16 Appendices

16.1 Study Information

16.1.1 Protocol and Protocol Amendments

The following protocols, amendments, and amendment summaries are provided:

Protocol Amendment 2	14 Aug 2008
Protocol Amendment 1 Addendum 2 (for France)	08 Nov 2007
Protocol Amendment 1 Addendum 1 (Administrative Change)	20 Jul 2007
Protocol Amendment 1	02 July 2007
Protocol Addendum 3 (for Germany – additional changes)	01 Nov 2006
Protocol Addendum 2 (for Hungary)	28 Jul 2006
Protocol Addendum 1 (for Germany)	06 Jul 2006
Original Protocol	10 Feb 2006

Clinical Study Protocol

Retigabine

A multicenter, open-label, long-term, safety, tolerability and efficacy study of retigabine in adult epilepsy patients with partial-onset seizures (Extension of Study VRX-RET-E22-302)

Protocol Number VRX-RET-E22-304

1. TITLE PAGE

STUDY TITLE:	A multicenter, open-label, long-term, safety, tolerability and efficacy study of retigabine in adult epilepsy patients with partial-onset seizures (Extension of Study VRX-RET-E22-302)
INVESTIGATIONAL PRODUCT:	Retigabine
IND NUMBER:	53,950
PROTOCOL NUMBER:	VRX-RET-E22-304, Amendment 2
PHASE:	3
SPONSOR:	Valeant Pharmaceuticals, North America One Enterprise Aliso Viejo, CA 92656 USA Main Office: [redacted] FAX: [redacted]
CONTRACT RESEARCH ORGANIZATION (CRO):	Quintiles, Inc. 5927 South Miami Blvd. Morrisville, NC 27560
CRO MEDICAL MONITOR:	[redacted] MD Director, Medical & Scientific Services Quintiles Global CRO Station House, Market Street, Bracknell RG12 1HX, UK Telephone: [redacted] Facsmile: [redacted]
COUNTRIES:	Western, Central and Eastern Europe, Australia, Israel, South Africa and the United States

2. PROTOCOL SIGN-OFF SHEET

PROTOCOL TITLE: A multicenter, open-label, long-term, safety, tolerability and efficacy study of retigabine in adult epilepsy patients with partial-onset seizures (Extension of Study VRX-RET-E22-302)

PROTOCOL NUMBER: VRX-RET-E22-304, Amendment 2

VERSION: 14 August 2008

Review[redacted]pproved by:

[redacted]
Sr. Director, Clinical Operations — 19 / AUG / 2008 Date

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Ph.D.
Director, Biostatistics — 18 / August / 2008 Date

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Sr. Director, Regulatory Affairs — 19 / August / 2008 Date

[redacted]
MD, PhD, ScM
V. P. Global Medical Affairs, Chief Medical Officer — 19 / Aug / 2008 Date

[redacted]
MD
Sr. V. P. Global Drug Development — 08 / 18 / 08 Date

3. SUMMARY OF REVISIONS

SECTION: **9.7.5 Discontinuation and Tapering of Study Medication**

*Added (see **bold** text)*

Patients who discontinue early from the open-label extension study will have their study medication tapered over a 3-week period, reducing their daily dose by one-third per week. After tapering has been completed, patients should return to the site immediately, and complete all assessments and evaluations scheduled for Visit 5, if patient discontinued early during the first year of the open-label extension study, complete all assessments and evaluations scheduled for Visit 8 if patient discontinued early during the second year of the open-label extension study, complete all assessments and evaluations scheduled for Visit 11 if patient discontinued early during the third year of the open-label extension study, ***and complete all assessments and evaluations scheduled for Visit 14 if patient discontinued early during the fourth year of the open-label extension study*** (Refer to Study Flow Chart in Appendix A).

REVISION: Added a fourth year visit to this procedure.

RATIONALE: This will allow patients, who enrolled early during the trial, to remain in the open label extension study until the study drug, retigabine, is approved and commercially available, or until the program is discontinued.

SECTION: **10.1 Study Flow Chart**

*Added (see **bold** text)*

- Study Visit 1 (at Month 1 ±3 days).
- Study Visit 1a for Hematological Monitoring (at Month 2 ±7 days)
- Study Visit 2 (at Month 3 ±7 days).
- Study Visit 2a for Hematological Monitoring (at Month 4 ±7 days)
- Study Visit 3 (at Month 6 ±7 days).
- Study Visit 3a for Hematological Monitoring (at Month 8 ±7 days)
- Study Visit 4 (at Month 9 ±7 days).
- Study Visit 4a for Hematological Monitoring (at Month 10 ±7 days)
- Study Visit 5 (at Month 12 ±7 days).
- Study Visit 6 (at Month 16 ±7 days).
- Study Visit 7 (at Month 20 ±7 days).
- Study Visit 8 (at Month 24 ±7 days).
- Study Visit 9 (at Month 28 ±7 days).
- Study Visit 10 (at Month 32 ±7 days).
- Study Visit 11 (at Month 36 ±7 days).
- ***Study Visit 12 (at Month 40 ±7 days).***
- ***Study Visit 13 (at Month 44 ±7 days).***
- ***Study Visit 14 (at Month 48 ±7 days).***

REVISION: Added fourth year visits and procedures.

RATIONALE: This will allow patients, who enrolled early during the trial, to remain in the open label extension study until the study drug, retigabine, is approved and commercially available, or until the program is discontinued.

SECTION: **10.3 Safety Assessments**

*First paragraph, added (see **bold** text)...*

Post-void residual (PVR) bladder ultrasounds to assess urinary retention and the American Urological Association (AUA) Symptom Index to assess urinary voiding function will also be performed during the first, **second, third and fourth** year of the open-label extension study.

REVISION: AUA and PVR assessments will be performed at visits 8, 11 and 14.

RATIONALE: To extend the urinary safety assessments after the first year of the trial.

SECTION: **10.3.2 Physical and Neurological Examinations**

*Added (see **bold** text)*

A complete physical and neurological examination will be performed annually at Visit 5, Visit 8, 11 **and Visit 14.** Brief neurological examinations will be performed at all other study visits, including visits 1, 2, 3, 4, 6, 7, 9, 10**, 12 and 13.**

RATIONALE: Added additional visits for a fourth year patient assessment.

REVISION: This will allow patients, who enrolled early during the trial, to remain in the open label extension study until the study drug, retigabine, is approved and commercially available, or until the program is discontinued.

SECTION: **10.3.3 Electrocardiograms**

*Added (see **bold** text)*

A 12-lead ECG will be performed at all study visits during the first year of the open-label extension study (Visits 1, 2, 3, 4, 5), and annually at Visits 8, 11 **and 14**...

REVISION: Added a fourth year visit for the ECG assessment.

RATIONALE: This will allow patients, who enrolled early during the trial, to remain in the open label extension study until the study drug, retigabine, is approved and commercially available, or until the program is discontinued.

SECTION: **10.3.5 Post-Void Residual (PVR) Bladder Ultrasound**

*Added (see **bold** text)...*

A post-void residual (PVR) bladder ultrasound to assess urinary retention will be performed at Visits 1, 2, 5, ***8, 11, and 14*** during the first, ***second, third, and fourth*** year of the open-label extension study.

REVISION: PVR assessments will be performed at visits 8, 11 and 14.

RATIONALE: To extend the urinary safety assessments after the first year (i.e., at the end of each subsequent year) of the study.

SECTION: **10.3.6 AUA Symptom Index**

*Added (see **bold** text)...*

An AUA Symptom Index to assess urinary voiding function will be performed at Visits 1, 2, 5, ***8, 11, and 14*** during the first, ***second, third, and fourth*** year of the open-label extension study.

REVISION: AUA assessments will be performed at visits 8, 11 and 14.

RATIONALE: To extend the urinary safety assessment after the first year (i.e., at the end of each subsequent year) of the study.

SECTION: **10.15.3 Visit 8 (Month 24)**

*Added (See **bold** text)...*

Patients will return for Study Visit 8 (Month 24). At this visit, the following evaluations will be performed:

- Seizure Diary (collection / review of current diary and dispensation of new diary)
- Complete Physical and Neurological Exam
- Vital Signs (BP, HR, and Temperature) and Body Weight
- ***AUA Symptom Index***
- ***PVR Bladder Ultrasound***
- Clinical Laboratory Tests (Blood Chemistries, Hematology, Urinalysis including microscopy)
- Serum Pregnancy Test
- 12-lead ECG
- Adverse Events
- Concomitant Medication
- QOLIE-31-P Questionnaire (completed by patient)
- Open-Label Study Medication (collect returned medication and dispense new medication)

REVISION: AUA and PVR assessments will be performed at visit 8.

RATIONALE: To extend the urinary safety assessments after the first year of the study.

SECTION: **10.15.6 Visit 11 (Month 36)**

*Added…(see **bold** text)*

Patients will return for Study Visit 11 (Month 36). At this visit, the following evaluations will be performed:

- Seizure Diary (collection / review of current diary and dispensation of new diary)
- Complete Physical and Neurological Exam
- Vital Signs (BP, HR, and Temperature) and Body Weight
- ***AUA Symptom Index***
- ***PVR Bladder Ultrasound***
- Clinical Laboratory Tests (Blood Chemistries, Hematology, Urinalysis including microscopy)
- Serum Pregnancy Test
- 12-lead ECG
- Adverse Events
- Concomitant Medication
- QOLIE-31-P Questionnaire (completed by patient)
- Open-Label Study Medication (collect returned medication and dispense new medication)

REVISION: AUA and PVR assessments will be performed at visit 11.

RATIONALE: To extend the urinary safety assessments after the first year of the study.

SECTION: *Added the following sections…*

10.15.7 Visit 12 (Month 40)

Patients will return for Study Visit 12 (Month 40). At this visit, the following evaluations will be performed:

- Seizure Diary (collection / review of current diary and dispensation of new diary)
- Brief Neurological Exam
- Vital Signs (BP, HR, and Temperature) and Body Weight
- Clinical Laboratory Tests (Blood Chemistries, Hematology, Urinalysis including microscopy)
- Adverse Events
- Concomitant Medication
- Open-Label Study Medication (Collect returned medication and dispense new medication)

10.15.8 Visit 13 (Month 44)

Patients will return for Study Visit 13 (Month 44). At this visit, the following evaluations will be performed:

- Seizure Diary (collection / review of current diary and dispensation of new diary)
- Brief Neurological Exam
- Vital Signs (BP, HR, and Temperature) and Body Weight
- Clinical Laboratory Tests (Blood Chemistries, Hematology, Urinalysis including microscopy)
- Adverse Events
- Concomitant Medication
- Open-Label Study Medication (Collect returned medication and dispense new medication)

10.15.9 Visit 14 (Month 48)

Patients will return for Study Visit 14 (Month 48). At this visit, the following evaluations will be performed:

- Seizure Diary (collection / review of current diary and dispensation of new diary)
- Complete Physical and Neurological Exam
- Vital Signs (BP, HR, and Temperature) and Body Weight
- AUA Symptom Index
- PVR Bladder Ultrasound
- Clinical Laboratory Tests (Blood Chemistries, Hematology, Urinalysis including microscopy)
- Serum Pregnancy Test
- 12-lead ECG
- Adverse Events
- Concomitant Medication
- QOLIE-31-P Questionnaire (completed by patient)

- Open-Label Study Medication (collect returned medication and dispense new medication)

REVISION: Added fourth year visits and procedures.

RATIONALE: This will allow patients, who enrolled early during the trial, to remain in the open label extension study until the study drug, retigabine, is approved and commercially available, or until the program is discontinued.

SECTION: **10.16 Tapering**

*Added (see **bold** text)*

During the first year, these patients should then return for a final visit to complete all assessments and evaluations scheduled for Study Visit 5. During the second year, these patients should then return for a final visit to complete all assessments and evaluations scheduled for Study Visit 8. During the third year, these patients should then return for a final visit to complete all assessments and evaluations scheduled for Study Visit 11. ***During the fourth year, these patients should then return for a final visit to complete all assessments and evaluations scheduled for Study Visit 14*** (Refer to Study Flow Chart in Appendix A).

REVISION: Added a fourth year visit for this procedure.

RATIONALE: This will allow patients, who enrolled early during the trial, to remain in the open label extension study until the study drug, retigabine, is approved and commercially available, or until the program is discontinued.

SECTION: **10.20 Early Termination**

*Added (see **bold** text)*

Patients who discontinue early during the first year of the open-label extension study will complete all assessments and evaluations scheduled for Study Visit 5. Patients who discontinue early during the second year of the open-label extension study will complete all assessments and evaluations scheduled for Study Visit 8. Patients who discontinue early during the third year of the open-label extension study will complete all assessments and evaluations scheduled for Study Visit 11 ***and complete all assessments and evaluations scheduled for Visit 14 if patient discontinued early during the fourth year of the open-label extension study*** (Refer to Study Flow Chart in Appendix A).

REVISION: Added a fourth year visit for this procedure.

RATIONALE: This will allow patients, who enrolled early during the trial, to remain in the open label extension study until the study drug, retigabine, is approved and commercially available, or until the program is discontinued.

SECTION: **Appendix A. Study Flowchart (REVISED)**

REVISION:
a. Added AUA and PVR assessments at visits 8 and 11.
b. Added fourth year visits (Visits 12, 13 and 14) and procedures.

RATIONALE:
a. To extend the urinary safety assessments after the first year of the study.
b. This will allow patients, who enrolled early during the trial, to remain in the open label extension study until the study drug, retigabine, is approved and commercially available, or until the program is discontinued.

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5. LIST OF ABBREVIATIONS

AE	=	Adverse event
AED	=	Antiepileptic drug
ALT	=	Alanine aminotransferase
ANCOVA	=	Analysis of covariance
ANOVA	=	Analysis of variance
APD	=	Action potential duration
AST	=	Aspartate aminotransferase
AUA	=	American Urological Association
AUC	=	Area under the curve
β-HCG	=	Beta human chorionic gonadotropin
BID	=	Twice a day
BMI	=	Body mass index
BP	=	Blood pressure
BUN	=	Blood urea nitrogen
CFR	=	Code of Federal Regulations
CGI	=	Clinical global impressions
CI	=	Confidence interval
C_{max}	=	Observed maximum plasma concentration
C_{min}	=	Observed minimum plasma concentration
CNS	=	Central nervous system
CPMP	=	Committee for Proprietary Medicinal Products
CRA	=	Clinical research associate
CRF	=	Case report form
CSR	=	Clinical study report
CT	=	Computerized tomography
CV	=	Curriculum vitae
CV%	=	Coefficient of variation
D-20443	=	Dihydrochloride salt of retigabine
ECG	=	Electrocardiogram
EDTA	=	Ethylenediaminetetraacetic acid
EEG	=	Electroencephalogram
EMEA	=	European Agency for the Evaluation of Medicinal Products
FDA	=	Food and Drug Administration
GABA	=	Gamma aminobutyric acid
GCP	=	Good Clinical Practice
hERG	=	Human ether-a-go-go related gene

HPF	=	High power field
HR	=	Heart rate
ICF	=	Informed consent form
ICH	=	International Conference on Harmonization
IEC	=	Independent Ethics Committee
ILAE	=	International League Against Epilepsy
IND	=	Investigational New Drug
IRB	=	Institutional Review Board
ISE	=	Integrated Summary of Efficacy
ISS	=	Integrated Summary of Safety
ITT	=	Intent to treat
i.v.	=	Intravenous
IVRS	=	Interactive Voice Response System
LFT	=	Liver function test
MAOI	=	Monamine oxidase inhibitor
MedDRA	=	Medical Dictionary for Regulatory Activities
MRI	=	Magnetic resonance imaging
msec	=	Milliseconds
MTD	=	Maximum tolerated dose
N	=	Number of patients
NAT	=	N-acetyl transferase
pH	=	Hydrogen Ion Concentration
PK	=	Pharmacokinetics
PGI	=	Patient global impressions
p.o.	=	Oral
PP	=	Per protocol
PVR	=	Post-void residual (bladder ultrasound)
QD	=	Once a day
QoL	=	Quality of Life
QOLIE-31-P	=	Quality of Life in Epilepsy-Problems Questionnaire
QTc	=	QT correction
QTcB	=	Bazett's QT correction
QTcF	=	Fridericia's QT correction
QTcI	=	Individual patient's QT correction
RBC	=	Red blood cell
REB	=	Research Ethics Board
SAE	=	Serious adverse event
SAP	=	Statistical Analysis Plan
SD	=	Standard deviation

SEM	=	Standard error of the mean
SUDEP	=	Sudden Unexplained Death in Epilepsy
$t_{1/2}$	=	Half life
TdP	=	Torsade des Pointes
TEAE	=	Treatment-emergent adverse event
TID	=	Three times a day
UDPGT	=	UDP-glucuronosyltransferase
UDS	=	unscheduled DNA synthesis
UGT	=	uridine diphosphate-glucuronosyltransferase
ULN	=	Upper limit of normal
URI	=	Upper respiratory infection
UTI	=	Urinary tract infection
Valeant	=	Valeant Pharmaceuticals, North America
VNS	=	Vagal nerve stimulator
WBC	=	White blood cell
WHO	=	World Health Organization

6. STUDY SYNOPSIS

TITLE:	A multicenter, open-label, long-term, safety, tolerability and efficacy study of retigabine in adult epilepsy patients with partial-onset seizures (Extension of Study VRX-RET-E22-302)
PHASE:	3
OBJECTIVES:	1. Primary: To evaluate the safety and tolerability of long-term therapy with retigabine administered as adjunctive therapy in adult epilepsy patients with partial-onset seizures, who completed the double-blind Study VRX-RET-E22-302. 2. Secondary: To evaluate efficacy of long-term treatment with retigabine and patient quality of life, evaluated through the QOLIE-31-P questionnaire.
STUDY DESIGN:	This is an open-label extension study of the placebo-controlled, double-blind Study VRX-RET-E22-302. Patients will be treated with 600-1200 mg/day of retigabine as an adjunct therapy to their current antiepileptic medications (AEDs) or vagal nerve stimulation as established in Study VRX-RET-E22-302. Treatment will be continued until retigabine is approved and commercially available, or until the program is discontinued, followed by a 3-week tapering period and a 30 day post study period for collection of Adverse Events (AEs).
SAMPLE SIZE:	All patients who complete Study VRX-RET-E22-302 are qualified to participate (up to approximately 510 patients).
NUMBER OF SITES:	This is a multicenter study involving approximately 55-60 study sites in the Western, Central, and Eastern Europe, Australia, Israel, South Africa and the United States.
TREATMENT GROUPS:	All patients will be treated with 600-1200 mg/day of retigabine as an adjunct therapy to their current antiepileptic medications (AEDs) or vagal nerve stimulation.
TREATMENT DURATION:	This study will allow the patients who complete Study VRX-RET-E22-302 to continue with retigabine until the drug is approved and commercially available, or until the program is discontinued.
FORMULATION:	Retigabine will be supplied by Valeant Pharmaceuticals, Noth America in bottles containing tablets in relevant strengths: 50 mg, 100 mg, or 300 mg.

KEY INCLUSION CRITERIA:	1. Patient has successfully completed the Maintenance and Transition phases of Study VRX-RET-E22-302 for the treatment of partial-onset seizures 2. Patient is expected to benefit from participation in the study in the opinion of the Investigator. 3. Women of childbearing potential and fertile males have to agree to use a medically acceptable method of birth control. Females must have a negative urine pregnancy test at Visit 0, which will be confirmed by the serum β-HCG pregnancy test at the last visit (Visit 11) of the Transition phase of Study VRX-RET-E22-302. A woman of childbearing potential is defined as a female who is biologically capable of becoming pregnant. A medically acceptable method of birth control includes an intrauterine device in place for at least 3 months, surgical sterilization (e.g. tubal ligation), or adequate barrier methods (e.g., diaphragm and foam). An oral contraceptive alone is not considered adequate for the purpose of this study. 4. In the opinion of the Investigator, patient is able to understand verbal and written instructions and will adhere to all study schedules and requirements. 5. Patient or legal guardian (if applicable) is informed, given ample time and opportunity to read and/or understand about his/her participation in the study, and has signed and dated the written informed consent form.
KEY EXCLUSION CRITERIA:	1. Patient meets any of the withdrawal criteria in the previous VRX-RET-E22-302 study or is experiencing an ongoing serious adverse event. 2. Patient is receiving any investigational drug or using any experimental device in addition to Retigabine for treatment of epilepsy or any other medical condition. 3. Patient has any other condition that would prevent compliance with the study procedures or proper reporting of AEs. 4. Female patient who has a positive pregnancy test at any time during the study.

EVALUATION CRITERIA:	• Efficacy: Patients will keep a seizure diary throughout the study. The anticonvulsant efficacy of retigabine will be evaluated by comparison of baseline seizure frequency (obtained during the 8-week baseline period of Study VRX-RET-E22-302) with seizure frequency obtained during retigabine therapy in this study. The primary efficacy variable will be the percentage change in the monthly seizure rate from the baseline phase to open-label treatment. The proportion of responders (patients experiencing ≥ 50% reduction in seizure frequency) from baseline to the open-label treatment phase will also be evaluated. • Safety: Safety will be assessed by measurements of vital signs, weight, clinical laboratory evaluations (blood chemistry, hematology, and urinalysis), 12-lead ECGs, physical and neurological examinations, and evaluations of adverse events. Patients will additionally be assessed using the American Urological Association Symptom Index to assess the urinary voiding function.
STATISTICAL ANALYSIS:	The safety population will include all patients who successfully complete the Transition phase of Study VRX-RET-E22-302 and were included in this long-term study. The Transition phase is the phase of Study VRX-RET-E22-302 during which patients were adjusted to a 300 mg TID dose of retigabine. No other population for analysis is defined for this long-term extension study. **Assessment of Efficacy:** "Monthly total partial seizure" as well as "monthly total seizure" rates will be calculated for the entire open-label part of Study VRX-RET-E22-304 and described statistically. Baseline monthly total partial seizure rate from Study VRX-RET-E22-302 will be used for the calculation of difference and % change in the open-label study. The % change will be classified into <0, [0, 25), [25, 50), [50, 75), [75, 100] with a description of the frequencies. The responder rate (defined as a reduction in seizure frequency ≥50%) is the sum of the upper two classes.

STATISTICAL ANALYSIS (cont):	**Assessment of Efficacy (cont):** The number of seizure free days, in percent to the individual duration of the open-label treatment, will be calculated and described statistically. In addition, frequencies for this percentage will be classified into [0, 25), [25, 50), [50, 75), [75, 95), [95,100), =100. The most upper class represents completely seizure free patients, the next class almost seizure free patients. Additional details will be provided in the Statistical Analysis Plan (SAP). **Assessment of Safety:** All adverse events will be encoded according to MedDRA 8.0. Treatment emergent adverse events (TEAE) will be analyzed, i.e. all adverse events starting or worsening between the start of the long-term open-label study up to 30 days after end of taper-off study drug at the completion of the open-label study. Incidences on preferred term and body system basis will be calculated for all TEAEs. In addition, all serious adverse events (SAEs) and all AEs leading to premature discontinuation will be presented as separate listings. A prospective analysis will be conducted in order to compare the results of this study to Study VRX-RET-E22-302. TEAE from both studies (double-blind and open-label extension) will be combined, i.e. each patient will be counted just once (with patient's respective TEAE). Other safety evaluations, such as vital signs, laboratory variables, ECG variables, AUA symptom index will be analyzed descriptively. Additional details will be provided in the Statistical Analysis Plan (SAP).

7. INTRODUCTION

7.1. Background

Epilepsy is among the most common neurological disorders, affecting approximately 50 million people worldwide. Classical antiepileptic drugs (AEDs) currently provide satisfactory seizure control in approximately 70% of patients; however, the remaining 30% of epilepsy patients are refractory to treatment. The partial onset seizure is the most common type of seizure that is uncontrolled in adult patients. The introduction of new AEDs (e.g., vigabatrin, lamotrigine, gabapentin, topiramate, levetiracetam, oxcarbazepine, zonisamide, and felbamate) during the last decade has increased therapeutic possibilities. However, data from recent clinical trials demonstrate that none of the newer AEDs provides adequate seizure control in all patients. The treatment of patients that do not respond to current AEDs remains a problem and motivates the continued search for compounds with high antiepileptic potential and low rates of side effects.

Retigabine (GKE-841 or D-23129), N-[2-amino-4(4-fluorobenzylamino)-phenyl] carbamic acid ethyl ester, is a new chemical entity discovered by ASTA Medica, Germany, and was acquired by Valeant Pharmaceuticals, North America (Valeant) for development as an AED for the treatment of partial onset seizures. It is a deaza analog of flupirtine, currently marketed in some regions as a centrally acting analgesic with ancillary muscle relaxing properties.

Two Phase 3 studies (VRX-RET-E22-301 and VRX-RET-E22-302) to compare the efficacy and safety of Retigabine (600 mg/day, 900 mg/day, or 1200 mg/day) to placebo as an adjunctive therapy in refractory patients with partial-onset seizures are currently being conducted. These studies are randomized, double-blind, placebo-controlled, multi-center, parallel-group trials enrolling a total of approximately 790 patients, globally. Because of the serious nature of epilepsy, the retigabine clinical program had foreseen that all patients who enter and complete a Phase 3 study with retigabine will be given the opportunity to continue treatment, if they consent and if the Principal Investigator feels they can benefit from continued retigabine treatment. Hence, an open-label extension protocol was designed for each double-blind study.

This study is the open-label extension of the Phase 3 Study VRX-RET-E22-302. VRX-RET-E22-302 is a randomized, double-blind, placebo-controlled, parallel-group, multicenter, study of 900 mg/day and 600 mg/day retigabine versus placebo. During the 4-week titration phase patients are titrated to the target dose. 510 patients are expected to be randomized to treatment. A 12-week maintenance phase follows. All patients who wish to enter the open-label extension protocol will enter a 4-week transition phase in

which their dose will be titrated to 300 mg TID in order to maintain the blind to the maximum extent. Thereafter, the patients could enter this extension study (Study VRX-RET-E22-304). Patients who do not wish to enter the open-label extension protocol will have their dose tapered over a 3-week period.

7.2. Pharmacology

Retigabine is a novel antiepileptic compound with a broad spectrum of activity and potent anticonvulsant properties.[1,2,3,4] Retigabine opens specific potassium channels called M channels linked to the KCNQ2/3 and KCNQ3/5 heteromultimeres, which are involved in the control of the excitability of neuronal cells.[5,6,7,8,9] Mutations in these channels were understood to be linked to benign neonatal familial convulsions.[10] This fact strongly supports the experimental evidence that M-channel activation may be a unique and powerful cellular target principle for the treatment of epilepsy. Retigabine also has a concentration-dependent ancillary mode of action by increasing gamma aminobutyric acid (GABA)-evoked currents. These effects, however, were seen at concentrations of 10 µmol/L, whereas the potassium channel-opening effects occur at concentrations as low as 0.1 µmol/L.[11,12]

Results from preclinical studies revealed that retigabine is effective in a broad range of animal models of epileptic seizures. Amygdala kindling is considered the most predictive animal model for human complex partial seizures.[13] In kindled rats, intraperitoneal or oral doses of retigabine as low as 0.01 mg/kg were effective in increasing the threshold for induction.[14] At a higher dose of 5 mg/kg retigabine also reduced seizure severity, seizure duration, and post-discharge duration in fully kindled rats.[14] A clear separation between antiepileptic and neurotoxic effects is evident in these preclinical models. In addition, preclinical testing has not revealed any tolerance, dependence, or withdrawal liabilities for retigabine.[15]

Retigabine is rapidly absorbed following p.o. (oral) administration with peak plasma concentrations being achieved 1-2 hours after dosing in mice and rats.[16,17] The absolute bioavailability ranged from 44% to 70%.[17] Retigabine is extensively distributed and rapidly eliminated from all tissues in rats over a 48- to 72-hour period after dosing.[18,19] Retigabine is primarily metabolized by acetylation, glucuronidation, and oxidation mechanisms in rats and by glucuronidation in dogs. The active N-acetyl metabolite of retigabine has a pharmacological profile similar to retigabine but is 20 times less potent.[20] The major route of excretion in rats and dogs is in feces, with some compound being excreted in urine.[21,22,23] In humans, retigabine is mainly metabolized by N-glucuronidation and N-acetylation, and is not metabolized by cytochrome P450 enzymes.[20] Retigabine has low protein binding in all species, including humans.[20] Both in vivo and in vitro studies suggest that retigabine is unlikely to have any important drug-drug interactions with commonly used drugs.[24,25,26,27]

7.3. Preclinical Safety Studies

Retigabine caused motor impairment in rodents in the rotarod test, but the doses necessary were 12 to 13 times higher than those active in models of epilepsy.[28] Neither retigabine nor its N-acetyl metabolite prolonged action potential duration (APD) in cat cardiac myocytes and dog Purkinje fibers, and in fact resulted in slight shortening of APD in these test systems.[29] At concentrations 17-20 times higher than those achieved at therapeutic doses in man, retigabine caused a slight prolongation in QT interval in the isolated guinea pig heart, as well as a slight reduction in K+ current through human ether-a-go-go related gene (hERG) channels.[30] However, retigabine did not affect ECG parameters in anesthetized dogs or conscious unrestrained dogs given daily doses for 7 days.[31] Retigabine may inhibit bladder contractions and micturition in rodents due to its ability to hyperpolarize and stabilize urinary bladder myocytes through activation of K+ channels.[32]

In acute and chronic toxicity studies in rats, CNS related clinical signs including hyperkinesia, hypokinesia, disturbed coordination, stilted gait, tremor and convulsions were observed.[33] In repeat dose toxicity studies in rodents, slight hepatocellular and thyroid follicular hypertrophy were observed and were considered to be adaptive.[34,35] In repeat-dose studies in dogs but not rodents, self-limiting hepatocellular degeneration was observed in regions adjacent to the gallbladder.[36,37] In rodents but not dogs, distended urinary bladder or urinary bladder ectasia was noted with occasional secondary inflammation and ulceration of bladder wall.[34,35,36,37]

No retigabine-related effects on reproductive function were observed in male or female rats in a fertility and general reproductive performance study. No teratogenic effects of retigabine were observed in rats or rabbits.[38,39] In a perinatal and postnatal toxicity study in rats, the administration of retigabine to mated females did not have significant effect on the development of the offspring, but at the highest dose level growth was slowed, early mortality increased, and auditory reflex development was retarded in relation to the delay in growth.[40] In juvenile rats, retigabine reduced food consumption at the maximum tolerated dose but did not affect growth, reflex development, motor activity, learning, memory, clinical pathology parameters, or reproductive performance.[41]

In genetic toxicity studies, the retigabine active substance, used to manufacture finished product, tested negative for mutagenicity in the AMES test. Some exceptions could be explained as false weakly positive results due to alterations of the Salmonella tester strains.[42,43] Retigabine was negative in 2 independent mammalian cell forward gene mutation assays in presence and absence of S-9.[42] Retigabine did not induce chromosome aberrations in cultured human lymphocytes following pulse treatment for 3 or 4 hours in the absence and presence of S-9.[43] Following continued treatment for 20 or 22 hours in this test system, retigabine induced chromosome aberrations, but only in

the absence of S-9. Retigabine tested negative in genetic toxicity studies relying for metabolism on unbroken cells where the required cofactors are present at their natural concentrations as in the in vivo micronucleus test in mice and in the in vivo / in vitro unscheduled DNA synthesis (UDS) assay in hepatocytes in rats.[44, 45, 46, 47, 48]

7.4. Clinical Studies

In open-label Phase 2 studies in patients with epilepsy, the majority of patients tolerated daily doses of up to 1200 mg administered orally in two or three divided doses. The most commonly observed treatment-emergent adverse effects were in the MedDRA system organ class of Nervous System Disorders. In a double-blind parallel group study comparing different titration rates (Study 3065A1-214), it has been shown that when the starting dose of retigabine is 300 mg/day (100 mg TID), the daily dose can be titrated to 1200 mg over a 6-week period with only 13% of patients discontinuing due to adverse events.

In a randomized, double-blind, placebo-controlled, parallel group study comprising 397 patients with epilepsy (Study 3065A1-205)[52], daily doses of 900 mg and 1200 mg (administered orally in three divided doses) caused a significant reduction in total partial seizure frequency compared with placebo. While a dose of 600 mg/day resulted in greater reduction of seizure frequency than placebo, the difference was not statistically significant. The majority of patients tolerated their treatment as prescribed, with a minority discontinuing from the study prematurely. The discontinuation rate due to adverse events in 1200 mg dose group was about 2.5 times that in placebo group. This is consistent with tolerability of other AEDs. The commonly observed adverse events were in the MedDRA system organ class of Nervous System Disorder and many of these were dose related and were more frequent with retigabine compared with placebo. There were few clinically important changes in vital signs, laboratory, or ECG parameters, or physical or neurological examinations.

Patients participating in Study 3065A1-205 were eligible for an open-label extension phase (Study 3065A1-212) if they experienced improvement in seizure control, did not experience adverse events that would prevent inclusion, and did not violate the double-blind study protocol. Patients who completed the interim (transition) phase of the double-blind portion of the study started with 300 mg TID, which could be increased weekly in increments of 150 mg/day, up to a maximum of 1200 mg daily. Concomitant AEDs could be adjusted to achieve the best efficacy/safety ratio. Patients who wished to discontinue retigabine during this open-label study entered a 3-week tapering period and a 10-day post-study follow-up period. Seizure frequency was recorded daily in a diary maintained by each patient. The efficacy of retigabine was evaluated by comparison of baseline seizure frequency (determined upon entry into the double-blind phase) with

seizure frequency during retigabine therapy in the extension study; this was calculated as a percentage change in total partial seizure frequency.

Of the 279 patients who completed Study 205, 222 enrolled in the open-label extension. The majority of these patients were white (213 or 95.9%) with a median age of 36 years. A total of 126 patients were male (56.8%) and 96 (43.2%) were female. The median duration of epilepsy at study entry was 20.7 years. Of these 222 patients, 18 (8%) discontinued within the first 3 months and 41 (18%) discontinued within 6 months. The most common cause for discontinuation was lack of efficacy. The most common daily dosage of retigabine was 900 mg (105 patients; 47.3%) and only a minority of the patients titrated the dosage to 1200 mg (53 patients; 23.9%). The median treatment duration during open-label extension phase was 358 days.

The median decrease in monthly total partial seizure frequency from baseline was 48.3%, which was similar to the results with the two highest retigabine dose groups (300 and 400 mg TID) in the randomized, double-blind phase. Patients assigned to the placebo group during the double-blind phase showed the largest seizure rate improvement during the extension phase. One hundred three patients (46.4%) showed a reduction in monthly total partial seizure frequency of 50%.

7.5. Safety and Tolerability

The safety and tolerability of various dosing regimens of retigabine were examined in healthy patients participating in human pharmacology studies and in patients with epilepsy in therapeutic trials.[53,54] A total of 404 healthy subjects participated in 18 human pharmacology studies. In a multiple dose-finding trial using fixed doses, regimens up to 200 mg twice a day (BID) were safe and well tolerated and the maximum tolerated dose was found to be 250 mg BID. However, after allowing for titration to the target dose, regimens up to 350 mg BID were tolerated without any dose-limiting adverse events (AEs). In general, central nervous system (CNS) AEs limited further dose increases.[55]

A total of 605 patients with epilepsy have been enrolled in clinical studies for retigabine. Retigabine was mostly administered as add-on therapy to various established background AEDs and to a minor extent as monotherapy by using various dose-titration regimens. The maximum tolerated dose (MTD) of retigabine when added to standard AEDs was 1200 mg/day. Retigabine was administered using BID and TID regimens. The most common AEs were CNS-related (e.g., somnolence, dizziness, confusion, speech disorder, vertigo, amnesia, thinking abnormal, tremor, incoordination, ataxia, nervousness, paresthesia, abnormal gait, diplopia, and abnormal vision) and appeared in a dose-dependent manner.[55] No AEs of retigabine on cardiac safety and in particular cardiac repolarization (QTc interval) were detected. While the AE pattern from human pharmacology and clinical trials is similar, it is interesting to note that MTDs in healthy

subjects appear to be different from those achieved in patients with epilepsy, despite the concomitant medication with standard AEDs in the latter group.

A complete description of preclinical pharmacology, toxicology, PK studies, and clinical safety and efficacy studies for retigabine can be found in the Investigator's Brochure.[56]

7.6. Pharmacokinetics

7.6.1. Absorption

In clinical trials, retigabine was rapidly absorbed within 2 hours after oral administration to healthy patients.[49] The N-acetylated metabolite of retigabine was also rapidly formed, following the parent compound by approximately 2 hours. Both retigabine and the N-acetylated metabolite of retigabine were eliminated with a half-life ($t_{1/2}$) of about 8 hours. At steady state, mean observed maximum concentration (C_{max}) and area under the curve (AUC) values of the N-acetylated metabolite were within 20% of the corresponding mean values of retigabine. The trough plasma concentrations of retigabine in the afternoon or evening were significantly lower than those in the morning, possibly related to slower metabolism during sleep. The pharmacokinetics (PK) of retigabine and the N-acetylated metabolite of retigabine were linearly dose proportional for doses from 100 to 350 mg.

7.6.2. Metabolism

Investigations of metabolism in humans indicate that retigabine is mainly metabolized by N-glucuronidation and N-acetylation, and is not metabolized by cytochrome P450 enzymes.[20] In vitro studies have shown that the glucuronidation is performed by several uridine diphosphate glucuronyltransferase (UGT) isozymes.[50] The PK of retigabine and the N-acetylated metabolite of retigabine in patients with epilepsy are comparable with those in healthy subjects.[51]

7.6.3. Excretion

The major route of excretion in rats and dogs is in feces, with some compound being excreted in urine.[21,22,23] In humans, retigabine is mainly metabolized by N-glucuronidation and N-acetylation, and is not metabolized by cytochrome P450 enzymes.[20] Retigabine has low protein binding in all species, including humans.[20] Both in vivo and in vitro studies suggest that retigabine is unlikely to have any important drug-drug interactions with commonly used drugs.[24,25,26,27]

8. STUDY OBJECTIVES

- Primary: To evaluate the safety and tolerability of long-term therapy with retigabine administered as adjunctive therapy in adult epilepsy patients with partial-onset seizures, who completed the double-blind Study VRX-RET-E22-302.

- Secondary: To evaluate efficacy of long-term treatment with retigabine and patient quality of life, evaluated through the QOLIE-31-P questionnaire.

9. STUDY DESIGN

This is an open-label extension study of the placebo controlled, double-blind Study VRX-RET-E22-302. Patients will be treated with 600-1200 mg/day of retigabine as an adjunct therapy to their current antiepileptic medications (AEDs) or vagal nerve stimulation as established in Study VRX-RET-E22-302. Following completion of the Transition Phase of the double-blind study (Study VRX-RET-E22-302), treatment in this open-label extension study will be continued until retigabine is approved and commercially available, or until the program is discontinued, followed by a 3-week tapering period and a 30 day post-study period for collection of adverse events.

9.1. Type of Study

Phase 3 open-label extension study for therapeutic use.

9.2. Study Population

Patients entering this study had to have participated in Study VRX-RET-E22-302, i.e. they had met eligibility criteria of that study and completed the double-blind phase.

9.3. Number of Study Sites

This is a multi-center open-label study involving approximately 55-60 study sites in Western, Central and Eastern Europe, Australia, Israel, South Africa and the United States.

9.4. Treatment Duration

Following completion of the Transition Phase of the double-blind study (Study VRX-RET-E22-302), treatment in this open-label extension study will be continued until retigabine is approved and commercially available, or until the program is discontinued, followed by a 3-week tapering period and a 30 day post-study period for collection of adverse events.

9.5. Patient Inclusion Criteria

For inclusion in the study, a patient must meet and comply with the following criteria:

1. Patient has successfully completed the Maintenance and Transition phases of Study VRX-RET-E22-302 for the treatment of partial-onset seizures
2. Patient is expected to benefit from participation in the study in the opinion of the Investigator.

3. Women of childbearing potential and fertile males have to agree to use a medically acceptable method of birth control and females shall have a negative urine pregnancy test at Visit 0, which will be confirmed by the serum β-HCG pregnancy test at the last visit (Visit 11) of the Transition phase of Study VRX-RET-E22-302. A woman of childbearing potential is defined as a female who is biologically capable of becoming pregnant. A medically acceptable method of birth control includes an intrauterine device in place for at least 3 months, surgical sterilization (e.g. tubal ligation), or adequate barrier methods (e.g., diaphragm and foam). An oral contraceptive alone is not considered adequate for the purpose of this study.
4. In the opinion of the Investigator, patient is able to understand verbal and written instructions and will adhere to all study schedules and requirements.
5. Patient or legal guardian (if applicable) is informed, given ample time and opportunity to read and/or understand about his/her participation in the study, and has signed and dated the written informed consent form.

9.6. Patient Exclusion Criteria

A patient is ineligible for entering Study VRX-RET-E22-304 if any of the following exclusion criteria are met:

1. Patient meets any of the withdrawal criteria in the previous VRX-RET-E22-302 study or is experiencing an ongoing serious adverse event.
2. Patient is receiving any investigational drug or using any experimental device in addition to Retigabine for treatment of epilepsy or any other medical condition.
3. Patient has any other condition that would prevent compliance with the study procedures or proper reporting of AEs.
4. Female patient who has a positive pregnancy test at any time during the study.

9.7. Study Medication

Study medication will be supplied by Valeant Pharmaceuticals, North America, as film-coated tablets containing 50 mg, 100 mg, or 300 mg of retigabine per tablet. Tablets will be packaged in induction sealed bottles. A sufficient supply of study medication will be provided to each site for completion of the trial, based on the number of patients enrolled, study visit schedule, and the daily doses of patients. Specific dosage instructions will be provided separately to the patient. All study medication will be dispensed by the pharmacy or an appropriately qualified member of the study staff assigned by the Principal Investigator to this task.

Patients will take the established background AEDs from their own prescriptions, and their use will be recorded.

9.7.1. Dosage Schedule and Mode of Administration

Patients who completed the Transition phase of Study VRX-RET-E22-302 will start with 300 mg three times a day (300 mg TID). Patients who were not able to tolerate the final dose adjustment (750 mg/day) during the last week of the Transition phase of Study VRX-RET-E22-302 will start with 200 mg three times a day (200 mg TID).

If, in the opinion of the Investigator, the patient was not receiving the maximum effective dose, the dose could be increased in weekly intervals of 150 mg/day, up to a maximum of 1200 mg daily (i.e. 400 mg TID). If adverse events considered to be secondary to retigabine occur, the total daily dose could be reduced by 150 mg/day every week, at Investigator discretion, as long as the dose is within 600-1200 mg/day.

At the investigator's discretion, patients may also start with another dose regimen that can be either BID or TID, and is not required to be equally distributed throughout the day (e.g., if a patient experiences somnolence and the investigator decides to dose the patient higher in the evening) as long as the total daily dose is within 600 -1200 mg/day.

After the patient has entered open-label treatment, the Investigator may add new AEDs, as long as these are approved AEDs. In addition, the existing background AED therapy can be adjusted to achieve the best efficacy/safety ratio, as needed, per Investigator discretion. If necessary, in the Investigator's judgment, all background AEDs can be discontinued to achieve monotherapy with retigabine.

