Randomized, double-blind, placebo-controlled trial of ezogabine (retigabine) in partial epilepsy

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ABSTRACT

Objective: To evaluate the efficacy and safety of ezogabine (United States adopted name)/retigabine (international nonproprietary name) (EZG[RTG]) 1,200 mg/day as adjunctive treatment in adults with drug-resistant epilepsy with partial-onset seizures with or without secondary generalization.

Methods: RESTORE 1 was a multicenter, randomized, double-blind, parallel-group trial. Following a prospective 8-week baseline phase, patients entered an 18-week double-blind treatment period (6-week forced dose titration to EZG[RTG] 1,200 mg/day in 3 equally divided doses or placebo, followed by a 12-week maintenance phase). Results were analyzed on an intent-to-treat basis for the entire 18-week period and for patients reaching the maintenance phase.

Results: In 306 patients randomized, 305 received EZG(RTG) 1,200 mg/day (n = 153) or placebo (n = 152). Median percent reduction in total partial-seizure frequency was 44.3% vs 17.5% ($p < 0.001$) for EZG(RTG) and placebo, respectively, during the 18-week double-blind period; responder rates (≥50% reduction in total partial-seizure frequency from baseline) were 44.4% vs 17.8% ($p < 0.001$). In 256 patients (EZG[RTG], 119; placebo, 137) entering the 12-week maintenance phase, median percent reduction in seizure frequency for EZG(RTG) vs placebo was 54.5% and 18.9% ($p < 0.001$), respectively; responder rates were 55.5% vs 22.6% ($p < 0.001$). The proportion of patients discontinuing due to treatment-emergent adverse events (TEAEs) was 26.8% (EZG[RTG]) vs 8.6% (placebo). Dizziness, somnolence, fatigue, confusion, dysarthria, urinary tract infection, ataxia, and blurred vision were the most common TEAEs reported by more patients treated with EZG(RTG) than placebo.

Conclusions: This study demonstrates that EZG(RTG) is effective as add-on therapy for reducing seizure frequency in patients with drug-resistant partial-onset seizures.

Classification of evidence: This study provides Class II evidence that EZG(RTG) 1,200 mg/day is effective as adjunctive therapy in adults with partial-onset seizures with or without secondary generalization. *Neurology*® 2011;76:1555–1563

GLOSSARY

AE = adverse event; **AED** = antiepileptic drug; **CGI-I** = Clinical Global Impression of Improvement; **EMA** = European Medicines Agency; **EZG** = ezogabine; **FDA** = Food and Drug Administration; **ILAE** = International League Against Epilepsy; **ITT** = intent-to-treat; **NNT** = number needed to treat; **PGI-I** = Patient Global Impression of Improvement; **PVR** = postvoid residual; **RTG** = retigabine; **TEAE** = treatment-emergent adverse event.

Treatment of patients with epilepsy who do not achieve adequate seizure control with current antiepileptic drugs (AEDs) (approximately 30%)[1] remains a major clinical problem and motivates the continued search for compounds with new mechanisms of action.

Potassium (K^+) channels play a central role in regulating neuronal excitability and represent a target for the treatment of epilepsy. Ezogabine (United States adopted name; EZG)/retigabine

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(international nonproprietary name; RTG) (N-[2-3amino-4-(4-fluorobenzylamino)-phenyl]-carbamic acid ethyl ester) is a first-in-class AED believed to enhance the activity and prolong the opening of neuron-specific KCNQ2/3 (K_v7.2/7.3) voltage-gated K^+ channels, thereby enhancing the M-current and suppressing epileptiform activity.[2-8] EZG(RTG) exhibits potent activity in a broad array of seizure/epilepsy models.[9-13]

EZG(RTG) is rapidly absorbed following oral administration and metabolized through glucuronidation. Kinetics are linear with no clinically significant food effect. EZG(RTG) and its metabolites are eliminated primarily by renal excretion, with a 6–10 hour half-life.[14-16]

To confirm positive results in a placebo-controlled dose-ranging study,[17] 2 multicenter, double-blind, placebo-controlled trials in adults with partial-onset seizures were undertaken: RESTORE 1 (Study 301), reported here, evaluated EZG (RTG) at the high-end 1,200 mg/day dose; RESTORE 2 (Study 302) explored lower doses (600 and 900 mg).[18]

METHODS

Standard protocol approvals, registration, and patient consents. RESTORE 1 (ClinicalTrials.gov identifier: NCT00232596) was conducted between August 2005 and January 2008 at 53 centers across the United States (n = 149), Canada (n = 20), Mexico (n = 54), Argentina (n = 33), and Brazil (n = 50), and complied with the International Conference on Harmonization Good Clinical Practice guidelines, Declaration of Helsinki, and applicable provisions of the United States Code of Federal Regulations, requirements of the European Medicines Agency (EMA), and national health authorities for Canada, Mexico, Argentina, and Brazil. Participants provided written informed consent before participation.

