrate their knowledge of the important safety information in the label for ezogabine. These employees will be available to respond to questions from patients and provide a copy of the Medication Guide.

8.4. Assessment of the Effectiveness of the Plan

8.4.1. Effectiveness of the Medication Guide

The Sponsor will work with FDA to develop qualitative research and a comprehension study to help assess effectiveness of the medication guide:

- Qualitative research to explore barriers to understanding the medication guide.
- Comprehension study to assess understanding of the medication guide. The study will be conducted using methods similar to those proposed in the April 2009 Draft Guidance for Industry: Label Comprehension Studies for Nonprescription Drug Products. The comprehension test will be conducted among a socioeconomically, racially, and geographically diverse group of patients with epilepsy.

8.4.2. Assessment of Healthcare Practitioners Knowledge

The Sponsor will work with FDA to develop a qualitative research study intended to assess the understanding of essential safety information of ezogabine by healthcare practitioners.

8.4.3. Assessment of Post Marketing Adverse Events of Interest

The goal of risk management for ezogabine is to minimize the occurrence and severity of identified adverse events, particularly those associated with urinary retention, and to continue assessment of possible risks in the post marketing setting. Specific assessments will include evaluation of:

- Case reports (spontaneous adverse event reports) indicative of urinary retention, particularly those requiring catheterization will be evaluated and will include assessment of whether directions for safe use were followed appropriately.
- Case reports (spontaneous adverse event reports) of cardiac arrhythmias, particularly those relating to QT prolongation or overdose will be evaluated to determine whether underlying risk factors were present.
- Case reports (spontaneous adverse event reports) of neuropsychiatric effects, particularly those occurring early in treatment will be evaluated to determine if the appropriate titration was used. In addition, reports will be reviewed to identify any reported accidents or injuries as a result of the effects of ezogabine.

8.4.4. Conclusion

With the implementation of the activities outlined above, important information on the safe and effective use of ezogabine will be appropriately communicated to healthcare professionals and patients. Modifications to the plan will be made as needed, based on post marketing assessments.

9. BENEFITS AND RISKS CONCLUSIONS

Despite the increased number of treatment options which have become available over the past 15 years, 30% of patients with partial-onset seizures remain uncontrolled. Moreover, patients with uncontrolled epilepsy have increased morbidity and risk of mortality, with SUDEP being the most common seizure related cause of death. Patients with epilepsy have significantly increased morbidity, including closed head injury, fractures, burns, dental injury and soft tissue injury related to seizures [Spitz, 1998; Wirrell, 2006]. Additional chronic co-morbidities include difficulties with memory, cognition, depression and sexual function. There remains a significant unmet medical need for the effective treatment of patients who do not respond to currently marketed AEDs, motivating the search for new compounds to treat patients with partial epilepsy.

Ezogabine, a selective, positive modulator of KCNQ/Kv7 channels, has a unique pharmacological profile not shared by current AEDs. It therefore offers a new and important adjunctive therapeutic option for patients not adequately treated with available AEDs.

9.1. Benefits of Ezogabine for Treatment of Epilepsy

In the pivotal efficacy studies (Studies 205, 301 and 302), patients had a diagnosis of epilepsy for an average of 22 years and over 75% were receiving treatment with at least two AEDs without adequate clinical benefit (median baseline seizure frequency 8 to 12 seizures per month). The results of these three adequate and well-controlled studies provide substantial evidence of effectiveness for ezogabine as the first of a new class of pharmacological treatments for adjunctive therapy in the treatment of partial onset seizures in adults, with or without secondary generalization.

The percent change from baseline in 28-Day total partial seizure frequency in the entire treatment period ranged from 23.4% to 44.3% across the dose range of 600 to 1200 mg/day ezogabine. The primary efficacy endpoint was supported by secondary efficacy endpoints. Across the dose range, 23.2% to 44.4% of patients had at least a 50% reduction in monthly seizure frequency during the entire treatment period. These studies confirm a dose-related increase in efficacy across the dose range of 600 to 1200 mg/day, whether defined in terms of the percent change from baseline or responder rate. Ezogabine demonstrated efficacy regardless of the number or type of AEDs to which it was added. In addition, long-term maintenance of efficacy of ezogabine has been demonstrated in 3 open-label extension trials.

9.2. Risks of Ezogabine for Treatment of Epilepsy

Ezogabine may cause dose related bladder dysfunction in some patients, an effect pharmacologically related to its effects on KCNQ channels. Urinary retention occurred in 7 of 813 patients (0.9%) treated with ezogabine compared to 2 of 427 patients (0.5%) receiving placebo in the PCTs and was infrequently associated with UTI. Of the 35 events of UTI in patients receiving ezogabine in the PCTs none was preceded by an AE of urinary retention. Events of urinary retention were reversible when recognized and treated promptly. A prospective epidemiological study of urinary retention following

ezogabine exposure will be conducted with the objective of quantifying the possible risk of urinary retention associated with exposure to ezogabine in a real world setting. A copy of the proposed study outline is provided in Appendix 11.5.

In the PCTs AEs possibly related to urinary crystals were reported more often in patients taking ezogabine than with placebo (9 [1%] versus 2 [0.5%]). There were 4 cases of nephrolithiasis in patients on ezogabine (all occurred with 1200 mg/day), and none on placebo.

In the PCTs, psychosis and hallucination were reported for a larger proportion of patients in the groups treated with ezogabine than placebo (32/813 [4%] versus 3/427 [$<1\%$]). These events appeared within the first 8 weeks of treatment in all dose-groups. When examined by study phase, over half the events were reported during titration (19/32). These types of events are not unique among AEDs.

Suicide-related events were not found to be higher on ezogabine than placebo; however, since these events are rare and may not have been detectable in the clinical development program, this potential risk will be the focus of class labelling and post-marketing risk management.

A clinically relevant effect of ezogabine on cardiac repolarization in patients at risk of QT prolongation cannot be excluded based on the results of the Thorough QT Study in healthy volunteers which demonstrated a slight (7 msec) and transient 1, 2 and 3 hours post-dose) effect of ezogabine on cardiac repolarization.

9.3. Conclusions

Epilepsy is a serious disease and is associated with decline in or worsening of memory, cognition, depression and sexual function in addition to high morbidity and mortality. Patients with uncontrolled seizures suffer social consequences including employment and lifestyle limitations.

Despite the fact that there are numerous AEDs currently marketed, nearly a third of patients are currently not adequately controlled. Ezogabine has demonstrated convincing efficacy with an acceptable safety profile. The Sponsor believes that the product labeling (and Medication Guide) and post marketing risk minimization activities that are being proposed will facilitate the safe and effective use of ezogabine.

Individualization of AED therapy on the basis of efficacy and tolerability remains the hallmark of current disease management. Although ezogabine may not be well tolerated in all patients, it offers a potentially meaningful treatment option for patients with uncontrolled epilepsy. In the context of the serious nature of epilepsy, current standard of care and available treatments, the benefit:risk profile is favorable and supports the use of ezogabine 600 to 1200 mg/day for the adjunctive treatment of partial onset seizures.

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11. APPENDICES

11.1. Appendix: Summary of Clinical Efficacy Studies

Table A 1 Summary of Other Secondary Efficacy Results in Studies 205, 301 and 302

	Study 205				Study 302			Study 301	
	Placebo	EZG 600 mg/day	EZG 900 mg/day	EZG 1200 mg/day	Placebo	EZG 600 mg/day	EZG 900 mg/day	Placebo	EZG 1200 mg/day
Percent Reduction in 28-Day Total Partial Seizure Frequency by Reduction Category (Double-Blind Phase) – ITT Double-Blind Population^a									
Percent Reduction, n (%)									
N	96	100	95	106	179	181	178	152	153
75 to 100%	8 (8)	9 (9)	10 (11)	14 (13)	12 (7)	16 (9)	27 (15)	6 (4)	27 (18)
50 to <75%	7 (7)	14 (14)	20 (21)	21 (20)	19 (11)	41 (23)	43 (24)	21 (14)	41 (27)
25 to <50%	18 (19)	25 (25)	22 (23)	29 (27)	39 (22)	38 (21)	41 (23)	37 (24)	20 (13)
>0 to <25%	34 (35)	23 (23)	15 (16)	17 (16)	43 (24)	38 (21)	24 (14)	33 (22)	26 (17)
No change or increase	29 (30)	29 (29)	28 (29)	25 (24)	66 (37)	48 (27)	43 (24)	55 (36)	39 (26)
P-value ^b	-	0.202	0.038	0.003	-	0.003	<0.001	-	<0.001
Percent Reduction in 28-Day Total Partial Seizure Frequency by Reduction Category (Maintenance Phase) – ITT Maintenance Population^a									
Percent Reduction, n (%)									
N	78	83	74	68	164	158	149	137	119
75 to 100%	8 (10)	11 (13)	12 (16)	15 (22)	11 (7)	27 (17)	30 (20)	13 (10)	38 (32)
50 to <75%	12 (15)	12 (14)	18 (24)	13 (19)	20 (12)	34 (22)	40 (27)	18 (13)	28 (24)
25 to <50%	17 (22)	26 (31)	15 (20)	17 (25)	32 (20)	30 (19)	36 (24)	31 (23)	16 (13)
>0 to <25%	19 (24)	10 (12)	11 (15)	11 (16)	51 (31)	30 (19)	13 (9)	34 (25)	17 (14)
No change or increase	22 (28)	24 (29)	18 (24)	12 (18)	50 (31)	37 (23)	30 (20)	41 (30)	20 (17)
P-value ^b	-	0.453	0.090	0.014	-	<0.001	<0.001	-	<0.001

	Study 205				Study 302			Study 301	
	Placebo	EZG 600 mg/day	EZG 900 mg/day	EZG 1200 mg/day	Placebo	EZG 600 mg/day	EZG 900 mg/day	Placebo	EZG 1200 mg/day
Percent of Patients who were Seizure Free (Double-Blind Phase) – ITT Double-Blind Population^a, n (%)									
N	96	100	95	106	179	181	178	152	153
n	96	99	95	106	176	179	175	150	151
Seizure-free	2 (2)	4 (4)	4 (4)	7 (7)	2 (1.1)	0	7 (4.0)	0	3 (2.0)
P-value ^c	-	0.683	0.444	0.175	-	n/a	0.104	-	0.248
Percent of Patients who were Seizure Free (Maintenance Phase) – ITT Maintenance Population^a, n (%)									
N	78	83	74	68	164	158	149	137	119
n	78	83	74	68	164	158	149	137	119
Seizure-free	3 (4)	2 (2)	4 (5)	6 (9)	2 (1.2)	5 (3.2)	7 (4.7)	2 (1.5)	9 (7.6)
P-value ^c	-	0.674	0.714	0.304	-	n/a	0.091	-	0.027
Percent of Seizure-Free Days (Double-Blind Phase) – ITT Double-Blind Population^a									
N	96	100	95	106	179	181	178	152	153
n	96	99	95	106	176	179	175	150	151
Mean ± SD	74.7 ± 20.52	74.6 ± 22.67	74.8 ± 23.90	74.4 ± 23.57	67.6 ± 27.71	70.7 ± 25.37	71.2 ± 28.48	65.0 ± 28.19	70.1 ± 29.12
Median (Range)	78.2 (1, 100)	82.1 (3, 100)	83.2 (2, 100)	80.4 (5, 100)	77.8 (0, 100)	79.5 (0, 99)	82.1 (0, 100)	77.3 (0, 98)	84.1 (0, 100)
P-value ^d	-	0.326	0.256	0.013	-	0.021	<0.001	-	<0.001
Percent of Seizure-Free Days (Maintenance Phase) – ITT Maintenance Population^a									
N	78	83	74	68	164	158	149	137	119
n	78	83	74	68	164	158	149	137	119
Mean ± SD	76.8 ± 19.70	75.8 ± 21.00	76.6 ± 22.82	74.5 ± 24.76	68.7 ± 27.02	72.3 ± 25.22	73.4 ± 28.42	66.3 ± 28.26	73.6 ± 28.60
Median (Range)	80.4 (2, 100)	82.1 (20, 100)	83.0 (2, 100)	81.8 (4, 100)	78.1 (0, 100)	81.6 (0, 100)	84.5 (0, 100)	78.2 (0, 100)	86.9 (0, 100)
P-value ^d	-	0.854	0.674	0.075	-	0.003	<0.001	-	<0.001

a. *Post hoc* analyses performed for Study 205

b. P-value from CMH test

c. P-value from Fisher's Exact test

d. P-value for treatment comparison versus placebo using non-parametric rank ANCOVA

Table A 2 Patients Reporting New Seizure Types During the Double-blind Phase That Were Not Reported at Baseline (ITT Double-Blind Population)

	Study 205 Randomized Population				Study 302 ITT Double-Blind Population			Study 301 ITT Double-Blind Population	
	Placebo	EZG 600 mg/day	EZG 900 mg/day	EZG 1200 mg/day	Placebo	EZG 600 mg/day	EZG 900 mg/day	Placebo	EZG 1200 mg/day
Seizure type									
N	N=97	N=101	N=95	N=106	N=179	N=181	N=178	N=152	N=153
Any new seizure type	15 (15.5)	16 (15.8)	8 (8.4)	15 (14.2)	24 (13.4)	24 (13.3)	25 (14.0)	33 (21.7)	42 (27.5)
Partial seizures without motor signs	6 (6.2)	8 (7.9)	3 (3.2)	4 (3.8)	9 (5.0)	8 (4.4)	12 (6.7)	12 (7.9)	17 (11.1)
Partial evolving to secondarily generalized	5 (5.2)	5 (5.0)	3 (3.2)	5 (4.7)	6 (3.4)	5 (2.8)	9 (5.1)	7 (4.6)	12 (7.8)
Complex partial seizures	2 (2.1)	0	2 (2.1)	1 (0.9)	1 (0.6)	4 (2.2)	0	5 (3.3)	11 (7.2)
Partial seizures with motor signs	2 (2.1)	2 (2.0)	4 (4.2)	2 (1.9)	5 (2.8)	6 (3.3)	3 (1.7)	11 (7.2)	7 (4.6)
Flurries	1 (1.0)	3 (3.0)	0	5 (4.7)	3 (1.7)	2 (1.1)	1 (0.6)	3 (2.0)	1 (0.7)
Tonic-clonic seizures	2 (2.1)	1 (1.0)	0	0	0	0	3 (1.7)	0	1 (0.7)
Atonic seizures	0	0	0	0	0	0	0	1 (0.7)	0
Tonic seizures	0	0	0	0	3 (1.7)	0	1 (0.6)	0	0
Unclassified seizures	0	1 (1.0)	0	0	0	1 (0.6)	0	0	0

11.2. Appendix: Supportive Efficacy Studies

A total of three Phase IIa studies are considered supporting efficacy studies. These studies are briefly described in the following sections.

11.2.1. Study 200/201

11.2.1.1. Study Design

Studies 200/201 (3065 A1-200/201) were the first multi-center studies in which ezogabine was investigated in patients with partial –onset seizures with or without secondary generalization. Given the similarity of the protocols, the efficacy data were pooled and reported within the one clinical study report. However the pharmacokinetic data derived from both protocols were reported separately in consideration of the differences in the PK sampling schedule across the study protocols.

Ezogabine was administered in an open-label fashion as add-on therapy to eligible patients (age 18 to 50 years) with partial-onset seizures with or without secondary generalization (patients who had at least eight seizures during the last 2 months and who had partial seizures treated with one to three AEDs).

The open-label uncontrolled studies were divided into three phases: baseline (2 months), treatment (consisting of a 3-month dose-titration period and a 3-month maintenance period); after completion of the treatment phase, patients were either tapered off ezogabine over a period of 3 weeks (25% dose reduction every week), or entered into a long-term follow-up study (Study 8017). During the treatment phases of Studies 200/201, concomitant AEDs were to remain constant.

The objectives of Study 200/201 were to define the minimum efficacious dose and the maximum tolerated dose for ezogabine as add-on treatment in patients with epilepsy. Safety, tolerability, pharmacokinetics and preliminary efficacy were evaluated in this study.

One of the objectives for this study was a determination of the optimal steps for titration and determination of the maximum tolerated dose depending on the patient's ability to tolerate study medication. Starting doses of ezogabine were 25 mg, 50mg, 100 mg, or 200 mg/day administered as a BID regimen depending on the dosing schedule that was assigned to study sites.

The original and amended dosing schedules across the two protocols permitted dose increases of 50 mg (slow titration), 100 mg (medium titration), or 200 mg (fast titration) at a minimum titration step period of 1 week so that 400 mg/day, 1200 mg/day, or 2400 mg/day respectively could be achieved. Patients were therefore treated according to individual titration schemes according to efficacy and tolerability that resulted in either the maximum daily dose allowed by the protocol or the maximum tolerated dose the patient achieved by the end of the titration period.

No changes in ezogabine dose at the end of the titration phase or concomitant AEDs were permitted during the maintenance period. These patients were eligible for entry into the extension study or the study medication was tapered at the discretion of the investigator.

Efficacy criteria were percent reduction from baseline in total partial seizure frequency and responder rate ($\geq 50\%$ reduction from baseline in seizure frequency) during the 3-month maintenance period (end of Week 24) or last study visit.

The safety population included all patients who took at least one dose of study medication. Analysis of efficacy was performed on the ITT population which was defined as all patients who took at least one dose of study medication and had at least one seizure assessment after Visit 1. A per-protocol analysis was also planned based on patients who entered the maintenance period and treated in accordance with the protocol i.e., no major protocol violations.

11.2.1.2. Demographics and Baseline Characteristics

The studies were conducted in six centers across three countries (Germany, Switzerland and Russia). Efficacy results from these two studies were combined because the studies had similar designs and study objectives with respect to identifying an optimal titration and maintenance dosing schedule for ezogabine in a similar patient population.

A total of 46 Caucasian patients (27 [59%] female and 19 [41%] male) with a mean age of 34 years (range 18 to 49 years) were included in the Safety and ITT populations. Thirty-eight patients were enrolled at five sites in Study 03065A1-200 and 8 patients at one site in Study 03065A1-201. In total, 11 (24%) patients discontinued study drug prematurely, 10 patients during the titration period and 1 patient during the maintenance period.

Patients had a long-standing history of epilepsy. The median total partial seizure frequency at baseline was 6.4 in the ITT population. All patients were taking concomitant AED therapy with the majority in the ITT population (31/46, 67%) receiving two (11/46, 23.9%) or three (20/46, 43.5%) AEDs. The majority of patients were taking carbamazepine and valproic acid as concomitant AEDs.

11.2.1.3. Efficacy

The median percent change in monthly total seizures and total partial seizure frequency in the maintenance phase (stabilization period) compared to baseline for the ITT population was -42.1% and -42.3% respectively.

The responder rate for total seizures in the ITT population in the maintenance phase was 30% in the most conservative imputation analysis where patients not entering the maintenance phase were classified as non-responders. The proportion of responders by maximum ezogabine dose for the maintenance period indicated that the therapeutic window for greatest efficacy was observed between ezogabine 400 to 1200 mg/day i.e., 5/16 (31%) patients at >400 to 800 mg/day and 6/10 (60%) patients at >800 to 1200 mg/day; and only 1 (25%) patient in the dose range ≤ 400 mg/day was classified as a

responder. Four patients (12% in the Per Protocol population) achieved doses greater than 1200 mg/day and in one patient a dose of 2400 mg/day was achieved, but in none of these patients was there evidence of efficacy based on the responder rate definition. None of the patients receiving doses >1200 mg/day were discontinued prematurely from study treatment.

In two separate analyses based on the per-protocol population, a medium dose class (>400 to 1200 mg/day) and a fast titration scheme (200 mg/week) was associated with the greatest proportion of responders. Doses below 400 mg/day did not appear to offer substantial efficacy.

The overall mean maintenance dose of ezogabine was 854 mg/day, with a dose range of 350 mg/day to 2400 mg/day administered as BID regimen. Titration schemes of ezogabine 100 mg/week or 200 mg/week allowed patients to achieve a higher maintenance dose, however the 200 mg/week titration scheme appeared to be less well tolerated (6 patients [33%] discontinued treatment during titration).

11.2.1.4. Study Conclusions

- In this first exploratory study for ezogabine in patients with partial epilepsy the three titration schemes investigated indicated that an appropriate therapeutic window for ezogabine in this patient population appeared to be between 400 mg/day and 1200 mg/day, with a maximum responder rate seen with 800 mg/day to 1200 mg/day, administered as a BID regimen. Titration schemes of between 100 mg/day and 200 mg/day weekly increments were sufficient to reach an efficacious dose within an appropriate time frame. However a rapid titration scheme of at least 100 mg/week appeared to be reasonable for further investigation.

11.2.2. Study 202

11.2.2.1. Study Design

Study 202 (Study 3065 A1-202) was a multi-center, open-label, uncontrolled safety, tolerability, and preliminary efficacy study of ezogabine administered as add-on therapy to patients with partial or generalized epilepsy currently receiving monotherapy with an established anticonvulsant. Eligible patients were 16 to 75 years of age, diagnosed with partial or generalized epilepsy, with a documented seizure frequency of at least two seizures per month receiving monotherapy with valproic acid, carbamazepine, phenytoin, or topiramate at stable doses for at least 5 weeks at the time of enrollment.

The primary objectives were to determine the highest tolerated dose of ezogabine and to evaluate the safety and tolerability of ascending doses of ezogabine administered first as add-on therapy and then as monotherapy. The secondary objectives were to evaluate the pharmacokinetic interaction of ezogabine in combination with the established AEDs described above. Preliminary efficacy of ezogabine administered first as add-on therapy and then as monotherapy was also assessed based on the criteria of percent reduction in total seizure frequency from both historical and pre-study baselines and the responder rate for total seizures only ($\geq 50\%$ reduction from pre-study baselines in seizure frequency) during the treatment period. The historical baseline seizure rate was calculated

from seizure rate in the 5 or 6 weeks prior to Visit 1. The pre-study baseline was calculated from information collected on the Seizure Record in the 2 to 3 weeks prior to Visit 2.

The titration scheme for ezogabine was amended several times during the study to accommodate adjustments to the speed of titration and to the maximum tolerated dose. Patients received starting ezogabine doses 100 to 200 mg/day (50 to 100 mg capsules BID) over the first 2 weeks. Doses could be increased further at weekly intervals by 100 to 200 mg/day to Day 47 (Week 6). In the first amendment, the starting dose was increased from 100 mg/day (50 mg BID) to 200 mg/day (100 mg BID) and the dose titration for ezogabine was changed from increases every 2 weeks up to a maximum dose of 1000 mg/day to increases every week up to a maximum dose of 2000 mg/day. The second amendment allowed the dosage regimen to be BID or TID and reduced the maximum daily dose of ezogabine from 2000 mg/day to 1600 mg/day. The third amendment required all newly enrolled patients to receive a TID regimen. In all amendments, beginning on Day 43 of study treatment after the pre-specified dose escalation scheme further adjustments to titrate daily doses above 1200 mg/day could be made in steps of 50 to 200 mg every 7 to 14 days to the maximum dose stipulated in the protocol and in accordance with the patient's requirements and investigator's discretion over the course up to Day 70 (Week 10). The maximum tolerated dosage regimen of ezogabine and the stable dosage regimen of background AED were maintained for 14 days. Background AEDs were subsequently tapered over a 14 day period and patients were maintained on ezogabine (monotherapy or with background AED at the lowest dose possible) maintenance treatment for a further 14 days. In the final phase (Day 112), patients either continued treatment with ezogabine in the extension study (Study 208), or the ezogabine dose was tapered by approximately 25% over 14 days to study completion (Day 126). While ezogabine was being tapered, the established AEDs were re-introduced by the investigator according to clinical need. Patients could continue in the study for a maximum of 153 days.

The efficacy analyses were assessed across four main on-therapy phases: i) titration (Low and Medium); ii) titration (High); iii) background AED tapering; and iv) maintenance phase. The L, M and H refer to the lowest, mid and highest doses of ezogabine during the titration phase. The titration L stage was when the patients were on their first and lowest dose of ezogabine. The length of L varied according to protocol amendment determining the speed of titration. The H titration stage was when patients were on their maximum dose of ezogabine in combination with their maximum dose of background AED. The titration M stage was the time between titration L and titration H. Secondary on-phase analyses including four further on-phase assessments that included assessment of efficacy across the entire treatment phase (all phases of the study combined) as well as sub-categories that mainly excluded the lowest part of the titration phase from the overall analysis.

Seizure rate was primarily calculated for total seizures since the trial included patients with both partial and generalized epilepsy. The historical baseline total seizure rate and the pre-study baseline total seizure rate were determined and the total seizure rate was calculated in both the four main on-therapy phases and the four secondary on-therapy phases.

In addition, the total partial seizure rate and total primary generalized seizure rate were calculated for the historical baseline, pre-study baseline and the four main on-therapy phases. The evaluations for total partial seizures were of particular clinical relevance with respect to informing dose recommendations in the patient populations to be included in the subsequent pivotal efficacy studies.

The safety population included all patients who took at least one dose of study medication. Analysis of efficacy was performed on the ITT population and two subgroups of the ITT population. The ITT population was defined as all patients who took at least one dose of study medication and had either a historical or pre-study baseline seizure record and had at least one seizure record whilst on ezogabine treatment.

Subgroups A and B of the ITT populations were i) subgroup A ITT population with ≥ 10 consecutive days in the maintenance phase i.e., on ezogabine alone and ii) subgroup B ITT population were patients with a primary diagnosis of partial epilepsy and pre-study baseline partial seizure rate (per 28 days) was ≥ 4 .

Descriptive statistics were produced across all analyses and no statistical comparisons were performed.

11.2.2.2. Demographics and Baseline Characteristics

A total of 60 patients (33 [55%] female and 27 [45%] male) with a mean age of 37 years (range 16 to 64 years) were included in the Safety population and the number of patients receiving the following concomitant AEDs were valproic acid (n=8), topiramate (n=11), phenytoin (n=19), and carbamazepine groups (n=22). A total of 59 patients were included in the evaluation of efficacy (ITT population). In both the Safety and ITT populations, the majority of patients were White (88%) and the majority (88%) had a primary diagnosis of partial epilepsy. A total of 8 (13%) patients discontinued the study due to adverse events regardless of background AED therapy.

11.2.2.3. Efficacy

Efficacy was assessed in terms of percent change in seizure rate from pre-study baseline and the responder rate. For both subgroups of the ITT population, the total seizure rate and percent change in total seizure rate were summarized in the four main on-therapy phases. The responder rate was also summarized by the four main on-therapy phases for the ITT population and the subgroup B ITT population i.e., patients with a primary diagnosis of partial epilepsy and pre-study baseline partial seizure rate (per 28 days) of ≥ 4 .

There was an approximately 20% reduction in median seizure rate for the population as a whole during ezogabine treatment phase (all periods combined) based on a reduction of the median total seizure frequency rate of 8.1 (pre-study baseline) to 6.4 for all study phases combine.

The overall median percent decrease in total seizure frequency during the titration phases was -19% (for the lowest and middle doses of ezogabine achieved during titration), -38%

(for the highest dose of ezogabine achieved during titration), -41% during the background AED taper phase, and -4% during the maintenance phase after the concomitant AED had been withdrawn. There was evidence of differences in efficacy by AED type, particularly with respect to concomitant administration of topiramate. However the small number of patients per group and the large variation on the seizure frequency across the patient group limited interpretation for efficacy by AED sub-type.

The overall median percentage change in the total seizure rate in the subgroup B ITT population was approximately -19% (for the lowest and middle doses of ezogabine achieved during titration), -40% (for the highest dose of ezogabine achieved during titration), -44% during the background AED taper phase and -33% during the maintenance phase after the concomitant AED had been withdrawn.

Similarly, there was a consistent increase in the number of responders (defined as 50% reduction in seizure frequency from baseline) with increase doses of ezogabine. The responder rates for the ITT population during the study varied between 33% (for the lowest and middle doses of ezogabine achieved during titration) and 44% (background AED taper phase) including 35% responder rate during the maintenance phase after the concomitant AED had been withdrawn.

The total percentage of responders in the ITT subgroup B analysis was 37% to 46% across the study phases. The responder rate during the maintenance phase alone was 43%. These findings were also corroborated in the analyses by seizure subtype.

There was large variation in the range of doses achieved by background AED type across the titration phase (75 to 1200 mg/day). The small numbers of patients in each AED subgroup precluded any meaningful evaluation of the influence of AED on the highest dose of ezogabine achieved during this phase. However the maximum doses of ezogabine achieved during the titration (H) phase varied between 400 to 1200 mg/day.

There was a slightly lower incidence of treatment-emergent adverse events (TEAEs) in patients administered ezogabine TID compared with a BID regimen (91% versus 100% respectively). Patients in the TID dosage regimen reported fewer central nervous system TEAEs than patients in the BID dose groups (64% versus 98% respectively).

11.2.2.4. Study Conclusions

- Based on the results of Study 202 ezogabine titrated up to 1200 mg/day (administered either as a BID or TID regimen) was associated with evidence of efficacy for total seizures. This included an analysis in patients with a primary diagnosis for total partial seizures. There was evidence for efficacy in reducing total partial seizures at the maximum ezogabine doses achieved during the high titration and background taper phase. The efficacy profiles were generally similar across the four AED subgroups.
- Pharmacokinetic data indicated no significant interaction of ezogabine on the pharmacokinetic profile of the AEDs studied. Carbamazepine and phenytoin increased the clearance of ezogabine by approximately 30%.

- Based on the efficacy results and adverse event profile, ezogabine 1200 mg/day (BID) was deemed the maximum tolerated dose in patients with epilepsy.
- Results from this study suggested that the fewer central nervous system TEAEs were seen in patients receiving ezogabine dosed TID versus BID.
- The results from this study were significant in informing the maximum dose selection and dosing regimen (TID) to be included in the Phase IIb dose-ranging study in patients with refractory total partial seizures.

11.2.3. Study 214

11.2.3.1. Study Design

Study 214 (Study 3065 A1-214) was a multi-center, randomized, double-blind, parallel-group, exploratory safety and tolerability study comparing three titration rate regimens of ezogabine in patients with refractory partial epilepsy. Eligible patients were 16 to 70 years with a diagnosis of partial epilepsy and a documented seizure frequency of ≥ 2 seizures per month during the 4 weeks before study evaluation. Eligible patients could be receiving one or two marketed AEDs (with the exception of vigabatrin and felbamate) at a stable dose for at least 1 month prior to screening. Patients could also be on VNS therapy and this counted as one AED towards the total of up to two AEDs. The study consisted of three phases: a 1 week screening/baseline phase, a 7-week double-blind titration phase, and a 3 week tapering phase for patients who did not enter the open-label extension study (Study 216) which followed the double-blind period.

The primary objective was to compare the safety and tolerability of three titration rates of ezogabine in this patient population. The secondary objective was to evaluate the efficacy of the three titration rates on seizure rate. This was assessed by reduction in total partial seizures and responder rate (50% reduction from baseline in partial seizure frequency) during the titration period. The primary efficacy variable for this study was defined as total partial seizures; total seizure was considered the secondary seizure category. The historical baseline i.e., seizure rate across the previous 4 weeks prior to the 1-week screening/baseline phase was used in deriving change in seizure rates across the titration phase.

The safety population included all patients who took at least one dose of study medication. Analysis of efficacy was performed on the ITT population which was defined as all patients who took at least one dose of study medication and had a historical baseline seizure record and had at least one seizure record while on ezogabine treatment. Two modified ITT populations based on exclusion of patients who withdrew due to adverse events as either the primary and/or secondary reason for withdrawal, respectively, were also part of the efficacy analyses.

All patients received a starting dose of ezogabine 300 mg/day (100 mg capsules TID). During the following days, study doses were increased by 150 mg every 2 days (Group 1: 24 patients), 150 mg every 4 days (Group 2: 25 patients) and 150 mg every 7 days (Group 3: 24 patients) up to a maximum target daily dose of 1200 mg. The maximum target dose was to be achieved on Day 13, Day 25, and Day 43 of administration in the respective titration groups. The planned duration of therapy was 49 days. All concomitant

AEDs were to remain constant during the ezogabine titration phase. If a patient could not tolerate the titration scheme and could not reach the target dose, the patient was withdrawn from the study.

11.2.3.2. Demographics and Baseline Characteristics

A total of 73 patients were enrolled in this study (24 in 150 mg/2 days titration group; 25 in ezogabine 150 mg/4 days titration group and 24 in 150 mg/7 days' titration group). All patients (n=73) were included in the Safety and ITT populations. A total of 25 (34%) patients withdrew prematurely from the study. The most common reason for withdrawal was due to adverse events: 10 (42%) in the 150 mg/2 days group, 7 (28%) in the 150 mg/4 days group and 3 (13%) in the 150 mg/7 days group.

A total of 73 patients (43 [59%] female and 30 [41%] male) with an average mean age of 38 years (range 17 to 68 years) were included in the Safety population. In both the Safety and ITT populations, the majority of patients were White (92%) and had a mean duration of illness of 22 years.

All patients were taking concomitant AED with no significant difference in use of concomitant background AEDs across the treatment groups. The majority of patients were taking carbamazepine and valproic acid as concomitant AEDs.

11.2.3.3. Tolerability

The primary analysis was the comparison of discontinuation rates due to adverse events reported as the primary reason across the three titration rate regimens. There was a statistically significant difference in discontinuations due to AEs between titrating upwards at ezogabine 150 mg every 2 days and the 150 mg every 7 days titration groups (43.5% versus 13.0% respectively, $p=0.024$, Fischer's Exact test); there was no significant difference between the 150 mg every 4 days and the 150 mg every 7 days groups (31.8% versus 13.0% respectively, $p=0.124$). Thus, the 150 mg every 2 days titration scheme was not acceptable when considering the discontinuation rate due to AE reported as primary reason.

A secondary analysis performed on discontinuation rates due to AE as primary or secondary reason showed, as with the primary efficacy analysis, the difference between the 150 mg every 2 days and the 150 mg every 7 days was statistically significant (43.5% versus 13.0% respectively, $p=0.024$, Fisher's Exact test). The difference between the 150 mg every 4 days and the 150 mg every 7 days approached statistical significance (37.5% versus 13.0% respectively, $p=0.055$).

11.2.3.4. Efficacy

The median total partial seizure frequency in the ITT population decreased by 61% in the 150 mg/2 days, 50% in the 150 mg every 4 days, and 21% in the 150 mg every 7 days groups during the titration phase; the results were similar for total seizure rate decreases. Responder rates for total seizures in the titration phase were 58% in the 150 mg every 2 days, 52% in the 150 mg every 4 days, and 33% in the 150 mg every 7 days respectively.

Responder rates for total partial seizure rates were not reported. No statistical analysis was performed to compare the effects of the three titration schemes on seizure control.

11.2.3.5. Conclusions

- A titration scheme of 150 mg every 7 days to a maximum tolerated dose of ezogabine 1200 mg/day i.e., over a 6-week titration period, was considered optimum with respect to the lowest discontinuation rates due to AEs. The results of Study 214 indicated that caution should be used if a titration scheme faster than 150 mg every 7 days is used to achieve a total daily dose of 1200 mg/day.

11.3. Appendix: Analysis by Seizure Sub-Type at Baseline

Table A 3 Responder Rate by Secondly Generalized Seizures Subgroup (Double-Blind Phase) – ITT Double-Blind Population (Studies 205, 301 and 302 Integrated)

	Placebo ^a	EZG 600 mg/day	EZG 900 mg/day	Placebo ^b	EZG 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
Responders	13 (16)	28 (28)	26 (27)	14 (18)	21 (25)
Adjusted Odds Ratio (95% CI) ^c		1.9 (0.9, 4.1)	2.0 (0.9, 4.1)		1.6 (0.7, 3.4)
P-value ^c		0.081	0.079		0.252
Patients without secondarily generalized seizures	N=193	N=180	N=175	N=168	N=174
n	192	177	174	166	173
Responders	33 (17)	52 (29)	74 (43)	28 (17)	82 (47)
Adjusted Odds Ratio (95% CI) ^c		2.1 (1.3, 3.4)	3.6 (2.2, 5.8)		4.7 (2.8, 7.9)
P-value ^c		0.004	<0.001		<0.001

Only patients with baseline and post-baseline seizures were included in the analysis.

Treatment by seizure subtype interaction (with or without secondarily generalized seizures) comparison vs placebo: ezogabine 600 mg/day vs placebo (p=0.877), ezogabine 900 mg/day vs placebo (p=0.186), ezogabine 1200 mg/day vs placebo (p=0.021).

- 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 is based on logistic regression.

Table A 4 Percent Change from Baseline in 28-Day Total Partial Seizure Frequency by Secondly Generalized Seizures Subgroup (Maintenance Phase) – ITT Maintenance Population (Studies 205, 301 and 302 Integrated)

	Placebo ^a	EZG 600 mg/day	EZG 900 mg/day	Placebo ^b	EZG 1200 mg/day
Secondarily generalized seizures					
Patients with secondarily generalized seizures	N=71	N=90	N=86	N=68	N=65
n	71	90	86	68	65
Mean ± SD	1.8 (194.40)	-4.5 (185.80)	-14.0 (99.66)	4.5 (175.23)	4.7 (132.26)
Median	-18.8	-34.6	-32.1	-18.8	-24.7
Range	-93, 1589	-100, 1653	-100, 714	-100, 1382	-100, 660
P-value ^c	-	0.157	0.093	-	0.223
Patients without secondarily generalized seizures	N=171	N=151	N=137	N=147	N=122
n	171	151	137	147	122
Mean ± SD	-13.6 ±51.95	-23.2 ±57.81	-37.3 ±53.07	-14.3 ±67.01	-48.0 ±48.53
Median	-18.5	-31.6	-45.6	-23.0	-57.5
Range	-100, 266	-100, 253	-100, 217	-100, 518	-100, 187
P-value ^c	-	0.012	<0.001	-	<0.001

Only patients with baseline and post-baseline seizures were included in the analysis.

Treatment by seizure subtype interaction (with or without secondarily generalized seizures) comparison vs placebo: ezogabine 600 mg/day vs placebo (p=0.770), ezogabine 900 mg/day vs placebo (p=0.086), ezogabine 1200 mg/day vs placebo (p=0.015).

- Consists of the placebo patients corresponding to the comparison with ezogabine 600 mg and 900 mg (Studies 205 and 302).
- Consists of the placebo patients corresponding to the comparison with ezogabine 1200 mg (Studies 205 and 301).
- Comparison vs placebo based on Rank Transformation Residual ANCOVA

Table A 5 Responder Rate by Seizure Type (Maintenance Phase) – ITT Maintenance Population (Studies 205, 301 and 302 Integrated)

	Placebo ^a	EZG 600 mg/day	EZG 900 mg/day	Placebo ^b	EZG 1200 mg/day
Simple partial seizures					
Patients with simple partial seizures	N=67	N=88	N=64	N=71	N=63
n	67	88	64	71	63
Responders	15 (22)	31 (35)	31 (48)	17 (24)	31 (49)
Adjusted Odds Ratio (95% CI) ^c		1.9 (0.9, 4.0)	3.6 (1.7, 7.7)		3.2 (1.5, 6.7)
P-value ^c		0.077	0.001		0.002
Patients without simple partial seizures	N=175	N=153	N=159	N=144	N=124
n	175	153	159	144	124
Responders	36 (21)	53 (35)	69 (43)	34 (24)	63 (51)
Adjusted Odds Ratio (95% CI) ^c		2.1 (1.3, 3.4)	3.0 (1.8, 4.9)		3.2 (1.9, 5.5)
P-value ^c		0.005	<0.001		<0.001
Complex partial seizures					
Patients with complex partial seizures	N=210	N=195	N=189	N=184	N=169
n	210	195	189	184	169
Responders	46 (22)	67 (34)	92 (49)	50 (27)	85 (50)
Adjusted Odds Ratio (95% CI) ^c		1.9 (1.2, 2.9)	3.5 (2.3, 5.4)		2.7 (1.7, 4.2)
P-value ^c		0.005	<0.001		<0.001
Patients without complex partial seizures	N=32	N=46	N=34	N=31	N=18
n	32	46	34	31	18
Responders	5 (16)	17 (37)	8 (24)	1 (3)	9 (50)
Adjusted Odds Ratio (95% CI) ^c		3.2 (1.0, 9.8)	1.7 (0.5, 5.9)		26.2 (2.9, 1276)
P-value ^c		0.047	0.415		<0.001 ^d

Continued

	Placebo ^a	EZG 600 mg/day	EZG 900 mg/day	Placebo ^b	EZG 1200 mg/day
Secondarily generalized seizures					
Patients with secondarily generalized seizures	N=71	N=90	N=86	N=68	N=65
n	71	90	86	68	65
Responders	15 (21)	32 (36)	33 (38)	16 (24)	23 (35)
Adjusted Odds Ratio (95% CI) ^c		2.1 (1.0, 4.2)	2.4 (1.2, 5.0)		1.8 (0.8, 3.8)
P-value ^c		0.051	0.016		0.142
Patients without secondarily generalized seizures	N=171	N=151	N=137	N=147	N=122
n	171	151	137	147	122
Responders	36 (21)	52 (34)	67 (49)	35 (24)	71 (58)
Adjusted Odds Ratio (95% CI) ^c		2.0 (1.2, 3.3)	3.7 (2.2, 6.1)		4.4 (2.6, 7.5)
P-value ^c		0.006	<0.001		<0.001

Only patients with baseline and post-baseline seizures were included in the analysis.