Patients who permanently discontinue open-label treatment will have their dose tapered by one-third every week.

Patients will be instructed on the administration procedures for study drug. Study medication will be administered orally with or without food. The 3 daily doses are to be administered with approximately an 8-hour interval between them (for example 7am, 3pm, 11pm). Patients will continue to take their established background AEDs from their own prescriptions.

9.7.2. Study Drug Storage

All study drug sent to the study centers must be stored under the conditions specified on the drug package label (15 – 30 °C / 59 – 86 °F) in a secure area accessible only to the Investigator and his/her designated staff. All study drugs should be stored and inventoried according to applicable government regulations and study procedures.

9.7.3. Study Drug Returns

Government regulations require that all investigational drug materials not used in clinical trials be returned before or at the completion of the study.

The Investigator will return the designated copies of the completed dispensing and inventory record.

9.7.4. Method of Assigning Study Medication to Patients

Study medication will be assigned to patients through a centralized Interactive Voice Response System (IVRS), as described in the IVRS user manual that will be provided to the sites. Sites will contact the IVRS to obtain the package number assignment(s) for patients at each scheduled study visit

Study personnel will select the study medication bottle(s) from their inventory that correspond to the package number(s) assigned by IVRS. Study personnel will complete the tear-off labels on the bottles, affix them to the Investigational Product Labels page found in the patient's paper source binder, and dispense the study medication (bottles) to the patient. At subsequent study visits, study personnel will follow the same procedures as described above, contacting the IVRS as instructed in the IVRS manual.

9.7.5. Discontinuation and Tapering of Study Medication

Patients who discontinue early from the open-label extension study will have their study medication tapered over a 3-week period, reducing their daily dose by one-third per week. After tapering has been completed, patients should return to the site immediately, and complete all assessments and evaluations scheduled for Visit 5, if patient discontinued early during the first year of the open-label extension study, complete all assessments and evaluations scheduled for Visit 8 if patient discontinued early during the second year of the open-label extension study, and complete all assessments and evaluations scheduled for Visit 11 if patient discontinued early during the third year of the open-label extension study, and complete all assessments and evaluations scheduled for Visit 14 if patient discontinued early during the fourth year of the open-label extension study (Refer to Study Flow Chart in Appendix A).

9.8. Assessment of Compliance

Patient compliance with the study drug dosing regimen will be assessed by counts of tablets remaining in the study medication bottles that are returned at each study visit. Compliance will be based on the medication the patient was scheduled to take for the days between study visits. In addition, information on the average total daily dose will be calculated, based on the number of tablets remaining or returned in each bottle.

Patients will be instructed to bring used and unused study medication bottles with them to each study visit for accountability purposes. Tablets from each bottle for each dose

strength (50 mg, 100 mg, 300 mg) will be counted and recorded to assess patient compliance and correct dosage taken. If a patient is deemed to be non-compliant with taking study medication, the patient should be counseled by the site. If the patient continues to be non-compliant, they should be withdrawn from the study.

Along with drug accountability logs, the CRF will capture the data which includes the prescribed dosage, dates of first dose and last dose, and the number of tablets returned from each bottle for each dose strength. The CRFs will also provide a classification in to poly- or monotherapy with retigabine.

9.9. Concomitant Therapy

9.9.1. Permitted Concomitant Medications

Patients will take the background AED as prescribed by their physician. If adverse events considered to be secondary to retigabine occur, the total daily dose could be reduced by 150 mg/day every week, at Investigator discretion, as long as the dose is within 600-1200 mg/day. The background AED therapy can be adjusted if a patient develops adverse events similar to the previously experienced reaction to that AED.

After patients enter the open-label extension study, the Investigator will be allowed to adjust background AEDs, as clinically indicated. As needed, the background AED therapy can be adjusted to achieve the best efficacy/safety ratio, per Investigator discretion. If necessary, in the Investigator judgment, all background AEDs can be discontinued to achieve monotherapy with retigabine. The dose and reason to use a concomitant medication shall be recorded in the CRFs.

9.9.2. Prohibited Medications

Use of felbamate and vigabatrin are prohibited. Concurrent use of any AEDs, or of any drug that could interfere with the absorption or metabolism of retigabine and background AED is also prohibited. Medications known to lower seizures (e.g. neuroleptics) and monoamine oxidase inhibitors (MAOIs) are not allowed.

9.10. Protocol Violations and Deviations

A deviation from the protocol is an unintended and/or unanticipated departure from the procedures and/or processes approved by the Sponsor and the IRB/IEC/REB and agreed to by the Investigator. Deviations usually have an impact on individual patients or a small group of patients. A protocol violation occurs when there is non-adherence to the protocol that results in a significant, additional risk to the patient, when the patient or Investigator has failed to adhere to critical protocol requirements (inclusion/exclusion criteria) and the patient was enrolled without prior Sponsor approval, or when there is non-adherence to FDA regulations and/or ICH GCP guidelines.

The Investigator or designee must document and explain any deviation or violation from the approved protocol. The Investigator may implement a deviation from, or a change of the protocol to eliminate an immediate hazard to study patients without prior IRB/IEC/REB approval. Immediately after the implemented deviation, violation or change to eliminate the immediate hazard to the study patient(s), the Investigator must submit a report explaining the reasons for the protocol deviation, violation or change to the Sponsor. If required, the regulatory authorities will be notified. The appropriate IRB/IEC/REB will be notified of specified, critical violations or violations that place patients at added, significant risk.

Protocol violations and deviations will be documented by the clinical monitor throughout the course of the monitoring visits. Investigators will be notified of violations and deviations and/or in writing by the monitor, and the Principal Investigator will be required to identify corrective action to eliminate future violations and deviations.

10. STUDY PROCEDURES

10.1. Study Flow Chart

As presented in the Study Flow Chart (see Appendix A), Study Visit 1 will have a window range of ±3 days. After Study Visit 1, all remaining study visits will have a window range of ±7 days around that visit day to accommodate individual schedules, as follows:

- Baseline for the open-label extension study corresponds to the assessments performed at the last visit of the Maintenance phase (Visit 9) of Study VRX-RET-E22-302 for all patients. The final, baseline eligibility assessment for the open-label extension study, including obtaining informed consent and dispensing open-label study medication will be performed at the last visit of the Transition phase (Visit 11) of Study VRX-RET-E22-302.
- Study Visit 1 (at Month 1 ±3 days)
- Study Visit 1a for Hematological Monitoring (at Month 2 ±7 days)
- Study Visit 2 (at Month 3 ±7 days)
- Study Visit 2a for Hematological Monitoring (at Month 4 ±7 days)
- Study Visit 3 (at Month 6 ±7 days)
- Study Visit 3a for Hematological Monitoring (at Month 8 ±7 days)
- Study Visit 4 (at Month 9 ±7 days)
- Study Visit 4a for Hematological Monitoring (at Month 10 ±7 days)

- Study Visit 5 (at Month 12 ±7 days).
- Study Visit 6 (at Month 16 ±7 days)
- Study Visit 7 (at Month 20 ±7 days).
- Study Visit 8 (at Month 24 ±7 days).
- Study Visit 9 (at Month 28 ±7 days).
- Study Visit 10 (at Month 32 ±7 days).
- Study Visit 11 (at Month 36 ±7 days).
- Study Visit 12 (at Month 40 ±7 days).
- Study Visit 13 (at Month 44 ±7 days).
- Study Visit 14 (at Month 48 ±7 days).

Each study month will be defined as 30 calendar days. If a patient visit occurs outside the visit window, the study clinical monitor (CRA) should be notified and the reason for the deviation noted. An attempt should be made to ensure that the patient returns for subsequent visits on schedule using the last visit of the Transition phase (Visit 11) of Study VRX-RET-E22-302, which corresponds to the final, baseline eligibility visit for the open-label extension study.

10.2. Efficacy Assessments

Patients will keep a seizure diary throughout the study. The anticonvulsant efficacy of retigabine will be evaluated by comparison of baseline seizure frequency (obtained during the 8-week baseline period of Study VRX-RET-E22-302) with seizure frequency obtained during retigabine therapy in this open-label extension study (VRX-RET-E22-304). The primary efficacy variable is the percentage change in the monthly seizure rate from the baseline phase to the open-label treatment phase. The proportion of responders (patients experiencing ≥ 50% reduction in seizure frequency) from baseline to the open-label treatment phase will also be evaluated.

10.3. Safety Assessments

Safety assessments will be evaluated, based on reports of AEs and results of vital signs (supine and standing blood pressure, pulse, and temperature), weight, clinical laboratory evaluations (blood chemistries, hematology and urinalysis including microscopy), a 12-lead ECG, and physical and neurological examinations. Post-void residual (PVR) bladder ultrasounds to assess urinary retention and the American Urological Association (AUA) Symptom Index to assess urinary voiding function will also be performed during the first, second, third and fourth year of the open-label extension study.

Clinical evaluations specific to hematology will be obtained on patients on a monthly basis for approximately 4 months and then every two months for the next 6 months. (See Appendix A for Study Flow Chart.)

10.3.1. Vital Sign Measurements and Weight

Complete vital sign measurements (including supine and standing blood pressure, heart rate, and temperature) will be obtained throughout the study at all visits. Evaluations of blood pressure and heart rate will be performed supine at each study visit, and again after the patient has been standing for approximately 2 minutes.

Weight [pounds (lb) or kilograms (kg)] will also be measured in ordinary indoor clothing (without shoes) and will be recorded at all study visits

Abnormal vital sign values that are deemed clinically significant by the Investigator will be reported as AEs in the study CRF.

10.3.2. Physical and Neurological Examinations

A complete physical and neurological examination will be performed annually at Visit 5, Visit 8, 11 and Visit 14. Brief neurological examinations will be performed at all other study visits, including visits 1, 2, 3, 4, 6, 7, 9, 10, 12 and 13.

10.3.3. Electrocardiograms

A 12-lead ECG will be performed at all study visits during the first year of the open-label extension study (Visits 1, 2, 3, 4, 5), and annually at Visits 8, 11 and 14. The ECG parameters that will be assessed are heart rate, PR interval, QRS interval, QT interval, and QTc interval. All ECG tracings will be sent to Quintiles ECG Services for central reading. Quintiles ECG Services will provide a central ECG analysis and transmit a feedback of preliminary results via facsimile to the investigation site within 24 hours. Trained technicians will read all ECGs manually, and any abnormal finding will then be over-read by board-certified cardiologists. QT intervals will be corrected using both Bazett's and Fridericia's formulas. For purposes of clinical study conduct, Bazett's QT correction will be used. For purposes of data analysis, Fridericia's QT correction will be considered as primary. Changes from baseline QTc interval will be monitored on an ongoing basis throughout this study.

Increases in Bazett's QTc interval of >60 msec from baseline or QTc interval of >500 msec anytime during the study should be confirmed on a repeat ECG. Any such occurrence shall result in notification of the Investigator and the study medical monitor for immediate review of the tracings and discussion with Valeant.

10.3.4. Laboratory Assessments

All clinical laboratory assessments will be performed by a central laboratory (Quintiles Central Laboratory Services), which will provide instructions and supplies to the study staff before study initiation. Results of the clinical laboratory assessments will be faxed back to the study site within 48 to 72 hours of sampling. Alert values will be reported to the Investigator via telephone. Approximately 7-mL sample of blood will be drawn for clinical chemistries and hematology assays. The laboratory assessments will include routine laboratory tests. The clinical laboratory evaluation will be performed at all study visits during the open-label extension study.

Because of the bladder toxicity observed in chronic toxicology studies in the rat and mouse, careful attention will be paid to plasma creatinine and blood urea nitrogen (BUN), microscopic findings on urinalysis, and any symptoms that might suggest incomplete bladder emptying (e.g., urinary tract infection, frequency, sensation of incomplete voiding, etc.). All patients will undergo urinalysis (including microscopy) at all study visits.

Any patient who has developed a clinically significant urinalysis abnormality will undergo further evaluation by an urologist (as clinically indicated) for any of the following:

- >5 red blood cells (RBC) per high power field (HPF) for males and postmenopausal females or >8 RBC/HPF for females
- >3 white blood cells(WBC) per high power field (HFP) for males and >12 WBC/HPF for females
- >1+ epithelial cells
- ≥1+ on all casts except Hyaline casts ≥2+
- >1+ blood for males and postmenopausal females
- ≥1+ trace protein [RBC; males and postmenopausal females] per high power field (HPF) or >5 white blood cells [WBC; must have 1 to few epithelial cells/HPF] per HPF, >occasional casts, >1+ blood [male and postmenopausal female patients] or >trace protein
- Have symptoms or AEs suggestive of possible hypotonicity of the bladder

The laboratory evaluations will include:

1. **Hematology:** hemoglobin, hematocrit, RBC count, WBC count with differential, and platelet count.

2. **Blood chemistries:** sodium, potassium, chloride, bicarbonate, glucose, cholesterol, creatinine, calcium, phosphorus, BUN, uric acid, total bilirubin, total protein, AST, ALT, and alkaline phosphatase levels.
3. **Pregnancy tests:**
   a. A urine pregnancy test will be performed at Visit 0 to immediately confirm non-pregnancy eligibility for female patients of child-bearing potential.
   b. A serum β-HCG pregnancy test for women of childbearing potential will be performed at Study Visit 5 and annually thereafter.
   c. A pregnancy test should be performed during the study whenever a woman's menstrual period is 5 days late.
4. **Routine urinalysis:** specific gravity, pH, protein/albumin, glucose/sugar, ketones/acetone, and hemoglobin/blood. In order to standardize measurements, Bayer multistix 8-SG or equivalent dipsticks will be used.
5. **Microscopic urinalysis:** RBC, WBC, casts, and crystals/cells.

All laboratory tests with values that become abnormal after drug administration will be repeated as clinically indicated until the values return to normal, or until the etiology has been determined and the condition considered stable. Abnormal laboratory test results that are considered to be clinically important by the Investigator will be reported as an AE in the CRF. A laboratory abnormality will not be considered an AE unless:

- Intervention is required.
- Changes in dose of retigabine are required (decrease, discontinued, interrupted).
- Other treatment/therapy is required.
- Associated with other diagnoses

Laboratory results will be reported to the Investigator who will review abnormal laboratory findings for clinical significance. The Investigator will note any laboratory test results of clinical concern, or values that were outside normal ranges and provide details of the relationship to study drug and the action taken. If a change in a laboratory value represents a medical condition, the medical condition will be listed in the AE record. If no correlation is possible, the direction of change (increase or decrease) rather than the actual value will be recorded.

Laboratory results specific to neutrophil counts will be flagged in the laboratory reports if the absolute neutrophil counts are $< 1.0 \times 10^3$. For all such cases, the investigator shall report these results in an expedited manner, whether or not they are considered a serious event.

Note: For all serious hematological events or infections, the investigator shall report these in an expedited fashion, whether they are considered unexpected or not.

10.3.5. Post-Void Residual (PVR) Bladder Ultrasound

A post-void residual (PVR) bladder ultrasound to assess urinary retention will be performed at Visits 1, 2, 5, 8, 11 and 14 during the first, second, third, and fourth year of the open-label extension study.

10.3.6. AUA Symptom Index

An AUA Symptom Index, a 7-item Likert-scored scale describing urinary bladder function, will be completed by the Investigator at Visits 1, 2, 5, 8, 11 and 14 during the first, second, third and fourth year of the open-label extension study, to assess the patient's urinary voiding function. The AUA Symptom Index is included in Appendix D of this protocol.

10.4. Quality of Life Assessments

The QOLIE-31-P (Version 2.0) will be utilized to assess quality of life. The QOLIE-31-P assessment must be completed by the patients. Patients who are cognitively impaired and cannot complete the QOLIE-31-P assessment may still participate in the study, by obtaining a waiver for QOLIE-31-P completion from the study medical monitor.

10.5. Baseline

Except for final study eligibility, informed consent and dispensation of open-label extension study medication, the Baseline assessments for the open-label extension study correspond to the assessments performed at the last visit of the Maintenance phase (Visit 9) of Study VRX-RET-E22-302 (See Study Flow Diagram - Appendix A). After completion of all study procedures on the last visit of the Transition phase (Visit 11) of Study VRX-RET-E22-302, patients will be allowed to enter this open-label extension study (VRX-RET-E22-304). All ongoing AEs and concomitant medications at the last visit of the Transition Phase (Visit 11) of Study VRX-RET-E22-302 will need to be transferred and captured on the appropriate open-label extension AE and Concomitant Medication CRF pages. The final study eligibility and informed consent for the open-label extension study should be performed at the last visit of the Transition phase (Visit 11) of Study VRX-RET-E22-302. A urine pregnancy test will be performed on female patients of child-bearing potential, to immediately confirm the non-pregnancy eligibility requirements tp enter the VRX-RET-E22-304 study. After confirmation of all final study eligibility requirements and obtaining proper informed consent, open-label study medication (sufficient supply of bottles at appropriate dose strengths = 50 mg, 100 mg, 300 mg) will be dispensed to patients, along with seizure diaries for completion until the next study visit (Visit 1 / Month 1).

10.6. Study Visit 1 (Month 1)

Patients will return for Study Visit 1 (Month 1). At this visit, the following evaluations will be performed:

- Seizure Diary (collection / review of current diary and dispensation of new diary)
- Brief Neurological Exam
- Vital Signs (BP, HR, and Temperature) and Body Weight
- Clinical Laboratory Tests (Blood Chemistries, Hematology, Urinalysis including microscopy)
- 12-lead ECG
- AUA Symptom Index
- PVR Bladder Ultrasound
- Adverse Events
- Concomitant Medication
- Open-Label Study Medication (collect returned medication and dispense new medication)

10.7. Study Visit 1a (Month 2)

Patients will return for Study Visit 1a (Month 2). At this visit, clinical laboratory tests, consisting of the following hematological evaluations (including a differential) will be performed:

- Hemoglobin
- Hematocrit
- RBC Count
- WBC Count
- Platelet count.

10.8. Study Visit 2 (Month 3)

Patients will return for Study Visit 2 (Month 3). At this visit, the following evaluations will be performed:

- Seizure Diary (collection / review of current diary and dispensation of new diary)
- Brief Neurological Exam

- Vital Signs (BP, HR, and Temperature) and Body Weight
- Clinical Laboratory Tests (Blood Chemistries, Hematology, Urinalysis including microscopy)
- 12-lead ECG
- AUA Symptom Index
- PVR Bladder Ultrasound
- Adverse Events
- Concomitant Medication
- QOLIE-31-P Questionnaire (completed by patient)
- Open-Label Study Medication (collect returned medication and dispense new medication)

10.9. Study Visit 2a (Month 4)

Patients will return for Study Visit 2a (Month 4). At this visit, clinical laboratory tests, consisting of the following hematological evaluations (including a differential) will be performed:

- Hemoglobin
- Hematocrit
- RBC Count
- WBC Count
- Platelet count.

10.10. Study Visit 3 (Month 6)

Patients will return for Study Visit 3 (Month 6). At this visit, the following evaluations will be performed:

- Seizure Diary (collection / review of current diary and dispensation of new diary)
- Brief Neurological Exam
- Vital Signs (BP, HR, and Temperature) and Body Weight
- Clinical Laboratory Tests (Blood Chemistries, Hematology, Urinalysis including microscopy)
- 12-lead ECG

- Adverse Events
- Concomitant Medication
- QOLIE-31-P Questionnaire (completed by patient)
- Open-Label Study Medication (collect returned medication and dispense new medication)

10.11. Study Visit 3a (Month 8)

Patients will return for Study Visit 3a (Month 8). At this visit, clinical laboratory tests, consisting of the following hematological evaluations (including a differential) will be performed:

- Hemoglobin
- Hematocrit
- RBC Count
- WBC Count
- Platelet count.

10.12. Study Visit 4 (Month 9)

Patients will return for Study Visit 4 (Month 9). At this visit, the following evaluations will be performed:

- Seizure Diary (collection / review of current diary and dispensation of new diary)
- Brief Neurological Exam
- Vital Signs (BP, HR, and Temperature) and Body Weight
- Clinical Laboratory Tests (Blood Chemistries, Hematology, Urinalysis including microscopy)
- 12-lead ECG
- Adverse Events
- Concomitant Medication
- QOLIE-31-P Questionnaire (completed by patient)
- Open-Label Study Medication (collect returned medication and dispense new medication)

10.13. Study Visit 4a (Month 10)

Patients will return for Study Visit 4a (Month 10). At this visit, clinical laboratory tests, consisting of the following hematological evaluations (including a differential), will be performed:

- Hemoglobin
- Hematocrit
- RBC Count
- WBC Count
- Platelet count.

10.14. Study Visit 5 (Month 12)

Patients will return for Study Visit 5 (Month 12). At this visit, the following evaluations will be performed:

- Seizure Diary (collection / review of current diary and dispensation of new diary)
- Complete Physical and Neurological Exam
- Vital Signs (BP, HR, and Temperature) and Body Weight
- Clinical Laboratory Tests (Blood Chemistries, Hematology, Urinalysis including microscopy)
- Serum Pregnancy Test
- 12-lead ECG
- AUA Symptom Index
- PVR Bladder Ultrasound
- Adverse Events
- Concomitant Medication
- QOLIE-31-P Questionnaire (completed by patient)
- Open-Label Study Medication (collect returned medication and dispense new medication)

10.15. Study Visits after the First Year

After the first year of open-label extension study, the study visits will occur every 4 months (3 visits per year), and will continue until retigabine is approved and

commercially available, or until the program is discontinued. The assessments for the first 2 study visits of each year will be identical, and the assessments for the last study visit of each year will be identical. To provide guidance, the following study visits and assessments will be performed during the second and third years of the open-label extension study:

10.15.1. Visit 6 (Month 16)

Patients will return for Study Visit 6 (Month 16), 4 months after Visit 5. At this visit, the following evaluations will be performed:

- Seizure Diary (collection / review of current diary and dispensation of new diary)
- Brief Neurological Exam
- Vital Signs (BP, HR, and Temperature) and Body Weight
- Clinical Laboratory Tests (Blood Chemistries, Hematology, Urinalysis including microscopy)
- Adverse Events
- Concomitant Medication
- Open-Label Study Medication (Collect returned medication and dispense new medication)

10.15.2. Visit 7 (Month 20)

Patients will return for Study Visit 7 (Month 20). At this visit, the following evaluations will be performed:

- Seizure Diary (collection / review of current diary and dispensation of new diary)
- Brief Neurological Exam
- Vital Signs (BP, HR, and Temperature) and Body Weight
- Clinical Laboratory Tests (Blood Chemistries, Hematology, Urinalysis including microscopy)
- Adverse Events
- Concomitant Medication
- Open-Label Study Medication (Collect returned medication and dispense new medication)

10.15.3. Visit 8 (Month 24)

Patients will return for Study Visit 8 (Month 24). At this visit, the following evaluations will be performed:

- Seizure Diary (collection / review of current diary and dispensation of new diary)
- Complete Physical and Neurological Exam
- Vital Signs (BP, HR, and Temperature) and Body Weight
- AUA Symptom Index
- PVR Bladder Ultrasound
- Clinical Laboratory Tests (Blood Chemistries, Hematology, Urinalysis including microscopy)
- Serum Pregnancy Test
- 12-lead ECG
- Adverse Events
- Concomitant Medication
- QOLIE-31-P Questionnaire (completed by patient)
- Open-Label Study Medication (collect returned medication and dispense new medication)

10.15.4. Visit 9 (Month 28)

Patients will return for Study Visit 9 (Month 28). At this visit, the following evaluations will be performed:

- Seizure Diary (collection / review of current diary and dispensation of new diary)
- Brief Neurological Exam
- Vital Signs (BP, HR, and Temperature) and Body Weight
- Clinical Laboratory Tests (Blood Chemistries, Hematology, Urinalysis including microscopy)
- Adverse Events
- Concomitant Medication
- Open-Label Study Medication (Collect returned medication and dispense new medication)

10.15.5. Visit 10 (Month 32)

Patients will return for Study Visit 10 (Month 32). At this visit, the following evaluations will be performed:

- Seizure Diary (collection / review of current diary and dispensation of new diary)
- Brief Neurological Exam
- Vital Signs (BP, HR, and Temperature) and Body Weight
- Clinical Laboratory Tests (Blood Chemistries, Hematology, Urinalysis including microscopy)
- Adverse Events
- Concomitant Medication
- Open-Label Study Medication (Collect returned medication and dispense new medication)

10.15.6. Visit 11 (Month 36)

Patients will return for Study Visit 11 (Month 36). At this visit, the following evaluations will be performed:

- Seizure Diary (collection / review of current diary and dispensation of new diary)
- Complete Physical and Neurological Exam
- Vital Signs (BP, HR, and Temperature) and Body Weight
- AUA Symptom Index
- PVR Bladder Ultrasound
- Clinical Laboratory Tests (Blood Chemistries, Hematology, Urinalysis including microscopy)
- Serum Pregnancy Test
- 12-lead ECG
- Adverse Events
- Concomitant Medication
- QOLIE-31-P Questionnaire (completed by patient)
- Open-Label Study Medication (collect returned medication and dispense new medication)

10.15.7. Visit 12 (Month 40)

Patients will return for Study Visit 12 (Month 40). At this visit, the following evaluations will be performed:

- Seizure Diary (collection / review of current diary and dispensation of new diary)
- Brief Neurological Exam
- Vital Signs (BP, HR, and Temperature) and Body Weight
- Clinical Laboratory Tests (Blood Chemistries, Hematology, Urinalysis including microscopy)
- Adverse Events
- Concomitant Medication
- Open-Label Study Medication (Collect returned medication and dispense new medication)

10.15.8. Visit 13 (Month 44)

Patients will return for Study Visit 13 (Month 44). At this visit, the following evaluations will be performed:

- Seizure Diary (collection / review of current diary and dispensation of new diary)
- Brief Neurological Exam
- Vital Signs (BP, HR, and Temperature) and Body Weight
- Clinical Laboratory Tests (Blood Chemistries, Hematology, Urinalysis including microscopy)
- Adverse Events
- Concomitant Medication
- Open-Label Study Medication (Collect returned medication and dispense new medication)

10.15.9. Visit 14 (Month 48)

Patients will return for Study Visit 14 (Month 48). At this visit, the following evaluations will be performed:

- Seizure Diary (collection / review of current diary and dispensation of new diary)
- Complete Physical and Neurological Exam
- Vital Signs (BP, HR, and Temperature) and Body Weight

- AUA Symptom Index
- PVR Bladder Ultrasound
- Clinical Laboratory Tests (Blood Chemistries, Hematology, Urinalysis including microscopy)
- Serum Pregnancy Test
- 12-lead ECG
- Adverse Events
- Concomitant Medication
- QOLIE-31-P Questionnaire (completed by patient)
- Open-Label Study Medication (collect returned medication and dispense new medication)

10.16. Tapering Period

All patients who discontinue early from study treatment during the open-label extension study will have their study medication tapered over a 3-week period, reducing their daily dose by one-third per week, and return immediately for a final visit. The patients will be instructed to take the tablets from their existing study medication bottles and to follow this tapering procedure:

- During the first week of tapering, patients will no longer take the afternoon dose.
- During the second week of tapering, patients will no longer take the morning and the afternoon doses.
- During the third week of tapering, patients will take no study medication (but will continue their existing background AEDs).

During the first year, these patients should then return for a final visit to complete all assessments and evaluations scheduled for Study Visit 5. During the second year, these patients should then return for a final visit to complete all assessments and evaluations scheduled for Study Visit 8. During the third year, these patients should then return for a final visit to complete all assessments and evaluations scheduled for Study Visit 11. During the fourth year, these patients should then return for a final visit to complete all assessments and evaluations scheduled for Study Visit 14 (Refer to Study Flow Chart in Appendix A).

During the tapering period, a new background AED should not be added until after the patient's final visit unless clinically necessary for patient safety. Unused current study medication bottles will be collected to ascertain compliance. Current study seizure

diaries will be collected and reviewed. Concomitant medications and AED usage will be documented, and adverse events will be recorded.

10.17. Replacement of Patients

Patients withdrawn from the study will not be replaced.

10.18. Unscheduled Visits

Unscheduled visits may be performed if required for assessments of laboratory parameters or clinical safety.

10.19. Laboratory Procedures

All clinical safety laboratory determinations will be performed by Quintiles Central Laboratory Services. The study staff will send the samples to the appropriate address (provided in the Central Laboratory Manual) by shipping them in the laboratory kits supplied by Quintiles Central Laboratory. Central laboratory reports will be sent to the Investigator for evaluation.

An Investigator may choose to use a local laboratory to evaluate a potential adverse event. However, for the purpose of this study, data from local laboratories will not be recorded or used in the analysis of safety. The Sponsor will not cover costs associated with the use of a local laboratory.

10.20. Early Termination / Withdrawal Visits

The Principal Investigator may discontinue a patient from the study for any of the following reasons: the patient no longer meets eligibility criteria, it is in the patient's best interest, patient preference, concurrent illness, noncompliance, etc. Patients will be informed prior to study entry that they are free to withdraw from the study at any time and for any reason. If a patient is discontinued from the study, the Investigator will immediately notify the Sponsor or the site CRA of the withdrawal.

Patients who withdraw from the study prior to completion for any reason (adverse event, withdrew consent, etc.) will have their study medication tapered over a 3-week period, reducing their daily dose by one-third per week and then return for a final visit. Patients who discontinue early during the first year of the open-label extension study will complete all assessments and evaluations scheduled for Study Visit 5. Patients who discontinue early during the second year of the open-label extension study will complete all assessments and evaluations scheduled for Study Visit 8. Patients who discontinue early during the third year of the open-label extension study will complete all assessments and evaluations scheduled for Study Visit 11 and complete all assessments and evaluations scheduled for Visit 14 if patient discontinued early during the fourth year of the open-label extension study (Refer to Study Flow Chart in Appendix A).

10.20.1. Reasons for Withdrawal

Patients are free to discontinue their participation in the study at any time and without prejudice to further treatment at their local site. The Investigator must withdraw any patient from the study if that patient requests to be withdrawn.

Patients withdrawn from the study will not be replaced, regardless of the reason for withdrawal. The patient's participation in this study may be discontinued due to the following reasons:

- Patient experiences an intolerable AE.
- Investigator decides patient has an "unsatisfactory response – efficacy."
- Patient becomes pregnant.
- Patient is unwilling or unable to continue the study.
- Patient is non-compliant with study procedures.
- Patient needs medication not allowed in the protocol.
- Any clinically significant change in patient's medical condition.
- Persistent ALT or aspartate aminotransferase (AST) above 3 times the ULN; will be confirmed by repeating laboratory assessment within 1 week.
- ALT or AST levels are above 5 times the ULN at any time during the study.
- Confirmed QTc prolongation defined as QTc (Bazett's) >500 msec or an increase in QTc (Bazett's) of >60 msec from baseline.
- Investigator decides that withdrawal from the study is in the best interest of the patient.
- Request of the Sponsor
- Hematological reasons or infections – for all such patients, the investigator shall report these in an expedited manner, whether or not they are considered serious or unexpected.

10.20.2. Handling of Withdrawals

If a patient is withdrawn from the study either at the patient's request or at the Investigator's decision or the patient fails to return, every effort should be made to determine the reason. This information will be recorded on the patient's case report form (CRF) and recorded by IVRS.

All patients who withdraw from the study prematurely, regardless of cause, should have their study medication tapered over a 3-week period, reducing their daily dose by one-

third per week, and follow the tapering procedures outlined in Section 9.12 (Tapering Period).

It is important to obtain follow up data for any patient withdrawn because of an AE, abnormal laboratory test, or ECG finding. In any case, every effort must be made to undertake safety follow up procedures.

11. STATISTICAL MEASUREMENTS, EVALUATIONS AND ANALYTICAL METHODS

11.1. Assessment of Efficacy

Monthly total seizure rates will be calculated for the entire open-label part of Study VRX-RET-E22-304 and described statistically. Monthly total seizure rates observed during the open-label extension period will be compared to the monthly total seizure rates observed during the Baseline phase of the double-blind study VRX-RET-E22-302. The percent change in monthly total seizure rates from the Baseline phase will be classified into <0, [0, 25), [25, 50), [50, 75), [75, 100] and described. The responder rate during the open-label study (defined as a reduction in seizure frequency ≥50%) will also be summarized using descriptive statistics.

The number of seizure free days, in percent to the individual duration of the open-label treatment, will be calculated and summarized using descriptive statistics. This percentage will be classified into [0, 25), [25, 50), [50, 75), [75, 95), [95,100), [=100] and described statistically.

All-cause withdrawal rates will be calculated as a percentage and respective "times to event" will be described by a Kaplan-Meier survival curve. Specific reasons for withdrawal will also be described separately.

This is an open-label extension study with the emphasis on safety. Efficacy is not the primary objective of this study unlike the double-blind study VRX-RET-E22-302. Descriptive statistics of efficacy measures such as number of patients, mean, standard deviation, median, minimum and maximum will be provided for continuous variables. The number and percentages in each category will be presented for categorical data. The pairwise t-test will be used to assess whether the retigabine treatment remains effective in the open-label extension study if necessary. The pairwise t-test may be sorted by the geographic region [Central/Eastern Europe vs. Rest of World (ROW)]. The safety assessments will use essentially the same descriptive statistics and pairwise t-test as mentioned above for efficacy. The complete details of efficacy analyses will be described in the Statistical Analysis Plan.

11.2. Assessment of Safety

Adverse events (AEs) will be monitored from the start of this extension study (informed consent provided by patient at the Baseline visit) until 30 days after administration of the last dose of study drug (end of study drug taper-off). Treatment-emergent adverse events (TEAEs) will be summarized with respect to overall incidence, as well as severity and relationship of the AEs to the study drugs. AEs that result in dose modification, discontinuation of the study drug, or serious adverse events will also be summarized

AEs with onset after the initiation of study drug and within 30 days after the last dose of study drug may be considered treatment-emergent. This will include any AE with onset prior to initiation of study drug that increased in severity during the treatment period. All reported AEs including those with onset more than 30 days after the last dose of study drug will be included in the data listings.

Abnormal changes in laboratory parameters that are not disease-related will be monitored and recorded throughout the study.

All adverse events will be encoded according to MedDRA 8.0. Treatment emergent adverse events (TEAE) will be analyzed, i.e. all adverse events starting or worsening between start of long-term extension study up to 30 days after end of study drug taper-off. Incidences on preferred term and body system basis will be calculated for all TEAEs.

Different categories for causality will be recorded in the CRFs, and these 4 categories (DEFINITE, PROBABLE, POSSIBLE, and NOT RELATED) are defined in Section 11.3 (Criteria for Determining Relationship to Study Drug) of this protocol.

In addition, all SAEs and all AEs leading to premature discontinuation will be presented as separate listings. TEAE from both studies (double-blind and open-label extension) will be combined, i.e. each patient will be counted just once (with patient's respective TEAE).

Other safety evaluations, such as vital signs, physical and neurological examinations, laboratory variables, ECG variables, post-void residual bladder ultrasound, and AUA symptom index will be analyzed descriptively.

Besides descriptive statistics of the safety evaluations will be presented, the incidence of TEAEs will be compared across treatment group using Fisher's Exact test, only for those events with an incidence of ≥ 5% over all treatment groups. Fisher's Exact test will be applied if necessary for other safety evaluations (vital signs, physical and neurological examinations, laboratory variables, etc.). QTc interval prolongations will be examined by using both Bazett's and Fridericia's QT correction formulas. The complete details of safety analyses will be described in the Statistical Analysis Plan.

11.3. Determination of Sample Size

Not applicable for this long-term extension study.

11.4. Additional Statistical Considerations

11.4.1. Analysis Population

The safety population will include all patients who successfully complete the Transition phase of Study VRX-RET-E22-302 and were included in this long-term study. The Transition phase is the phase of Study VRX-RET-E22-302 during which patients were adjusted to a 300 mg TID dose. No other population for analysis is defined for this long-term extension.

11.4.2. Handling of Missing Data

No imputation will be made for missing data in the safety analyses, with the exception of incomplete date variables regarding adverse events onset date that is necessary for defining treatment-emergent adverse events. More details on imputation of partial dates will be provided in the statistical analysis plan.

12. ADVERSE EVENTS

An adverse event (AE) is defined as any untoward clinical occurrence in a patient administered a pharmaceutical drug product that does not necessarily have a causal relationship with the study drug. An AE can therefore be any unfavorable and unintended sign (including an abnormal laboratory finding), symptom or disease temporarily associated with the use of a drug product, whether or not related to the drug product.

The presence or occurrence of any of those clinical manifestations and/or alterations in clinical laboratory test results that are either present before participation in this study or that are part of the normal fluctuations or progression of their pre-study health state, will not engender an AE report to the health authorities. Clinical manifestations and/or abnormal laboratory values measured during the study that are a sign of worsening of the patient's pre-study health status or that are new findings may, if clinically relevant, be an AE reportable to the health authorities. Abnormal laboratory values represent adverse events when they are indicative of a disease or defect (e.g., reduced hematocrit resulting in anemia), necessitate intervention (e.g., administration of packed red blood cells or other therapies), or result in dose reduction or permanent discontinuation of the drug product.

Throughout the course of the study, AEs will be monitored and recorded on the patients' source documents and CRFs. The onset, seriousness, intensity, duration, actions taken, effect on study drug administration (e.g., discontinuation), the potential relationship to the study drug, as well as the date of resolution, if any, will be recorded.

12.1. Definition and Grading Intensity

Serious Adverse Events

A serious adverse event (SAE) is an event that results in any of the following outcomes:

- Death.
- Life-threatening adverse experience.
- Hospitalization (unplanned hospital stay) or prolongation of existing hospitalization.
- Persistent or significant disability/incapacity.
- Congenital anomaly/birth defect.

Important medical events that may not result in death, be life-threatening or require hospitalization may be considered serious adverse events when, based on appropriate medical judgment, they may jeopardize the subject and may require medical or surgical intervention to prevent one of the outcomes listed above.

Planned hospitalization or surgery for a condition present prior to the participant's enrollment in the study will not meet the definition of an SAE.

12.2. Intensity

The relationship to the study drug and the intensity of an AE should be assessed by the Investigator using the following guidelines:

MILD	=	Causing no limitation of usual activities; the patient may experience slight discomfort.
MODERATE	=	Causing some limitation of usual activities; the patient may experience annoying discomfort; may warrant intervention.
SEVERE	=	Causing inability to carry out usual activities; the patient may experience intolerable discomfort or pain; warrants intervention.

12.3. Criteria for Determining Relationship to Drug

The Investigator should assess the relationship of the adverse event to the study drug according to the following guidelines:

DEFINITE	=	An event that follows a reasonable temporal sequence from administration of the drug or in which the drug level has been established in body fluids or tissue; that follows a known or expected response pattern to the suspected drug; and that is confirmed by improvement on stopping or reducing the dosage of the drug, and reappearance of the reaction on repeated exposure.

PROBABLE = An event that follows a reasonable temporal sequence from administration of the drug; that follows a known or expected response pattern to the suspected drug; that is confirmed by stopping or reducing the dosage of the drug; and that could not be reasonably explained by the known characteristics of the patient's clinical state.

POSSIBLE = An event that follows a reasonable temporal sequence from administration of the drug; that follows a known or expected response pattern to the suspected drug; but that could readily be produced by a number of other factors.

NOT RELATED = Any event that does not meet the above criteria.

12.4. Reporting of Adverse Events

All AEs should be recorded on the appropriate CRFs. All SAEs, whether or not deemed drug-related or expected, must be recorded on the CRFs and SAE forms and reported by the Investigator to the CRO (Quintiles Pharmacovigilance) assigned by the Sponsor within 24 hours by telephone and facsimile.

Complete details of SAE contact information for Quintiles Pharmacovigilance will be provided to sites in each of the participating countries in the Study Reference Manual.

A written report for an SAE must follow within 24 hours of the initial notification, including a full description of the event and any sequelae. This includes events that occur while enrolled in the study or within the Follow-Up Period. The Investigator shall comply with all applicable regulations and report all SAEs according to the requirements of their Institutional Review Board (IRB), Independent Ethics Committee (IEC) or Research Ethics Board (REB).

12.4.1. Adverse Events Follow-Up

AEs will be recorded from the start of this extension study (informed consent provided by patient at the Baseline visit) until 30 days after administration of the last dose of study medication (end of study medication taper-off). All post-treatment events will be collected through spontaneous reporting by the patient. All AEs and SAEs will be followed until the event resolves, the condition stabilizes, the event is otherwise explained, or the patient is lost to follow up. The Investigator is responsible for ensuring that follow up includes any supplemental investigations as may be indicated to elucidate the nature and/or causality of the AE. This may include additional laboratory tests or investigations, histopathological examinations, or consultation with other health care professionals, as is practical.

13. DOSE MODIFICATIONS

Patients will be treated with 600-1200 mg/day of retigabine as an adjunct therapy to their current antiepileptic medications (AEDs) or vagal nerve stimulation as established in Study VRX-RET-E22-302.

If, in the opinion of the Investigator, the patient was not receiving the maximum effective dose, the dose could be increased in weekly intervals of 150 mg/day, up to a maximum of 1200 mg daily (i.e., 400 mg TID). If adverse events considered to be secondary to retigabine occur, the total daily dose could be reduced by 150 mg/day every week, at Investigator discretion, as long as the dose is within 600-1200 mg/day.

After the patient has entered open-label treatment, the Investigator may add new AEDs, as long as these are approved AEDs. In addition, the existing background AED therapy can be adjusted to achieve the best efficacy/safety ratio, as needed, per Investigator discretion. If necessary, in the Investigator's judgment, all background AEDs can be discontinued to achieve monotherapy with retigabine.

Patients who permanently discontinue open-label treatment will have their dose tapered by one-third every week.

If a patient experiences a serious adverse event that is categorized to be "life-threatening," all study medication must be discontinued immediately.

All dose modifications and reason(s) must be documented in the patient's source documents and the CRF.

14. MONITORING

The Sponsor or designee will monitor this clinical trial through visits scheduled to check the adequacy of staff and facilities, and to ensure adherence to the protocol, study procedures and applicable regulations. The clinical monitor will also assess proper CRF completion and retention. The Investigator and clinical staff are expected to allocate sufficient time to permit adequate review of the study's progress. The Investigator will permit trial-related monitoring, audits, IRB/IEC review and regulatory inspection(s), providing direct access to source data/documents.

15. QUALITY ASSURANCE AND QUALITY CONTROL

The Sponsor or designee will implement and maintain quality assurance and quality control systems with Standard Operating Procedures (SOPs) to ensure that this clinical trial is conducted and data are generated, documented (recorded) and reported in

compliance to the protocol, Good Clinical Practice (GCP) standards, ICH and other applicable regulations.

The Sponsor is responsible for securing agreement among collaborating parties to ensure direct access to clinical-trial-related sites and material to ensure that all data are reliable and have been processed correctly.