Patients. Eligible patients were men and women aged 18–75 years with drug-resistant partial epilepsy characterized by simple or complex partial-onset seizures, with or without secondary generalization according to the 1981 International League Against Epilepsy (ILAE) Classification of Epileptic Seizures, a 28-day partial seizure frequency of ≥4 seizures over 8 weeks, and currently receiving a stable regimen of 1–3 background AEDs with or without vagus nerve stimulator. Drug-resistant epilepsy was defined, consistent with the ILAE definition,[19] as continued occurrence of partial seizures despite treatment with at least 2 approved AEDs alone or in combination, administered in adequate doses for a sufficient period to document treatment failure (for detailed inclusion/exclusion criteria, see table e-1 on the *Neurology*® Web site at www.neurology.org).

Study design. This multinational, multicenter, randomized, double-blind, parallel-group, placebo-controlled trial comprised an 8-week prospective baseline phase for patients meeting screening criteria and an 18-week double-blind treatment period (6-week dose titration phase and 12-week maintenance phase; figure e-1). Background AEDs or their dose or VNS settings were kept constant throughout the study. Patients or caregivers recorded seizure type and frequency, adverse events (AEs), and concomitant treatment in daily diaries. Eligible patients were randomized 1:1 in a blinded fashion to EZG(RTG) 400 mg TID or placebo. A central randomization schedule was generated by an independent team at the collaborating contract research organization. Drug kit numbers were assigned by an interactive voice response system. Blinding was maintained by identical packaging for EZG(RTG) and placebo.

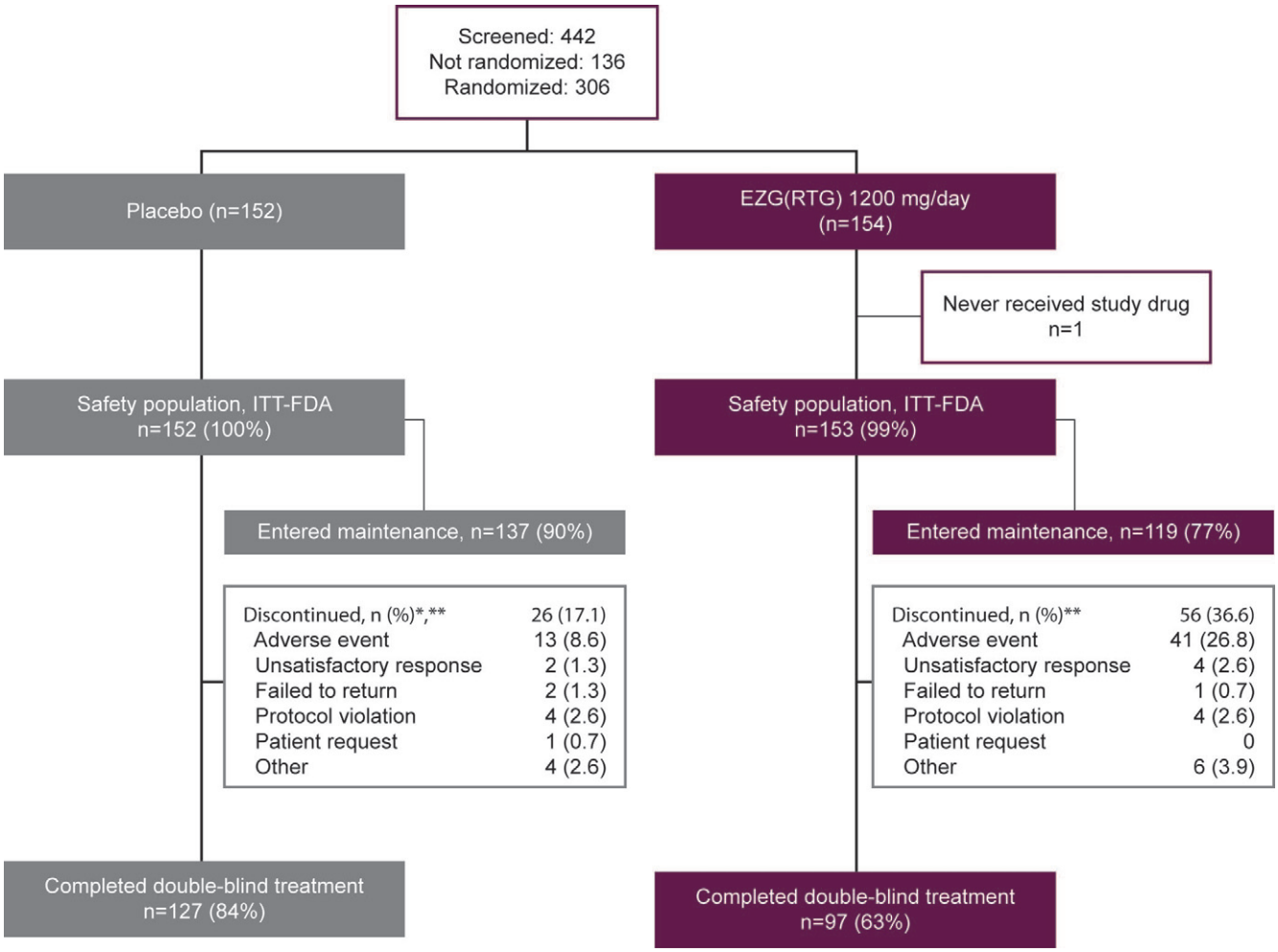
During the double-blind period, EZG(RTG) or matching placebo were taken TID at approximately 8-hour intervals. The 300 mg/day (100 mg TID) starting dose was increased weekly in 150-mg/day increments to achieve the target dosage of 1200 mg/day at week 6. In week 7, a single dosage reduction of 150 mg/day was allowed for intolerability (maintenance dosage, 1,050 mg/day). All patients who received at least 1 dose of study drug were included in the intent-to-treat (ITT) analyses in accordance with randomized dose. Patients unable to achieve 1,200 mg/day or tolerate 1,050 mg/day discontinued the study. Patient dosing compliance was monitored by counting tablets remaining in blister cards.