Treatment by seizure subtype interaction (with or without secondarily generalized seizures) comparison vs placebo: ezogabine 600 mg/day vs placebo (p=0.967), ezogabine 900 mg/day vs placebo (p=0.359), ezogabine 1200 mg/day vs placebo (p=0.055)

- Consists of the placebo patients corresponding to the comparison with ezogabine 600 mg and 900 mg (Studies 205 and 302).
- Consists of the placebo patients corresponding to the comparison with ezogabine 1200 mg (Studies 205 and 301).
- Comparison vs placebo is based on logistic regression.
- Comparison vs placebo is based on exact logistic regression.

11.4. Appendix: Liver Function in the All Phase II/III Grouping

Similar to the Pivotal Controlled Trials grouping, there was a low incidence of high PCC values ($\geq 3 \times \text{ULN}$) for AST or ALT post-baseline, although there was an increase over the incidence at baseline (Table A 6).

Nine patients had AST $\geq 5 \times \text{ULN}$ post baseline and one patient had an elevation of AST $\geq 10 \times \text{ULN}$ (Table A 6). Seventeen patients had elevated ALT $\geq 5 \times \text{ULN}$ post baseline and 3 patients had elevations of $\geq 10 \times \text{ULN}$.

As summarized in Table A 6, 17 patients had AST and/or ALT $\geq 5 \times \text{ULN}$ (9 patients had both AST and ALT $\geq 5 \times \text{ULN}$). Nine patients were withdrawn due to LFT AEs. Mini narratives for all cases of AST or ALT $\geq 5 \times \text{ULN}$ are included below.

Patients randomized to placebo in parent study:

- Patient 302-50107/304-50107, a 55-year-old Caucasian female receiving ezogabine 600mg/day along with carbamazepine and topiramate (had received placebo in the double-blind phase), had elevated transaminases from study Day 144 (day 41 of ezogabine), and elevated AST (208 IU/L) and ALT (274 IU/L) on Day 157. Transaminases remained elevated and the patient discontinued from the study (and ezogabine) on Day 164 due to the adverse event of increase liver function tests. No followup laboratory evaluations are available.
- Patient 301-10211/303-10211, a 22-year-old Hispanic female receiving ezogabine 1200 mg/day along with carbamazepine (had received placebo in the double-blind phase), had elevated AST (190 IU/L) and ALT (261 IU/L) on study Day 169 (Day 43 of ezogabine). The patient continued in the study on a reduced ezogabine dose. Transaminases remained elevated and the patient discontinued from the study on Day 176 due to the serious adverse event of liver function abnormalities. Her last dose of ezogabine was on Day 197. At followup on Day 225, AST and ALT had returned to within normal limits.
- Patient 304-50711 was a 33-year-old Caucasian female with a history of hepatitis B receiving ezogabine 900 mg/day (had received placebo in the double-blind phase) along with topiramate. She had elevated ALT (40 IU/L) beginning on Day 147 of ezogabine and ALT continued to increase to 146 IU/L on Day 218. The patient was discontinued from the study due to the adverse events of hepatitis and liver enzyme elevation. Her last dose of ezogabine was Day 225. The patient was hospitalized and diagnosed with drug induced hepatitis on Day 238. On Day 252, AST and ALT peaked with values of 571 IU/L and 1017 IU/L respectively. On Day 274 the patient had recovered from the event.
- Patient 301-01403/303-01403, a 46 year old Caucasian female receiving ezogabine 1200 mg/day (had received placebo in the double-blind phase) along with levetiracetam and lamotrigine, had an elevated ALT (192 IU/L) on study Day 166 (day 43 of ezogabine). The patient's ezogabine dose was decreased and she continued in the study. ALT continued to fluctuate between normal and abnormal, however, the patient remains ongoing in Study 303.

- Patient 301-15210/303-15210, a 43 year old Hispanic female receiving ezogabine 1200 mg/day (had received placebo in the double-blind phase) along with carbamazepine, clonazepam, and topiramate, had an elevated ALT (262 IU/L) on study Day 168 (day 44 of ezogabine) She was discontinued from the study due to the serious adverse event of increase of transaminases. Her last dose of ezogabine was on Day 183. On Day 190, at her final study visit, laboratory results were ALT 59 IU/L and AST 26 IU/L. Serology results from a blood draw on Day 200 were borderline for hepatitis C.
- Patient 304-55516 was a 23-year-old Caucasian female receiving ezogabine 600 mg/day (had received placebo in the double-blind phase) along with levetiracetam, lamotrigine, and gabapentin. She had elevated ALT (338 IU/L) on Day 383 of ezogabine and ALT (329 IU/L) on Day 393. She remains in the study and ALT returned to within normal limits on Day 512.

Patients randomized to ezogabine in parent study

- Patient 301-03506/303-03506, a 42-year-old Caucasian female receiving 1050 mg/day ezogabine along with phenytoin and phenobarbital, had elevated AST (228 IU/L) and ALT (379 IU/L) on Day 141 and of ALT (273 IU/L) on Day 155. The patient discontinued from the study due to the serious adverse event of elevated liver transaminases and her last dose of ezogabine was on Day 148. At her last visit (Day 162), AST and ALT had improved to 56 and 115 IU/L, respectively.
- Patient 303-10210, a 25-year-old Hispanic female receiving ezogabine 1200mg/day along with carbamazepine, had elevated AST (390 IU/L) and ALT (474 IU/L) on Day 441 and AST (253 IU/L) and ALT (311 IU/L) on Day 448. The patient discontinued from the study due to the adverse event of liver enzyme elevation. Her last dose of ezogabine was on Day 463 and transaminases returned to normal on Day 476.
- Patient 304-85314, a 61-year-old Caucasian male receiving ezogabine 900 mg/day along with carbamazepine and phenobarbital, had elevated transaminases from Day 169, (AST 246 IU/L and ALT 282 IU/L) on Day 232 and ALT (250 IU/L) on Day 260. Transaminases remained elevated and the patient discontinued from the study due to the adverse event of liver enzyme elevation. His last dose of ezogabine was on Day 247. On Day 288, AST and ALT levels decreased to 115 IU/L and 165 IU/L, respectively.
- Patient 212-00206, a 28-year-old Caucasian male receiving ezogabine 1100 mg/day along with levetiracetam, phenobarbital, and phenytoin, had an elevated AST of 302 IU/L on Day 204. The patient continued in the study and AST had normalized by Day 243.
- Patient 205-01016/212-0387, a 20-year-old Black male receiving ezogabine 900 mg/day along with oxcarbazepine, had elevated ALT on Day 141 (331 IU/L) and on Day 148 (532 IU/L). The patient was withdrawn from the study due to the adverse event of elevated liver enzymes. His last dose of ezogabine was on Day 151 and ALT decreased to 48 IU/L on Day 207.

- Patient 304-85206, a 25-year-old Caucasian female receiving ezogabine, 900 mg/day (had received placebo in the double-blind phase) along with carbamazepine had elevated ALT (186 IU/L) on study Day 175 (day 63 of ezogabine) and 318 IU/L on Day 185. The patient was withdrawn from the study due to the adverse event of elevated liver transaminases. She took her last dose of ezogabine on Day 203. ALT was 33 IU/L on Day 218.
- Patients 205-00471, 301-10511, 302-60214 and 302-25213 were previously discussed.
- Patient 202-100011, a 57-year-old Caucasian female receiving ezogabine 400 mg/day along with valproic acid, had elevated AST of 215 IU/L on Day 91, and 341 IU/L on Day 97 (ALT values on these days were 112 IU/L and 131 IU/L, respectively). The patient discontinued both ezogabine and valproic acid and was started on gabapentin. Transaminases returned to normal within 2 months.

There was a low incidence (<1.0%) of total bilirubin values meeting the high PCC criterion (≥ 2 mg/dL) (Table A 6). Most patients with elevated total bilirubin had single isolated occurrences. Two patients had more than one high total bilirubin value:

- Patient 202-120001, a 36 year old Caucasian male taking ezogabine 1200 mg/day along with phenytoin had an elevation of total bilirubin meeting the PCC criterion of 34.2 umol/L on Day 81. The patient continued in the study and had elevated bilirubin values at Day 123 and 140. None of these findings were noted as adverse events. The patient continued into study 208 and total bilirubin returned to within normal limits by Day 172.
- Patient 202-120005, a 17 year old Hispanic female, taking 1000 mg/day of ezogabine along with carbamazepine had two isolated events of elevated bilirubin on Day 74 and Day 158. Neither event was reported as an adverse event and the patient continued on into study 208. Total bilirubin remained within normal limits up to the patient's final visit on Day 1545.

There was a low incidence (<1.0%) of alkaline phosphatase values meeting the high PCC criterion ($\geq 3 \times$ ULN) (Table A 6).

As observed in the Pivotal Controlled Trials grouping, there were no reports of patients who met criteria for Hy's Law.

Table A 6 Liver Function Indices of Potential Clinical Concern (Safety Population: All Phase II/III Combined)

		Percentage of Patients (n/N)
		EZG (N=1365)
AST		
PCC high	B	<1.0 (4/1339)
(≥3 x ULN)	P-B	1.6 (21/1303)
(≥5 x ULN)	P-B	<1.0 (9/1303)
(≥10 x ULN)	P-B	<1.0 (1/1303)
ALT		
PCC high	B	<1.0 (2/1339)
(≥3 x ULN)	P-B	3.1 (40/1302)
(≥5 x ULN)	P-B	1.3 (17/1302)
(≥10 x ULN)	P-B	<1.0 (3/1302)
Alkaline phosphatase		
PCC high	B	<1.0 (1/1330)
(≥3 x ULN)	P-B	<1.0 (2/1299)
Total bilirubin		
PCC high	B	<1.0 (3/1334)
	P-B	<1.0 (9/1298)

B=baseline; P-B=post-baseline

11.5. Appendix: Urinary Retention Epidemiology Study Draft Protocol Outline

APPENDIX 11.5:

DRAFT PROTOCOL SUMMARY: POST MARKETING EPIDEMIOLOGY STUDY OF URINARY RETENTION FOLLOWING EZOGABINE EXPOSURE

Rationale

A post-marketing safety surveillance study using a United States (US) claims database coupled with medical records review will be implemented to determine the risk of urinary retention (UR) associated with exposure to polytherapy antiepileptic drug (AED) regimens containing ezogabine (EZG) in a real-world setting. The risk of UR among epilepsy patients treated with EZG containing polytherapy regimens will be compared to the risk among epilepsy patients treated with other AED polytherapy regimens. In addition, EZG users will be described in terms of their demographic characteristics, concomitant medication use, and co-morbid medical conditions associated with UR.

Objective(s)

The objective of the study is to quantify the risk of UR associated with exposure to EZG in a real-world setting. Specific aims include the following:

1. To determine the magnitude of the risk and time to onset of UR associated with post-marketing use of EZG.
2. To determine whether the risk and time to onset of UR varies according to age, concomitant antiepileptic drug use, and underlying co-morbidities.
3. To describe patients receiving EZG in terms of demographics, co-morbidities and concomitant AED use.
4. To quantify the proportions of EZG users
 - a. receiving medication potentially associated with UR.
 - b. with conditions pre-disposing to UR.
5. To monitor for off label use of EZG.

Study Design

The study will use health insurance claims data within the Healthcore Integrated Research Database (HIRDsm) to initially identify treated epilepsy patients. The database captures information on diagnoses, procedures, and diagnostic or interventional workups associated with inpatient hospitalizations and outpatient visits (including laboratory results from blood samples), as well as prescription drug use for individuals covered by the healthcare plans offered by Wellpoint. This is the largest privately insured health benefits company in the United States.

This prospective cohort study of treated epilepsy patients will, from the time of EZG launch, capture patients starting a new AED polytherapy treatment. Patients classified as exposed to any polytherapy including EZG and polytherapy not including EZG will be followed until the first of a case of UR, change in AED polytherapy, loss to follow up or the end of the study (when the pre-specified sample size of EZG users has been attained).

Study Endpoints/Assessments

The primary study outcome will be UR during study follow-up. ICD-9 diagnosis codes will be used to identify cases of UR from the HIRDsm. Cases will be considered overall and then stratified by severity. Severe cases of UR will be identified according to such criteria as a hospitalization with a claim for UR or a claim for UR and a claim for catheterization or other procedures indicating severe UR. Diagnostic codes will be validated via a medical chart review study.

Analysis

The primary analysis will concentrate on individuals using AED polytherapy, given the initial EZG indication of adjunctive therapy for partial seizures. The incidence of UR (with associated confidence intervals), as well the cumulative incidence, will be calculated for individuals receiving EZG and non-EZG polytherapy combinations.

Poisson regression will be used to assess potential associations between UR and exposure and UR and baseline patient characteristics. Incidence rate ratios for UR will be reported as well as rate differences between exposure groups.

In addition, Poisson regression will be used to compare the cumulative incidence of UR at set time intervals post EZG (or alternative therapy) initiation. For example, the cumulative incidence of UR will be compared between EZG and non-EZG polytherapy users at 1, 3, 6, 12 and 24 months post therapy initiation to investigate time to onset of UR.

The duration of the prospective cohort study will be determined by market uptake of EZG. An analytical study will only be completed once a pre-specified EZG sample size, as per power calculation, has been reached to ensure an adequately powered study. As it could take several years to reach the pre-specified EZG sample size, descriptive analyses will be completed every six months post EZG launch. These analyses will describe:

- The characteristics of EZG users in terms of demographics, co-morbidities and concomitant use of AEDs and medications associated with an increased risk of UR;
- The incidence of UR in EZG users. The incidence among EZG users will be compared descriptively to the UR incidence calculated from a historical cohort of polytherapy treated epilepsy patients from the pre-EZG time period of the HIRDsm. The historical data will be used as a benchmark against which to monitor for a large increase in risk of UR associated with EZG use prior to adequate sample sizes for an analytical study.
- Off label use of EZG. This analysis will use a different population denominator assessing usage of EZG outside of the epilepsy polytherapy cohort within the HIRD.

Finally, a medical record validation will be conducted to validate the accuracy of UR diagnosis, based on ICD-9 codes, and to assess the etiological role of AEDs in association with UR in the claims data.

Project Timeline

The prospective study cohorts will be built within the HIRDsm following the launch of EZG.

Semi-annual reports will be produced describing:

- Characteristics of EZG users
- Descriptive comparison of the incidence of UR in EZG users versus the historical cohort of AED polytherapy users from the pre-EZG launch period of the HIRD.
- Prevalence of off label use

Power calculations will consider

- Precision for a range of potential UR incidence estimates associated with different sample sizes and
- Sample sizes needed to detect pre-specified differences in UR incidence between exposure groups with adequate power.

These calculations will be re-run using background UR incidence estimates from the historical cohort. This, together with market uptake of EZG, will be used to estimate overall study duration and will be reported within semi-annual updates.

11.6. Appendix: Targeted Follow Up Questionnaire

APPENDIX 11.6: TARGETED FOLLOW-UP QUESTIONNAIRE FOR VOIDING DYSFUNCTION/URINARY RETENTION (DRAFT)

Targeted Follow Up Questionnaire EZOGABINE AND URINARY RETENTION		
Patient/subject ID, DOB/initials:	Sex/weight (is patient obese if weight unknown):	CASE No:
Description of the Event:		
Prior to the event did the patient report any of the following?	Yes	No
1. Dysuria	<input type="checkbox"/>	<input type="checkbox"/>
2. Urinary hesitation	<input type="checkbox"/>	<input type="checkbox"/>
3. Poor urinary stream	<input type="checkbox"/>	<input type="checkbox"/>
4. Nocturia	<input type="checkbox"/>	<input type="checkbox"/>
Was the event associated with?		
1. Urinary tract infection	<input type="checkbox"/>	<input type="checkbox"/>
2. Any change in background medication	<input type="checkbox"/>	<input type="checkbox"/>
Medical History		
Does the patient have a history of any of the following conditions?	Yes	No
1. Benign prostatic hypertrophy	<input type="checkbox"/>	<input type="checkbox"/>
2. Any other disorder associated with bladder outflow obstruction	<input type="checkbox"/>	<input type="checkbox"/>
3. Neurological disease with bladder dysfunction, for example multiple sclerosis	<input type="checkbox"/>	<input type="checkbox"/>
4. Renal calculi	<input type="checkbox"/>	<input type="checkbox"/>
If yes, please describe:		

Medication History	Yes	No
Has the patient take any of the following medicines prior the event?		
1. Anticholinergic drugs for detrusor instability, for example tolterodine.	<input type="checkbox"/>	<input type="checkbox"/>
2. Other drugs with anticholinergic properties, for example:	<input type="checkbox"/>	<input type="checkbox"/>
a. Amitriptyline	<input type="checkbox"/>	<input type="checkbox"/>
b. Loperamide	<input type="checkbox"/>	<input type="checkbox"/>
c. Chlorpheniramine	<input type="checkbox"/>	<input type="checkbox"/>
3. Sympathomimetic drugs, for example pseudoephedrine	<input type="checkbox"/>	<input type="checkbox"/>
Diagnostic Tests:	Yes	No
Please provide a summary of main results of abnormal laboratory values / investigations (or provide copies of relevant results):		
Were urea and electrolytes measured?	<input type="checkbox"/>	<input type="checkbox"/>
If yes, please indicate dates and results:		
Was a renal ultrasound performed?	<input type="checkbox"/>	<input type="checkbox"/>
If yes, please describe result (or attach a copy of the report)		
Outcome:	Yes	No
1. Did the patient require urinary bladder catheterisation?	<input type="checkbox"/>	<input type="checkbox"/>
2. Has the patient discontinued therapy with ezogabine?	<input type="checkbox"/>	<input type="checkbox"/>
3. Has bladder function returned to normal?	<input type="checkbox"/>	<input type="checkbox"/>
4. If continuing with ezogabine, are there ongoing urinary symptoms. If so please describe:	<input type="checkbox"/>	<input type="checkbox"/>

11.7. Appendix: Renal/Urinary Events (NDA Data Cut-Off: 30 June 2008)

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1. BACKGROUND

The 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. Other work has suggested the possibility of a central effect in addition to the local effects on the bladder myocytes [Streng, 2004].

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.

This document provides a summary of renal and urinary events reported with ezogabine as of the 30 June 2008 integrated ISS database cut off date for the original application. In addition, serious and severe renal and urinary events from ongoing clinical trials up to the submission cut-off date of 31 December 2008 are provided. This document focuses on the Pivotal Controlled Trials and All Phase II/III Combined study groupings.

2. OVERALL SEARCH STRATEGY

2.1. Methodology for Capturing Urinary/Renal Events of Interest

A search was conducted on the pooled ISS data sets for the Pivotal Controlled Trials (Studies 205, 301, and 302) and the All Phase II/ III Combined studies (includes primary efficacy studies and open label extension studies; integrated ISS database cut-off date of 30 June 2008) using MedDRA preferred terms relating to the renal/urinary tract identified by three sponsor physicians.

Table 1 Preferred Terms Used for Identifying Renal/Urinary AEs

SOC	Preferred Term MedDRA Version (Derived from Pooled Safety Data-set)	FDA required search terms
Renal and Urinary Disorders	Atonic urinary bladder; bilirubinuria; bladder discomfort; bladder diverticulum; bladder pain; bladder spasm; calculus bladder; calculus ureteric; chromaturia; costovertebral angle tenderness; crystalluria; dysuria; glomerulonephritis; glycosuria; haematuria; hydronephrosis; hypertonic bladder; leukocyturia; micturition disorder; micturition frequency decreased; micturition urgency; nephritis; nephrolithiasis; nephropathy toxic; neurogenic bladder; nocturia; oliguria; pollakiuria; polyuria; proteinuria; psychogenic dysuria; pyuria; renal colic; renal cyst; renal failure; renal failure acute; renal pain; strangury; terminal dribbling; ureteric stenosis; urethral pain; urethral stenosis; urinary hesitation; urinary incontinence; urinary retention; urinary tract disorder; urinary tract pain; urine abnormality; urine flow decreased; urine odor abnormal	urinary, bladder, calculi, incontinence, renal, urinary retention
Investigations	Bacteria urine; blood creatinine increased; blood urea increased; blood urine present; crystal urine; crystal urine present; glucose urine present; protein urine; protein urine present; red blood cells urine; red blood cells urine positive; residual urine volume; urinary casts; urinary sediment abnormal; urinary sediment; urine analysis; urine analysis abnormal; urine color abnormal; urine leukocyte; urine output decreased; urine output increased; white blood cells urine; white blood cells urine positive;	urinary tract infection; calculi
Infections and Infestations	Asymptomatic bacteriuria; bacteriuria; cystitis; genitourinary tract infection; kidney infection; pyelonephritis; urinary tract infection; urinary tract infection bacterial; urosepsis;	urinary tract infection
General Disorders and Administration Site Conditions	Microlithiasis	calculi

Provided in [Figure 1](#) are the steps followed in order to identify cases involving AEs of possible interest related to the kidneys, bladder and urinary tract.

Figure 1 Search Strategy for Identifying Cases of Renal/Urinary AEs

Step 1

A broad list of preferred terms (PT) and verbatim terms has been selected from ISS AE listings. FDA suggested verbatim terms have been mapped to the selected ISS PTs.



Step 2

The resulting list from Step 1 was reviewed by Sponsor physicians and terms that were judged consistent with urinary/renal involvement (SOCs of Renal and Urinary Disorders; Investigations; Infections and Infestations and General Disorders and Administration Site Conditions) were identified.



Step 3

Renal /urinary disorder PTs were further assigned to one of 4 categories: Voiding Dysfunction and Urinary retention; Renal Dysfunction; UTIs and related Signs and Symptoms and Urinary Crystals.



Step 4

Narratives were written for all renal / urinary events of severe intensity (consistent with Pre-NDA agreement)



Step 5

Clinical review of narratives were undertaken by sponsor physicians to ensure events represent cases of renal /urinary events of special interest as designated by the FDA



Step 6

‘Patient profiles’ were generated for all cases of non serious, non-severe adverse events in lieu of narratives

2.2. Description of assessments leading to generation of narratives and patient profiles:

Step 1: Generation of a broad screen

A computerized search strategy was implemented to identify AEs relevant to the safety topic of special interest. AEs identified using the broad search criteria were not considered to be cases. Rather, they were a comprehensive list of all AEs requiring further evaluation in order to determine whether or not they were judged as potential cases of AEs relevant to safety topics of special interest.

Step 2: Initial filtering to potential AEs of safety topics of special interest

Unique preferred and verbatim term combinations relating to the renal/urinary tract were identified from the ISS AE listings by three sponsor physicians. A data cut-off date of 30 June 2008, consistent with the integrated ISS database cut-off was used. A check was run to ensure all the FDA requested verbatim terms and text strings fell within the preferred terms identified using this search strategy, and any potential new preferred/verbatim term combinations were added.

Step 3: Categorization of renal / urinary events

Preferred terms from this search were further evaluated by sponsor physicians to the following sub – categories where possible:

- Voiding Dysfunction and Urinary Retention
- Renal Dysfunction (renal failure)
- UTIs and Related Signs and Symptoms
- Urinary Crystals

All other events were assigned to an ‘other’ category where it was not possible to confidently assign to a specific sub-category at this stage

Step 4: Narratives for potential renal/urinary events

Narratives for all renal / urinary cases of **severe intensity** were written up to June 30, 2008, consistent with the integrated ISS database cut-off. These were presented under the 4 sub - categories listed in step 3. Any other severe renal / urinary event not previously sub -categorized were listed under ‘other’.

Step 5: Clinical review of narratives

Each narrative was reviewed by a physician to ensure events represent cases of renal /urinary events of special interest as designated by the FDA and that the event was listed in the appropriate sub category.

Step 6: ‘Patient profile’s for non serious / non severe renal/urinary events

For non-serious, non-severe renal/urinary adverse events identified from step 2, key information captured in the case report form was presented in a detailed patient profile.

3. RESULTS

3.1. Overall Discussion of Renal/Urinary Disorders

3.1.1. Pivotal Controlled Trials (Studies 205, 301 and 302)

3.1.1.1. Incidence of Adverse Events

During the double-blind phase of randomized controlled trials, renal and urinary disorders AEs were reported for greater proportions of patients in the Total EZG group than the placebo group (17% versus 12.9%) ([Table 2](#)).

The relative risk of reporting a renal/urinary disorder event was calculated as follows:

$$\frac{(\text{No. of patients with event in ezogabine group} / \text{Total no. of patients in ezogabine group})}{(\text{No. of patients with event in placebo group} / \text{Total no. of patients in placebo group})}$$

The relative risk of reporting a renal/urinary disorder in the Total EZG 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 EZG group were 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%).

In addition to the events belonging to the renal and urinary disorders SOC, urinary tract infections (which are classified under the infections and infestations SOC) are also examined here to better understand the overall effect of the drug on the urinary tract. Events of urinary tract infection were slightly more common in placebo than ezogabine. Overall, 4.7% of patients from the placebo group compared to 4.3% of patients from the ezogabine group reported urinary tract infections. UTI’s are further discussed in [Section 3.2.2.1](#).

Dysuria, chromaturia, urine analysis abnormal and polyuria appeared to show a dose related increase. Although UTIs also increased across the ezogabine dose groups, UTI was only more common than placebo in the 1200mg/day group with no overall excess over placebo.

Table 2 Adverse Events of Renal/Urinary Disorders Reported by 2 or more Patients in Any Treatment Group (Safety Population: PCT, 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 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)
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)

Most renal/urinary events in the Total EZG group were first reported in the initial 8 weeks of treatment with the majority appearing within the first 28 days. Sixteen/813 (2%) were reported during day 1 to 7, 9/793 (1%) between days 8 to 13; 32/781 (4.1%) between days 14 to 27; and 41/746 (5.5%) between days 28 to 55.

Results by Study Phase (Titration and Maintenance) are presented in [Table 3](#). During titration the number of patients reporting events in the placebo, 600 mg/day and 900 doses mg/day were similar, but the rate at 1200mg was higher.

During the maintenance phase, the rate of events was similar for placebo, 600 and 900 mg/day, but higher for 1200mg/day. Between titration and maintenance the rate increased by approximately 50% in both placebo and the 1200mg groups. This may be explained as a factor of time on treatment with more events being reported during the longer maintenance phase as opposed to the titration phase.

Table 3 Adverse Events of Common (Reported in at Least 2% of Patients) Renal/Urinary Disorders Reported by Study Phase (Titration and Maintenance) in Any Treatment Group (Safety Population: PCT, 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)
Titration Phase					
Any event	26 (6.1)	20 (7.1)	21 (7.7)	37 (14.3)	78 (9.6)
Urinary tract infection	7 (1.6)	2 (0.7)	4 (1.5)	11 (4.2)	17 (2.1)
Dysuria	3 (0.7)	3 (1.1)	2 (0.7)	6 (2.3)	11 (1.4)
Preferred Term	Placebo N=383	Ezogabine			
		600 mg/day (N=243)	900 mg/day (N=226)	1200 mg/day (N=189)	Total (N=658)
	Maintenance Phase				
Any event	33 (8.6)	20 (8.2)	16 (7.1)	40 (21.2)	76 (11.6)
Urinary tract infection	12 (3.1)	2 (0.8)	4 (1.8)	15 (7.9)	21 (3.2)
Dysuria	1 (0.3)	2 (0.8)	3 (1.3)	6 (3.2)	11 (1.7)
Urinary Hesitation	3 (0.8)	3 (1.2)	1 (0.4)	4 (2.1)	8 (1.2)

A total of 138 patients in the Total EZG group reported renal/urinary events. Of these, the majority of reported events were a maximum intensity of mild (100/138, 72.5%); 31/138 (22.5%) were moderate, and 7/138 (5%) were severe in intensity. In the placebo group, 40/55 (73%) events were mild, 14/55 (25.5%) events were moderate and 1/55 (1.8%) event was severe in intensity.

A summary table of all renal/urinary events of severe intensity is in [Table 4](#). A listing of all severe cases is provided in [Table 9](#).

Table 4 Adverse Events of Renal/Urinary Disorders of Severe Intensity in Any Treatment Group (Safety Population: PCT, 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 event	1 (0.2)	1 (0.4)	4 (1.5)	2 (0.8)	7 (0.9)
Urinary retention	0	0	1 (0.4)	0	1 (0.1)
Renal Colic	0	0	1 (0.4)	0	1 (0.1)
Urethral pain	1 (0.2)	0	0	0	0
Bladder spasm	0	0	0	1 (0.4)	1 (0.1)
Renal failure	0	1 (0.4)	0	0	1 (0.1)
Urinary tract infection	0	0	1 (0.4)	1 (0.4)	2 (0.2)
Residual urine volume	0	0	1 (0.4)	0	1 (0.1)

There were more severe cases of renal/urinary disorders in the Total EZG group than placebo. There was no clear dose relationship. Two cases of UTIs of severe intensity were reported.

3.1.1.2. Serious Adverse Events Due to Renal/Urinary Disorders

There were 5 SAEs relating to Renal/Urinary Disorders in 4 (<1%) patients in the Total EZG group compared to 1 (0.2%) SAE for a patient on placebo.

Listings of the individual patients are presented in [Table 5](#).

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.

Table 5 **Serious Adverse Events Due to Renal/Urinary Disorders (Safety Population: PCT, 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
205	000448	53/C/F	600 (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	

C= Caucasian, H = Hispanic, A = Asian, M = Male, F = Female, UNK= Unknown

3.1.1.3. Discontinuations Due to Renal/Urinary Disorders

Nine patients discontinued due to renal/urinary events ([Table 6](#)). Of these 3 (0.7%) patients were in the placebo treatment group. Six (0.7%) patients treated with ezogabine withdrew: 1 case each of UTI, renal failure, hematuria, atonic urinary bladder, urinary retention and nephritis. There was no clear pattern to onset of event leading to discontinuation. Most cases occurred in the 600 mg/day group. One patient in the 1200mg/day group actually received 1050mg/day at the time of AE leading to discontinuation.

Table 6 Discontinuations Due to Renal/Urinary Disorders (Safety Population: PCT, 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

C= Caucasian, H = Hispanic, A = Asian, M = Male, F = Female, UNK = Unknown

3.1.2. All Ph II/III Combined

3.1.2.1. Incidence of Adverse Events

A summary of renal and urinary disorder AEs reported by ezogabine-treated patients in the All Phase II/III Combined studies is presented in [Table 7](#).

Table 7 Adverse Events of Renal/Urinary Disorders Reported by 2 or more Patients (Safety Population: All Phase II/III Combined)

Preferred Term	Number (%) of Patients EZG (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)

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.

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.

During the combined Phase II/III studies most events were mild in intensity (228/346 events, 66%); 95/346 (27%) events were a maximum intensity of moderate while 22/346 (6%) were severe. [Table 8](#) summarizes all severe cases of renal/urinary disorders.

**Table 8 Adverse Events of Renal/Urinary Disorders of Severe Intensity
(Safety Population: All Phase II/III Combined)**

Preferred Term	Number (%) of Patients EZG (N=1365)
Any event	22 (1.6)
Urinary tract infections	5 (0.4)
Urinary retention	3 (0.2)
Renal Colic	3 (0.2)
Urinary hesitation	2 (0.1)
Residual urine volume	2 (0.1)
Hematuria	2 (0.1)
Renal failure	1 (<0.1)
Renal failure acute	1 (<0.1)
Urosepsis	1 (<0.1)
Red blood cells urine	1 (<0.1)
Blood creatinine increased	1 (<0.1)
Nephrolithiasis	1 (<0.1)
Micturition Frequency decreased	1 (<0.1)
Bladder Spasm	1 (<0.1)

Twenty three patients reported severe events related to renal/urinary disorders ([Table 9](#)). [Table 9](#) summarizes all severe AEs reporting renal/urinary disorders reported as of the 31 December 2008 submission cut-off date. This included one case reported between 30th June 2008 and 31st December 2008 ([Patient 303-000902](#), who reported urinary retention at a ezogabine dose of 900 mg/day).

Approximately half of the severe AEs were also SAEs. The majority of AEs resolved.

**Table 9 Listings of Severe Adverse Events of Renal/Urinary Disorders
(Safety Population: All Phase II/III Combined)**

Study	Patient ID	Age/Race/ Gender	Actual Dose at time of AE Mg/day	Preferred Term	Day of onset	SAE Y/N	Resolved Y/N	Withdrawn Y/N
212	000286	37/C/M	600.0	Urinary Tract Infection	444	N	Y	UNK
212	000110	42/C/F	800.0	Urinary Tract Infection	64	N	Y	N
212	000693	22/C/F	600.0	Urosepsis	170	Y	Y	Y
301	010206	46/H/F	750.0	Urinary Tract Infection	19	N	Y	UNK
302 ¹	025509	47/C/F	600.0	Urinary Tract Infection	118	Y	Y	UNK
					119	Y	Y	UNK
302	055506	47/C/M	450.0	Urinary Tract Infection	13	N	Y	UNK
208	000013	39/C/F	400.0	Nephrolithiasis	114	Y	Y	N
			700.0	Hematuria	560	Y	Y	N
			600.0	Renal Colic	681	Y	Y	UNK
			1200.0	Renal Failure Acute	986	Y	Y	UNK
208	000017	18/C/F	1200.0	Renal Failure Acute	986	Y	Y	UNK
205	000125	39/C/M	900.0	Renal Colic	43	Y	Y	N
212	000184	33/C/M	1150.0	Renal Colic	266	Y	Y	UNK
205	000448	53/C/F	600.0	Renal Failure	20	Y	N	Y
214	000015	30/C/M	450.0	Blood Creatinine Increased	14	N	Y	N
301 ¹	000103	20/C/F	918.8	Hematuria	43	Y	Y	UNK
303	001416	70/C/M	1200.0	Urinary Hesitation	274	N	Y	UNK
303	002512	42/C/F	1200.0	Red Blood Cells Urine	46	N	Y	UNK
303	003505	30/C/M	1050.0	Urinary Retention	81	N	N	Y
303	000902	39/C/M	900	Urinary retention	872	Y	Y	N
301 ¹	003901	58/C/M	600.0	Micturition Frequency Decreased	17	N	Y	Y
			714.3	Urinary Retention	28	Y	Y	Y
301	010308	69/H/M	60.0	Bladder Spasm	15	N	Y	UNK
302	030301	48/C/F	900.0	Urinary Retention	29	N	Y	Y
302 / 304	050102	45/C/F	825.0	Residual Urine Volume	57	N	Y	UNK
304	055505	58/C/F	750.0	Residual Urine Volume	168	N	Y	UNK
304	055510	37/C/M	900.0	Urinary Hesitation	29	N	Y	UNK

C = Caucasian, H = Hispanic, A = Asian, X = Other, M = Male, F = Female. UNK = Unknown

NOTE: Bolded patient numbers represent new reports between 1 January 2008 and 31 December 2008

1. Reported in the transition phase of the parent study.

3.1.2.2. Renal/Urinary SAEs

Sixteen (1%) patients reported a total of 20 SAEs due to renal/urinary disorders (Table 10).

The most commonly reported was urinary retention reported in 4 (0.3%) patients, followed by urinary tract infections and renal colic, reported in 3 (0.2%) patients each, and hematuria, reported in 2 (0.1%) patients.

Table 10 Serious Adverse Events Due to Renal/Urinary Disorders (Safety Population: All Phase II/III Combined)

Study	Patient ID	Age/Race/ Gender	Actual Dose at time of AE mg/day	Preferred Term	Day of onset	Resolved Y/N	Withdrawn Y/N
205	000125	39/C/M	900	Renal colic	43, 49	Y	N
205	000448	53/C/F	600	Renal failure	20	Y	Y
302	025108	31/C/F	600	Urinary retention	19	Y	N
302	025405	34/C/F	600	Atonic urinary bladder	21	Y	Y
			UNK	Urinary incontinence	63	Y	
212	000693	22/C/F	600	Urosepsis	170	Y	Y
303	000103 ^a	20/C/F	1200	Urinary tract infection	97	Y	N
301	010607	31/H/F	1400	Urinary tract infection	137	Y	N
302	025509	26/C/F	600	Urinary tract infection	118	Y	N
208	000013	39/C/F	700	Hematuria	560	Y	N
			600	Hematuria	681		
			600	Renal colic	681		
208	000017	18/C/F	1200	Renal failure acute	986	Y	N
212	000184	33/C/M	1150	Renal colic	266	Y	N
301	000103 ^a	20/C/F	918.8	Hematuria	43	Y	N
303	000902	39/C/M	990	Urinary retention	698	Y	Y
303	003505	30/C/M	1050	Urinary retention	81	Ongoing	Y
301	003901	58/C/M	600	Urinary retention	28	Y	Y
304	050710	24/C/M	0	Hydronephrosis	166	Y	Y
304	060306	52/C/M	600	Nephropathy toxic	455	Y	Y

C = Caucasian, H = Hispanic, A = Asian, M = Male, F = Female, UNK = unknown

Note: Bolded Patient numbers represent newly reported between 1 January 2008 and 30 June 2008.

a. Patient 000103 is listed twice, but for different studies: 301 and 303.

Two reports are of interest. Patient 25405 from Study 302 reported decreased bladder sensation and associated urinary incontinence 21 days after receiving ezogabine 600 mg daily. Subsequently, urinary incontinence was reported after 63 days of treatment. These events were classified as atonic bladder; however, repeat bladder ultrasounds documented PVRs generally less than 100 mL, with a maximum value of 159 mL. Patient was withdrawn from the study and the events resolved.

Patient 60306 from Study 304 was hospitalized due to reported drug-related nephropathy 455 days after receiving therapy with ezogabine 900 mg daily plus valproate (unknown dose). Chemistry values, including creatinine and BUN, were near or slightly above the upper limit of normal ranges throughout treatment in Study 302 and 304. Upon hospitalization, drug taper was begun and the patient was discharged one week later. Serum chemistries normalized within approximately 1 month after discontinuation of ezogabine.

3.1.2.3. Discontinuations Due to Renal/Urinary AEs

Fourteen (1%) patients reported a total of 15 AEs due to renal/urinary disorders (Table 11).

Table 11 Discontinuations Due to Renal/Urinary Events (Safety Population: All Phase II/III Combined)

Study	Patient ID	Age/Race/Gender	Actual Dose at time of AE mg/day	Preferred Term	Day of Onset	SAE Y/N	Resolved Y/N
302	070101	22/C/F	600	Urinary tract infection	77	N	Y
205	000448	53/C/F	600	Renal failure	20	Y	N
301	001303	26/C/M	1050	Hematuria	42	N	Y
302	025405	34/C/F	600	Atonic urinary bladder	21	Y	Y
302	030301	48/C/F	900	Urinary retention	29	N	Y
302	090509	49/C/M	377.8	Nephritis	81	N	Y
212	000528	39/C/M	800	Urinary tract infection	206	N	Y
212	000693	22/C/F	600	Urosepsis	170	Y	Y
303	003505	30/C/M	1050	Urinary retention	81	Y	N
				Micturition frequency decreased	17 ¹	N	Y
301	003901	58/C/M	714.3	Urinary retention	28 ¹	Y	
304	050710	24/C/M	0	Hydronephrosis	166	Y	Y
304	060306	52/C/M	600	Nephropathy toxic	455	Y	Y
304	070201	36/C/M	750	Urinary retention	501	N	Y
304	070310	31/C/F	900	Urinary retention	171	N	N

C = Caucasian, H = Hispanic, A = Asian, M = Male, F = Female.