16. DRUG ACCOUNTABILITY

The Investigator must maintain accurate records of the study medication received from the Sponsor, including date received, number of units received and lot number. The Investigator must also ensure that the drug supplies are kept secured and accounted for with access limited to those authorized by the Investigator. The study coordinator or designee must maintain accurate records of all study medication received to be able to reconcile the dispensing logs at the end of the study. The study drug records must be readily available for inspection by the study monitor and/or auditor. No medication (new or used) can be returned to the Sponsor (or its designee) or disposed of at the research unit until the Sponsor's clinical monitor has verified the accuracy of the study medication records at the site and indicated whether the medication should be destroyed at the site or returned to the Sponsor (or its designee), in which case the study monitor must indicate the name and address of the individual to whom the returned materials should be shipped.

17. LABELING AND PACKAGING OF STUDY MEDICATION

The study drug will be packaged and labeled in a manner consistent with the study design and applicable regulations. The study drug shall be identified as an investigational compound. The study protocol number will be identified on the unit label. Designated site personnel shall record the drug unit on the drug dispensing logs when the study drug is dispensed.

Each bottle of retigabine tablets (50 mg, 100 mg, or 300 mg per tablet) will be labeled with the protocol number, a unique package number, the name of the study medication, the use-by date, the Valeant address, and any additional information required by local regulations. In addition, spaces will be included for recording patient number/initials, visit number, and dated dispensed. Specific dosage instructions will be provide separately to the patient. A sufficient supply of study medication will be provided to each site for completion of trial, based on the number of patients enrolled, study visit schedule, and the daily doses of patients.

All study medication will be dispensed by the pharmacy or an appropriately qualified member of the study staff assigned by the Principal Investigator to this task.

18. DATA HANDLING AND RECORDKEEPING

18.1. Records

The Investigator must maintain all documents and records, copies or originals, relating to the conduct of this trial. This documentation includes, but is not limited to protocols, CRFs, advertising for patient participation, AE reports, patient source data, correspondence with health authorities and IRB/IEC/REB, consent forms, Investigator's curriculum vitae, monitor visit logs, laboratory reference ranges and laboratory certification or quality control procedures and laboratory director curriculum vitae. The Investigator and affiliated institution should maintain the trial documents as required by the applicable regulations. The Investigator and affiliated institution should take measures to prevent accidental or premature destruction of documents. Clinical trial documents must be kept in the clinical site's archives indefinitely, unless written authorization is obtained from the Sponsor.

Federal regulations require that records of drug disposition, CRFs, and all reports of this investigation shall be retained by the Investigator for a minimum of 15 years after notification by Valeant that the regulatory authorities have been notified of the study's termination, or 2 years after approval of the marketing application. If the Investigator is unable to retain the study documents for the required amount of time, Valeant must be informed of the individual who will be assuming this responsibility. These documents shall be retained for a longer period, however, if required by applicable regulatory requirement(s) or if needed by the Sponsor.

18.2. Case Report Forms

All entries on a CRF are ultimately the responsibility of the Investigator, who is expected to review each form for completeness, accuracy and legibility before signing. All forms must be filled out by using black ink. Errors should be lined out but not obliterated and the correction inserted, initialed, dated and an explanation provided (if not evident). A CRF must be completed for each participant who has given informed consent. The CRFs and source documents must be made available to the study monitor for review at the time of the monitoring visits.

19. INSTITUTIONAL REVIEW BOARD

This study is to be conducted in accordance with Institutional Review Board (IRB) regulations (US 21 CFR, Part 56) or applicable Independent Ethics Committee (IEC) regulations. The IRB/IEC must review and approve the following documents, if applicable:

- Trial protocol and amendment(s).

- Written informed consent form(s) and consent form updates.
- Patient recruitment procedures (e.g., advertisements).
- Written information to be provided to patients.
- Investigator's Brochure (IB) and available safety information.
- Information about payments and compensation available to patients.

The IRB/IEC approval should be in writing, clearly identifying the trial, the documents reviewed including informed consent and date of the review. The Investigator has the responsibility to provide the Sponsor with the written IRB/IEC approval prior to initiating any study-related procedures. The Investigator also has the responsibility to inform the IRB/IEC of serious and unexpected AEs and provide the IRB/IEC with a final report upon study completion.

20. COMPLIANCE WITH THE DECLARATION OF HELSINKI

This study is to be conducted in compliance with the Declaration of Helsinki (Appendix C).

21. INFORMED CONSENT

Prior to participation in a study, the patient or patient's legal representative must sign an IRB/IEC approved written informed consent form. The approved written informed consent must abide to all applicable laws in regards to the safety and confidentiality of the patients. To obtain and document informed consent, the Investigator should comply with applicable regulations; adhere to GCP standards and the ethical principles in the Declaration of Helsinki (Appendix C).

The language in the oral and written information about the trial, including the written informed consent form should be as non-technical as practical and should be understandable to the patient or patient's legal representative and the impartial witness, where applicable. Before informed consent is obtained, the Investigator should provide the patient or patient's legal representative ample time and opportunity to inquire about the trial and to decide whether or not to participate.

All questions about the trial should be answered to the satisfaction of the patient or the patient's legal representative. The written informed consent form should be signed and personally dated by the patient or patient's legal representative, and by the person who conducted the informed consent discussion. Patients will be informed that participation is voluntary and that he/she can withdraw from the study at any time. A signed copy of the consent form must be given to the patient, and this fact will be documented in the CRFs.

22. CHANGES TO THE PROTOCOL

The Investigator shall not implement any deviation or change to the protocol without approval by the Sponsor and prior review and documented approval and favorable opinion from the IRB/IEC/REB. The only exception is when it is necessary to eliminate immediate hazards to study patients or when changes involve only logistical or administrative aspects of the study (e.g., change in monitors, change in phone numbers).

Although the Sponsor has every intention of completing the study, the Sponsor reserves the right to discontinue the study at any time for clinical or administrative reasons.

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Appendix A. Study Flow Chart (REVISED)

Study Procedures	Baseline[1]	Open-Label Extension – First Year[2,3]									Open-Label Extension - Second Year and Onward[2,3]								
	V 0	V 1	V 1a[9]	V 2	V 2a[9]	V 3	V 3a[9]	V 4	V 4a[9]	V 5[4]	V 6	V 7	V 8[4]	V 9	V 10	V 11[4]	V 12	V 13	V 14[4]
	Mo 0	Mo 1	Mo 2	Mo 3	Mo 4	Mo 6	Mo 8	Mo 9	Mo 10	Mo 12	Mo 16	Mo 20	Mo 24	Mo 28	Mo 32	Mo 36	Mo 40	Mo 44	Mo 48
Eligibility/ICF	X																		
Physical & Neuro Exam	X									X			X			X			X
Brief Neuro Exam		X		X		X		X			X	X		X	X		X	X	
Vital Signs (BP, HR, & Temp) & Wt[5]	X	X		X		X		X		X	X	X	X	X	X	X	X	X	X
12 Lead ECG	X	X		X		X		X		X			X			X			X
Blood Chem & Hematology	X	X		X		X		X		X	X	X	X	X	X	X	X	X	X
Hematological Evaluation			X		X		X		X										
Urinalysis (including Microscopy)	X	X		X		X		X		X	X	X	X	X	X	X	X	X	X
AUA Symptom Index[7]	X	X		X						X			X			X			X
PVR Bladder Ultrasound[7]	X	X		X						X			X			X			X
Serum Preg Test[6]	X									X			X			X			X
Urine Preg Test[6]	X																		

Study Procedures	Baseline[1]	Open-Label Extension – First Year[2,3]									Open-Label Extension - Second Year and Onward[2,3]								
	V 0	V 1	V 1a[9]	V 2	V 2a[9]	V 3	V 3a[9]	V 4	V 4a[9]	V 5[4]	V 6	V 7	V 8[4]	V 9	V 10	V 11[4]	V 12	V 13	V 14[4]
	Mo 0	Mo 1	Mo 2	Mo 3	Mo 4	Mo 6	Mo 8	Mo 9	Mo 10	Mo 12	Mo 16	Mo 20	Mo 24	Mo 28	Mo 32	Mo 36	Mo 40	Mo 44	Mo 48
Seizure Diary Review	X	X		X		X		X		X	X	X	X	X	X	X	X	X	X
AE Evaluation	X	X		X		X		X		X	X	X	X	X	X	X	X	X	X
Concomitant Medication	X	X		X		X		X		X	X	X	X	X	X	X	X	X	X
QOLIE-31-P Questionnaire	X			X		X		X		X			X			X			X
Dispense OLE Study Meds[8]	X	X		X		X		X		X	X	X	X	X	X	X	X	X	X
Collect Returned OLE Study Meds		X		X		X		X		X	X	X	X	X	X	X	X	X	X

1. Baseline for the open-label extension study corresponds to the assessments performed at the last visit of the Maintenance phase (Visit 9) of Study VRX-RET-E22-302 for all patients. The final, baseline eligibility assessment for the open-label extension study, including obtaining informed consent and dispensing open-label study medication will be performed at the last visit of the Transition phase (Visit 11) of Study VRX-RET-E22-302.
2. Study Visit 1 will have a window range of ±3 days. After Study Visit 1, all remaining study visits will have a window range of ±7 days around that visit day to accommodate individual schedules. Each study month will be defined as 30 calendar days. If a patient visit occurs outside the visit window, the study clinical monitor (CRA) should be notified and the reason for the deviation noted. An attempt should be made to ensure that the patient returns for subsequent visits on schedule using the last visit of the Transition phase (Visit 11) of Study VRX-RET-E22-302, which corresponds to the final, Baseline eligibility visit for the open-label extension study.
3. This open-label extension study will be continued until retigabine is approved and commercially available, or until the program is discontinued, followed by a 3-week tapering period and a 30 day post-study period for collection of adverse events. After the first year, the study visits will occur every 4 months (3 visits per year). After the first year, the assessments for the first 2 study visits of each year (e.g. Visits 6, 7, 9, 10, 12, and 13) will be identical, and the assessments for the last study visit of each year (e.g. Visits 8, 11, and 14) will be identical.
4. All patients who discontinue early from study treatment during the open-label extension study will have their study medication tapered over a 3-week period, reducing their daily dose by one-third per week, and then return for a final visit. Patients who discontinue early during the first year of the open-label extension study will complete all assessments and evaluations scheduled for Study Visit 5. Patients who discontinue early during the second year of the open-label extension study will complete all assessments and evaluations scheduled for Study Visit 8. Patients who discontinue early during the third year of the open-label extension study will complete all assessments and evaluations scheduled for Study Visit 11. Patients who discontinue early during the fourth year of the open-label extension study will complete all assessments and evaluations scheduled for Study Visit 14. Also, all adverse events should be followed and collected up to until 30 days after administration of the last dose of study drug (end of study drug taper-off).
5. Supine and standing blood pressure, heart rate.
6. In addition to the scheduled pregnancy tests, a pregnancy test should be performed during the study whenever a woman's menstrual period is 5 days late.
7. The AUA Symptom Index and the PVR bladder ultrasound will only be performed during the first, second, third, and fourth year of the open-label extension study (Visits 1, 2, 5, 8, 11, and 14).
8. Dispensation of study medication is not applicable at the final study visit, if a patient has discontinued early or completed the open-label extension study.
9. Study visits added per FDA comments that the open label extension trial should include more frequent hematological monitoring. These are now in-line with the hematological monitoring frequencies per the VRX-RET-E22-302, double-blind trial.

Appendix B. Medical Association Declaration of Helsinki

Ethical Principles for Medical Research Involving Human Subjects

Adopted by the 18th WMA General Assembly, Helsinki, Finland, June 1964, and amended by the

29th WMA General Assembly, Tokyo, Japan, October 1975

35th WMA General Assembly, Venice, Italy, October 1983

41st WMA General Assembly, Hong Kong, September 1989

48th WMA General Assembly, Somerset West, Republic of South Africa, October 1996

and the 52nd WMA General Assembly, Edinburgh, Scotland, October 2000

Note of Clarification on Paragraph 29 added by the WMA General Assembly, Washington 2002

Note of Clarification on Paragraph 30 added by the WMA General Assembly, Tokyo 2004

INTRODUCTION

1. The World Medical Association has developed the Declaration of Helsinki as a statement of ethical principles to provide guidance to physicians and other participants in medical research involving human subjects. Medical research involving human subjects includes research on identifiable human material or identifiable data.
2. It is the duty of the physician to promote and safeguard the health of the people. The physician's knowledge and conscience are dedicated to the fulfillment of this duty.
3. The Declaration of Geneva of the World Medical Association binds the physician with the words, "The health of my patient will be my first consideration," and the International Code of Medical Ethics declares that, "A physician shall act only in the patient's interest when providing medical care which might have the effect of weakening the physical and mental condition of the patient."
4. Medical progress is based on research which ultimately must rest in part on experimentation involving human subjects.

5. In medical research on human subjects, considerations related to the well-being of the human subject should take precedence over the interests of science and society.
6. The primary purpose of medical research involving human subjects is to improve prophylactic, diagnostic and therapeutic procedures and the understanding of the aetiology and pathogenesis of disease. Even the best proven prophylactic, diagnostic, and therapeutic methods must continuously be challenged through research for their effectiveness, efficiency, accessibility and quality.
7. In current medical practice and in medical research, most prophylactic, diagnostic and therapeutic procedures involve risks and burdens.
8. Medical research is subject to ethical standards that promote respect for all human beings and protect their health and rights. Some research populations are vulnerable and need special protection. The particular needs of the economically and medically disadvantaged must be recognized. Special attention is also required for those who cannot give or refuse consent for themselves, for those who may be subject to giving consent under duress, for those who will not benefit personally from the research and for those for whom the research is combined with care.
9. Research Investigators should be aware of the ethical, legal and regulatory requirements for research on human subjects in their own countries as well as applicable international requirements. No national ethical, legal or regulatory requirement should be allowed to reduce or eliminate any of the protections for human subjects set forth in this Declaration.

BASIC PRINCIPLES FOR ALL MEDICAL RESEARCH

10. It is the duty of the physician in medical research to protect the life, health, privacy, and dignity of the human subject.
11. Medical research involving human subjects must conform to generally accepted scientific principles, be based on a thorough knowledge of the scientific literature, other relevant sources of information, and on adequate laboratory and, where appropriate, animal experimentation.
12. Appropriate caution must be exercised in the conduct of research which may affect the environment, and the welfare of animals used for research must be respected.
13. The design and performance of each experimental procedure involving human subjects should be clearly formulated in an experimental protocol. This protocol should be submitted for consideration, comment, guidance, and where appropriate, approval to a specially appointed ethical review committee, which must be independent of the Investigator, the sponsor or any other kind of undue influence. This independent

committee should be in conformity with the laws and regulations of the country in which the research experiment is performed. The committee has the right to monitor ongoing trials. The researcher has the obligation to provide monitoring information to the committee, especially any serious adverse events. The researcher should also submit to the committee, for review, information regarding funding, sponsors, institutional affiliations, other potential conflicts of interest and incentives for subjects.

14. The research protocol should always contain a statement of the ethical considerations involved and should indicate that there is compliance with the principles enunciated in this Declaration.
15. Medical research involving human subjects should be conducted only by scientifically qualified persons and under the supervision of a clinically competent medical person. The responsibility for the human subject must always rest with a medically qualified person and never rest on the subject of the research, even though the subject has given consent.
16. Every medical research project involving human subjects should be preceded by careful assessment of predictable risks and burdens in comparison with foreseeable benefits to the subject or to others. This does not preclude the participation of healthy volunteers in medical research. The design of all studies should be publicly available.
17. Physicians should abstain from engaging in research projects involving human subjects unless they are confident that the risks involved have been adequately assessed and can be satisfactorily managed. Physicians should cease any investigation if the risks are found to outweigh the potential benefits or if there is conclusive proof of positive and beneficial results.
18. Medical research involving human subjects should only be conducted if the importance of the objective outweighs the inherent risks and burdens to the subject. This is especially important when the human subjects are healthy volunteers.
19. Medical research is only justified if there is a reasonable likelihood that the populations in which the research is carried out stand to benefit from the results of the research.
20. The subjects must be volunteers and informed participants in the research project.
21. The right of research subjects to safeguard their integrity must always be respected. Every precaution should be taken to respect the privacy of the subject, the confidentiality of the patient's information and to minimize the impact of the study on the subject's physical and mental integrity and on the personality of the subject.
22. In any research on human beings, each potential subject must be adequately informed of the aims, methods, sources of funding, any possible conflicts of interest, institutional

affiliations of the researcher, the anticipated benefits and potential risks of the study and the discomfort it may entail. The subject should be informed of the right to abstain from participation in the study or to withdraw consent to participate at any time without reprisal. After ensuring that the subject has understood the information, the physician should then obtain the subject's freely-given informed consent, preferably in writing. If the consent cannot be obtained in writing, the non-written consent must be formally documented and witnessed.

23. When obtaining informed consent for the research project the physician should be particularly cautious if the subject is in a dependent relationship with the physician or may consent under duress. In that case the informed consent should be obtained by a well-informed physician who is not engaged in the investigation and who is completely independent of this relationship.

24. For a research subject who is legally incompetent, physically or mentally incapable of giving consent or is a legally incompetent minor, the Investigator must obtain informed consent from the legally authorized representative in accordance with applicable law. These groups should not be included in research unless the research is necessary to promote the health of the population represented and this research cannot instead be performed on legally competent persons.

25. When a subject deemed legally incompetent, such as a minor child, is able to give assent to decisions about participation in research, the Investigator must obtain that assent in addition to the consent of the legally authorized representative.

26. Research on individuals from whom it is not possible to obtain consent, including proxy or advance consent, should be done only if the physical/mental condition that prevents obtaining informed consent is a necessary characteristic of the research population. The specific reasons for involving research subjects with a condition that renders them unable to give informed consent should be stated in the experimental protocol for consideration and approval of the review committee. The protocol should state that consent to remain in the research should be obtained as soon as possible from the individual or a legally authorized surrogate.

27. Both authors and publishers have ethical obligations. In publication of the results of research, the Investigators are obliged to preserve the accuracy of the results. Negative as well as positive results should be published or otherwise publicly available. Sources of funding, institutional affiliations and any possible conflicts of interest should be declared in the publication. Reports of experimentation not in accordance with the principles laid down in this Declaration should not be accepted for publication.

ADDITIONAL PRINCIPLES FOR MEDICAL RESEARCH COMBINED WITH MEDICAL CARE

28. The physician may combine medical research with medical care, only to the extent that the research is justified by its potential prophylactic, diagnostic or therapeutic value. When medical research is combined with medical care, additional standards apply to protect the patients who are research subjects.
29. The benefits, risks, burdens and effectiveness of a new method should be tested against those of the best current prophylactic, diagnostic, and therapeutic methods. This does not exclude the use of placebo, or no treatment, in studies where no proven prophylactic, diagnostic or therapeutic method exists.[1]
30. At the conclusion of the study, every patient entered into the study should be assured of access to the best proven prophylactic, diagnostic and therapeutic methods identified by the study.[2]
31. The physician should fully inform the patient which aspects of the care are related to the research. The refusal of a patient to participate in a study must never interfere with the patient-physician relationship.
32. In the treatment of a patient, where proven prophylactic, diagnostic and therapeutic methods do not exist or have been ineffective, the physician, with informed consent from the patient, must be free to use unproven or new prophylactic, diagnostic and therapeutic measures, if in the physician's judgment it offers hope of saving life, re-establishing health or alleviating suffering. Where possible, these measures should be made the object of research, designed to evaluate their safety and efficacy. In all cases, new information should be recorded and, where appropriate, published. The other relevant guidelines of this Declaration should be followed.

---

[1] **Note of clarification on paragraph 29 of the WMA Declaration of Helsinki**

The WMA hereby reaffirms its position that extreme care must be taken in making use of a placebo-controlled trial and that in general this methodology should only be used in the absence of existing proven therapy. However, a placebo-controlled trial may be ethically acceptable, even if proven therapy is available, under the following circumstances:

- Where for compelling and scientifically sound methodological reasons its use is necessary to determine the efficacy or safety of a prophylactic, diagnostic or therapeutic method; or

- Where a prophylactic, diagnostic or therapeutic method is being investigated for a minor condition and the patients who receive placebo will not be subject to any additional risk of serious or irreversible harm.

All other provisions of the Declaration of Helsinki must be adhered to, especially the need for appropriate ethical and scientific review.

[2] Note of clarification on paragraph 30 of the WMA Declaration of Helsinki

The WMA hereby reaffirms its position that it is necessary during the study planning process to identify post-trial access by study participants to prophylactic, diagnostic and therapeutic procedures identified as beneficial in the study or access to other appropriate care. Post-trial access arrangements or other care must be described in the study protocol so the ethical review committee may consider such arrangements during its review.

9.10.2004

Appendix C. American Urological Association Symptom Index

This section contained Clinical Outcome Assessment data collection questionnaires or indices, which are protected by copyright laws and therefore have been excluded.

Reference:

Barry MJ, et al. (1992). The American Urological Association symptom index for benign prostatic hyperplasia. Journal of Urology, 148: 1549–1557.

Appendix D. Protocol Agreement

PROTOCOL TITLE:

A multicenter, open-label, long-term, safety, tolerability and efficacy study of retigabine in adult epilepsy patients with partial-onset seizures (Extension of study VRX-RET-E22-302).

PROTOCOL NO: VRX-RET-E22-304

This document is a confidential communication of Valeant Pharmaceuticals, North America. The authorized Investigator agrees to personally conduct or supervise the conduct of this study as outlined in the current protocol. No changes will be made to the protocol without prior written approval from Valeant Pharmaceuticals, North America, except to protect the safety, rights and welfare of the study participants and always in compliance with all applicable Good Clinical Practices (GCP), as well as International Conference on Harmonization (ICH) and regulatory requirements. Acceptance of this document constitutes the agreement by the Investigator that no unpublished information contained herein will be published or disclosed without prior written approval from Valeant Pharmaceuticals, North America.

I have read this protocol in its entirety and agree to conduct the study accordingly.

_____ _____

Signature: Date
Principal Investigator

_____

Printed Name

COUNTRY SPECIFIC ADDENDUM FOR FRANCE

PROTOCOL:	A Multicenter, Open-label, Long-term, Safety, Tolerability and Efficacy Study of Retigabine in Adult Epilepsy Patients with Partial-onset Seizures (Extension of Study VRX-RET-E22-302)
INVESTIGATIONAL PRODUCT:	Retigabine (50 mg, 100 mg or 300 mg tablets)
PROTOCOL NUMBER:	VRX-RET-E22-304 – Amendment 1 (Addendum 2)
EUDRACT NUMBER:	2006-000956-42
IND NUMBER:	53,950
SPONSOR:	Valeant Pharmaceuticals North America One Enterprise Aliso Viejo, CA 92656, USA Telephone: [redacted] Facsimile:
CONTRACT RESEARCH ORGANIZATION:	Quintiles, Inc. 5927 South Miami Blvd. Morrisville, NC 27560 USA
MEDICAL MONITOR:	[redacted] MD Quintiles Hungary, Ltd Budafoki ut 91-93 H-1117 Budapest Tel: [redacted] Facsimile: [redacted]

Protocol Sign-Off Sheet

Protocol Title: A Multicenter, Open-label, Long-term, Safety, Tolerability and Efficacy Study of Retigabine in Adult Epilepsy Patients with Partial-onset Seizures

(Extension of Study VRX-RET-E22-302)

Protocol Number: VRX-RET-E22-304 – Amendment 1 (Addendum 2)

Version: November 8, 2007

Reviewed and Approved by:

[redacted]
Director, Clinical Operations

08 / NOV / 2007
Date

[redacted] PhD
Director, Biostatistics

09 / NOV / 2007
Date

[redacted]
Senior Director, Regulatory Affairs

09 / Nov / 2007
Date

[redacted] VP Global Safety and Pharmacovigilance 09/Nov/2007
MD, PhD.
VP Global Medical Affairs, Chief Medical Officer

11 / 9 / 07
Date

[redacted] MD
Senior VP Global Drug Development

11 / 8 / 07
Date

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PROTOCOL ADDENDUM SUMMARY

OBJECTIVE:	Monthly serum pregnancy tests will be conducted for all applicable female subjects of childbearing potential participating in the Retigabine VRX-RET-E22-304 trial in France.
RATIONAL:	This is an additional safety requirement requested by the French Competent Authorities (AFSSAPS).
SELECTION OF PATIENTS:	Female subjects of childbearing potential who participate in the Retigabine VRX-RET-E22-304 trial in France will be required to visit the study clinic for monthly (i.e., occurring every 30 days) serum pregnancy tests.
COLLABORATING SITES:	All sites conducting the Retigabine VRX-RET-E22-304 study in France will be required to adhere to this protocol addendum.
PREGNANCY SAMPLE COLLECTION:	Urine and serum pregnancy tests will be conducted as described in the main study protocol. *Additional serum pregnancy tests will be performed so that female subjects of child-bearing potential will undergo monthly serum testing during the time they are active in the study.* (See Appendix I Study Visit Schedule. Pages included reflect modifications only)
LABORATORY: KITS:	For additional serum pregnancy tests, sites shall utilize the serum pregnancy kits available in the Unscheduled/Retest kits from QLAB.
INFORMED CONSENT:	The Patient Informed Consent (PIC) will be amended to reflect the additional monthly site visits for serum pregnancy tests of all applicable female subjects of childbearing potential. The amended consent will only be provided to female patients of childbearing potential for completion. (See Appendix II for sample PIC. Pages included reflect modifications only.)

This addendum shall be submitted to the Competent Authority, the CEC and ECs, as applicable.

APPENDIX I: PROTOCOL CHANGES

(Revisions to page 31 of Protocol Amendment 1)

SECTION 10: STUDY PROCEDURES

(Changes are in bold)

10.1 Study Flow Chart

- Study Visit 1 (at Month 1 ±3 days)
- Study Visit 1a for Hematological Monitoring (at Month 2 ±7 days)
- Study Visit 2 (at Month 3 ±7 days)
- Study Visit 2a for Hematological Monitoring (at Month 4 ±7 days)
- **Study Visit 2b for Serum Pregnancy Testing (at Month 5±3 days)**
- Study Visit 3 (at Month 6 ±7 days)
- **Study Visit 3aa for Serum Pregnancy Testing (at Month 7±3 days)**
- Study Visit 3a for Hematological Monitoring (at Month 8 ±7 days)
- Study Visit 4 (at Month 9 ±7 days)
- Study Visit 4a for Hematological Monitoring (at Month 10 ±7 days)
- **Study Visit 4b for Serum Pregnancy Testing (at Month 11±3 days)**
- Study Visit 5 (at Month 12 ±7 days).
- **Study Visit 5a for Serum Pregnancy Testing (at Month 13±3 days)**
- **Study Visit 5b for Serum Pregnancy Testing (at Month 14±3 days)**
- **Study Visit 5c for Serum Pregnancy Testing (at Month 15±3 days)**
- Study Visit 6 (at Month 16 ±7 days)
- **Study Visit 6a for Serum Pregnancy Testing (at Month 17±3 days)**
- **Study Visit 6b for Serum Pregnancy Testing (at Month 18±3 days)**
- **Study Visit 6c for Serum Pregnancy Testing (at Month 19±3 days)**
- Study Visit 7 (at Month 20 ±7 days).
- **Study Visit 7a for Serum Pregnancy Testing (at Month 21±3 days)**
- **Study Visit 7b for Serum Pregnancy Testing (at Month 22±3 days)**
- **Study Visit 7c for Serum Pregnancy Testing (at Month 23±3 days)**
- Study Visit 8 (at Month 24 ±7 days).

- **Study Visit 8a for Serum Pregnancy Testing (at Month 25±3 days)**
- **Study Visit 8b for Serum Pregnancy Testing (at Month 26±3 days)**
- **Study Visit 8c for Serum Pregnancy Testing (at Month 27±3 days)**
- Study Visit 9 (at Month 28 ±7 days).
- **Study Visit 9a for Serum Pregnancy Testing (at Month 29±3 days)**
- **Study Visit 9b for Serum Pregnancy Testing (at Month 30±3 days)**
- **Study Visit 9c for Serum Pregnancy Testing (at Month 31±3 days)**
- Study Visit 10 (at Month 32 ±7 days).
- **Study Visit 10a for Serum Pregnancy Testing (at Month 33±3 days)**
- **Study Visit 10b for Serum Pregnancy Testing (at Month 34±3 days)**
- **Study Visit 10c for Serum Pregnancy Testing (at Month 35±3 days)**
- Study Visit 11 (at Month 36 ±7 days).

Study Visit Schedule

(Revisions to Page 61 of Protocol Amendment 1)

Study Procedures	Baseline[1]	Open-Label Extension – First Year [2,3]											
	V 0	V 1	V 1a[9]	V 2	V 2a[9]	V2b	V 3	V3aa	V 3a[9]	V 4	V 4a[9]	V 4b	V 5[4]
	Mnth 0	Mnth 1	Mnth 2	Mnth 3	Mnth 4	Mnth 5	Mnth 6	Mnth 7	Mnth 8	Mnth 9	Mnth 10	Mnth 11	Mnth 12
Eligibility/ICF	X												
Physical & Neuro Exam	X												X
Brief Neuro Exam		X		X			X			X			
Vital Signs (BP, HR, & Temp) & Wt[5]	X	X		X			X			X			X
12 Lead ECG	X	X		X			X			X			X
Blood Chem & Hematology	X	X		X			X			X			X
Hematological Evaluation			X		X				X		X		
Urinalysis (including Microscopy)	X	X		X			X			X			X
AUA Symptom Index[7]	X	X		X									X
PVR Bladder Ultrasound[7]	X	X		X									X
Serum Preg Test[6]	X	X	X	X	X	X	X	X	X	X	X	X	X
Urine Preg Test[6]	X												
Seizure Diary Review	X	X		X			X			X			X
AE Evaluation	X	X		X			X			X			X
Concomitant Medication	X	X		X			X			X			X
QOLIE-31-P Questionnaire	X			X			X			X			X
Dispense OLE Study Meds[8]	X	X		X			X			X			X
Collect Returned OLE Study Meds		X		X			X			X			X

Study Visit Schedule (Continued)

Study Procedures	Open-Label Extension – Second Year and Onward [2,3]																							
	V5a	V5b	V5c	V 6	V 6a	V 6b	V 6c	V 7	V 7a	V 7b	V 7c	V 8[4]	V 8a	V 8b	V 8c	V 9	V 9a	V 9b	V 9c	V 10	V 10a	V 10b	V 10c	V 11[4]
	Mnth 13	Mnth 14	Mnth 15	Mnth 16	Mnth 17	Mnth 18	Mnth 19	Mnth 20	Mnth 21	Mnth 22	Mnth 23	Mnth 24	Mnth 25	Mnth 26	Mnth 27	Mnth 28	Mnth 29	Mnth 30	Mnth 31	Mnth 32	Mnth 33	Mnth 34	Mnth 35	Mnth 36
Eligibility/ICF																								
Physical & Neuro												X												X
Brief Neuro Exam				X				X								X				X				
Vital Signs (BP, HR, & Temp) & Wt[5]				X				X				X				X				X				X
12 Lead ECG												X												X
Blood Chem & Hematology				X				X				X				X				X				X
Hematological																								
Urinalysis (including Microscopy)				X				X				X				X				X				X
AUA Symptom Index[7]																								
PVR Bladder																								
Serum Preg Test[6]	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
Urine Preg Test[6]																								
Seizure Diary Review				X				X				X				X				X				X
AE Evaluation				X				X				X				X				X				X
Concomitant				X				X				X				X				X				X
QOLIE-31-P Questionnaire												X												X
Dispense OLE Study Meds[8]				X				X				X				X				X				X
Collect Returned OLE Study Meds				X				X				X				X				X				X

APPENDIX II: Informed Consent Revisions

Sample of Modified Informed Consent

(See deleted and **bold** font for sections to be modified)

THIS APPLIES TO APPLICABLE FEMALE PTS OF CHILD-BEARING POTENTIAL, ONLY

Title: A MULTICENTER, OPEN-LABEL, LONG-TERM, SAFETY, TOLERABILITY AND EFFICACY STUDY OF RETIGABINE IN ADULT EPILEPSY PATIENTS WITH PARTIAL-ONSET SEIZURES (EXTENSION OF STUDY VRX-RET-E22-302)

Protocol #: VRX-RET-E22-304, Amendment 1 – Addendum 2

Sponsor: Valeant Pharmaceuticals North America
One Enterprise
Aliso Viejo, CA 92656

Investigator Name: <insert>

Address: <insert>

Procedures

During ~~the first year of~~ this Open-Label study you will be asked to visit the research clinic ~~9 times~~ **once a month (every 30 days) until you withdraw or complete the study.** ~~These visits will occur on months 1, 2, 3, 4, 6, 8, 9, 10 and 12. Thereafter, you will be asked to visit the research clinic 3 times a year. Each visit, after the first year, will be approximately 4 months apart.~~ Clinic visits may last about 1½ to 2 hours depending on what study procedures are scheduled for that day.

The following procedures will be done at various times throughout the study:

(1) Physical exams (including weight)
(2) Neurological exams
(3) Blood pressure, heart rate (once while lying down and once after standing for 2 minutes) and temperature
(4) 12-lead ECGs (electrical tracing of your heart)
(5) Blood samples (approximately 1.5 teaspoons or 7 mL each time) to determine your overall health
(6) Serum pregnancy tests and urine pregnancy test (if you are a female of child-bearing potential)
(7) Urine will be collected for routine urinalysis. If at any time during the study your routine urinalysis results show abnormalities, your study doctor may ask you to see an urologist for additional safety evaluation.
(8) You will meet with your study doctor and research staff to provide information on how you are feeling, and if there have been any changes in your current medications
(9) You will be asked to complete some questionnaires (either by yourself or with your study doctor) on your bladder function and how your illness affects your daily life
(10) You will be asked to continue to complete a study seizure diary which research staff will review and collect at every study visit.
(11) Bladder ultrasounds during the first year.
(12) You will be asked to return all unused study medication from the previous visit.

For details on when procedures will be done, please see Appendix II: Study Visit Schedule.

Informed Consent Study Visit Schedule

Procedure	1st Year											
	Month 1	Month 2	Month 3	Month 4	Month 5	Month 6	Month 7	Month 8	Month 9	Month 10	Month 11	Month 12
Physical Exam												X
Neurological Exam	X		X			X			X			X
ECG	X		X			X			X			X
Blood Pressure, Heart Rate, Temperature & Weight	X		X			X			X			X
Blood Sample	X	X	X	X		X		X	X	X		X
Serum Pregnancy Test	X	X	X	X	X	X	X	X	X	X	X	X
Urine Sample Collection	X		X			X			X			X
Health and Medication Discussion	X		X			X			X			X
Questionnaires			X			X			X			X
Seizure Diary Review	X		X			X			X			X
Bladder Ultrasound	X		X									X
Collection of Returned Study Medication / Dispense Study Medication	X		X									X
Procedure	**Every Year After 1st Year**											
	Month 1	Month 2	Month 3	Month 4	Month 5	Month 6	Month 7	Month 8	Month 9	Month 10	Month 11	Month 12
Physical Exam												X
Neurological Exam				X				X				X
ECG												X
Blood Pressure, Heart Rate, Temperature & Weight				X				X				X
Blood Sample				X				X				X
Serum Pregnancy Test	X	X	X	X	X	X	X	X	X	X	X	X
Urine Sample Collection				X				X				X
Health and Medication Discussion				X				X				X
Questionnaires												X
Seizure Diary Review				X				X				X
Bladder Ultrasound												
Collection of Returned Study Medication / Dispense Study Medication												

APPENDIX III: Protocol Agreement

This document is a confidential communication of Valeant Pharmaceuticals North America. The authorized investigator agrees to personally conduct or supervise the conduct of this investigational study as outlined in protocol VRX-RET-E22-304 Amendment 1 – Addendum 2. No changes will be made to the protocol Amendment 1- Addendum 2 without prior written approval from Valeant Pharmaceuticals, except to protect the safety, rights and welfare of the study subjects, and always in compliance with all applicable regulations. Acceptance of this document constitutes the agreement by the investigator that no unpublished information contained herein will be published or disclosed without prior written approval from Valeant Pharmaceuticals North America.

I have read this protocol VRX-RET-E22-304, Amendment 1 –Addendum 2 and agree to conduct the study accordingly.

_____ _____

Signature of Principal Investigator Date

_____

Name of Principal Investigator (please print)

ADMINSTRATIVE CHANGE

PROTOCOL: A Multicenter, Open-Label, Long-Term, Safety, Tolerability and Efficacy Study of Retigabine in Adult Epilepsy Patients with Partial-Onset Seizures (Extension Study of VRX-RET-E22-302)

INVESTIGATIONAL PRODUCT: Retigabine
50 mg, 100 mg and 300 mg tablets

PROTOCOL NUMBER: VRX-RET-E22-304 – Amendment 1 (Addendum 1)

EUDRACT NUMBER: 2005-002182-36

IND NUMBER: 53,950

SPONSOR: Valeant Pharmaceuticals North America
One Enterprise
Aliso Viejo, CA 92656, USA
Telephone: [redacted]
Facsimile:

CONTRACT RESEARCH ORGANIZATION: Quintiles, Inc.
5927 South Miami Blvd.
Morrisville, NC 27560 USA

MEDICAL MONITOR: [redacted] MD
Quintiles Hungary Ltd
H-1117 Budapest
Budafoki ut 91-93
Telephone: [redacted]
Facsimile [redacted]

Reviewed and Approved by:

[redacted]
irector, Clinical Operations

25 / Jul / 2007
Date

[redacted]
PhD
Director, Biostatistics

25 / July / 2007
Date

[redacted]
Senior Director, Regulatory Affairs

27 / July / 2007
Date

[redacted]
MD, PhD.
VP Global Medical Affairs, Chief Medical Officer

26 / July / 2007
Date

[redacted]
MD
Senior VP Global Drug Development

7 / 26 / 2007
Date

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PROTOCOL ADDENDUM SUMMARY

OBJECTIVE: Protocol VRX-RET-E22-304 will be amended to include the participation of patients at sites in the United States. Currently only sites outside the US, primarily in Western, Central and Eastern Europe, in addition to sites in Israel, South Africa and Australia are conducting this trial.

RATIONAL: As the VRX-RET-E22-302 double-blind trial was amended to include US patients in order to meet the study timelines of patient enrollment, so too, is the VRX-RET-E22-304 open-label extension study being amended to allow those US patients who have completed the double-blind 302 trial the opportunity to move into the open-label 304 study.

SELECTION OF PATIENTS: The selection of patients (i.e., inclusion/exclusion criteria) will remain the same for the US sites as is currently being implemented for those sites outside the US conducting the VRX-RET-E22-304 trial.

INFORMED CONSENT: The Informed Consent will be drafted to reflect the US FDA requirements regarding the protection of human subjects in clinical research.

This addendum shall be submitted to the Regulatory Authorities, IRBs, CECs and ECs, as applicable.

APPENDIX I

Statement of Investigator

This document is a confidential communication of Valeant Pharmaceuticals North America. The authorized investigator agrees to personally conduct or supervise the conduct of this investigational study as outlined in protocol VRX-RET-E22-304, Amendment 1, Addendum 1. No changes will be made to Amendment 1, Addendum 1 of this protocol without prior written approval from Valeant Pharmaceuticals North America, except to protect the safety, rights and welfare of the study subjects, and always in compliance with all applicable regulations.

Acceptance of this document constitutes the agreement by the investigator that no unpublished information contained herein will be published or disclosed without prior written approval from Valeant Pharmaceuticals North America.

I have read protocol VRX-RET-E22-304, Amendment 1, Addendum 1 and agree to conduct the study accordingly.

_____ _____

Signature of Principal Investigator Date

_____

Name of Principal Investigator (please print)

Clinical Study Protocol

Retigabine

A multicenter, open-label, long-term, safety, tolerability and efficacy study of retigabine in adult epilepsy patients with partial-onset seizures (Extension of Study VRX-RET-E22-302)

Protocol Number VRX-RET-E22-304

1. TITLE PAGE

STUDY TITLE:	A multicenter, open-label, long-term, safety, tolerability and efficacy study of retigabine in adult epilepsy patients with partial-onset seizures (Extension of Study VRX-RET-E22-302)
INVESTIGATIONAL PRODUCT:	Retigabine
IND NUMBER:	53,950
PROTOCOL NUMBER:	VRX-RET-E22-304, Amendment 1
PHASE:	3
SPONSOR:	Valeant Pharmaceuticals, North America One Enterprise Aliso Viejo, CA 92656 USA Main Office: [redacted] FAX: [redacted]
CONTRACT RESEARCH ORGANIZATION (CRO):	Quintiles, Inc. 5927 South Miami Blvd. Morrisville, NC 27560
CRO MEDICAL MONITOR:	[redacted] MD Quintiles Hungary, Ltd Budafoki ut 91-93 H-1117 Budapest Tel: [redacted] Facsimile: [redacted]
COUNTRIES:	Western, Central and Eastern Europe, Australia, Israel, and South Africa

2. PROTOCOL SIGN-OFF SHEET

PROTOCOL TITLE: A multicenter, open-label, long-term, safety, tolerability and efficacy study of retigabine in adult epilepsy patients with partial-onset seizures (Extension of Study VRX-RET-E22-302)

PROTOCOL NUMBER: VRX-RET-E22-304

VERSION: July 2, 2007

Reviewed and Approved by:

[redacted]
Director, Clinical Operations
05 / Jul / 2007
Date

[redacted] PhD
Director, Biostatistics
05 / July / 2007
Date

[redacted]
Sr. Director, Regulatory Affairs
05 / July / 2007
Date

[redacted] MD, PhD.
VP Global Medical Affairs, Chief Medical Officer
5 / July / 2007.
Date

[redacted] MD
Sr. V. P. Global Drug Development
5 / July / 2007
Date

3. SUMMARY OF REVISIONS

SECTION: **1. TITLE PAGE, section Sponsor**

REVISION: **Amended to read (see bold text)**

Valeant ~~Research and Developemnt~~ **Pharmaceuticals, North America**
~~3300 Hyland Ave~~. **One Enterprise**
~~Costa Mesa~~ **Aliso Viejo**, CA 926~~2~~**5**6 USA
Main office. [redacted]
Facsimile: [redacted]

RATIONALE: To provide new address and contact information of Sponsor.

SECTION: **1. TITLE PAGE, section CRO Medical Monitor**

REVISION: **Amended to read (see bold text)**

[redacted] MD
Quintiles ~~GmbH~~ **Hungary Ltd**.
~~Hugenottenelee 167~~ **Budafoki ut 91-93**
~~D-63263 Neu-Isenberg~~ **H-1117 Budapest**
Tel. [redacted] ~~Ext.~~
Facsimile: [redacted]

RATIONALE: To provide new address and contact information of CRO Medical Monitor.

SECTION: **3. SUMMARY OF REVISIONS**

REVISION: Added new Section 3. SUMMARY OF REVISIONS. All sections after this have been renumbered.

RATIONALE: This section was added to describe what has been modified in Amendment 1 of the VRX-RET-E22-304 protocol.

SECTION: Throughout the protocol

REVISION: *IS:* **….Valeant Pharmaceuticals, North America…**

WAS: **…Valeant Research and Development…**

RATIONALE: Due to company restructuring, the legal entity known as Valeant Research & Development has been folded into Valeant Pharmaceuticals, North America.