Study measurements. Two primary endpoints meeting evidentiary requirements of the US Food and Drug Administration (FDA) and EMA, respectively, were selected: percent change in 28-day total partial-seizure frequency from baseline to 18-week double-blind period (titration/maintenance phases) (FDA); and responder rate, defined as the proportion of patients experiencing a ≥50% reduction in 28-day total partial-seizure frequency from baseline to maintenance phase (EMA). Total partial seizures was the sum of all simple partial seizures with or without motor signs, complex partial seizures, partial seizures evolving to secondary generalization, partial status epilepticus, convulsive status epilepticus, +10 if flurries present. Additional efficacy endpoints included distribution of patients across seizure frequency reduction categories, proportion of seizure-free patients, percent of treatment days without seizures, and Clinical/Patient Global Impressions of Improvement (CGI–I, PGI–I), which consisted of a 7-point Likert scale from 1 (very much improved) to 7 (very much worse). Lower scores represented improvement. Tolerability and safety were monitored with AE assessments based on patient/caregiver reporting in seizure diaries and at study visits, vital signs, neurologic/physical examinations, clinical laboratory assessments, and EKG tracings. AEs were coded using the Medical Directory for Regulatory Activities. Due to urinary system findings observed in preclinical toxicology studies, urinary bladder function was assessed at specified visits by administering the American Urologic Association Symptom Index[20] and postvoid residual (PVR) bladder ultrasound.

Statistical analysis. Statistical analysis was supervised by Robin White, MS, GlaxoSmithKline. Sample size determination was based on the proportion of patients with ≥50% seizure reduction for EZG(RTG) 1,200 mg/day and placebo in the previous dose-ranging study.[17] A total of 250 patients (125 per group) was considered sufficient for 85% power to detect a 17% difference in responder rate with Type I error at 5%, requiring that 280 patients (140 per arm) be randomized to allow for a 10% rate of early treatment discontinuation.

Monthly (28-day) seizure frequency was calculated for baseline, the 18-week double-blind period, and 12-week maintenance phase. For patients who discontinued prematurely during

Figure 1 Patient disposition



EZG(RTG) = ezogabine (retigabine); FDA = Food and Drug Administration; ITT = intent-to-treat. *One patient discontinued after being considered a completer. **Primary reason for discontinuation with possibly >1 reason.

titration or maintenance, monthly seizure rate for the double-blind period was calculated using all observed data up to time of discontinuation. The safety and ITT populations in efficacy analyses comprised all randomized patients who received at least one dose of study drug. Patients who did not provide any post-dosing seizure diary data were considered nonresponders. The population for maintenance phase analyses comprised patients who received at least one dose of study drug during the maintenance phase and provided at least one maintenance phase seizure diary entry (regardless of whether seizures occurred or not).

Baseline homogeneity was assessed by one-way analysis of variance with treatment as a factor for continuous demographic and baseline characteristics in the safety population, and by Fisher exact test for categorical characteristics. Efficacy assessments were performed using 2-sided tests at the 0.05 significance level. A stratified nonparametric rank analysis of covariance model was used to evaluate percent change in seizure frequency and percent of seizure-free treatment days. Fisher exact test was used to analyze responder rates. Cochran-Mantel-Haenszel statistics were used to analyze seizure category distribution.

For each region, only one of the 2 prespecified endpoints was considered primary (i.e., the endpoint which met evidentiary requirements of the region) and the other was considered a key secondary endpoint. To account for multiple comparisons, the primary endpoint was assessed at the 5% level. If this was significant, the key secondary endpoint was assessed at the 5% level. If this was significant, other secondary endpoints were then assessed. Numbers needed to treat (NNT) were calculated post hoc for the EMA endpoint using Bandolier methodology.[21]

RESULTS

Patient disposition. Of 442 screened patients who entered baseline from August 2005 to January 2008, 306 were randomized (EZG[RTG], 154; placebo, 152). Disposition is further delineated in figure 1.

Patient characteristics. EZG(RTG) and placebo groups were generally well-balanced for demographics and epilepsy characteristics at baseline in the ITT population (table 1).