1. Events occurred on days 17 and 28 of the long-term extension study

Note: Bolded Patient numbers represent newly reported between 1 January 2008 and 31 December 2008.

There was no clear pattern to onset of event leading to discontinuation, with cases being clustered both earlier (between days 20-81) and later (166 to 455 days) in treatment. Most cases clustered around the 600 mg/day dose. One patient in the 1200mg/day group actually received 1050 mg/day at the time of AE leading to discontinuation.

3.2. Renal/Urinary Event Sub-Groups

3.2.1. Voiding Dysfunction and Urinary Retention

For this document, the following preferred terms were used to identify events related to voiding dysfunction and urinary retention: atonic urinary bladder; residual urine volume; bladder discomfort; bladder disorder; bladder diverticulum; bladder pain; calculus bladder; dysuria (verbatim terms difficulty in initiating micturition and difficulty initiating ,micturition), hypertonic bladder, micturition disorder; micturition frequency decreased; micturition urgency; neurogenic bladder; oliguria; pollakiuria; strangury; urinary hesitation; urinary retention; urinary tract disorder; urine flow decreased.

3.2.1.1. Pivotal Controlled Trials (Studies 205, 301 and 302)

Adverse events possibly related to voiding dysfunction and urinary retention were reported more frequently in patients receiving ezogabine (43 [5%] patients in the Total EZG group versus 11 [3%] patients in the placebo group) (Table 12).

The most common event reported was urinary hesitation (2%), followed by residual urine volume (1%). All other events were reported at <1%. All events were reported more frequently in Total EZG group compared with placebo, with the exception of micturition urgency. Although the largest effects for the 'any event' category were seen in the high dose group (1200 mg/day), there was no consistent dose relationship pattern for individual preferred terms.

Table 12 Adverse Events of Voiding Dysfunction and Urinary Retention (Safety Population: PCT, 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 event	11 (2.6)	12 (4.3)	13 (4.8)	18 (6.9)	43 (5.3)
Urinary hesitation	4 (0.9)	6 (2.1)	3 (1.1)	9 (3.5)	18 (2.2)
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)
Bladder disorder	1 (0.2)	1 (0.4)	0	1 (0.4)	2 (0.2)
Hypertonic bladder	0	1 (0.4)	0	1 (0.4)	2 (0.2)
Micturition frequency decreased	0	2 (0.7)	0	0	2 (0.2)
Urine flow decreased	2 (0.5)	1 (0.4)	0	1 (0.4)	2 (0.2)
Micturition urgency	3 (0.7)	0	0	1 (0.4)	1 (0.1)
Atonic urinary bladder	0	0	1 (0.4)	0	1 (0.1)
Bladder diverticulum	0	0	1 (0.4)	0	1 (0.1)
Bladder pain	0	0	0	1 (0.4)	1 (0.1)
Bladder spasm	0	0	0	1 (0.4)	1 (0.1)
Dysuria	0	0	1 (0.4)	0	1 (0.1)
Micturition disorder	0	1 (0.4)	0	0	1 (0.1)
Oliguria	0	0	0	1 (0.4)	1 (0.1)
Urinary incontinence	0	0	1 (0.4)	0	1 (0.1)
Urinary tract disorder	1 (0.2)	0	0	0	0

Although urinary hesitation was reported more frequently in the Total EZG group than in placebo, there did not seem to be a dose relationship, with 6 events in the 600 mg/day group, 3 events in the 900 mg/day group and 9 events in the 1200 mg/day group. Most events (16/18) of urinary hesitation were of mild intensity (2% Total EZG vs 0.2% Placebo), while 2 (0.4%) were of moderate intensity. None of the events were classified as severe or serious and none led to discontinuation from the studies. Events occurred more frequently in the first 8 weeks of treatment.

AEs of residual urine volume were reported by 8 (1%) patients in the Total EZG group and 1 (0.2%) patient in the placebo group. More events were reported in the 900 mg/day

and 1200 mg/day groups. There were 3 (0.4%) reports of mild residual urine volume, 4 (0.5%) reports of moderate intensity and 1 (0.1%) report of severe intensity versus 1 (0.2%) report of moderate intensity on placebo. There were no SAEs or discontinuations due to this AE. The majority of reported events were seen between days 56-84; this was the earliest time-point beyond baseline where PVRs were measured.

Urinary retention was reported by 7 (0.9%) of patients in the total EZG group versus 2 (0.5%) in the placebo group. The majority of events occurred during the first 8 weeks of treatment. There was no apparent dose relationship, with 1 report in the 600mg/day group, 4 in the 900 mg/day group and 2 in the 1200 mg/day group. There were 3 SAEs (Patients 301- 005203, 302-025108 and 302-025405), one patient on placebo and two on 900 mg/day (Table 5). All of the patients recovered and continued in the study. Slightly more males than females reported urinary retention (14, 2.1% vs 12, 1.7%).

3.2.1.2. All Phase II/III Combined

AEs relating to voiding dysfunction and urinary retention in the All Phase II/III Combined studies are presented in Table 13.

Table 13 Adverse Events of Voiding Dysfunction and Urinary Retention (Safety Population: All Phase II/III Combined)

Preferred Term	Number (%) of Patients EZG (N=1365)
Any event	115 (8.4)
Urinary hesitation	42 (3.1)
Urinary retention	26 (1.9)
Residual urine volume	15 (1.1)
Urine flow decreased	8 (0.6)
Micturition frequency decreased	6 (0.4)
Urinary incontinence	6 (0.4)
Oliguria	5 (0.4)
Bladder disorder	4 (0.3)
Micturition disorder	4 (0.3)
Micturition urgency	4 (0.3)
Bladder spasm	3 (0.2)
Hypertonic bladder	2 (0.1)
Neurogenic bladder	2 (0.1)
Atonic urinary bladder	1 (<0.1)
Bladder discomfort	1 (<0.1)
Bladder diverticulum	1 (<0.1)
Bladder pain	1 (<0.1)
Calculus bladder	1 (<0.1)
Dysuria	1 (<0.1)
Nocturia	1 (<0.1)
Strangury	1 (<0.1)
Urinary tract disorder	1 (<0.1)

The most common PT was urinary hesitation, which was reported by 3% of patients. This was slightly higher than in the Pivotal Controlled Trials (2.2%). Most events of urinary hesitation were mild (31/42, 74%). There were 2 reported events of severe intensity. Slightly more males than females reported urinary hesitation (25, 3.8% vs 17, 2.4%).

The second most common was urinary retention. The majority of events were mild to moderate in severity (23/26, 88%), and most patients continued in the study. Events tended to occur during the first 3 months of treatment. More males (14, 2.1%) than females (12, 2%) reported urinary retention. There were 5 SAEs (Patients 302-025108, 302-025405, 303-000902, 303-003505 and 301-003901. Five patients withdrew due to urinary retention.

Five patients required catheterization to aid in urine voiding. Brief narratives are provided here.

Patient 205-000448 was a 53-year-old Australian female who was receiving 200 mg TID of ezogabine as an add on therapy for the treatment of temporal lobe epilepsy. Therapy with ezogabine began on 05 April 2000 and the patient received ezogabine for just over one month when she was admitted to the hospital after a history of 11 days of symptoms of myalgia, fatigue, cough, sweats and polydipsia and laboratory findings of elevated liver function tests and mild renal failure with BUN of 12.3 (normal <9), and creatinine of 190 (normal <124). On the day of admission (06-May-2000) the patient felt unwell and had symptoms of abdominal pain and orthopnea with pulmonary edema, and findings of nystagmus and urinary retention on examination. On 06-May-2000, a catheter was used to evacuate 1.5 L of urine from the bladder. Ezogabine was discontinued. Urinalysis showed many leukocytes but no growth was seen on urine cultures. On an unknown date an ultrasound scan revealed some dilatation of the upper urinary tract (ureters and kidneys). The investigator and medical monitor considered the urinary retention and renal failure to be serious and possibly related to ezogabine.

Patient 301-005203 was a 55-year-old Canadian male. He was receiving study medication of placebo when he was hospitalized for increased seizures on 11 September 2006, approximately four weeks after initiating study medication. He developed urinary retention the day after admission on 12 September 2006, and had his hospitalization extended by one day. The urinary retention resolved with one time bladder catheterization on 12 September 2006. Urine culture from the day of urinary retention showed no growth. The patient had no urinary retention when he first entered the clinical study. This patient continued on study medication and completed the 301 study. He has rolled over into the 303 open label extension trial. The investigator considered the urinary retention to be serious because of prolonged hospitalization and unrelated to study medication. An alternative basis for the urinary retention was not provided.

Patient 303-03505 was a 31 year old Caucasian male previously randomized to placebo in Study 301 who experienced psychomotor agitation and urinary retention after 82 days on ezogabine (overall Day 211 of study). The patient presented to the ER after approximately 18 hours of urinary retention. A PVR ultrasound in the ER showed 900 mL of urine. The patient was described as uncooperative and in distress in the ER. After

some difficulties, eventual insertion of a Foley catheter revealed approximately 1200 mL of urine. Past medical history included a traumatic brain injury, rattlesnake bite with antivenom treatment, hypertension, sleep apnea, gastroesophageal reflux disease, and a VNS implant. Concomitant medications included carbamazepine, pregabalin, lamotrigine, and pantoprazole. The study medication was withdrawn immediately and the patient was taught self catheterizations on 19 Feb 2008. Urodynamic studies on 24 Mar 2008 indicated normal bladder compliance, a sensation of fullness upon filling, no leak with valsalva maneuvers, but an inability to void during the exam. No EMG activity was noted. PVR volume was 882 mL. The patient continued intermittent self-catheterizations. A follow-up PVR in a urology office on 5 May 2008 was 91 mL. Additional follow-up information on 9 July 2008 revealed some interval improvement. The patient was voiding spontaneously on a regular basis, but continued to require intermittent catheterizations, although less frequently than before. The event is considered ongoing and still followed at this time.

Patient 303-00902 was a 39 year old Caucasian male who experienced post-ictal psychosis and urinary retention after 691 days on ezogabine. Past medical history included decreased cognition and auditory hallucinations. Concomitant medications included oxcarbazepine, pregabalin, levetiracetam, sertraline, multivitamins, coenzyme, and glucosamine. Urologic consultation in the hospital revealed an enlarged prostate and a PVR volume of 700 mL. The patient was discharged with a Foley catheter and recovered from the event after 8 days. The patient remained in the study. Additional PVR volumes from the database at baseline, Day 68, Day 126, Day 196, Day 252, and Day 532 were normal at 37, 37, 17, 10, 40 and 17 mL, respectively.

Patient 304-50102 was a 46 y/o Caucasian female who was randomized to ezogabine 900 mg/day during the double blind phase of Study 302 and reported urinary retention after 57 days on study medication. Past medical history included a traumatic brain injury. Concomitant medications included carbamazepine and clobazam. Because the patient reported an excellent therapeutic response, she decided to remain in the study and began self-catheterization on 6 May 2007. During Study 304, PVR volume was elevated during Month 1 and Month 12 at 200 mL and 150 mL, respectively. The patient eventually withdrew from the study on 8 Nov 2007 due to increased seizures. During the patient's follow-up visit on 28 Nov 2007, the patient reported she no longer required self-catheterizations and had no more voiding problems. Overall, PVR volumes from the clinical database at baseline, Day 57, Day 112, Day 168, Day 231, and Day 505 were 7, 60, 180, 200, 95, and 150 mL, respectively.

The third most common preferred term was residual volume increased, reported at 1% (comparable to the Pivotal Controlled Trials at 1%). Most reported events were mild 7 (0.5%) or moderate 6 (0.4%); there were 2 (0.1%) severe events reported. None of these patients discontinued, or were SAEs.

All other AEs were reported at <1%. Six patients withdrew (5 urinary retention, 1, atonic bladder). There were 5 SAEs (4 urinary retention and 1 atonic urinary bladder) (Table 10).

3.2.1.3. Summary

Voiding dysfunction and urinary retention occur at a higher frequency in patients receiving ezogabine than in patients receiving placebo. Across both the Pivotal Controlled Trials and All Phase II/III Combined study groupings, the most commonly reported event related to voiding dysfunction was urinary hesitation. Most of the events were mild in intensity and patients were able to continue in the study. Where events necessitated withdrawal of patients from the study, their symptoms generally returned to normal suggesting reversibility consistent with a pharmacological effect. Only one patient had any residual effects after discontinuation of study drug. This patient had a complicated course following severe urinary retention including a concurrent SAE of psychomotor agitation and resultant delay in seeking medical treatment, demonstrated improvement by regaining spontaneous urination but continued to require intermittent self-catheterization.

3.2.2. Urinary Tract Infections and Related Signs and Symptoms

The following preferred terms were used to identify events related to urinary tract infections and related signs and symptoms: asymptomatic bacteriuria; bacteriuria; urinary tract infection; urinary tract infection bacterial; urosepsis; bacteria urine; dysuria (verbatim terms: burning on micturition, burning on micturition/dysuria, burning sensation with urinating, burning with urination-UTI, disuria, dyssuria, dysunia, dysuria, dysuria worsening, mictional burning, painful micturition, stinging sensation on micturition, temporary and cutting pains below abdomen + urethra after urination, urinary burning sensation, urinary burns and urinary discomfort); glomerulonephritis.

3.2.2.1. Pivotal Controlled Trials

During ezogabine trials, urinary tract infections were diagnosed primarily based on the principal investigator's clinical assessment of the patient's signs and symptoms and urinalysis results. Urine cultures were not typically performed as they were not required per protocol. Overall, most urinary tract infections were not confirmed by urine cultures.

Urinary tract infection-related AEs for patients in the pivotal controlled trials are shown in [Table 14](#).

Table 14 Adverse Events of Urinary Tract Infections and Related Signs and Symptoms in Any Treatment Group (Safety Population: PCT, 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 event	33 (7.7)	18 (6.4)	16 (5.9)	38 (14.7)	72 (8.9)
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)	3 (1.1)	10 (3.9)	17 (2.1)
Urine analysis abnormal	4 (0.9)	2 (0.7)	3 (1.1)	8 (3.1)	13 (1.6)
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)
Cystitis	1 (0.2)	1 (0.4)	0	1 (0.4)	2 (0.2)
Pyuria	0	0	1 (0.4)	0	1 (0.1)
Urethral pain	1 (0.2)	1 (0.4)	0	0	1 (0.1)
Bacteria urine	0	0	1 (0.4)	0	1 (0.1)
White blood cells urine	0	1 (0.4)	0	0	1 (0.1)
Urine odor abnormal	0	0	0	1 (0.4)	1 (0.1)
White blood cells urine positive	1 (0.2)	0	0	0	0

During the pivotal controlled trials, UTI-related AEs were reported in similar proportions of patients in ezogabine versus placebo treatment groups (8.9% Total EZG group versus 7.7%).

Overall, the most common single preferred term reported was UTI (4.3% Total EZG group, 4.7% placebo group) followed by dysuria (2.1% Total EZG vs 0.7% placebo). UTI and urine analysis abnormal both showed a dose-related increase, with the most events reported in the 1200mg/day group. Most UTI events occurred during days 28-56, were mild in intensity (27, 33%), and resulted in withdrawal of only one patient. There were 2 severe cases, one each on 900mg/day and 1200 mg/day; both patients continued in the study. There were no SAEs of UTI (Table 5).

Examination of the data revealed that the overall frequency of the reported preferred term UTIs across the three studies was highly variable. UTIs were less common in the 600 mg/day and 900 mg/day dose groups than in placebo (1.8% and 3.3% versus 4.7%), but more common in the 1200 mg/day group than placebo (8.1% versus 4.7%) (Table 14). Over half (54%) of the UTIs in placebo and ezogabine combined (31 out of 57) were reported in Study 301 alone with a UTI rate of 10.2%. This study was also the smallest of the three trials, accounting for only 24.5% (305 out of 1240) of the total patients. By comparison, the overall rate of UTIs in Study 302 and 205 was 2.4% and 3.3%, respectively.

Further examination of the Study 301 data also revealed that 3 sites enrolling 11% (33/305) of patients accounted for 39% of the UTIs in the study (12 out of 31). Sites 102, 105 and 107, all in Mexico, reported 5, 4, and 3 UTIs, respectively. In these three sites, 18 patients were randomized to placebo, with 5 reporting UTIs. Fifteen patients were randomized to ezogabine 1200 mg/day, with 7 reporting UTIs. In Study 302, UTIs were

reported in 2% of patients on placebo (4/179), 2% on 600 mg/day (4/181), and 2.8% on 900 mg/day (5/178). In Study 205, UTIs were reported by 4.2% on placebo (4/96), 2.0% on 600 mg/day (2/100), 4% on 900 mg/day (4/95), and 2.8% on 1200 mg/day (3/106).

This reporting bias confounds the evaluation of the relationship of UTIs and ezogabine dose.

3.2.2.2. All Phase II/III Combined

Adverse events of Urinary tract infections and related signs and symptoms are presented in [Table 15](#).

Table 15 Adverse Events of Urinary Tract Infections (Safety Population: All Phase II/III Combined)

Preferred Term	Number (%) of Patients EZG (N=1365)
Any event	191 (14.0)
Urinary tract infection	105 (7.7)
Urine analysis abnormal	35 (2.6)
Dysuria	31 (2.3)
Leukocyturia	12 (0.9)
Cystitis	8 (0.6)
Bacteriuria	7 (0.5)
Bacteria urine	5 (0.4)
Bacteria urine identified	4 (0.3)
Kidney infection	2 (0.1)
Pyelonephritis	2 (0.1)
Urinary tract infection bacterial	2 (0.1)
Urethral pain	2 (0.1)
Urinary tract pain	2 (0.1)
White blood cells urine	2 (0.1)
Asymptomatic bacteriuria	1 (<0.1)
Urosepsis	1 (<0.1)
Pyuria	1 (<0.1)
Urinary tract disorder	1 (<0.1)
Urine odor abnormal	1 (<0.1)
Blood urine present	1 (<0.1)
Urine leukocyte esterase	1 (<0.1)
White blood cell count increased	1 (<0.1)

UTI related signs and symptoms were reported in 14% of patients. This was higher than the Pivotal Controlled Trials group (9%). Urinary tract infection was the most common AE, and was reported by 8% of all patients, which was approximately twice as high as the Pivotal Controlled Trials (4.3%). All other AEs were reported at approximately the same rate as the Pivotal Controlled Trials. There were some gender differences as UTIs with 10% of females versus 5% of males reporting in the ezogabine group. There did not seem to be any specific pattern of onset. The majority of cases were mild 69 (5%).

There were 5 (0.4%) severe cases of UTIs. There were 3 SAEs of UTIs, and one of urosepsis (Patients 301-010607, 302-025509, 303-000103 and 212-000693). One of the four patients withdrew from the study due to a urinary event (urosepsis, Patient 212-000693).

3.2.2.3. Summary

UTIs were reported at comparable rates in the total ezogabine population versus placebo, but the 1200mg dose group did have a higher rate. The rate in placebo was higher than the 600 or 900mg dose group. A closer examination of the data revealed a pattern of UTI's across the three pivotal studies that was highly variable with more frequent reporting of UTIs in Study 301, especially in the 1200mg/day group. There was no clear pattern of onset of symptoms. There was a higher incidence in the Phase II/III combined population, probably due to the longer reporting period captured in this population. Most UTIs were mild and resolved with treatment. As expected, UTIs were reported more commonly in females than in males. Based on these data, there does not appear to be any significant overall increase in UTIs with ezogabine therapy or any clear dose relationship among those who did report events.

3.2.3. Renal Dysfunction

The following preferred terms were used to identify events related to renal dysfunction (renal failure) : blood urea increased; hematuria; hydronephrosis; leukocyturia; nephritis; nocturia; oliguria; pollakiuria; polyuria; proteinuria; psychogenic dysuria; pyuria; renal cyst; renal failure; renal failure acute; renal pain; blood urine increased.

3.2.3.1. Pivotal Controlled Trials (Studies 205, 301 and 302)

Renal dysfunction-related AEs for patients in the pivotal controlled trials are shown in [Table 16](#).

Table 16 Adverse Events of Renal Dysfunction in Any Treatment Group (Safety Population: PCT, 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 event	0	3 (1.1)	1 (0.4)	0	4 (0.5)
Urine output decreased	0	1 (0.4)	0	0	1 (0.1)
Urine output increased	0	0	1 (0.4)	0	1 (0.1)
Nephritis	0	1 (0.4)	0	0	1 (0.1)
Renal failure	0	1 (0.4)	0	0	1 (0.1)

During the pivotal controlled trials events possibly related to renal dysfunction were reported only in patients receiving ezogabine compared with placebo (4, 0.5% vs 0). Most events were reported in the 600 mg/day group. There were no events in the 1200 mg/day group. There was 1 SAE ([Patient 205-000448](#)) with mild renal failure secondary

to urinary retention; this patient was withdrawn from the study. A brief narrative was presented in Section 3.2.1.2.

3.2.3.2. All Phase II/III Combined

AEs relating to renal dysfunction in the All Phase II/III Combined studies are presented in Table 17.

Table 17 Adverse Events of Renal Dysfunction in Any Treatment Group (Safety Population: All Phase II/III Combined)

Preferred Term	Number (%) of Patients EZG (N=1365)
Any event	9 (0.7)
Blood creatinine increased	2 (0.1)
Nephritis	1 (<0.1)
Nephropathy toxic	1 (<0.1)
Renal failure	1 (<0.1)
Renal failure acute	1 (<0.1)
Renal pain	1 (<0.1)
Blood urea increased	1 (<0.1)
Urine output decreased	1 (<0.1)
Urine output increased	1 (<0.1)

Renal dysfunction was reported in 9 (0.7%) patients receiving ezogabine. The 6 additional events seen in the All Phase II/III Combined group were 2 cases of blood creatinine increased, and 1 each of nephropathy toxic, renal failure acute, renal pain and blood urea increased. There were 2 additional SAEs reported in this population: 1 SAE of with nephropathy toxic and was withdrawn from the study (Patient 304-060306 taking 600 mg/day), and 1 SAE of renal failure acute (Patient 208-000017 taking 1200 mg/day).

3.2.3.3. Summary

Adverse events related to renal dysfunction were uncommon in clinical trials of ezogabine.

3.2.4. Urinary Crystals

Urinary crystals having the microscopic appearance of bilirubin have been described in urine samples collected during the Phase III trials (Studies 301, 302, 303 and 304). This involved 15% of patients (127 out of 843) and only occurred in patients who received active drug; there have been no reports in any of the other phase I or phase II ezogabine studies. The crystals were not associated with any trends in clinical symptoms and no effects on relevant laboratory data or post-void residual urine volume (PVR) have been observed in these patients.

A formal analysis was performed to determine the nature of the crystals, and to ensure that there were no untoward effects resulting from these crystals. A comparison of clinical and biochemical profiles between patients who reported crystals and those who did not is reproduced in Section 3.4.3 of this document. In addition, a chemical analysis of urine samples containing crystals determined that the crystal were not bilirubin. .

The following preferred terms were used to identify events possibly related to urinary crystals: crystal urine present; urine analysis abnormal; calculus ureteric; crystalluria; nephrolithiasis, renal colic. Although calculus ureteric, nephrolithiasis and renal colic were included in the search, there has been no evidence that urinary crystals seen in the phase III studies are associated with stone formation or its sequelae.

3.2.4.1. Pivotal Controlled Trials (Studies 205, 301 and 302)

AEs possibly relating to urinary crystals in the All Phase II/III Combined studies are presented in Table 18.

Table 18 Adverse Events of Urinary Crystals Reported in Any Treatment Group (Safety Population: PCT, 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 event	2 (0.5)	1 (0.4)	2 (0.7)	6 (2.3)	9 (1.1)
Nephrolithiasis	0	0	0	4 (1.5)	4 (0.5)
Renal colic	1 (0.2)	0	2 (0.7)	1 (0.4)	3 (0.4)
Crystalluria	0	1 (0.4)	0	0	1 (0.1)
Urine analysis abnormal	1 (0.2)	0	0	1 (0.4)	1 (0.1)

AEs possibly related to urinary crystals were reported more often in the Total Ezogabine group than in the placebo group (9, 1.1% vs 2, 0.5%).

Nephrolithiasis was the most common event reported, and was seen in 4 (0.5%) patients. The 4 patients with nephrolithiasis came from the ezogabine 1200 mg/day group in Study 301. One of the patients (00901 from Study 301) had a prior history of nephrolithiasis in 2002. Another patient (20210 from Study 301) reported concomitant use of topiramate, an AED associated with nephrolithiasis. The other two patients (000302 from Study 301 and 020221 from Study 301) had no known predisposing factors for nephrolithiasis. None of the patients with nephrolithiasis had any laboratory reports of bilirubin crystals.

Renal colic was also reported in 3 (0.4%) patients receiving ezogabine; one patient (205-000125) reported renal colic as an SAE (Table 10).

3.2.4.2. All Phase II/III Combined

AEs possibly relating to urinary crystals in the All Phase II/III Combined studies are presented in Table 19.

Table 19 Adverse Events of Urinary Crystals Reported in Any Treatment Group (Safety Population: All Phase II/III Combined)

Preferred Term	Number (%) of Patients EZG (N=1365)
Any event	22 (1.6)
Nephrolithiasis	9 (0.7)
Renal colic	7 (0.5)
Crystalluria	2 (0.1)
Crystal urine present	2 (0.1)
Urine analysis abnormal	2 (0.1)
Calculus ureteric	1 (<0.1)
Crystal urine	1 (<0.1)

More patients reported urinary crystals in the All Phase II/III Combined population than in the Pivotal Controlled Trials group (2% vs 1%). The most common event was nephrolithiasis, seen in an additional 5 patients; 8/9 (89%) of all cases were mild / moderate in intensity. The events reported for 2 additional patients in the All Phase II/III Combined studies (208-000013 and 212-000184) were SAEs ([Table 10](#)).

An additional observation of chromaturia has been identified and occurred at a higher rate in EZG vs placebo (1.6% vs, 0.2%) ([Table 2](#)). The reason for the discoloured urine is unclear but may be related to the bilirubin-like nature of the crystals which have been observed. There appeared to be a dose effect, with 2 (0.7%), 4 (1.5%) and 7 (2.7%) in the 600mg/day, 900 mg/day and 1200mg/day groups respectively ([Table 2](#)). There was similar incidence reported in the All Phase II/III Combined population (23/1365, 1.7%) ([Table 7](#)). There were no clinical sequelae to this observation. All reports of chromaturia were mild or moderate, and there were no gender differences in reporting.

3.2.4.3. Summary

Urinary crystals having the microscopic appearance of bilirubin were first indentified incidentally and intermittently on urine microscopy during the Phase III trials. These urinary crystals only occurred in patients who received active drug. No unusual trends in symptoms, AEs, laboratory findings, or PVR volumes were seen in these patients and initial analysis has not yielded any evidence that these are actually bilirubin, but may be ezogabine or ezogabine metabolite crystals that may occur post void as a result of specimen handling. A specific laboratory assessment of the isolated urinary crystals confirmed that the precipitate was not bilirubin. The refractory properties of the bilirubin-like crystals may account for the reports of chromaturia.

3.3. Clinical chemistry

There were no clear differences between the placebo group and the ezogabine groups for any renal function clinical chemistry indices (creatinine, BUN and uric acid) at baseline and there were no meaningful changes over time for creatinine. Slight increases in BUN and uric acid were apparent from Week 2 but did not appear to increase further over time

and there was no evidence of a dose relationship. Clinically significant findings of BUN and creatinine for all populations were uncommon and do not indicate any harmful effects of the drug on the renal and urinary system.

3.4. Other Urinary Assessments

3.4.1. American Urological Association Symptom Index

The American Urological Association Symptom Index (AUA SI) scale was administered in the Phase III double-blind studies (Studies 301 and 302) and their extensions (Studies 303 and 304). 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 [Barry, 1992a; Barry, 1992b]. 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. In Studies 301 and 302, AUA SI scores were measured at baseline, during the titration phase (Week 4 or 6), early in the maintenance phase (Week 8 or 10), late in the maintenance phase (Week 16 or 18) and at the time of study completion or discontinuation (designated as Week 20 or 22, but could be at any time if the patient withdrew early). All Week 20 or 22 results were obtained after the patient had stopped the study drug. In Studies 303 and 304, AUA SI scores were measured at 1, 3, and 12 months of open-label treatment.

This document presents integrated summaries for both the Pivotal Controlled Trials and All Phase II/III combined groups and presents changes from baseline in addition to absolute scores.

3.4.1.1. Central Tendency and Change from Baseline

3.4.1.1.1. Pivotal Controlled Trials (Studies 205, 301, and 302)

In the Pivotal Controlled Trial grouping, results indicate that mean AUA SI Total scores for both the placebo and Total EZG groups remained relatively stable throughout the study (Table 20), although there was considerable variability. The majority of scores were in the “mild” range for both placebo and Total EZG groups throughout the study.

Table 20 **Change from Baseline in American Urological Association Symptom Index Total Scores (Safety Population: PCT, Studies 205, 301, and 302)**

Statistic	Placebo (N=427)	EZG 600 mg/day (N=281)	EZG 900 mg/day (N=273)	EZG 1200 mg/day (N=259)	EZG Total (N=813)
Baseline phase Mean (SD)	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)
Change from Baseline to:					
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)
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)

3.4.1.1.2. All Phase II/III Combined

In the All Phase II/III Combined grouping, mean AUA SI scores were similar to those reported in the Pivotal Controlled Trials. Mean scores remained low and consistent throughout the study suggesting no worsening of urinary symptoms with long term treatment.

3.4.1.2. Shift Analyses

3.4.1.2.1. Pivotal Controlled Trials (Studies 205, 301, and 302)

In patients with AUA SI scores in the “mild” range at baseline, 5/237 (2.1%), 23/161 (14.3%), 20/149 (13.4%), 25/111 (22.5%) patients in the placebo, 600, 900, and 1200 mg/day groups, respectively had shifts to “moderate” or “severe” at any point post baseline. Shift in category from mild to moderate or severe was more frequent in all ezogabine dose groups compared with placebo and appeared to be dose related.

3.4.1.2.2. All Phase II/III Combined

Consistent with the Pivotal Controlled Trials, of patients with AUA SI scores in the “mild” range at baseline, 108/664 (16.3%) had shifts to “moderate” or “severe” at any point post baseline in the All Phase II/III Combined group.

3.4.1.3. Summary

Urinary investigation findings were consistent with the known pharmacologic effect of ezogabine on bladder function and consistent with clinical signs and symptoms leading to AE reports related to urinary retention in patients taking ezogabine.

In the Pivotal Controlled Trials (Studies 205, 301, and 302):

- Mean American Urological Association Symptom Index (AUA SI) Total scores remained relatively stable in both the placebo and ezogabine groups. In patients with AUA SI scores in the “mild” range at baseline, 5/237 (2.1%), 23/161 (14.3%), 20/149 (13.4%), 25/111 (22.5%) patients in the placebo, 600, 900, and 1200 mg/day groups, respectively had shifts to “moderate” or “severe” at any point post baseline.

AUA SI mean scores in the All Phase II/III Combined grouping remained low with long term exposure, suggesting no worsening of effects with long term treatment.

3.4.2. Post-Void Residual Volume

Post-void residual urine (PVR) volumes were measured by bladder ultrasound in the Phase III double-blind studies (Studies 301 and 302) and their open-label extensions (Studies 303 and 304). In Studies 301 and 302, ultrasounds were performed at baseline, early in the maintenance phase (Week 8 or 10), late in the maintenance phase (Week 16 or 18), and at the time of study completion or discontinuation (designated as “Week 20” or “22”, but could be at any time point during the study if the patient withdrew). All Week 20 or 22 results were obtained after the patient had stopped taking the study drug. In Studies 303 and 304, bladder ultrasounds were performed at approximately 1, 3, and 12 months of open-label treatment.

This document presents integrated summaries for both the Pivotal Controlled Trials and All Phase II/III Combined groups. Mean values and changes from baseline are presented for the integrated study groupings. However, for purposes of this document, a PVR greater than 150 mL was considered a value of potential clinical concern; ranges of PVR are not presented.

3.4.2.1. Pivotal Controlled Trials (Studies 205, 301 and 302)

In the Pivotal Controlled Trials grouping, mean PVR bladder volumes were similar at baseline between placebo and all ezogabine dose groups ([Table 21](#)). Mean change from baseline in PVR bladder volume increased in the Total EZG group compared with a decrease in the placebo group, however no consistent effect was seen over time. These findings are consistent with the clinical signs and symptoms leading to AE reports related

to urinary retention in patients taking ezogabine. In most patients, PVR returned to baseline after discontinuation of treatment.

Table 21 Baseline and Change from Baseline in Post-Void Residual Bladder Urine Volume (Safety Population: PCT, Studies 205, 301, and 302)

Statistic	Placebo (N=427)	EZG 600 mg/day (N=281)	EZG 900 mg/day (N=273)	EZG 1200 mg/day (N=259)	EZG Total (N=813)
Baseline phase	n=313	n=178	n=168	n=143	n=489
Mean (SD)	19.7 (48.8)	17.4 (30.6)	21.5 (40.6)	30.1 (74.3)	22.5 (50.3)
Change from Baseline to:					
Week 8	n=146	n=130	n=115	n=5	n=250
Mean (SD)	-0.5 (24.9)	10.2 (69.6)	4.6 (47.3)	14.6 (39.8)	7.7 (59.7)
Week 10	n=110	n=2	n=3	n=85	n=90
Mean (SD)	-4.9 (47.1)	-34.0 (48.1)	-39.7 (65.3)	22.3 (90.6)	19.0 (89.7)
Week 16	n=136	n=117	n=97	n=2	n=216
Mean (SD)	-3.1 (29.1)	12.9 (82.8)	-1.0 (49.4)	-23.5 (3.5)	6.3 (69.6)
Week 18	n=92	n=4	n=1	n=63	n=68
Mean (SD)	-9.7 (43.4)	-8.5 (20.2)	0	9.4 (56.6)	8.2 (54.8)

3.4.2.1.1. Post-Void Residual Bladder Ultrasound Values of Potential Clinical Concern

In the Pivotal Controlled Trials grouping, values of PCC on PVR bladder ultrasound were measured at any time post baseline in 3/295 (1.0%), 12/155 (7.7%), 10/136 (7.4%), 11/109 (10.1%) patients in the placebo, 600, 900, and 1200 mg/day groups, respectively. In patients without PCC values at baseline, values of PCC were measured at any time post baseline in 3/275 (1.1%), 12/150 (8.0%), 7/126 (5.6%), 7/97 (7.2%) patients in the placebo, 600, 900, and 1200 mg/day groups, respectively.

3.4.2.2. All Phase II/III Combined

In the All Phase II/III Combined grouping, mean PVR volume remained low with long term exposure to ezogabine ([Table 22](#)).

Table 22 Baseline and Change from Baseline in Post-Void Residual Bladder Urine Volume - (Safety Population: All Phase II/III Combined)

	Number of Patients	PVR Volume (ml)
	EZG (N=1365)	
Total Population Baseline mean(\pm SD)	758	19.6 (43.8)
Change from Baseline mean(\pm SD)		
Week 8	364	6.7 (55.0)
Week 10	176	16.8 (72.8)
Week 16	283	5.1 (61.5)
Week 18	171	6.1 (46.4)
Week 24	185	3.6 (58.1)
Week 32	251	5.6 (61.9)
Week 38	79	2.3 (57.8)
Week 56	73	5.5 (36.2)
Week 74	83	-1.0 (58.1)

3.4.2.2.1. Post-Void Residual Bladder Ultrasound Values of Potential Clinical Concern

In the All Phase II/III Combined grouping, 53/642 (8.3%) of patients had values of PCC on PVR bladder ultrasound measured at any time post baseline. In patients without PCC values at baseline, values of PCC were measured at any time post baseline in 42/607 (6.9%) of patients. This finding is consistent with the Pivotal Controlled Trials, suggesting no worsening of effect with long term exposure to ezogabine.

3.4.2.3. Summary

Mean change from baseline in PVR bladder volume increased in the Total EZG group compared with a decrease in the placebo group, however, no consistent effect was seen over time. PVR volumes of PCC were noted at any time post baseline in 3/295 (1.0%), 12/155 (7.7%), 10/136 (7.4%), 11/109 (10.1%) patients in the placebo, 600, 900, and 1200 mg/day groups, respectively.

PVR mean scores in the All Phase II/III Combined grouping remained low with long term exposure, suggesting no worsening of effects with long term treatment.

3.4.3. Relationship Between Urinary Crystals and Urinalysis and Laboratory Parameters

Table 23 below compares relevant clinical data in patients from Studies 301, 302, 303 and 304 who have reported urinary crystals at least once (Crystal Formers) versus patients who have never reported these crystals (Non-crystal Formers). Key data including urine specific gravity, pH, BUN/urea, creatinine, serum bilirubin, AST, ALT, alkaline phosphatase, and PVR volumes are examined in Crystal Formers and Non-crystal Formers.

Table 23 Comparison of Phase 3 Laboratory Data between Patients who have Reported Bilirubin Crystals at least once (Crystal formers) versus Patients who have never Reported Bilirubin Crystals (Non-Crystal formers)

Lab Test	Crystal Former ^a	N (number of lab tests) ^b	Mean	Standard Deviation	p-value of mean difference
Urine Specific Gravity	Y N	1117 8758	1.021 1.020	0.008 0.008	<0.0001
Urine pH	Y N	1121 8770	5.808 5.833	0.591 0.634	0.1989
BUN/Urea (mmol/L)	Y N	1133 8910	4.749 4.686	1.513 1.552	0.1935
Creatinine (umol/L)	Y N	1122 8715	70.229 74.407	13.708 15.283	<0.0001
Serum bilirubin (umol/L)	Y N	1132 8836	7.829 7.772	3.526 3.552	0.6116
AST (IU/L)	Y N	1133 8904	21.488 22.254	11.088 13.145	0.0603
ALT (IU/L)	Y N	1132 8891	22.845 23.782	16.786 18.463	0.1046
Alkaline phosphatase (IU/L)	Y N	1134 8891	79.865 83.741	31.019 31.486	<0.0001
PVR (mL)	Y N	430 3151	17.886 24.110	41.820 57.223	0.0295

- Y = patients who reported at least 1 treatment emergent occurrence of bilirubin crystals in a urine specimen during any visit in a phase 3 study; N = patients who have never reported any bilirubin crystals.
- Indicates the total number of a lab tests available for calculation of mean, SD, and p-value. Does not equal the number of occurrences of bilirubin crystals. A patient was considered a crystal former if the patient had 1 occurrence of this event. All available lab tests throughout the study from a crystal former would then be included in the analysis

As indicated in [Table 23](#), all mean laboratory parameters for both groups (crystal formers and non-crystal formers) were well within normal ranges. Statistically, there was a very slight difference in specific gravity between patients with and without crystals (1.021 versus 1.020). However, there were no clinically meaningful differences in specific gravity or pH to suggest any urinary abnormalities in patients with these crystals. Mean BUN and creatinine levels were similar for both groups and suggested no renal dysfunction related to the crystals. Mean serum bilirubin and other liver function tests were similar in both groups and well within normal limits. This would appear to provide evidence against bilirubin crystallization in the urine due to a lack of evidence for hyperbilirubinemia, jaundice, or liver/biliary disease in patients with crystals. Finally, PVR volumes were normal and on average lower in patients with crystals than those without, further suggesting no evidence for any bladder dysfunction related to this unusual finding.