SECTION: **6. STUDY SYNOPSIS, subsection "KEY INCLUSION CRITERIA"**
and
9.5 Inclusion Criteria, subsection 3

REVISION: **Amended to read (see bold text):**

…females *[deleted]* ~~had to~~ **shall** have a negative *[added]* **urine pregnancy test at Visit 0**, **which will be confirmed by the** serum β-HCG pregnancy test at the last visit *[added]* **(Visit 11)** of the Transition phase of Study VRX-RET-E22-302…

RATIONALE: The urine pregnancy test has been added to provide immediate confirmation regarding non-pregnant eligibility requirements for female patients of child-bearing potential.

SECTION: **6. STUDY SYNOPSIS, subsection, "KEY EXCLUSION CRITERIA"**
and
9.6 Exclusion Criteria

REVISION: *[Added]*

4. Female patient who has a positive pregnancy test at any time during the study.

RATIONALE: To more clearly define pregnancy exclusion criteria for female subjects participating in the VRX-RET-E22-304 trial.

SECTION: **9.7.1 Dosage Schedule and Mode of Administration**

REVISION: *[Added]*

At the investigator's discretion, patients may also start with another dose regimen that can be either BID or TID, and is not required to be equally distributed throughout the day (e.g., if a patient experiences somnolence and the investigator decides to dose the patient higher in the evening) as long as the total daily dose is within 600 -1200 mg/day.

RATIONALE: To allow more flexibility for the investigator to tailor drug dispensation specific to a patient's needs for maximum benefit of the study medication.

SECTION: **10.1 Study Flow Chart**

REVISION: Added the following visits to the current visit schedule:

- **Study Visit 1a for Hematological Monitoring (at Month 2 ±7 days)**
- **Study Visit 2a for Hematological Monitoring (at Month 4 ±7 days)**
- **Study Visit 3a for Hematological Monitoring (at Month 8 ±7 days)**
- **Study Visit 4a for Hematological Monitoring (at Month 10 ±7 days)**

Added the following under each new study visit section

Patients will return for Study Visit … At this visit, clinical laboratory tests, consisting of the following hematological evaluations (including a differential) will be performed:

- **Hemoglobin**
- **Hematocrit**
- **RBC Count**
- **WBC Count**
- **Platelet count**

RATIONALE: Added study visits per FDA comment that open label extension trials should include more frequent hematological monitoring. These are now in-line with the hematological monitoring frequencies of the double-blind VRX-RET-E22-302 trial.

SECTION: **10.3. SAFETY ASSESSMENTS**

REVISION: *[Added]*

Clinical evaluations specific to hematology will be obtained on patients on a monthly basis for approximately 4 months and then every two months for the next 6 months. (See Appendix A for Study Flow Chart.)

RATIONALE: Added paragraph per FDA comments that the open label extension trial should include more frequent hematological monitoring. These are now in-line with the hematological monitoring frequencies per the VRX-RET-E22-302, double-blind trial.

SECTION: **10.3.4 LABORATORY ASSESSMENTS, subsection 3**

REVISION: *IS:*

3. Pregnancy tests:

a. A urine pregnancy test will be performed at Visit 0 to immediately confirm non-pregnancy eligibility requirements for female patients of child-bearing potential.

b. A serum β-HCG pregnancy test for women of childbearing potential will be performed at Study Visit 5 and annually thereafter.

c. A pregnancy test should be performed during the study whenever a woman's menstrual period is 5 days late.

WAS:

3. Pregnancy tests: a serum β-HCG pregnancy test for women of childbearing potential will be performed at Study Visit 5 and annually thereafter. In addition to the scheduled pregnancy tests, a pregnancy test should be performed during the study whenever a woman's menstrual period is 5 days late.

RATIONALE: Reformatted to identify various pregnancy test requirements. Added urine pregnancy test at Visit 0 to provide immediate test results to determine non-pregnant eligibility of female patients of child-bearing potential.

SECTION: **10.3.4 LABORATORY ASSESSMENTS**

REVISION: *Added the following paragraphs*

Laboratory results specific to neutrophil counts will be flagged in the laboratory reports if the absolute neutrophil counts are < 1.0 x 10^3. For all such cases, the investigator shall report these results in an expedited manner, whether or not they are considered a serious event.

Note: For all serious hematological events or infections, the investigator shall report these in an expedited fashion, whether they are considered unexpected or not.

RATIONALE: Added per FDA comments requesting expedited reporting of patients with neutrophil counts < 1.0 x 10^3 and who have serious hematological events or infections.

SECTION: **10.5 BASELINE**

REVISION: **Amended to read (see bold text):**

…The final study eligibility…for the open-label extension study *[deleted]* ~~will~~ *[added]* **should** be performed at the last visit of the Transition phase... *[added]* **A urine pregnancy test will be performed on female patients of child-bearing potential at Visit 0 to immediately confirm the non-pregnancy eligibility requirements to enter the VRX-RET-E22-304 study.** After confirmation of *[added]* **all** final study eligibility *[added]* **requirements…** open-label study medication…will be dispensed…

RATIONALE: Added urine pregnancy test at Visit 0 to provide immediate test results to determine eligibility of female patients of child-bearing potential.

SECTION: **10.20.1 REASON FOR WITHDRAWAL**

REVISION: *Added bullet point*

- **Hematological reasons or infections – for all such patients, the investigator shall report these in an expedited manner, whether or not they are considered serious or unexpected.**

RATIONALE: Added per FDA comment requesting expedited reporting of all patient discontinuations because of hematological reasons or infections.

SECTION: **11.1 ASSESSMENT OF EFFICACY**

REVISION: *(deleted last paragraph)*

~~Besides the categorical analysis mentioned above, the continuous efficacy measurements (such as percent change in monthly total seizure rate from the baseline, etc.) will be analyzed by analysis of covariance (ANCOVA) with treatment and center as fixed factors and the baseline value of the efficacy measurement as covariate. Rank analysis of covariance will be used if necessary; however adjusted means will not be presented because the data are ranked. The responder rates will be analyzed to check the consistency of treatment response in double-blind and open-label extension studies. The complete details of efficacy analyses will be described in the Statistical Analysis Plan.~~

REVISION (cont): ***replaced with:***

This is an open-label extension study with the emphasis on safety. Efficacy is not the primary objective of this study unlike the double-blind study VRX-RET-E22-302. Descriptive statistics of efficacy measures such as number of patients, mean, standard deviation, median, minimum and maximum will be provided for continuous variables. The number and percentages in each category will be presented for categorical data. The pairwise t-test will be used to assess whether the retigabine treatment remains effective in the open-label extension study if necessary. The pairwise t-test may be sorted by the geographic region [Central/Eastern Europe vs. Rest of World (ROW)]. The safety assessments will use essentially the same descriptive statistics and pairwise t-test as mentioned above for efficacy. The complete details of efficacy analyses will be described in the Statistical Analysis Plan.

RATIONALE: As this is an open-label extension study with the emphasis on safety, as opposed to the VRX-RET-E22-302 double-blind study, which emphasizes both safety and efficacy, the statistical methods for this open-label extension study required revision to address the safety factor appropriately.

SECTION: **APPENDIX A. Study flow chart:**

REVISION: Added the following visits to the current visit schedule:

V 1a - Month 2
V 2a - Month 4
V 3a - Month 8
V 4a - Month 10

Under Study Procedures column, added a new row entitled “Hematological Evaluation.” In this new row, placed an “X” under columns V1a, V2a, V3a and V4a

RATIONALE: Added study visits per FDA comment that open label extension trials should include more frequent hematological monitoring.

SECTION: **APPENDIX A. Study flow chart:**

REVISION: Under Study Procedures column, added a new row entitled “Urine Pregnancy Test.” In this new row, placed an “X” under Visit 0.

RATIONALE: Added Urine Pregnancy Test as a new study procedure to be conducted at Visit 0 to provide immediate test results to determine non-pregnancy eligibility requirements for females of child-bearing potential.

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5. LIST OF ABBREVIATIONS

AE	=	Adverse event
AED	=	Antiepileptic drug
ALT	=	Alanine aminotransferase
ANCOVA	=	Analysis of covariance
ANOVA	=	Analysis of variance
APD	=	Action potential duration
AST	=	Aspartate aminotransferase
AUA	=	American Urological Association
AUC	=	Area under the curve
β-HCG	=	Beta human chorionic gonadotropin
BID	=	Twice a day
BMI	=	Body mass index
BP	=	Blood pressure
BUN	=	Blood urea nitrogen
CFR	=	Code of Federal Regulations
CGI	=	Clinical global impressions
CI	=	Confidence interval
C_{max}	=	Observed maximum plasma concentration
C_{min}	=	Observed minimum plasma concentration
CNS	=	Central nervous system
CPMP	=	Committee for Proprietary Medicinal Products
CRA	=	Clinical research associate
CRF	=	Case report form
CSR	=	Clinical study report
CT	=	Computerized tomography
CV	=	Curriculum vitae
CV%	=	Coefficient of variation
D-20443	=	Dihydrochloride salt of retigabine
ECG	=	Electrocardiogram
EDTA	=	Ethylenediaminetetraacetic acid
EEG	=	Electroencephalogram
EMEA	=	European Agency for the Evaluation of Medicinal Products
FDA	=	Food and Drug Administration
GABA	=	Gamma aminobutyric acid
GCP	=	Good Clinical Practice
hERG	=	Human ether-a-go-go related gene

HPF	=	High power field
HR	=	Heart rate
ICF	=	Informed consent form
ICH	=	International Conference on Harmonization
IEC	=	Independent Ethics Committee
ILAE	=	International League Against Epilepsy
IND	=	Investigational New Drug
IRB	=	Institutional Review Board
ISE	=	Integrated Summary of Efficacy
ISS	=	Integrated Summary of Safety
ITT	=	Intent to treat
i.v.	=	Intravenous
IVRS	=	Interactive Voice Response System
LFT	=	Liver function test
MAOI	=	Monamine oxidase inhibitor
MedDRA	=	Medical Dictionary for Regulatory Activities
MRI	=	Magnetic resonance imaging
msec	=	Milliseconds
MTD	=	Maximum tolerated dose
N	=	Number of patients
NAT	=	N-acetyl transferase
pH	=	Hydrogen Ion Concentration
PK	=	Pharmacokinetics
PGI	=	Patient global impressions
p.o.	=	Oral
PP	=	Per protocol
PVR	=	Post-void residual (bladder ultrasound)
QD	=	Once a day
QoL	=	Quality of Life
QOLIE-31-P	=	Quality of Life in Epilepsy-Problems Questionnaire
QTc	=	QT correction
QTcB	=	Bazett's QT correction
QTcF	=	Fridericia's QT correction
QTcI	=	Individual patient's QT correction
RBC	=	Red blood cell
REB	=	Research Ethics Board
SAE	=	Serious adverse event
SAP	=	Statistical Analysis Plan
SD	=	Standard deviation

SEM	=	Standard error of the mean
SUDEP	=	Sudden Unexplained Death in Epilepsy
$t_{1/2}$	=	Half life
TdP	=	Torsade des Pointes
TEAE	=	Treatment-emergent adverse event
TID	=	Three times a day
UDPGT	=	UDP-glucuronosyltransferase
UDS	=	unscheduled DNA synthesis
UGT	=	uridine diphosphate-glucuronosyltransferase
ULN	=	Upper limit of normal
URI	=	Upper respiratory infection
UTI	=	Urinary tract infection
Valeant	=	Valeant Pharmaceuticals, North America
VNS	=	Vagal nerve stimulator
WBC	=	White blood cell
WHO	=	World Health Organization

6. STUDY SYNOPSIS

TITLE:	A multicenter, open-label, long-term, safety, tolerability and efficacy study of retigabine in adult epilepsy patients with partial-onset seizures (Extension of Study VRX-RET-E22-302)
PHASE:	3
OBJECTIVES:	1. Primary: To evaluate the safety and tolerability of long-term therapy with retigabine administered as adjunctive therapy in adult epilepsy patients with partial-onset seizures, who completed the double-blind Study VRX-RET-E22-302. 2. Secondary: To evaluate efficacy of long-term treatment with retigabine and patient quality of life, evaluated through the QOLIE-31-P questionnaire.
STUDY DESIGN:	This is an open-label extension study of the placebo-controlled, double-blind Study VRX-RET-E22-302. Patients will be treated with 600-1200 mg/day of retigabine as an adjunct therapy to their current antiepileptic medications (AEDs) or vagal nerve stimulation as established in Study VRX-RET-E22-302. Treatment will be continued until retigabine is approved and commercially available, or until the program is discontinued, followed by a 3-week tapering period and a 30 day post study period for collection of Adverse Events (AEs).
SAMPLE SIZE:	All patients who complete Study VRX-RET-E22-302 are qualified to participate (up to approximately 510 patients).
NUMBER OF SITES:	This is a multicenter study involving approximately 55-60 study sites in the Western, Central, and Eastern Europe, Australia, Israel, and South Africa.
TREATMENT GROUPS:	All patients will be treated with 600-1200 mg/day of retigabine as an adjunct therapy to their current antiepileptic medications (AEDs) or vagal nerve stimulation.
TREATMENT DURATION:	This study will allow the patients who complete Study VRX-RET-E22-302 to continue with retigabine until the drug is approved and commercially available, or until the program is discontinued.
FORMULATION:	Retigabine will be supplied by Valeant Pharmaceuticals, Noth America in bottles containing tablets in relevant strengths: 50 mg, 100 mg, or 300 mg.

KEY INCLUSION CRITERIA:	1. Patient has successfully completed the Maintenance and Transition phases of Study VRX-RET-E22-302 for the treatment of partial-onset seizures 2. Patient is expected to benefit from participation in the study in the opinion of the Investigator. 3. Women of childbearing potential and fertile males have to agree to use a medically acceptable method of birth control. Females must have a negative urine pregnancy test at Visit 0, which will be confirmed by the serum β-HCG pregnancy test at the last visit (Visit 11) of the Transition phase of Study VRX-RET-E22-302. A woman of childbearing potential is defined as a female who is biologically capable of becoming pregnant. A medically acceptable method of birth control includes an intrauterine device in place for at least 3 months, surgical sterilization (e.g. tubal ligation), or adequate barrier methods (e.g., diaphragm and foam). An oral contraceptive alone is not considered adequate for the purpose of this study. 4. In the opinion of the Investigator, patient is able to understand verbal and written instructions and will adhere to all study schedules and requirements. 5. Patient or legal guardian (if applicable) is informed, given ample time and opportunity to read and/or understand about his/her participation in the study, and has signed and dated the written informed consent form.
KEY EXCLUSION CRITERIA:	1. Patient meets any of the withdrawal criteria in the previous VRX-RET-E22-302 study or is experiencing an ongoing serious adverse event. 2. Patient is receiving any investigational drug or using any experimental device in addition to Retigabine for treatment of epilepsy or any other medical condition. 3. Patient has any other condition that would prevent compliance with the study procedures or proper reporting of AEs. 4. Female patient who has a positive pregnancy test at any time during the study.

EVALUATION CRITERIA:	• Efficacy: Patients will keep a seizure diary throughout the study. The anticonvulsant efficacy of retigabine will be evaluated by comparison of baseline seizure frequency (obtained during the 8-week baseline period of Study VRX-RET-E22-302) with seizure frequency obtained during retigabine therapy in this study. The primary efficacy variable will be the percentage change in the monthly seizure rate from the baseline phase to open-label treatment. The proportion of responders (patients experiencing ≥ 50% reduction in seizure frequency) from baseline to the open-label treatment phase will also be evaluated. • Safety: Safety will be assessed by measurements of vital signs, weight, clinical laboratory evaluations (blood chemistry, hematology, and urinalysis), 12-lead ECGs, physical and neurological examinations, and evaluations of adverse events. Patients will additionally be assessed using the American Urological Association Symptom Index to assess the urinary voiding function.
STATISTICAL ANALYSIS:	The safety population will include all patients who successfully complete the Transition phase of Study VRX-RET-E22-302 and were included in this long-term study. The Transition phase is the phase of Study VRX-RET-E22-302 during which patients were adjusted to a 300 mg TID dose of retigabine. No other population for analysis is defined for this long-term extension study. **Assessment of Efficacy:** "Monthly total partial seizure" as well as "monthly total seizure" rates will be calculated for the entire open-label part of Study VRX-RET-E22-304 and described statistically. Baseline monthly total partial seizure rate from Study VRX-RET-E22-302 will be used for the calculation of difference and % change in the open-label study. The % change will be classified into <0, [0, 25), [25, 50), [50, 75), [75, 100] with a description of the frequencies. The responder rate (defined as a reduction in seizure frequency ≥50%) is the sum of the upper two classes.

STATISTICAL ANALYSIS (cont):	**Assessment of Efficacy (cont):** The number of seizure free days, in percent to the individual duration of the open-label treatment, will be calculated and described statistically. In addition, frequencies for this percentage will be classified into [0, 25), [25, 50), [50, 75), [75, 95), [95,100), =100. The most upper class represents completely seizure free patients, the next class almost seizure free patients. Additional details will be provided in the Statistical Analysis Plan (SAP). **Assessment of Safety:** All adverse events will be encoded according to MedDRA 8.0. Treatment emergent adverse events (TEAE) will be analyzed, i.e. all adverse events starting or worsening between the start of the long-term open-label study up to 30 days after end of taper-off study drug at the completion of the open-label study. Incidences on preferred term and body system basis will be calculated for all TEAEs. In addition, all serious adverse events (SAEs) and all AEs leading to premature discontinuation will be presented as separate listings. A prospective analysis will be conducted in order to compare the results of this study to Study VRX-RET-E22-302. TEAE from both studies (double-blind and open-label extension) will be combined, i.e. each patient will be counted just once (with patient's respective TEAE). Other safety evaluations, such as vital signs, laboratory variables, ECG variables, AUA symptom index will be analyzed descriptively. Additional details will be provided in the Statistical Analysis Plan (SAP).

7. INTRODUCTION

7.1. Background

Epilepsy is among the most common neurological disorders, affecting approximately 50 million people worldwide. Classical antiepileptic drugs (AEDs) currently provide satisfactory seizure control in approximately 70% of patients; however, the remaining 30% of epilepsy patients are refractory to treatment. The partial onset seizure is the most common type of seizure that is uncontrolled in adult patients. The introduction of new AEDs (e.g., vigabatrin, lamotrigine, gabapentin, topiramate, levetiracetam, oxcarbazepine, zonisamide, and felbamate) during the last decade has increased therapeutic possibilities. However, data from recent clinical trials demonstrate that none of the newer AEDs provides adequate seizure control in all patients. The treatment of patients that do not respond to current AEDs remains a problem and motivates the continued search for compounds with high antiepileptic potential and low rates of side effects.

Retigabine (GKE-841 or D-23129), N-[2-amino-4(4-fluorobenzylamino)-phenyl] carbamic acid ethyl ester, is a new chemical entity discovered by ASTA Medica, Germany, and was acquired by Valeant Pharmaceuticals, North America (Valeant) for development as an AED for the treatment of partial onset seizures. It is a deaza analog of flupirtine, currently marketed in some regions as a centrally acting analgesic with ancillary muscle relaxing properties.

Two Phase 3 studies (VRX-RET-E22-301 and VRX-RET-E22-302) to compare the efficacy and safety of Retigabine (600 mg/day, 900 mg/day, or 1200 mg/day) to placebo as an adjunctive therapy in refractory patients with partial-onset seizures are currently being conducted. These studies are randomized, double-blind, placebo-controlled, multi-center, parallel-group trials enrolling a total of approximately 790 patients, globally. Because of the serious nature of epilepsy, the retigabine clinical program had foreseen that all patients who enter and complete a Phase 3 study with retigabine will be given the opportunity to continue treatment, if they consent and if the Principal Investigator feels they can benefit from continued retigabine treatment. Hence, an open-label extension protocol was designed for each double-blind study.

This study is the open-label extension of the Phase 3 Study VRX-RET-E22-302. VRX-RET-E22-302 is a randomized, double-blind, placebo-controlled, parallel-group, multicenter, study of 900 mg/day and 600 mg/day retigabine versus placebo. During the 4-week titration phase patients are titrated to the target dose. 510 patients are expected to be randomized to treatment. A 12-week maintenance phase follows. All patients who wish to enter the open-label extension protocol will enter a 4-week transition phase in

which their dose will be titrated to 300 mg TID in order to maintain the blind to the maximum extent. Thereafter, the patients could enter this extension study (Study VRX-RET-E22-304). Patients who do not wish to enter the open-label extension protocol will have their dose tapered over a 3-week period.

7.2. Pharmacology

Retigabine is a novel antiepileptic compound with a broad spectrum of activity and potent anticonvulsant properties.[1,2,3,4] Retigabine opens specific potassium channels called M channels linked to the KCNQ2/3 and KCNQ3/5 heteromultimeres, which are involved in the control of the excitability of neuronal cells.[5,6,7,8,9] Mutations in these channels were understood to be linked to benign neonatal familial convulsions.[10] This fact strongly supports the experimental evidence that M-channel activation may be a unique and powerful cellular target principle for the treatment of epilepsy. Retigabine also has a concentration-dependent ancillary mode of action by increasing gamma aminobutyric acid (GABA)-evoked currents. These effects, however, were seen at concentrations of 10 µmol/L, whereas the potassium channel-opening effects occur at concentrations as low as 0.1 µmol/L.[11,12]

Results from preclinical studies revealed that retigabine is effective in a broad range of animal models of epileptic seizures. Amygdala kindling is considered the most predictive animal model for human complex partial seizures.[13] In kindled rats, intraperitoneal or oral doses of retigabine as low as 0.01 mg/kg were effective in increasing the threshold for induction.[14] At a higher dose of 5 mg/kg retigabine also reduced seizure severity, seizure duration, and post-discharge duration in fully kindled rats.[14] A clear separation between antiepileptic and neurotoxic effects is evident in these preclinical models. In addition, preclinical testing has not revealed any tolerance, dependence, or withdrawal liabilities for retigabine.[15]

Retigabine is rapidly absorbed following p.o. (oral) administration with peak plasma concentrations being achieved 1-2 hours after dosing in mice and rats.[16,17] The absolute bioavailability ranged from 44% to 70%.[17] Retigabine is extensively distributed and rapidly eliminated from all tissues in rats over a 48- to 72-hour period after dosing.[18,19] Retigabine is primarily metabolized by acetylation, glucuronidation, and oxidation mechanisms in rats and by glucuronidation in dogs. The active N-acetyl metabolite of retigabine has a pharmacological profile similar to retigabine but is 20 times less potent.[20] The major route of excretion in rats and dogs is in feces, with some compound being excreted in urine.[21,22,23] In humans, retigabine is mainly metabolized by N-glucuronidation and N-acetylation, and is not metabolized by cytochrome P450 enzymes.[20] Retigabine has low protein binding in all species, including humans.[20] Both in vivo and in vitro studies suggest that retigabine is unlikely to have any important drug-drug interactions with commonly used drugs.[24,25,26,27]

7.3. Preclinical Safety Studies

Retigabine caused motor impairment in rodents in the rotarod test, but the doses necessary were 12 to 13 times higher than those active in models of epilepsy.[28] Neither retigabine nor its N-acetyl metabolite prolonged action potential duration (APD) in cat cardiac myocytes and dog Purkinje fibers, and in fact resulted in slight shortening of APD in these test systems.[29] At concentrations 17-20 times higher than those achieved at therapeutic doses in man, retigabine caused a slight prolongation in QT interval in the isolated guinea pig heart, as well as a slight reduction in K+ current through human ether-a-go-go related gene (hERG) channels.[30] However, retigabine did not affect ECG parameters in anesthetized dogs or conscious unrestrained dogs given daily doses for 7 days.[31] Retigabine may inhibit bladder contractions and micturition in rodents due to its ability to hyperpolarize and stabilize urinary bladder myocytes through activation of K+ channels.[32]

In acute and chronic toxicity studies in rats, CNS related clinical signs including hyperkinesia, hypokinesia, disturbed coordination, stilted gait, tremor and convulsions were observed.[33] In repeat dose toxicity studies in rodents, slight hepatocellular and thyroid follicular hypertrophy were observed and were considered to be adaptive.[34,35] In repeat-dose studies in dogs but not rodents, self-limiting hepatocellular degeneration was observed in regions adjacent to the gallbladder.[36,37] In rodents but not dogs, distended urinary bladder or urinary bladder ectasia was noted with occasional secondary inflammation and ulceration of bladder wall.[34,35,36,37]

No retigabine-related effects on reproductive function were observed in male or female rats in a fertility and general reproductive performance study. No teratogenic effects of retigabine were observed in rats or rabbits.[38,39] In a perinatal and postnatal toxicity study in rats, the administration of retigabine to mated females did not have significant effect on the development of the offspring, but at the highest dose level growth was slowed, early mortality increased, and auditory reflex development was retarded in relation to the delay in growth.[40] In juvenile rats, retigabine reduced food consumption at the maximum tolerated dose but did not affect growth, reflex development, motor activity, learning, memory, clinical pathology parameters, or reproductive performance.[41]

In genetic toxicity studies, the retigabine active substance, used to manufacture finished product, tested negative for mutagenicity in the AMES test. Some exceptions could be explained as false weakly positive results due to alterations of the Salmonella tester strains.[42,43] Retigabine was negative in 2 independent mammalian cell forward gene mutation assays in presence and absence of S-9.[42] Retigabine did not induce chromosome aberrations in cultured human lymphocytes following pulse treatment for 3 or 4 hours in the absence and presence of S-9.[43] Following continued treatment for 20 or 22 hours in this test system, retigabine induced chromosome aberrations, but only in

the absence of S-9. Retigabine tested negative in genetic toxicity studies relying for metabolism on unbroken cells where the required cofactors are present at their natural concentrations as in the in vivo micronucleus test in mice and in the in vivo / in vitro unscheduled DNA synthesis (UDS) assay in hepatocytes in rats.[44, 45, 46, 47, 48]

7.4. Clinical Studies

In open-label Phase 2 studies in patients with epilepsy, the majority of patients tolerated daily doses of up to 1200 mg administered orally in two or three divided doses. The most commonly observed treatment-emergent adverse effects were in the MedDRA system organ class of Nervous System Disorders. In a double-blind parallel group study comparing different titration rates (Study 3065A1-214), it has been shown that when the starting dose of retigabine is 300 mg/day (100 mg TID), the daily dose can be titrated to 1200 mg over a 6-week period with only 13% of patients discontinuing due to adverse events.

In a randomized, double-blind, placebo-controlled, parallel group study comprising 397 patients with epilepsy (Study 3065A1-205)[52], daily doses of 900 mg and 1200 mg (administered orally in three divided doses) caused a significant reduction in total partial seizure frequency compared with placebo. While a dose of 600 mg/day resulted in greater reduction of seizure frequency than placebo, the difference was not statistically significant. The majority of patients tolerated their treatment as prescribed, with a minority discontinuing from the study prematurely. The discontinuation rate due to adverse events in 1200 mg dose group was about 2.5 times that in placebo group. This is consistent with tolerability of other AEDs. The commonly observed adverse events were in the MedDRA system organ class of Nervous System Disorder and many of these were dose related and were more frequent with retigabine compared with placebo. There were few clinically important changes in vital signs, laboratory, or ECG parameters, or physical or neurological examinations.

Patients participating in Study 3065A1-205 were eligible for an open-label extension phase (Study 3065A1-212) if they experienced improvement in seizure control, did not experience adverse events that would prevent inclusion, and did not violate the double-blind study protocol. Patients who completed the interim (transition) phase of the double-blind portion of the study started with 300 mg TID, which could be increased weekly in increments of 150 mg/day, up to a maximum of 1200 mg daily. Concomitant AEDs could be adjusted to achieve the best efficacy/safety ratio. Patients who wished to discontinue retigabine during this open-label study entered a 3-week tapering period and a 10-day post-study follow-up period. Seizure frequency was recorded daily in a diary maintained by each patient. The efficacy of retigabine was evaluated by comparison of baseline seizure frequency (determined upon entry into the double-blind phase) with

seizure frequency during retigabine therapy in the extension study; this was calculated as a percentage change in total partial seizure frequency.

Of the 279 patients who completed Study 205, 222 enrolled in the open-label extension. The majority of these patients were white (213 or 95.9%) with a median age of 36 years. A total of 126 patients were male (56.8%) and 96 (43.2%) were female. The median duration of epilepsy at study entry was 20.7 years. Of these 222 patients, 18 (8%) discontinued within the first 3 months and 41 (18%) discontinued within 6 months. The most common cause for discontinuation was lack of efficacy. The most common daily dosage of retigabine was 900 mg (105 patients; 47.3%) and only a minority of the patients titrated the dosage to 1200 mg (53 patients; 23.9%). The median treatment duration during open-label extension phase was 358 days.

The median decrease in monthly total partial seizure frequency from baseline was 48.3%, which was similar to the results with the two highest retigabine dose groups (300 and 400 mg TID) in the randomized, double-blind phase. Patients assigned to the placebo group during the double-blind phase showed the largest seizure rate improvement during the extension phase. One hundred three patients (46.4%) showed a reduction in monthly total partial seizure frequency of 50%.

7.5. Safety and Tolerability

The safety and tolerability of various dosing regimens of retigabine were examined in healthy patients participating in human pharmacology studies and in patients with epilepsy in therapeutic trials.[53,54] A total of 404 healthy subjects participated in 18 human pharmacology studies. In a multiple dose-finding trial using fixed doses, regimens up to 200 mg twice a day (BID) were safe and well tolerated and the maximum tolerated dose was found to be 250 mg BID. However, after allowing for titration to the target dose, regimens up to 350 mg BID were tolerated without any dose-limiting adverse events (AEs). In general, central nervous system (CNS) AEs limited further dose increases.[55]

A total of 605 patients with epilepsy have been enrolled in clinical studies for retigabine. Retigabine was mostly administered as add-on therapy to various established background AEDs and to a minor extent as monotherapy by using various dose-titration regimens. The maximum tolerated dose (MTD) of retigabine when added to standard AEDs was 1200 mg/day. Retigabine was administered using BID and TID regimens. The most common AEs were CNS-related (e.g., somnolence, dizziness, confusion, speech disorder, vertigo, amnesia, thinking abnormal, tremor, incoordination, ataxia, nervousness, paresthesia, abnormal gait, diplopia, and abnormal vision) and appeared in a dose-dependent manner.[55] No AEs of retigabine on cardiac safety and in particular cardiac repolarization (QTc interval) were detected. While the AE pattern from human pharmacology and clinical trials is similar, it is interesting to note that MTDs in healthy

subjects appear to be different from those achieved in patients with epilepsy, despite the concomitant medication with standard AEDs in the latter group.

A complete description of preclinical pharmacology, toxicology, PK studies, and clinical safety and efficacy studies for retigabine can be found in the Investigator's Brochure.[56]

7.6. Pharmacokinetics

7.6.1. Absorption

In clinical trials, retigabine was rapidly absorbed within 2 hours after oral administration to healthy patients.[49] The N-acetylated metabolite of retigabine was also rapidly formed, following the parent compound by approximately 2 hours. Both retigabine and the N-acetylated metabolite of retigabine were eliminated with a half-life ($t_{1/2}$) of about 8 hours. At steady state, mean observed maximum concentration (C_{max}) and area under the curve (AUC) values of the N-acetylated metabolite were within 20% of the corresponding mean values of retigabine. The trough plasma concentrations of retigabine in the afternoon or evening were significantly lower than those in the morning, possibly related to slower metabolism during sleep. The pharmacokinetics (PK) of retigabine and the N-acetylated metabolite of retigabine were linearly dose proportional for doses from 100 to 350 mg.

7.6.2. Metabolism

Investigations of metabolism in humans indicate that retigabine is mainly metabolized by N-glucuronidation and N-acetylation, and is not metabolized by cytochrome P450 enzymes.[20] In vitro studies have shown that the glucuronidation is performed by several uridine diphosphate glucuronyltransferase (UGT) isozymes.[50] The PK of retigabine and the N-acetylated metabolite of retigabine in patients with epilepsy are comparable with those in healthy subjects.[51]

7.6.3. Excretion

The major route of excretion in rats and dogs is in feces, with some compound being excreted in urine.[21,22,23] In humans, retigabine is mainly metabolized by N-glucuronidation and N-acetylation, and is not metabolized by cytochrome P450 enzymes.[20] Retigabine has low protein binding in all species, including humans.[20] Both in vivo and in vitro studies suggest that retigabine is unlikely to have any important drug-drug interactions with commonly used drugs.[24,25,26,27]

8. STUDY OBJECTIVES

- Primary: To evaluate the safety and tolerability of long-term therapy with retigabine administered as adjunctive therapy in adult epilepsy patients with

partial-onset seizures, who completed the double-blind Study VRX-RET-E22-302.

- Secondary: To evaluate efficacy of long-term treatment with retigabine and patient quality of life, evaluated through the QOLIE-31-P questionnaire.

9. STUDY DESIGN

This is an open-label extension study of the placebo controlled, double-blind Study VRX-RET-E22-302. Patients will be treated with 600-1200 mg/day of retigabine as an adjunct therapy to their current antiepileptic medications (AEDs) or vagal nerve stimulation as established in Study VRX-RET-E22-302. Following completion of the Transition Phase of the double-blind study (Study VRX-RET-E22-302), treatment in this open-label extension study will be continued until retigabine is approved and commercially available, or until the program is discontinued, followed by a 3-week tapering period and a 30 day post-study period for collection of adverse events.

9.1. Type of Study

Phase 3 open-label extension study for therapeutic use.

9.2. Study Population

Patients entering this study had to have participated in Study VRX-RET-E22-302, i.e. they had met eligibility criteria of that study and completed the double-blind phase.

9.3. Number of Study Sites

This is a multi-center open-label study involving approximately 55-60 study sites in Western, Central and Eastern Europe, Australia, Israel, and South Africa.

9.4. Treatment Duration

Following completion of the Transition Phase of the double-blind study (Study VRX-RET-E22-302), treatment in this open-label extension study will be continued until retigabine is approved and commercially available, or until the program is discontinued, followed by a 3-week tapering period and a 30 day post-study period for collection of adverse events.

9.5. Patient Inclusion Criteria

For inclusion in the study, a patient must meet and comply with the following criteria:

1. Patient has successfully completed the Maintenance and Transition phases of Study VRX-RET-E22-302 for the treatment of partial-onset seizures

2. Patient is expected to benefit from participation in the study in the opinion of the Investigator.
3. Women of childbearing potential and fertile males have to agree to use a medically acceptable method of birth control and females shall have a negative urine pregnancy test at Visit 0, which will be confirmed by the serum β-HCG pregnancy test at the last visit (Visit 11) of the Transition phase of Study VRX-RET-E22-302. A woman of childbearing potential is defined as a female who is biologically capable of becoming pregnant. A medically acceptable method of birth control includes an intrauterine device in place for at least 3 months, surgical sterilization (e.g. tubal ligation), or adequate barrier methods (e.g., diaphragm and foam). An oral contraceptive alone is not considered adequate for the purpose of this study.
4. In the opinion of the Investigator, patient is able to understand verbal and written instructions and will adhere to all study schedules and requirements.
5. Patient or legal guardian (if applicable) is informed, given ample time and opportunity to read and/or understand about his/her participation in the study, and has signed and dated the written informed consent form.

9.6. Patient Exclusion Criteria

A patient is ineligible for entering Study VRX-RET-E22-304 if any of the following exclusion criteria are met:

1. Patient meets any of the withdrawal criteria in the previous VRX-RET-E22-302 study or is experiencing an ongoing serious adverse event.
2. Patient is receiving any investigational drug or using any experimental device in addition to Retigabine for treatment of epilepsy or any other medical condition.
3. Patient has any other condition that would prevent compliance with the study procedures or proper reporting of AEs.
4. Female patient who has a positive pregnancy test at any time during the study.

9.7. Study Medication

Study medication will be supplied by Valeant Pharmaceuticals, North America, as film-coated tablets containing 50 mg, 100 mg, or 300 mg of retigabine per tablet. Tablets will be packaged in induction sealed bottles. A sufficient supply of study medication will be provided to each site for completion of the trial, based on the number of patients enrolled, study visit schedule, and the daily doses of patients. Specific dosage instructions will be provided separately to the patient. All study medication will be

dispensed by the pharmacy or an appropriately qualified member of the study staff assigned by the Principal Investigator to this task.

Patients will take the established background AEDs from their own prescriptions, and their use will be recorded.

9.7.1. Dosage Schedule and Mode of Administration

Patients who completed the Transition phase of Study VRX-RET-E22-302 will start with 300 mg three times a day (300 mg TID). Patients who were not able to tolerate the final dose adjustment (750 mg/day) during the last week of the Transition phase of Study VRX-RET-E22-302 will start with 200 mg three times a day (200 mg TID).

If, in the opinion of the Investigator, the patient was not receiving the maximum effective dose, the dose could be increased in weekly intervals of 150 mg/day, up to a maximum of 1200 mg daily (i.e. 400 mg TID). If adverse events considered to be secondary to retigabine occur, the total daily dose could be reduced by 150 mg/day every week, at Investigator discretion, as long as the dose is within 600-1200 mg/day.

At the investigator's discretion, patients may also start with another dose regimen that can be either BID or TID, and is not required to be equally distributed throughout the day (e.g., if a patient experiences somnolence and the investigator decides to dose the patient higher in the evening) as long as the total daily dose is within 600 -1200 mg/day.

After the patient has entered open-label treatment, the Investigator may add new AEDs, as long as these are approved AEDs. In addition, the existing background AED therapy can be adjusted to achieve the best efficacy/safety ratio, as needed, per Investigator discretion. If necessary, in the Investigator's judgment, all background AEDs can be discontinued to achieve monotherapy with retigabine.

Patients who permanently discontinue open-label treatment will have their dose tapered by one-third every week.

Patients will be instructed on the administration procedures for study drug. Study medication will be administered orally with or without food. The 3 daily doses are to be administered with approximately an 8-hour interval between them (for example 7am, 3pm, 11pm). Patients will continue to take their established background AEDs from their own prescriptions.

9.7.2. Study Drug Storage

All study drug sent to the study centers must be stored under the conditions specified on the drug package label (15 – 30 °C / 59 – 86 °F) in a secure area accessible only to the Investigator and his/her designated staff. All study drugs should be stored and inventoried according to applicable government regulations and study procedures.

9.7.3. Study Drug Returns

Government regulations require that all investigational drug materials not used in clinical trials be returned before or at the completion of the study.

The Investigator will return the designated copies of the completed dispensing and inventory record.

9.7.4. Method of Assigning Study Medication to Patients

Study medication will be assigned to patients through a centralized Interactive Voice Response System (IVRS), as described in the IVRS user manual that will be provided to the sites. Sites will contact the IVRS to obtain the package number assignment(s) for patients at each scheduled study visit

Study personnel will select the study medication bottle(s) from their inventory that correspond to the package number(s) assigned by IVRS. Study personnel will complete the tear-off labels on the bottles, affix them to the Investigational Product Labels page found in the patient's paper source binder, and dispense the study medication (bottles) to the patient. At subsequent study visits, study personnel will follow the same procedures as described above, contacting the IVRS as instructed in the IVRS manual.

9.7.5. Discontinuation and Tapering of Study Medication

Patients who discontinue early from the open-label extension study will have their study medication tapered over a 3-week period, reducing their daily dose by one-third per week. After tapering has been completed, patients should return to the site immediately, and complete all assessments and evaluations scheduled for Visit 5, if patient discontinued early during the first year of the open-label extension study, complete all assessments and evaluations scheduled for Visit 8 if patient discontinued early during the second year of the open-label extension study, and complete all assessments and evaluations scheduled for Visit 11 if patient discontinued early during the third year of the open-label extension study (Refer to Study Flow Chart in Appendix A).

9.8. Assessment of Compliance

Patient compliance with the study drug dosing regimen will be assessed by counts of tablets remaining in the study medication bottles that are returned at each study visit. Compliance will be based on the medication the patient was scheduled to take for the days between study visits. In addition, information on the average total daily dose will be calculated, based on the number of tablets remaining or returned in each bottle.

Patients will be instructed to bring used and unused study medication bottles with them to each study visit for accountability purposes. Tablets from each bottle for each dose strength (50 mg, 100 mg, 300 mg) will be counted and recorded to assess patient compliance and correct dosage taken. If a patient is deemed to be non-compliant with

taking study medication, the patient should be counseled by the site. If the patient continues to be non-compliant, they should be withdrawn from the study.

Along with drug accountability logs, the CRF will capture the data which includes the prescribed dosage, dates of first dose and last dose, and the number of tablets returned from each bottle for each dose strength. The CRFs will also provide a classification in to poly- or monotherapy with retigabine.

9.9. Concomitant Therapy

9.9.1. Permitted Concomitant Medications

Patients will take the background AED as prescribed by their physician. If adverse events considered to be secondary to retigabine occur, the total daily dose could be reduced by 150 mg/day every week, at Investigator discretion, as long as the dose is within 600-1200 mg/day. The background AED therapy can be adjusted if a patient develops adverse events similar to the previously experienced reaction to that AED.

After patients enter the open-label extension study, the Investigator will be allowed to adjust background AEDs, as clinically indicated. As needed, the background AED therapy can be adjusted to achieve the best efficacy/safety ratio, per Investigator discretion. If necessary, in the Investigator judgment, all background AEDs can be discontinued to achieve monotherapy with retigabine. The dose and reason to use a concomitant medication shall be recorded in the CRFs.

9.9.2. Prohibited Medications

Use of felbamate and vigabatrin are prohibited. Concurrent use of any AEDs, or of any drug that could interfere with the absorption or metabolism of retigabine and background AED is also prohibited. Medications known to lower seizures (e.g. neuroleptics) and monoamine oxidase inhibitors (MAOIs) are not allowed.

9.10. Protocol Violations and Deviations

A deviation from the protocol is an unintended and/or unanticipated departure from the procedures and/or processes approved by the Sponsor and the IRB/IEC/REB and agreed to by the Investigator. Deviations usually have an impact on individual patients or a small group of patients. A protocol violation occurs when there is non-adherence to the protocol that results in a significant, additional risk to the patient, when the patient or Investigator has failed to adhere to critical protocol requirements (inclusion/exclusion criteria) and the patient was enrolled without prior Sponsor approval, or when there is non-adherence to FDA regulations and/or ICH GCP guidelines.

The Investigator or designee must document and explain any deviation or violation from the approved protocol. The Investigator may implement a deviation from, or a change of the protocol to eliminate an immediate hazard to study patients without prior

IRB/IEC/REB approval. Immediately after the implemented deviation, violation or change to eliminate the immediate hazard to the study patient(s), the Investigator must submit a report explaining the reasons for the protocol deviation, violation or change to the Sponsor. If required, the regulatory authorities will be notified. The appropriate IRB/IEC/REB will be notified of specified, critical violations or violations that place patients at added, significant risk.

Protocol violations and deviations will be documented by the clinical monitor throughout the course of the monitoring visits. Investigators will be notified of violations and deviations and/or in writing by the monitor, and the Principal Investigator will be required to identify corrective action to eliminate future violations and deviations.