Efficacy. Median percent reduction in monthly seizure frequency over the double-blind period was EZG(RTG) 44.3% vs placebo 17.5% ($p < 0.001$,

Table 1 Demographics and baseline characteristics[a]

	Placebo (n = 152)	EZG(RTG) (n = 153)
Age, y	36.7 (11.6)	37.7 (12.6)
Range	18–64	18–71
Women, n (%)	80 (52.6)	85 (55.6)
Ethnicity, n (%)		
White	78 (51.3)	90 (58.8)
Hispanic	47 (30.9)	39 (25.5)
Black	15 (9.9)	15 (9.8)
Weight, kg	75.2 (22.8)	77.8 (21.7)
Height, cm	166.8 (10.6)	166.7 (10.1)
BMI, kg/m^2	26.9 (7.6)	27.8 (6.9)
Epilepsy duration, y	23.1 (12.8)	23.7 (13.0)
Treatment at baseline, n (%)		
1 AED	21 (13.8)	32 (20.9)
2 AEDs	70 (46.1)	79 (51.6)
3 AEDs	61 (40.1)	42 (27.5)
VNS	17 (11.2)	12 (7.8)
Baseline monthly partial-onset seizure frequency, median	11.3	12.1

Abbreviations: AED = antiepileptic drug; BMI = body mass index; EZG(RTG) = ezogabine (retigabine) 1,200 mg/day; VNS = vagus nerve stimulator.
[a] Values are mean (SD) unless otherwise stated.

figure 2A), and the responder rate was 44.4% vs 17.8% ($p < 0.001$, figure 2B). Among patients completing titration and entering maintenance, median percent reduction in seizure frequency during the maintenance phase was EZG(RTG) 54.5% vs placebo 18.9% ($p < 0.001$, figure 2A), with responder rates of 55.5% vs 22.6% ($p < 0.001$, figure 2B).

Distribution across seizure frequency reduction categories significantly favored EZG(RTG) over placebo for both the double-blind period and maintenance phase ($p < 0.001$; Cochran-Mantel-Haenszel test): a larger proportion of EZG(RTG)-treated patients were in the 50%–<75% or 75%–100% seizure reduction categories, while a larger proportion of placebo-treated patients were in the no seizure reduction, <25%, or 25%–<50% reduction categories (with maintenance phase categorization in accordance with EMA guidance) (figure 3).

There were no significant differences between groups for patients who were seizure-free for the entire double-blind period (EZG[RTG], 3/151 [2%]; placebo, 0/150 [0%]). However, for those patients completing the trial, more patients treated with EZG(RTG) than placebo were seizure-free during the entire maintenance phase (EZG[RTG], 5/97 [5.2%]; placebo, 1/127 [0.8%]; $p = 0.087$). Median percentage of seizure-free days was significantly greater for EZG(RTG) than placebo during both the double-blind period and maintenance phase ($p < 0.001$, see table e-2). The NNT for the ITT-EMA primary endpoint was 3.0 for EZG(RTG) 1,200 mg/day.

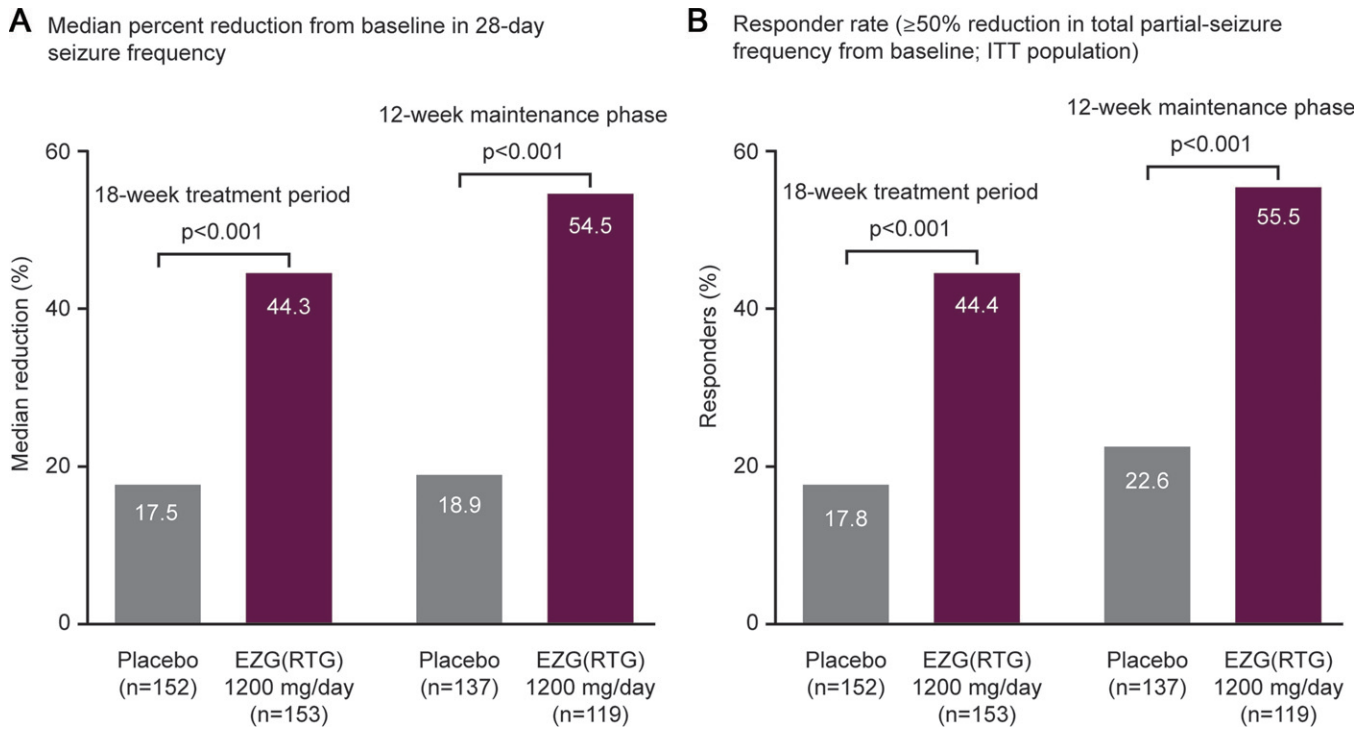
Mean score for CGI–I during the double-blind period was significantly better for EZG(RTG) than placebo (2.9 vs 3.2, $p = 0.020$); corresponding scores during the maintenance phase were 2.7 vs 3.2 ($p = 0.002$). There was no significant difference between EZG(RTG) and placebo for PGI–I scores in the double-blind period (3.1 vs 3.0), and corresponding scores for the maintenance phase were 2.9 for both groups.