3.5. Independent Review of Renal and Urinary Events

An independent review of the available data for ezogabine was conducted by Dr. Claus Roehrborn. Much of his review focused on the use of AUA-SI and PVR as predictors of lower urinary tract events. His review of available data concluded that there was a low risk of serious lower urinary tract events with ezogabine and that routine PVR and AUA-SI monitoring would be impractical. Available data did not allow conclusions regarding a contraindication or discontinuation of treatment based on abnormal AUA-SI or PVR.

Because Dr. Roehrborn's review included most of the data available from the ezogabine clinical development program, in particular the controlled clinical trials, a second independent review was not conducted.

4. RENAL AND URINARY DISORDER DISCUSSION AND CONCLUSION

Ezogabine affects the urinary bladder in rodent models inhibiting micturition and has the potential to cause such effects in humans. However, in clinical studies, the effects were limited in frequency and severity, and were generally reversible following withdrawal of therapy.

In double-blind studies more adverse events related to renal and urinary symptoms were reported for ezogabine than placebo (17 % vs 12.9%). Discontinuations due to these events were uncommon.

Overall, nearly all the AEs were mild to moderate in intensity. There was no dose effect in terms of severity or seriousness. There were few SAEs (<1%) and few discontinuations (3 [0.7%] placebo vs 6 [0.7%] ezogabine). All patients in the Pivotal Controlled Trials who reported clinically significant AEs or SAEs leading to discontinuation recovered while either remaining in the study or after discontinuation.

In the All Phase II/III Combined group, 25.3% of patients treated with ezogabine reported renal and urinary disorder AEs. Most events were of mild or moderate intensity. There were more SAEs reported in this population vs the Pivotal Controlled Trials group (2% vs <0.7%), with the most common SAE being urinary retention. Few patients discontinued (1.0%) and most patients recovered while remaining on the study, or after discontinuation.

Within the voiding dysfunction / urinary retention subgroup approximately 2% of patients reported urinary hesitancy; approximately 1% reported urinary retention and residual urine volume. Serious AEs and discontinuations due to these AEs were uncommon (<1% and <1%, respectively), and there were no deaths. Although the largest effects for the 'any event' category were seen in the high dose group (1200 mg/day), there was no consistent dose relationship pattern for individual preferred terms. The only patient with any residual abnormalities after dose decrease or discontinuation had a prolonged period before seeking and obtaining appropriate medical attention.

In the Pivotal Controlled Trial group, results indicate that mean AUA SI scores for both the placebo and Total EZG groups remained relatively stable throughout the study, although there was considerable variability. The majority of scores were in the “mild” range for both placebo and Total EZG groups throughout the study. Mean change from baseline in PVR bladder volume increased in the Total EZG group compared with a decrease in the placebo group, however, no consistent effect was seen over time. AUA SI and PVR mean scores in the All Phase II/III Combined group remained low with long term exposure, suggesting no worsening of effects with long term treatment.

The severity of clinical symptoms (urinary retention, hesitation, bladder pain) rather than PVR volumes or AUA SI scores alone should dictate the management of urinary tract disorders as high PVR volumes and AUA SI scores alone tended not to be predictive of serious adverse events.

Urinary tract infection-related AEs were reported by 9% of ezogabine-treated patients in the randomized controlled trials (compared with 8% of placebo patients), and 14% of patients in the All Phase II/III Combined studies. Most UTIs were mild and resolved with treatment. As expected, UTIs were reported more commonly in females than in males. Ezogabine treatment does not seem to be associated with UTIs, despite there being an apparent increase in incidence at the 1200 mg/day group. This finding reflects diagnostic bias based on disproportionate reporting from 3 sites in Mexico. In the general population, UTIs are common diagnoses in both men and women. Women in particular, have a lifetime risk for UTI of over 50% [Griebing, 2005a]. Data from NHANES-III (Third National Health and Nutritional Examination Survey) show that the incidence of UTI in women per 12 months was 13,320/100,000 or 13% annually [Griebing, 2005a]. In men, the incidence per 12 months was 2318/100,000 or 2% annually [Griebing, 2005b].

During the pivotal controlled trials, events possibly related to renal dysfunction (renal failure) were reported only in patients receiving ezogabine (4, <1% vs 0). Most events (3, 1%) were reported in the 600 mg/day group. There were no events in the 1200 mg/day group. There was 1 SAE of mild renal failure; this patient was withdrawn from the study. Overall, there were no clinically abnormal trends in laboratory tests that would indicate any safety issues. Although at certain time points urea levels demonstrated slight increases, all mean urea values remained well within normal ranges for all treatment groups at all time points. Clinically significant findings of urea and creatinine for all populations were uncommon and do not indicate any harmful effects of the drug on the renal and urinary system. Thus, there was no evidence that ezogabine treatment is associated with renal dysfunction (renal failure) based on review of adverse events and laboratory data.

Urinary crystals having the microscopic appearance of bilirubin have been described intermittently in urine samples during the Phase III trials. These urinary crystals only occurred in patients who received active drug. No unusual trends in symptoms, AEs, laboratory findings, or PVR volumes were seen in these patients and initial analysis has not yielded any evidence that these are actually bilirubin. Nephrolithiasis and calculus ureteric were uncommon and occurred at a frequency of <1% in ezogabine (9/1365). In the general population, nephrolithiasis is considered the most common chronic kidney

condition with over 5% of US population diagnosed [[Worcester](#), 2008; [Saigal](#), 2005]. In another report, the lifetime prevalence has been described to be as high as 15% in the United States and Europe [[Mente](#), 2007].

Based on the mechanism of action of ezogabine it is plausible that it may induce a feeling of urinary hesitancy in some patients. In addition, there is a slight excess in the pivotal controlled trials for ezogabine treated over placebo treated patients for urinary hesitancy and urinary retention adverse events. However, the aggregate data for urinary tract infection from the pivotal controlled trials and the open label extension studies are inconsistent and as such do not provide compelling evidence of a causal association for ezogabine and urinary tract infection or other potentially serious outcomes, based on AE reporting from these trials.

Furthermore, the majority of renal and urinary AEs were mild with most patients able to continue treatment without difficulties. In the small number of severe or serious cases of bladder dysfunction, withdrawal from ezogabine and prompt medical intervention provided relief of symptoms and a return to normal bladder function. Most patients did not require withdrawal from treatment due to urinary AEs. Those who did withdraw generally recovered rapidly, suggesting a readily reversible effect of the study drug on bladder function. The Prescribing Information (PI) and Medication Guide will contain language on the potential of lower urinary tract symptoms and in particular the risk of urinary retention.

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**11.8. Appendix: Renal and Urinary Disorders (Safety Data Cut-off:
2 October 2009)**

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1. INTRODUCTION

This document provides an update to previously reported information regarding renal and urinary events with ezogabine described in the original application ([Appendix 11.7](#)). It also presents important new information on urinalysis results reported in the post-herpetic neuralgia (PHN) study VRX-RET-E22-NP201 (referred to as Study NP201 throughout remainder of document).

Notes to Reviewer:

- For data entered in the “Any Event” row in the AE tables, unique patients are counted only once irrespective of the number of TEAEs they may have actually reported. An increase for the 120-Day reporting period compared to the ISS reporting period represents the addition of a patient or patients who reported NO TEAEs during the ISS reporting period, but reported at least 1 TEAE between the ISS and 120 Day update cut-off dates.
- For individual TEAE events displayed in the AE tables, the entries represent the number and percentage of patients reporting a specific TEAE during the specified reporting period. This means that if patients reported different TEAEs, they may be included in more than 1 row. However, if they reported more than 1 episode of the same TEAE they will be counted only once within that specific AE row
An increase for the 120-Day reporting period compared to the ISS reporting period represents a patient who did not report a specific TEAE during the ISS reporting period, but subsequently reported it during the 120-Day reporting period. Note if a patient reported any TEAE in the ISS, additional TEAEs reported by the same patient would not result in an increase to the ANY EVENT row, but would result in an increase to the specific TEAE row.

2. ALL PHASE II/III COMBINED

For background information and methodology for searching for TEAE terms related to renal and urinary disorders, refer to [Appendix 11.7](#).

2.1. Overall Incidence of Adverse Events

Five patients reported renal/urinary TEAEs for the first time during the 120-Day Safety Update reporting period bringing the overall total to 351/1365 (26%) ([Table 1](#)). Results were similar to those reported in the original ISS.

There were no new renal and urinary disorders SAEs.

Table 1 Adverse Events of Renal/Urinary Disorders Reported by 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
Any event	346 (25.3)	351 (25.7)
Urinary tract infection	105 (7.7)	107 (7.8)
Urinary hesitation	42 (3.1)	42 (3.1)
Urinalysis abnormal	35 (2.6)	35 (2.6)
Dysuria	33 (2.4)	33 (2.4)
Urinary retention	26 (1.9)	26 (1.9)
Hematuria	24 (1.8)	25 (1.8)
Chromaturia	23 (1.7)	23 (1.7)
Polyuria	22 (1.6)	23 (1.7)
Residual urine volume	15 (1.1)	16 (1.2)
Blood urine present	12 (0.9)	12 (0.9)
Leukocyturia	12 (0.9)	13 (1.0)
Proteinuria	12 (0.9)	13 (1.0)
Nephrolithiasis	9 (0.7)	10 (0.7)
Urine flow decreased	8 (0.6)	8 (0.6)
Cystitis	8 (0.6)	10 (0.7)
Bacteriuria	7 (0.5)	7 (0.5)
Urinary sediment present	7 (0.5)	7 (0.5)
Renal colic	7 (0.5)	7 (0.5)
Micturition frequency decreased	6 (0.4)	6 (0.4)
Urinary incontinence ^a	6 (0.4)	5 (0.4)
Oliguria	5 (0.4)	5 (0.4)
Bacteria urine	5 (0.4)	5 (0.4)
Bacteria urine identified	4 (0.3)	4 (0.3)
Bilirubinuria	4 (0.3)	4 (0.3)
Bladder disorder	4 (0.3)	4 (0.3)
Costovertebral angle tenderness	4 (0.3)	4 (0.3)
Micturition disorder	4 (0.3)	4 (0.3)
Micturition urgency	4 (0.3)	4 (0.3)
Bladder spasm	3 (0.2)	3 (0.2)
Pollakiuria	3 (0.2)	3 (0.2)
Red blood cells urine	3 (0.2)	3 (0.2)
Bladder pain	1 (<0.1)	2 (0.1)
Crystalluria	2 (0.1)	2 (0.1)
Hypertonic bladder	2 (0.1)	2 (0.1)
Neurogenic bladder	2 (0.1)	2 (0.1)
Urethral pain	2 (0.1)	2 (0.1)
Urinary tract disorder	2 (0.1)	2 (0.1)
Urinary tract pain	2 (0.1)	2 (0.1)
Urine abnormality	2 (0.1)	2 (0.1)
Kidney infection	2 (0.1)	2 (0.1)
Pyelonephritis	2 (0.1)	2 (0.1)
Urinary tract infection bacterial	2 (0.1)	2 (0.1)
Blood creatinine increased	2 (0.1)	2 (0.1)
Crystal urine present	2 (0.1)	3 (0.2)

Preferred Term	Number (%) of Patients EZG (N=1365)	
Protein urine	2 (0.1)	2 (0.1)
Red blood cells urine positive	2 (0.1)	2 (0.1)
White blood cells urine	2 (0.1)	2 (0.1)
Strangury	1 (<0.1)	2 (0.1)

- a. For 1 patient (303-36-3602), the verbatim term was changed from 'URINARY INCONTINENCE' in the original ISS to 'PROLAPS BLADDER' in the 120-Day Safety Update and therefore this patients' preferred terms changed from 'URINARY INCONTINENCE' to 'BLADDER PROLAPSE' and thus this event does not appear in this summary table.

Note: those events highlighted in gray have a higher incidence than the original ISS.

Table 2 summarizes all severe cases of renal and urinary disorders TEAEs. During the reporting period, 1 patient reported a new severe TEAE (hematuria). Most events were mild (229/351, 65%); 99/351 (28%) were moderate and 23/351 (7%) were severe. Results were similar to those reported in the original ISS.

**Table 2 Adverse Events of Renal/Urinary Disorders of Severe Intensity
(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
Any event	22 (1.6)	23 (1.7)
Urinary tract infections	5 (0.4)	5 (0.4)
Urinary retention	3 (0.2)	3 (0.2)
Renal Colic	3 (0.2)	3 (0.2)
Urinary hesitation	2 (0.1)	2 (0.1)
Residual urine volume	2 (0.1)	2 (0.1)
Hematuria	2 (0.1)	3 (0.2)
Renal failure	1 (<0.1)	1 (<0.1)
Renal failure acute	1 (<0.1)	1 (<0.1)
Urosepsis	1 (<0.1)	1 (<0.1)
Red blood cells urine	1 (<0.1)	1 (<0.1)
Blood creatinine increased	1 (<0.1)	1 (<0.1)
Nephrolithiasis	1 (<0.1)	1 (<0.1)
Micturition Frequency decreased	1 (<0.1)	1 (<0.1)
Bladder Spasm	1 (<0.1)	1 (<0.1)

Note: those events highlighted in gray have a higher incidence than the original ISS.

2.2. Discontinuations Due to Renal/Urinary TEAEs

Two new patients reported a renal/urinary TEAE leading to withdrawal during the 120-Day Safety Update reporting period. Combined with the 14 patients who reported renal/urinary TEAEs leading to withdrawal in the original ISS, a total of 16 (1.2%) patients reported renal/urinary-related TEAEs leading to withdrawal in this study grouping. The types and incidences of renal/urinary TEAEs leading to withdrawal were

similar to those reported in the original ISS. One patient reported urinary hesitation and 1 patient reported urinary retention (Table 3). These data are consistent with those reported in the original ISS.

Table 3 Discontinuations Due to Renal/Urinary Events (Safety Population: All Phase II/III Combined)

Study	Patient ID	Age/Race/Gender	Actual Dose at time of AE mg/day	Preferred Term	Day of Onset	SAE Y/N	Resolved Y/N
304	035402	36/C/F	900	Urinary hesitation	168	N	Y
304	065408	38/C/F	750	Urinary retention	582	N	Y

C= Caucasian, F = Female.

2.3. Voiding Dysfunction and Urinary Retention

Three patients reported voiding dysfunction and urinary retention-related TEAEs for the first time during the 120-Day Safety Update reporting period bringing the overall total to 118 (9%) (Table 4); 1 patient reported residual urine volume, 1 patient reported strangury and 1 patient reported benign prostatic hyperplasia (Table 4). The types and incidences of voiding dysfunction and urinary retention TEAEs were otherwise similar to those reported in the original ISS.

Table 4 Adverse Events of Voiding Dysfunction and Urinary Retention Reported 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)	
	ISS Integrated data Cut-Off: 30 June 2008	120-Day Safety Data Cut-off: 2 October 2009
Any event	115 (8.4)	118 (8.6)
Urinary hesitation	42 (3.1)	42 (3.1)
Urinary retention	26 (1.9)	26 (1.9)
Residual urine volume	15 (1.1)	16 (1.2)
Urine flow decreased	8 (0.6)	8 (0.6)
Micturition frequency decreased	6 (0.4)	6 (0.4)
Urinary incontinence ^a	6 (0.4)	5 (0.4)
Oliguria	5 (0.4)	5 (0.4)
Bladder disorder	4 (0.3)	4 (0.3)
Micturition disorder	4 (0.3)	4 (0.3)
Micturition urgency	4 (0.3)	4 (0.3)
Bladder spasm	3 (0.2)	3 (0.2)
Hypertonic bladder	2 (0.1)	2 (0.1)
Neurogenic bladder	2 (0.1)	2 (0.1)
Strangury	1 (<0.1)	2 (0.1)
Benign prostatic hyperplasia	0	1 (<0.1)

a. For 1 patient (303-36-3602), the verbatim term was changed from 'URINARY INCONTINENCE' in the original ISS to 'PROLAPS BLADDER' in the 120-Day Safety Update and therefore this subjects' preferred terms changed from 'URINARY INCONTINENCE' to 'BLADDER PROLAPSE' and thus this event does not appear in this summary table.

Note: those events highlighted in gray have a higher incidence than the original ISS.

2.4. Urinary Tract Infections and Related Signs and Symptoms

Four patients reported UTI-related TEAE for the first time during the 120-Day Safety Update reporting period bringing the overall total to 195 (14%) (Table 5); 2 patients reported UTI, 1 patient reported leukocyturia and 2 patients reported cystitis. The types and incidences of UTI-related TEAEs were otherwise similar to those reported in the original ISS.

Table 5 Adverse Events of Urinary Tract Infections 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
Any event	191 (14.0)	195 (14.3)
Urinary tract infection	105 (7.7)	107 (7.8)
Urine analysis abnormal	35 (2.6)	35 (2.6)
Dysuria	31 (2.3)	31 (2.3)
Leukocyturia	12 (0.9)	13 (1.0)
Cystitis	8 (0.6)	10 (0.7)
Bacteriuria	7 (0.5)	7 (0.5)
Bacteria urine	5 (0.4)	5 (0.4)
Bacteria urine identified	4 (0.3)	4 (0.3)
Kidney infection	2 (0.1)	2 (0.1)
Pyelonephritis	2 (0.1)	2 (0.1)
Urinary tract infection bacterial	2 (0.1)	2 (0.1)
Urethral pain	2 (0.1)	2 (0.1)
Urinary tract pain	2 (0.1)	2 (0.1)
White blood cells urine	2 (0.1)	2 (0.1)

Note: those events highlighted in gray have a higher incidence than the original ISS.

2.5. Renal Dysfunction

There were no new events relating to renal/urinary dysfunction during the 120-Day Safety Update reporting period.

2.6. Urinary Crystals and Nephrolithiasis

Nephrolithiasis was reported by 1 patient for the first time during the 120-day reporting period bringing the total to 10 (1%) and the overall total number of patients reporting urinary crystal-related TEAEs to 23 (2%) (Table 6). Brief narratives for all subjects reporting nephrolithiasis are presented in Section 2.6.1.

One patient also reported a TEAE of crystal urine present. The types and incidences of urinary crystal-related TEAEs were otherwise similar to those reported in the original ISS.

Table 6 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: 30 June 2008	120-Day Safety Data Cut-off: 2 October 2009
Any event	22 (1.6)	23 (1.7)
Nephrolithiasis	9 (0.7)	10 (0.7)
Renal colic	7 (0.5)	7 (0.5)
Crystalluria	2 (0.1)	2 (0.1)
Crystal urine present	2 (0.1)	3 (0.2)
Urine analysis abnormal	2 (0.1)	2 (0.1)
Calculus ureteric	1 (<0.1)	1 (<0.1)
Crystal urine	1 (<0.1)	1 (<0.1)

Note: those events highlighted in gray have a higher incidence than the original ISS.

2.6.1. Brief Narratives for Patients with Nephrolithiasis

Patient 3065A1-205-042-000848/212-042-000482 was a 33-year-old Caucasian male who was randomized to treatment with 900 mg of ezogabine along with carbamazepine (Hermolepsin) when he had a kidney stone of moderate severity on 19 Dec 2000 (Day 138). The event was reported as resolved on the same day, but was later updated to 'persisted' on Day 278. He continued in the study and was referred to a urology consult. However, no treatment information was provided.

Patient 3065A1-20212-00014/20879-00013 was a 39-year-old female with a history of nephrolithiasis, renal colic, pyelonephritis, and S/P surgery for kidney stones, who was taking ezogabine 400 mg/day along with phenytoin when she began experiencing mild pain at the both renal angles, left more than right, on 25 Feb 1999 (Day 96). Beginning on 15 Mar 1999 (Day 114), the patient developed severe left renal pain, reported to be from a kidney stone, along with nausea and vomiting. It is unknown if she passed a stone. The patient continued in the study and was taking 700 mg of ezogabine monotherapy when she had 2 consecutive hospitalizations, on 03 Jun 2000 (Day 560) and 10 Jun 2000 (Day 567), due to recurrent left flank pain. There was hematuria associated with the first event, but a cystoscopy with retrograde pyelogram was negative for renal stones. There was no hematuria present during the second event. The patient continued on 600 mg of ezogabine when she was re-admitted on 02 Oct 2000 (Day 681) with right renal colic and gross hematuria. She did not pass a stone and a number of diagnostic tests (cystoscopy, renal angiogram, biopsy, and post-biopsy CAT scan of the left kidney) did not reveal any etiology of the hematuria. The patient was discharged from the hospital as hematuria had subsided and continued in the study.

Patient 214-012-000116/216-012-000093 was a 32-year-old Caucasian male with a history of kidney stone in 1997 who was taking ezogabine 800 mg/day in combination with Dilantin and Keppra when he had a mild kidney stone on 09 Oct 2001 (Day 109).

The event was reported as resolved on the same day, but no other information, including treatment details, was provided. The patient continued in the study.

Patient 301-20221 was a 36- year-old Caucasian male who was taking ezogabine 1200 mg/day in combination with topiramate, lamotrigine and clobazam when he had a mild nephric lithiasis on 20 Aug 2007 (Day 70). A urinalysis collected on the same day had results within normal ranges. The event was reported as resolved without sequelae on 15 Oct 2007 (Day 126), but no additional details, including the treatment information, were provided. The patient continued in the study without interruption.

Patient 301-00302 was a 32- year-old Caucasian male who was taking 950 mg of ezogabine daily in combination with Depakote and Tegretol XR in the maintenance phase of the double-blinded study when he passed a kidney stone on 06 Sep 2006 (Day 96). He recovered on the same day and continued in the study.

Patient 301-00901 was a 38- year-old Caucasian male, with a history of kidney stones in 2001 and 2002, who was taking 1050 mg of ezogabine daily in combination with levetiracetam when he reported back discomfort beginning on 25 Feb 2006 (Day 52) followed by hematuria and penile pain on 28 Feb 2006 (Day 55). He was diagnosed with a kidney stone on 01 Mar 2006 (Day 56) via X-rays and abdominal/pelvic CT scans. He took a prophylactic treatment with Keflex 2000 mg for 7 days following a cystoscopy on 14 Mar 2006. Additional information on treatment of the event was not available. The subject recovered without sequelae on 12 Apr 2006 (Day 98) and continued in the study without interruption.

Patient 301-20210 was a 37- year-old Caucasian female had mild renal lithiasis on 19 Jan 2007 (Day 49), 7 days after she had permanently stopped taking 1050 mg of ezogabine per day, without tapering, during the maintenance phase of the study. Concomitant antiepileptics included lamotrigine and clobazam. At the time of the final study visit, the event was ongoing. No further details, including treatment of the event, were provided.

Patient 303-20413 was a 34-year-old African-American female who was taking ezogabine 1200 mg/day (had received placebo in the double-blind phase) in combination with phenytoin and clonazepam when she had renal calculus of moderate severity on 05 Oct 2007 (Day 263). She was treated with Etoricoxib and Hioscine until the event resolved without sequelae on 09 Oct 2007 (Day 267).

Patient 304-70204 was a 35-year-old Caucasian male who was receiving ezogabine, at a dose of 1200 mg/day, along with pregabalin and carbamazepine, when he experienced 2 episodes of mild renal microlithiasis, on 28 Feb 2008 (Day 564) and 04 Mar 2008 (Day 569), each resolving on the same day. No additional information, including treatment details, was provided. The patient continued in the study with no actions taken with ezogabine.

Patient 303-02511 was a 21-year-old Caucasian female who was taking ezogabine 1000 mg daily (had received ezogabine 1200 mg in the double-blinded study) in combination with topiramate and clonazepam when she developed a kidney stone on 26 Jun 2009

(Day 995), managed with Toradol 30 mg for 1 day. The event was reported as resolved without sequelae on 01 Jul 2009 (Day 1000), however it was not specified if the patient passed the stone. She continued in the study with no changes to ezogabine.

2.6.2. Discussion of Nephrolithiasis

Nephrolithiasis is a common condition; with as many as 13% of men and 7% of women in the United States expected to have at least 1 kidney stone during their lifetime [Goldfarb, 2009]. In addition, medical claims data demonstrated a prevalence rate for nephrolithiasis in adults between 18 and 64 years of age of 1.12% per for the year 2000 [Saigal, 2005]. Furthermore, the prevalence of kidney stones is increasing, perhaps because they are associated with hypertension, diabetes, obesity, chronic kidney disease, and the metabolic syndrome, all of which are on the increase. Secondary prevention recommendations include dietary modification with increasing fluid intake, restricting dietary sodium and reducing excessive meat consumption [Goldfarb, 2009].

Considering the common occurrence of nephrolithiasis, it is not surprising that a number of events of nephrolithiasis have been reported in the All Phase II/III Combined Grouping. Up to the cut-off date for this 120-Day Update, 10 cases of nephrolithiasis have been reported out of 1365 patients who have received ezogabine. Factoring in long term exposure within this grouping that comprises 1420 patient-years it provides a prevalence rate of 7.0 per 1,000 patient years of exposure.

This prevalence is consistent with the rate reported in the medical literature and as such does not support a causal association between ezogabine treatment and the occurrence of nephrolithiasis.

2.7. American Urological Association Symptom Index

2.7.1. Central tendency

Mean American Urological Association Symptom Index (AUA SI) scores remained low and consistent suggesting no worsening of urinary symptoms with long term treatment.

2.7.2. Shift

Consistent with the original ISS, 111/664 (17%) patients with AUA SI scores in the “mild” range at baseline had shifts to “moderate” or “severe” post baseline .

2.8. Post-Void Residual Volume

2.8.1. Post-Void Residual Bladder Ultrasound Values of Potential Clinical Concern

During the 120-Day reporting period, Post-Void Residual Volume (PVR) values of potential clinical concern were reported for 2 patients post baseline bringing the overall total to 55/642 (9%) of which 9 had PVR values of potential clinical concern at baseline.

3. URINALYSIS FINDINGS

3.1. Study VRX-RET-E22-NP201 (Post-Herpetic Neuropathic Pain)

3.1.1. Overview

Positive urine dipstick protein readings were reported in up to one-third of ezogabine-treated PHN patients enrolled in Study NP201 when assessed up to 96 hours after sample collection by a fully automated urine chemistry analyzer. In comparison, protein was detected in the urine specimens of no more than 10% of placebo patients. Concurrently, urine turbidity was reported for nearly all (96%) ezogabine-treated patients compared with approximately one-third of placebo patients, and abnormal urine color was reported in nearly half of ezogabine-treated patients, but in only 3% of placebo patients. No clinically meaningful changes in renal function were detected on other laboratory assessments, and no AEs were associated with the unexpected urinalysis findings which completely resolved with gradual ezogabine withdrawal over 3 weeks.

It is considered that these findings are likely to result from the *in vitro* degradation of renally-excreted ezogabine and ezogabine metabolites to produce urine discoloration and turbidity. Such changes might have interfered either directly or indirectly with the semi-quantitative analyses performed by the specific central laboratory facility utilized in the study. This hypothesis is supported by the following collective observations:

- the apparent connection between turbidity, color and positive protein dipstick readings, and the complete and rapid reversal to pre-treatment levels following ezogabine discontinuation;
- the lack of any associated clinical signs or symptoms;
- the sporadic nature of findings within subjects; the lack of precedence within other studies in the ezogabine development program;
- Eighty-four percent (84%) of an oral dose of ezogabine is excreted renally with 36% of the total dose excreted as unchanged ezogabine. The intrinsic solubility of ezogabine in the pH range of 5-7 is low (70-80 µg/mL). It is considered likely that the reported turbidity, color and positive protein dipstick readings are associated with excreted ezogabine and/or its metabolites.

This hypothesis is considered further below.

3.1.2. Introduction

Study NP201 was a Phase IIa, randomized, double-blind, placebo-controlled, proof-of-concept study conducted in the US and South Africa to evaluate the efficacy of maximally tolerated doses (MTD) of 300-900mg/day of ezogabine in reducing pain associated with post-herpetic neuralgia (PHN). It consisted of a 21-day Screening Phase; a 1-week Baseline Phase; a Titration Phase of up to 6 weeks in order to achieve the MTD; a 4-week Maintenance Phase; and a 3-week Taper Phase (treatment withdrawal).

A total of 187 patients were randomised to treatment (2:1 ezogabine: placebo) with 125 receiving ezogabine and 62 receiving placebo. Patients had a median age of 64 years (minimum 22 years; maximum 84 years); most were White (80%) and gender was reasonably balanced (54% female; 47% male).

Urine samples were collected at Baseline; Weeks 2, 4 and 6 of the Titration Phase; Weeks 2 and 4 of the Maintenance Phase; and at the end of the Taper Phase. Urine specimen stabilizing tablets [Cargille Stabilur® Tablet] were added at site and samples were shipped at ambient temperature to Covance Central Laboratory Services for urinalysis up to 96 hours after collection.

3.1.3. Urinalysis Methodology

Urinalysis was conducted using a fully automated system (iQ®200) that performs complete urinalyses on unspun specimens (International Remote Imaging Systems [IRIS], Inc., Chatsworth CA). The iQ200 system incorporates the iQ®200 Automated Urine Microscopy Analyzer (iQ200) and the AUTION MAX™ AX-4280 Automated Urine Chemistry Analyzer (AX-4280) to provide a fully integrated chemical and microscopic analysis.

The AX-4280 identifies and processes bar-coded specimen tubes in 10-position racks by mixing, sampling, and analyzing automatically. A 1.0 mL urine sample is aspirated, aliquots are deposited on AUTION 9EB strips, and the remainder of the sample is taken to a spectrophotometer and a refractometer for color, clarity and specific gravity measurements. Results for glucose, protein, bilirubin, urobilinogen, pH, blood, ketones, nitrite, leukocyte esterase, specific gravity (SG), color and clarity are rapidly provided.

3.1.3.1. Protein Detection

The protein pad on the AUTION 9EB multi-reagent strip is based on the Protein Error of Indicators [Free, 1957] which depends on the ability of amino groups in proteins to bind to and alter the color of acid-base indicators. At a constant pH any color change that happens to an indicator is attributed to protein. The test area of the reagent strip is impregnated with an indicator, tetrabromophenol blue, buffered to pH 3.0. At this pH it is yellow in the absence of protein. Protein forms a complex with the dye turning it green or bluish green. The intensity of blue color formed with protein is proportional to the amount of protein present, representing a typical negative reaction and 5 positive colors signifying “trace,” 30, 100 and 300 mg and greater than 600mg protein per 100 ml. The values are also designated as 1+, 2+, 3+ and 4+, respectively.

3.1.4. Significant Urinalysis Results

3.1.4.1. Protein

At the Baseline Visit, the incidence of $\geq 1+$ automated dipstick urinalysis protein readings was slightly lower in ezogabine-treated patients compared with patients who received placebo (4% versus 10%, respectively) (Table 7). However, during treatment, up to one-third of ezogabine-treated patients had $\geq 1+$ readings (by Maintenance Week 4), whereas

the incidence of $\geq 1+$ readings in patients who received placebo never exceeded the baseline level.

Readings rarely exceeded 1+ and returned rapidly to normal by Taper Week 3.

Table 7 Frequency of Protein Results: At Least 1+ (Safety Population: Study NP201)

Visit	Ezogabine 150-900mg/day (N=125)		Placebo (N=62)	
	N	Number (%) of patients	N	Number (%) of patients
Baseline	125	5 (4.0)	62	6 (9.7)
Titration Week 2	115	16 (13.9)	58	5 (8.6)
Titration Week 4	92	22 (23.9)	54	2 (3.7)
Titration Week 6	46	12 (26.1)	48	1 (2.1)
Maintenance Week 2	87	27 (31.0)	55	4 (7.3)
Maintenance Week 4	77	26 (33.8)	53	2 (3.8)
Taper Week 3	84	5 (6.0)	57	4 (7.0)

Note: Baseline = last non-missing observation before taking study medication.

3.1.4.2. Urine Clarity

At the Baseline Visit, the proportion of patients with clear urine was slightly lower in the ezogabine-treated group compared with patients who received placebo (75% versus 84%, respectively) (Table 8). However, during treatment the majority of patients receiving ezogabine produced urine that was either cloudy or hazy (up to 96% at Maintenance Week 4). In contrast, the proportion of placebo patients with cloudy or hazy urine never exceeded 32% (Taper Week 3).

Urine clarity in ezogabine-treated patients returned to baseline levels by the end of Taper Week 3.

Table 8 Urinalysis Findings: Urine Clarity (Safety Population: Study NP201)

Visit (N=EZG/Placebo)	Number (%) of Patients					
	Ezogabine 150-900mg/day (N=125)			Placebo (N=62)		
	Category			Category		
	Clear	Cloudy	Hazy	Clear	Cloudy	Hazy
Baseline (N=125/62)	94 (75.2)	2 (1.6)	29 (23.2)	52 (83.9)	2 (3.2)	8 (12.9)
Titration Week 2 (N=115/58)	10 (8.7)	46 (40.0)	59 (51.3)	44 (75.9)	1 (1.7)	13 (22.4)
Titration Week 4 (N=92/54)	9 (9.8)	58 (63.0)	25 (27.2)	42 (77.8)	0	12 (22.2)
Titration Week 6 (N=46/48)	4 (8.7)	32 (69.6)	10 (21.7)	37 (77.1)	0	11 (22.9)
Maintenance Week 2 (N=87/55)	8 (9.2)	57 (65.5)	22 (25.3)	45 (81.8)	3 (5.5)	7 (12.7)
Maintenance Week 4 (N=77/53)	3 (3.9)	56 (72.7)	18 (23.4)	39 (73.6)	0	14 (26.4)
Taper Week 3 (N=84/57)	63 (75.0)	3 (3.6)	18 (21.4)	39 (68.4)	6 (10.5)	12 (21.1)

Note: Baseline = last non-missing observation before taking study medication.

3.1.4.3. Urine Color

Urine color is influenced by a number of factors, including some foods and drugs that are known to produce unusually colored urine. Urine concentration also determines the range of normal tone that varies from colorless to yellow.

At Baseline, urine color was well matched between treatment groups with only 2 (3%) placebo patients producing abnormally colored urine (orange) (Table 9). However, during treatment, the urine from a substantial proportion of ezogabine-treated patients was reported as being orange or brown (up to 48% at Titration Week 6). Urine color in patients who received placebo remained normal throughout most of the study.

Color changes resolved rapidly and returned to normal by the end of Taper Week 3.

Table 9 Urinalysis Findings: Urine Color (Safety Population: Study NP201)

Visit (N=EZG/Placebo)	Number (%) of Patients							
	Ezogabine 150-900mg/day (N=125)				Placebo (N=62)			
	Category				Category			
	Colorless	Yellow	Orange	Brown	Colorless	Yellow	Orange	Brown
Baseline (N=125/62)	13 (10.4)	112 (89.6)	0	0	10 (16.1)	50 (80.6)	2 (3.2)	0
Titration Week 2 (N=115/58)	3 (2.6)	83 (72.2)	12 (10.4)	17 (14.8)	8 (13.8)	50 (86.2)	0	0
Titration Week 4 (N=92/54)	2 (2.2)	58 (63.0)	13 (14.1)	19 (20.7)	10 (18.5)	44 (81.5)	0	0
Titration Week 6 (N=46/48)	3 (6.5)	21 (45.7)	9 (19.6)	13 (28.3)	6 (12.5)	42 (87.5)	0	0
Maintenance Week 2 (N=87/55)	4 (4.6)	54 (62.1)	7 (8.0)	22 (25.3)	8 (14.5)	47 (85.5)	0	0
Maintenance Week 4 (N=77/53)	6 (7.8)	37 (48.1)	9 (11.7)	25 (32.5)	14 (26.4)	39 (73.6)	0	0
Taper Week 3 (N=84/57)	21 (25.0)	62 (73.8)	1 (1.2)	0	16 (28.1)	40 (70.2)	0	1 (1.8)

Note: Baseline = last non-missing observation before taking study medication.

3.1.5. Further Evaluations

Supplementary data were generated and additional analyses performed in order to attempt to better understand the clinical relevance of the unexpected urinalysis findings.

3.1.5.1. Correlation between Urine Findings

A third (34%) of patients had $\geq 1+$ dipstick protein readings by Maintenance Week 4 (26/77) with the proportion of such patients who also had colored and/or cloudy urine ranging from 63% (10/16) at Titration Week 2 to 100% (12/12) at Titration Week 6 (Table 10).

Table 10 Rates of At Least 1+ Dipstick Protein Readings in Ezogabine 150-900 mg Patients and Subsets with Cloudy Urine, Abnormally Colored Urine, and the Combination of both Urine Cloudiness and Abnormal Color (Safety Population: Study NP201)

Visit	N	Number (%) of patients Ezogabine 150-900 mg/day			
		All Ezogabine	Cloudy Urine Subset	Colored Urine Subset	Cloudy/Colored Urine Subset
Baseline	125	5 (4.0)	0	0	0
Titration Week 2	115	16 (13.9)	12 (10.4)	12 (10.4)	10 (8.7)
Titration Week 4	92	22 (23.9)	17 (18.5)	17 (18.5)	15 (16.3)
Titration Week 6	46	12 (26.1)	12 (26.1)	10 (21.7)	10 (21.7)
Maintenance Week 2	87	27 (31.0)	23 (26.4)	21 (24.1)	21 (24.1)
Maintenance Week 4	77	26 (33.8)	24 (31.2)	23 (29.9)	22 (28.6)
Taper Week 3	84	5 (6.0)	2 (2.4)	1 (1.2%)	1 (1.2)

3.1.5.2. Non-Urine Markers of Renal Function

3.1.5.2.1. Blood Urea Nitrogen

Table 11 provides a summary of blood urea nitrogen (BUN) levels showing marginal increases from baseline in ezogabine-treated patients. The increases were not reported as AEs by investigators and are not considered clinically significant.

Table 11 BUN (mmol/L): Observed Means and Standard Deviations and Change From Baseline by Week (Safety Population: Study NP201)

Timepoint	Ezogabine 150-900mg (N=125)			Placebo (N=62)		
	N	Mean (STD)	Change from Baseline Mean (STD)	N	Mean (STD)	Change from Baseline Mean (STD)
Baseline	125	5.9 (1.71)	-	62	5.6 (1.53)	-
Titration Week 2	120	6.2 (1.73)	0.3 (1.45)	59	5.6 (1.59)	0.0 (1.14)
Titration Week 4	95	6.6 (1.84)	0.7 (1.64)	54	5.5 (1.66)	-0.1 (1.13)
Titration Week 6	47	6.4 (1.78)	0.7 (1.80)	49	5.5 (1.77)	-0.1 (1.45)
Maintenance Week 2	85	6.2 (1.69)	0.4 (1.55)	57	5.7 (1.72)	0.2 (1.36)
Maintenance Week 4	76	6.5 (1.89)	0.7 (1.65)	54	5.5 (1.67)	0.0 (1.32)
Taper Week 3	84	6.0 (1.58)	0.1 (1.56)	58	5.9 (1.90)	0.4 (1.38)

Note: Baseline = last non-missing observation before taking study medication.

Note: Only subjects with both baseline and post-baseline data are included at each timepoint.

3.1.5.2.2. Serum Creatinine

Table 12 provides a summary of serum creatinine levels showing marginal increases in ezogabine-treated patients. The increases were not reported as AEs by investigators and are not considered clinically significant.

Table 12 Serum Creatinine (mmol/L): Observed Means and Standard Deviations and Change From Baseline by Week (Safety Population: Study NP201)

Timepoint	Ezogabine 150-900mg (N=125)			Placebo (N=62)		
	N	Mean (STD)	Change from Baseline Mean (STD)	N	Mean (STD)	Change from Baseline Mean (STD)
Baseline	125	77.3 (16.69)		62	76.0 (18.82)	
Titration Week 2	120	78.7 (20.84)	1.3 (10.98)	59	75.4 (17.60)	-0.4 (8.62)
Titration Week 4	95	77.5 (18.48)	1.6 (9.75)	54	75.1 (19.19)	-0.7 (6.78)
Titration Week 6	47	80.3 (19.25)	2.5 (8.20)	49	73.5 (17.48)	-1.7 (8.08)
Maintenance Week 2	85	79.1 (18.52)	2.7 (8.26)	57	75.7 (18.80)	-0.6 (7.02)
Maintenance Week 4	76	82.8 (25.98)	5.3 (22.01)	54	76.1 (18.41)	-0.2 (9.13)
Taper Week 3	84	80.7 (17.19)	3.7 (9.26)	58	75.7 (18.94)	-0.5 (8.36)

Note: Baseline = last non-missing observation before taking study medication.