10. STUDY PROCEDURES

10.1. Study Flow Chart

As presented in the Study Flow Chart (see Appendix A), Study Visit 1 will have a window range of ±3 days. After Study Visit 1, all remaining study visits will have a window range of ±7 days around that visit day to accommodate individual schedules, as follows:

- Baseline for the open-label extension study corresponds to the assessments performed at the last visit of the Maintenance phase (Visit 9) of Study VRX-RET-E22-302 for all patients. The final, baseline eligibility assessment for the open-label extension study, including obtaining informed consent and dispensing open-label study medication will be performed at the last visit of the Transition phase (Visit 11) of Study VRX-RET-E22-302.
- Study Visit 1 (at Month 1 ±3 days)
- Study Visit 1a for Hematological Monitoring (at Month 2 ±7 days)
- Study Visit 2 (at Month 3 ±7 days)
- Study Visit 2a for Hematological Monitoring (at Month 4 ±7 days)
- Study Visit 3 (at Month 6 ±7 days)
- Study Visit 3a for Hematological Monitoring (at Month 8 ±7 days)
- Study Visit 4 (at Month 9 ±7 days)
- Study Visit 4a for Hematological Monitoring (at Month 10 ±7 days)
- Study Visit 5 (at Month 12 ±7 days).
- Study Visit 6 (at Month 16 ±7 days)

- Study Visit 7 (at Month 20 ±7 days).
- Study Visit 8 (at Month 24 ±7 days).
- Study Visit 9 (at Month 28 ±7 days).
- Study Visit 10 (at Month 32 ±7 days).
- Study Visit 11 (at Month 36 ±7 days).

Each study month will be defined as 30 calendar days. If a patient visit occurs outside the visit window, the study clinical monitor (CRA) should be notified and the reason for the deviation noted. An attempt should be made to ensure that the patient returns for subsequent visits on schedule using the last visit of the Transition phase (Visit 11) of Study VRX-RET-E22-302, which corresponds to the final, baseline eligibility visit for the open-label extension study.

10.2. Efficacy Assessments

Patients will keep a seizure diary throughout the study. The anticonvulsant efficacy of retigabine will be evaluated by comparison of baseline seizure frequency (obtained during the 8-week baseline period of Study VRX-RET-E22-302) with seizure frequency obtained during retigabine therapy in this open-label extension study (VRX-RET-E22-304). The primary efficacy variable is the percentage change in the monthly seizure rate from the baseline phase to the open-label treatment phase. The proportion of responders (patients experiencing ≥ 50% reduction in seizure frequency) from baseline to the open-label treatment phase will also be evaluated.

10.3. Safety Assessments

Safety assessments will be evaluated, based on reports of AEs and results of vital signs (supine and standing blood pressure, pulse, and temperature), weight, clinical laboratory evaluations (blood chemistries, hematology and urinalysis including microscopy), a 12-lead ECG, and physical and neurological examinations. Post-void residual (PVR) bladder ultrasounds to assess urinary retention and the American Urological Association (AUA) Symptom Index to assess urinary voiding function will also be performed during the first year of the open-label extension study.

Clinical evaluations specific to hematology will be obtained on patients on a monthly basis for approximately 4 months and then every two months for the next 6 months. (See Appendix A for Study Flow Chart.)

10.3.1. Vital Sign Measurements and Weight

Complete vital sign measurements (including supine and standing blood pressure, heart rate, and temperature) will be obtained throughout the study at all visits. Evaluations of

blood pressure and heart rate will be performed supine at each study visit, and again after the patient has been standing for approximately 2 minutes.

Weight [pounds (lb) or kilograms (kg)] will also be measured in ordinary indoor clothing (without shoes) and will be recorded at all study visits

Abnormal vital sign values that are deemed clinically significant by the Investigator will be reported as AEs in the study CRF.

10.3.2. Physical and Neurological Examinations

A complete physical and neurological examination will be performed annually at Visit 5, Visit 8, and Visit 11. Brief neurological examinations will be performed at all other study visits, including visits 1, 2, 3, 4, 6, 7, 9, and 10.

10.3.3. Electrocardiograms

A 12-lead ECG will be performed at all study visits during the first year of the open-label extension study (Visits 1, 2, 3, 4, 5), and annually at Visits 8 and 11. The ECG parameters that will be assessed are heart rate, PR interval, QRS interval, QT interval, and QTc interval. All ECG tracings will be sent to Quintiles ECG Services for central reading. Quintiles ECG Services will provide a central ECG analysis and transmit a feedback of preliminary results via facsimile to the investigation site within 24 hours. Trained technicians will read all ECGs manually, and any abnormal finding will then be over-read by board-certified cardiologists. QT intervals will be corrected using both Bazett's and Fridericia's formulas. For purposes of clinical study conduct, Bazett's QT correction will be used. For purposes of data analysis, Fridericia's QT correction will be considered as primary. Changes from baseline QTc interval will be monitored on an ongoing basis throughout this study.

Increases in Bazett's QTc interval of >60 msec from baseline or QTc interval of >500 msec anytime during the study should be confirmed on a repeat ECG. Any such occurrence shall result in notification of the Investigator and the study medical monitor for immediate review of the tracings and discussion with Valeant.

10.3.4. Laboratory Assessments

All clinical laboratory assessments will be performed by a central laboratory (Quintiles Central Laboratory Services), which will provide instructions and supplies to the study staff before study initiation. Results of the clinical laboratory assessments will be faxed back to the study site within 48 to 72 hours of sampling. Alert values will be reported to the Investigator via telephone. Approximately 7-mL sample of blood will be drawn for clinical chemistries and hematology assays. The laboratory assessments will include routine laboratory tests. The clinical laboratory evaluation will be performed at all study visits during the open-label extension study.

Because of the bladder toxicity observed in chronic toxicology studies in the rat and mouse, careful attention will be paid to plasma creatinine and blood urea nitrogen (BUN), microscopic findings on urinalysis, and any symptoms that might suggest incomplete bladder emptying (e.g., urinary tract infection, frequency, sensation of incomplete voiding, etc.). All patients will undergo urinalysis (including microscopy) at all study visits.

Any patient who has developed a clinically significant urinalysis abnormality will undergo further evaluation by an urologist (as clinically indicated) for any of the following:

- >5 red blood cells (RBC) per high power field (HPF) for males and postmenopausal females or >8 RBC/HPF for females
- >3 white blood cells(WBC) per high power field (HFP) for males and >12 WBC/HPF for females
- >1+ epithelial cells
- ≥1+ on all casts except Hyaline casts ≥2+
- >1+ blood for males and postmenopausal females
- ≥1+ trace protein [RBC; males and postmenopausal females] per high power field (HPF) or >5 white blood cells [WBC; must have 1 to few epithelial cells/HPF] per HPF, >occasional casts, >1+ blood [male and postmenopausal female patients] or >trace protein
- Have symptoms or AEs suggestive of possible hypotonicity of the bladder

The laboratory evaluations will include:

1. **Hematology:** hemoglobin, hematocrit, RBC count, WBC count with differential, and platelet count.
2. **Blood chemistries:** sodium, potassium, chloride, bicarbonate, glucose, cholesterol, creatinine, calcium, phosphorus, BUN, uric acid, total bilirubin, total protein, AST, ALT, and alkaline phosphatase levels.
3. **Pregnancy tests:**
   a. A urine pregnancy test will be performed at Visit 0 to immediately confirm non-pregnancy eligibility for female patients of child-bearing potential.
   b. A serum β-HCG pregnancy test for women of childbearing potential will be performed at Study Visit 5 and annually thereafter.
   c. A pregnancy test should be performed during the study whenever a woman's menstrual period is 5 days late.

4. **Routine urinalysis:** specific gravity, pH, protein/albumin, glucose/sugar, ketones/acetone, and hemoglobin/blood. In order to standardize measurements, Bayer multistix 8-SG or equivalent dipsticks will be used.
5. **Microscopic urinalysis:** RBC, WBC, casts, and crystals/cells.

All laboratory tests with values that become abnormal after drug administration will be repeated as clinically indicated until the values return to normal, or until the etiology has been determined and the condition considered stable. Abnormal laboratory test results that are considered to be clinically important by the Investigator will be reported as an AE in the CRF. A laboratory abnormality will not be considered an AE unless:

- Intervention is required.
- Changes in dose of retigabine are required (decrease, discontinued, interrupted).
- Other treatment/therapy is required.
- Associated with other diagnoses

Laboratory results will be reported to the Investigator who will review abnormal laboratory findings for clinical significance. The Investigator will note any laboratory test results of clinical concern, or values that were outside normal ranges and provide details of the relationship to study drug and the action taken. If a change in a laboratory value represents a medical condition, the medical condition will be listed in the AE record. If no correlation is possible, the direction of change (increase or decrease) rather than the actual value will be recorded.

Laboratory results specific to neutrophil counts will be flagged in the laboratory reports if the absolute neutrophil counts are $< 1.0 \times 10^3$. For all such cases, the investigator shall report these results in an expedited manner, whether or not they are considered a serious event.

Note: For all serious hematological events or infections, the investigator shall report these in an expedited fashion, whether they are considered unexpected or not.

10.3.5. Post-Void Residual (PVR) Bladder Ultrasound

A post-void residual (PVR) bladder ultrasound to assess urinary retention will be performed at Visits 1, 2, and 5, during the first year of the open-label extension study.

10.3.6. AUA Symptom Index

An AUA Symptom Index, a 7-item Likert-scored scale describing urinary bladder function, will be completed by the Investigator at Visits 1, 2, and 5, during the first year of

the open-label extension study, to assess the patient's urinary voiding function. The AUA Symptom Index is included in Appendix D of this protocol.

10.4. Quality of Life Assessments

The QOLIE-31-P (Version 2.0) will be utilized to assess quality of life. The QOLIE-31-P assessment must be completed by the patients. Patients who are cognitively impaired and cannot complete the QOLIE-31-P assessment may still participate in the study, by obtaining a waiver for QOLIE-31-P completion from the study medical monitor.

10.5. Baseline

Except for final study eligibility, informed consent and dispensation of open-label extension study medication, the Baseline assessments for the open-label extension study correspond to the assessments performed at the last visit of the Maintenance phase (Visit 9) of Study VRX-RET-E22-302 (See Study Flow Diagram - Appendix A). After completion of all study procedures on the last visit of the Transition phase (Visit 11) of Study VRX-RET-E22-302, patients will be allowed to enter this open-label extension study (VRX-RET-E22-304). All ongoing AEs and concomitant medications at the last visit of the Transition Phase (Visit 11) of Study VRX-RET-E22-302 will need to be transferred and captured on the appropriate open-label extension AE and Concomitant Medication CRF pages. The final study eligibility and informed consent for the open-label extension study should be performed at the last visit of the Transition phase (Visit 11) of Study VRX-RET-E22-302. A urine pregnancy test will be performed on female patients of child-bearing potential, to immediately confirm the non-pregnancy eligibility requirements tp enter the VRX-RET-E22-304 study. After confirmation of all final study eligibility requirements and obtaining proper informed consent, open-label study medication (sufficient supply of bottles at appropriate dose strengths = 50 mg, 100 mg, 300 mg) will be dispensed to patients, along with seizure diaries for completion until the next study visit (Visit 1 / Month 1).

10.6. Study Visit 1 (Month 1)

Patients will return for Study Visit 1 (Month 1). At this visit, the following evaluations will be performed:

- Seizure Diary (collection / review of current diary and dispensation of new diary)
- Brief Neurological Exam
- Vital Signs (BP, HR, and Temperature) and Body Weight
- Clinical Laboratory Tests (Blood Chemistries, Hematology, Urinalysis including microscopy)
- 12-lead ECG

- AUA Symptom Index
- PVR Bladder Ultrasound
- Adverse Events
- Concomitant Medication
- Open-Label Study Medication (collect returned medication and dispense new medication)

10.7. Study Visit 1a (Month 2)

Patients will return for Study Visit 1a (Month 2). At this visit, clinical laboratory tests, consisting of the following hematological evaluations (including a differential) will be performed:

- Hemoglobin
- Hematocrit
- RBC Count
- WBC Count
- Platelet count.

10.8. Study Visit 2 (Month 3)

Patients will return for Study Visit 2 (Month 3). At this visit, the following evaluations will be performed:

- Seizure Diary (collection / review of current diary and dispensation of new diary)
- Brief Neurological Exam
- Vital Signs (BP, HR, and Temperature) and Body Weight
- Clinical Laboratory Tests (Blood Chemistries, Hematology, Urinalysis including microscopy)
- 12-lead ECG
- AUA Symptom Index
- PVR Bladder Ultrasound
- Adverse Events
- Concomitant Medication
- QOLIE-31-P Questionnaire (completed by patient)

- Open-Label Study Medication (collect returned medication and dispense new medication)

10.9. Study Visit 2a (Month 4)

Patients will return for Study Visit 2a (Month 4). At this visit, clinical laboratory tests, consisting of the following hematological evaluations (including a differential) will be performed:

- Hemoglobin
- Hematocrit
- RBC Count
- WBC Count
- Platelet count.

10.10. Study Visit 3 (Month 6)

Patients will return for Study Visit 3 (Month 6). At this visit, the following evaluations will be performed:

- Seizure Diary (collection / review of current diary and dispensation of new diary)
- Brief Neurological Exam
- Vital Signs (BP, HR, and Temperature) and Body Weight
- Clinical Laboratory Tests (Blood Chemistries, Hematology, Urinalysis including microscopy)
- 12-lead ECG
- Adverse Events
- Concomitant Medication
- QOLIE-31-P Questionnaire (completed by patient)
- Open-Label Study Medication (collect returned medication and dispense new medication)

10.11. Study Visit 3a (Month 8)

Patients will return for Study Visit 3a (Month 8). At this visit, clinical laboratory tests, consisting of the following hematological evaluations (including a differential) will be performed:

- Hemoglobin

- Hematocrit
- RBC Count
- WBC Count
- Platelet count.

10.12. Study Visit 4 (Month 9)

Patients will return for Study Visit 4 (Month 9). At this visit, the following evaluations will be performed:

- Seizure Diary (collection / review of current diary and dispensation of new diary)
- Brief Neurological Exam
- Vital Signs (BP, HR, and Temperature) and Body Weight
- Clinical Laboratory Tests (Blood Chemistries, Hematology, Urinalysis including microscopy)
- 12-lead ECG
- Adverse Events
- Concomitant Medication
- QOLIE-31-P Questionnaire (completed by patient)
- Open-Label Study Medication (collect returned medication and dispense new medication)

10.13. Study Visit 4a (Month 10)

Patients will return for Study Visit 4a (Month 10). At this visit, clinical laboratory tests, consisting of the following hematological evaluations (including a differential), will be performed:

- Hemoglobin
- Hematocrit
- RBC Count
- WBC Count
- Platelet count.

10.14. Study Visit 5 (Month 12)

Patients will return for Study Visit 5 (Month 12). At this visit, the following evaluations will be performed:

- Seizure Diary (collection / review of current diary and dispensation of new diary)
- Complete Physical and Neurological Exam
- Vital Signs (BP, HR, and Temperature) and Body Weight
- Clinical Laboratory Tests (Blood Chemistries, Hematology, Urinalysis including microscopy)
- Serum Pregnancy Test
- 12-lead ECG
- AUA Symptom Index
- PVR Bladder Ultrasound
- Adverse Events
- Concomitant Medication
- QOLIE-31-P Questionnaire (completed by patient)
- Open-Label Study Medication (collect returned medication and dispense new medication)

10.15. Study Visits after the First Year

After the first year of open-label extension study, the study visits will occur every 4 months (3 visits per year), and will continue until retigabine is approved and commercially available, or until the program is discontinued. The assessments for the first 2 study visits of each year will be identical, and the assessments for the last study visit of each year will be identical. To provide guidance, the following study visits and assessments will be performed during the second and third years of the open-label extension study:

10.15.1. Visit 6 (Month 16)

Patients will return for Study Visit 6 (Month 16), 4 months after Visit 5. At this visit, the following evaluations will be performed:

- Seizure Diary (collection / review of current diary and dispensation of new diary)
- Brief Neurological Exam
- Vital Signs (BP, HR, and Temperature) and Body Weight

- Clinical Laboratory Tests (Blood Chemistries, Hematology, Urinalysis including microscopy)
- Adverse Events
- Concomitant Medication
- Open-Label Study Medication (Collect returned medication and dispense new medication)

10.15.2. Visit 7 (Month 20)

Patients will return for Study Visit 7 (Month 20). At this visit, the following evaluations will be performed:

- Seizure Diary (collection / review of current diary and dispensation of new diary)
- Brief Neurological Exam
- Vital Signs (BP, HR, and Temperature) and Body Weight
- Clinical Laboratory Tests (Blood Chemistries, Hematology, Urinalysis including microscopy)
- Adverse Events
- Concomitant Medication
- Open-Label Study Medication (Collect returned medication and dispense new medication)

10.15.3. Visit 8 (Month 24)

Patients will return for Study Visit 8 (Month 24). At this visit, the following evaluations will be performed:

- Seizure Diary (collection / review of current diary and dispensation of new diary)
- Complete Physical and Neurological Exam
- Vital Signs (BP, HR, and Temperature) and Body Weight
- Clinical Laboratory Tests (Blood Chemistries, Hematology, Urinalysis including microscopy)
- Serum Pregnancy Test
- 12-lead ECG
- Adverse Events
- Concomitant Medication

- QOLIE-31-P Questionnaire (completed by patient)
- Open-Label Study Medication (collect returned medication and dispense new medication)

10.15.4. Visit 9 (Month 28)

Patients will return for Study Visit 9 (Month 28). At this visit, the following evaluations will be performed:

- Seizure Diary (collection / review of current diary and dispensation of new diary)
- Brief Neurological Exam
- Vital Signs (BP, HR, and Temperature) and Body Weight
- Clinical Laboratory Tests (Blood Chemistries, Hematology, Urinalysis including microscopy)
- Adverse Events
- Concomitant Medication
- Open-Label Study Medication (Collect returned medication and dispense new medication)

10.15.5. Visit 10 (Month 32)

Patients will return for Study Visit 10 (Month 32). At this visit, the following evaluations will be performed:

- Seizure Diary (collection / review of current diary and dispensation of new diary)
- Brief Neurological Exam
- Vital Signs (BP, HR, and Temperature) and Body Weight
- Clinical Laboratory Tests (Blood Chemistries, Hematology, Urinalysis including microscopy)
- Adverse Events
- Concomitant Medication
- Open-Label Study Medication (Collect returned medication and dispense new medication)

10.15.6. Visit 11 (Month 36)

Patients will return for Study Visit 11 (Month 36). At this visit, the following evaluations will be performed:

- Seizure Diary (collection / review of current diary and dispensation of new diary)
- Complete Physical and Neurological Exam
- Vital Signs (BP, HR, and Temperature) and Body Weight
- Clinical Laboratory Tests (Blood Chemistries, Hematology, Urinalysis including microscopy)
- Serum Pregnancy Test
- 12-lead ECG
- Adverse Events
- Concomitant Medication
- QOLIE-31-P Questionnaire (completed by patient)
- Open-Label Study Medication (collect returned medication and dispense new medication)

10.16. Tapering Period

All patients who discontinue early from study treatment during the open-label extension study will have their study medication tapered over a 3-week period, reducing their daily dose by one-third per week, and return immediately for a final visit. The patients will be instructed to take the tablets from their existing study medication bottles and to follow this tapering procedure:

- During the first week of tapering, patients will no longer take the afternoon dose.
- During the second week of tapering, patients will no longer take the morning and the afternoon doses.
- During the third week of tapering, patients will take no study medication (but will continue their existing background AEDs).

During the first year, these patients should then return for a final visit to complete all assessments and evaluations scheduled for Study Visit 5. During the second year, these patients should then return for a final visit to complete all assessments and evaluations scheduled for Study Visit 8. During the third year, these patients should then return for a final visit to complete all assessments and evaluations scheduled for Study Visit 11 (Refer to Study Flow Chart in Appendix A).

During the tapering period, a new background AED should not be added until after the patient's final visit unless clinically necessary for patient safety. Unused current study medication bottles will be collected to ascertain compliance. Current study seizure

diaries will be collected and reviewed. Concomitant medications and AED usage will be documented, and adverse events will be recorded.

10.17. Replacement of Patients

Patients withdrawn from the study will not be replaced.

10.18. Unscheduled Visits

Unscheduled visits may be performed if required for assessments of laboratory parameters or clinical safety.

10.19. Laboratory Procedures

All clinical safety laboratory determinations will be performed by Quintiles Central Laboratory Services. The study staff will send the samples to the appropriate address (provided in the Central Laboratory Manual) by shipping them in the laboratory kits supplied by Quintiles Central Laboratory. Central laboratory reports will be sent to the Investigator for evaluation.

An Investigator may choose to use a local laboratory to evaluate a potential adverse event. However, for the purpose of this study, data from local laboratories will not be recorded or used in the analysis of safety. The Sponsor will not cover costs associated with the use of a local laboratory.

10.20. Early Termination / Withdrawal Visits

The Principal Investigator may discontinue a patient from the study for any of the following reasons: the patient no longer meets eligibility criteria, it is in the patient's best interest, patient preference, concurrent illness, noncompliance, etc. Patients will be informed prior to study entry that they are free to withdraw from the study at any time and for any reason. If a patient is discontinued from the study, the Investigator will immediately notify the Sponsor or the site CRA of the withdrawal.

Patients who withdraw from the study prior to completion for any reason (adverse event, withdrew consent, etc.) will have their study medication tapered over a 3-week period, reducing their daily dose by one-third per week and then return for a final visit. Patients who discontinue early during the first year of the open-label extension study will complete all assessments and evaluations scheduled for Study Visit 5. Patients who discontinue early during the second year of the open-label extension study will complete all assessments and evaluations scheduled for Study Visit 8. Patients who discontinue early during the third year of the open-label extension study will complete all assessments and evaluations scheduled for Study Visit 11 (Refer to Study Flow Chart in Appendix A).

10.20.1. Reasons for Withdrawal

Patients are free to discontinue their participation in the study at any time and without prejudice to further treatment at their local site. The Investigator must withdraw any patient from the study if that patient requests to be withdrawn.

Patients withdrawn from the study will not be replaced, regardless of the reason for withdrawal. The patient's participation in this study may be discontinued due to the following reasons:

- Patient experiences an intolerable AE.
- Investigator decides patient has an "unsatisfactory response – efficacy."
- Patient becomes pregnant.
- Patient is unwilling or unable to continue the study.
- Patient is non-compliant with study procedures.
- Patient needs medication not allowed in the protocol.
- Any clinically significant change in patient's medical condition.
- Persistent ALT or aspartate aminotransferase (AST) above 3 times the ULN; will be confirmed by repeating laboratory assessment within 1 week.
- ALT or AST levels are above 5 times the ULN at any time during the study.
- Confirmed QTc prolongation defined as QTc (Bazett's) >500 msec or an increase in QTc (Bazett's) of >60 msec from baseline.
- Investigator decides that withdrawal from the study is in the best interest of the patient.
- Request of the Sponsor
- Hematological reasons or infections – for all such patients, the investigator shall report these in an expedited manner, whether or not they are considered serious or unexpected.

10.20.2. Handling of Withdrawals

If a patient is withdrawn from the study either at the patient's request or at the Investigator's decision or the patient fails to return, every effort should be made to determine the reason. This information will be recorded on the patient's case report form (CRF) and recorded by IVRS.

All patients who withdraw from the study prematurely, regardless of cause, should have their study medication tapered over a 3-week period, reducing their daily dose by one-

third per week, and follow the tapering procedures outlined in Section 9.12 (Tapering Period).

It is important to obtain follow up data for any patient withdrawn because of an AE, abnormal laboratory test, or ECG finding. In any case, every effort must be made to undertake safety follow up procedures.

11. STATISTICAL MEASUREMENTS, EVALUATIONS AND ANALYTICAL METHODS

11.1. Assessment of Efficacy

Monthly total seizure rates will be calculated for the entire open-label part of Study VRX-RET-E22-304 and described statistically. Monthly total seizure rates observed during the open-label extension period will be compared to the monthly total seizure rates observed during the Baseline phase of the double-blind study VRX-RET-E22-302. The percent change in monthly total seizure rates from the Baseline phase will be classified into <0, [0, 25), [25, 50), [50, 75), [75, 100] and described. The responder rate during the open-label study (defined as a reduction in seizure frequency ≥50%) will also be summarized using descriptive statistics.

The number of seizure free days, in percent to the individual duration of the open-label treatment, will be calculated and summarized using descriptive statistics. This percentage will be classified into [0, 25), [25, 50), [50, 75), [75, 95), [95,100), [=100] and described statistically.

All-cause withdrawal rates will be calculated as a percentage and respective "times to event" will be described by a Kaplan-Meier survival curve. Specific reasons for withdrawal will also be described separately.

This is an open-label extension study with the emphasis on safety. Efficacy is not the primary objective of this study unlike the double-blind study VRX-RET-E22-302. Descriptive statistics of efficacy measures such as number of patients, mean, standard deviation, median, minimum and maximum will be provided for continuous variables. The number and percentages in each category will be presented for categorical data. The pairwise t-test will be used to assess whether the retigabine treatment remains effective in the open-label extension study if necessary. The pairwise t-test may be sorted by the geographic region [Central/Eastern Europe vs. Rest of World (ROW)]. The safety assessments will use essentially the same descriptive statistics and pairwise t-test as mentioned above for efficacy. The complete details of efficacy analyses will be described in the Statistical Analysis Plan.

11.2. Assessment of Safety

Adverse events (AEs) will be monitored from the start of this extension study (informed consent provided by patient at the Baseline visit) until 30 days after administration of the last dose of study drug (end of study drug taper-off). Treatment-emergent adverse events (TEAEs) will be summarized with respect to overall incidence, as well as severity and relationship of the AEs to the study drugs. AEs that result in dose modification, discontinuation of the study drug, or serious adverse events will also be summarized

AEs with onset after the initiation of study drug and within 30 days after the last dose of study drug may be considered treatment-emergent. This will include any AE with onset prior to initiation of study drug that increased in severity during the treatment period. All reported AEs including those with onset more than 30 days after the last dose of study drug will be included in the data listings.

Abnormal changes in laboratory parameters that are not disease-related will be monitored and recorded throughout the study.

All adverse events will be encoded according to MedDRA 8.0. Treatment emergent adverse events (TEAE) will be analyzed, i.e. all adverse events starting or worsening between start of long-term extension study up to 30 days after end of study drug taper-off. Incidences on preferred term and body system basis will be calculated for all TEAEs.

Different categories for causality will be recorded in the CRFs, and these 4 categories (DEFINITE, PROBABLE, POSSIBLE, and NOT RELATED) are defined in Section 11.3 (Criteria for Determining Relationship to Study Drug) of this protocol.

In addition, all SAEs and all AEs leading to premature discontinuation will be presented as separate listings. TEAE from both studies (double-blind and open-label extension) will be combined, i.e. each patient will be counted just once (with patient's respective TEAE).

Other safety evaluations, such as vital signs, physical and neurological examinations, laboratory variables, ECG variables, post-void residual bladder ultrasound, and AUA symptom index will be analyzed descriptively.

Besides descriptive statistics of the safety evaluations will be presented, the incidence of TEAEs will be compared across treatment group using Fisher's Exact test, only for those events with an incidence of ≥ 5% over all treatment groups. Fisher's Exact test will be applied if necessary for other safety evaluations (vital signs, physical and neurological examinations, laboratory variables, etc.). QTc interval prolongations will be examined by using both Bazett's and Fridericia's QT correction formulas. The complete details of safety analyses will be described in the Statistical Analysis Plan.

11.3. Determination of Sample Size

Not applicable for this long-term extension study.

11.4. Additional Statistical Considerations

11.4.1. Analysis Population

The safety population will include all patients who successfully complete the Transition phase of Study VRX-RET-E22-302 and were included in this long-term study. The Transition phase is the phase of Study VRX-RET-E22-302 during which patients were adjusted to a 300 mg TID dose. No other population for analysis is defined for this long-term extension.

11.4.2. Handling of Missing Data

No imputation will be made for missing data in the safety analyses, with the exception of incomplete date variables regarding adverse events onset date that is necessary for defining treatment-emergent adverse events. More details on imputation of partial dates will be provided in the statistical analysis plan.

12. ADVERSE EVENTS

An adverse event (AE) is defined as any untoward clinical occurrence in a patient administered a pharmaceutical drug product that does not necessarily have a causal relationship with the study drug. An AE can therefore be any unfavorable and unintended sign (including an abnormal laboratory finding), symptom or disease temporarily associated with the use of a drug product, whether or not related to the drug product.

The presence or occurrence of any of those clinical manifestations and/or alterations in clinical laboratory test results that are either present before participation in this study or that are part of the normal fluctuations or progression of their pre-study health state, will not engender an AE report to the health authorities. Clinical manifestations and/or abnormal laboratory values measured during the study that are a sign of worsening of the patient's pre-study health status or that are new findings may, if clinically relevant, be an AE reportable to the health authorities. Abnormal laboratory values represent adverse events when they are indicative of a disease or defect (e.g., reduced hematocrit resulting in anemia), necessitate intervention (e.g., administration of packed red blood cells or other therapies), or result in dose reduction or permanent discontinuation of the drug product.

Throughout the course of the study, AEs will be monitored and recorded on the patients' source documents and CRFs. The onset, seriousness, intensity, duration, actions taken, effect on study drug administration (e.g., discontinuation), the potential relationship to the study drug, as well as the date of resolution, if any, will be recorded.

12.1. Definition and Grading Intensity

Serious Adverse Events

A serious adverse event (SAE) is an event that results in any of the following outcomes:

- Death.
- Life-threatening adverse experience.
- Hospitalization (unplanned hospital stay) or prolongation of existing hospitalization.
- Persistent or significant disability/incapacity.
- Congenital anomaly/birth defect.

Important medical events that may not result in death, be life-threatening or require hospitalization may be considered serious adverse events when, based on appropriate medical judgment, they may jeopardize the subject and may require medical or surgical intervention to prevent one of the outcomes listed above.

Planned hospitalization or surgery for a condition present prior to the participant's enrollment in the study will not meet the definition of an SAE.

12.2. Intensity

The relationship to the study drug and the intensity of an AE should be assessed by the Investigator using the following guidelines:

MILD = Causing no limitation of usual activities; the patient may experience slight discomfort.

MODERATE = Causing some limitation of usual activities; the patient may experience annoying discomfort; may warrant intervention.

SEVERE = Causing inability to carry out usual activities; the patient may experience intolerable discomfort or pain; warrants intervention.

12.3. Criteria for Determining Relationship to Drug

The Investigator should assess the relationship of the adverse event to the study drug according to the following guidelines:

DEFINITE = An event that follows a reasonable temporal sequence from administration of the drug or in which the drug level has been established in body fluids or tissue; that follows a known or expected response pattern to the suspected drug; and that is confirmed by improvement on stopping or reducing the dosage

of the drug, and reappearance of the reaction on repeated exposure.

PROBABLE = An event that follows a reasonable temporal sequence from administration of the drug; that follows a known or expected response pattern to the suspected drug; that is confirmed by stopping or reducing the dosage of the drug; and that could not be reasonably explained by the known characteristics of the patient's clinical state.

POSSIBLE = An event that follows a reasonable temporal sequence from administration of the drug; that follows a known or expected response pattern to the suspected drug; but that could readily be produced by a number of other factors.

NOT RELATED = Any event that does not meet the above criteria.

12.4. Reporting of Adverse Events

All AEs should be recorded on the appropriate CRFs. All SAEs, whether or not deemed drug-related or expected, must be recorded on the CRFs and SAE forms and reported by the Investigator to the CRO (Quintiles Pharmacovigilance) assigned by the Sponsor within 24 hours by telephone and facsimile.

Complete details of SAE contact information for Quintiles Pharmacovigilance will be provided to sites in each of the participating countries in the Study Reference Manual.

A written report for an SAE must follow within 24 hours of the initial notification, including a full description of the event and any sequelae. This includes events that occur while enrolled in the study or within the Follow-Up Period. The Investigator shall comply with all applicable regulations and report all SAEs according to the requirements of their Institutional Review Board (IRB), Independent Ethics Committee (IEC) or Research Ethics Board (REB).

12.4.1. Adverse Events Follow-Up

AEs will be recorded from the start of this extension study (informed consent provided by patient at the Baseline visit) until 30 days after administration of the last dose of study medication (end of study medication taper-off). All post-treatment events will be collected through spontaneous reporting by the patient. All AEs and SAEs will be followed until the event resolves, the condition stabilizes, the event is otherwise explained, or the patient is lost to follow up. The Investigator is responsible for ensuring that follow up includes any supplemental investigations as may be indicated to elucidate the nature and/or causality of the AE. This may include additional laboratory tests or investigations,

histopathological examinations, or consultation with other health care professionals, as is practical.

13. DOSE MODIFICATIONS

Patients will be treated with 600-1200 mg/day of retigabine as an adjunct therapy to their current antiepileptic medications (AEDs) or vagal nerve stimulation as established in Study VRX-RET-E22-302.

If, in the opinion of the Investigator, the patient was not receiving the maximum effective dose, the dose could be increased in weekly intervals of 150 mg/day, up to a maximum of 1200 mg daily (i.e., 400 mg TID). If adverse events considered to be secondary to retigabine occur, the total daily dose could be reduced by 150 mg/day every week, at Investigator discretion, as long as the dose is within 600-1200 mg/day.

After the patient has entered open-label treatment, the Investigator may add new AEDs, as long as these are approved AEDs. In addition, the existing background AED therapy can be adjusted to achieve the best efficacy/safety ratio, as needed, per Investigator discretion. If necessary, in the Investigator's judgment, all background AEDs can be discontinued to achieve monotherapy with retigabine.

Patients who permanently discontinue open-label treatment will have their dose tapered by one-third every week.

If a patient experiences a serious adverse event that is categorized to be "life-threatening," all study medication must be discontinued immediately.

All dose modifications and reason(s) must be documented in the patient's source documents and the CRF.

14. MONITORING

The Sponsor or designee will monitor this clinical trial through visits scheduled to check the adequacy of staff and facilities, and to ensure adherence to the protocol, study procedures and applicable regulations. The clinical monitor will also assess proper CRF completion and retention. The Investigator and clinical staff are expected to allocate sufficient time to permit adequate review of the study's progress. The Investigator will permit trial-related monitoring, audits, IRB/IEC review and regulatory inspection(s), providing direct access to source data/documents.

15. QUALITY ASSURANCE AND QUALITY CONTROL

The Sponsor or designee will implement and maintain quality assurance and quality control systems with Standard Operating Procedures (SOPs) to ensure that this clinical trial is conducted and data are generated, documented (recorded) and reported in compliance to the protocol, Good Clinical Practice (GCP) standards, ICH and other applicable regulations.

The Sponsor is responsible for securing agreement among collaborating parties to ensure direct access to clinical-trial-related sites and material to ensure that all data are reliable and have been processed correctly.

16. DRUG ACCOUNTABILITY

The Investigator must maintain accurate records of the study medication received from the Sponsor, including date received, number of units received and lot number. The Investigator must also ensure that the drug supplies are kept secured and accounted for with access limited to those authorized by the Investigator. The study coordinator or designee must maintain accurate records of all study medication received to be able to reconcile the dispensing logs at the end of the study. The study drug records must be readily available for inspection by the study monitor and/or auditor. No medication (new or used) can be returned to the Sponsor (or its designee) or disposed of at the research unit until the Sponsor's clinical monitor has verified the accuracy of the study medication records at the site and indicated whether the medication should be destroyed at the site or returned to the Sponsor (or its designee), in which case the study monitor must indicate the name and address of the individual to whom the returned materials should be shipped.

17. LABELING AND PACKAGING OF STUDY MEDICATION

The study drug will be packaged and labeled in a manner consistent with the study design and applicable regulations. The study drug shall be identified as an investigational compound. The study protocol number will be identified on the unit label. Designated site personnel shall record the drug unit on the drug dispensing logs when the study drug is dispensed.

Each bottle of retigabine tablets (50 mg, 100 mg, or 300 mg per tablet) will be labeled with the protocol number, a unique package number, the name of the study medication, the use-by date, the Valeant address, and any additional information required by local regulations. In addition, spaces will be included for recording patient number/initials, visit number, and dated dispensed. Specific dosage instructions will be provide

separately to the patient. A sufficient supply of study medication will be provided to each site for completion of trial, based on the number of patients enrolled, study visit schedule, and the daily doses of patients.

All study medication will be dispensed by the pharmacy or an appropriately qualified member of the study staff assigned by the Principal Investigator to this task.

18. DATA HANDLING AND RECORDKEEPING

18.1. Records

The Investigator must maintain all documents and records, copies or originals, relating to the conduct of this trial. This documentation includes, but is not limited to protocols, CRFs, advertising for patient participation, AE reports, patient source data, correspondence with health authorities and IRB/IEC/REB, consent forms, Investigator's curriculum vitae, monitor visit logs, laboratory reference ranges and laboratory certification or quality control procedures and laboratory director curriculum vitae. The Investigator and affiliated institution should maintain the trial documents as required by the applicable regulations. The Investigator and affiliated institution should take measures to prevent accidental or premature destruction of documents. Clinical trial documents must be kept in the clinical site's archives indefinitely, unless written authorization is obtained from the Sponsor.

Federal regulations require that records of drug disposition, CRFs, and all reports of this investigation shall be retained by the Investigator for a minimum of 15 years after notification by Valeant that the regulatory authorities have been notified of the study's termination, or 2 years after approval of the marketing application. If the Investigator is unable to retain the study documents for the required amount of time, Valeant must be informed of the individual who will be assuming this responsibility. These documents shall be retained for a longer period, however, if required by applicable regulatory requirement(s) or if needed by the Sponsor.

18.2. Case Report Forms

All entries on a CRF are ultimately the responsibility of the Investigator, who is expected to review each form for completeness, accuracy and legibility before signing. All forms must be filled out by using black ink. Errors should be lined out but not obliterated and the correction inserted, initialed, dated and an explanation provided (if not evident). A CRF must be completed for each participant who has given informed consent. The CRFs and source documents must be made available to the study monitor for review at the time of the monitoring visits.

19. INSTITUTIONAL REVIEW BOARD

This study is to be conducted in accordance with Institutional Review Board (IRB) regulations (US 21 CFR, Part 56) or applicable Independent Ethics Committee (IEC) regulations. The IRB/IEC must review and approve the following documents, if applicable:

- Trial protocol and amendment(s).
- Written informed consent form(s) and consent form updates.
- Patient recruitment procedures (e.g., advertisements).
- Written information to be provided to patients.
- Investigator's Brochure (IB) and available safety information.
- Information about payments and compensation available to patients.

The IRB/IEC approval should be in writing, clearly identifying the trial, the documents reviewed including informed consent and date of the review. The Investigator has the responsibility to provide the Sponsor with the written IRB/IEC approval prior to initiating any study-related procedures. The Investigator also has the responsibility to inform the IRB/IEC of serious and unexpected AEs and provide the IRB/IEC with a final report upon study completion.

20. COMPLIANCE WITH THE DECLARATION OF HELSINKI

This study is to be conducted in compliance with the Declaration of Helsinki (Appendix C).

21. INFORMED CONSENT

Prior to participation in a study, the patient or patient's legal representative must sign an IRB/IEC approved written informed consent form. The approved written informed consent must abide to all applicable laws in regards to the safety and confidentiality of the patients. To obtain and document informed consent, the Investigator should comply with applicable regulations; adhere to GCP standards and the ethical principles in the Declaration of Helsinki (Appendix C).

The language in the oral and written information about the trial, including the written informed consent form should be as non-technical as practical and should be understandable to the patient or patient's legal representative and the impartial witness, where applicable. Before informed consent is obtained, the Investigator should provide

the patient or patient's legal representative ample time and opportunity to inquire about the trial and to decide whether or not to participate.

All questions about the trial should be answered to the satisfaction of the patient or the patient's legal representative. The written informed consent form should be signed and personally dated by the patient or patient's legal representative, and by the person who conducted the informed consent discussion. Patients will be informed that participation is voluntary and that he/she can withdraw from the study at any time. A signed copy of the consent form must be given to the patient, and this fact will be documented in the CRFs.

22. CHANGES TO THE PROTOCOL

The Investigator shall not implement any deviation or change to the protocol without approval by the Sponsor and prior review and documented approval and favorable opinion from the IRB/IEC/REB. The only exception is when it is necessary to eliminate immediate hazards to study patients or when changes involve only logistical or administrative aspects of the study (e.g., change in monitors, change in phone numbers).

Although the Sponsor has every intention of completing the study, the Sponsor reserves the right to discontinue the study at any time for clinical or administrative reasons.

23. REFERENCES

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56 Investigator's Brochure. Retigabine (D-23129), Valeant Research & Development, Edition Number 6, 13 June 2005.