Tolerability and safety. During double-blind treatment, 91.5% of EZG(RTG)-treated patients vs 84.9% of placebo-treated patients experienced treatment-emergent AEs (TEAEs). The most common were CNS-related (table 2). The most common reported by more EZG(RTG)- than placebo-treated patients included dizziness, somnolence (which were the most common TEAEs causing reduction of EZG[RTG] dosage), fatigue, confusion, dysarthria, urinary tract infection, ataxia, blurred vision, tremor, and nausea. The majority (>80%) of TEAEs were of mild or moderate severity. For EZG(RTG), the majority emerged during titration. With the exception of confusion, the incidence of newly emergent TEAEs generally declined during the maintenance phase. TEAEs most commonly associated with discontinuation for EZG(RTG) (>3% of patients) were dizziness, confusion, somnolence, and fatigue.

The most common psychiatric disorder TEAE was confusional state (EZG[RTG], 14% vs placebo, 2%), followed by anxiety (5% vs 3%) and disorientation (5% vs 1%). The majority of TEAEs reported as confusional state in EZG(RTG)-treated patients were judged to be mild or moderate in intensity (5 [3.3%] and 15 [9.8%] patients, respectively), with 2 (1.3%) patient reports of confusional state considered severe. Hallucinations and visual hallucinations were experienced by 3 (2%) and 4 (3%) patients, respectively, for EZG(RTG), with no reports of either AE for placebo. Depression was reported by a higher percentage of patients treated with placebo (5%) than EZG(RTG) (1%).

A total of 19 (12.4%) EZG(RTG)-treated patients and 8 (5.3%) placebo-treated patients experienced serious TEAEs, which were most commonly classified as nervous system disorders (EZG[RTG], 4%; placebo, 1%), psychiatric disorders (EZG[RTG], 3%; placebo, 1%), or metabolism/nutritional disorders (EZG[RTG], 2%; placebo, 0%).

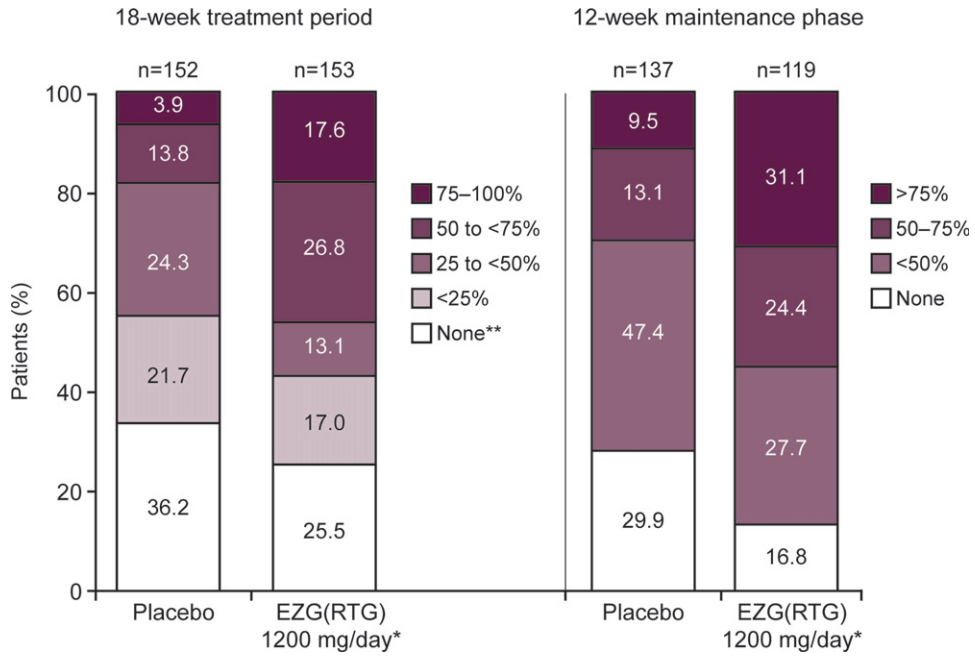
Figure 2 Primary efficacy endpoints for intent-to-treat (ITT) (A) Food and Drug Administration and (B) European Medicines Agency populations



EZG(RTG) = ezogabine (retigabine). The *p* values are based on nonparametric rank analysis of covariance for median percent seizure reduction, and Fisher exact test for responder rates.