Note: Only subjects with both baseline and post-baseline data are included at each timepoint.

3.1.5.3. Adverse Events

Of note, there was 1 report of renal impairment following treatment with ezogabine (1/125; 1%) that was considered mild, required no action and the subject completed the study (Table 13). There were also 2 reports of renal cysts; 1 each for placebo and ezogabine.

There were no other notable differences between treatment groups.

Table 13 Number of Renal and Urinary Disorder TEAEs Reported During the Double-Blind Phase of Study NP201

Preferred term	Number (%) of Patients	
	Ezogabine 150-900mg/day (N=125)	Placebo (N=62)
Urinary Retention	4 (3.2)	1 (1.6)
Micturition Frequency Decreased	3 (2.4)	0
Dysuria	2 (1.6)	0
Urinary Incontinence	2 (1.6)	0
Urobilinuria	2 (1.6)	0
Bladder Pain	1 (0.8)	0
Chromaturia	1 (0.8)	0
Haematuria	1 (0.8)	0
Nephrolithiasis	1 (0.8)	1 (1.6)
Pollakiuria	1 (0.8)	2 (3.2)
Renal Cyst	1 (0.8)	1 (1.6)
Renal Impairment	1 (0.8)	0
Renal Pain	1 (0.8)	0
Urinary Hesitation	1 (0.8)	0
Urine Flow Decreased	1 (0.8)	0
Urine Odour Abnormal	1 (0.8)	0
Micturition Urgency	0	1 (1.6)
Nocturia	0	1 (1.6)
Proteinuria	0	2 (3.2)

3.2. Pivotal Controlled Trials (Studies 205, 301 and 302)

Integrated urinalysis data for the Pivotal Controlled Trials (PCT) grouping (Studies 205, 301, and 302) are summarized in [Table 14](#).

There was no indication that ezogabine had any adverse effect on urinalysis.

Table 14 Summary of Urinalysis Evaluations at Any Post-Baseline Visit (Safety Population: PCT, Studies 205, 301, and 302)

	Percentage of Patients (n/N)				
	Placebo (N=427)	EZG 600 mg/day (N=281)	EZG 900 mg/day (N=273)	EZG 1200 mg/day (N=259)	EZG Total (N=813)
Blood present	97/412 (23.5)	57/269 (21.2)	46/260 (17.7)	48/247 (19.4)	151/776 (19.5)
Amorphous crystals present	62/412 (15.0)	99/269 (36.8)	89/260 (34.2)	12/247 (4.9)	200/776 (25.8)
Amorphous phosphate crystals present	19/412 (4.6)	2/269 (0.7)	5/260 (1.9)	9/247 (3.6)	16/776 (2.1)
Amorphous urate crystals present	55/412 (13.3)	25/269 (9.3)	27/260 (10.4)	56/247 (22.7)	108/776 (13.9)
Uric acid crystals present	32/412 (7.8)	29/269 (10.8)	33/260 (12.7)	35/247 (14.2)	97/776 (12.5)
Calcium oxalate crystals present	113/412 (27.4)	69/269 (25.7)	65/260 (25.0)	60/247 (24.3)	194/776 (25.0)
Glucose present	6/412 (1.5)	1/269 (0.4)	1/260 (0.4)	2/247 (0.8)	4/776 (0.5)
Hyaline casts present	57/412 (13.8)	24/269 (8.9)	25/260 (9.6)	13/247 (5.3)	62/776 (8.0)
Ketones present	14/412 (3.4)	3/269 (1.1)	6/260 (2.3)	7/247 (2.8)	16/776 (2.1)
Protein present	100/412 (24.3)	51/269 (19.0)	51/260 (19.6)	63/247 (25.5)	165/776 (21.3)
RBCs present	305/412 (74.0)	179/269 (66.5)	176/260 (67.7)	153/247 (61.9)	508/776 (65.5)
WBCs present	321/412 (77.9)	167/269 (62.1)	159/260 (61.2)	168/247 (68.0)	494/776 (63.7)

3.3. Integrated Clinical Pharmacology Studies (VRX-RET-E22-103 and VRX-RET-E22-106)

Integrated data for a subset of the Integrated Clinical Pharmacology grouping that included long term exposure to ezogabine (VRX-RET-E22-103 and VRX-RET-E22-106) are summarized in [Table 15](#). The data are not considered to be of clinical significance.

Table 15 Summary of Urinalysis Evaluations at Any Post-Base (Safety Population: Integrated Clinical Pharmacology Studies- VRX-103 and VRX-106)

	Percentage of Patients (n/N)	
	EZG Total (N=813)	
Bacteria present	9/70 (12.9)	
Blood present	3/70 (4.3)	
Color (yellow)	40/70 (57.1)	
Glucose present	0	
Ketones present	3/70 (4.3)	
Protein present	1/70 (1.4)	
RBCs present	17/70 (24.3)	
WBCs present	17/70 (24.3)	

3.4. Hypothesis Testing

In order to assess the validity of the hypothesis that the urinary findings in Study NP201 are the consequence of ezogabine degradation subsequently interfering with the urinalysis methodology employed in this study thus producing false positive protein results; an initial exploratory evaluation of urine specimens collected from ezogabine-treated patients in an ongoing exploratory study is being performed and a more comprehensive study to further evaluate previously stated hypothesis is planned.

3.4.1. Urinalysis Sub-Study (Study VRX-RET-E22-303, Amendment 2)

Open-label extension Study 303 was amended to provide an initial opportunity for the rapid exploration of the supposition regarding the urinary findings in Study NP201. The amendment enabled male and female patients enrolled in Study 303 to voluntarily provide urine samples for further evaluation. On-site tests of the urine samples included immediate visual dipstick evaluation for protein, blood, leukocytes, nitrite, pH, and specific gravity (SG) with the clarity and color of the urine being noted. Urine samples were also divided into aliquots and simultaneously sent to both Covance and Quintiles central laboratories for automated urinalysis. The Quintiles central laboratory (Qlabs) was utilized extensively in the Phase III epilepsy studies and is conducting the routine safety testing for the extension studies. Therefore the addition of Covance central laboratory enables a direct comparison of the effects of different laboratory methodologies on urinalysis outcomes. In order to correct for urinary concentration, quantify how much protein was actually excreted in urine samples and therefore establish whether any urinalysis protein readings were false positives, a spot urine microalbumin:creatinine ratio was also determined at each laboratory (a urine albumin:creatinine ratio correlates well with the amount of albumin excreted over 24 hours using a “gold standard” 24-hour urine collection [Saudan, 1997; Kashif, 2003; Phelan, 2004; Price, 2005; Dwyer, 2008; NICE, 2008] and has greater sensitivity for detecting low levels of protein than a protein:creatinine ratio [NICE, 2008]).

Table 16 summarizes the results of on-site urine examination and subsequent central laboratory urinalysis (Covance and Qlabs) of 35 specimens collected from 16 patients during January 2010 (some patients provided more than 1 sample on different days to enable the expeditious reporting of the results for the 120-Day Safety Update).

Visual inspection of the freshly voided urine specimens by investigator site staff indicated that approximately two-thirds were clear (71%; 25/35) and normal (yellow) in color (66%; 23/35). Furthermore, on-site urine dipstick protein readings were considered positive for only 6% (2/35) of specimens (1 at the 1+ level, and 1 at the 2+ level).

Covance and Qlabs urinalysis results of aliquots of the same specimens 1-3 days following collection provide somewhat discordant results between certain parameters (Table 16). As observed in Study NP201, the Covance urinalysis results indicate a relatively high proportion of 1+ protein readings (26%; 9/35), turbidity (100%; 35/35) and discoloration (29%; 10/35 orange/brown). In comparison, the Qlabs data generally reflect those from the epilepsy clinical development program with only a few positive

protein readings (6%; 2/35), little abnormal coloration (3%; 1/35) and less than half of the specimens were turbid (46%; 16/35).

Microalbumin:creatinine ratios compare well between the Covance and Quintiles central laboratories.

Table 16 Summary of Urinalysis Evaluations (Safety Population: Study VRX-RET-E22-303, Amendment 2)

Urinalysis Parameter	Category	Site (N=35)	Covance (N=35)	Quintiles (N=35)
Clarity	Clear	25/35 (71.4%)	0/35	19/35 (54.3%)
	Cloudy	2/35 (5.7%)	20/35 (57.1%)	6/35 (17.1%)
	Hazy	8/35 (22.9%)	15/35 (42.9%)	0/35
	Turbid	0/35	0/35	10/35 (28.6%)
Color	Brown	0/35	6/35 (17.1%)	0/35
	Green	0/35	0/35	1/35 (2.9%)
	Orange	12/35 (34.3%)	4/35 (11.4%)	0/35
	Yellow	23/35 (65.7%)	25/35 (71.4%)	34/35 (97.1%)
Protein	Absent ^a	33/35 (94.3%)	26/35 (74.3%)	33/35 (94.3%)
	Present ^a	2/35 (5.7%)	9/35 (25.7%)	2/35 (5.7%)
Microalbumin:creatinine ratio (mg/g)	Mean	N/A ^b	15.1	13.5
	STD ^c		23.9	22.9
	Median		7.0	7.0
	Minimum		4.0	4.0
	Maximum		109	105

a. Absent = Trace or Negative; Present = 1+ or 2+ (30mg/dL or 100mg/dL, respectively)

b. N/A = Not Applicable

c. STD = Standard Deviation

A summary of patients with urine specimens with positive urine protein readings and/or abnormal microalbumin:creatinine ratios is presented in [Table 17](#). Also presented are the corresponding urine color and urine clarity readings for all of these patients.

Three patients had abnormal microalbumin:creatinine ratios reported by at least 1 central laboratory ([Table 17](#)). One of these 3 patients who had a relatively high microalbumin:creatinine ratio (>100mg/g) also had corresponding urine dipstick protein readings of $\geq 1+$ at 2 different timepoints as assessed by both the investigator site and the 2 central laboratories. This African-American male patient (Patient 303-041-04105) was initially randomized to treatment with ezogabine 1200mg/day in Study VRX-RET-E22-301 (Study 301) and subsequently transitioned into the open-label extension Study 303. Urinalysis readings at the Screening and Baseline Visits in Study 301 indicate trace levels of protein. Subsequent urinalysis at visits after initiating treatment with ezogabine indicated mostly 1+ urinalysis protein readings (2+ on one occasion; trace readings on 2 other occasions). The protein readings seemed to correlate with specific gravity readings suggestive of more dilute urine at Screening/Baseline and more concentrated urine during treatment. Serum creatinine remained fairly constant ranging from 0.8mg/dL at baseline to a maximum of 1.1mg/dL. Blood urea nitrogen levels ranged from 9mg/dL at baseline to a maximum of 22mg/dL. The other 2 patients had microalbumin:creatinine ratios that

were just outside the normal range (normal range $\leq 30\text{mg/g}$), although for 1 of the patients at 1 timepoint, conflicting results were obtained from the central laboratories, with 1 laboratory reporting a normal microalbumin:creatinine ratio. At other timepoints for this patient a few days earlier, the microalbumin:creatinine ratios were all within the normal range. Neither sites nor central laboratories indicated the presence of urinary protein for either of these 2 patients.

Seven other urine specimens from 4 patients were reported to contain protein (1+) by Covance, but not by investigator sites or Qlabs. Covance also indicated that all of these samples were cloudy or hazy, and many were discolored (brown). Investigator sites and Qlabs also indicated some of the specimens to be hazy, cloudy or turbid, but, whilst investigator sites indicated some specimens to be discolored (orange), Qlabs indicated the majority of the specimens were a normal yellow. Importantly, the microalbumin:creatinine ratios were within the normal range for all of these samples that strongly suggests that while some factor may be interfering with the dipstick assessment of protein, particularly at Covance this does not impact the more robust assessment of proteinuria using the microalbumin:creatinine ratio.

Table 17 Summary of Urinalysis Evaluations for Patients with Positive Urine Protein Readings and/or Out of Range Microalbumin:Creatinine Ratios (Safety Population: Study VRX-RET-E22-303, Amendment 2)

Subject No	Study Day	Microalbumin:creatinine ratio (mg/g)		Protein			Clarity			Colour		
		Covance	Qlabs	Site	Covance	Qlabs	Site	Covance	Qlabs	Site	Covance	Qlabs
303-000001-000103	1267	32	32	Neg	Trace	Neg	Clear	Cloudy	Clear	Orange	Yellow	Yellow
303-000001-000106	1226	7	6	Neg	1+	Trace	Clear	Cloudy	Clear	Orange	Brown	Yellow
303-000002-000202	1396	9	7	Neg	1+	Trace	Hazy	Cloudy	Cloudy	Yellow	Brown	Yellow
	1400	7	5	Neg	1+	Trace	Cloudy	Cloudy	Cloudy	Yellow	Brown	Yellow
	1403	7	6	Trace	1+	Trace	Hazy	Hazy	Cloudy	Orange	Yellow	Yellow
303-000014-001406	1047	16	12	Trace	1+	Trace	Clear	Cloudy	Turbid	Orange	Brown	Yellow
	1048	5	5	Neg	Neg	Neg	Clear	Hazy	Turbid	Yellow	Yellow	Yellow
	1052	12	9	Neg	Trace	Trace	Hazy	Hazy	Turbid	Yellow	Yellow	Yellow
303-000014-001415	974	7	8	Neg	Neg	Neg	Hazy	Cloudy	Cloudy	Orange	Yellow	Yellow
	975	9	8	Neg	Trace	Trace	Clear	Cloudy	Turbid	Yellow	Yellow	Yellow
	979	35	9	Trace	Neg	Trace	Clear	Hazy	Turbid	Orange	Yellow	Yellow
303-000041-004105	1111	105	101	2+	1+	1+	Clear	Cloudy	Clear	Yellow	Brown	Green
	1112	109	105	1+	1+	1+	Clear	Cloudy	Clear	Yellow	Brown	Yellow
303-000041-004106	1090	7	4	Trace	1+	Trace	Cloudy	Hazy	Turbid	Yellow	Yellow	Yellow
	1091	7	4	Trace	1+	Trace	Hazy	Hazy	Clear	Orange	Yellow	Yellow

Note: cells highlighted in gray show correlations between investigator site and central laboratory assessments of spot urine microalbumin:creatinine ratios, protein, clarity and color for all patients with abnormal protein findings.

3.4.2. Study RTG114137

This is a planned clinical pharmacology study to assess the impact of urine sample handling procedures (interval between collection and analysis; role of specimen stabilizers) on urinalysis outcomes in healthy males and females aged 40 to 65 years receiving ezogabine doses of 300mg/day to 900mg/day for 4 weeks. Urine samples will be collected on 5 occasions over the treatment period. As the study will also explore the potential impact of urine osmolality, on 2 of these occasions urine samples will be collected from patients following 24-hour fluid restriction. All urine specimens will be divided into a number of aliquots, treated with 2 different types of stabilizers and urinalysis will be performed on both fresh urine and on urine that has been stored at room temperature for 24 and 72 hours. All samples will be frozen and stored after completion of tests. Urinalysis will be performed using the iQ200 system as used in Study NP201 and in case of positivity for protein in the fresh urine sample the total protein:creatinine ratio will be measured. Proposed timelines for the study are: first subject visit in April 2010; last subject visit in September 2010; data analysis completed in December 2010.

3.5. Discussion

In Study NP201, nearly all urine specimens from ezogabine-treated patients were hazy or cloudy; half became abnormally colored and around a third tested positive for the presence of protein when evaluated by an automated urine chemistry analyzer at a central laboratory up to 96 hours after urine collection. In contrast, the majority of patients who received placebo had normal urine color; turbidity increased only marginally and protein readings remained similar to those at baseline. It is considered unlikely that these findings are of clinical concern and may be due to false positive observations. This inference is supported by a number of corroborating factors as discussed below.

3.5.1. Nature of Urinary Findings

In Study NP201, differences from baseline in dipstick protein readings of $\geq 1+$ were evident between placebo and ezogabine-treated patients from Week 2 of the Treatment Phase. The differences between the 2 groups progressively increased throughout treatment until the end of the Maintenance Phase (Week 4). Similarly up to 96% of urine specimens from ezogabine-treated patients were hazy or cloudy and up to 49% were abnormally colored (orange or brown) during treatment/maintenance. Thereafter, gradual lowering of the ezogabine dose to eventual discontinuation over a 3 week Taper Phase resulted in the return of urine protein, turbidity and color readings to pre-treatment levels. The rapid onset of the changes and their subsequent rapid and complete resolution support the likelihood of a chemical as opposed to a pathological cause for the observed findings. This is further substantiated by the non-urine markers of renal function (serum creatinine and BUN) that showed only small clinically insignificant changes with exposure.

3.5.2. Crystalluria

Urinary crystals having the microscopic appearance of bilirubin were first identified incidentally and intermittently on urine microscopy during the Phase III trials of

ezogabine in epilepsy. These urinary crystals only occurred in patients who received ezogabine. No unusual trends in symptoms, AEs, laboratory findings, or post-void residual (PVR) volumes were seen in these patients and a chemical analysis of the crystals determined that they were not bilirubin, but may be ezogabine or ezogabine metabolite crystals.

Urinary crystals (e.g. calcium oxalate, uric acid, calcium phosphate, triple phosphate) are common and vary according to urine pH [Fogazzi, 1996]. Cloudy urine often is a result of precipitated crystals [Simerville, 2005] and therefore it is not improbable that either normal urine crystallization, or ezogabine or metabolite crystal formation, or a combination of these amorphous forms may account for the reports of crystalluria in the epilepsy studies. Furthermore the refractory properties of the bilirubin-like crystals together with ezogabine color formation in solution over time may contribute to the reports of chromaturia in the epilepsy studies and the extensive turbidity and discoloration in Study NP201 (1 AE of “crystal urine present” was reported in this study).

3.5.3. Impact of Automated Dipstick Urinalysis

The ideal test for the assessment of protein does not exist [Phelan, 2004]. Dipstick urinalysis is relatively cheap and convenient but is associated with widely varying sensitivities and specificities [Halligan, 1999; NICE, 2008]. False positive (and false negative) protein results are not unusual [Hindberg, 1978; Kashif, 2003; Phelan, 2004; Gangaram, 2005; Simerville, 2005; Abebe, 2008; Dwyer, 2008] and although the use of automated urinalysis devices improves accuracy compared with visual inspection [Peele, 1977; Saudan, 1997] high false positive rates are still common [Kyle, 2008] particularly at the 1+ level [Saudan, 1997; Phelan, 2004; Dwyer, 2008].

Compared with the epilepsy clinical development program where only a small proportion of ezogabine-treated patients reported proteinuria, the observation of positive protein results in up to one-third of PHN patients in Study NP201 not only underpins the difficulties in comparing tests of diagnostic accuracy between studies [Waugh, 2001], but suggests that the different methodologies employed by the respective central laboratories may account for the variations observed between the 2 patient populations. This is likely supported by:

- the fact that the majority of urine protein readings were at the recognised high false positive (1+) level;
- that there is a strong correlation between high urine protein, turbidity and color levels (i.e. conditions likely to overwhelm the automated analyzer despite the presence of a dual wavelength reflectance and a color compensation pad to limit interferences from color, turbidity or drugs).

Data from the urinary sub-study of patients from Study 303 suggest that minor differences between central laboratories in factors such as specimen handling, transport and storage conditions, specimen stabilizers, analysis timing, and analytical methodologies may indeed result in dissimilar results. The results from this sub-study show that whilst immediate post-void dipstick testing and subjective visual examination of urine samples indicate mostly normal urine color, clarity and protein levels; the

transfer of aliquots of the same specimens to 2 central laboratories for automated urinalysis 1-3 days post-collection can result in different outcomes despite general similarities in the overall methodological processes employed by the respective laboratories.

In this sub-study, urinalysis data from the Covance central laboratory show proportions of patients to have 1+ dipstick protein readings, urinary turbidity and urinary discoloration similar to those observed for Study NP201. In comparison, urinalysis data from the Quintiles central laboratory for the very same urine specimens show few positive protein readings, with urine discoloration and turbidity reported in only a small proportion of samples. Of significance, the inclusion of an estimation of spot urine microalbumin:creatinine ratio by both central laboratories provides reassurance that the discrepancies resulting from the minor differences between their respective semi-quantitative urinalysis methodologies can be put into context with the majority of the urinary protein findings clearly being false positive readings.

Three patients had microalbumin:creatinine ratios that are considered to be outside of the normal range. For 2 of these patients, the fact that their ratios were only marginally higher than normal and that neither sites nor central laboratories detected the presence of any significant urinary protein, suggests that the ratios may not be clinically significant and probably due to chance, particularly as for 1 of the patients the central laboratories produced highly conflicting results at 1 assessment timepoint, whilst normal ratios were reported by both laboratories for the same patient only a few days earlier. For the third patient, urinary protein was detected by both the investigator site and the 2 central laboratories and the microalbumin:creatinine ratios are clearly outside the normal range. Examination of other urinary parameters for this patient as provided by Covance and Qlabs do not indicate any obvious cause that may be responsible for the apparent proteinuria in this patient. Examination of urinalysis data for this patient who also received ezogabine in Study 301 showed that the patient had raised, but not progressive, urinalysis protein readings throughout his participation in the study. However, these were not associated with any changes in creatinine or blood urea nitrogen, and no AEs were reported for the patient.

3.5.4. Conclusion

In conclusion, protein findings in 11% (4/35) of specimens is in line with the reported rates for urinary protein detected by urinalysis for both placebo- and ezogabine-treated patients in the epilepsy clinical development program. A more likely true rate of proteinuria of 1/16 (6%) patients (2/35 specimens) provides further reassurance that ezogabine is unlikely to be associated with the development of kidney disease. The apparent excess of positive protein readings in the Covance analysis does not match that reported by the site or the other central laboratory and is in conflict with the microalbumin:creatinine ratios from both laboratories. As such, this demonstrates a potential for false positive urinalysis protein readings arising from the Covance methodology. The planned clinical pharmacology study RTG114137 will explore the potential underlying mechanisms that may have been responsible for the Covance results in both this sub-study and Study NP201 and consequently will seek to provide more definitive evidence that ezogabine does not cause proteinuria.

3.6. References

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11.9. Appendix: Full Narratives for Patients Requiring Catheterization

PATIENT 205-000448

Protocol#: 3065A1-205-AU/EU/US	Site ID: 032
Age of patient at study entry: 53 Sex: Female Ethnic Origin: White	
Reason for narrative: Serious adverse event (hospitalisation)	
Study Treatment/Dose: Ezogabine 200 mg TID	
Date therapy started : 05 Apr 2000	Date of last dose: 06 May 2000
Adverse event (preferred term): Kidney failure	
Adverse event (verbatim term): Renal failure and Abnormal liver function tests.	Severity: Moderate
Start date of AE: 24 Apr 2000	End date of AE: 13 May 2000
Duration of AE: 20 days	Treatment emergent? Yes
Relation to therapy (investigator): Probably	Relation to therapy (monitor): Possibly
Patient has another narrative? No	

Significant past medical history: Vitiligo of unknown origin; Hysterectomy; Motor vehicle accident at the age of 18 where she was briefly knocked unconscious; Base of skull fracture at age 46 (fall during a seizure). The patient had partial complex epilepsy diagnosed 1974, beginning early in her first and only pregnancy. Her seizures have usually manifested themselves as repetitive opening closing of left hand, chewing movements, inappropriate actions, and abnormal responses the outside world. She has on a few occasions experienced secondary generalisation of seizures with tonic-clonic convulsions. The patient's partial, complex epilepsy has at all times been resistant to medical treatment. During her participation in the Ezogabine protocol, the patient has been receiving Valproate 1000 mg daily and Carbamazepine 800 mg daily as concomitant background AED treatment.

The patient was screened for suitability in the study on 08 Feb 2000. Her baseline screening tests including ECG, Holter monitor, echocardiogram, routine blood tests and thyroid function tests were normal apart from a mild depression of T3 and T4 (ascribed to Carbamazepine).

The patient initially experienced adverse symptoms on 24 Apr 2000, complaints including non-specific symptoms like myalgia, fatigue, cough, polydipsia and sweats. Over the next four days the patient felt some improvement and she was seen on 28 Apr 2000 by the investigator for a scheduled visit (visit 4); upon examination the patient presented with a normal general and neurological examination apart from mild ataxia and nystagmus. The usual blood tests were taken and the patient was sent home receiving unchanged concomitant AED's and continuing the Ezogabine trial medication.

Over the next days the patient became increasingly affected by aches, lethargy and sweats, and she developed tremors. Her urinary pattern changed to frequent visits to the

toilet with small volumes of urine delivered and she became increasingly constipated. The patient had no complaints of dysuria, fever or abdominal pains.

On 06 May 2000 results from the blood tests taken 28 Apr 2000 were reviewed. These revealed renal failure and mild to moderate derangement of liver function tests:

Creatinine: 0.38 mmol/L Normal range: 0.04 - 0.10

Urea: 22.9 mmol/L Normal range: 2.5 - 8.5

Sodium: 130 mmol/L Normal range: 135 - 149

Potassium: 5.3 mmol/L Normal range: 3.6 - 5.4

AST: 29 U/L Normal range: 0 - 50

ALT: 60 U/L Normal range: < 50

GGT: 780 U/L Normal range: 5 - 40

Bilirubin: 23 μ mol/L Normal range: < 20

Alkaline Phos: 152 U/L Normal range: 40 - 125

CRP: 328 mg/L Normal range: < 12

The patient was admitted to the hospital on this date. Examination of the patient demonstrated slight basal crackles bilaterally at lungs, faintly yellow sclerae, and a distended and slightly tender abdomen. No fever was recorded. The patient was catheterised and immediately delivered 1500 ml of cloudy urine (positive for protein but not for blood or glucose). Blood tests were done:

Creatinine: 0.40 mmol/L Normal range: 0.06 - 0.10

Urea: 24.8 mmol/L Normal range: 3.0 - 6.6

Sodium: 129 mmol/L Normal range: 136 - 144

Potassium: 4.7 mmol/L Normal range: 3.4 - 4.8

AST: 40 U/L Normal range: 1 - 30

ALT: 61 U/L Normal range: 1 - 40

GGT: 625 U/L Normal range: 1 - 25

Bilirubin: 34 μ mol/L Normal range: < 20

Alkaline Phos: 125 U/L Normal range: 30 - 110

On the basis of the above symptoms and laboratory tests the patient was diagnosed with acute renal failure secondary to urinary retention. The latter was thought to be on the basis of either infection or study medication. The patient was started on gentamicin and ampicillin and study medication was discontinued on 07 May 2000.

During the following days the patient went into recovery polyuria phase and delivered large amounts of discoloured urine (excretion of Bilirubin?) and on 09 May 2000 visualisation of the kidneys demonstrated dilation of renal pelvis and swollen kidneys bilaterally. Urinary cultures were all clear and antibiotics were discontinued on 10 May 2000. The patient's laboratory values rapidly improved. Thus, on 10 May, the following was recorded:

Creatinine: 0.16 mmol/L	Normal range: 0.06 - 0.10
Urea: 10.2 mmol/L	Normal range: 3.0 - 6.6
Sodium: 142 mmol/L	Normal range: 136 - 144
Potassium: 3.2 mmol/L	Normal range: 3.4 - 4.8
AST: 57 U/L	Normal range: 1 - 30
ALT: 82 U/L	Normal range: 1 - 40
GGT: 496 U/L	Normal range: 1 - 25
Bilirubin: 18 μ mol/L	Normal range: < 20
Alkaline Phos: 115 U/L	Normal range: 30 – 110

During the course of her recovery polyuria phase the patient passed approximately 3.5 L of urine per day. As expected, this considerable change in fluid balance caused deviations in the patient's electrolytes and made supplementation with saline and Caltrate necessary during the hospitalisation. The patient kept improving and was discharged on 13 May 2000.

The specific cause of urinary retention/post-renal obstruction was never established. Thus, the relationship to the study drug remains to be confirmed/refuted. The patient is now well and has no sequelae.

PATIENT 301-005203

Serious adverse event			
Study / Subject No:		VRX-RET-E22-301 / 05203	
Age (yrs) / Sex / Race:		55 / Male / Caucasian	
Event term: (verbatim / PT)		Increased seizures / Convulsion Urinary retention / Urinary retention	
Oral study drug:		Placebo	
Study drug start - end dates:		19 Aug 2006 – Continuing	
Date maintenance phase began:		30 Sep 2006	
Last dose of study drug taken:		Continued into open label extension study	
Concomitant antiepileptic therapy (start date):		Carbamazepine (1997) Clobazam (1997) Lamotrigine (May 1999)	
Adverse event as reported by investigator:	Adverse event as coded:	SAE:	DC'd due to AE:
Increased seizures	Convulsion	Yes ^a	No
Urinary retention	Urinary retention	Yes ^b	No
(a Hospitalization)			
(b Prolongation of hospital stay)			

Case summary:

This 55-year-old Caucasian male randomized to treatment with placebo in combination with carbamazepine, clobazam, and lamotrigine, with a history of a left cerebral vascular accident and right hemiparesis, was hospitalized for increased seizures on 11 Sep 2006 (Day 24). The patient's hospital stay was prolonged due to an episode of urinary retention (Day 25).

This patient began treatment with blinded placebo on 19 Aug 2006 and reached maintenance treatment on 30 Sep 2006. On 11 Sep 2006, the patient experienced 3 complex partial seizures at home and 5 complex partial seizures in the emergency room over an 8 hour period. The seizures were more frequent, but not more severe, than his baseline seizures. Ten days prior to the event, carbamazepine and lamotrigine levels were within normal therapeutic levels. On the day of the event, carbamazepine levels were within therapeutic levels, CBC results were normal, and sodium was 134 mmol/L (normal range, 135-145 mmol/L). On 12 Sep 2006, an electroencephalogram (EEG) revealed a disturbance in the cerebral cortical function involving the left cerebral hemisphere and potentially epileptogenic abnormalities in the left mid-temporal and left parietal regions, which were consistent with the results of the patient's previous EEGs. On the same day, the patient was started on pantoprazole and rabeprazole for 2 days and experienced urinary retention, which was treated with an in-and-out catheterization. A routine microscopic urinalysis and urine culture were negative.

A postvoid residual (PVR) measurement of urine volume, conducted on 17 Aug 2006, revealed a pre-void volume of 147 cc and a PVR volume no greater than 20 cc, with a bladder described as "unremarkable". The patient did not have any additional seizures in

the hospital and did not experience any further difficulty voiding. No action was taken with the blinded study drug and the patient remained in the study. The patient was discharged from the hospital on 13 Sep 2006 (Day 26).

The investigator considered the increased seizures as possibly related to blinded study drug (placebo) and the urinary retention as not related. The sponsor considered the increased seizures as unexpected and possibly related to blinded placebo and the urinary retention as unexpected and not related.

Selected test results are presented in the tables below.

Date	Day	Carbamazepine (µg/mL)	Lamotrigine (µg/mL)
18 Aug 2006	-1	9.8	5.4
01 Sep 2006	14	9.0	5.1
28 Sep 2006	41	7.5	–
12 Oct 2006	55	9.4	5.5
27 Dec 2006	131	7.7	–
Therapeutic range		4 – 12	10 – 60

Source: Clinical Study Laboratory

Visit	Date	Day	Post-void residual urine
volume (cc)			
Baseline	17 Aug 2007	-2	20
Week 10	02 Nov 2007	76	14
Week 18	27 Dec 2006	131	3
Normal range			<50

Medical history:

Left cerebral vascular accident (1950-continuing), right hemianopia (1950-continuing), right hemiatrophy (1950-continuing), right hemiparesis (1950-continuing), complex partial seizures (1952, continuing), partial seizures evolving to secondary generalized seizures (1952, continuing).

Anxiety (1996-continuing).

Hypertension (2006-continuing), colon polyps (1997), recurrent rectal bleeding (1998), anal fissures (1998), hemorrhoids (1998, continuing), chronic iron deficiency anemia (1999-continuing), hiatal hernia (1999-continuing), peptic ulcer disease (1999-2000), upper gastrointestinal bleed (2000), H. pylori positive (2000, continuing), cholelithiasis with cholecystectomy (Dec 2001), fractured right mandible (1993), left leg infected sebaceous cyst (Aug 2000), acrochordon/benign fibrous skin tag (unknown date, continuing), scar from a burn on the right sacral area (unknown date, continuing).

Concomitant medications other than AEDs:

haloperidol (anxiety) 1990 – Continuing

paroxetine (anxiety) 1990 – Continuing

omeprazole (hiatal hernia) 2000 – Continuing

ferrous gluconate (chronic anemia) 2003 – Continuing

folic acid (chronic anemia) 14 Jul 2004 – Continuing

quinapril (hypertension) Jan 2006 – Continuing

PATIENT 303-03505

Serious Adverse event leading to discontinuation of study drug treatment/Urinary Retention			
Study / Subject No:		VRX-RET-E22-303-03505 (1)	
Age (yrs) / Sex / Race:		30 / Male / Caucasian	
Event term: (verbatim / PT)		Psychomotor Agitation / Psychomotor hyperactivity Urinary Retention / Urinary Retention	
Oral study drug:		Ezogabine open label	
Randomization in study 301:		Placebo	
First dose of study drug taken::		30 Nov 2007	
Last dose of study drug taken:		(Day 83)	
Concomitant antiepileptic therapy			
Concomitant antiepileptic therapy (start date):		Lamotrigine 800 mg (Continuing) Pregabalin 800 mg (Continuing) Carbamazepine 1600 mg (Continuing)	
Adverse event as reported by investigator:	Adverse event as coded:	SAE:	DC'd due to AE:
Psychomotor Agitation Urinary Retention	Psychomotor hyperactivity Urinary Retention	Yes Yes	Yes Yes

Case summary:

This 30-year-old Caucasian male, with a history of partial epilepsy, psychomotor agitation, motorcycle accident with head trauma leading to placement of a vagal nerve stimulator, was part of an open label ezogabine study. He was taking ezogabine in combination with lamotrigine, pregabalin, and carbamazepine when 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.

This patient began treatment with the study drug on 30 Nov 2007 (Day 1), during the transition phase of study 301. The patient began the open label treatment on 09 Jan 2008 (Day 41), at a dose of 1200 mg/day. On 23 Jan 2008 (Day 55), the patient was sent to the emergency room (ER) and was admitted to the hospital for observation over night due to psychomotor agitation, urinary retention and upper respiratory infection. A Foley catheter was inserted in the ER and 1200 cc of urine was evacuated. Study drug was reduced to 1050 mg/day on 23 Jan 2008 (Day 55) and stopped on 20 Feb 2008 (Day 83). On 08 Feb 2008 (Day 71), a bladder ultrasound revealed 122 cc of retained urine and on 18 Feb 2008 (Day 81) another ultrasound revealed 900 cc of retained urine in his bladder.

The psychomotor agitation event was resolved on 19 Feb 2008 (Day 82). The patient was referred to a urologist for a urodynamic study which demonstrated a neurogenic bladder. The plan was to self catheterize intermittently, and a trial of flomax with follow-up in 6 weeks. A computed tomography (CT) scan of abdomen and pelvis on 17 Mar 2008 (Day 109) was unremarkable. At a follow-up visit to the urology clinic on 05 May 2008 (Day 158), the patient reported improvement and PVR in the office revealed 91 cc of residual urine. On 03 Jun 2008 (Day 187), the patient reported improved symptoms and the ability to spontaneously void and was self catheterizing less frequently. On 09 Jul 2008 (Day 223), the patient's voiding diary revealed that he spontaneously voided 340 cc per void versus 280 cc per catheterizations during the week of 06 Jul 2008 (Day 220). The urinary retention event was confirmed as ongoing on 25 Feb 2009 (Day 434) by the investigator.

The events of psychomotor agitation and urinary retention were assessed by the investigator as possibly related to study drug and the primary reason for study withdrawal.

Medical history:

Partial epilepsy, hypertension, sleep apnea requiring CPAP, GERD, motorcycle accident with head trauma leading to a vagal nerve stimulator implantation.

Concomitant medications other than AEDs:

Flomax (Continuing)

Pantoprazole 20 mg (Continuing)

PATIENT 303-00902

Serious adverse event			
Study / Subject No:		VRX-RET-E22-303-00902	
Age (yrs) / Sex / Race:		39 / Male / Caucasian	
Event term: (verbatim / PT)		Postictal psychosis / Epileptic psychosis Urinary retention / Urinary retention Flurry of seizures worsening of the condition / Epilepsy Urinary retention / Urinary retention	
Oral study drug:		Ezogabine open label	
Randomization in study 301:		400 mg TID	
Study drug start - end dates:		06 Apr 2006	
First dose of study drug taken:		N/A	
Last dose of study drug taken:			
Concomitant antiepileptic therapy (start date):		Pregabalin 800 mg (Continuing) Levetiracetam 2500 mg (Continuing) Oxycarbazepine 1200 mg (Continuing) Carbamazepine 1200 mg (Continuing)	
Adverse event as reported by investigator:	Adverse event as coded:	SAE:	DC'd due to AE:
Urinary retention (03 Mar 2008)	Urinary retention	Yes	No
Postictal psychosis	Epileptic psychosis	Yes	No
Urinary retention (20 Aug 2008)	Urinary retention	Yes	No
Flurry of seizures worsening of the condition	Epilepsy	Yes	No

Case summary:

This 39-year-old Caucasian male, with a history of partial epilepsy, vagal nerve stimulator, cognitive disturbances, auditory hallucinations, right anterior temporal brain lobectomy, right temporal lobectomy and frontal topectomy was part of an open label ezogabine study. He was taking ezogabine in combination with pregabalin, levetiracetam, oxycarbazepine, and carbamazepine when he was hospitalized for postictal psychosis and urinary retention on 01 Mar 2008 (Day 696).

This patient began treatment with the study drug on 06 Apr 2006 (Day 1), during the titration phase of study 301. The patient began the open label treatment on 20 Sep 2006 (Day 168), at a dose of 1050 mg/day. Study drug was reduced to 900 mg/day on 18 Oct 2006 (Day 196). On 01 Mar 2008 (Day 696), he was brought to the emergency room after being found wandering. He received an unspecified dose of lorazepam and was released the same day after his cognition reportedly cleared. On 02 Mar 2008 (Day 697), he reported "questionable" hallucinations. On 03 Mar 2008 (Day 698), the patient visited the investigator's office where he was noted to be very confused and unresponsive with

dilated pupils. The patient was given 3 mg of lorazepam in the office over the period of approximately 1-1.5 hours. His cognition improved but he appeared drowsy. The patient was noted to have an abrasion and ecchymosis on the right side of his head and he was referred to the emergency room (ER) on 01 Mar 2008 (Day 696). A computed tomography (CT scan) performed in the ER was negative for hemorrhage. The patient was admitted to the hospital for epilepsy monitoring for postictal psychosis and urinary retention. A CT scan on that day demonstrated large areas of encephalomalacia in the right hemisphere with some dilatation overlying the right lateral ventricle, and several nonspecific foci of hypodensity within the white matter of the cerebral hemisphere. On 04 Mar 2008 (Day 699), a urology consult was obtained and a bladder scan revealed PVR urine volume of 700 cc and a foley catheter was placed. The urologist's opinion was that the urinary retention may have been due to an obstructive voiding problem secondary to benign prostatic hypertrophy, or a functional neurogenic bladder, or anticholinergic effect of medications. While receiving ezogabine therapy, the patient's prior PVR volume ranged from 10 to 40 cc (the PVR volumes on 22 Mar 2006 (Day -16) were 37 cc; on 12 Jun 2006 (Day 68) 37cc; on 09 Aug 2006 (Day 126) 17 cc; on 18 Oct 2006 (Day 194) 10 cc; on 13 Dec 2006 (Day 252) 40 cc, and on 19 Sept 2007 (Day 532) 17 cc).

On 20 Aug 2008 (Day 868), he was admitted to the hospital due to flurry of seizures and urinary retention. The patient was catheterized on 24 Aug 2008 (Day 872) and 990 cc of urine was collected and the patient was started on flomax 0.4 mg. The event of postictal psychosis was resolved on 04 Mar 2008 (Day 699) without sequelae and the patient was discharged from the hospital. The first urinary retention episode was resolved on 11 Mar 2008 (Day 706) without sequelae. The flurry of seizures and second episode of urinary retention were resolved on 27 Aug 2008 (Day 875).