Appendix A. Study Flow Chart (REVISED)

Study Procedures	Baseline[1]	Open-Label Extension – First Year[2,3]									Open-Label Extension - Second Year and Onward[2,3]					
	V 0	V 1	V 1a[9]	V 2	V 2a[9]	V 3	V 3a[9]	V 4	V 4a[9]	V 5[4]	V 6	V 7	V 8[4]	V 9	V 10	V 11[4]
	Mnth 0	Mnth 1	Mnth 2	Mnth 3	Mnth 4	Mnth 6	Mnth 8	Mnth 9	Mnth 10	Mnth 12	Mnth 16	Mnth 20	Mnth 24	Mnth 28	Mnth 32	Mnth 36
Eligibility/ICF	X															
Physical & Neuro Exam	X									X			X			X
Brief Neuro Exam		X		X		X		X			X	X		X	X	
Vital Signs (BP, HR, & Temp) & Wt[5]	X	X		X		X		X		X	X	X	X	X	X	X
12 Lead ECG	X	X		X		X		X		X			X			X
Blood Chem & Hematology	X	X		X		X		X		X	X	X	X	X	X	X
Hematological Evaluation			X		X		X		X							
Urinalysis (including Microscopy)	X	X		X		X		X		X	X	X	X	X	X	X
AUA Symptom Index[7]	X	X		X						X						
PVR Bladder Ultrasound[7]	X	X		X						X						
Serum Preg Test[6]	X									X			X			X
Urine Preg Test[6]	X															

Study Procedures	Baseline[1]	Open-Label Extension – First Year[2,3]									Open-Label Extension - Second Year and Onward[2,3]					
	V 0	V 1	V 1a[9]	V 2	V 2a[9]	V 3	V 3a[9]	V 4	V 4a[9]	V 5[4]	V 6	V 7	V 8[4]	V 9	V 10	V 11[4]
	Mnth 0	Mnth 1	Mnth 2	Mnth 3	Mnth 4	Mnth 6	Mnth 8	Mnth 9	Mnth 10	Mnth 12	Mnth 16	Mnth 20	Mnth 24	Mnth 28	Mnth 32	Mnth 36
Seizure Diary Review	X	X		X		X		X		X	X	X	X	X	X	X
AE Evaluation	X	X		X		X		X		X	X	X	X	X	X	X
Concomitant Medication	X	X		X		X		X		X	X	X	X	X	X	X
QOLIE-31-P Questionnaire	X			X		X		X		X			X			X
Dispense OLE Study Meds[8]	X	X		X		X		X		X	X	X	X	X	X	X
Collect Returned OLE Study Meds		X		X		X		X		X	X	X	X	X	X	X

1. Baseline for the open-label extension study corresponds to the assessments performed at the last visit of the Maintenance phase (Visit 9) of Study VRX-RET-E22-302 for all patients. The final, baseline eligibility assessment for the open-label extension study, including obtaining informed consent and dispensing open-label study medication will be performed at the last visit of the Transition phase (Visit 11) of Study VRX-RET-E22-302.
2. Study Visit 1 will have a window range of ±3 days. After Study Visit 1, all remaining study visits will have a window range of ±7 days around that visit day to accommodate individual schedules. Each study month will be defined as 30 calendar days. If a patient visit occurs outside the visit window, the study clinical monitor (CRA) should be notified and the reason for the deviation noted. An attempt should be made to ensure that the patient returns for subsequent visits on schedule using the last visit of the Transition phase (Visit 11) of Study VRX-RET-E22-302, which corresponds to the final, Baseline eligibility visit for the open-label extension study.
3. This open-label extension study will be continued until retigabine is approved and commercially available, or until the program is discontinued, followed by a 3-week tapering period and a 30 day post-study period for collection of adverse events. After the first year, the study visits will occur every 4 months (3 visits per year). After the first year, the assessments for the first 2 study visits of each year (e.g. Visits 6, 7, 9 and 10) will be identical, and the assessments for the last study visit of each year (e.g. Visits 8 and 11) will be identical.
4. All patients who discontinue early from study treatment during the open-label extension study will have their study medication tapered over a 3-week period, reducing their daily dose by one-third per week, and then return for a final visit. Patients who discontinue early during the first year of the open-label extension study will complete all assessments and evaluations scheduled for Study Visit 5. Patients who discontinue early during the second year of the open-label extension study will complete all assessments and evaluations scheduled for Study Visit 8. Patients who discontinue early during the third year of the open-label extension study will complete all assessments and evaluations scheduled for Study Visit 11. Also, all adverse events should be followed and collected up to until 30 days after administration of the last dose of study drug (end of study drug taper-off).
5. Supine and standing blood pressure, heart rate.
6. In addition to the scheduled pregnancy tests, a pregnancy test should be performed during the study whenever a woman's menstrual period is 5 days late.
7. The AUA Symptom Index and the PVR bladder ultrasound will only be performed during the first year of the open-label extension study (Visits 1, 2, and 5).
8. Dispensation of study medication is not applicable at the final study visit, if a patient has discontinued early or completed the open-label extension study.
9. Study visits added per FDA comments that the open label extension trial should include more frequent hematological monitoring. These are now in-line with the hematological monitoring frequencies per the VRX-RET-E22-302, double-blind trial.

Appendix A. Study Flow Chart (ORIGINAL)

Study Procedures	Baseline[1]	Open-Label Extension – First Year[2,3]					Open-Label Extension - Second Year and Onward[2,3]					
	Visit 0	Visit 1	Visit 2	Visit 3	Visit 4	Visit 5[4]	Visit 6	Visit 7	Visit 8[4]	Visit 9	Visit 10	Visit 11[4]
	Month 0	Month 1	Month 3	Month 6	Month 9	Month 12	Month 16	Month 20	Month 24	Month 28	Month 32	Month 36
Eligibility/Informed Consent	X											
Physical and Neurological Exam	X					X			X			X
Brief Neurological Exam		X	X	X	X		X	X		X	X	
Vital Signs (BP, HR, and Temperature) and Weight[5]	X	X	X	X	X	X	X	X	X	X	X	X
12 Lead ECG	X	X	X	X	X	X			X			X
Blood Chemistry and Hematology	X	X	X	X	X	X	X	X	X	X	X	X
Urinalysis (including Microscopy)	X	X	X	X	X	X	X	X	X	X	X	X
AUA Symptom Index[7]	X	X	X			X						
PVR Bladder Ultrasound[7]	X	X	X			X						
Serum Pregnancy Test[6]	X					X			X			X
Seizure Diary Review	X	X	X	X	X	X	X	X	X	X	X	X
AE Evaluation	X	X	X	X	X	X	X	X	X	X	X	X

Study Procedures	Baseline[1]	Open-Label Extension – First Year[2,3]					Open-Label Extension - Second Year and Onward[2,3]					
	Visit 0	Visit 1	Visit 2	Visit 3	Visit 4	Visit 5[4]	Visit 6	Visit 7	Visit 8[4]	Visit 9	Visit 10	Visit 11[4]
	Month 0	Month 1	Month 3	Month 6	Month 9	Month 12	Month 16	Month 20	Month 24	Month 28	Month 32	Month 36
Concomitant Medication	X	X	X	X	X	X	X	X	X	X	X	X
QOLIE-31-P Questionnaire	X		X	X	X	X			X			X
Dispense Open-Label Study Medication[8]	X	X	X	X	X	X	X	X	X	X	X	X
Collect Returned Open-Label Study Medication		X	X	X	X	X	X	X	X	X	X	X

1. Baseline for the open-label extension study corresponds to the assessments performed at the last visit of the Maintenance phase (Visit 9) of Study VRX-RET-E22-302 for all patients. The final, baseline eligibility assessment for the open-label extension study, including obtaining informed consent and dispensing open-label study medication will be performed at the last visit of the Transition phase (Visit 11) of Study VRX-RET-E22-302.
2. Study Visit 1 will have a window range of ±3 days. After Study Visit 1, all remaining study visits will have a window range of ±7 days around that visit day to accommodate individual schedules. Each study month will be defined as 30 calendar days. If a patient visit occurs outside the visit window, the study clinical monitor (CRA) should be notified and the reason for the deviation noted. An attempt should be made to ensure that the patient returns for subsequent visits on schedule using the last visit of the Transition phase (Visit 11) of Study VRX-RET-E22-302, which corresponds to the final, Baseline eligibility visit for the open-label extension study.
3. This open-label extension study will be continued until retigabine is approved and commercially available, or until the program is discontinued, followed by a 3-week tapering period and a 30 day post-study period for collection of adverse events. After the first year, the study visits will occur every 4 months (3 visits per year). After the first year, the assessments for the first 2 study visits of each year (e.g. Visits 6, 7, 9 and 10) will be identical, and the assessments for the last study visit of each year (e.g. Visits 8 and 11) will be identical.
4. All patients who discontinue early from study treatment during the open-label extension study will have their study medication tapered over a 3-week period, reducing their daily dose by one-third per week, and then return for a final visit. Patients who discontinue early during the first year of the open-label extension study will complete all assessments and evaluations scheduled for Study Visit 5. Patients who discontinue early during the second year of the open-label extension study will complete all assessments and evaluations scheduled for Study Visit 8. Patients who discontinue early during the third year of the open-label extension study will complete all assessments and evaluations scheduled for Study Visit 11. Also, all adverse events should be followed and collected up to until 30 days after administration of the last dose of study drug (end of study drug taper-off).
5. Supine and standing blood pressure, heart rate.
6. In addition to the scheduled pregnancy tests, a pregnancy test should be performed during the study whenever a woman's menstrual period is 5 days late.
7. The AUA Symptom Index and the PVR bladder ultrasound will only be performed during the first year of the open-label extension study (Visits 1, 2, and 5).
8. Dispensation of study medication is not applicable at the final study visit, if a patient has discontinued early or completed the open-label extension study.

Appendix B. Medical Association Declaration of Helsinki

Ethical Principles for Medical Research Involving Human Subjects

Adopted by the 18th WMA General Assembly, Helsinki, Finland, June 1964, and amended by the

29th WMA General Assembly, Tokyo, Japan, October 1975

35th WMA General Assembly, Venice, Italy, October 1983

41st WMA General Assembly, Hong Kong, September 1989

48th WMA General Assembly, Somerset West, Republic of South Africa, October 1996

and the 52nd WMA General Assembly, Edinburgh, Scotland, October 2000

Note of Clarification on Paragraph 29 added by the WMA General Assembly, Washington 2002

Note of Clarification on Paragraph 30 added by the WMA General Assembly, Tokyo 2004

INTRODUCTION

1. The World Medical Association has developed the Declaration of Helsinki as a statement of ethical principles to provide guidance to physicians and other participants in medical research involving human subjects. Medical research involving human subjects includes research on identifiable human material or identifiable data.
2. It is the duty of the physician to promote and safeguard the health of the people. The physician's knowledge and conscience are dedicated to the fulfillment of this duty.
3. The Declaration of Geneva of the World Medical Association binds the physician with the words, "The health of my patient will be my first consideration," and the International Code of Medical Ethics declares that, "A physician shall act only in the patient's interest when providing medical care which might have the effect of weakening the physical and mental condition of the patient."
4. Medical progress is based on research which ultimately must rest in part on experimentation involving human subjects.

5. In medical research on human subjects, considerations related to the well-being of the human subject should take precedence over the interests of science and society.
6. The primary purpose of medical research involving human subjects is to improve prophylactic, diagnostic and therapeutic procedures and the understanding of the aetiology and pathogenesis of disease. Even the best proven prophylactic, diagnostic, and therapeutic methods must continuously be challenged through research for their effectiveness, efficiency, accessibility and quality.
7. In current medical practice and in medical research, most prophylactic, diagnostic and therapeutic procedures involve risks and burdens.
8. Medical research is subject to ethical standards that promote respect for all human beings and protect their health and rights. Some research populations are vulnerable and need special protection. The particular needs of the economically and medically disadvantaged must be recognized. Special attention is also required for those who cannot give or refuse consent for themselves, for those who may be subject to giving consent under duress, for those who will not benefit personally from the research and for those for whom the research is combined with care.
9. Research Investigators should be aware of the ethical, legal and regulatory requirements for research on human subjects in their own countries as well as applicable international requirements. No national ethical, legal or regulatory requirement should be allowed to reduce or eliminate any of the protections for human subjects set forth in this Declaration.

BASIC PRINCIPLES FOR ALL MEDICAL RESEARCH

10. It is the duty of the physician in medical research to protect the life, health, privacy, and dignity of the human subject.
11. Medical research involving human subjects must conform to generally accepted scientific principles, be based on a thorough knowledge of the scientific literature, other relevant sources of information, and on adequate laboratory and, where appropriate, animal experimentation.
12. Appropriate caution must be exercised in the conduct of research which may affect the environment, and the welfare of animals used for research must be respected.
13. The design and performance of each experimental procedure involving human subjects should be clearly formulated in an experimental protocol. This protocol should be submitted for consideration, comment, guidance, and where appropriate, approval to a specially appointed ethical review committee, which must be independent of the Investigator, the sponsor or any other kind of undue influence. This independent

committee should be in conformity with the laws and regulations of the country in which the research experiment is performed. The committee has the right to monitor ongoing trials. The researcher has the obligation to provide monitoring information to the committee, especially any serious adverse events. The researcher should also submit to the committee, for review, information regarding funding, sponsors, institutional affiliations, other potential conflicts of interest and incentives for subjects.

14. The research protocol should always contain a statement of the ethical considerations involved and should indicate that there is compliance with the principles enunciated in this Declaration.
15. Medical research involving human subjects should be conducted only by scientifically qualified persons and under the supervision of a clinically competent medical person. The responsibility for the human subject must always rest with a medically qualified person and never rest on the subject of the research, even though the subject has given consent.
16. Every medical research project involving human subjects should be preceded by careful assessment of predictable risks and burdens in comparison with foreseeable benefits to the subject or to others. This does not preclude the participation of healthy volunteers in medical research. The design of all studies should be publicly available.
17. Physicians should abstain from engaging in research projects involving human subjects unless they are confident that the risks involved have been adequately assessed and can be satisfactorily managed. Physicians should cease any investigation if the risks are found to outweigh the potential benefits or if there is conclusive proof of positive and beneficial results.
18. Medical research involving human subjects should only be conducted if the importance of the objective outweighs the inherent risks and burdens to the subject. This is especially important when the human subjects are healthy volunteers.
19. Medical research is only justified if there is a reasonable likelihood that the populations in which the research is carried out stand to benefit from the results of the research.
20. The subjects must be volunteers and informed participants in the research project.
21. The right of research subjects to safeguard their integrity must always be respected. Every precaution should be taken to respect the privacy of the subject, the confidentiality of the patient's information and to minimize the impact of the study on the subject's physical and mental integrity and on the personality of the subject.
22. In any research on human beings, each potential subject must be adequately informed of the aims, methods, sources of funding, any possible conflicts of interest, institutional

affiliations of the researcher, the anticipated benefits and potential risks of the study and the discomfort it may entail. The subject should be informed of the right to abstain from participation in the study or to withdraw consent to participate at any time without reprisal. After ensuring that the subject has understood the information, the physician should then obtain the subject's freely-given informed consent, preferably in writing. If the consent cannot be obtained in writing, the non-written consent must be formally documented and witnessed.

23. When obtaining informed consent for the research project the physician should be particularly cautious if the subject is in a dependent relationship with the physician or may consent under duress. In that case the informed consent should be obtained by a well-informed physician who is not engaged in the investigation and who is completely independent of this relationship.

24. For a research subject who is legally incompetent, physically or mentally incapable of giving consent or is a legally incompetent minor, the Investigator must obtain informed consent from the legally authorized representative in accordance with applicable law. These groups should not be included in research unless the research is necessary to promote the health of the population represented and this research cannot instead be performed on legally competent persons.

25. When a subject deemed legally incompetent, such as a minor child, is able to give assent to decisions about participation in research, the Investigator must obtain that assent in addition to the consent of the legally authorized representative.

26. Research on individuals from whom it is not possible to obtain consent, including proxy or advance consent, should be done only if the physical/mental condition that prevents obtaining informed consent is a necessary characteristic of the research population. The specific reasons for involving research subjects with a condition that renders them unable to give informed consent should be stated in the experimental protocol for consideration and approval of the review committee. The protocol should state that consent to remain in the research should be obtained as soon as possible from the individual or a legally authorized surrogate.

27. Both authors and publishers have ethical obligations. In publication of the results of research, the Investigators are obliged to preserve the accuracy of the results. Negative as well as positive results should be published or otherwise publicly available. Sources of funding, institutional affiliations and any possible conflicts of interest should be declared in the publication. Reports of experimentation not in accordance with the principles laid down in this Declaration should not be accepted for publication.

ADDITIONAL PRINCIPLES FOR MEDICAL RESEARCH COMBINED WITH MEDICAL CARE

28. The physician may combine medical research with medical care, only to the extent that the research is justified by its potential prophylactic, diagnostic or therapeutic value. When medical research is combined with medical care, additional standards apply to protect the patients who are research subjects.

29. The benefits, risks, burdens and effectiveness of a new method should be tested against those of the best current prophylactic, diagnostic, and therapeutic methods. This does not exclude the use of placebo, or no treatment, in studies where no proven prophylactic, diagnostic or therapeutic method exists.[1]

30. At the conclusion of the study, every patient entered into the study should be assured of access to the best proven prophylactic, diagnostic and therapeutic methods identified by the study.[2]

31. The physician should fully inform the patient which aspects of the care are related to the research. The refusal of a patient to participate in a study must never interfere with the patient-physician relationship.

32. In the treatment of a patient, where proven prophylactic, diagnostic and therapeutic methods do not exist or have been ineffective, the physician, with informed consent from the patient, must be free to use unproven or new prophylactic, diagnostic and therapeutic measures, if in the physician's judgment it offers hope of saving life, re-establishing health or alleviating suffering. Where possible, these measures should be made the object of research, designed to evaluate their safety and efficacy. In all cases, new information should be recorded and, where appropriate, published. The other relevant guidelines of this Declaration should be followed.

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[1] Note of clarification on paragraph 29 of the WMA Declaration of Helsinki

The WMA hereby reaffirms its position that extreme care must be taken in making use of a placebo-controlled trial and that in general this methodology should only be used in the absence of existing proven therapy. However, a placebo-controlled trial may be ethically acceptable, even if proven therapy is available, under the following circumstances:

- Where for compelling and scientifically sound methodological reasons its use is necessary to determine the efficacy or safety of a prophylactic, diagnostic or therapeutic method; or

- Where a prophylactic, diagnostic or therapeutic method is being investigated for a minor condition and the patients who receive placebo will not be subject to any additional risk of serious or irreversible harm.

All other provisions of the Declaration of Helsinki must be adhered to, especially the need for appropriate ethical and scientific review.

[2] Note of clarification on paragraph 30 of the WMA Declaration of Helsinki

The WMA hereby reaffirms its position that it is necessary during the study planning process to identify post-trial access by study participants to prophylactic, diagnostic and therapeutic procedures identified as beneficial in the study or access to other appropriate care. Post-trial access arrangements or other care must be described in the study protocol so the ethical review committee may consider such arrangements during its review.

9.10.2004

Appendix C. American Urological Association Symptom Index

This section contained Clinical Outcome Assessment data collection questionnaires or indices, which are protected by copyright laws and therefore have been excluded.

Reference:

Barry MJ, et al. (1992). The American Urological Association symptom index for benign prostatic hyperplasia. Journal of Urology, 148: 1549–1557.

Appendix D. Protocol Agreement

PROTOCOL TITLE:

A multicenter, open-label, long-term, safety, tolerability and efficacy study of retigabine in adult epilepsy patients with partial-onset seizures (Extension of study VRX-RET-E22-302).

PROTOCOL NO: VRX-RET-E22-304

This document is a confidential communication of Valeant Pharmaceuticals, North America. The authorized Investigator agrees to personally conduct or supervise the conduct of this study as outlined in the current protocol. No changes will be made to the protocol without prior written approval from Valeant Pharmaceuticals, North America, except to protect the safety, rights and welfare of the study participants and always in compliance with all applicable Good Clinical Practices (GCP), as well as International Conference on Harmonization (ICH) and regulatory requirements. Acceptance of this document constitutes the agreement by the Investigator that no unpublished information contained herein will be published or disclosed without prior written approval from Valeant Pharmaceuticals, North America.

I have read this protocol in its entirety and agree to conduct the study accordingly.

_____ _____

Signature: Date
Principal Investigator

_____

Printed Name

COUNTRY SPECIFIC ADDENDUM FOR GERMANY

PROTOCOL: A multicenter, open-label, long-term, safety, tolerability and efficacy study of retigabine in adult epilepsy patients with partial-onset seizures (Extension of Study VRX-RET-E22-302)

INVESTIGATIONAL PRODUCT: Retigabine
50 mg., 100 mg. or 300 mg. tablets

PROTOCOL NUMBER: VRX-RET-E22-304 – Addendum 3

EUDRACT NUMBER: 2006-000956-42

IND NUMBER: 53,950

SPONSOR: Valeant Research & Development
3300 Hyland Ave.
Costa Mesa, CA 92626, USA
Telephone: [redacted]
Facsimile:

CONTRACT RESEARCH ORGANIZATION: Quintiles, Inc.
5927 South Miami Blvd.
Morrisville, NC 27560 USA

MEDICAL MONITOR: [redacted] MD
Quintiles GmbH
Hugenottenallee 167
D-63263 Neu-Isenburg, Germany
Telephone: [redacted] Ext [redacted]
Facsimile: [redacted]

Reviewed and Approved by:

[redacted]
Director, Clinical Operations

01 Nov 2006
Date

[redacted]
Sr. Director, Regulatory Affairs

02 Nov 2006
Date

[redacted]
MD, M
Chief Medical Officer

01 Nov. 2006
Date

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PROTOCOL ADDENDUM SUMMARY

OBJECTIVE: To modify and clarify sections of the Patient Informed Consent (PIC) and/or VRX-RET-E22-304 protocol.

RATIONAL: These changes are being incorporated in response to comments received from the [redacted] and the German Federal Regulatory Authority (BfArM).

SELECTION OF PATIENTS: All male and female subjects who wish to participate in the Retigabine VRX-RET-E22-304 protocol in Germany.

COLLABORATING SITES: All sites conducting the Retigabine VRX-RET-E22-304 study in Germany.

PROTOCOL MODIFICATIONS: The following modifications will be implemented:

1) VRX-RET-E22-304 protocol –
   a) All paragraphs referring to patient consent will only apply to those patients in the study who are able to consent themselves (i.e., any language referring to legal guardian/representative providing patient consent will be invalid). (CEC request to be in compliance with current German law.)
   b) References to *Appendix C* Declaration of Helsinki in Sections 19 and 20 shall be replaced with *Appendix B* Declaration of Helsinki. (BfArM)

2) PIC – The verbiage requesting the patient take part in the 304 study if he/she and the PI deem it is of benefit, has been moved to the first paragraph of the PIC. (CEC)

3) VRX-RET-E22-304 protocol and PIC –
   a) All paragraphs which include the verbiage: "…or until the program is discontinued…" *add: due to the availability of new findings impacting your (PIC) patient (protocol) safety.* (CEC)

3) VRX-RET-E22-304 protocol and PIC (cont) –

b) All paragraphs which include the verbiage: "*...an intrauterine device...*" shall be replaced with "*...a hormonal intrauterine device...*" (BfArM request to guarantee a Pearl index lower than 1% for highly effective contraceptive protection)

This addendum shall be submitted to the German Federal Regulatory Authority (BfArM) and the [redacted] for their review and approval. This shall also be submitted to the local ECs, as appropriate.

APPENDIX I

Sample of Modified Informed Consent – edited English version

(see **bold font** for sections to be modified)

PATIENT INFORMATION AND DECLARATION OF CONSENT FORM TO TAKE PART IN A CLINICAL STUDY

Study Title: A MULTICENTER, OPEN-LABEL, LONG-TERM, SAFETY, TOLERABILITY AND EFFICACY STUDY OF RETIGABINE IN ADULT EPILEPSY PATIENTS WITH PARTIAL-ONSET SEIZURES (EXTENSION OF STUDY VRX-RET-E22-302)

Protocol #: VRX-RET-E22-304

Sponsor: Valeant Research & Development
3300 Hyland Ave., Costa Mesa, CA USA

European Representative: Quintiles Ltd.
Station House
Market Street, Bracknell
UK EH14 4AP

Investigator Name:

Address:

Dear Patient,

You are being asked to participate in a clinical study because you have been diagnosed with epilepsy with partial-onset seizures and you have completed the Transition phase of the double blind study VRX-RET-E22-302 *(A Randomized, Double-Blind, Placebo-Controlled, MultiCenter, Parallel-Group Phase 3 Study to Determine the Efficacy and Safety of Two Doses of Retigabine (900 mg/day and 600 mg/day) Used as Adjunctive Therapy in Refractory Epilepsy Patients with Partial-Onset Seizures)*. In addition, in the opinion of your study doctor you may continue to benefit from treatment with retigabine.

Clinical drug studies are required to obtain information on investigational substances. Clinical trials include only patients who choose voluntarily to take part. Please take your time to make your decision. Discuss it with your friends and family.

PURPOSE AND BACKGROUND

The investigator and the sponsor are doing this Open-Label study to continue to learn more about the investigational drug retigabine and to learn how safe and tolerable retigabine is when taken for a longer period of time. An investigational drug is a drug that is still being tested and has not been approved for sale.

The same sites and the same patients who participated in the double-blind study (VRX-RET-E22-302) may participate in this open-label study.

If you have questions about or do not understand something in this informed consent form, you should ask the study doctor. Before you decide if you want to participate in the study, you may take home this form to think about or discuss it with family or friends before making your decision. Do not sign this form unless you are satisfied with the answers to your questions and decide that you want to be part of this study.

Being in this study does not replace your regular medical care.

HOW LONG WILL I BE IN THE STUDY?

If you decide to participate, you may receive retigabine until it is approved and commercially available (can be prescribed by doctors through their usual medical practice), which is projected to be through the end of 2008, or until the program is discontinued **due to the availability of new findings impacting your safety**.

INFORMATION ON THE STUDY MEDICATION

In this Open-Label study all patients will be treated with retigabine. You and your doctor will know what dose of retigabine you will be receiving. In addition, your study doctor will be allowed to adjust your retigabine dose between 600 mg–1200 mg a day, depending on your needs. You will continue to receive your other antiepileptic medications (AEDs) including vagal nerve stimulation (VNS) as you have been through your own prescription. Your study doctor may also add new AEDs or decide to adjust the dosage of your current AEDs, depending on your needs. Also depending on your needs, your study doctor may decide to stop your dosage of all your AEDs and only treat you with retigabine.

No matter what dose of retigabine you will receive, you will be asked to take retigabine tablets 3 times a day at around 8 hours apart.

APPENDIX II

Statement of Investigator

This document is a confidential communication of Valeant Research & Development, Inc. The authorized investigator agrees to personally conduct or supervise the conduct of this investigational study as outlined in this protocol Addendum 3. No changes will be made to the protocol Addendum 3 without prior written approval from Valeant Research & Development, Inc., except to protect the safety, rights and welfare of the study subjects, and always in compliance with all applicable regulations. Acceptance of this document constitutes the agreement by the investigator that no unpublished information contained herein will be published or disclosed without prior written approval from Valeant Research & Development, Inc.

I have read this protocol Addendum 3 and agree to conduct the study accordingly.

_____ _____

Signature of Principal Investigator Date

_____

Name of Principal Investigator (please print)

COUNTRY SPECIFIC ADDENDUM FOR HUNGARY

PROTOCOL: A multicenter, open-label, long-term, safety, tolerability and efficacy study of retigabine in adult epilepsy patients with partial-onset seizures (Extension of Study VRX-RET-E22-302)

INVESTIGATIONAL PRODUCT: Retigabine
50 mg., 100 mg. or 300 mg. tablets

PROTOCOL NUMBER: VRX-RET-E22-304 – Addendum 2

EUDRACT NUMBER: 2006-000956-42

IND NUMBER: 53,950

SPONSOR: Valeant Research & Development
3300 Hyland Ave.
Costa Mesa, CA 92626, USA
Telephone: [redacted]
Facsimile: [redacted]

CONTRACT RESEARCH ORGANIZATION: Quintiles, Inc.
5927 South Miami Blvd.
Morrisville, NC 27560 USA

MEDICAL MONITOR: [redacted] MD
Quintiles GmbH
Hugenottenallee 167
D-63263 Neu-Isenburg, Germany
Telephone: [redacted] Ext [redacted]
Facsimile: [redacted]

Reviewed and Approved by:

[redacted]
Director, Clinical Operations

01 August 2006
Date

[redacted]
Sr. Director, Regulatory Affairs

01 August 2006
Date

[redacted] MD, MPH
Chief Medical Officer

01 August 2006
Date

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PROTOCOL ADDENDUM SUMMARY

OBJECTIVE: An additional liver enzyme test, known as gamma-glutamyl transferase (GGT), will be performed on patients participating in the Retigabine VRX-RET-E22-304 trial.

RATIONAL: This is an added safety requirement being requested by the [redacted] in conjunction with the Regulatory Authority of Hungary, for liver function testing.

SELECTION OF PATIENTS: All male and female subjects participating in the Retigabine VRX-RET-E22-304 trial in Hungary will be required to submit a blood sample for GGT testing at each scheduled visit.

COLLABORATING SITES: All sites conducting the Retigabine VRX-RET-E22-304 study in Hungary will take an additional blood draw from each patient during their scheduled visit and submit the sample to their local lab for GGT analysis.

All sites must provide this addendum to their local ECs for review and approval.

INFORMED CONSENT: The Informed Consent Form (ICF) will be amended to reflect the change in the patient's total blood volume to be drawn for lab analysis. (See Appendix 2 for sample ICF.)

The amended ICF shall be submitted to the appropriate ECs for review and approval.

APPENDIX I

Sample Collection and Lab Review for GGT Testing

General Instructions:

Patients participating in this study will be required to have an additional blood draw for gamma-glutamyl transferase (GGT) testing. The blood sample for GGT analysis will consist of approximately 5 mL. This will be collected and placed in a separate tube from the other 7 mL blood draw that is required for the clinical chemistries and hematology assays that are part of this study protocol. Furthermore, the additional 5 mL sample will be sent to the site's local lab, with a laboratory requisition for GGT analysis.

Once the site receives the results for the GGT analysis from their local lab, the PI will review for abnormal lab results. Should there be any abnormal results, the same requirements will apply as indicated in section 5.6.4 Laboratory Assessments of the study protocol. The GGT lab report shall be initialed and dated by the PI to indicate his review of the results and included in the patients' source documents.

Collection Time Points for GGT testing:

The additional GGT sample will be drawn during each patient's scheduled visit.

Laboratory Collection Kits and Requisitions:

These will be supplied by the local lab as appropriate.

Sample of Modified Informed Consent – edited English version

(see deleted and **bold** font for section to be modified)

PATIENT CONSENT TO PARTICIPATE IN A CLINICAL RESEARCH STUDY

Title: A MULTICENTER, OPEN-LABEL, LONG-TERM, SAFETY, TOLERABILITY AND EFFICACY STUDY OF RETIGABINE IN ADULT EPILEPSY PATIENTS WITH PARTIAL-ONSET SEIZURES (EXTENSION OF STUDY VRX-RET-E22-302)

Protocol #: VRX-RET-E22-304

Sponsor: Valeant Research & Development
3300 Hyland Ave., Costa Mesa, CA USA
telephone number [redacted]
fax number [redacted]
e-mail address: [redacted]

Investigator Name:

Address: [include telephone number, fax number and e-mail address]

PURPOSE AND BACKGROUND

This is a clinical trial (a type of research study). Clinical trials include only patients who choose to take part. Please take your time to make your decision. Discuss it with your friends and family.

You are being asked to participate in this Open-Label study because you have completed the Transition phase of the double-blind study VRX-RET-E22-302 *(A Randomized, Double-Blind, Placebo-Controlled, MultiCenter, Parallel-Group Phase 3 Study to Determine the Efficacy and Safety of Two Doses of Retigabine (900 mg/day and 600 mg/day) Used as Adjunctive Therapy in Refractory Epilepsy Patients with Partial-Onset Seizures).* In addition, in the opinion of your study doctor you may continue to benefit from treatment with retigabine.

Dr. *<insert Principal Investigator>* and the sponsor, Valeant Research & Development, are doing this Open-Label study to continue to learn more about the investigational drug retigabine and to learn how safe and tolerable retigabine is when taken for a longer period of time. An investigational drug is a drug that is still being tested and has not been approved for sale.

The same sites and the same patients who participated in the double-blind study (VRX-RET-E22-302) may participate in this open-label study.

If you have questions about or do not understand something in this informed consent form, you should ask the study doctor. Before you decide if you want to participate in the study, you may take home a copy of this form to think about or discuss it with family or friends before making your decision. Do not sign this form unless you are satisfied with the answers to your questions and decide that you want to be part of this study.

Your decision to take part in this study is voluntary. You are free to either take part or not take part in this study.

Being in this study does not replace your regular medical care.

HOW LONG WILL I BE IN THE STUDY?

If you decide to participate, you may receive retigabine until it is approved and commercially available (can be prescribed by doctors through their usual medical practice) or until the program is discontinued.

WHAT IS INVOLVED IN THE STUDY?

Dosing

In this Open-Label study all patients will be treated with retigabine. You and your doctor will know what dose of retigabine you will be receiving. In addition, your study doctor will be allowed to adjust your retigabine dose between 600 mg–1200 mg a day, depending on your needs. You will continue to receive your other antiepileptic medications (AEDs) including vagal nerve stimulation (VNS) as you have been through your own prescription. Your study doctor may also add new AEDs or decide to adjust the dosage of your current AEDs, depending on your needs. Also depending on your needs, your study doctor may decide to stop your dosage of all your AEDs and only treat you with retigabine.

No matter what dose of retigabine you will receive, you will be asked to take retigabine tablets 3 times a day at around 8 hours apart.

Procedures

During the first year of this Open-Label study you will be asked to visit the research clinic 5 times. These visits will occur on months 1, 3, 6, 9, and 12. Thereafter, you will then be asked to visit the research clinic 3 times a year. Each visit will be approximately 4 months apart. Clinic visits will last about 1½ to 2 hours depending on what study procedures are scheduled for that day.

The following procedures will be done at various times throughout the study:

(1) Physical exams (including weight)
(2) Neurological exams
(3) Blood pressure, heart rate (once while lying down and once after standing for 2 minutes) and temperature
(4) 12-lead ECGs (electrical tracing of your heart)
(5) Blood samples (approximately *[delete]* ~~1.5 teaspoons or 7 mL~~ *[add]* **12 ml** each time) to determine your overall health
(6) Serum pregnancy tests (if you are a female of child-bearing potential)

APPENDIX III

Statement of Investigator

This document is a confidential communication of Valeant Research & Development, Inc. The authorized investigator agrees to personally conduct or supervise the conduct of this investigational study as outlined in this protocol Addendum 1. No changes will be made to the protocol Addendum 1 without prior written approval from Valeant Research & Development, Inc., except to protect the safety, rights and welfare of the study subjects, and always in compliance with all applicable regulations. Acceptance of this document constitutes the agreement by the investigator that no unpublished information contained herein will be published or disclosed without prior written approval from Valeant Research & Development, Inc.

I have read this protocol Addendum 2 and agree to conduct the study accordingly.

_____ _____

Signature of Principal Investigator Date

_____

Name of Principal Investigator (please print)

COUNTRY SPECIFIC ADDENDUM FOR GERMANY

PROTOCOL: A multicenter, open-label, long-term, safety, tolerability and efficacy study of retigabine in adult epilepsy patients with partial-onset seizures (Extension of Study VRX-RET-E22-302)

INVESTIGATIONAL PRODUCT: Retigabine
50 mg., 100 mg. or 300 mg. tablets

PROTOCOL NUMBER: VRX-RET-E22-304 – Addendum 1

EUDRACT NUMBER: 2006-000956-42

IND NUMBER: 53,950

SPONSOR: Valeant Research & Development
3300 Hyland Ave.
Costa Mesa, CA 92626, USA
Telephone: [redacted]
Facsimile:

CONTRACT RESEARCH ORGANIZATION: Quintiles, Inc.
5927 South Miami Blvd.
Morrisville, NC 27560 USA

MEDICAL MONITOR: [redacted] MD
Quintiles GmbH
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D-63263 Neu-Isenburg, Germany
Telephone: [redacted] Ext [redacted]
Facsimile: [redacted]

Reviewed and Approved by:

[redacted]
Director, Clinical Operations

20 July 2006
Date

[redacted]
Sr. Director, Regulatory Affairs

21 July 2006
Date

[redacted] MD, MPH,
Chief Medical Officer

20 July 2006
Date

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PROTOCOL ADDENDUM SUMMARY

OBJECTIVE: A study end date for patients wishing to participate in the Retigabine Protocol VRX-RET-E22-304 trial is being added. The end date is projected to be through the end of 2008, or until the program is discontinued.

RATIONAL: This is a Clinical Trial Insurance requirement for Germany in collaboration with the [redacted]

SELECTION OF PATIENTS: All male and female subjects who wish to participate in the Retigabine VRX-RET-E22-304 protocol in Germany shall be informed of the study end date.

COLLABORATING SITES: All sites conducting the Retigabine VRX-RET-E22-304 study in Germany must provide this addendum to their local ECs for review and approval.

INFORMED CONSENT: The Informed Consent will be amended to reflect the change in this addendum. The amended consent shall be submitted to the appropriate ECs for review and approval.

APPENDIX I

Sample of Modified Informed Consent – edited English version

(see **bold font** for section to be modified)

PATIENT INFORMATION AND DECLARATION OF CONSENT FORM
TO TAKE PART IN A CLINICAL STUDY

Study Title: A MULTICENTER, OPEN-LABEL, LONG-TERM, SAFETY, TOLERABILITY AND EFFICACY STUDY OF RETIGABINE IN ADULT EPILEPSY PATIENTS WITH PARTIAL-ONSET SEIZURES (EXTENSION OF STUDY VRX-RET-E22-302)

Protocol #: VRX-RET-E22-304

Sponsor: Valeant Research & Development
3300 Hyland Ave., Costa Mesa, CA USA

European Representative: Quintiles Ltd.
Station House
Market Street, Bracknell
UK EH14 4AP

Investigator Name:

Address:

Dear Patient,

Your doctor has invited you to take part in a clinical study. Clinical drug studies are required to obtain information on investigational substances. Clinical trials include only patients who choose voluntarily to take part. Please take your time to make your decision. Discuss it with your friends and family.

PURPOSE AND BACKGROUND

You are being asked to participate in this Open-Label study because you have completed the Transition phase of the double-blind study VRX-RET-E22-302 *(A Randomized, Double-Blind, Placebo-Controlled, MultiCenter, Parallel-Group Phase 3 Study to Determine the Efficacy and*

Safety of Two Doses of Retigabine (900 mg/day and 600 mg/day) Used as Adjunctive Therapy in Refractory Epilepsy Patients with Partial-Onset Seizures). In addition, in the opinion of your study doctor you may continue to benefit from treatment with retigabine.

The investigator and the sponsor are doing this Open-Label study to continue to learn more about the investigational drug retigabine and to learn how safe and tolerable retigabine is when taken for a longer period of time. An investigational drug is a drug that is still being tested and has not been approved for sale.

The same sites and the same patients who participated in the double-blind study (VRX-RET-E22-302) may participate in this open-label study.

If you have questions about or do not understand something in this informed consent form, you should ask the study doctor. Before you decide if you want to participate in the study, you may take home this form to think about or discuss it with family or friends before making your decision. Do not sign this form unless you are satisfied with the answers to your questions and decide that you want to be part of this study.

Being in this study does not replace your regular medical care.

HOW LONG WILL I BE IN THE STUDY?

If you decide to participate, you may receive Retigabine until it is approved and commercially available (can be prescribed by doctors through their usual medical practice), which is projected to be through the end of 2008, or until the program is discontinued.

INFORMATION ON THE STUDY MEDICATION

In this Open-Label study all patients will be treated with retigabine. You and your doctor will know what dose of retigabine you will be receiving. In addition, your study doctor will be allowed to adjust your retigabine dose between 600 mg–1200 mg a day, depending on your needs. You will continue to receive your other antiepileptic medications (AEDs) including vagal nerve stimulation (VNS) as you have been through your own prescription. Your study doctor may also add new AEDs or decide to adjust the dosage of your current AEDs, depending on your needs. Also depending on your needs, your study doctor may decide to stop your dosage of all your AEDs and only treat you with retigabine.

No matter what dose of retigabine you will receive, you will be asked to take retigabine tablets 3 times a day at around 8 hours apart.

APPENDIX II

Statement of Investigator

This document is a confidential communication of Valeant Research & Development, Inc. The authorized investigator agrees to personally conduct or supervise the conduct of this investigational study as outlined in this protocol Addendum 1. No changes will be made to the protocol Addendum 1 without prior written approval from Valeant Research & Development, Inc., except to protect the safety, rights and welfare of the study subjects, and always in compliance with all applicable regulations. Acceptance of this document constitutes the agreement by the investigator that no unpublished information contained herein will be published or disclosed without prior written approval from Valeant Research & Development, Inc.

I have read this protocol Addendum 1 and agree to conduct the study accordingly.

_____ _____

Signature of Principal Investigator Date

_____

Name of Principal Investigator (please print)

Clinical Study Protocol

Retigabine

A multicenter, open-label, long-term, safety, tolerability and efficacy study of retigabine in adult epilepsy patients with partial-onset seizures (Extension of Study VRX-RET-E22-302)

Protocol Number VRX-RET-E22-304

1. TITLE PAGE

STUDY TITLE:	A multicenter, open-label, long-term, safety, tolerability and efficacy study of retigabine in adult epilepsy patients with partial-onset seizures (Extension of Study VRX-RET-E22-302)
INVESTIGATIONAL PRODUCT:	Retigabine
IND NUMBER:	53,950
PROTOCOL NUMBER:	VRX-RET-E22-304
PHASE:	3
SPONSOR:	Valeant Research & Development 3300 Hyland Avenue Costa Mesa, CA 92626 USA Main Office: [redacted] FAX: [redacted]
CONTRACT RESEARCH ORGANIZATION (CRO):	Quintiles, Inc. 5927 South Miami Blvd. Morrisville, NC 27560
CRO MEDICAL MONITOR:	[redacted] MD Quintiles GmbH Hugenottenallee 167 D-63263 Neu-Isenberg, Germany Tel: [redacted] Ext. [redacted] Facsimile: [redacted]
COUNTRIES:	Western, Central and Eastern Europe, Australia, Israel, and South Africa

VALEANT
Research & Development

2. PROTOCOL SIGN-OFF SHEET

PROTOCOL TITLE: A multicenter, open-label, long-term, safety, tolerability and efficacy study of retigabine in adult epilepsy patients with partial-onset seizures (Extension of Study VRX-RET-E22-302)

PROTOCOL NUMBER: VRX-RET-E22-304

VERSION: February 10, 2006

Reviewed and Approved By:

[redacted]
Associate Director [redacted]ical Operations
2 / 10 / 2006
Date

[redacted]
PhD
Vice Pres[redacted]ent [redacted]ou[redacted]rs
10 / FEB / 2006
Date

[redacted]
PhD
[redacted]ctor, Biometrics
10 / Feb / 2006
Date

[redacted]
PhD
Vice President, Drug Development
2 / 10 / 2006
Date

[redacted]
PhD
Senior Director, Clinical Research
2 / 10 / 06
Date

[redacted]
MD, PhD
Consultant, Neurologist

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4. LIST OF ABBREVIATIONS

AE	=	Adverse event
AED	=	Antiepileptic drug
ALT	=	Alanine aminotransferase
ANCOVA	=	Analysis of covariance
ANOVA	=	Analysis of variance
APD	=	Action potential duration
AST	=	Aspartate aminotransferase
AUA	=	American Urological Association
AUC	=	Area under the curve
β-HCG	=	Beta human chorionic gonadotropin
BID	=	Twice a day
BMI	=	Body mass index
BP	=	Blood pressure
BUN	=	Blood urea nitrogen
CFR	=	Code of Federal Regulations
CGI	=	Clinical global impressions
CI	=	Confidence interval
C_{max}	=	Observed maximum plasma concentration
C_{min}	=	Observed minimum plasma concentration
CNS	=	Central nervous system
CPMP	=	Committee for Proprietary Medicinal Products
CRA	=	Clinical research associate
CRF	=	Case report form
CSR	=	Clinical study report
CT	=	Computerized tomography
CV	=	Curriculum vitae
CV%	=	Coefficient of variation
D-20443	=	Dihydrochloride salt of retigabine
ECG	=	Electrocardiogram
EDTA	=	Ethylenediaminetetraacetic acid
EEG	=	Electroencephalogram
EMEA	=	European Agency for the Evaluation of Medicinal Products
FDA	=	Food and Drug Administration
GABA	=	Gamma aminobutyric acid
GCP	=	Good Clinical Practice
hERG	=	Human ether-a-go-go related gene

HPF	=	High power field
HR	=	Heart rate
ICF	=	Informed consent form
ICH	=	International Conference on Harmonization
IEC	=	Independent Ethics Committee
ILAE	=	International League Against Epilepsy
IND	=	Investigational New Drug
IRB	=	Institutional Review Board
ISE	=	Integrated Summary of Efficacy
ISS	=	Integrated Summary of Safety
ITT	=	Intent to treat
i.v.	=	Intravenous
IVRS	=	Interactive Voice Response System
LFT	=	Liver function test
MAOI	=	Monamine oxidase inhibitor
MedDRA	=	Medical Dictionary for Regulatory Activities
MRI	=	Magnetic resonance imaging
msec	=	Milliseconds
MTD	=	Maximum tolerated dose
N	=	Number of patients
NAT	=	N-acetyl transferase
pH	=	Hydrogen Ion Concentration
PK	=	Pharmacokinetics
PGI	=	Patient global impressions
p.o.	=	Oral
PP	=	Per protocol
PVR	=	Post-void residual (bladder ultrasound)
QD	=	Once a day
QoL	=	Quality of Life
QOLIE-31-P	=	Quality of Life in Epilepsy-Problems Questionnaire
QTc	=	QT correction
QTcB	=	Bazett's QT correction
QTcF	=	Fridericia's QT correction
QTcI	=	Individual patient's QT correction
RBC	=	Red blood cell
REB	=	Research Ethics Board
SAE	=	Serious adverse event
SAP	=	Statistical Analysis Plan
SD	=	Standard deviation

SEM	=	Standard error of the mean
SUDEP	=	Sudden Unexplained Death in Epilepsy
$t_{1/2}$	=	Half life
TdP	=	Torsade des Pointes
TEAE	=	Treatment-emergent adverse event
TID	=	Three times a day
UDPGT	=	UDP-glucuronosyltransferase
UDS	=	unscheduled DNA synthesis
UGT	=	uridine diphosphate-glucuronosyltransferase
ULN	=	Upper limit of normal
URI	=	Upper respiratory infection
UTI	=	Urinary tract infection
Valeant	=	Valeant Research & Development
VNS	=	Vagal nerve stimulator
WBC	=	White blood cell
WHO	=	World Health Organization

5. STUDY SYNOPSIS

TITLE:	A multicenter, open-label, long-term, safety, tolerability and efficacy study of retigabine in adult epilepsy patients with partial-onset seizures (Extension of Study VRX-RET-E22-302)
PHASE:	3
OBJECTIVES:	1. Primary: To evaluate the safety and tolerability of long-term therapy with retigabine administered as adjunctive therapy in adult epilepsy patients with partial-onset seizures, who completed the double-blind Study VRX-RET-E22-302. 2. Secondary: To evaluate efficacy of long-term treatment with retigabine and patient quality of life, evaluated through the QOLIE-31-P questionnaire.
STUDY DESIGN:	This is an open-label extension study of the placebo-controlled, double-blind Study VRX-RET-E22-302. Patients will be treated with 600-1200 mg/day of retigabine as an adjunct therapy to their current antiepileptic medications (AEDs) or vagal nerve stimulation as established in Study VRX-RET-E22-302. Treatment will be continued until retigabine is approved and commercially available, or until the program is discontinued, followed by a 3-week tapering period and a 30 day post study period for collection of Adverse Events (AEs).
SAMPLE SIZE:	All patients who complete Study VRX-RET-E22-302 are qualified to participate (up to approximately 510 patients).
NUMBER OF SITES:	This is a multicenter study involving approximately 55-60 study sites in the Western, Central, and Eastern Europe, Australia, Israel, and South Africa.
TREATMENT GROUPS:	All patients will be treated with 600-1200 mg/day of retigabine as an adjunct therapy to their current antiepileptic medications (AEDs) or vagal nerve stimulation.
TREATMENT DURATION:	This study will allow the patients who complete Study VRX-RET-E22-302 to continue with retigabine until the drug is approved and commercially available, or until the program is discontinued.
FORMULATION:	Retigabine will be supplied by Valeant Research & Development in bottles containing tablets in relevant strengths: 50 mg, 100 mg, or 300 mg.