One patient in each treatment group died during the double-blind study. For placebo, one death due to collapsed lung with respiratory failure was considered unrelated to treatment. For EZG(RTG), death of an obese patient with hypertensive cardiovascular disease and moderate fasting hyperglycemia at base-

Figure 3 Cumulative distribution of percentage reduction from baseline seizure frequency



EZG(RTG) = ezogabine (retigabine). Percentages do not add up to 100% due to rounding. *$p < 0.001$; *p* values based on Cochran-Mantel-Haenszel test. **Two patients in each arm with no efficacy measure were included.

Table 2 Treatment-emergent adverse events and discontinuation rates during the 18-week treatment period (≥5% of patients in the EZG[RTG] 1,200 mg/day treatment group)[a]

	Placebo (n = 152)		EZG(RTG) (n = 153)	
Preferred term, n (%)	Incidence	Discontinued	Incidence	Discontinued
Dizziness	21 (13.8)	3 (2.0)	62 (40.5)	14 (9.2)
Somnolence	27 (17.8)	2 (1.3)	48 (31.4)	6 (3.9)
Fatigue	12 (7.9)	0	24 (15.7)	5 (3.3)
Confusional state[b]	3 (2.0)	1 (0.7)	22 (14.4)	10 (6.5)
Dysarthria	3 (2.0)	0	19 (12.4)	4 (2.6)
Headache	28 (18.4)	0	19 (12.4)	2 (1.3)
Urinary tract infection	13 (8.6)	0	18 (11.8)	0
Ataxia	6 (3.9)	1 (0.7)	18 (11.8)	4 (2.6)
Vision blurred	4 (2.6)	0	18 (11.8)	2 (1.3)
Tremor	6 (3.9)	0	17 (11.1)	4 (2.6)
Nausea	10 (6.6)	0	16 (10.5)	4 (2.6)
Speech disorder	0	0	13 (8.5)	1 (0.7)
Influenza	8 (5.3)	0	12 (7.8)	0
Memory impairment	7 (4.6)	0	12 (7.8)	1 (0.7)
Diplopia	4 (2.6)	0	10 (6.5)	3 (2.0)
Gait disturbance	3 (2.0)	0	10 (6.5)	2 (1.3)
Vertigo	4 (2.6)	2 (1.3)	9 (5.9)	1 (0.7)
Constipation	3 (2.0)	0	9 (5.9)	0
Balance disorder	1 (0.7)	0	9 (5.9)	1 (0.7)
Urinary hesitation	1 (0.7)	0	9 (5.9)	0
Vomiting	8 (5.3)	1 (0.7)	8 (5.2)	2 (1.3)
Anxiety	4 (2.6)	0	8 (5.2)	2 (1.3)
Dysuria	2 (1.3)	0	8 (5.2)	0
Disturbance in attention	1 (0.7)	0	8 (5.2)	3 (2.0)
Disorientation	1 (0.7)	1 (0.7)	8 (5.2)	0

Abbreviations: AE = adverse event; EZG(RTG) = ezogabine (retigabine) 1,200 mg/day.
[a] Patients are not listed for the same AE in multiple rows, but could be represented in 2 rows for a separate and distinct AE (e.g., dizziness and confusional state). Each row describes a separate and distinct AE (by preferred term).
[b] Includes the following verbatim terms: confusion, intermittent confusion, general confusion, absent mindedness, muddled thoughts, transient confusion, and episodic confusion.

line from subsequent diabetic ketoacidosis was considered possibly related to treatment.

No clinically abnormal results or trends in laboratory values, EKGs, vital signs, or physical/neurologic examinations indicative of safety issues were observed except for rare transient abnormal liver function tests. At the end of the double-blind period, mean body weight increased by 2.6 kg (EZG[RTG]) and 0.3 kg (placebo) (an increase of 3.5% and 0.4%, respectively), and 18.5% (17/92) of EZG(RTG)-treated patients had increases of ≥7% from baseline vs 3.1% (4/127) for placebo. No patient discontinued due to weight gain, and patients with clinically significant weight gain (increases of ≥7% from baseline values) did not report edema.

A small increase in mean PVR volume was observed with EZG(RTG) early in treatment, which did not increase over time. Urinary system TEAEs, most commonly urinary tract infection, urinary hesitation, dysuria, and chromaturia, occurred in more patients assigned to EZG(RTG) than placebo, were not serious, and typically improved or resolved spontaneously or with treatment discontinuation. Urinary retention was reported by 1 EZG(RTG)- and 2 placebo-treated patients. Fifteen EZG(RTG)- and 6 placebo-treated patients had increased PVR volumes of >100 mL from baseline; however, urinary system TEAEs were generally not associated with elevated PVR volumes collected at specified study visits.