The investigator assessed the event of postictal psychosis as unrelated to study drug and the first episode of urinary retention as serious criterion of medically significant event and possibly related to study drug. The event of flurry of seizures was assessed as unrelated to study drug by the investigator and the second episode of urinary retention as medically significant event and possibly related to study drug.

Medical history:

Postictal confusion, cognitive disturbance, auditory hallucinations, brain lobectomy- right anterior temporal, right temporal lobectomy and frontal topectomy, occasional fatigue and dizziness, diarrhea, upper respiratory infection, oral fungal infection, fractured nose, bilateral arm tremors, irritability, poor short and long term memory situational depression, occasional lightheadedness, bilateral knee-leg jerks.

Concomitant medications other than AEDs:

Multivitamins 1 tab (ongoing), CoQ10 100 mg (ongoing), Glucosamine w/ Chondroitin

Sulfates 3000 mg (ongoing), Vitamin A 1 tab (ongoing), Zolof 50 mg (ongoing),

Topiramate 400 mg (ongoing), Flomax 0.4 mg (ongoing)

PATIENT 304-50102

Serious adverse event leading to discontinuation of study drug treatment			
Study / Subject No:		VRX-RET-E22-304 / 50102	
Age (yrs) / Sex / Race:		45/ Female / Caucasian	
Event term: (verbatim / PT)		Exacerbation of seizure frequency / Epilepsy	
Oral study drug:		Ezogabine open label	
Randomization in study 302:		Ezogabine 300 mg TID	
First dose of study drug taken::		22 Jun 2006 (Day 1)	
Ezogabine start - end dates, Study 304:		08 Nov 2006 – 05 Oct 2007	
Last dose of study drug taken:		Day 471	
Concomitant antiepileptic therapy (start date)a:		Carbamazepine 1200 mg/day (2004) Clobazam 30 mg/day (2004) a Changes to AED therapy during open-label treatment are detailed below.	
Adverse event as reported by investigator:	Adverse event as coded:	SAE:	DC'd due to AE:
Exacerbation of seizure frequency	Epilepsy	Yes ^a	Yes

Hospitalization.

Case summary:

This 45-year-old Caucasian female, taking ezogabine in combination with carbamazepine and clobazam for control of complex partial seizures and partial seizures evolving to secondary generalization resulting from head trauma, had ongoing adverse events of hyponatremia and postvoid residual urine volume from Study 302. She experienced epilepsy (reported as exacerbation of seizure frequency) on 09 Oct 2007 (Day 475) that led to hospitalization and discontinuation of study drug treatment.

This patient took her first dose of blinded ezogabine on 22 Jun 2006 (Day 1) during titration phase of Study 302, completed maintenance and transition phases taking ezogabine 900 mg/day, and began open-label treatment on 08 Nov 2006 (Day 140) at a reduced dose of 600 mg/day. She was mildly hyponatremic beginning 26 Jul 2006 (Day 35) of Study 302 and was water-restricted for the condition. Mild somnolence, dysarthria, and gait disturbance were noted beginning 08 Oct 2007 (Day 474). On 09 Oct 2007, the patient began to experience an increase in the frequency of her seizures over her baseline frequency of 5 complex partial seizures per month. Her dose of carbamazepine was decreased to 1000 mg/day on 09 Oct 2007. The patient was admitted to the hospital on 18 Oct 2007. The patient was withdrawn from the study because of the exacerbation of seizure frequency. The patient was discharged from the hospital on 26 Oct 2007. The increased seizure frequency resolved by 28 Nov 2007.

The investigator assessed the exacerbation of seizure frequency as possibly related to ezogabine. The sponsor assessed the event as expected and unrelated to ezogabine.

Selected seizure frequency data is presented in the table below.

Study Period	Visit Dates	Number of partial seizures	Number of days	Seizures per 28 days
302 Baseline	24 Apr 2006 22 Jun 2006	55	59	26.10
302 Double-Blind	22 Jun 2006 10 Oct 2006	43	111	10.85
304 Visit 0 – 1	08 Nov 2006 06-Dec-06	7	30	6.53
304 Visit 1 - 2	06 Dec 2006 07 Feb 2007	9	60	4.20
304 Visit 2 – 3	07 Feb 2007 06 May 2007	25	90	7.78
304 Visit 3 - 4	06 May 2007 08 Aug 2007	0	90	0.00
304 NA	08 Aug 2007 05 Oct 2007	0	62	0.00

Medical history:

Complex partial seizures and partial seizures evolving to secondary generalization since 1983. Etiology: head trauma (1973).

Asthma (1964, continuing), depressed skull fracture and surgical repair (left parietooccipital; 1973), dyslipidemia (2006, continuing).

Concomitant medications other than AEDs:

simvastatin (dyslipidemia) 11 Aug 2006 – Continuing

gentamicin 06 May 2007 and 27 May 2007

Dose adjustments to concomitant AEDs:

clobazam 30 mg/day 2004 - Continuing

carbamazepine 1200 mg/day 2004 – 08 Oct 2007

1000 mg/day 09 Oct 2007 - Continuing

11.10. Appendix: Roehrborn: Urinary Safety of Ezogabine

1 URINARY SAFETY OF RETIGABINE

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August 17, 2008

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1.1 Introduction

The functions of the lower urinary tract can be simplified into two major tasks:

- Storage of urine in the bladder
- Voiding of urine and emptying the bladder

Disorders of the lower urinary tract can equally affect either one or the other of these two vital functions and the associated symptoms are referred to as storage or voiding symptoms, making up together the bulk of what is referred to as lower urinary tract symptoms or LUTS.

LUTS are assessed and measured by a standardized instrument known as the International Prostate Symptom Score (IPSS) or as the AUA Symptom Index, which consists of seven self administered questions which are rated from 0–5 each for a total score running from 0–35 (Barry, Fowler et al. 1992; Barry, Fowler FJ et al. 1992; Barry, Fowler et al. 1995). By convention, a score from 0–7 is consistent with mild symptoms (usually implying no need for any treatment), a score from 8–18 is consistent with moderate and one from 19–35 points with severe symptoms, the latter two groups being usually bothered by their symptoms and desirous of treatment for them. There is also a single disease specific quality of life question that is often added to the AUA Symptom Index, which asks the patient how he would feel if he had to live with his symptoms for the rest of his life. The answer, ranging from delighted to terrible or from 0–6 points, gives an excellent initial insight into whether or not the patient may wish to have treatment or rather just monitor his condition.

Studies such as the Olmsted County Study of Urinary Symptoms in Men (Chute, Panser et al. 1993; Guess, Chute et al. 1993), the UREPIK study (Boyle, Robertson et al. 2003) and more recently the Boston Area Community Study (BACH) give excellent insight into the distribution of the AUA Symptom Index in age stratified men and women. Recently the data from the BACH and UREPIK study were published together allowing a clear insight into the frequency of moderate to severe symptoms in men and women from different geographic and ethnic backgrounds (Robertson, Link et al. 2007) (Figure 1). Populations in their 40s accordingly have mild symptoms only in 80–90%, in their 50s in 70–80%, in their 60s in 65–75% and in their 70s still in more than 50%.

From the longitudinal follow-up in the Olmsted County Study we have data to examine the increase in the AUA Symptom Index in men (Jacobsen, Girman et al. 1996). Overall, there was an average increase in American Urological Association Symptom Index of approximately 0.18 (95% confidence interval 0.13 to 0.24) points per year of follow-up. The average annual symptom score slope and variability in slope increased with patient age at baseline from a mean of 0.05 ± 1.06 (standard deviation) per year among men in the forties to 0.44 ± 1.35 per year for men in the sixties, and decreased to 0.14 ± 1.42 per year for men in the seventies. A typical person age 40 may thus have a score of 6 and in 10 years this may increase to 7 points by the age of 50. In the

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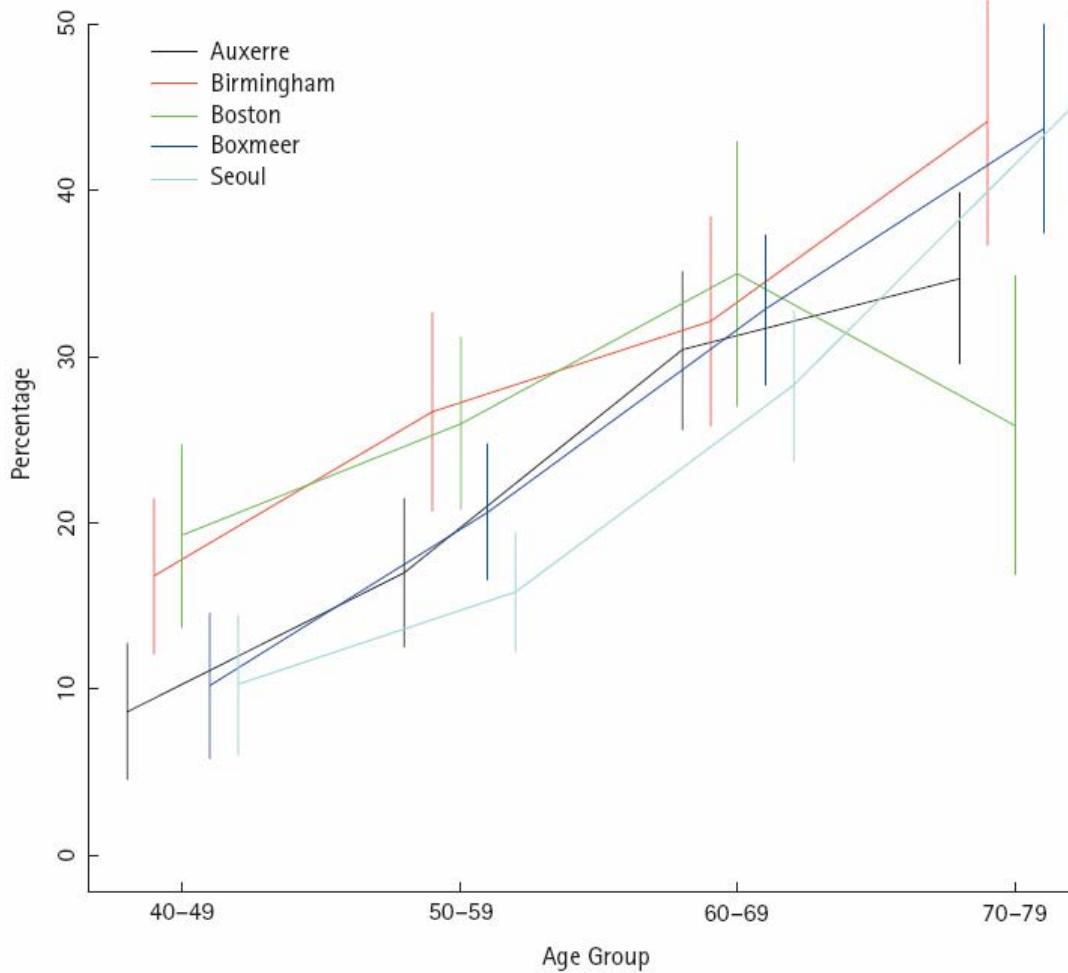
next decade it may increase to 9 points and in his 60s he may experience an increase of 5 points to 14 points by the time he reaches the age of 70. A comparison of the increase in AUA Symptom Index and the single QoL question was provided recently by Kok et al (Kok, Bohnen et al. 2005), who compared the results from the Krimpen study with those from Olmsted County and Japan.

Table 1 Annual I-PSS and I-PSS-QOL Change in 3 Comparable Studies

Baseline Age	Krimpen	Olmstead County	Japan
I-PSS			
50–59	0.05	0.30	–0.10
60–69	0.31	0.60	–0.20
70–79	0.41	0.38	–0.20
I-PSS-QOL			
50–59	0.00	–0.00	–0.01
60–69	0.01	0.05	–0.27
70–79	0.01	–0.03	0.20

[Table 1](#): Annual AUA Symptom Index and QoL changes by decade of life in three different studies in Europe, USA and Japan.

Figure 1 Frequency of Moderate to Severe Symptoms by Decade of Life in the BACH and UREPIK Study Centers



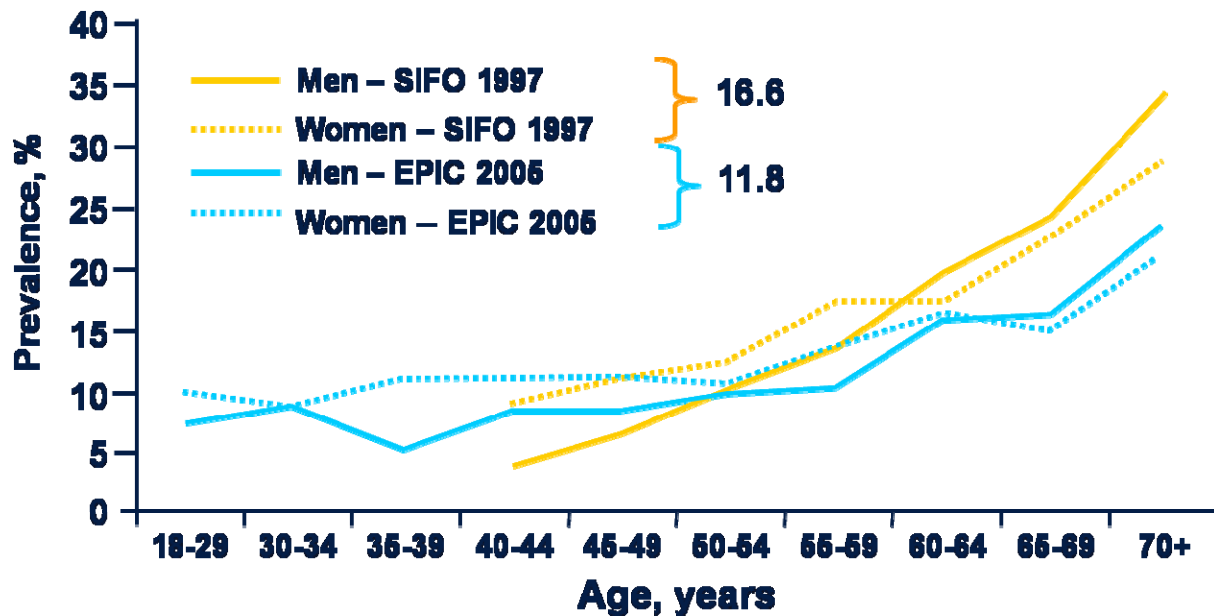
Source: (Robertson, Link et al. 2007)

AUA Symptom Index Scoring Instrument

Urinary Symptoms		Not at all	Less than one time in five	Less than half the time	About half the time	More than half the time	Almost always
1	Over the past month, how often have you had a sensation of not emptying your bladder completely after you finished urinating?	0	1	2	3	4	5
2	Over the past month, how often have you had to urinate again less than 2 hours after you finished urinating?	0	1	2	3	4	5
3	Over the past month, how often have you found you stopped and started again several times while urinating?	0	1	2	3	4	5
4	Over the past month, how often have you found it difficult to postpone urination?	0	1	2	3	4	5
5	Over the past month, how often have you had a weak urinary stream?	0	1	2	3	4	5
6	Over the past month, how often have you had to push or strain to begin urination?	0	1	2	3	4	5
7	Over the past month, how many times did you typically get up to urinate from the time you went to bed until the time you got up in the morning?	Never 0	1 time 1	2 times 2	3 times 3	4 times 4	5 or more Times 5
Total for Urinary Symptoms:							

The term Overactive Bladder or OAB refers to a constellation of irritative or storage symptoms including frequency, urgency and urge incontinence, items that are not captured entirely by the AUA Symptom Index. Excellent population based studies are available to demonstrate that in free living populations of men and women the prevalence of OAB increases also with age, starting at the age of 40–44 and reaches an overall population prevalence of 12–17% in these two large studies (Milsom, Abrams et al. 2001; Irwin, Milsom et al. 2006).

Figure 2 **Prevalence of OAB Symptoms in Age Stratified Men and Women from Two Large Population Based Studies**



Source: (Milsom, Abrams et al. 2001; Irwin, Milsom et al. 2006).

While OAB and LUTS refer to the subjective assessment of functional disorders of the lower urinary tract, there are also objective measures which are frequently used to determine the proper function or dysfunction of the interaction between bladder in its role as storage organ versus expelling force by muscular contraction, the bladder neck and in men the prostate as a source of obstruction, and the external urinary sphincter. Aside from complex measurements such as invasive urodynamics, the following more simple parameters are often reported:

1. Voided volume (VV): the amount of urine eliminated in a single voiding act (ml)
2. Functional bladder capacity (FBC): the highest volume voided in a single void per a single person
3. Post void residual urine (PVR): the amount of urine retained in the bladder after a single voiding act (ml)
 - a. Typically measured by either ultrasonography or catheterization
4. Total Bladder capacity (TBC): the sum of voided volume (VV) + PVR (ml)
5. Voiding efficiency: VV/TBC expressed as percent
 - b. Eg: patient voids 200 ml and retains 150 ml for a TBC of 350 ml. $200/350 = 57\%$ voiding efficiency
6. Peak urinary flowrate (PUF): the maximum speed at which the urine is passed from the bladder to the outside measured in ml/sec

Regarding 24 hr voided volumes and the FBC, excellent age stratified data are available for men from the Krimpen Study in the Netherlands (Table 2 and Table 3) (Blanker, Groeneveld et al. 2001). The average voided volume per void ranges from 267 to 224 ml, and the FBC from 420 to 350 ml for men in their 50s to those in their 70s. Table 3 illustrates the effect of age, reduced PUF, drinking habits and COPD on the FBC.

Table 2 Twenty-Four Hour Voided Volumes, Average Volume Per Void, and Functional Bladder Capacity by Age Strata

	Age Strata (Yr)					
	50-54 (n = 301)	55-59 (n = 373)	60-64 (n = 343)	65-69 (n = 279)	70-78 (n = 146)	Total (n = 1446)
24-hour voided volume (mL)						
Median	1500	1400	1550	1530	1563	1506*
25 th to 75 th percentiles	1118-2000	1095-1900	1180-1950	1200-2025	1200-1902	1160-1950
Average volume/void (mL)						
Median	267	250	248	238	224	246
25 th to 75 th percentiles	210-346	198-331	193-316	172-300	183-271	192-349
Functional bladder capacity (mL)						
Median	420	400	400	375	350	400
25th to 75th percentiles	305-518	300-548	300-500	280-500	300-450	300-500

*Analysis of variance test for linear trend, P = 0.12.

Source: (Blanker, Groeneveld et al. 2001)

Table 3 **Determinants of Functional Bladder Capacity**

	Univariate Analyses		Multivariate Analyses	
	Mean FBC (mL)	P Value	Mean FBC (mL) and Difference to Constant Value (95% CI)	P Value
Constant			518 (482 to 554)	
Age strata (yr)				
50–54 (reference, constant)	438			
55–59	434	0.742	–2 (–26 to 23)	0.880
60–64	414	0.060	–18 (–43 to 7)	0.160
65–69	402	0.006	–28 (–9 to –1)	0.042
70–78	379	0.000	–43 (–75 to –11)	0.009
Prostate enlargement (>30 cm ³)				
No (reference, constant)	428			
Yes	408	0.028	Not significant	0.811
Reduced flow rate (<15 mL/s)				
No (reference, constant)	483			
Yes	398	0.000	–73 (–93 to –53)	<0.001
Drinking habits				
No alcohol (reference, constant)	416			
1–2 units/day	406	0.342	–16 (–37 to 5)	0.124
>2 units/day	463	0.000	+32 (6 to 59)	0.017
COPD				
Men without (reference, constant)	417			
Men with	465	0.018	+54 (14 to 95)	0.009

Key: FBC = functional bladder capacity; CI = confidence interval; COPD = chronic obstructive pulmonary disease.
Source: (Blanker, Groeneveld et al. 2001)

It is generally accepted that PVR in healthy young adults is under 30 ml. In a very old study residual urine in normal volunteers ranges from 0.0 to 2.3 ml with a mean of 0.5 ml (Hinman and Cox 1967) and 78% of normal men have PVR values <5 ml and 100% of <12 ml (Di Mare, Fish et al. 1963). It is also recognized that there is considerable intraindividual variability (Bruskewitz, Iversen et al. 1982; Birch, G et al. 1988).

A study from Japan in 76 men and 88 women with a mean age of 56 and 52, respectively, suggested an average PVR of 20 ml and an average voiding efficiency (Table 4, labeled as BE (%)) of 86–87% (Ku and Oh 2006).

Table 4 Comparison of Urodynamic Findings in Men and Women

Urodynamic parameters	Male (n = 76)	Female (n = 88)	P-value
Voiding parameters			
Uroflowmetry			
Q _{max} (ml/sec)	10 (7.3–14.9)	16.4 (11–22.7)	<0.001 ^a
Q _{ave} (ml/sec)	5 (3–7)	7 (5–10)	<0.001 ^a
Voided volume (ml)	137.5 (82.3–276.5)	147.5 (90.3–256.3)	0.806 ^a
PVR (ml)	20 (10–57.5)	20 (10–50)	0.189 ^a
BVE (%)	87.1 (67.2–91.4)	85.9 (76.5–92.9)	0.091 ^a
Pressure-flow study			
Q _{max} (ml/sec)	12 (8.6–13.8)	18 (14–24)	<0.001 ^a
Voided volume (ml)	279 (203.3–411)	277 (212.3–368)	0.679 ^a
PdetQ _{max} (cm H ₂ O)	45 (38–55)	33 (23.3–47.8)	0.001 ^a
Pdet.open (cm H ₂ O)	48 (39–67.3)	27 (19–45)	<0.001 ^a
Pdet.clos (cm H ₂ O)	27 (17.8–36)	19 (12–33)	0.271 ^a
BOOI	22.5 (9.8–34.5)	–5 (–26.3–14.8)	<0.001 ^a
BCI	104.5 (91–126.5)	133 (107–156.5)	<0.001 ^a
Storage parameters			
Filling cystometry			
Maximal cystometric capacity (ml)	391 (262.3–450)	373.5 (311–450)	0.352 ^a
Uninhibited contraction	13 (17.1%)	18 (20.5%)	0.585 ^b
Urethral function tests			
MUCP (cm H ₂ O)	76 (58–92)	73.5 (57.3–100)	0.875 ^a

Data presented at medians (25th–75th centiles) or numbers (%).

Q_{max}, maximum flow rate; Q_{ave}, Average flow rate; PVR, post-void residual; BVE, bladder voiding efficiency; PdetQ_{max}, detrusor pressure at maximal flow rate; Pdet.open, opening detrusor pressure; Pdet.clos, closing detrusor pressure; BOOI, bladder outlet obstruction index; BCI, bladder contractility index; MUCP, maximum urethral closure pressure.

^aStudent *t*-test.

^bChi-square test.

Source: (Ku and Oh 2006)

There are few if any age stratified population based assessments of PVR values published (Rule, Jacobson et al. 2005) (Jacobsen, Girman et al. 2001). Rule et al described the natural history of post-void residual (PVR) and voided volume (VV) in men participating in the Olmsted County Study. A random sample of community dwelling men (529 men 40 to 79 years old) were followed with a sonographic PVR and VV every 2 years for up to 12 years (median 5 examinations). The median annual change (slope) for PVR was 2.2% (p=0.03) and for VV was -2.1% (p <0.0001). There was considerable variability in PVR slopes (25th percentile -11%, 75th percentile 18%). A rapid increase in PVR slope (greater than 80th percentile) was more likely in men with a baseline American Urological Association Symptom Index greater than 7 (age adjusted odds ratio [OR]1.6, 95% CI 1.0 to 2.5). There was less variability in VV slopes (25th percentile -(Rule, Jacobson et al. 2005) 8.0%, 75th percentile 3.1%). A rapid decrease in VV slope (less than 20th percentile) was more likely in men with baseline age 70 to 79 years than

40 to 49 years (OR 3.9, 95% CI 2.1 to 7.2) and in men with a baseline PVR greater than 50 ml (age adjusted OR 2.1, 95% CI 1.2 to 3.6) (Figure 3 and Table 5)

Table 5 Annual Percent Change in PVR and VV

Baseline Age Group (No. Pts)	Median % Change (Q1, Q3)	
	PVR Slope	VV Slope
40–79 (529)	2.2 (–11, 18)	–2.1 (–8.0, 3.1)
40–49 (230)	1.8 (–9.2, 15)	–1.3 (–6.5, 3.7)
50–59 (139)	4.3 (–8.5, 22)	–1.1 (–5.9, 3.3)
60–69 (95)	2.6 (–16, 22)	–4.3 (–12, 1.6)
70–79 (65)	–2.6 (–19, 19)	–4.6 (–20, –0.3)

Source: (Rule, Jacobson et al. 2005)

Figure 3 Predicted PVR and Voided Volumes Versus Age from the Olmsted County Study

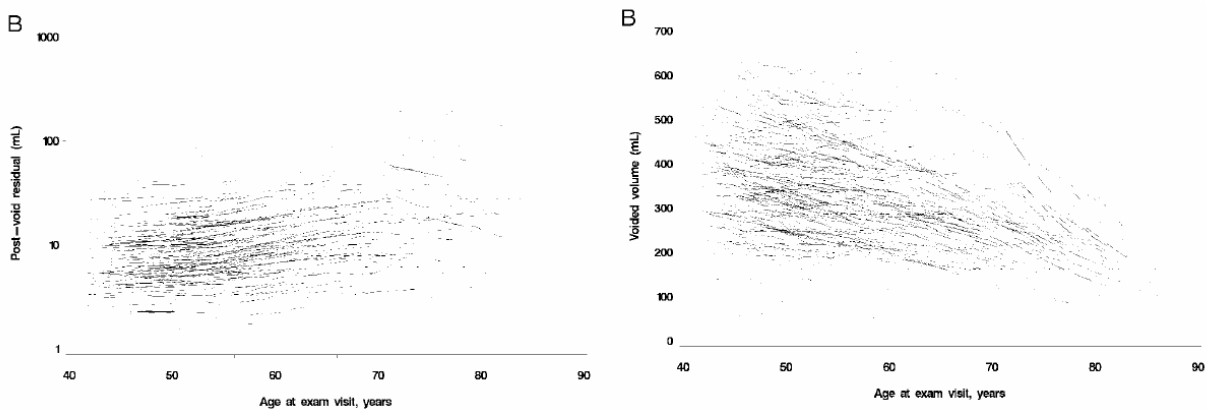
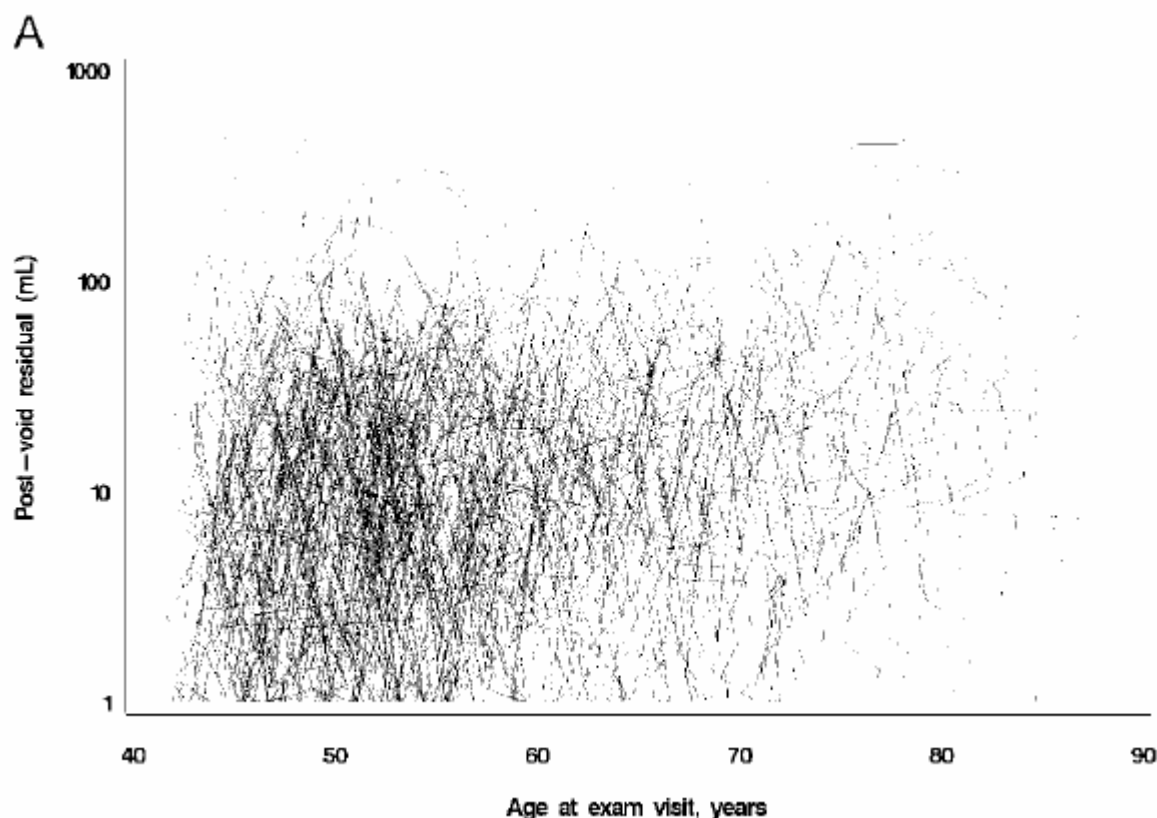


Figure 3: Each curve represents individual subject based on smoothed group averages (mixed effects regression model with age group, time, and age group – time covariates) (Rule, Jacobson et al. 2005).

While in individual patients occasionally a PVR of >100 ml was recorded (Figure 4), the smooth curved averages based on the regression model in Figure 3 suggest this to be a rare event.

Figure 4 Plot of Observed Post-void Residuals Showing Variability

Source: (Rule, Jacobson et al. 2005)

Figure 4: Plot of observed post-void residuals showing variability. Each line represents individual subject with age. (Rule, Jacobson et al. 2005)

A completely different picture emerges, however, when one assess the literature for PVR values in men with LUTS and BPH, where the average PVR value is usually significantly higher as seen in a meta-analysis of 6 studies involving the alpha blocker alfuzosin (Figure 5) (McNeill, Hargreave et al. 2001). At baseline the average PVR was around 100 ml with a range from 50-350 ml. 50% had a PVR of <100, and 20% of over 150 ml.

It must be noted that in these studies and in almost all LUTS and BPH studies thresholds are imposed and patients with PVR values above such thresholds are NOT allowed to enroll. While the thresholds differ, commonly used thresholds are between 150 and 350 ml. This naturally limits our ability to understand the natural history of PVR in men with LUTS and BPH, and the implications of higher PVRs on events such as infections, acute urinary retention and need for surgery, hydronephrosis, renal insufficiency and others. Urinary tract infections, hydronephrosis and renal insufficiency are distinctly rare as was shown in the 5 year MTOPS study, were few patients experienced a UTI and none of the 3047 patients developed renal insufficiency over the 5 years of follow up (McConnell, Roehrborn et al. 2003).

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This leaves progression to the total inability to urinate – acute urinary retention or AUR – as the one outcome to study that does occur with reasonable frequency and which in many cases leads to a subsequent surgical procedure.

Table 6 Characteristics of Participants in Six BPH Studies Involving 1470 Patients

Characteristic	Overall Population (n = 1470)
Age (yr)	64.5 ± 7.4 (42–89)
Symptom duration (mo)	39.5 ± 34.0 (1–240)
Boyarsky total score	9.5 ± 2.6 (2–20)
Q _{max} (mL/s)	9.8 ± 4.0 (2–46)
PVR volume (mL)	106.1 ± 54.5 (50–350)
No. of patients (%) with baseline PVR volume of	
50–100 mL	748 (51)
100–150 mL	439 (30)
≥150 mL	283 (19)

Key: Q_{max} = maximum urinary flow rate; PVR = postvoid residual (urine).

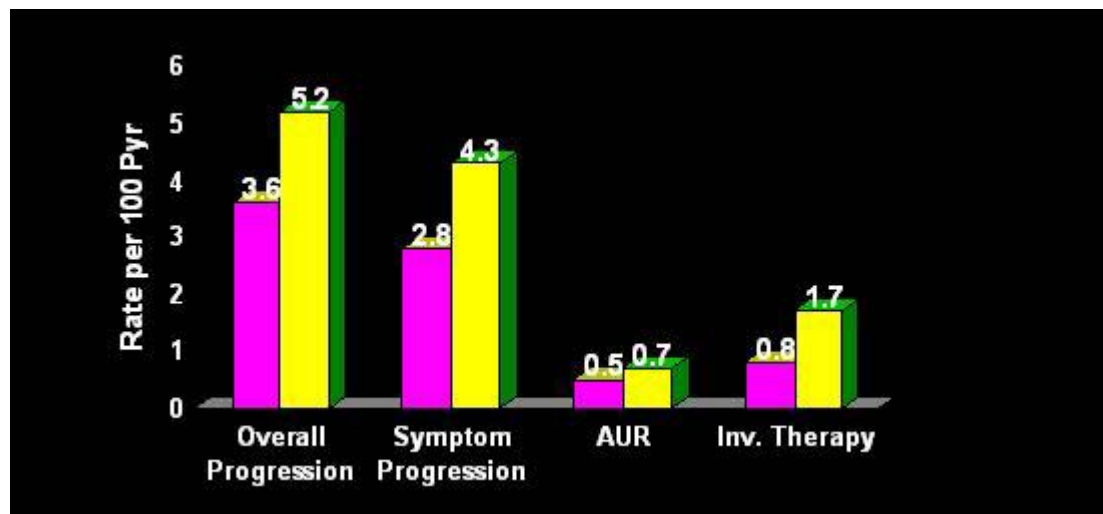
Data presented as the mean ± SD, with the range in parentheses, unless otherwise noted.

Source: (McNeill, Hargreave et al. 2001)

In a recent review article PVR did not appear to be a strong predictor of acute urinary retention (AUR). Mochtar et al did not find any significant associations between urinary retention and PVR (at both above and below 300 ml) in men treated with alpha blockers (N=389) or watchful waiting (N=553) (Mochtar, Kiemeny et al. 2006). Conversely, Klarskov et al found that men were 3.6 times more likely to have a recurrence of AUR if they had a PVR of 500 ml or greater than men with a PVR of less than 500 ml (Klarskov, Andersen et al. 1987). Men with spontaneous AUR and a PVR of 500 ml or greater were 6.8 times more likely to have a subsequent episode of AUR than men with precipitated AUR and PVR less than 500 ml. In a 10-year followup study of 1,068 men with BOO, only age and larger prostate volumes were predictive of AUR; PVR and other urodynamic parameters were not predictive (Thomas, Cannon et al. 2005). However, it should be noted that a large portion of the original cohort was lost to followup in this study. A greater risk was noted if PVR increased rapidly while voided volume declined rapidly (Rule, Jacobson et al. 2005). The same investigators also found that PVR of >100 is associate with an increased risk for developing chronic renal insufficiency in community dwelling men (Rule, Jacobson et al. 2005) Two other researchers found that increased PVR might be associated with developing chronic urinary retention or AUR, although the number of events was small (Neal, Styles et al. 1987).

Perhaps the best set of data to assess the impact of PVR upon longer term consequences such as symptomatic worsening (by at least 4 points), AUR and invasive therapy is the MTOPS study (McConnell, Roehrborn et al. 2003).

Figure 5 Absolute Rates of Overall Progression and Symptomatic Progress, AUR and Invasive Therapies in Placebo Treated Patients in the MTOPS Study Over 5 Years of Follow-up (purple < 39 and yellow > 39 ml)



Source: (McConnell, Roehrborn et al. 2003)

When stratifying the over 700 men in the placebo group by the median PVR of 39 ml, the rate of overall progression (defined as an increase of at least 4 points above baseline in the AUA symptom score, AUR, urinary incontinence, renal insufficiency, or recurrent urinary tract infection) per 100 patient years was 3.6 vs 5.2 in men with a PVR below or above the median ($p=0.0008$). Both the risk for symptomatic worsening and the risk for surgery were significantly higher in men with PVR >39 ml, but not the risk for AUR (n.s.).

A more detailed analysis of PVR and outcomes was conducted using the placebo treated patients in the MTOPS study (Table 7 and Table 8). Men in the higher PVR quartiles were slightly older, had higher AUA Symptom Index scores, larger glands and higher PSA values and a lower PUF or Qmax (Roehrborn, Kaplan et al. 2005).

Table 7 Placebo Treated patients in MTOPS stratified in quartiles of PVR

PVR (ml)	<12	12–39	40–93	>93
Mean±SD	2.7 ± 3.7	25.2 ± 8.1	69.2 ± 15.3	182 ± 90.8
Age	62.1	62.4	62.6	63.4
AUA Symptom Index	16.0	16.8	16.7	18.1
Prostate Volume - mL	33.9	34.7	37.1	39.6
Qmax	10.7	10.6	10.4	10.2
PSA	2.1	2.3	2.4	2.7

Source: (Roehrborn, Kaplan et al. 2005)

Table 8 Rates, Relative Risk and 95% Confidence Interval for Overall Progression, Symptom Progression and AUR for Placebo Treated Patients in MTOPS, 1st Quartile with PVR <12 ml as Reference Group

Quartile	<12 ml	12–39 ml	40–93 ml	>93 ml
Mean \pm 95% CI	2.7 \pm 3.7	25.2 \pm 8.1	69.2 \pm 15.3	182 \pm 90.8
Overall Progression	3.92	3.21 / 0.81 0.46 – 1.42	4.94 / 1.11 0.66 – 1.89	5.93 / 1.42 0.84 – 2.4
Symptom Progression	3.01	2.34 / 0.77 0.4 – 1.47	4.12 / 1.18 0.65 – 2.13	4.52 / 1.45 0.8 – 2.64
Acute Retention	0.68	0.37 / 0.46 0.1 – 2.12	0.69 / 0.90 0.24 – 3.43	0.85 / 0.98 0.26 – 3.65

Source: (Roehrborn, Kaplan et al. 2005)

Compared to the 1st quartile, men in the 3rd and 4th quartile with a mean PVR of 70 and 180 ml had a 1.1, 1.2 and 0.9 relative risk for overall progression, symptom progression and AUR (3rd) and a 1.4, 1.5 and 1.0 relative risk for overall progression, symptom progression and AUR (4th quartile).

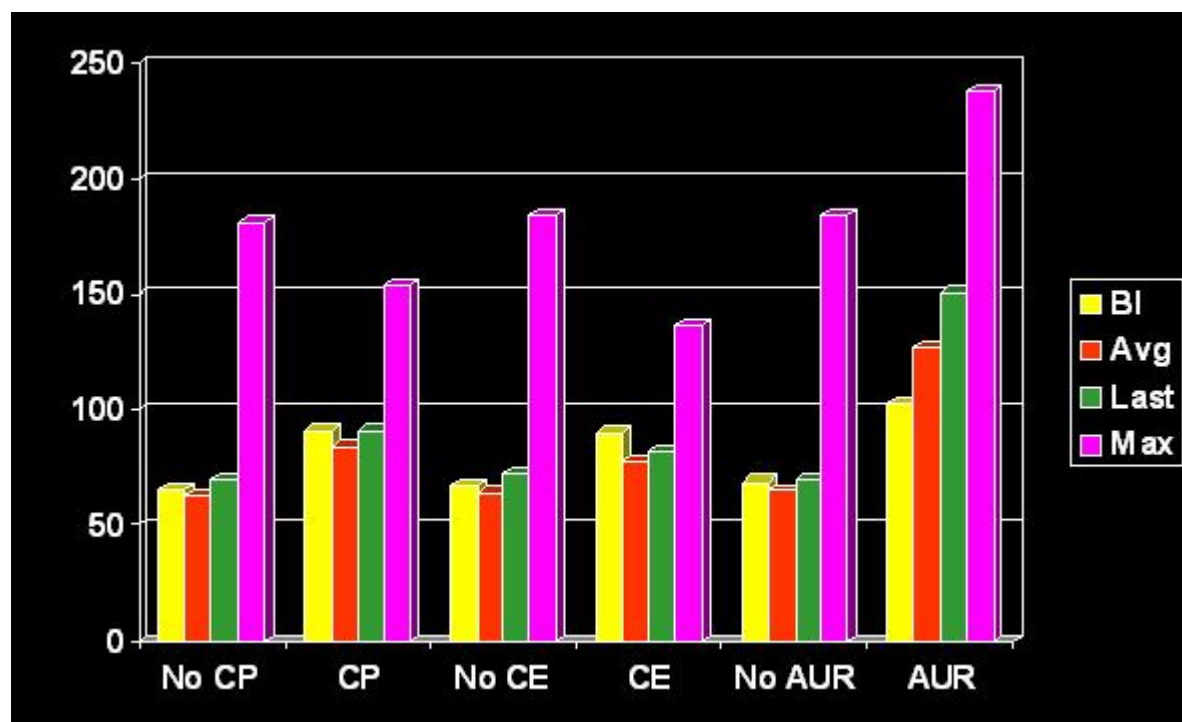
Figure 6 is of particular interest. Men who experienced either a confirmed progression event or an endpoint started out with slightly higher baseline PVRs, had higher average PVRs and a higher last observed PVR compared to those who did not reach either event.