KEY INCLUSION CRITERIA:	1. Patient has successfully completed the Maintenance and Transition phases of Study VRX-RET-E22-302 for the treatment of partial-onset seizures 2. Patient is expected to benefit from participation in the study in the opinion of the Investigator. 3. Women of childbearing potential and fertile males have to agree to use a medically acceptable method of birth control and females had to have a negative serum β-HCG pregnancy test at the last visit of the Transition phase of Study VRX-RET-E22-302. A woman of childbearing potential is defined as a female who is biologically capable of becoming pregnant. A medically acceptable method of birth control includes an intrauterine device in place for at least 3 months, surgical sterilization (e.g. tubal ligation), or adequate barrier methods (e.g., diaphragm and foam). An oral contraceptive alone is not considered adequate for the purpose of this study. 4. In the opinion of the Investigator, patient is able to understand verbal and written instructions and will adhere to all study schedules and requirements. 5. Patient or legal guardian (if applicable) is informed, given ample time and opportunity to read and/or understand about his/her participation in the study, and has signed and dated the written informed consent form.
KEY EXCLUSION CRITERIA:	1. Patient meets any of the withdrawal criteria in the previous VRX-RET-E22-302 study or is experiencing an ongoing serious adverse event. 2. Patient is receiving any investigational drug or using any experimental device in addition to Retigabine for treatment of epilepsy or any other medical condition. 3. Patient has any other condition that would prevent compliance with the study procedures or proper reporting of AEs.

EVALUATION CRITERIA:

- Efficacy: Patients will keep a seizure diary throughout the study. The anticonvulsant efficacy of retigabine will be evaluated by comparison of baseline seizure frequency (obtained during the 8-week baseline period of Study VRX-RET-E22-302) with seizure frequency obtained during retigabine therapy in this study. The primary efficacy variable will be the percentage change in the monthly seizure rate from the baseline phase to open-label treatment. The proportion of responders (patients experiencing ≥ 50% reduction in seizure frequency) from baseline to the open-label treatment phase will also be evaluated.
- Safety: Safety will be assessed by measurements of vital signs, weight, clinical laboratory evaluations (blood chemistry, hematology, and urinalysis), 12-lead ECGs, physical and neurological examinations, and evaluations of adverse events. Patients will additionally be assessed using the American Urological Association Symptom Index to assess the urinary voiding function.

STATISTICAL ANALYSIS:

The safety population will include all patients who successfully complete the Transition phase of Study VRX-RET-E22-302 and were included in this long-term study. The Transition phase is the phase of Study VRX-RET-E22-302 during which patients were adjusted to a 300 mg TID dose of retigabine. No other population for analysis is defined for this long-term extension study.

Assessment of Efficacy:

"Monthly total partial seizure" as well as "monthly total seizure" rates will be calculated for the entire open-label part of Study VRX-RET-E22-304 and described statistically.

Baseline monthly total partial seizure rate from Study VRX-RET-E22-302 will be used for the calculation of difference and % change in the open-label study. The % change will be classified into <0, [0, 25), [25, 50), [50, 75), [75, 100] with a description of the frequencies. The responder rate (defined as a reduction in seizure frequency ≥50%) is the sum of the upper two classes.

The number of seizure free days, in percent to the individual duration of the open-label treatment, will be calculated and described statistically. In addition, frequencies for this percentage will be classified into [0, 25), [25, 50), [50, 75), [75, 95), [95,100), =100. The most upper class represents completely seizure free patients, the next class almost seizure free patients.

Additional details will be provided in the Statistical Analysis Plan (SAP).

Assessment of Safety:

All adverse events will be encoded according to MedDRA 8.0. Treatment emergent adverse events (TEAE) will be analyzed, i.e. all adverse events starting or worsening between the start of the long-term open-label study up to 30 days after end of taper-off study drug at the completion of the open-label study. Incidences on preferred term and body system basis will be calculated for all TEAEs. In addition, all serious adverse events (SAEs) and all AEs leading to premature discontinuation will be presented as separate listings. A prospective analysis will be conducted in order to compare the results of this study to Study VRX-RET-E22-302.

TEAE from both studies (double-blind and open-label extension) will be combined, i.e. each patient will be counted just once (with patient's respective TEAE).

Other safety evaluations, such as vital signs, laboratory variables, ECG variables, AUA symptom index will be analyzed descriptively.

Additional details will be provided in the Statistical Analysis Plan (SAP).

6. INTRODUCTION

6.1. Background

Epilepsy is among the most common neurological disorders, affecting approximately 50 million people worldwide. Classical antiepileptic drugs (AEDs) currently provide satisfactory seizure control in approximately 70% of patients; however, the remaining 30% of epilepsy patients are refractory to treatment. The partial onset seizure is the most common type of seizure that is uncontrolled in adult patients. The introduction of new AEDs (e.g., vigabatrin, lamotrigine, gabapentin, topiramate, levetiracetam, oxcarbazepine, zonisamide, and felbamate) during the last decade has increased therapeutic possibilities. However, data from recent clinical trials demonstrate that none of the newer AEDs provides adequate seizure control in all patients. The treatment of patients that do not respond to current AEDs remains a problem and motivates the continued search for compounds with high antiepileptic potential and low rates of side effects.

Retigabine (GKE-841 or D-23129), N-[2-amino-4(4-fluorobenzylamino)-phenyl] carbamic acid ethyl ester, is a new chemical entity discovered by ASTA Medica, Germany, and was acquired by Valeant Research & Development (Valeant) for development as an AED for the treatment of partial onset seizures. It is a deaza analog of flupirtine, currently marketed in some regions as a centrally acting analgesic with ancillary muscle relaxing properties.

Two Phase 3 studies (VRX-RET-E22-301 and VRX-RET-E22-302) to compare the efficacy and safety of Retigabine (600 mg/day, 900 mg/day, or 1200 mg/day) to placebo as an adjunctive therapy in refractory patients with partial-onset seizures are currently being conducted. These studies are randomized, double-blind, placebo-controlled, multi-center, parallel-group trials enrolling a total of approximately 790 patients, globally. Because of the serious nature of epilepsy, the retigabine clinical program had foreseen that all patients who enter and complete a Phase 3 study with retigabine will be given the opportunity to continue treatment, if they consent and if the Principal Investigator feels they can benefit from continued retigabine treatment. Hence, an open-label extension protocol was designed for each double-blind study.

This study is the open-label extension of the Phase 3 Study VRX-RET-E22-302. VRX-RET-E22-302 is a randomized, double-blind, placebo-controlled, parallel-group, multicenter, study of 900 mg/day and 600 mg/day retigabine versus placebo. During the 4-week titration phase patients are titrated to the target dose. 510 patients are expected to be randomized to treatment. A 12-week maintenance phase follows. All patients who wish to enter the open-label extension protocol will enter a 4-week transition phase in which their dose will be titrated to 300 mg TID in order to maintain the blind to the maximum extent. Thereafter, the patients could enter this extension study (Study VRX-RET-E22-304). Patients who do not

wish to enter the open-label extension protocol will have their dose tapered over a 3-week period.

6.2. Pharmacology

Retigabine is a novel antiepileptic compound with a broad spectrum of activity and potent anticonvulsant properties.[1,2,3,4] Retigabine opens specific potassium channels called M channels linked to the KCNQ2/3 and KCNQ3/5 heteromultimeres, which are involved in the control of the excitability of neuronal cells.[5,6,7,8,9] Mutations in these channels were understood to be linked to benign neonatal familial convulsions.[10] This fact strongly supports the experimental evidence that M-channel activation may be a unique and powerful cellular target principle for the treatment of epilepsy. Retigabine also has a concentration-dependent ancillary mode of action by increasing gamma aminobutyric acid (GABA)-evoked currents. These effects, however, were seen at concentrations of 10 µmol/L, whereas the potassium channel-opening effects occur at concentrations as low as 0.1 µmol/L.[11,12]

Results from preclinical studies revealed that retigabine is effective in a broad range of animal models of epileptic seizures. Amygdala kindling is considered the most predictive animal model for human complex partial seizures.[13] In kindled rats, intraperitoneal or oral doses of retigabine as low as 0.01 mg/kg were effective in increasing the threshold for induction.[14] At a higher dose of 5 mg/kg retigabine also reduced seizure severity, seizure duration, and post-discharge duration in fully kindled rats.[14] A clear separation between antiepileptic and neurotoxic effects is evident in these preclinical models. In addition, preclinical testing has not revealed any tolerance, dependence, or withdrawal liabilities for retigabine.[15]

Retigabine is rapidly absorbed following p.o. (oral) administration with peak plasma concentrations being achieved 1-2 hours after dosing in mice and rats.[16,17] The absolute bioavailability ranged from 44% to 70%.[17] Retigabine is extensively distributed and rapidly eliminated from all tissues in rats over a 48- to 72-hour period after dosing.[18,19] Retigabine is primarily metabolized by acetylation, glucuronidation, and oxidation mechanisms in rats and by glucuronidation in dogs. The active N-acetyl metabolite of retigabine has a pharmacological profile similar to retigabine but is 20 times less potent.[20] The major route of excretion in rats and dogs is in feces, with some compound being excreted in urine.[21,22,23] In humans, retigabine is mainly metabolized by N-glucuronidation and N-acetylation, and is not metabolized by cytochrome P450 enzymes.[20] Retigabine has low protein binding in all species, including humans.[20] Both in vivo and in vitro studies suggest that retigabine is unlikely to have any important drug-drug interactions with commonly used drugs.[24,25,26,27]

6.3. Preclinical Safety Studies

Retigabine caused motor impairment in rodents in the rotarod test, but the doses necessary were 12 to 13 times higher than those active in models of epilepsy.[28] Neither retigabine nor

its N-acetyl metabolite prolonged action potential duration (APD) in cat cardiac myocytes and dog Purkinje fibers, and in fact resulted in slight shortening of APD in these test systems.[29] At concentrations 17-20 times higher than those achieved at therapeutic doses in man, retigabine caused a slight prolongation in QT interval in the isolated guinea pig heart, as well as a slight reduction in K+ current through human ether-a-go-go related gene (hERG) channels.[30] However, retigabine did not affect ECG parameters in anesthetized dogs or conscious unrestrained dogs given daily doses for 7 days.[31] Retigabine may inhibit bladder contractions and micturition in rodents due to its ability to hyperpolarize and stabilize urinary bladder myocytes through activation of K+ channels.[32]

In acute and chronic toxicity studies in rats, CNS related clinical signs including hyperkinesia, hypokinesia, disturbed coordination, stilted gait, tremor and convulsions were observed.[33] In repeat dose toxicity studies in rodents, slight hepatocellular and thyroid follicular hypertrophy were observed and were considered to be adaptive.[34,35] In repeat-dose studies in dogs but not rodents, self-limiting hepatocellular degeneration was observed in regions adjacent to the gallbladder.[36,37] In rodents but not dogs, distended urinary bladder or urinary bladder ectasia was noted with occasional secondary inflammation and ulceration of bladder wall.[34,35,36,37]

No retigabine-related effects on reproductive function were observed in male or female rats in a fertility and general reproductive performance study. No teratogenic effects of retigabine were observed in rats or rabbits.[38,39] In a perinatal and postnatal toxicity study in rats, the administration of retigabine to mated females did not have significant effect on the development of the offspring, but at the highest dose level growth was slowed, early mortality increased, and auditory reflex development was retarded in relation to the delay in growth.[40] In juvenile rats, retigabine reduced food consumption at the maximum tolerated dose but did not affect growth, reflex development, motor activity, learning, memory, clinical pathology parameters, or reproductive performance.[41]

In genetic toxicity studies, the retigabine active substance, used to manufacture finished product, tested negative for mutagenicity in the AMES test. Some exceptions could be explained as false weakly positive results due to alterations of the Salmonella tester strains.[42,43] Retigabine was negative in 2 independent mammalian cell forward gene mutation assays in presence and absence of S-9.[42] Retigabine did not induce chromosome aberrations in cultured human lymphocytes following pulse treatment for 3 or 4 hours in the absence and presence of S-9.[43] Following continued treatment for 20 or 22 hours in this test system, retigabine induced chromosome aberrations, but only in the absence of S-9. Retigabine tested negative in genetic toxicity studies relying for metabolism on unbroken cells where the required cofactors are present at their natural concentrations as in the in vivo micronucleus test in mice and in the in vivo / in vitro unscheduled DNA synthesis (UDS) assay in hepatocytes in rats.[44, 45, 46, 47, 48]

6.4. Clinical Studies

In open-label Phase 2 studies in patients with epilepsy, the majority of patients tolerated daily doses of up to 1200 mg administered orally in two or three divided doses. The most commonly observed treatment-emergent adverse effects were in the MedDRA system organ class of Nervous System Disorders. In a double-blind parallel group study comparing different titration rates (Study 3065A1-214), it has been shown that when the starting dose of retigabine is 300 mg/day (100 mg TID), the daily dose can be titrated to 1200 mg over a 6-week period with only 13% of patients discontinuing due to adverse events.

In a randomized, double-blind, placebo-controlled, parallel group study comprising 397 patients with epilepsy (Study 3065A1-205)[52], daily doses of 900 mg and 1200 mg (administered orally in three divided doses) caused a significant reduction in total partial seizure frequency compared with placebo. While a dose of 600 mg/day resulted in greater reduction of seizure frequency than placebo, the difference was not statistically significant. The majority of patients tolerated their treatment as prescribed, with a minority discontinuing from the study prematurely. The discontinuation rate due to adverse events in 1200 mg dose group was about 2.5 times that in placebo group. This is consistent with tolerability of other AEDs. The commonly observed adverse events were in the MedDRA system organ class of Nervous System Disorder and many of these were dose related and were more frequent with retigabine compared with placebo. There were few clinically important changes in vital signs, laboratory, or ECG parameters, or physical or neurological examinations.

Patients participating in Study 3065A1-205 were eligible for an open-label extension phase (Study 3065A1-212) if they experienced improvement in seizure control, did not experience adverse events that would prevent inclusion, and did not violate the double-blind study protocol. Patients who completed the interim (transition) phase of the double-blind portion of the study started with 300 mg TID, which could be increased weekly in increments of 150 mg/day, up to a maximum of 1200 mg daily. Concomitant AEDs could be adjusted to achieve the best efficacy/safety ratio. Patients who wished to discontinue retigabine during this open-label study entered a 3-week tapering period and a 10-day post-study follow-up period. Seizure frequency was recorded daily in a diary maintained by each patient. The efficacy of retigabine was evaluated by comparison of baseline seizure frequency (determined upon entry into the double-blind phase) with seizure frequency during retigabine therapy in the extension study; this was calculated as a percentage change in total partial seizure frequency.

Of the 279 patients who completed Study 205, 222 enrolled in the open-label extension. The majority of these patients were white (213 or 95.9%) with a median age of 36 years. A total of 126 patients were male (56.8%) and 96 (43.2%) were female. The median duration of epilepsy at study entry was 20.7 years. Of these 222 patients, 18 (8%) discontinued

within the first 3 months and 41 (18%) discontinued within 6 months. The most common cause for discontinuation was lack of efficacy. The most common daily dosage of retigabine was 900 mg (105 patients; 47.3%) and only a minority of the patients titrated the dosage to 1200 mg (53 patients; 23.9%). The median treatment duration during open-label extension phase was 358 days.

The median decrease in monthly total partial seizure frequency from baseline was 48.3%, which was similar to the results with the two highest retigabine dose groups (300 and 400 mg TID) in the randomized, double-blind phase. Patients assigned to the placebo group during the double-blind phase showed the largest seizure rate improvement during the extension phase. One hundred three patients (46.4%) showed a reduction in monthly total partial seizure frequency of 50%.

6.5. Safety and Tolerability

The safety and tolerability of various dosing regimens of retigabine were examined in healthy patients participating in human pharmacology studies and in patients with epilepsy in therapeutic trials.[53,54] A total of 404 healthy subjects participated in 18 human pharmacology studies. In a multiple dose-finding trial using fixed doses, regimens up to 200 mg twice a day (BID) were safe and well tolerated and the maximum tolerated dose was found to be 250 mg BID. However, after allowing for titration to the target dose, regimens up to 350 mg BID were tolerated without any dose-limiting adverse events (AEs). In general, central nervous system (CNS) AEs limited further dose increases.[55]

A total of 605 patients with epilepsy have been enrolled in clinical studies for retigabine. Retigabine was mostly administered as add-on therapy to various established background AEDs and to a minor extent as monotherapy by using various dose-titration regimens. The maximum tolerated dose (MTD) of retigabine when added to standard AEDs was 1200 mg/day. Retigabine was administered using BID and TID regimens. The most common AEs were CNS-related (e.g., somnolence, dizziness, confusion, speech disorder, vertigo, amnesia, thinking abnormal, tremor, incoordination, ataxia, nervousness, paresthesia, abnormal gait, diplopia, and abnormal vision) and appeared in a dose-dependent manner.[55] No AEs of retigabine on cardiac safety and in particular cardiac repolarization (QTc interval) were detected. While the AE pattern from human pharmacology and clinical trials is similar, it is interesting to note that MTDs in healthy subjects appear to be different from those achieved in patients with epilepsy, despite the concomitant medication with standard AEDs in the latter group.

A complete description of preclinical pharmacology, toxicology, PK studies, and clinical safety and efficacy studies for retigabine can be found in the Investigator's Brochure.[56]

6.6. Pharmacokinetics

6.6.1. Absorption

In clinical trials, retigabine was rapidly absorbed within 2 hours after oral administration to healthy patients.[49] The N-acetylated metabolite of retigabine was also rapidly formed, following the parent compound by approximately 2 hours. Both retigabine and the N-acetylated metabolite of retigabine were eliminated with a half-life ($t_{1/2}$) of about 8 hours. At steady state, mean observed maximum concentration (C_{max}) and area under the curve (AUC) values of the N-acetylated metabolite were within 20% of the corresponding mean values of retigabine. The trough plasma concentrations of retigabine in the afternoon or evening were significantly lower than those in the morning, possibly related to slower metabolism during sleep. The pharmacokinetics (PK) of retigabine and the N-acetylated metabolite of retigabine were linearly dose proportional for doses from 100 to 350 mg.

6.6.2. Metabolism

Investigations of metabolism in humans indicate that retigabine is mainly metabolized by N-glucuronidation and N-acetylation, and is not metabolized by cytochrome P450 enzymes.[20] In vitro studies have shown that the glucuronidation is performed by several uridine diphosphate glucuronyltransferase (UGT) isozymes.[50] The PK of retigabine and the N-acetylated metabolite of retigabine in patients with epilepsy are comparable with those in healthy subjects.[51]

6.6.3. Excretion

The major route of excretion in rats and dogs is in feces, with some compound being excreted in urine.[21,22,23] In humans, retigabine is mainly metabolized by N-glucuronidation and N-acetylation, and is not metabolized by cytochrome P450 enzymes.[20] Retigabine has low protein binding in all species, including humans.[20] Both in vivo and in vitro studies suggest that retigabine is unlikely to have any important drug-drug interactions with commonly used drugs.[24,25,26,27]

7. STUDY OBJECTIVES

- Primary: To evaluate the safety and tolerability of long-term therapy with retigabine administered as adjunctive therapy in adult epilepsy patients with partial-onset seizures, who completed the double-blind Study VRX-RET-E22-302.
- Secondary: To evaluate efficacy of long-term treatment with retigabine and patient quality of life, evaluated through the QOLIE-31-P questionnaire.

8. STUDY DESIGN

This is an open-label extension study of the placebo controlled, double-blind Study VRX-RET-E22-302. Patients will be treated with 600-1200 mg/day of retigabine as an adjunct therapy to their current antiepileptic medications (AEDs) or vagal nerve stimulation as established in Study VRX-RET-E22-302. Following completion of the Transition Phase of the double-blind study (Study VRX-RET-E22-302), treatment in this open-label extension study will be continued until retigabine is approved and commercially available, or until the program is discontinued, followed by a 3-week tapering period and a 30 day post-study period for collection of adverse events.

8.1. Type of Study

Phase 3 open-label extension study for therapeutic use.

8.2. Study Population

Patients entering this study had to have participated in Study VRX-RET-E22-302, i.e. they had met eligibility criteria of that study and completed the double-blind phase.

8.3. Number of Study Sites

This is a multi-center open-label study involving approximately 55-60 study sites in Western, Central and Eastern Europe, Australia, Israel, and South Africa.

8.4. Treatment Duration

Following completion of the Transition Phase of the double-blind study (Study VRX-RET-E22-302), treatment in this open-label extension study will be continued until retigabine is approved and commercially available, or until the program is discontinued, followed by a 3-week tapering period and a 30 day post-study period for collection of adverse events.

8.5. Patient Inclusion Criteria

For inclusion in the study, a patient must meet and comply with the following criteria:

1. Patient has successfully completed the Maintenance and Transition phases of Study VRX-RET-E22-302 for the treatment of partial-onset seizures
2. Patient is expected to benefit from participation in the study in the opinion of the Investigator.
3. Women of childbearing potential and fertile males have to agree to use a medically acceptable method of birth control and females had to have a negative serum β-HCG pregnancy test at the last visit of the Transition phase of Study VRX-RET-E22-302. A woman of childbearing potential is defined as a female who is biologically capable of becoming pregnant. A medically acceptable method of birth control includes an

intrauterine device in place for at least 3 months, surgical sterilization (e.g. tubal ligation), or adequate barrier methods (e.g., diaphragm and foam). An oral contraceptive alone is not considered adequate for the purpose of this study.

4. In the opinion of the Investigator, patient is able to understand verbal and written instructions and will adhere to all study schedules and requirements.
5. Patient or legal guardian (if applicable) is informed, given ample time and opportunity to read and/or understand about his/her participation in the study, and has signed and dated the written informed consent form.

8.6. Patient Exclusion Criteria

A patient is ineligible for entering Study VRX-RET-E22-304 if any of the following exclusion criteria are met:

1. Patient meets any of the withdrawal criteria in the previous VRX-RET-E22-302 study or is experiencing an ongoing serious adverse event.
2. Patient is receiving any investigational drug or using any experimental device in addition to Retigabine for treatment of epilepsy or any other medical condition.
3. Patient has any other condition that would prevent compliance with the study procedures or proper reporting of AEs.

8.7. Study Medication

Study medication will be supplied by Valeant Research & Development, as film-coated tablets containing 50 mg, 100 mg, or 300 mg of retigabine per tablet. Tablets will be packaged in induction sealed bottles. A sufficient supply of study medication will be provided to each site for completion of the trial, based on the number of patients enrolled, study visit schedule, and the daily doses of patients. Specific dosage instructions will be provided separately to the patient. All study medication will be dispensed by the pharmacy or an appropriately qualified member of the study staff assigned by the Principal Investigator to this task.

Patients will take the established background AEDs from their own prescriptions, and their use will be recorded.

8.7.1. Dosage Schedule and Mode of Administration

Patients who completed the Transition phase of Study VRX-RET-E22-302 will start with 300 mg three times a day (300 mg TID). Patients who were not able to tolerate the final dose adjustment (750 mg/day) during the last week of the Transition phase of Study VRX-RET-E22-302 will start with 200 mg three times a day (200 mg TID).

If, in the opinion of the Investigator, the patient was not receiving the maximum effective dose, the dose could be increased in weekly intervals of 150 mg/day, up to a maximum of

1200 mg daily (i.e. 400 mg TID). If adverse events considered to be secondary to retigabine occur, the total daily dose could be reduced by 150 mg/day every week, at Investigator discretion, as long as the dose is within 600-1200 mg/day.

After the patient has entered open-label treatment, the Investigator may add new AEDs, as long as these are approved AEDs. In addition, the existing background AED therapy can be adjusted to achieve the best efficacy/safety ratio, as needed, per Investigator discretion. If necessary, in the Investigator's judgment, all background AEDs can be discontinued to achieve monotherapy with retigabine.

Patients who permanently discontinue open-label treatment will have their dose tapered by one-third every week.

Patients will be instructed on the administration procedures for study drug. Study medication will be administered orally with or without food. The 3 daily doses are to be administered with approximately an 8-hour interval between them (for example 7am, 3pm, 11pm). Patients will continue to take their established background AEDs from their own prescriptions.

8.7.2. Study Drug Storage

All study drug sent to the study centers must be stored under the conditions specified on the drug package label (15 – 30 °C / 59 – 86 °F) in a secure area accessible only to the Investigator and his/her designated staff. All study drugs should be stored and inventoried according to applicable government regulations and study procedures.

8.7.3. Study Drug Returns

Government regulations require that all investigational drug materials not used in clinical trials be returned before or at the completion of the study.

The Investigator will return the designated copies of the completed dispensing and inventory record.

8.7.4. Method of Assigning Study Medication to Patients

Study medication will be assigned to patients through a centralized Interactive Voice Response System (IVRS), as described in the IVRS user manual that will be provided to the sites. Sites will contact the IVRS to obtain the package number assignment(s) for patients at each scheduled study visit

Study personnel will select the study medication bottle(s) from their inventory that correspond to the package number(s) assigned by IVRS. Study personnel will complete the tear-off labels on the bottles, affix them to the Investigational Product Labels page found in the patient's paper source binder, and dispense the study medication (bottles) to the patient. At subsequent study visits, study personnel will follow the same procedures as described above, contacting the IVRS as instructed in the IVRS manual.

8.7.5. Discontinuation and Tapering of Study Medication

Patients who discontinue early from the open-label extension study will have their study medication tapered over a 3-week period, reducing their daily dose by one-third per week. After tapering has been completed, patients should return to the site immediately, and complete all assessments and evaluations scheduled for Visit 5, if patient discontinued early during the first year of the open-label extension study, complete all assessments and evaluations scheduled for Visit 8 if patient discontinued early during the second year of the open-label extension study, and complete all assessments and evaluations scheduled for Visit 11 if patient discontinued early during the third year of the open-label extension study (Refer to Study Flow Chart in Appendix A).

8.8. Assessment of Compliance

Patient compliance with the study drug dosing regimen will be assessed by counts of tablets remaining in the study medication bottles that are returned at each study visit. Compliance will be based on the medication the patient was scheduled to take for the days between study visits. In addition, information on the average total daily dose will be calculated, based on the number of tablets remaining or returned in each bottle.

Patients will be instructed to bring used and unused study medication bottles with them to each study visit for accountability purposes. Tablets from each bottle for each dose strength (50 mg, 100 mg, 300 mg) will be counted and recorded to assess patient compliance and correct dosage taken. If a patient is deemed to be non-compliant with taking study medication, the patient should be counseled by the site. If the patient continues to be non-compliant, they should be withdrawn from the study.

Along with drug accountability logs, the CRF will capture the data which includes the prescribed dosage, dates of first dose and last dose, and the number of tablets returned from each bottle for each dose strength. The CRFs will also provide a classification in to poly- or monotherapy with retigabine.

8.9. Concomitant Therapy

8.9.1. Permitted Concomitant Medications

Patients will take the background AED as prescribed by their physician. If adverse events considered to be secondary to retigabine occur, the total daily dose could be reduced by 150 mg/day every week, at Investigator discretion, as long as the dose is within 600-1200 mg/day. The background AED therapy can be adjusted if a patient develops adverse events similar to the previously experienced reaction to that AED.

After patients enter the open-label extension study, the Investigator will be allowed to adjust background AEDs, as clinically indicated. As needed, the background AED therapy can be adjusted to achieve the best efficacy/safety ratio, per Investigator discretion. If necessary, in

the Investigator judgment, all background AEDs can be discontinued to achieve monotherapy with retigabine. The dose and reason to use a concomitant medication shall be recorded in the CRFs.

8.9.2. Prohibited Medications

Use of felbamate and vigabatrin are prohibited. Concurrent use of any AEDs, or of any drug that could interfere with the absorption or metabolism of retigabine and background AED is also prohibited. Medications known to lower seizures (e.g. neuroleptics) and monoamine oxidase inhibitors (MAOIs) are not allowed.

8.10. Protocol Violations and Deviations

A deviation from the protocol is an unintended and/or unanticipated departure from the procedures and/or processes approved by the Sponsor and the IRB/IEC/REB and agreed to by the Investigator. Deviations usually have an impact on individual patients or a small group of patients. A protocol violation occurs when there is non-adherence to the protocol that results in a significant, additional risk to the patient, when the patient or Investigator has failed to adhere to critical protocol requirements (inclusion/exclusion criteria) and the patient was enrolled without prior Sponsor approval, or when there is non-adherence to FDA regulations and/or ICH GCP guidelines.

The Investigator or designee must document and explain any deviation or violation from the approved protocol. The Investigator may implement a deviation from, or a change of the protocol to eliminate an immediate hazard to study patients without prior IRB/IEC/REB approval. Immediately after the implemented deviation, violation or change to eliminate the immediate hazard to the study patient(s), the Investigator must submit a report explaining the reasons for the protocol deviation, violation or change to the Sponsor. If required, the regulatory authorities will be notified. The appropriate IRB/IEC/REB will be notified of specified, critical violations or violations that place patients at added, significant risk.

Protocol violations and deviations will be documented by the clinical monitor throughout the course of the monitoring visits. Investigators will be notified of violations and deviations and/or in writing by the monitor, and the Principal Investigator will be required to identify corrective action to eliminate future violations and deviations.

9. STUDY PROCEDURES

9.1. Study Flow Chart

As presented in the Study Flow Chart (see Appendix A), Study Visit 1 will have a window range of ±3 days. After Study Visit 1, all remaining study visits will have a window range of ±7 days around that visit day to accommodate individual schedules, as follows:

- Baseline for the open-label extension study corresponds to the assessments performed at the last visit of the Maintenance phase (Visit 9) of Study VRX-RET-E22-302 for all patients. The final, baseline eligibility assessment for the open-label extension study, including obtaining informed consent and dispensing open-label study medication will be performed at the last visit of the Transition phase (Visit 11) of Study VRX-RET-E22-302.
- Study Visit 1 (at Month 1 ±3 days).
- Study Visit 2 (at Month 3 ±7 days).
- Study Visit 3 (at Month 6 ±7 days).
- Study Visit 4 (at Month 9 ±7 days).
- Study Visit 5 (at Month 12 ±7 days).
- Study Visit 6 (at Month 16 ±7 days).
- Study Visit 7 (at Month 20 ±7 days).
- Study Visit 8 (at Month 24 ±7 days).
- Study Visit 9 (at Month 28 ±7 days).
- Study Visit 10 (at Month 32 ±7 days).
- Study Visit 11 (at Month 36 ±7 days).

Each study month will be defined as 30 calendar days. If a patient visit occurs outside the visit window, the study clinical monitor (CRA) should be notified and the reason for the deviation noted. An attempt should be made to ensure that the patient returns for subsequent visits on schedule using the last visit of the Transition phase (Visit 11) of Study VRX-RET-E22-302, which corresponds to the final, baseline eligibility visit for the open-label extension study.

9.2. Efficacy Assessments

Patients will keep a seizure diary throughout the study. The anticonvulsant efficacy of retigabine will be evaluated by comparison of baseline seizure frequency (obtained during the 8-week baseline period of Study VRX-RET-E22-302) with seizure frequency obtained during retigabine therapy in this open-label extension study (VRX-RET-E22-304). The primary efficacy variable is the percentage change in the monthly seizure rate from the baseline phase to the open-label treatment phase. The proportion of responders (patients experiencing ≥ 50% reduction in seizure frequency) from baseline to the open-label treatment phase will also be evaluated.

9.3. Safety Assessments

Safety assessments will be evaluated, based on reports of AEs and results of vital signs (supine and standing blood pressure, pulse, and temperature), weight, clinical laboratory evaluations (blood chemistries, hematology and urinalysis including microscopy), a 12-lead ECG, and physical and neurological examinations. Post-void residual (PVR) bladder ultrasounds to assess urinary retention and the American Urological Association (AUA) Symptom Index to assess urinary voiding function will also be performed during the first year of the open-label extension study.

9.3.1. Vital Sign Measurements and Weight

Complete vital sign measurements (including supine and standing blood pressure, heart rate, and temperature) will be obtained throughout the study at all visits. Evaluations of blood pressure and heart rate will be performed supine at each study visit, and again after the patient has been standing for approximately 2 minutes.

Weight [pounds (lb) or kilograms (kg)] will also be measured in ordinary indoor clothing (without shoes) and will be recorded at all study visits

Abnormal vital sign values that are deemed clinically significant by the Investigator will be reported as AEs in the study CRF.

9.3.2. Physical and Neurological Examinations

A complete physical and neurological examination will be performed annually at Visit 5, Visit 8, and Visit 11. Brief neurological examinations will be performed at all other study visits, including visits 1, 2, 3, 4, 6, 7, 9, and 10.

9.3.3. Electrocardiograms

A 12-lead ECG will be performed at all study visits during the first year of the open-label extension study (Visits 1, 2, 3, 4, 5), and annually at Visits 8 and 11. The ECG parameters that will be assessed are heart rate, PR interval, QRS interval, QT interval, and QTc interval. All ECG tracings will be sent to Quintiles ECG Services for central reading. Quintiles ECG Services will provide a central ECG analysis and transmit a feedback of preliminary results via facsimile to the investigation site within 24 hours. Trained technicians will read all ECGs manually, and any abnormal finding will then be over-read by board-certified cardiologists. QT intervals will be corrected using both Bazett's and Fridericia's formulas. For purposes of clinical study conduct, Bazett's QT correction will be used. For purposes of data analysis, Fridericia's QT correction will be considered as primary. Changes from baseline QTc interval will be monitored on an ongoing basis throughout this study.

Increases in Bazett's QTc interval of >60 msec from baseline or QTc interval of >500 msec anytime during the study should be confirmed on a repeat ECG. Any such occurrence shall

result in notification of the Investigator and the study medical monitor for immediate review of the tracings and discussion with Valeant.

9.3.4. Laboratory Assessments

All clinical laboratory assessments will be performed by a central laboratory (Quintiles Central Laboratory Services), which will provide instructions and supplies to the study staff before study initiation. Results of the clinical laboratory assessments will be faxed back to the study site within 48 to 72 hours of sampling. Alert values will be reported to the Investigator via telephone. Approximately 7-mL sample of blood will be drawn for clinical chemistries and hematology assays. The laboratory assessments will include routine laboratory tests. The clinical laboratory evaluation will be performed at all study visits during the open-label extension study.

Because of the bladder toxicity observed in chronic toxicology studies in the rat and mouse, careful attention will be paid to plasma creatinine and blood urea nitrogen (BUN), microscopic findings on urinalysis, and any symptoms that might suggest incomplete bladder emptying (e.g., urinary tract infection, frequency, sensation of incomplete voiding, etc.). All patients will undergo urinalysis (including microscopy) at all study visits.

Any patient who has developed a clinically significant urinalysis abnormality will undergo further evaluation by an urologist (as clinically indicated) for any of the following:

- >5 red blood cells (RBC) per high power field (HPF) for males and postmenopausal females or >8 RBC/HPF for females
- >3 white blood cells(WBC) per high power field (HFP) for males and >12 WBC/HPF for females
- >1+ epithelial cells
- ≥1+ on all casts except Hyaline casts ≥2+
- >1+ blood for males and postmenopausal females
- ≥1+ trace protein [RBC; males and postmenopausal females] per high power field (HPF) or >5 white blood cells [WBC; must have 1 to few epithelial cells/HPF] per HPF, >occasional casts, >1+ blood [male and postmenopausal female patients] or >trace protein
- Have symptoms or AEs suggestive of possible hypotonicity of the bladder

The laboratory evaluations will include:

1. **Hematology:** hemoglobin, hematocrit, RBC count, WBC count with differential, and platelet count.

2. **Blood chemistries:** sodium, potassium, chloride, bicarbonate, glucose, cholesterol, creatinine, calcium, phosphorus, BUN, uric acid, total bilirubin, total protein, AST, ALT, and alkaline phosphatase levels.
3. **Pregnancy tests:** a serum β-HCG pregnancy test for women of childbearing potential will be performed at Study Visit 5 and annually thereafter. In addition to the scheduled pregnancy tests, a pregnancy test should be performed during the study whenever a woman's menstrual period is 5 days late.
4. **Routine urinalysis:** specific gravity, pH, protein/albumin, glucose/sugar, ketones/acetone, and hemoglobin/blood. In order to standardize measurements, Bayer multistix 8-SG or equivalent dipsticks will be used.
5. **Microscopic urinalysis:** RBC, WBC, casts, and crystals/cells.

All laboratory tests with values that become abnormal after drug administration will be repeated as clinically indicated until the values return to normal, or until the etiology has been determined and the condition considered stable. Abnormal laboratory test results that are considered to be clinically important by the Investigator will be reported as an AE in the CRF. A laboratory abnormality will not be considered an AE unless:

- Intervention is required.
- Changes in dose of retigabine are required (decrease, discontinued, interrupted).
- Other treatment/therapy is required.
- Associated with other diagnoses.

Laboratory results will be reported to the Investigator who will review abnormal laboratory findings for clinical significance. The Investigator will note any laboratory test results of clinical concern, or values that were outside normal ranges and provide details of the relationship to study drug and the action taken. If a change in a laboratory value represents a medical condition, the medical condition will be listed in the AE record. If no correlation is possible, the direction of change (increase or decrease) rather than the actual value will be recorded.

9.3.5. Post-Void Residual (PVR) Bladder Ultrasound

A post-void residual (PVR) bladder ultrasound to assess urinary retention will be performed at Visits 1, 2, and 5, during the first year of the open-label extension study.

9.3.6. AUA Symptom Index

An AUA Symptom Index, a 7-item Likert-scored scale describing urinary bladder function, will be completed by the Investigator at Visits 1, 2, and 5, during the first year of the open-label extension study, to assess the patient's urinary voiding function. The AUA Symptom Index is included in Appendix D of this protocol.

9.4. Quality of Life Assessments

The QOLIE-31-P (Version 2.0) will be utilized to assess quality of life. The QOLIE-31-P assessment must be completed by the patients. Patients who are cognitively impaired and cannot complete the QOLIE-31-P assessment may still participate in the study, by obtaining a waiver for QOLIE-31-P completion from the study medical monitor.

9.5. Baseline

Except for final study eligibility, informed consent and dispensation of open-label extension study medication, the Baseline assessments for the open-label extension study correspond to the assessments performed at the last visit of the Maintenance phase (Visit 9) of Study VRX-RET-E22-302 (See Study Flow Diagram - Appendix A). After completion of all study procedures on the last visit of the Transition phase (Visit 11) of Study VRX-RET-E22-302, patients will be allowed to enter this open-label extension study (VRX-RET-E22-304). All ongoing AEs and concomitant medications at the last visit of the Transition Phase (Visit 11) of Study VRX-RET-E22-302 will need to be transferred and captured on the appropriate open-label extension AE and Concomitant Medication CRF pages. The final study eligibility and informed consent for the open-label extension study will be performed at the last visit of the Transition phase (Visit 11) of Study VRX-RET-E22-302. After confirmation of final study eligibility and obtaining proper informed consent, open-label study medication (sufficient supply of bottles at appropriate dose strengths = 50 mg, 100 mg, 300 mg) will be dispensed to patients, along with seizure diaries for completion until the next study visit (Visit 1 / Month 1).