DISCUSSION This study demonstrated a statistically significant reduction in seizure frequency with the addition of EZG(RTG) 1,200 mg/day in patients with drug-resistant epilepsy with partial-onset seizures. This study validates the therapeutic potential of EZG(RTG) in patients with partial-onset seizures and corroborates findings from a previous double-blind, placebo-controlled, dose-ranging study.[17]

RESTORE 1 evaluated a high dose of EZG(RTG) (1,200 mg/day) vs the 600 and 900 mg/day doses in the companion RESTORE 2 study. As expected, titration to high-dose EZG(RTG) 1,200 mg/day confirmed efficacy, but also led to tolerability issues in some patients. The 2 primary efficacy outcomes for RESTORE 1 were met: median percent reduction in 28-day total partial-seizure frequency from baseline to double-blind treatment period was significantly higher in EZG(RTG)-treated patients than placebo, as was the maintenance phase responder rate. For lower EZG(RTG) doses evaluated in RESTORE 2, EZG(RTG) 600 and 900 mg/day significantly increased median percent reduction in 28-day total partial-seizure frequency from baseline to double-blind period (27.9% [$p = 0.007$] and 39.9% [$p < 0.001$], respectively) vs placebo (15.9%) and significantly increased the maintenance phase responder rate (38.6% and 47.0%, respectively [both $p < 0.001$]) vs placebo (18.9%).[18]

Complete seizure freedom is difficult to achieve in patients with drug-resistant epilepsy over the course of a clinical trial. Seizure freedom data reported in this study with EZG(RTG) are consistent with those for other AEDs, when expressed over the entire 12-week maintenance phase in the completers population (5.2% [5/97 patients]) or in the "pragmatic ITT" population (defined as patients who were seizure-free for the entire duration of the study using the ITT population as the denominator; 3.3% [5/153 patients]).[22] An increase in seizure-free days can

also have significant patient benefits. Compared with placebo, the addition of EZG(RTG) produced an 11% increase in mean percentage of days patients were seizure-free during the maintenance phase, which translates to an additional 7.3 seizure-free days/12 weeks (31.7 days/year, table e-2). This gain compares favorably with results reported of 11–24 additional seizure-free days per year for levetiracetam,[23] lamotrigine,[24] and pregabalin.[25]

With titration over 6 weeks to EZG(RTG) 1,200 mg/day, 26.8% of EZG(RTG)-assigned patients discontinued due to TEAEs vs 8.6% for placebo. These discontinuation rates are similar to those reported in recent double-blind, placebo-controlled studies evaluating upper dosage limits of new AEDs: fixed-dose pregabalin 600 mg/day, 24–33% vs placebo, 5–7%[26,27]; highest-dose lacosamide (600 mg/day), 30% vs placebo, 5%[28]; and eslicarbazepine 1,200 mg/day, 20% vs placebo, 4%.[29] In RESTORE 2, 8%, 17%, and 26% of patients receiving placebo, EZG(RTG) 600, and 900 mg/day, respectively, discontinued treatment due to a TEAE.[18]

The most frequently observed AEs associated with AEDs are CNS-related.[30] The most common EZG(RTG)-associated TEAEs in this study were dizziness and somnolence. For most patients, these events were mild or moderate in severity and did not result in discontinuation or dosage modification. In some patients, CNS events such as dizziness appeared to be transient peak-dose effects that resolved over the dosing interval. In addition, the most common CNS TEAEs occurred during titration and generally diminished with continued therapy.

In repeated-dose studies in rodents and, to a lesser extent, in dogs, EZG(RTG) was associated with bladder and minor renal changes. These may have reflected inhibition of bladder contractility and urinary retention secondary to the effects of EZG(RTG) on KCNQ2–5 (K_v7.2–7.5) channels in bladder muscle.[31] Although EZG(RTG) 1,200 mg/day was associated with mild increases in PVR urine volume early in treatment, these volumes stabilized or declined with continued therapy. Elevations in PVR urine volume were not associated with serious urinary TEAEs or with discontinuation of therapy for either EZG(RTG) or placebo. Of the 15 (9.8%) patients with elevated PVR volumes, the majority (9 patients) were asymptomatic with renal/urinary-related AEs reported in 6 patients. Moreover, increasing age did not appear to be associated with an increased risk of elevated PVR volumes. Voiding dysfunction TEAEs were more common with EZG(RTG), but were generally of mild or moderate intensity and improved/resolved spontaneously or with treatment discontinuation. As with other drugs with the potential to affect urinary function (e.g., anticholinergics or tricyclic antidepressants), patients receiving EZG(RTG) should be made aware of the potential for bladder dysfunction and the need to maintain regular urinary voiding.

TEAEs coded as psychiatric consisted mostly of confusion and disorientation. Visual hallucinations rarely occurred. However, depression, a side effect of several other AEDs, most notably levetiracetam, tiagabine, topiramate, and vigabatrin, occurred less often in EZG(RTG) than placebo-treated patients.

CGI–I, as determined by the treating team, improved more in EZG(RTG)- than placebo-treated patients. There was no difference in PGI–I between groups, although mean scores in both groups improved. This is not surprising, considering patients were force-titrated to a dose which may, for some, have been supratherapeutic.

The KCNQ (K_v7) family of K^+ channels includes KCNQ1 (K_v7.1) channels, which play a key role in cardiac action potential repolarization. However, channel-opening effects of EZG(RTG), which are specific to KCNQ2–5 (K_v7.2–7.5) channels, do not affect KCNQ1 (K_v7.1) activity at clinically relevant concentrations,[7,8,32,33] and EZG(RTG) was not associated with clinically relevant adverse cardiovascular changes measured as blood pressure, pulse, or EKG. Relative to placebo, EZG(RTG) did not adversely affect hematology tests. Clinically significant liver function test abnormalities were infrequent, did not involve simultaneous abnormalities in bilirubin, and improved or normalized, often while patients continued EZG(RTG) treatment. Results from RESTORE 1 support the previous double-blind, placebo-controlled study[17] that demonstrated that EZG(RTG) is effective compared with placebo when used as adjunctive treatment to other AEDs in adults with partial-onset seizures with or without secondary generalization. This first-in-class AED, with good efficacy and a novel mechanism of action that opens neuronal K^+ channels resulting in dampened neuronal hyperexcitability, provides a valuable therapeutic option for patients with drug-resistant epilepsy with partial-onset seizures, with acceptable tolerability at high dose.