Regarding AUR, the situation is more complex. The placebo treated men eventually experiencing an AUR event started out with 100 ml PVR at baseline vs approximately 70 ml for those who did not, their average PVR prior to the AUR event was higher and the last PVR observed prior to AUR was 150 ml. The maximum observed PVR in this cohort was nearly 250 ml and higher than in any other group (Figure 6).

The conclusions from this analysis are that (Roehrborn, Kaplan et al. 2005):

- High baseline PVR predicts progression in placebo treated patients
- Patients experiencing AUR had higher PVR at baseline, but also during follow up and at last visit before event suggesting AUR being the end result of increasing amounts of PVR at least in some cases
- Compared to other parameters such as age, PSA and prostate volume, PVR is a weak predictor of progression

Figure 6 Baseline (BL), Average (avg), Last Observed (last), and Maximum Recorded (max) PVR Value in Placebo Treated Patients in MTOPS Stratified by Whether or Not They Experienced Confirmed Progression or Not (CP), a Confirmed Endpoint or Not (CE) or AUR



Source: (Roehrborn, Kaplan et al. 2005)

The data presented and discussed up to this point represent the state of our knowledge regarding subjective and objective measures of the storage and voiding function of the lower urinary tract. There is reasonably good data regarding age stratified storage, voiding and OAB symptoms for men and women, as well as data regarding the annual increase in the symptom burden. There are fewer age stratified data regarding flow rates, voided volumes, voiding efficiency, bladder capacity and post void residual urine, and certainly fewer data regarding annual changes of these parameters. However, based on available data “normal” values may be defined and reasonable projection may be made as to the changes of these values over time.

The most difficult question is how these subjective and objective measures relate to outcomes of significance. The problems with the available data fall into several categories: limited data from female populations/patients; outcomes in general are rare and associations weak; in almost all treatment trials artificial thresholds imposed at enrollment limit ability to study the predictive nature of the parameters.

Nonetheless, it does appear that at least in men diagnosed with BPH, an increasing amount of PVR is associated with an increasing risk of AUR, as well as symptomatic worsening.

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Whether such associations would hold true in women, or older men without diagnosed BPH, or younger men is a matter of concern and interest, but not readily answerable due to absence of reliable data.

It is on this background that changes in subjective symptoms and objective voiding parameters under novel medical therapies may be judged as to whether or not they have deleterious consequences to the lower urinary tract.

1.2 The Compound

Retigabine (GKE 841 or D-23129), N-[2-amino-4(4-fluorobenzylamino)-phenyl] carbamic acid ethyl ester, is a new chemical entity in development for treatment of epilepsy. It is a deaza analog of flupirtine, a product currently marketed in Europe as a centrally acting analgesic with ancillary muscle-relaxing properties. Retigabine is a novel antiepileptic compound with a broad spectrum of activity and potent anticonvulsant properties (Armand et al, 1999; 2000; Rostock et al, 1996; Tober et al, 1996). The principle anticonvulsant properties are thought to be enhancement of the M-current by binding to KCNQ2/3 potassium channels, stabilizing them in an open conformation, which dampens neuronal hyperexcitability (Rundfeldt and Netzer 2000; Wuttke et al, 2005). Valeant Pharmaceuticals North America is investigating retigabine primarily as an adjunctive treatment for partial-onset seizures in patients with refractory epilepsy.

1.3 Potential Impact on Lower Urinary Tract Function

A recent review by Andersson listed a large number of potential pharmacological approaches to influence lower urinary tract function, LUTS and OAB (Andersson 2007). Potassium channels have been implicated in the function of the lower urinary tract. In addition, Normandi et al showed that potassium channel activators, adenylate cyclase stimulators, or endothelin antagonists all may have utility against the dynamic component of outflow obstruction secondary to BPH (Normandin and Lodge 1996). Any compound that affects potassium channels may thus inadvertently lead to changes in lower urinary tract function, LUTS and OAB, some of which may be undesired. Specifically, a compound such as retigabine, by dampening neuronal hyperexcitability, may decrease contractility of the detrusor muscle and thereby induce one or more of the following:

- Increase in obstructive voiding symptoms such as hesitancy, straining, intermittency, slow stream
- Subjective sensation of not emptying bladder
- Objective increase in post void residual urine (PVR)
- Reduction in the urinary flow rate

Such changes may be assumed to secondarily lead to urinary tract infections (UTI) due to stagnant urine, backpressure upon the ureters and kidneys with loss of renal function, inability to urinate at all or acute urinary retention (AUR), formation of bladder stones secondary to infection

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in the stagnant urine, and other such consequences. From the MTOPS study, it is well understood that even in men with BPH, significant LUTS and varying amounts of PVR, episodes of UTIs are extremely rare and in five years of following 3,047 men not a single patient developed renal failure due to BPH (McConnell, Roehrborn et al. 2003). In a study comparing watchful waiting and TURP in men with moderate symptoms, only 1 of 276 patients assigned to watchful waiting developed a bladder stone in 3 years of follow-up (Wasson, Reda et al. 1995). In older surgical series, urinary tract infections (UTIs) constitute the main indication for surgical intervention in about 12%. Although one might intuitively assume that increased amounts of residual urine would predispose to the development of UTIs, clear evidence is lacking. Hunter and colleagues cited a rate of 5.2% self-reported episodes of UTI in a cross-sectional survey of 2002 men in Madrid, Spain (Hunter, Berra-Unamuno et al. 1996). The best data to date come from the MTOPS study, where the incidence of UTIs in the placebo-treated patients was only 0.1 per 100 patient-years (McConnell, Roehrborn et al. 2003). Incontinence is one of the most feared complications from surgical intervention for BPH. Although it may be the result of BPH secondary to overdistention of the bladder (overflow incontinence) or to detrusor instability, estimated to affect up to one half or more of all obstructed patients (urge incontinence) (McConnell, Barry et al. 1994; McConnell, MJ et al. 1994), it is also associated with aging, and in a community study an incidence of incontinence of 24% and 49% in men and women older than 50 years was reported (Roberts et al. 1998). In the VA cooperative study, a 4% incidence of incontinence in both the surgical and conservative treatment arms was reported (Wasson, Reda et al. 1995). The self-reported rate of incontinence in a cross-sectional study in 2002 Spanish men was 6.1% (Hunter, Berra-Unamuno et al. 1996). In MTOPS the rate of socially unacceptable incontinence was 0.3 per 100 patient-years (McConnell, Roehrborn et al. 2003). The Agency for Health Care Policy and Research (AHCPR) BPH guidelines reported a mean of 13.6% (range from 0.3% to 30%) of patients presenting for TURP with evidence of renal failure based on predominantly older studies (McConnell, Barry et al. 1994). Patients in renal failure have an increased risk for complications following TURP compared with patients with normal renal function (25% versus 17%) and the mortality increases up to sixfold (Holtgrewe and Valk 1962; Melchior, Valk et al. 1974). The term silent obstruction or silent prostatism has been used to describe the constellation of asymptomatic patients who eventually develop renal failure resulting from bladder outlet obstruction, a case both rare and important. In the VA cooperative study, only 3 of 280 surgically treated patients and 1 of 276 patients in the watchful waiting arm developed renal azotemia, defined as a doubling of serum creatinine from baseline (Wasson, Reda et al. 1995). In none of the cohort or population-based studies have cases of renal failure clearly attributable to BPH been reported. However, the self-reported rate of an episode of renal failure in a cross-sectional study in 2002 Spanish men was 2.4%. In MTOPS, there was not a single case of renal insufficiency related to BPH in over 3000 men observed for over 4 years. One has to be careful, however, not to overinterpret these findings. Participants in MTOPS were screened at

baseline, and one might argue that some at higher risk for developing renal failure were excluded from participation.

From these observations one can conclude that even in men with documented LUTS, BPH and often significant obstructive voiding symptoms and PVRs, development of such negative outcomes is reasonably rare, leading many to suggest that BPH is mostly a quality of life issue and less a serious health concern.

A compound such as retigabine is aimed at women and men with epileptic seizures, a population very different from a population of elderly men enrolled in a BPH treatment study such as the MTOPS trial.

The target population will be (a) younger, (b) have less severe if any lower urinary tract symptoms, and (c) many of the treated patients will be female. Implications of voiding symptoms, detrusor contractility, PVR and long term outcomes in women are less well understood, but due to the absence of a prostate as a potentially obstructing organ, any consequences observed in men should be significantly less common in age matched female patients.

Nonetheless, it is reasonable and prudent to focus particular attention on those adverse events (AEs) that may be attributable to the effect of retigabine on the lower urinary tract in men and women when assessing the safety of the compound. The obvious choices for monitoring are the International Prostate Symptom Score or AUA Symptom Index score, which may be used in both men and women to assess severity and frequency of lower urinary tract symptoms and the amount of PVR measured by transabdominal ultrasonography in a reliable and non-invasive manner (Hartnell, Kiely et al. 1987; Massagli, Cardenas et al. 1989; Ruud Bosch 1995). The AUA Symptom Index score is a seven question self administered questionnaire which asks 4 voiding/obstructive and 3 storage/irritative question, each of which may be answered by a likert scale from 0-5 for a total score of 35 points. The instrument has been validated and found reliable and sensitive to changes induced by treatment (Barry, Fowler et al. 1992; Barry, Fowler FJ et al. 1992; Barry, Girman et al. 1995). By convention, a score of 7 or less is thought to represent mild, a score from 8-18 moderate and a score from 19-35 severe symptoms.

1.4 Urinary Safety Profile of Retigabine

1.4.1 Nonclinical Studies

Retigabine's effects on urinary bladder function were first evaluated in nonclinical studies. In preclinical studies, retigabine was found to inhibit bladder contractions and micturition in rodents, most likely due to its ability to hyperpolarize and thereby stabilize urinary bladder myocytes through activation of certain K^+ channels. In vitro studies in bladder myocytes from rats and guinea pigs also suggested that the effects on the urinary bladder in vivo were most likely mediated by retigabine's ability to hyperpolarize bladder muscle by opening certain KCNQ-encoded K^+ channels.

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1.4.2 Randomized, Controlled Trials

Patients who received at least 1 dose of study drug in the Phase 2b (Study 205) and Phase 3 (Study 301 and 302) randomized, double-blind, placebo-controlled studies are included in the Randomized, Controlled Trials Safety Analysis Set. This set includes 813 patients who received retigabine, and 427 patient who received placebo.

1.4.3 Overall Phase 2/3 Retigabine Trials

Patients who received at least 1 dose of retigabine in any Phase 2 or 3 study were included in the Overall Phase 2/3 Retigabine Safety Analysis Set. Patients who participated in both a randomized study and the subsequent open label extension study (such as Study 301 and the open label extension Study 303) 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. This set includes 1365 patients who received retigabine.

1.4.4 Treatment Emergent Adverse Events

1.4.4.1 Randomized, Controlled Trials

Data from the three studies mentioned above (Study 205, 301, and 302) comprised the randomized, controlled trials. A total of 427 patients from the placebo group and 813 patients from the total retigabine group are included.

1.4.4.2 Renal and Urinary Treatment Emergent Adverse Events

Table 9 Overall Renal and Urinary Disorder Adverse Events Reported by 2 or More Patients in the Total Retigabine Treatment Group During Randomized, Controlled Trials

System organ class	Placebo n (%) (N=427)	Retigabine, n (%)			TOTAL (N=813)
		600 mg/day (N=281)	900 mg/day (N=273)	1200 mg/day (N=259)	
Any Renal and Urinary Disorder Adverse Event	24 (5.6)	30 (10.7)	23 (8.4)	41 (15.8)	94 (11.6)
Dysuria	3 (<1.0)	4 (1.4)	6 (2.2)	10 (3.9)	20 (2.5)
Urinary hesitation	4 (<1.0)	6 (2.1)	3 (1.1)	8 (3.1)	18 (2.2)
Hematuria	3 (<1.0)	6 (2.1)	3 (1.5)	4 (1.5)	13 (1.6)
Chromaturia	1 (<1.0)	2 (<1.0)	4 (1.5)	7 (2.7)	13 (1.6)
Polyuria	7 (1.6)	2 (<1.0)	3 (1.1)	6 (2.3)	11 (1.4)
Urinary retention	2 (<1.0)	1 (<1.0)	4 (1.5)	2 (<1.0)	7 (<1.0)
Nephrolithiasis	0	0	0	4 (1.5)	4 (<1.0)
Leukocyturia	2 (<1.0)	3 (1.1)	0	0	3 (<1.0)
Proteinuria	3 (<1.0)	3 (1.1)	0	0	3 (<1.0)
Renal colic	1 (<1.0)	0	2 (<2.0)	1 (<1.0)	3 (<1.0)
Micturition disorder	0	1 (<1.0)	0	1 (<1.0)	2 (<1.0)
Micturition frequency decreased	1 (<1.0)	2 (<1.0)	0	0	2 (<1.0)
Urine flow decreased	1 (<1.0)	1 (<1.0)	0	1 (<1.0)	2 (<1.0)
Bladder disorder	1 (<1.0)	1 (<1.0)	0	1 (<1.0)	2 (<1.0)
Hypertonic bladder	0	1 (<1.0)	0	1 (<1.0)	2 (<1.0)
Crystalluria	0	2 (<1.0)	0	0	2 (<1.0)

Adverse events are presented in descending order of incidence in the total retigabine population.

TEAE=treatment-emergent adverse event.

During randomized, controlled trials, adverse events (AEs) belonging to the renal and urinary disorders system organ class (SOC) were reported by greater proportions of patients in the total retigabine group than the placebo group (11.6% versus 5.6%). The most common renal and urinary disorder AEs in the retigabine group was dysuria. It is difficult to interpret the term ‘dysuria’ correctly in this context as it could mean a large number of different voiding symptoms. The term hesitation is of greater interest as the compound presumably may reduce the contractility of the bladder and the urinary flow. While there seems to be a numerically greater proportion of men in the active drug groups experiencing this AE, there is no dose effect noted.

The next table lists the special interest AE in the category of voiding dysfunction. While TEAEs related to voiding dysfunction were reported in slightly larger percentages of patients receiving retigabine, there was no apparent dose relationship for any of the individual adverse events.

Table 10 Event of Special Interest: Voiding Dysfunction-related TEAEs – Randomized Controlled Trial Safety Analysis Set

Preferred Term	Placebo n (%) (N=427)	Retigabine, n (%)			
		600 mg/day (N=281)	900 mg/day (N=273)	1200 mg/day (N=259)	TOTAL (N=813)
Any event	7 (1.6)	13 (4.6)	8 (2.9)	14 (5.4)	35 (4.3)
Urinary hesitation	4 (<1.0)	6 (2.1)	3 (1.1)	8 (3.1)	18 (2.2)
Urinary retention	2 (<1.0)	1 (<1.0)	4 (1.5)	2 (<1.0)	7 (<1.0)
Micturition disorder	0	1 (<1.0)	0	1 (<1.0)	2 (<1.0)
Micturition frequency decreased	1 (<1.0)	2 (<1.0)	0	0	2 (<1.0)
Urine flow decreased	1 (<1.0)	1 (<1.0)	0	1 (<1.0)	2 (<1.0)
Bladder disorder	1 (<1.0)	1 (<1.0)	0	1 (<1.0)	2 (<1.0)
Hypertonic bladder	0	1 (<1.0)	0	1 (<1.0)	2 (<1.0)
Urine output decreased	0	1 (<1.0)	0	0	1 (<1.0)
Atonic urinary bladder	0	0	1(<1.0)	0	1 (<1.0)

Adverse events are presented in descending order of incidence in the total retigabine population.

TEAE=treatment-emergent adverse event.

1.4.4.3 Urinary Tract Infections during Randomized, Controlled Trials

During randomized, controlled trials, events of urinary tract infection were reported with similar frequency in the placebo and total retigabine groups. A total of 4.9% of patients from the placebo group (21 out of 427) compared to 4.4% from the total retigabine group (36 out of 813) reported events of urinary tract infection. There appeared to be a possible dose effect among the retigabine groups, as UTIs were reported by 2.1% of the 600 mg/day group, 3.3% of the 900 mg/day group, and 8.1% of the 1200 mg/day group. As with renal and urinary disorders AEs, most UTIs were mild in intensity. This suggests that whatever the effects of retigabine on voiding function may be, such changes do not appear to increase the likelihood of a UTI in controlled trials.

Urinary Tract Infections and Related Signs and Symptoms

Similar to the special interest category of voiding dysfunction, all events that could be related to urinary tract infection were also included in a special interest category of Urinary Tract Infections and Related Signs and Symptoms.

Urinary tract infection TEAEs for patients in the randomized, controlled trials are shown in [Table 11](#).

Table 11 Event of Special Interest – TEAEs of Urinary Tract Infections and Related Signs and Symptoms – Randomized Controlled Trial Safety Analysis Set

Preferred Term	Placebo n (%) (N=427)	Retigabine, n (%)			
		600 mg/day (N=281)	900 mg/day (N=273)	1200 mg/day (N=259)	TOTAL (N=813)
Any event	30 (7.0)	14 (5.0)	14 (5.1)	31 (12.0)	59 (7.3)
Patients with lower UTI or Related Signs and Symptoms	30 (7.0)	14 (5.0)	14 (5.1)	30 (11.6)	58 (7.1)
Urinary tract infection	20 (4.7)	5 (1.8)	9 (3.3)	20 (7.7)	34 (4.2)
Urine analysis abnormal	4 (<1.0)	2 (<1.0)	3 (1.1)	8 (3.1)	13 (1.6)
Bacteriuria	1 (<1.0)	2 (<1.0)	1 (<1.0)	0	3 (<1.0)
Leukocyturia	2 (<1.0)	3 (1.1)	0	0	3 (<1.0)
Cystitis	1 (<1.0)	1 (<1.0)	0	1 (<1.0)	2 (<1.0)
Bacteria urine	0	0	1 (<1.0)	0	1 (<1.0)
Bacteria urine identified	1 (<1.0)	0	0	1 (<1.0)	1 (<1.0)
Blood urine present	1 (<1.0)	0	0	1 (<1.0)	1 (<1.0)
White blood cells urine	0	1 (<1.0)	0	0	1 (<1.0)
Pyuria	0	0	1 (<1.0)	0	1 (<1.0)
White blood cells urine positive	1 (<1.0)	0	0	0	0
Patients with upper UTI or Related Signs and Symptoms	0	0	0	1 (<1.0)	1 (<1.0)
Costovertebral angle tenderness	0	0	0	1 (<1.0)	1 (<1.0)

Adverse events are presented in descending order of incidence in the total retigabine population.
TEAE=treatment-emergent adverse event.

TEAEs related to urinary tract infections were reported with similar frequency in both placebo and retigabine treatment groups during randomized, controlled trials: 7.0% of the placebo group and 7.3% of the total retigabine group.

1.4.4.4 Overall Phase 2/3 Retigabine Trials

Treatment-emergent adverse event data for the overall phase 2/3 trials included data from a total of 13 studies, many of which were long-term extension studies. A total of 1365 patients comprised the safety population. Urinary hesitation and dysuria was reported in 2.6 and 2.1% of these patients, respectively, 7.9% reported a UTI, and 0.6% withdrew due to AEs. These data suggest long-term urinary tract safety of retigabine in open label extension studies.

1.4.4.5 Section 2 Summary and Conclusions

In randomized, controlled trials, although numerically there were more AEs reported related to the urinary tract for retigabine vs placebo (11.6 vs 5.6%), there was no clear dose relationship and the only term related to voiding dysfunction that was reported by more than 1% of patients on retigabine was hesitancy (2.2%) affecting one out of 50 patient. UTI related AEs were reported with similar frequency of 7.3 vs 7.0%, respectively. Discontinuations due to AEs were very rare.

In the overall phase 2/3 retigabine studies urinary hesitation and dysuria was reported in 2.2 and 2.5% of patients, respectively, 7.9% reported a UTI, and 0.6% withdrew due to AEs. These data suggest long-term urinary tract safety of retigabine in open label extension studies.

Taken the information of the controlled trials and the open label extension trials in aggregate, there is very little in the way of a signal in terms of voiding dysfunction, and increased risk for urinary retention with subsequent UTI or other outcomes. While it is possible and even plausible that the mechanism of action of retigabine induces the feeling of hesitancy in some patients, it is certainly not apparent that this increases the risk for serious outcomes based on AE reporting in these trials.

It will be of further interest to focus on the two tools discussed in previous paragraphs, namely the AUA Symptom Index or American Urological Association Symptom Score (AUA Symptom Index) and PVR measurements, to determine if systematic changes in subjective symptoms or objective measures occur under retigabine treatment.

1.4.5 American Urological Association Symptom Index Scores

The two tables summarize the baseline and follow-up AUA Symptom Index in trials 301 and 302.

1.4.5.1 AUA Symptom Index Scores from Study 301 (Placebo versus Retigabine 1200 mg/day)

Table 12 American Urological Association Symptom Index Scores in Study 301 – Descriptive Statistics

Statistic	Placebo (N=152)	RTG 1200 mg (N=153)
Baseline phase	n = 151	n = 149
Mean ± SD	4.0 ± 4.73	5.1 ± 6.46
Median	2.0	2.0
Range (minimum, maximum)	0, 20	0, 30
Week 6 (titration phase ^a)	n = 137	n = 117
Mean ± SD	3.6 ± 4.92	5.0 ± 6.66
Median	2.0	2.0
Range (minimum, maximum)	0, 25	0, 28
Week 10 (maintenance phase ^a)	n = 126	n = 115
Mean ± SD	3.7 ± 5.27	5.3 ± 6.80
Median	1.0	2.0
Range (minimum, maximum)	0, 27	0, 29
Week 18 (end of maintenance phase ^a)	n = 120	n = 89
Mean ± SD	3.3 ± 4.64	4.1 ± 5.27
Median	1.5	2.0
Range (minimum, maximum)	0, 25	0, 24
Week 22 (end of study ^a) ^b	n = 6	n = 7
Mean ± SD	3.0 ± 4.34	5.1 ± 6.07
Median	1.0	4.0
Range (minimum, maximum)	0, 11	0, 18

^a Phase is assigned by visit windows and may not reflect the dosage taken at that particular time point

^b End of study assessments occur after the patient is off study drug

N=number of patients in the population; n=number of patients with an observation; RTG=retigabine;

SD=standard deviation; TID=three times daily.

1.4.5.2 AUA Symptom Index Scores from Study 302 (Placebo versus retigabine 600 mg/day and 900 mg/day)

Table 13 American Urological Association Symptom Index Scores in Study 302 – Descriptive Statistics

Statistic	Placebo (N=179)	RTG 600 mg/day (N=181)	RTG 900 mg/day (N=178)
Baseline phase	n = 179	n = 181	n = 177
Mean ± SD	3.2 ± 5.19	2.8 ± 4.77	2.7 ± 3.86
Median	1.0	1.0	1.0
Range (minimum, maximum)	0, 29	0, 27	0, 18
Week 4 (titration phase ^a)	n = 166	n = 167	n = 162
Mean ± SD	2.7 ± 4.48	2.7 ± 4.72	2.8 ± 4.67
Median	1.0	1.0	0.0
Range (minimum, maximum)	0, 27	0, 23	0, 25
Week 8 (titration phase ^a)	n = 157	n = 152	n = 139
Mean ± SD	2.9 ± 4.94	2.9 ± 4.77	2.7 ± 5.05
Median	0.0	1.0	1.0
Range (minimum, maximum)	0, 29	0, 24	0, 24
Week 16 (maintenance phase ^a)	n = 149	n = 133	n = 130
Mean ± SD	2.7 ± 4.68	2.3 ± 4.67	2.4 ± 4.27
Median	1.0	0.0	0.0
Range (minimum, maximum)	0, 22	0, 29	0, 21
Week 20 (end of study ^{a,b})	n = 6	n = 2	n = 8
Mean ± SD	2.0 ± 3.52	7.0 ± 9.90	2.8 ± 6.20
Median	0.5	7.0	0.5
Range (minimum, maximum)	0, 9	0, 14	0, 18

^a Phase is assigned by visit windows and may not reflect the dosage taken at that particular time point

^b End of study assessments occur after the patient is off study drug

N=number of patients in the population; n=number of patients with an observation; RTG=retigabine; SD=standard deviation

In aggregate there are no numerical and certainly no significant changes observed from baseline in the AUA Symptom Index in either trial 301 or 302. In trial 301 the 1200 mg active drug group started at a higher score and ended at a similarly higher score compared to placebo.

It should be noted that the population in both of these studies was on average 37 years old and represents equal proportions of men and women. Based on previous discussion, one might assume that in fact 90% of all participants would score in the mild or <8 point categories, and in fact the mean and SD in both trials at baseline and during follow-up suggest that this is in fact the case.

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Table 14 Demographic and Other Baseline Characteristics Trial 301

Variable	Placebo (N=152)	RTG 1200 mg/day (N=153)	Total (N=305)	p-value
Age (years)				
Mean \pm SD	36.7 \pm 11.63	37.7 \pm 12.55	37.2 \pm 12.09	p=0.464 ^a
Sex (n[%])				p=0.646 ^b
Male	72 (47.4)	68 (44.4)	140 (45.9)	
Female	80 (52.6)	85 (55.6)	165 (54.1)	
Race (n[%])				p=0.719 ^b
Caucasian	78 (51.3)	90 (58.8)	168 (55.1)	
African-American (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)	
Height (cm)				
Mean \pm SD	166.8 \pm 10.57	166.7 \pm 10.06	166.8 \pm 10.30	p=0.930 ^a
Weight (kg)				
Mean \pm SD	75.2 \pm 22.75	77.8 \pm 21.73	76.5 \pm 22.25	p=0.308 ^a
BMI (kg/m ²)				
Mean \pm SD	26.9 \pm 7.63	27.8 \pm 6.88	27.4 \pm 7.27	p=0.282 ^a

^a p-value for treatment comparison using one-way analysis of variance model.

^b p-value for treatment comparison using Fisher's Exact test.

BMI=body mass index; n=number of patients with the observation; N=number of patients in the population;
RTG=retigabine; SD=standard deviation;

Table 15 AUA Symptom Index Score by Age Category – Placebo Safety Population – Study 301

Placebo													
Visit #	Age Category	Male				Female				Total			
		N	Mean	Median	STD	N	Mean	Median	STD	N	Mean	Median	STD
3	<40	50	3.2	1.0	5.0	45	2.8	2.0	3.0	95	3.0	1.0	4.2
	>=40	22	5.5	4.0	5.6	35	5.6	3.0	5.0	57	5.6	4.0	5.2
6	<40	46	2.8	1.0	5.5	40	2.6	2.0	2.4	86	2.7	1.0	4.3
	>=40	21	5.9	3.0	6.7	31	4.6	3.0	4.4	52	5.1	3.0	5.4
9	<40	42	2.6	1.0	5.8	39	3.7	1.0	5.0	81	3.1	1.0	5.4
	>=40	20	4.9	3.5	4.3	30	4.3	2.0	5.3	50	4.5	3.0	4.9
11	<40	39	3.5	1.0	6.1	35	2.4	1.0	3.4	74	3.0	1.0	5.0
	>=40	19	4.2	3.0	4.3	30	3.3	2.0	3.8	49	3.6	3.0	4.0
16	<40	15	2.9	2.0	3.2	15	3.9	1.0	6.9	30	3.4	1.0	5.3
	>=40	6	4.3	5.0	3.4	7	4.6	1.0	6.9	13	4.5	3.0	5.4
111	<40	2	0.0	0.0	0.0	2	0.0	0.0	0.0				
	>=40	1	1.0	1.0	2	8.5	8.5	3.5	3	6.0	6.0	5.0	

Table 16 AUA Symptom Index Score by Age Category – Retigabine 1200 mg/day Safety Population – Study 301

Retigabine 1200 mg													
Visit #	Age Category	Male				Female				Total			
		N	Mean	Median	STD	N	Mean	Median	STD	N	Mean	Median	STD
3	<40	45	3.7	1.0	5.3	45	3.7	2.0	5.2	90	3.7	2.0	5.2
3	≥40	21	9.7	8.0	8.9	39	6.1	4.0	6.5	60	7.4	5.0	7.6
6	<40	41	3.3	1.0	5.0	37	5.0	3.0	6.2	78	4.1	2.0	5.6
6	≥40	16	7.5	5.5	8.5	29	5.7	3.0	6.7	45	6.3	3.0	7.4
9	<40	37	4.3	2.0	5.5	31	4.7	2.0	6.2	68	4.5	2.0	5.8
9	≥40	14	9.4	6.5	10.0	25	6.5	2.0	8.2	39	7.5	2.0	8.8
11	<40	33	3.0	1.0	4.8	31	3.5	2.0	4.5	64	3.2	1.0	4.7
11	≥40	11	7.9	7.0	6.4	24	3.1	2.0	4.0	35	4.6	3.0	5.3
16	<40	13	2.6	0.0	4.6	21	2.8	0.0	5.4	34	2.7	0.0	5.0
16	≥40	8	8.9	8.0	8.5	19	3.1	1.0	4.1	27	4.8	1.0	6.2
111	<40					2	8.0	8.0	9.9	2	8.0	8.0	9.9
111	≥40					1	14.0	14.0		1	14.0	14.0	

An analysis of the AUA Symptom Index or AUA SS stratified by gender and age (< vs ≥ 40 years) helps to further understand the impact of retigabine on LUTS (Tables 15 and 16 from Study 301 above). In the placebo and retigabine 1200 mg groups, and in both men and women, the patients ≥ 40 yrs have higher AUA Symptom Index compared to those <40 yrs at baseline. Over time, however, there are no discernible or systematic changes in the AUA Symptom Index in either male or female participants, in either the placebo or retigabine groups, or in those < or ≥ 40 yrs.

This suggest the absence of a group effect of retigabine on AUA Symptom Index in either men or women, but also the absence of an effect in those ≥ 40 years, who have a higher baseline AUA Score and theoretically might be at greater risk to experience AUA score progression due to underlying bladder (women) or bladder/prostate (men) problems.

1.5 Section Summary and Conclusions

- Overall, AUA Symptom Index scores were similar between the placebo and retigabine groups in the double blinded studies (Study 301 and 302).
- No significant changes were seen for any treatment group from baseline to follow-up in either men or women in studies 301[303] or 302[304]
- Mean scores for placebo and all retigabine groups consistently remained within the none-to-mild symptom range (≤ 7) at all time points for the overall population
 - AUA Symptom Index scores during the long term studies were similarly low and consistent throughout the trials, suggesting no worsening in bladder symptoms with long term therapy
- When stratifying the participants by age (decade of life [data not shown] or < vs ≥ 40 yrs), higher AUA Symptom Index are observed at baseline in both men and women, but none of the groups experience a progression in AUA score over time either in the placebo or the retigabine treated patients
 - Data from the open label long term extension verify the absence of a systematic increase in AUA score in either men or women, stratified either by decade of life or by < vs ≥ 40 years of age in retigabine treated patients in either studies 301[303] or 302[304]

1.6 Post-void Residual Urine Volumes

Post-void residual urine volumes were measured by bladder ultrasound in the Phase 3 double-blind studies (Studies 301 and 302) and their open-label extensions (Studies 303 and 304). In Studies 301 and 302, ultrasounds were performed at baseline, early in the maintenance phase (Week 8 or 10), late in the maintenance phase (Week 16 or 18), and at the time of study completion or withdrawal if the patient chose not to continue into the open label (designated as “Week 20” or “22”, but could be at any time point during the study if the patient withdrew). In

Studies 303 and 304, bladder ultrasounds were performed at approximately 1, 3, and 12 months of open-label treatment.

1.6.1 Mean Changes from Baseline

1.6.1.1 PVR Ultrasounds from Study 301 (Placebo versus Retigabine 1200 mg/day)

PVR bladder ultrasound results from Study 301 are shown below in [Table 17](#).

Table 17 Baseline and Change From Baseline in Post-void Residual Bladder Urine Volume in Study 301 (Safety Population)

Statistic	Placebo (N=152)	Change from baseline ^b	RTG 400 mg TID (N=153)	Change from baseline ^b
Baseline phase	n = 142		n = 145	
Mean ± SD	20.9 ± 36.42		29.7 ± 73.81	
Median	10.0		11.0	
Range (minimum, maximum)	0, 261		0, 774	
Week 10 (maintenance phase ^a)	n = 127	n = 120	n = 97	n = 94
Mean ± SD	18.8 ± 31.53	-3.2 ± 44.01	53.4 ± 124.35	20.3 ± 86.6
Median	7.0	-1.0	11.0	0.0
Range (minimum, maximum)	0, 200	-211, 190	0, 800	-163, 413
Week 18 (maintenance phase ^a)	n = 115	n = 108	n = 91	n = 87
Mean ± SD	16.3 ± 27.08	-7.8 ± 41.02	43.8 ± 84.35	8.4 ± 69.13
Median	6.0	-2.5	13.0	0.0
Range (minimum, maximum)	0, 162	-258, 110	0, 490	-284, 257
Week 22 (end of study ^{a,c})	n = 38	n = 36	n = 56	n = 55
Mean ± SD	16.3 ± 40.8	-4.9 ± 48.14	13.8 ± 23.08	-7.8 ± 23.59
Median	4.5	-2.5	5.0	-4.0
Range (minimum, maximum)	0, 246	-83, 234	0, 136	-91, 55

^a Phase is assigned by visit windows and may not reflect the dosage taken at that particular time point

^b In order to calculate change from baseline, a patient had to have a result at both baseline and that particular time point

^c End of study assessments occur after the patient is off study drug

N=number of patients in the population; n=number of patients with an observation; RTG=retigabine; SD=standard deviation; TID=three times daily.

At baseline of Study 301, mean PVR urine volumes were somewhat greater for the retigabine group (29.7 mL) than the placebo group (20.9 mL). In both groups the PVR was well within the ranges observed previously to be considered as normal in this age population of men and women. While there were virtually no changes in PVR in the placebo group, in the retigabine group the PVR increased at week 10 only to decrease again towards the end of the study below baseline values.

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1.6.1.2 PVR Ultrasounds from Study 302 (Placebo versus Retigabine 600 mg/day and 900 mg/day)

A summary of PVR bladder volumes from Study 302 is presented in [Table 18](#).

Table 18 Baseline and Change From Baseline in Post-void Residual Bladder Urine Volumes in Study 302 (Safety Population)

Statistic	Placebo (N=179)	RTG 600 mg/day (N=181)	RTG 900 mg/day (N=178)
Baseline phase	n = 178	n = 180	n = 173
Mean ± SD	18.74 ± 56.04	17.42 ± 30.4	23.08 ± 42.52
Median	3.0	5.0	8.0
Range (minimum, maximum)	0, 629	0, 195	0, 272
Week 8 (maintenance phase ^a)	n = 151	n = 142	n = 125
Mean ± SD	14.19 ± 27.91	32.74 ± 82.77	23.58 ± 42.26
Median	4.0	4.5	3.0
Range (minimum, maximum)	0, 215	0, 660	0, 179
Change from baseline ^b to Week 8 (maintenance phase ^a)	n = 150	n = 141	n = 123
Mean ± SD	-1.0 ± 28.44	15.7 ± 82.41	2.2 ± 48.82
Median	0.0	0.0	0.0
Range (minimum, maximum)	-140, 148	-195, 540	-162, 165
Week 16 (maintenance phase ^a)	n = 149	n = 134	n = 113
Mean ± SD	12.89 ± 30.0	27.74 ± 81.63	20.13 ± 37.49
Median	3.0	3.5	6.0
Range (minimum, maximum)	0, 299	0, 735	0, 246
Change from baseline ^b to Week 16 (maintenance phase ^a)	n = 148	n = 133	n = 112
Mean ± SD	-1.5 ± 34.25	12.0 ± 78.4	-3.3 ± 48.5
Median	0.0	0.0	0.0
Range (minimum, maximum)	-185, 232	-195, 609	-262, 173
Week 20 (end of study ^a)	n = 27	n = 35	n = 51
Mean ± SD	48.1 ± 148.56	16.7 ± 23.51	27.0 ± 43.68
Median	4.0	7.0	10.0
Range (minimum, maximum)	0, 742	0, 88	0, 176
Change from baseline ^b to Week 20 (end of study ^{a,c})	n = 27	n = 35	n = 48
Mean ± SD	6.3 ± 49.51	-6.7 ± 30.77	-5.2 ± 47.68
Median	0.0	0.0	0.0
Range (minimum, maximum)	-68, 189	-141, 73	-217, 141

^a Phase is assigned by visit windows and may not reflect the dosage taken at that particular time point

^b In order to calculate change from baseline, a patient had to have a result at both baseline and at that particular time point

^c End of study assessments occur after the patient is off study drug

N=number of patients in the population; n=number of patients with an observation; RTG=retigabine; SD=standard deviation.

In Study 302, most patients in all treatment groups also exhibited low PVR volumes of <100 mL at either baseline or follow-up. At all time points (Baseline, Week 8, Week 16, and Week 20/End of Study), over 90% of patients in all treatment groups exhibited low PVR volumes of less than 100 mL (see [Table 20](#)).

1.6.1.3 Categorical Stratification by PVR Volume

PVR volumes were also divided into 4 categories based on actual measured volumes in the following table (Categories were: <100 mL, ≥100 to <200, ≥200 to <400, and ≥400).