9.6. Study Visit 1 (Month 1)

Patients will return for Study Visit 1 (Month 1). At this visit, the following evaluations will be performed:

- Seizure Diary (collection / review of current diary and dispensation of new diary)
- Brief Neurological Exam
- Vital Signs (BP, HR, and Temperature) and Body Weight
- Clinical Laboratory Tests (Blood Chemistries, Hematology, Urinalysis including microscopy)
- 12-lead ECG
- AUA Symptom Index
- PVR Bladder Ultrasound
- Adverse Events
- Concomitant Medication

- Open-Label Study Medication (collect returned medication and dispense new medication)

9.7. Study Visit 2 (Month 3)

Patients will return for Study Visit 2 (Month 3). At this visit, the following evaluations will be performed:

- Seizure Diary (collection / review of current diary and dispensation of new diary)
- Brief Neurological Exam
- Vital Signs (BP, HR, and Temperature) and Body Weight
- Clinical Laboratory Tests (Blood Chemistries, Hematology, Urinalysis including microscopy)
- 12-lead ECG
- AUA Symptom Index
- PVR Bladder Ultrasound
- Adverse Events
- Concomitant Medication
- QOLIE-31-P Questionnaire (completed by patient)
- Open-Label Study Medication (collect returned medication and dispense new medication)

9.8. Study Visit 3 (Month 6)

Patients will return for Study Visit 3 (Month 6). At this visit, the following evaluations will be performed:

- Seizure Diary (collection / review of current diary and dispensation of new diary)
- Brief Neurological Exam
- Vital Signs (BP, HR, and Temperature) and Body Weight
- Clinical Laboratory Tests (Blood Chemistries, Hematology, Urinalysis including microscopy)
- 12-lead ECG
- Adverse Events
- Concomitant Medication
- QOLIE-31-P Questionnaire (completed by patient)

- Open-Label Study Medication (collect returned medication and dispense new medication)

9.9. Study Visit 4 (Month 9)

Patients will return for Study Visit 4 (Month 9). At this visit, the following evaluations will be performed:

- Seizure Diary (collection / review of current diary and dispensation of new diary)
- Brief Neurological Exam
- Vital Signs (BP, HR, and Temperature) and Body Weight
- Clinical Laboratory Tests (Blood Chemistries, Hematology, Urinalysis including microscopy)
- 12-lead ECG
- Adverse Events
- Concomitant Medication
- QOLIE-31-P Questionnaire (completed by patient)
- Open-Label Study Medication (collect returned medication and dispense new medication)

9.10. Study Visit 5 (Month 12)

Patients will return for Study Visit 5 (Month 12). At this visit, the following evaluations will be performed:

- Seizure Diary (collection / review of current diary and dispensation of new diary)
- Complete Physical and Neurological Exam
- Vital Signs (BP, HR, and Temperature) and Body Weight
- Clinical Laboratory Tests (Blood Chemistries, Hematology, Urinalysis including microscopy)
- Serum Pregnancy Test
- 12-lead ECG
- AUA Symptom Index
- PVR Bladder Ultrasound
- Adverse Events
- Concomitant Medication

- QOLIE-31-P Questionnaire (completed by patient)
- Open-Label Study Medication (collect returned medication and dispense new medication)

9.11. Study Visits after the First Year

After the first year of open-label extension study, the study visits will occur every 4 months (3 visits per year), and will continue until retigabine is approved and commercially available, or until the program is discontinued. The assessments for the first 2 study visits of each year will be identical, and the assessments for the last study visit of each year will be identical. To provide guidance, the following study visits and assessments will be performed during the second and third years of the open-label extension study:

9.11.1. Visit 6 (Month 16)

Patients will return for Study Visit 6 (Month 16), 4 months after Visit 5. At this visit, the following evaluations will be performed:

- Seizure Diary (collection / review of current diary and dispensation of new diary)
- Brief Neurological Exam
- Vital Signs (BP, HR, and Temperature) and Body Weight
- Clinical Laboratory Tests (Blood Chemistries, Hematology, Urinalysis including microscopy)
- Adverse Events
- Concomitant Medication
- Open-Label Study Medication (Collect returned medication and dispense new medication)

9.11.2. Visit 7 (Month 20)

Patients will return for Study Visit 7 (Month 20). At this visit, the following evaluations will be performed:

- Seizure Diary (collection / review of current diary and dispensation of new diary)
- Brief Neurological Exam
- Vital Signs (BP, HR, and Temperature) and Body Weight
- Clinical Laboratory Tests (Blood Chemistries, Hematology, Urinalysis including microscopy)
- Adverse Events

- Concomitant Medication
- Open-Label Study Medication (Collect returned medication and dispense new medication)

9.11.3. Visit 8 (Month 24)

Patients will return for Study Visit 8 (Month 24). At this visit, the following evaluations will be performed:

- Seizure Diary (collection / review of current diary and dispensation of new diary)
- Complete Physical and Neurological Exam
- Vital Signs (BP, HR, and Temperature) and Body Weight
- Clinical Laboratory Tests (Blood Chemistries, Hematology, Urinalysis including microscopy)
- Serum Pregnancy Test
- 12-lead ECG
- Adverse Events
- Concomitant Medication
- QOLIE-31-P Questionnaire (completed by patient)
- Open-Label Study Medication (collect returned medication and dispense new medication)

9.11.4. Visit 9 (Month 28)

Patients will return for Study Visit 9 (Month 28). At this visit, the following evaluations will be performed:

- Seizure Diary (collection / review of current diary and dispensation of new diary)
- Brief Neurological Exam
- Vital Signs (BP, HR, and Temperature) and Body Weight
- Clinical Laboratory Tests (Blood Chemistries, Hematology, Urinalysis including microscopy)
- Adverse Events
- Concomitant Medication
- Open-Label Study Medication (Collect returned medication and dispense new medication)

9.11.5. Visit 10 (Month 32)

Patients will return for Study Visit 10 (Month 32). At this visit, the following evaluations will be performed:

- Seizure Diary (collection / review of current diary and dispensation of new diary)
- Brief Neurological Exam
- Vital Signs (BP, HR, and Temperature) and Body Weight
- Clinical Laboratory Tests (Blood Chemistries, Hematology, Urinalysis including microscopy)
- Adverse Events
- Concomitant Medication
- Open-Label Study Medication (Collect returned medication and dispense new medication)

9.11.6. Visit 11 (Month 36)

Patients will return for Study Visit 11 (Month 36). At this visit, the following evaluations will be performed:

- Seizure Diary (collection / review of current diary and dispensation of new diary)
- Complete Physical and Neurological Exam
- Vital Signs (BP, HR, and Temperature) and Body Weight
- Clinical Laboratory Tests (Blood Chemistries, Hematology, Urinalysis including microscopy)
- Serum Pregnancy Test
- 12-lead ECG
- Adverse Events
- Concomitant Medication
- QOLIE-31-P Questionnaire (completed by patient)
- Open-Label Study Medication (collect returned medication and dispense new medication)

9.12. Tapering Period

All patients who discontinue early from study treatment during the open-label extension study will have their study medication tapered over a 3-week period, reducing their daily

dose by one-third per week, and return immediately for a final visit. The patients will be instructed to take the tablets from their existing study medication bottles and to follow this tapering procedure:

- During the first week of tapering, patients will no longer take the afternoon dose.
- During the second week of tapering, patients will no longer take the morning and the afternoon doses.
- During the third week of tapering, patients will take no study medication (but will continue their existing background AEDs).

During the first year, these patients should then return for a final visit to complete all assessments and evaluations scheduled for Study Visit 5. During the second year, these patients should then return for a final visit to complete all assessments and evaluations scheduled for Study Visit 8. During the third year, these patients should then return for a final visit to complete all assessments and evaluations scheduled for Study Visit 11 (Refer to Study Flow Chart in Appendix A).

During the tapering period, a new background AED should not be added until after the patient's final visit unless clinically necessary for patient safety. Unused current study medication bottles will be collected to ascertain compliance. Current study seizure diaries will be collected and reviewed. Concomitant medications and AED usage will be documented, and adverse events will be recorded.

9.13. Replacement of Patients

Patients withdrawn from the study will not be replaced.

9.14. Unscheduled Visits

Unscheduled visits may be performed if required for assessments of laboratory parameters or clinical safety.

9.15. Laboratory Procedures

All clinical safety laboratory determinations will be performed by Quintiles Central Laboratory Services. The study staff will send the samples to the appropriate address (provided in the Central Laboratory Manual) by shipping them in the laboratory kits supplied by Quintiles Central Laboratory. Central laboratory reports will be sent to the Investigator for evaluation.

An Investigator may choose to use a local laboratory to evaluate a potential adverse event. However, for the purpose of this study, data from local laboratories will not be recorded or used in the analysis of safety. The Sponsor will not cover costs associated with the use of a local laboratory.

9.16. Early Termination / Withdrawal Visits

The Principal Investigator may discontinue a patient from the study for any of the following reasons: the patient no longer meets eligibility criteria, it is in the patient's best interest, patient preference, concurrent illness, noncompliance, etc. Patients will be informed prior to study entry that they are free to withdraw from the study at any time and for any reason. If a patient is discontinued from the study, the Investigator will immediately notify the Sponsor or the site CRA of the withdrawal.

Patients who withdraw from the study prior to completion for any reason (adverse event, withdrew consent, etc.) will have their study medication tapered over a 3-week period, reducing their daily dose by one-third per week and then return for a final visit. Patients who discontinue early during the first year of the open-label extension study will complete all assessments and evaluations scheduled for Study Visit 5. Patients who discontinue early during the second year of the open-label extension study will complete all assessments and evaluations scheduled for Study Visit 8. Patients who discontinue early during the third year of the open-label extension study will complete all assessments and evaluations scheduled for Study Visit 11 (Refer to Study Flow Chart in Appendix A).

9.16.1. Reasons for Withdrawal

Patients are free to discontinue their participation in the study at any time and without prejudice to further treatment at their local site. The Investigator must withdraw any patient from the study if that patient requests to be withdrawn.

Patients withdrawn from the study will not be replaced, regardless of the reason for withdrawal. The patient's participation in this study may be discontinued due to the following reasons:

- Patient experiences an intolerable AE.
- Investigator decides patient has an "unsatisfactory response – efficacy."
- Patient becomes pregnant.
- Patient is unwilling or unable to continue the study.
- Patient is non-compliant with study procedures.
- Patient needs medication not allowed in the protocol.
- Any clinically significant change in patient's medical condition.
- Persistent ALT or aspartate aminotransferase (AST) above 3 times the ULN; will be confirmed by repeating laboratory assessment within 1 week.
- ALT or AST levels are above 5 times the ULN at any time during the study.

- Confirmed QTc prolongation defined as QTc (Bazett's) >500 msec or an increase in QTc (Bazett's) of >60 msec from baseline.
- Investigator decides that withdrawal from the study is in the best interest of the patient.
- Request of the Sponsor.

9.16.2. Handling of Withdrawals

If a patient is withdrawn from the study either at the patient's request or at the Investigator's decision or the patient fails to return, every effort should be made to determine the reason. This information will be recorded on the patient's case report form (CRF) and recorded by IVRS.

All patients who withdraw from the study prematurely, regardless of cause, should have their study medication tapered over a 3-week period, reducing their daily dose by one-third per week, and follow the tapering procedures outlined in Section 9.12 (Tapering Period).

It is important to obtain follow up data for any patient withdrawn because of an AE, abnormal laboratory test, or ECG finding. In any case, every effort must be made to undertake safety follow up procedures.

10. STATISTICAL MEASUREMENTS, EVALUATIONS AND ANALYTICAL METHODS

10.1. Assessment of Efficacy

Monthly total seizure rates will be calculated for the entire open-label part of Study VRX-RET-E22-304 and described statistically. Monthly total seizure rates observed during the open-label extension period will be compared to the monthly total seizure rates observed during the Baseline phase of the double-blind study VRX-RET-E22-302. The percent change in monthly total seizure rates from the Baseline phase will be classified into <0, [0, 25), [25, 50), [50, 75), [75, 100] and described. The responder rate during the open-label study (defined as a reduction in seizure frequency ≥50%) will also be summarized using descriptive statistics.

The number of seizure free days, in percent to the individual duration of the open-label treatment, will be calculated and summarized using descriptive statistics. This percentage will be classified into [0, 25), [25, 50), [50, 75), [75, 95), [95,100), [=100] and described statistically.

All-cause withdrawal rates will be calculated as a percentage and respective "times to event" will be described by a Kaplan-Meier survival curve. Specific reasons for withdrawal will also be described separately.

Besides the categorical analysis mentioned above, the continuous efficacy measurements (such as percent change in monthly total seizure rate from the baseline, etc.) will be analyzed by analysis of covariance (ANCOVA) with treatment and center as fixed factors and the baseline value of the efficacy measurement as covariate. Rank analysis of covariance will be used if necessary; however adjusted means will not be presented because the data are ranked. The responder rates will be analyzed to check the consistency of treatment response in double-blind and open label extension studies. The complete details of efficacy analyses will be described in the Statistical Analysis Plan.

10.2. Assessment of Safety

Adverse events (AEs) will be monitored from the start of this extension study (informed consent provided by patient at the Baseline visit) until 30 days after administration of the last dose of study drug (end of study drug taper-off). Treatment-emergent adverse events (TEAEs) will be summarized with respect to overall incidence, as well as severity and relationship of the AEs to the study drugs. AEs that result in dose modification, discontinuation of the study drug, or serious adverse events will also be summarized

AEs with onset after the initiation of study drug and within 30 days after the last dose of study drug may be considered treatment-emergent. This will include any AE with onset prior to initiation of study drug that increased in severity during the treatment period. All reported AEs including those with onset more than 30 days after the last dose of study drug will be included in the data listings.

Abnormal changes in laboratory parameters that are not disease-related will be monitored and recorded throughout the study.

All adverse events will be encoded according to MedDRA 8.0. Treatment emergent adverse events (TEAE) will be analyzed, i.e. all adverse events starting or worsening between start of long-term extension study up to 30 days after end of study drug taper-off. Incidences on preferred term and body system basis will be calculated for all TEAEs.

Different categories for causality will be recorded in the CRFs, and these 4 categories (DEFINITE, PROBABLE, POSSIBLE, and NOT RELATED) are defined in Section 11.3 (Criteria for Determining Relationship to Study Drug) of this protocol.

In addition, all SAEs and all AEs leading to premature discontinuation will be presented as separate listings. TEAE from both studies (double-blind and open-label extension) will be combined, i.e. each patient will be counted just once (with patient's respective TEAE).

Other safety evaluations, such as vital signs, physical and neurological examinations, laboratory variables, ECG variables, post-void residual bladder ultrasound, and AUA symptom index will be analyzed descriptively.

Besides descriptive statistics of the safety evaluations will be presented, the incidence of TEAEs will be compared across treatment group using Fisher's Exact test, only for those events with an incidence of ≥ 5% over all treatment groups. Fisher's Exact test will be applied if necessary for other safety evaluations (vital signs, physical and neurological examinations, laboratory variables, etc.). QTc interval prolongations will be examined by using both Bazett's and Fridericia's QT correction formulas. The complete details of safety analyses will be described in the Statistical Analysis Plan.

10.3. Determination of Sample Size

Not applicable for this long-term extension study.

10.4. Additional Statistical Considerations

10.4.1. Analysis Population

The safety population will include all patients who successfully complete the Transition phase of Study VRX-RET-E22-302 and were included in this long-term study. The Transition phase is the phase of Study VRX-RET-E22-302 during which patients were adjusted to a 300 mg TID dose. No other population for analysis is defined for this long-term extension.

10.4.2. Handling of Missing Data

No imputation will be made for missing data in the safety analyses, with the exception of incomplete date variables regarding adverse events onset date that is necessary for defining treatment-emergent adverse events. More details on imputation of partial dates will be provided in the statistical analysis plan.

11. ADVERSE EVENTS

An adverse event (AE) is defined as any untoward clinical occurrence in a patient administered a pharmaceutical drug product that does not necessarily have a causal relationship with the study drug. An AE can therefore be any unfavorable and unintended sign (including an abnormal laboratory finding), symptom or disease temporarily associated with the use of a drug product, whether or not related to the drug product.

The presence or occurrence of any of those clinical manifestations and/or alterations in clinical laboratory test results that are either present before participation in this study or that are part of the normal fluctuations or progression of their pre-study health state, will not engender an AE report to the health authorities. Clinical manifestations and/or abnormal laboratory values measured during the study that are a sign of worsening of the patient's pre-study health status or that are new findings may, if clinically relevant, be an AE reportable to the health authorities. Abnormal laboratory values represent adverse events when they are indicative of a disease or defect (e.g., reduced hematocrit resulting in

anemia), necessitate intervention (e.g., administration of packed red blood cells or other therapies), or result in dose reduction or permanent discontinuation of the drug product.

Throughout the course of the study, AEs will be monitored and recorded on the patients' source documents and CRFs. The onset, seriousness, intensity, duration, actions taken, effect on study drug administration (e.g., discontinuation), the potential relationship to the study drug, as well as the date of resolution, if any, will be recorded.

11.1. Definition and Grading Intensity

Serious Adverse Events

A serious adverse event (SAE) is an event that results in any of the following outcomes:

- Death.
- Life-threatening adverse experience.
- Hospitalization (unplanned hospital stay) or prolongation of existing hospitalization.
- Persistent or significant disability/incapacity.
- Congenital anomaly/birth defect.

Important medical events that may not result in death, be life-threatening or require hospitalization may be considered serious adverse events when, based on appropriate medical judgment, they may jeopardize the subject and may require medical or surgical intervention to prevent one of the outcomes listed above.

Planned hospitalization or surgery for a condition present prior to the participant's enrollment in the study will not meet the definition of an SAE.

11.2. Intensity

The relationship to the study drug and the intensity of an AE should be assessed by the Investigator using the following guidelines:

MILD	=	Causing no limitation of usual activities; the patient may experience slight discomfort.
MODERATE	=	Causing some limitation of usual activities; the patient may experience annoying discomfort; may warrant intervention.
SEVERE	=	Causing inability to carry out usual activities; the patient may experience intolerable discomfort or pain; warrants intervention.

11.3. Criteria for Determining Relationship to Drug

The Investigator should assess the relationship of the adverse event to the study drug according to the following guidelines:

DEFINITE = An event that follows a reasonable temporal sequence from administration of the drug or in which the drug level has been established in body fluids or tissue; that follows a known or expected response pattern to the suspected drug; and that is confirmed by improvement on stopping or reducing the dosage of the drug, and reappearance of the reaction on repeated exposure.

PROBABLE = An event that follows a reasonable temporal sequence from administration of the drug; that follows a known or expected response pattern to the suspected drug; that is confirmed by stopping or reducing the dosage of the drug; and that could not be reasonably explained by the known characteristics of the patient's clinical state.

POSSIBLE = An event that follows a reasonable temporal sequence from administration of the drug; that follows a known or expected response pattern to the suspected drug; but that could readily be produced by a number of other factors.

NOT RELATED = Any event that does not meet the above criteria.

11.4. Reporting of Adverse Events

All AEs should be recorded on the appropriate CRFs. All SAEs, whether or not deemed drug-related or expected, must be recorded on the CRFs and SAE forms and reported by the Investigator to the CRO (Quintiles Pharmacovigilance) assigned by the Sponsor within 24 hours by telephone and facsimile.

Complete details of SAE contact information for Quintiles Pharmacovigilance will be provided to sites in each of the participating countries in the Study Reference Manual.

A written report for an SAE must follow within 24 hours of the initial notification, including a full description of the event and any sequelae. This includes events that occur while enrolled in the study or within the Follow-Up Period. The Investigator shall comply with all applicable regulations and report all SAEs according to the requirements of their Institutional Review Board (IRB), Independent Ethics Committee (IEC) or Research Ethics Board (REB).

11.4.1. Adverse Events Follow-Up

AEs will be recorded from the start of this extension study (informed consent provided by patient at the Baseline visit) until 30 days after administration of the last dose of study medication (end of study medication taper-off). All post-treatment events will be collected through spontaneous reporting by the patient. All AEs and SAEs will be followed until the event resolves, the condition stabilizes, the event is otherwise explained, or the patient is lost to follow up. The Investigator is responsible for ensuring that follow up includes any

supplemental investigations as may be indicated to elucidate the nature and/or causality of the AE. This may include additional laboratory tests or investigations, histopathological examinations, or consultation with other health care professionals, as is practical.

12. DOSE MODIFICATIONS

Patients will be treated with 600-1200 mg/day of retigabine as an adjunct therapy to their current antiepileptic medications (AEDs) or vagal nerve stimulation as established in Study VRX-RET-E22-302.

If, in the opinion of the Investigator, the patient was not receiving the maximum effective dose, the dose could be increased in weekly intervals of 150 mg/day, up to a maximum of 1200 mg daily (i.e. 400 mg TID). If adverse events considered to be secondary to retigabine occur, the total daily dose could be reduced by 150 mg/day every week, at Investigator discretion, as long as the dose is within 600-1200 mg/day.

After the patient has entered open-label treatment, the Investigator may add new AEDs, as long as these are approved AEDs. In addition, the existing background AED therapy can be adjusted to achieve the best efficacy/safety ratio, as needed, per Investigator discretion. If necessary, in the Investigator's judgment, all background AEDs can be discontinued to achieve monotherapy with retigabine.

Patients who permanently discontinue open-label treatment will have their dose tapered by one-third every week.

If a patient experiences a serious adverse event that is categorized to be "life-threatening," all study medication must be discontinued immediately.

All dose modifications and reason(s) must be documented in the patient's source documents and the CRF.

13. MONITORING

The Sponsor or designee will monitor this clinical trial through visits scheduled to check the adequacy of staff and facilities, and to ensure adherence to the protocol, study procedures and applicable regulations. The clinical monitor will also assess proper CRF completion and retention. The Investigator and clinical staff are expected to allocate sufficient time to permit adequate review of the study's progress. The Investigator will permit trial-related monitoring, audits, IRB/IEC review and regulatory inspection(s), providing direct access to source data/documents.

14. QUALITY ASSURANCE AND QUALITY CONTROL

The Sponsor or designee will implement and maintain quality assurance and quality control systems with Standard Operating Procedures (SOPs) to ensure that this clinical trial is conducted and data are generated, documented (recorded) and reported in compliance to the protocol, Good Clinical Practice (GCP) standards, ICH and other applicable regulations.

The Sponsor is responsible for securing agreement among collaborating parties to ensure direct access to clinical-trial-related sites and material to ensure that all data are reliable and have been processed correctly.

15. DRUG ACCOUNTABILITY

The Investigator must maintain accurate records of the study medication received from the Sponsor, including date received, number of units received and lot number. The Investigator must also ensure that the drug supplies are kept secured and accounted for with access limited to those authorized by the Investigator. The study coordinator or designee must maintain accurate records of all study medication received to be able to reconcile the dispensing logs at the end of the study. The study drug records must be readily available for inspection by the study monitor and/or auditor. No medication (new or used) can be returned to the Sponsor (or its designee) or disposed of at the research unit until the Sponsor's clinical monitor has verified the accuracy of the study medication records at the site and indicated whether the medication should be destroyed at the site or returned to the Sponsor (or its designee), in which case the study monitor must indicate the name and address of the individual to whom the returned materials should be shipped.

16. LABELING AND PACKAGING OF STUDY MEDICATION

The study drug will be packaged and labeled in a manner consistent with the study design and applicable regulations. The study drug shall be identified as an investigational compound. The study protocol number will be identified on the unit label. Designated site personnel shall record the drug unit on the drug dispensing logs when the study drug is dispensed.

Each bottle of retigabine tablets (50 mg, 100 mg, or 300 mg per tablet) will be labeled with the protocol number, a unique package number, the name of the study medication, the use-by date, the Valeant address, and any additional information required by local regulations. In addition, spaces will be included for recording patient number/initials, visit number, and dated dispensed. Specific dosage instructions will be provide separately to the patient. A sufficient supply of study medication will be provided to each site for completion of trial,

based on the number of patients enrolled, study visit schedule, and the daily doses of patients.

All study medication will be dispensed by the pharmacy or an appropriately qualified member of the study staff assigned by the Principal Investigator to this task.

17. DATA HANDLING AND RECORDKEEPING

17.1. Records

The Investigator must maintain all documents and records, copies or originals, relating to the conduct of this trial. This documentation includes, but is not limited to protocols, CRFs, advertising for patient participation, AE reports, patient source data, correspondence with health authorities and IRB/IEC/REB, consent forms, Investigator's curriculum vitae, monitor visit logs, laboratory reference ranges and laboratory certification or quality control procedures and laboratory director curriculum vitae. The Investigator and affiliated institution should maintain the trial documents as required by the applicable regulations. The Investigator and affiliated institution should take measures to prevent accidental or premature destruction of documents. Clinical trial documents must be kept in the clinical site's archives indefinitely, unless written authorization is obtained from the Sponsor.

Federal regulations require that records of drug disposition, CRFs, and all reports of this investigation shall be retained by the Investigator for a minimum of 15 years after notification by Valeant that the regulatory authorities have been notified of the study's termination, or 2 years after approval of the marketing application. If the Investigator is unable to retain the study documents for the required amount of time, Valeant must be informed of the individual who will be assuming this responsibility. These documents shall be retained for a longer period, however, if required by applicable regulatory requirement(s) or if needed by the Sponsor.

17.2. Case Report Forms

All entries on a CRF are ultimately the responsibility of the Investigator, who is expected to review each form for completeness, accuracy and legibility before signing. All forms must be filled out by using black ink. Errors should be lined out but not obliterated and the correction inserted, initialed, dated and an explanation provided (if not evident). A CRF must be completed for each participant who has given informed consent. The CRFs and source documents must be made available to the study monitor for review at the time of the monitoring visits.

18. INSTITUTIONAL REVIEW BOARD

This study is to be conducted in accordance with Institutional Review Board (IRB) regulations (US 21 CFR, Part 56) or applicable Independent Ethics Committee (IEC) regulations. The IRB/IEC must review and approve the following documents, if applicable:

- Trial protocol and amendment(s).
- Written informed consent form(s) and consent form updates.
- Patient recruitment procedures (e.g., advertisements).
- Written information to be provided to patients.
- Investigator's Brochure (IB) and available safety information.
- Information about payments and compensation available to patients.

The IRB/IEC approval should be in writing, clearly identifying the trial, the documents reviewed including informed consent and date of the review. The Investigator has the responsibility to provide the Sponsor with the written IRB/IEC approval prior to initiating any study-related procedures. The Investigator also has the responsibility to inform the IRB/IEC of serious and unexpected AEs and provide the IRB/IEC with a final report upon study completion.

19. COMPLIANCE WITH THE DECLARATION OF HELSINKI

This study is to be conducted in compliance with the Declaration of Helsinki (Appendix C).

20. INFORMED CONSENT

Prior to participation in a study, the patient or patient's legal representative must sign an IRB/IEC approved written informed consent form. The approved written informed consent must abide to all applicable laws in regards to the safety and confidentiality of the patients. To obtain and document informed consent, the Investigator should comply with applicable regulations; adhere to GCP standards and the ethical principles in the Declaration of Helsinki (Appendix C).

The language in the oral and written information about the trial, including the written informed consent form should be as non-technical as practical and should be understandable to the patient or patient's legal representative and the impartial witness, where applicable. Before informed consent is obtained, the Investigator should provide the patient or patient's legal representative ample time and opportunity to inquire about the trial and to decide whether or not to participate.

All questions about the trial should be answered to the satisfaction of the patient or the patient's legal representative. The written informed consent form should be signed and personally dated by the patient or patient's legal representative, and by the person who conducted the informed consent discussion. Patients will be informed that participation is voluntary and that he/she can withdraw from the study at any time. A signed copy of the consent form must be given to the patient, and this fact will be documented in the CRFs.

21. CHANGES TO THE PROTOCOL

The Investigator shall not implement any deviation or change to the protocol without approval by the Sponsor and prior review and documented approval and favorable opinion from the IRB/IEC/REB. The only exception is when it is necessary to eliminate immediate hazards to study patients or when changes involve only logistical or administrative aspects of the study (e.g., change in monitors, change in phone numbers).

Although the Sponsor has every intention of completing the study, the Sponsor reserves the right to discontinue the study at any time for clinical or administrative reasons.

22. REFERENCES

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Appendix A. Study Flow Chart

Study Procedures	Baseline[1]	Open-Label Extension – First Year[2,3]					Open-Label Extension - Second Year and Onward[2,3]					
	Visit 0	Visit 1	Visit 2	Visit 3	Visit 4	Visit 5[4]	Visit 6	Visit 7	Visit 8[4]	Visit 9	Visit 10	Visit 11[4]
	Month 0	Month 1	Month 3	Month 6	Month 9	Month 12	Month 16	Month 20	Month 24	Month 28	Month 32	Month 36
Eligibility/Informed Consent	X											
Physical and Neurological Exam	X					X			X			X
Brief Neurological Exam		X	X	X	X		X	X		X	X	
Vital Signs (BP, HR, and Temperature) and Weight[5]	X	X	X	X	X	X	X	X	X	X	X	X
12 Lead ECG	X	X	X	X	X	X			X			X
Blood Chemistry and Hematology	X	X	X	X	X	X	X	X	X	X	X	X
Urinalysis (including Microscopy)	X	X	X	X	X	X	X	X	X	X	X	X
AUA Symptom Index[7]	X	X	X			X						
PVR Bladder Ultrasound[7]	X	X	X			X						
Serum Pregnancy Test[6]	X					X			X			X
Seizure Diary Review	X	X	X	X	X	X	X	X	X	X	X	X
AE Evaluation	X	X	X	X	X	X	X	X	X	X	X	X

Study Procedures	Baseline[1]	Open-Label Extension – First Year[2,3]					Open-Label Extension - Second Year and Onward[2,3]					
	Visit 0	Visit 1	Visit 2	Visit 3	Visit 4	Visit 5[4]	Visit 6	Visit 7	Visit 8[4]	Visit 9	Visit 10	Visit 11[4]
	Month 0	Month 1	Month 3	Month 6	Month 9	Month 12	Month 16	Month 20	Month 24	Month 28	Month 32	Month 36
Concomitant Medication	X	X	X	X	X	X	X	X	X	X	X	X
QOLIE-31-P Questionnaire	X		X	X	X	X			X			X
Dispense Open-Label Study Medication[8]	X	X	X	X	X	X	X	X	X	X	X	X
Collect Returned Open-Label Study Medication		X	X	X	X	X	X	X	X	X	X	X

1. Baseline for the open-label extension study corresponds to the assessments performed at the last visit of the Maintenance phase (Visit 9) of Study VRX-RET-E22-302 for all patients. The final, baseline eligibility assessment for the open-label extension study, including obtaining informed consent and dispensing open-label study medication will be performed at the last visit of the Transition phase (Visit 11) of Study VRX-RET-E22-302.
2. Study Visit 1 will have a window range of ±3 days. After Study Visit 1, all remaining study visits will have a window range of ±7 days around that visit day to accommodate individual schedules. Each study month will be defined as 30 calendar days. If a patient visit occurs outside the visit window, the study clinical monitor (CRA) should be notified and the reason for the deviation noted. An attempt should be made to ensure that the patient returns for subsequent visits on schedule using the last visit of the Transition phase (Visit 11) of Study VRX-RET-E22-302, which corresponds to the final, Baseline eligibility visit for the open-label extension study.
3. This open-label extension study will be continued until retigabine is approved and commercially available, or until the program is discontinued, followed by a 3-week tapering period and a 30 day post-study period for collection of adverse events. After the first year, the study visits will occur every 4 months (3 visits per year). After the first year, the assessments for the first 2 study visits of each year (e.g. Visits 6, 7, 9 and 10) will be identical, and the assessments for the last study visit of each year (e.g. Visits 8 and 11) will be identical.
4. All patients who discontinue early from study treatment during the open-label extension study will have their study medication tapered over a 3-week period, reducing their daily dose by one-third per week, and then return for a final visit. Patients who discontinue early during the first year of the open-label extension study will complete all assessments and evaluations scheduled for Study Visit 5. Patients who discontinue early during the second year of the open-label extension study will complete all assessments and evaluations scheduled for Study Visit 8. Patients who discontinue early during the third year of the open-label extension study will complete all assessments and evaluations scheduled for Study Visit 11. Also, all adverse events should be followed and collected up to until 30 days after administration of the last dose of study drug (end of study drug taper-off).
5. Supine and standing blood pressure, heart rate.
6. In addition to the scheduled pregnancy tests, a pregnancy test should be performed during the study whenever a woman's menstrual period is 5 days late.
7. The AUA Symptom Index and the PVR bladder ultrasound will only be performed during the first year of the open-label extension study (Visits 1, 2, and 5).
8. Dispensation of study medication is not applicable at the final study visit, if a patient has discontinued early or completed the open-label extension study.

Appendix B. World Medical Association Declaration of Helsinki

Ethical Principles for Medical Research Involving Human Subjects

Adopted by the 18th WMA General Assembly, Helsinki, Finland, June 1964, and amended by the

29th WMA General Assembly, Tokyo, Japan, October 1975

35th WMA General Assembly, Venice, Italy, October 1983

41st WMA General Assembly, Hong Kong, September 1989

48th WMA General Assembly, Somerset West, Republic of South Africa, October 1996

and the 52nd WMA General Assembly, Edinburgh, Scotland, October 2000

Note of Clarification on Paragraph 29 added by the WMA General Assembly, Washington 2002

Note of Clarification on Paragraph 30 added by the WMA General Assembly, Tokyo 2004

INTRODUCTION

1. The World Medical Association has developed the Declaration of Helsinki as a statement of ethical principles to provide guidance to physicians and other participants in medical research involving human subjects. Medical research involving human subjects includes research on identifiable human material or identifiable data.
2. It is the duty of the physician to promote and safeguard the health of the people. The physician's knowledge and conscience are dedicated to the fulfillment of this duty.
3. The Declaration of Geneva of the World Medical Association binds the physician with the words, "The health of my patient will be my first consideration," and the International Code of Medical Ethics declares that, "A physician shall act only in the patient's interest when providing medical care which might have the effect of weakening the physical and mental condition of the patient."
4. Medical progress is based on research which ultimately must rest in part on experimentation involving human subjects.

5. In medical research on human subjects, considerations related to the well-being of the human subject should take precedence over the interests of science and society.
6. The primary purpose of medical research involving human subjects is to improve prophylactic, diagnostic and therapeutic procedures and the understanding of the aetiology and pathogenesis of disease. Even the best proven prophylactic, diagnostic, and therapeutic methods must continuously be challenged through research for their effectiveness, efficiency, accessibility and quality.
7. In current medical practice and in medical research, most prophylactic, diagnostic and therapeutic procedures involve risks and burdens.
8. Medical research is subject to ethical standards that promote respect for all human beings and protect their health and rights. Some research populations are vulnerable and need special protection. The particular needs of the economically and medically disadvantaged must be recognized. Special attention is also required for those who cannot give or refuse consent for themselves, for those who may be subject to giving consent under duress, for those who will not benefit personally from the research and for those for whom the research is combined with care.
9. Research Investigators should be aware of the ethical, legal and regulatory requirements for research on human subjects in their own countries as well as applicable international requirements. No national ethical, legal or regulatory requirement should be allowed to reduce or eliminate any of the protections for human subjects set forth in this Declaration.

BASIC PRINCIPLES FOR ALL MEDICAL RESEARCH

10. It is the duty of the physician in medical research to protect the life, health, privacy, and dignity of the human subject.
11. Medical research involving human subjects must conform to generally accepted scientific principles, be based on a thorough knowledge of the scientific literature, other relevant sources of information, and on adequate laboratory and, where appropriate, animal experimentation.
12. Appropriate caution must be exercised in the conduct of research which may affect the environment, and the welfare of animals used for research must be respected.
13. The design and performance of each experimental procedure involving human subjects should be clearly formulated in an experimental protocol. This protocol should be submitted for consideration, comment, guidance, and where appropriate, approval to a specially appointed ethical review committee, which must be independent of the Investigator, the sponsor or any other kind of undue influence. This independent

committee should be in conformity with the laws and regulations of the country in which the research experiment is performed. The committee has the right to monitor ongoing trials. The researcher has the obligation to provide monitoring information to the committee, especially any serious adverse events. The researcher should also submit to the committee, for review, information regarding funding, sponsors, institutional affiliations, other potential conflicts of interest and incentives for subjects.

14. The research protocol should always contain a statement of the ethical considerations involved and should indicate that there is compliance with the principles enunciated in this Declaration.
15. Medical research involving human subjects should be conducted only by scientifically qualified persons and under the supervision of a clinically competent medical person. The responsibility for the human subject must always rest with a medically qualified person and never rest on the subject of the research, even though the subject has given consent.
16. Every medical research project involving human subjects should be preceded by careful assessment of predictable risks and burdens in comparison with foreseeable benefits to the subject or to others. This does not preclude the participation of healthy volunteers in medical research. The design of all studies should be publicly available.
17. Physicians should abstain from engaging in research projects involving human subjects unless they are confident that the risks involved have been adequately assessed and can be satisfactorily managed. Physicians should cease any investigation if the risks are found to outweigh the potential benefits or if there is conclusive proof of positive and beneficial results.
18. Medical research involving human subjects should only be conducted if the importance of the objective outweighs the inherent risks and burdens to the subject. This is especially important when the human subjects are healthy volunteers.
19. Medical research is only justified if there is a reasonable likelihood that the populations in which the research is carried out stand to benefit from the results of the research.
20. The subjects must be volunteers and informed participants in the research project.
21. The right of research subjects to safeguard their integrity must always be respected. Every precaution should be taken to respect the privacy of the subject, the confidentiality of the patient's information and to minimize the impact of the study on the subject's physical and mental integrity and on the personality of the subject.
22. In any research on human beings, each potential subject must be adequately informed of the aims, methods, sources of funding, any possible conflicts of interest, institutional affiliations of the researcher, the anticipated benefits and potential risks of the study and

the discomfort it may entail. The subject should be informed of the right to abstain from participation in the study or to withdraw consent to participate at any time without reprisal. After ensuring that the subject has understood the information, the physician should then obtain the subject's freely-given informed consent, preferably in writing. If the consent cannot be obtained in writing, the non-written consent must be formally documented and witnessed.

23. When obtaining informed consent for the research project the physician should be particularly cautious if the subject is in a dependent relationship with the physician or may consent under duress. In that case the informed consent should be obtained by a well-informed physician who is not engaged in the investigation and who is completely independent of this relationship.

24. For a research subject who is legally incompetent, physically or mentally incapable of giving consent or is a legally incompetent minor, the Investigator must obtain informed consent from the legally authorized representative in accordance with applicable law. These groups should not be included in research unless the research is necessary to promote the health of the population represented and this research cannot instead be performed on legally competent persons.

25. When a subject deemed legally incompetent, such as a minor child, is able to give assent to decisions about participation in research, the Investigator must obtain that assent in addition to the consent of the legally authorized representative.

26. Research on individuals from whom it is not possible to obtain consent, including proxy or advance consent, should be done only if the physical/mental condition that prevents obtaining informed consent is a necessary characteristic of the research population. The specific reasons for involving research subjects with a condition that renders them unable to give informed consent should be stated in the experimental protocol for consideration and approval of the review committee. The protocol should state that consent to remain in the research should be obtained as soon as possible from the individual or a legally authorized surrogate.

27. Both authors and publishers have ethical obligations. In publication of the results of research, the Investigators are obliged to preserve the accuracy of the results. Negative as well as positive results should be published or otherwise publicly available. Sources of funding, institutional affiliations and any possible conflicts of interest should be declared in the publication. Reports of experimentation not in accordance with the principles laid down in this Declaration should not be accepted for publication.

ADDITIONAL PRINCIPLES FOR MEDICAL RESEARCH COMBINED WITH MEDICAL CARE

28. The physician may combine medical research with medical care, only to the extent that the research is justified by its potential prophylactic, diagnostic or therapeutic value. When medical research is combined with medical care, additional standards apply to protect the patients who are research subjects.

29. The benefits, risks, burdens and effectiveness of a new method should be tested against those of the best current prophylactic, diagnostic, and therapeutic methods. This does not exclude the use of placebo, or no treatment, in studies where no proven prophylactic, diagnostic or therapeutic method exists.[1]

30. At the conclusion of the study, every patient entered into the study should be assured of access to the best proven prophylactic, diagnostic and therapeutic methods identified by the study.[2]

31. The physician should fully inform the patient which aspects of the care are related to the research. The refusal of a patient to participate in a study must never interfere with the patient-physician relationship.

32. In the treatment of a patient, where proven prophylactic, diagnostic and therapeutic methods do not exist or have been ineffective, the physician, with informed consent from the patient, must be free to use unproven or new prophylactic, diagnostic and therapeutic measures, if in the physician's judgment it offers hope of saving life, re-establishing health or alleviating suffering. Where possible, these measures should be made the object of research, designed to evaluate their safety and efficacy. In all cases, new information should be recorded and, where appropriate, published. The other relevant guidelines of this Declaration should be followed.

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[1] Note of clarification on paragraph 29 of the WMA Declaration of Helsinki

The WMA hereby reaffirms its position that extreme care must be taken in making use of a placebo-controlled trial and that in general this methodology should only be used in the absence of existing proven therapy. However, a placebo-controlled trial may be ethically acceptable, even if proven therapy is available, under the following circumstances:

- Where for compelling and scientifically sound methodological reasons its use is necessary to determine the efficacy or safety of a prophylactic, diagnostic or therapeutic method; or

- Where a prophylactic, diagnostic or therapeutic method is being investigated for a minor condition and the patients who receive placebo will not be subject to any additional risk of serious or irreversible harm.

All other provisions of the Declaration of Helsinki must be adhered to, especially the need for appropriate ethical and scientific review.

[2] Note of clarification on paragraph 30 of the WMA Declaration of Helsinki

The WMA hereby reaffirms its position that it is necessary during the study planning process to identify post-trial access by study participants to prophylactic, diagnostic and therapeutic procedures identified as beneficial in the study or access to other appropriate care. Post-trial access arrangements or other care must be described in the study protocol so the ethical review committee may consider such arrangements during its review.

9.10.2004

Appendix C. American Urological Association Symptom Index

This section contained Clinical Outcome Assessment data collection questionnaires or indices, which are protected by copyright laws and therefore have been excluded.

Reference:

Barry MJ, et al. (1992). The American Urological Association symptom index for benign prostatic hyperplasia. Journal of Urology, 148: 1549–1557.

Appendix D. Protocol Agreement

PROTOCOL TITLE:

A multicenter, open-label, long-term, safety, tolerability and efficacy study of retigabine in adult epilepsy patients with partial-onset seizures (Extension of study VRX-RET-E22-302).

PROTOCOL NO: VRX-RET-E22-304

This document is a confidential communication of Valeant Research & Development. The authorized Investigator agrees to personally conduct or supervise the conduct of this study as outlined in the current protocol. No changes will be made to the protocol without prior written approval from Valeant Research & Development, except to protect the safety, rights and welfare of the study participants and always in compliance with all applicable Good Clinical Practices (GCP), as well as International Conference on Harmonization (ICH) and regulatory requirements. Acceptance of this document constitutes the agreement by the Investigator that no unpublished information contained herein will be published or disclosed without prior written approval from Valeant Research & Development.

I have read this protocol in its entirety and agree to conduct the study accordingly.

_____ _____

Signature: Date
Principal Investigator

_____

Printed Name