AUTHOR CONTRIBUTIONS

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academic authors about the statements made in the final report. J.A. French was a study investigator, contributed to the conception, design, and conduct of the study, contributed to data analysis and interpretation, and oversaw the development of the manuscript. She takes responsibility for the data, accuracy of the data analysis, and the conduct of the research. B.W. Abou-Khalil, R.F. Leroy, and E.M.T. Yacubian were study investigators and contributed to interpretation of the data and revision of the manuscript. P. Shin contributed to the conception, design, oversight, and conduct of the study, to the data analysis and interpretation, and to the revision of the manuscript. S. Hall contributed to the data analyses and interpretations and contributed to the revision of the manuscript. H. Mansbach contributed to the conduct of the study, data analysis and interpretation, and to the revision of the manuscript. V. Nohria contributed to the conception, design, and conduct of the study, and to data analysis and interpretation. He contributed to the first and subsequent drafts of the manuscript.

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DISCLOSURE

Dr. French has served on scientific advisory boards for UCB, Johnson & Johnson, Eisai Inc., Novartis, Valeant Pharmaceuticals International, Icagen, Inc., Ikano Therapeutics Inc., Sepracor Inc., and Marinus Pharmaceuticals, Inc.; has received funding for travel from UCB, Kyowa Hakko Kirin Pharma, Inc., Eisai Inc., Johnson & Johnson, Valeant Pharmaceuticals International, and GlaxoSmithKline; serves as an Associate Editor of *Epilepsy Currents* and Supplement Editor for *Epileptic Disorders*; estimates that 30% of her time is spent in outpatient epilepsy practice; receives research support from the Epilepsy Therapy Development Project, FACES, Johnson & Johnson, Eisai Inc., UCB, SK Bio-Pharmaceuticals, Valeant Pharmaceuticals International, Vertex Pharmaceuticals, Pfizer Inc, Merck Serono, the NIH, and the Epilepsy Research Foundation; and serves as President of the Epilepsy Study Consortium, which receives money from multiple pharmaceutical companies. A fixed 20% of her NYU salary is paid by the study consortium, some of which may come from consulting fees from GlaxoSmithKline, Pfizer Inc, UCB, Johnson & Johnson, Cyberonics, Inc., SCHWARZ PHARMA, Ortho-McNeil-Janssen Pharmaceuticals, Inc., Eisai Inc., Jazz Pharmaceuticals, Ovation Pharmaceuticals, Endo Pharmaceuticals, Bial Pharmaceuticals, NeuroVista Corporation, Valeant Pharmaceuticals International, Icagen, Inc., Supernus Pharmaceuticals, Inc., Ikano Therapeutics Inc., SK Bio-Pharmaceuticals, TaroPharma, NeuroTherapeutics Pharma, Inc., Sepracor Inc., and Novartis. Dr. Abou-Khalil serves as a consultant for UCB and receives research support from Valeant Pharmaceuticals International, UCB, SCHWARZ PHARMA, Marinus Pharmaceuticals, Inc., Ortho McNeill, GlaxoSmithKline, Pfizer Inc, and Abbott. Dr. Leroy serves on speakers' bureaus for and has received speaker honoraria from GlaxoSmithKline, UCB, and Cyberonics, Inc.; and receives research support from UCB, Schwartz Biomedical, LLC., Lundbeck Inc. (Ovation), King Pharmaceuticals, Pfizer Inc, GlaxoSmithKline, Valeant Pharmaceuticals International, Novartis, Eisai Inc., Sepacor Inc., Johnson & Johnson, and Bial. Dr. Yacubian serves on scientific advisory boards for Novartis, Abbott, and Johnson & Johnson; and has received funding for travel and speaker honoraria from Abbott and Novartis. P. Shin was an employee of Valeant Pharmaceuticals North America at the time of the study. Dr. Hall is an employee of and holds stock and stock options in Valeant Pharmaceuticals North America. Dr. Mansbach was an employee of Valeant Pharmaceuticals North America at the time of the study; has served as a consultant for and received funding for travel from GlaxoSmithKline; and holds stock in Valeant Pharmaceuticals International. Dr. Nohria was a paid consultant to Valeant Pharmaceuticals North America during the course of the study and the preparation of this manuscript; serves on a scientific advisory board for Antisense Pharma GmbH; serves/has served as a consultant for UCB/SCHWARZ PHARMA, Archimedes Pharma, Shire plc, Marinus Pharmaceuticals, Inc., Upsher-Smith Laboratories, and Antisense Pharma; and is a non-executive director of Allergy Therapeutics plc, in which he holds stock, and an executive officer of Alaven Pharmaceutical LLC.

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