Table 19 Post-void Residual Bladder Urine Volume in Study 301 by Category (Safety Population)

Timepoint and Category of PVR volume	Placebo (N=152)	RTG 1200 mg/day (N=153)
Baseline phase	n = 142	n = 145
<100 mL	137 (96.5%)	138 (95.2%)
≥100 mL, <200 mL	3 (2.1%)	5 (3.4%)
≥200 mL, <400 mL	2 (1.4%)	1 (0.7%)
≥400 mL	0	1 (0.7%)
Week 10 (maintenance phase ^a)	n = 127	n = 97
<100 mL	122 (96.1%)	85 (87.6%)
≥100 mL, <200 mL	4 (3.1%)	4 (4.1%)
≥200 mL, <400 mL	1 (0.8%)	5 (5.2%)
≥400 mL	0	3 (3.1%)
Week 18 (maintenance phase ^a)	n = 115	n = 91
<100 mL	112 (97.4%)	82 (90.1%)
≥100 mL, <200 mL	3 (2.6%)	4 (4.4%)
≥200 mL, <400 mL	0	3 (3.3%)
≥400 mL	0	2 (2.2%)
Week 22 (end of study ^a) ^b	n = 38	n = 56
<100 mL	37 (97.4%)	55 (98.2%)
≥100 mL, <200 mL	0	1 (1.8%)
≥200 mL, <400 mL	1 (2.6%)	0
≥400 mL	0	0

^a Phase is assigned by visit windows and may not reflect the dosage taken at that particular time point

^b End of study assessments occur after the patient is off study drug

N=number of patients in the population; n=number of patients with an observation; RTG=retigabine;

Table 20 Post-void Residual Bladder Urine Volume in Study 302 by Different Categories (Safety Population)

Timepoint and Category of PVR volume	Placebo (N=179)	RTG 600 mg/day (N=181)	RTG 900 mg/day (N=178)
Baseline phase	n = 178	n = 180	n = 173
<100 mL	173 (97.2%)	174 (96.7%)	163 (94.2%)
≥100 mL, <200 mL	3 (1.7%)	6 (3.3%)	8 (4.6%)
≥200 mL, <400 mL	1 (0.6%)	0	2 (1.2%)
≥400 mL	1 (0.6%)	0	0
Week 8 (maintenance phase ^a)	n = 151	n = 142	n = 125
<100 mL	146 (96.7%)	131 (92.3%)	115 (92.0%)
≥100 mL, <200 mL	4 (2.6%)	5 (3.5%)	10 (8.0%)
≥200 mL, <400 mL	1 (0.7%)	4 (2.8%)	0
≥400 mL	0	2 (1.4%)	0
Week 16 (maintenance phase ^a)	n = 149	n = 134	n = 113
<100 mL	148 (99.3%)	125 (93.3%)	109 (96.5%)
≥100 mL, <200 mL	0	4 (3.0%)	3 (2.7%)
≥200 mL, <400 mL	1 (0.7%)	4 (3.0%)	1 (0.9%)
≥400 mL	0	1 (0.7%)	0
Week 20 (end of study ^{a,b})	n = 27	n = 35	n = 51
<100 mL	25 (92.6%)	35 (100%)	46 (90.2%)
≥100 mL, <200 mL	0	0	5 (9.8%)
≥200 mL, <400 mL	1 (3.7%)	0	0
≥400 mL	1 (3.7%)	0	0

^a Phase is assigned by visit windows and may not reflect the dosage taken at that particular time point

^b End of study assessments occur after the patient is off study drug

N=number of patients in the population; n=number of patients with an observation; RTG=retigabine.

As the two tables above illustrate, >90% of patients in all treatment groups with the single exception of the week 10 1200 mg dosage retained <100 ml of PVR throughout the study, a value that in the MTOPS was found to be a threshold above which the risk of outcomes increased in the placebo treated cohort.

1.6.1.4 Shift in PVR from Baseline

The number and percent of patients with shifts in PVR bladder urine volume from baseline are shown for Study 301 in [Table 21](#).

Table 21 **Number and Percent of Patients with Shifts from Baseline in Post-void Residual Bladder Urine Volume (Safety Population) – Study 301**

	Baseline			
	<100 mL	≥100 mL, <200 mL	≥200 mL, <400 mL	≥400 mL
Placebo, n (%)				
Week 10 (Visit 9) (n=120)				
<100 mL	110 (91.7)	3 (2.5)	2 (1.7)	0
≥100 mL, <200 mL	4 (3.3)	0	0	0
≥200 mL, <400 mL	1 (0.8)	0	0	0
≥400 mL	0	0	0	0
Week 18 (Visit 11) (n=108)				
<100 mL	102 (94.4)	2 (1.9)	2 (1.9)	0
≥100 mL, <200 mL	2 (1.9)	0	0	0
≥200 mL, <400 mL	0	0	0	0
≥400 mL	0	0	0	0
Retigabine, n (%)				
Week 10 (Visit 9) (n=94)				
<100 mL	80 (85.1)	2 (2.1)	0	0
≥100 mL, <200 mL	3 (3.2)	0	1 (1.1)	0
≥200 mL, <400 mL	4 (4.3)	1 (1.1)	0	0
≥400 mL	1 (1.1)	1 (1.1)	0	1 (1.1)
Week 18 (Visit 11) (n=87)				
<100 mL	75 (86.2)	3 (3.4)	0	0
≥100 mL, <200 mL	4 (4.6)	0	0	0
≥200 mL, <400 mL	2 (2.3)	0	1 (1.1)	0
≥400 mL	0	1 (1.1)	0	1 (1.1)

Table 22 Number and Percent of Patients with Shifts from Baseline in Post-void Residual Bladder Urine Volume (Safety Population) – Study 302

	Baseline			
	<100 mL	≥100 mL, <200 mL	≥200 mL, <400 mL	≥400 mL
Placebo, n (%)				
Week 8 (Visit 7) (n=150)				
<100 mL	144 (96.0)	2 (1.3)	0	0
≥100 mL, <200 mL	2 (1.3)	0	1 (0.7)	0
≥200 mL, <400 mL	1 (0.7)	0	0	0
≥400 mL	0	0	0	0
Week 16 (Visit 9) (n=148)				
<100 mL	144 (97.3)	2 (1.4)	1 (0.7)	0
≥100 mL, <200 mL	0	0	0	0
≥200 mL, <400 mL	1 (0.7)	0	0	0
≥400 mL	0	0	0	0
Retigabine 600 mg/day, n (%)				
Week 8 (Visit 7) (n=141)				
<100 mL	125 (88.7)	5 (3.5)	0	0
≥100 mL, <200 mL	5 (3.5)	0	0	0
≥200 mL, <400 mL	4 (2.8)	0	0	0
≥400 mL	1 (0.7)	1 (0.7)	0	0
Week 16 (Visit 9) (n=133)				
<100 mL	120 (90.2)	4 (3.0)	0	0
≥100 mL, <200 mL	4 (3.0)	0	0	0
≥200 mL, <400 mL	4 (3.0)	0	0	0
≥400 mL	0	1 (0.8)	0	0
Retigabine 900 mg/day, n (%)				
Week 8 (Visit 7) (n=123)				
<100 mL	107 (87.0)	6 (4.9)	0	0
≥100 mL, <200 mL	9 (7.3)	0	1 (0.8)	0
≥200 mL, <400 mL	0	0	0	0
≥400 mL	0	0	0	0
Week 16 (Visit 9) (n=112)				
<100 mL	102 (91.1)	5 (4.5)	1 (0.9)	0
≥100 mL, <200 mL	2 (1.8)	1 (0.9)	0	0
≥200 mL, <400 mL	0	1 (0.9)	0	0
≥400 mL	0	0	0	0

In study 301 9.1% and 7.4% respectively in the 1200 mg dose group experienced an increase from <100 ml PVR at baseline to >100 ml at week 10 and 18, compared to 4.3% and 1.9% in the placebo group.

In study 302 the corresponding numbers were 2.0% and 0.7% in the placebo group, 7.4 and 6.3% in the 600 mg dose group and 7.8 and 1.9% in the 900 mg dose group.

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Table 23 PVR Volumes by Age Category– Placebo Safety Population – Study 301

Placebo													
Visit #	Age Category	Male				Female				Total			
		N	Mean	Median	STD	N	Mean	Median	STD	N	Mean	Median	STD
3	<40	44	18.0	5.0	32.3	42	26.6	10.5	51.8	86	22.2	10.0	42.9
	>=40	21	20.6	10.0	28.9	35	17.8	10.0	19.7	56	18.8	10.0	23.4
9	<40	39	12.8	6.0	22.4	39	28.0	8.0	45.9	78	20.4	7.0	36.7
	>=40	20	23.8	12.0	28.3	29	11.2	7.0	11.8	49	16.3	8.0	20.9
11	<40	35	13.4	4.0	26.6	35	21.2	7.0	36.5	70	17.3	5.0	31.9
	>=40	15	11.0	8.0	14.2	30	16.7	10.5	18.6	45	14.8	8.0	17.3
16	<40	13	34.9	14.0	66.0	13	6.5	4.0	8.5	26	20.7	5.5	48.3
	>=40	6	11.8	6.0	15.0	6	1.8	0.0	3.0	12	6.8	2.0	11.6
111	<40	1	0.0	0.0							1	0.0	0.0
	>=40	1	37.0	37.0							1	37.0	37.0

Table 24 PVR Volumes by Age Category – Retigabine 1200 mg/day Safety Population – Study 301

Retigabine 1200 mg QD													
Visit #	Age Category	Male				Female				Total			
		N	Mean	Median	STD	N	Mean	Median	STD	N	Mean	Median	STD
3	<40	42	38.6	15.0	118.1	43	30.1	11.0	58.5	85	34.3	12.0	92.4
3	>=40	21	30.1	18.0	41.0	39	19.5	7.0	27.1	60	23.2	11.0	32.7
9	<40	34	57.9	11.0	151.2	27	66.1	10.0	135.5	61	61.5	11.0	143.4
9	>=40	13	46.3	8.0	120.6	23	35.8	13.0	54.2	36	39.6	13.0	82.9
11	<40	31	51.5	15.0	100.6	28	53.3	9.5	102.1	59	52.3	12.0	100.4
11	>=40	12	21.3	12.5	21.9	20	32.3	15.5	44.1	32	28.1	14.0	37.3
16	<40	12	7.1	4.0	8.6	19	7.5	1.0	10.6	31	7.4	3.0	9.8
16	>=40	7	14.6	10.0	20.7	18	24.6	14.0	34.7	25	21.8	10.0	31.3
111	<40					2	10.0	10.0	14.1	2	10.0	10.0	14.1
	>=40					1	0.0	0.0		1	0.0	0.0	

To better understand the potential impact of retigabine on PVR, several further analyses were performed by calculating mean and median PVR values for studies 301[303] and 302[304] for men and women, stratified by decade of life and by age < or ≥40 yrs of age.

The tables above (Table 23 and Table 24) illustrate that in neither men nor women < or ≥40 years of age was there a significant or sustained change in PVR from baseline through end of study visit in either the placebo or the retigabine treatment groups. Similar results were obtained for studies 302 and the long term extension studies 303 and 304, and when stratifying the groups by decade of life, although the small number of patients in their 50s and 60s and above limits the ability to study age stratified PVR trends stratified by decade of life.

Neither mean group changes nor changes in PVR stratified by decade of life or < vs ≥40 years of age suggests any systematic effect of retigabine on PVR measures.

The categorical PVR tables and the PVR shift tables suggest that individual patients experienced increases in PVR from one to the next category. These were, however, often isolated events and on subsequent visits the PVR value in most cases was noted to be again in the lower category.

The following sections analyze the relationship between PVR measure and treatment emergent adverse events, as well as the correlations between PVR measures and AUA Symptom Indices.

1.6.1.5 Treatment Emergent Abnormal PVR in 301 and 302**Table 25 Details of Patients With Treatment-emergent Abnormal PVR Urine Volumes in Study 301**

Patient no ^a	PVR urine vol (mL)			Related AE	Day (Wk) of AE	Action	Outcome
	BL	Week 10	Week 18				
Retigabine 400 mg TID (n = 153)							
00108	196	582	12	Urinary hesitation	39 (6)	Reduced	Resolved
				Residual urine	69 (10)	Other	Resolved
00122	0	655	183	Residual urine volume	69 (10)	Other	Ongoing
00124	94	298	32	Urge incontinence	2 (1)	Other	Resolved
				Residual urine volume	70 (10)	Other	Ongoing
01701	32	445	60	Oliguria	0 (0)	None	Resolved
				Oliguria	70 (10)	None	Resolved
02110	32	306	267	None			
02515	100	136	—	None			
03402	42	358	200	None			
04106	0	50	110	None			
05107	196	394	453	None			
15204	15	188	41	None			
15212	43	113	99	None			
15306	774	800	490	None			
20106	11	104	9	Dysuria	35 (5)	None	Resolved
				Urinary hesitancy	43 (6)	None	Ongoing
20308	32	Unk	113	Dysuria	53 (8)	Conmed	Resolved
20421	24	243	22	None			
Placebo (n = 152)							
02506	85	122	131	Urinary tract infection	80 (11)	Conmed	Resolved
02509	10	200	22	None			
10601	12	115	1	None			
15202	12	79	122	None			
15207	29	156	21	None			
15214	7	199	2	Dysuria	0 (0)	None	Resolved
			100	Dysuria	25 (3)	Conmed	Resolved
20204	—	8	162	None			

^a Includes patients with PVR urine volume results that were elevated at baseline (≥ 100 mL) but worsened post-baseline.

AE = adverse events, Conmed = concomitant medication, PVR = post-void residual

Fifteen out of 153 patients (9.8%) in the retigabine 1200 mg/day group exhibited treatment-emergent elevations in PVR volumes. Four of the 15 patients in this group had elevated PVR volumes at baseline. Among the 15 patients, only 6 reported corresponding renal and urinary-related AEs. The majority of patients with increases in PVR volume reported no urinary adverse events. In the placebo group, among 7 patients (4.6%) with treatment-emergent elevations in

PVR urine volume, 2 had related AEs of dysuria and urinary tract infection. None of the patients in the retigabine group reported any UTIs.

Table 26 Details of Patients With Treatment-emergent Abnormal PVR Volumes (≥ 100 mL) or worsening of PVR Volumes in Study 302

PVR urine vol (mL)							
Patient no ^a	BL	Week 8	Week 16	Related AE	Day (Wk) of AE	Action	Outcome
Retigabine 300 mg TID (n = 178)							
25215	30	156	83	Urinary retention	56 (8)	None	Ongoing
25405*	29	159	83	Bladder atonia	21 (3)	Disc.	Resolved
				Urge incontinence	63 (9)	Other	Resolved
30301	38	101 ^b	—	Urinary retention	29 (5)	Disc.	Resolved
40119	115	0	246	Residual urine volume	114 (17)	None	Ongoing
40144	41	128 ^b	—	None			
40604	35	150 ^b	—	None			
40701	31	150	40	Haematuria	29 (5)	None	Resolved
				UTI	42 (6)	None	Resolved
				Residual urine volume	58 (9)	None	Resolved
45307	0	156	28	None			
45310	14	179	8	None			
50102*	7	60	180	Residual urine volume	57 (9)	None	Ongoing
50603	13	139	57	None			
55506	20	110	8	UTI	13 (2)	None	Resolved
65210	78	137	18	Polyuria	8 (2)	None	Resolved
				Urine analysis abnormal	43 (6)	Other	Resolved
80310	78	176 ^b	—	None			
85103	9	123	150 ^b	None			
90211	0	80	141	None			
Retigabine 200 mg TID (n = 181)							
25107*	23	330	19b	Nerve root compression	43 (7)	Other, Disc.	Resolved
35402	30	0	150	None			
40125	0	0	125	None			
40138	0	246	229	None			
40901	23	328	336	UTI	92 (14)	Conmed	Resolved
45109	0	0	107	Chromaturia	0 (0)	None	Ongoing
50509	63	175	53	None			
60601	7	143	0	Hypertonic bladder	49 (7)	None	Resolved
60604	0	88	270	Bladder disorder	56 (8)	None	Ongoing
				Neurogenic bladder	130 (19)	None	Ongoing
65302	0	114	0	None			
70101	20	175	30 ^b	UTI	42 (6)	Conmed	Resolved
				UTI	77 (11)	Disc.	Resolved
70117	0	400	0	None			
70601	43	165	6	None			
80304	120	660	—	Urinary hesitation	27 (4)	None	Ongoing

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PVR urine vol (mL)							
Patient no ^a	BL	Week 8	Week 16	Related AE	Day (Wk) of AE	Action	Outcome
85403	33	215	100	Dysuria	29 (5)	None	Ongoing
90206	126	26	735	None			
90502	45	0	324	Dysuria	0 (0)	None	Resolved
				Dysuria	71 (11)	Conmed	Resolved
				Haematuria	71 (11)	None	Resolved
				Residual urine volume	113 (17)	None	Ongoing
Placebo (n = 179)							
40166	68	118	86	None			
40132	67	215	299	None			
50701	87	78	276	None			
80314	629	—	742 ^b	None			

^a Includes patients with PVR urine volume results that were abnormal at baseline (≥ 100 mL) but worsened post-baseline.

^b PVR volume was from an early termination visit. Patient off drug at the time of this PVR volume

* Patient reported a urinary related SAE during the study

AE = adverse events, Conmed = concomitant medication, PVR = post-void residual

A summary of patients with treatment-emergent abnormal PVR results or post-baseline increases in PVR urine volumes and corresponding urinary-related AEs was presented in [Table 25](#) and [Table 26](#).

As [Table 26](#) above indicates, 16 out of 178 patients (9.0%) in the 900 mg/day group exhibited treatment-emergent elevations in PVR volume. Among the 16 patients, half of the patients (8 out of 16) reported no corresponding urinary AEs. In the 8 patients who did report urinary AEs, most were able to continue in the study. Two of the 8 patients with AEs reported SAEs related to urinary symptoms. One of these patients was able to continue in the study. The other patient discontinued but recovered from the SAE. Two of the AEs reported in this treatment group were UTIs. Both UTIs recovered without treatment. Overall, only 2 patients in the 900 mg/day group discontinued due to urinary symptoms. In both cases, patients who discontinued from the study recovered from their events.

Among the 17 patients (9.4%) in the 600 mg/day group with treatment-emergent PVR abnormalities, about half (8 out of 17) again reported no corresponding urinary AEs. In this group, there were 2 patients who discontinued from the study due to urinary related AEs. Both patients recovered after discontinuing from the study. One reported an SAE of nerve root compression described earlier. The other was an event of UTI which also recovered after discontinuation. Overall, 2 of the 17 patients with elevated PVR volumes reported UTIs during the study. Both patients also recovered.

In the placebo group, 4 patients (2.2%) reported treatment emergent PVR volume abnormalities. There were no AEs related to PVR volume abnormalities in the placebo group.

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1.6.1.6 PVR in Long Term Open Label Extension 303 and 304

PVR Volumes from Study 303 (Open Label Extension of Study 301)

At baseline, mean PVR urine volume was 29.6 mL. During Study 303, mean PVR volumes showed slight decreases over time with volumes of 29.9 mL, 28.1 mL, and 24.4 mL at Month 1, Month 3, and Month 12, respectively. Mean change from baseline was +4.2mL at Month 1, +0.8 mL at Month 3, and -12.6 mL at Month 12. Overall, long term exposure to retigabine did not appear to result in worsening of bladder function as measured by PVR volume. More than 90% of patients maintained a PVR of <100 ml throughout the study.

PVR Volumes from Study 304 (Open Label Extension of Study 302)

At baseline, mean PVR urine volumes for patients in this study was 18.4 mL. Means remained relatively constant during the study at 20.5 mL at Month 1, 22.6 mL at Month 3, and 18.2 mL at Month 12. Mean change from baseline was +3.7 mL at Month 1, +6.5 mL at Month 3, and -0.36 mL at Month 12. Overall, no worsening of bladder function as measured by PVR volumes was noted with long term exposure to retigabine. More than 90% of patients maintained a PVR of <100 ml throughout the study.

1.6.1.7 Section Summary and Conclusions

Compared to placebo, there appears to be a modest effect on mean PVR urine volume with retigabine 600 mg/day and 1200 mg/day; however, there was no significant effect with retigabine 900 mg/day. Drug effects on PVR volume appear to be readily reversible, as patients who discontinued retigabine reported lower mean PVR volumes during end-of-study assessments than at baseline. Median PVR urine volumes for all groups were low during the study and relatively unchanged during the double-blind phase. In long-term studies, mean PVR volumes were also low, suggesting no overall worsening of bladder function with extended exposure to retigabine.

Although PVR volumes could be helpful in confirming the diagnosis of urinary retention, elevated PVR volumes were not strongly associated with adverse events of voiding dysfunction or urinary retention.

1.6.2 Correlation Between Subjective (AUA Symptom Index) and Objective (PVR) Measures

The following tables list patients in controlled studies 301 and 302 and open label extension studies 303 and 304, who experienced increases in PVR and presents the AUA Symptom Index score at the time of PVR measurement in an effort to better understand the relationship between subjective and objective parameters.

Table 27 PVR and AUA Data from Study 301 (Retigabine 1200 mg/day vs Placebo)

		Time Point of Test (PVR/AUA)							
Patient ^a (demo.)	Test	BL	Week 6	Week 10	Week 18	Related AE	Day (Wk) of AE	Action	Outcome
Retigabine 1200 mg/day (n = 153)									
00108 (39y F)	PVR	196	—	582	12	Urinary hesitation	39 (6)	Reduced	Resolved
	AUA	10	10	18	6	Residual urine	69 (10)	Other	Resolved
00122 (44y F)	PVR	0	—	655	183	Residual urine volume	69 (10)	Other	Ongoing
	AUA	0	2	3	2				
00124 (39y M)	PVR	94	—	298	32	Urge incontinence	2 (1)	Other	Resolved
	AUA	3	4	9	8	Residual urine volume	70 (10)	Other	Ongoing
01701 (50y M)	PVR	32	—	445	60	Oliguria	0 (0)	None	Resolved
	AUA	10	6	17	15	Oliguria	70 (10)	None	Resolved
02110 (27y M)	PVR	32	—	306	267	None			
	AUA	5	—	7	9				
02515 (53y F)	PVR	100	—	136	—	None			
	AUA	1	1	0	0				
03402 (29y F)	PVR	42	—	358	200	None			
	AUA	2	1	2	0				
04106 (24y F)	PVR	0	—	50	110	None			
	AUA	7	6	3	0				
05107 (33y F)	PVR	196	—	394	453	None			
	AUA	0	0	0	1				
15204 (23y M)	PVR	15	—	188	41	None			
	AUA	0	2	5	1				
15212 (41y F)	PVR	43	—	113	99	None			
	AUA	7	2	1	3				
15306 (25y M)	PVR	774	—	800	490	None			
	AUA	0	0	0	1				
20106 (24y F)	PVR	11	—	104	9	Dysuria	35 (5)	None	Resolved
	AUA	5	9	2	4	Urinary hesitancy	43 (6)	None	Ongoing
20308 (27y M)	PVR	32	—	Unk	113	Dysuria	53 (8)	Conmed	Resolved
	AUA	0	0	1	0				
20421 (45y F)	PVR	24	—	243	22	None			
	AUA	1	17	12	0				
Placebo (n = 152)									
02506 (38y M)	PVR	85	—	122	131	Urinary tract infection	80 (11)	Conmed	Resolved
	AUA	0	6	0	12				
02509 (24y F)	PVR	10	—	200	22	None			
	AUA	5	5	2	5				
10601 (31y M)	PVR	12	—	115	1	None			
	AUA	1	1	1	2				

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		Time Point of Test (PVR/AUA)							
Patient ^a (demo.)	Test	BL	Week 6	Week 10	Week 18	Related AE	Day (Wk) of AE	Action	Outcome
15202 (35y M)	PVR AUA	12 1	— 1	79 1	122 1	None			
15207 (26y F)	PVR AUA	29 4	— 1	156 0	21 2	None			
15214 (26y F)	PVR AUA	7 1	— 2	100 0	2 0	Dysuria Dysuria	0 (0) 25 (3)	None Conmed	Resolved Resolved
20204 (39y F)	PVR AUA	— 3	— 4	8 5	162 5	None			

^a Includes patients with PVR urine volume results that were elevated at baseline (≥ 100 mL) but worsened post-baseline.

BL = baseline, AE = adverse events, Conmed = concomitant medication, PVR = post-void residual

Table 28 PVR and AUA Data from Study 302 (Retigabine 900 mg/day vs Retigabine 600 mg/day vs Placebo)

		Time Point of Test (PVR/AUA)							
Patient ^a (demo.)	Test	BL	Week 6	Week 8	Week 16	Related AE	Day (Wk) of AE	Action	Outcome
Retigabine 900 mg/day (n = 178)									
25215 (47y M)	PVR AUA	30 7	— 15	156 21	83 11	Urinary retention	56 (8)	None	Ongoing
25405* (34y F)	PVR AUA	29 2	— 3	159 23	83 ^b 21 ^b	Bladder atonia Urge incontinence	21 (3) 63 (9)	Disc. Other	Resolved Resolved
30301 (47y F)	PVR AUA	38 7	— 7	101 ^b 4 ^b	— —	Urinary retention	29 (5)	Disc.	Resolved
40119 (57y F)	PVR AUA	115 0	— 0	0 0	246 4	Residual urine volume	114 (17)	None	Ongoing
40144 (63y M)	PVR AUA	41 2	— —	128 ^b 3 ^b	— —	None			
40604 (60y M)	PVR AUA	35 6	— 8	150 ^b 3 ^b	— —	None			
40701* (62y M)	PVR AUA	31 1	— 1	150 1	40 1	Haematuria UTI Residual urine volume	29 (5) 42 (6) 58 (9)	None None None	Resolved Resolved Resolved
45307 (24y M)	PVR AUA	0 1	— 0	156 0	28 0	None			
45310 (19y M)	PVR AUA	14 2	— 1	179 3	8 5	None			

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		Time Point of Test (PVR/AUA)							
Patient ^a (demo.)	Test	BL	Week 6	Week 8	Week 16	Related AE	Day (Wk) of AE	Action	Outcome
50102* (45y F)	PVR AUA	7 1	— 0	60 0	180 0	Residual urine volume	57 (9)	None	Ongoing
50603 (54y M)	PVR AUA	13 1	— 0	139 1	57 1	None			
55506 (47y M)	PVR AUA	20 9	— 11	110 2	8 0	UTI	13 (2)	None	Resolved
65210 (22y M)	PVR AUA	78 10	— 4	137 4	18 5	Polyuria Urine analysis abnormal	8 (2) 43 (6)	None Other	Resolved Resolved
80310 (64y F)	PVR AUA	78 0	— 0	176 ^b 0 ^b	— —	None			
85103 (57y F)	PVR AUA	9 3	— 0	123 0	150 ^b 2 ^b	None			
90211 (37y M)	PVR AUA	0 4	— 4	80 5	141 7	None			
Retigabine 600 mg/day (n = 181)									
25107* (62y F)	PVR AUA	23 4	— 0	330 12	19 ^b 2 ^b	Nerve root compression	43 (7)	Other, Disc.	Resolved
35402 (36y F)	PVR AUA	30 0	— 0	0 0	150 0	None			
40125 (40y F)	PVR AUA	0 0	— 0	0 0	125 0	None			
40138 (33y M)	PVR AUA	0 0	— 0	246 0	229 0	None			
40901 (61y F)	PVR AUA	23 6	— 20	328 12	336 —	UTI	92 (14)	Conmed	Resolved
45109 (31y M)	PVR AUA	0 0	— 3	0 0	107 1	Chromaturia	0 (0)	None	Ongoing
50509 (38y M)	PVR AUA	63 0	— 0	175 1	53 0	None			
60601 (28y M)	PVR AUA	7 4	— 3	143 3	0 2	Hypertonic bladder	49 (7)	None	Resolved
60604 (18y F)	PVR AUA	0 0	— 0	88 0	270 1	Bladder disorder Neurogenic bladder	56 (8) 130 (19)	None None	Ongoing Ongoing
65302 (51y F)	PVR AUA	0 3	— 4	114 0	0 0	None			
70101 (22y F)	PVR AUA	20 0	— 0	175 1	30 ^b 29 ^b	UTI UTI	42 (6) 77 (11)	Conmed Disc.	Resolved Resolved
70117 (65y M)	PVR AUA	0 1	— 1	400 2	0 2	None			
70601 (37y M)	PVR AUA	43 1	— 0	165 2	6 4	None			

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		Time Point of Test (PVR/AUA)							
Patient ^a (demo.)	Test	BL	Week 6	Week 8	Week 16	Related AE	Day (Wk) of AE	Action	Outcome
80304 (56y M)	PVR AUA	120 0	— 7	660 13	— —	Urinary hesitation	27 (4)	None	Ongoing
85403 (42y M)	PVR AUA	33 2	— 3	215 7	100 10	Dysuria	29 (5)	None	Ongoing
90206 (39y M)	PVR AUA	126 4	— 4	26 2	735 2	None			
90502 (44y M)	PVR	45	—	0	324	Dysuria	0 (0)	None	Resolved
	AUA	0	3	0	0	Dysuria	71 (11)	Conmed	Resolved
						Haematuria	71 (11)	None	Resolved
						Residual urine volume	113 (17)	None	Ongoing
Placebo (n = 179)									
40116 (48y M)	PVR AUA	68 0	— 0	118 0	86 0	None			
40132 (37y M)	PVR AUA	67 0	— 0	215 0	299 0	None			
50701 (42y F)	PVR AUA	87 4	— 4	78 4	276 8 ^b	None			
80314 (56y M)	PVR AUA	629 0	— 6	— 2	742 ^b 2 ^b	None			

^a Includes patients with PVR urine volume results that were abnormal at baseline (≥ 100 mL) but worsened post-baseline. Demo. = demographic information (age, sex)

^b PVR/AUA was from an early termination visit. Patient off drug at the time of this assessment

* Patient reported an urinary related SAE during the study

BL = baseline, AE = adverse events, Conmed = concomitant medication, PVR = post-void residual

Table 29 PVR and AUA Data from Study 303 (Open Label Extension of Study 301)

		Time Point of Test (PVR/AUA)							
Patient ^a (demo.)	Test	BL	Month 1	Month 3	Month 12	Related AE	Day of AE	Action	Outcome
Retigabine (n = 176)									
00108 (39y F)	PVR AUA	196 10	244 21	109 16	16 3	None			
00124 (39y M)	PVR AUA	94 3	110 6	230 3	59 5	None			
00304 (37y F)	PVR AUA	261 0	231 0	533 0	10 0	None			
00801 (46y M)	PVR AUA	63 5	122 0	15 0	210 5	Urinary retention	509		
00808 (30y M)	PVR AUA	0 3	106 4	16 4	— —	None			
01204 (29y M)	PVR AUA	130 0	132 0	60 0	12 1	None			
01501 (52y M)	PVR AUA	— 21	167 6	35 7	39 1	None			
02110 (27y M)	PVR AUA	32 5	319 2	44 1	— —	None			
02506 (38y F)	PVR AUA	85 0	42 3	115 8	220 6	UTI	171	Conmed	Resolved
02512 (42y F)	PVR AUA	50 11	40 2	118 1	— —	Blood urine Protein urine Red cells urine	172 172 172	Other Other Other	Resolved Resolved Resolved
03402 (29y F)	PVR AUA	42 2	40 4	152 11	13 3	None			
20107 28y M)	PVR AUA	15 1	0 1	210 1	— —	None			
20110 (26y F)	PVR AUA	5 1	127 9	— —	— —	None			
20423 (20y F)	PVR AUA	24 5	135 3	— —	— —	None			

^a Includes patients with PVR urine volume results that were elevated at baseline (≥ 100 mL) but worsened post-baseline. Demo. = demographic information (age, sex)

BL = baseline visit from Study 301, AE = adverse events, Conmed = concomitant medication, PVR = post-void residual

Table 30 PVR and AUA Data from Study 304 (Open Label Extension of Study 302)

		PVR urine vol (mL)							
Patient ^a (demo.)	Test	BL	Month 1	Month 3	Month 12	Related AE	Day of AE	Action ^b	Outcome
Retigabine (n = 294)									
40107 (42y F)	PVR	0	0	180	—	None			
	AUA	0	0	3	—				
40125 (40y F)	PVR	0	0	137	—	None			
	AUA	0	0	0	—				
40901 (61y F)	PVR	23	0	138	—	UTI	173	None	Resolved
	AUA	6	6	5	—				
45306 (50y F)	PVR	0	33	124	—	None			
	AUA	0	0	0	—				
50102 (45y F)	PVR	7	100	95	150	Urinary retention	56	Disc.	Resolved
	AUA	1	0	0	0				
50506 (20y F)	PVR	125	265	75	95	None			
	AUA	0	0	0	0				
55207 (40y F)	PVR	22	12	120	—	None			
	AUA	0	0	0	—				
55303 (18y M)	PVR	0	7	216	—	None			
	AUA	0	0	0	—				
55304 (22y M)	PVR	0	147	3	0	None			
	AUA	0	0	0	0				
55410 (18y M)	PVR	1	2	315	2	None			
	AUA	0	0	0	0				
55505 (58y F)	PVR	16	170	61	109	None			
	AUA	2	4	7	2				
60209 (20y M)	PVR	5	190	0	—	Residual urine vol. Urinary tract disorder	179 235	Reduced dose Reduced dose	Resolved Resolved
	AUA	0	0	3	—				
60604 (18y F)	PVR	0	122	182	8	None			
	AUA	0	0	0	0				
60605 (37y M)	PVR	0	118	138	—	Neurogenic bladder	184	None	
	AUA	2	1	0	—				
70110 (26y M)	PVR	188	90	215	—	None			
	AUA	0	2	0	—				
70201 (35y M)	PVR	0	—	67	102	Urinary retention	501	Disc.	Resolved
	AUA	12	3	0	11				
70601 (37y M)	PVR	43	300	—	—	None			
	AUA	1	1	—	—				
80304 (56y M)	PVR	120	—	375	—	None			
	AUA	0	17	6	13				

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Patient ^a (demo.)	Test	PVR urine vol (mL)				Related AE	Day of AE	Action ^b	Outcome
		BL	Month 1	Month 3	Month 12				
80404 (22y M)	PVR	140	166	—	—	None			
	AUA	0	0	—	—				
85403 (42y M)	PVR	33	270	63	0	Urinary retention	170	None	Resolved
	AUA	2	10	5	3	Urinary retention	233	None	

^a Includes patients with PVR urine volume results that were abnormal at baseline but worsened post-baseline. Demo.
= demographic information (age, sex)

^b Disc = discontinued

BL = baseline visit from Study 302, AE = adverse events, Conmed = concomitant medication, PVR = post-void residual

When scrutinizing these four tables (and listings of PVR and corresponding AUA Symptom Index, the following observations can be made:

- Single or multiple elevated PVR values occur in women and men at a similar rate
- Single or multiple elevated PVR values occur independent of age in this cohort of patients with a mean age of 37 years
- Baseline PVR does not predict sudden increases in PVR values
- Single elevated PVR values most often are followed by a lower PVR at next visit, ie, there is no progression noticeable
- Baseline AUA Symptom Index does not predict sudden increases in PVR values
- There is except in very few cases no correlation between increases in PVR and increases in AUA Symptom Index, suggesting that for the most part these PVR elevations are asymptomatic
- Single or multiple occurrences of elevated PVR are not routinely associated with relevant AEs reported
- Single or multiple occurrences of elevated PVR are not often associated with reported UTIs

1.7 Serious Adverse Events of Urinary Retention

Regarding serious adverse events of urinary retention Valeant provided a document entitled “FDA Requested SAE Narratives Regarding Urinary Retention”. According to this document, as of 11-Aug-2008, a search of the safety database at Valeant Pharmaceuticals International retrieved **eight (8)** serious adverse events and **two (2)** non-serious adverse events related to urinary retention described in clinical trials with retigabine.

Table 31 Ten Cases of Serious AEs of Urinary Retention (Abbreviated)

Age	Sex	Dosage	Description
63	Female	600 mg	Increased PVR, diagnosed with L5/S1 nerve root compression, resolved after surgery
32	Female	900 mg	Increased PVR during titration, resolved and pt remained in study on medication
34	Female	900 mg	Developed incontinence and PVR of 159 ml, resolved after discontinuation of drug
55	Male	Placebo	4 wks after initiation admitted for seizures, had AUR and required catheter, resolved, remained on study medication
53	Female	600 mg	1 mo into treatment admitted with pulmonary edema and AUR, drug discontinued, no sequelae, no f/u
58	Male	1200 mg	Developed retention to > 500 ml during transition phase on active drug; discontinued, resolved with no sequelae
46	Female	Open label	Developed AUR with PVR of > 1000 ml, performed CIC and continued on drug (good clinical results), eventually discontinued drug, resolved with no sequelae
62	Female	900 mg	UTI with some temporary increase in PVR, resolved, <u>downgraded to not serious</u>
31	Male	Open label	<i>Admitted with psychomotor agitation and PVR of 900. Multiple issues including possible poisonous snake bite, at time of last contact still on CIC up to tid with varying amounts of voided vs retained urine</i>
41	Male	Open label	PVR 700 ml, resolved without further intervention, subsequent PVRs were wnl

Of the ten cases, six involved female patients, four male patients. The involved patients appear to be older than the average for the entire study cohort. One was on placebo, nine on varying doses of retigabine, several in open label studies. In nine patients the event resolved, while in one younger male patient (*italics*) it is ongoing with the patient performing self catheterization. A detailed review of this patient reveals other factors of interest, such as admission for psychomotor agitation, history of poisonous snake bite during study participation, hypertension, sleep apnea, vagal nerve stimulator implantation, gastroesophageal reflux disease and psychomotor agitation. Concomitant medications included carbamazepine, lamotrigine, pregabalin and pantoprazole.

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The invasive urodynamic study performed was made available to me and it is not clear from this study whether or not the patient has neurogenic bladder disorder and if so, what the particular characteristics of such may be.

The fact that these ten episodes involve younger and older and male and female participants on dosages ranging from 600 to 1200 mg retigabine does not allow firm conclusions regarding the risk of retigabine for certain populations nor recommendations for specific monitoring. However, one must also consider that with approximately 100 patient years of exposure to placebo and over 900 patient years of exposure to retigabine to date, the overall rates of *serious* adverse events of urinary retention are similar in placebo (1 per 100 patient years) and active drug (7 per > 900 patient years).

1.8 Overall Summary and Conclusions

- Based on the known population based data regarding subjective and objective measures of lower urinary tract function such as AUA Symptom Index and PVR, and based on the known changes over time in such measures from population based data, the changes in AUA Symptom Index and PVR observed in studies 301, 302, 303 and 304 with retigabine over a wide range of dosages, in men and women with a mean age of 37 years, indicate a low risk to induce over time serious outcomes regarding the lower urinary tract
 - There are virtually no group changes noticed in the AUA Symptom Index and only few individual patients experience temporary increases in AUA Symptom Index, not necessarily correlating to relevant AE reporting
 - There are no group changes in the amount of PVR. While some patients experience (mostly temporary) increases in PVR, these are NOT correlated to AE reporting, AUA Symptom Index increases or any other measurable outcomes. Furthermore, such increases in PVR even in at risk men with BPH have not been found to be reliable predictor of serious outcomes
- Single and multiple increases in PVR occur in men and women, both above and below the mean age in studies 301[303] and 302[304]. No sub-population appears to be at greater risk compared to the entire population and thus no specific recommendation regarding monitoring of any subgroups can be made
- It is both impractical and not indicated based on the data from studies 301[303] and 302[304] to recommend routine measurement of PVR or AUA Symptom Index in women or men about to be treated with retigabine
- The data from studies 301[303] and 302[304] do not allow conclusions regarding a contraindication to retigabine treatment based on any such parameters, nor regarding discontinuation of therapy if changes in AUA Symptom Index or PVR are observed

- A careful and detailed review of the ten cases of serious AEs related to urinary retention do not reveal a particular pattern that would lend itself to restrictions, contraindication or other monitoring recommendations. Furthermore, the overall rates of *serious* adverse events of urinary retention are similar in placebo (1 per 100 patient years) and active drug (7 per > 900 patient years) when calculated based on total exposure in all studies.
- The package insert (PI) should perhaps contain relevant language to draw physicians attention to the observed risks of worsening of lower urinary tract symptoms and increases in post void residual urine. The risk for having a single or sustained increase in symptom score either by a certain threshold or by an absolute value, is very similar between retigabine and placebo treated patients. By similar analyses, the risk for increases in post void residual urine volume by any definition is slightly higher in retigabine treated patients compared to placebo without evidence that this is causing subsequent serious adverse events. This is demonstrated in the following table from (data from studies 301 and 302, analyses provided by Valeant upon request of author):

	Placebo	Retigabine
Isolated or repeated increase in symptom score <u>to</u> > 7 points	20.85% (69 / 331)	20.31% (104 / 512)
Isolated or repeated increase in symptom score <u>by</u> ≥4 points from baseline	15.71% (52 / 331)	16.60% (85 / 512)
Sustained increase in symptom score <u>by</u> ≥4 points from baseline	4.23% (14 / 331)	4.69% (24/512)
Isolated or repeated increase in PVR <u>to</u> ≥100 ml	3.63% (12 / 331)	8.98% (46 / 512)
Isolated or repeated increase in PVR <u>by</u> ≥100 ml from baseline	1.81% (6 / 331)	7.03% (36 / 512)
Sustained increase in PVR <u>by</u> ≥ 100 ml from baseline	0.30% (1 / 331)	1.17% (6 / 512)

- It might be reasonable to suggest non-invasive measurement of PVR or referral to a urologist for such measurement in those patients who spontaneously report urinary hesitancy during the course of treatment with retigabine

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