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Efficacy and safety of retigabine/ezogabine as adjunctive therapy in adult Asian patients with drug-resistant partial-onset seizures: A randomized, placebo-controlled Phase III study

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ABSTRACT

Purpose: The purpose of this study was to evaluate the efficacy and safety of adjunctive retigabine/ezogabine (RTG/EZG) therapy in Asian adults with partial-onset seizures.
Methods: A Phase III, randomized, double-blind, placebo-controlled, parallel-group study was conducted at 26 centers in Asia. Eligible patients were randomized in a 1:1:1 ratio to receive RTG/EZG 600 mg/day (200 mg 3 times daily), RTG/EZG 900 mg/day (300 mg 3 times daily), or placebo. The study consisted of an 8-week screening/baseline phase, followed by a 16-week treatment phase (4-week titration phase and 12-week maintenance phase).
Results: The study was terminated early because of emerging safety information on RTG/EZG (i.e., retinal pigmentation and skin/mucosal discoloration) from long-term trials. Of 132 patients screened and 76 randomized, 75 (placebo, n = 25; RTG/EZG 600 mg/day, n = 26; RTG/EZG 900 mg/day, n = 24) received at least 1 dose of the study drug and were included in the safety and intent-to-treat populations. The responder rate (≥50% reduction in 28-day total partial-onset seizure frequency) was 31% with RTG/EZG 600 mg/day and 17% with RTG/EZG 900 mg/day versus 0% with placebo. Median percent change from baseline in 28-day total partial-onset seizure frequency during the maintenance phase was −33.90% and −22.46% with RTG/EZG 600 and 900 mg/day, respectively, versus −22.21% with placebo. No new safety concerns were identified.
Conclusions: Insufficient data were obtained to permit definitive conclusions. However, the results appear to be broadly in line with those from previous studies that included primarily Caucasian patients.

1. Introduction

Retigabine (RTG; international nonproprietary name)/ezogabine (EZG; United States adopted name) is an antiepileptic drug (AED) that has recently been approved for the adjunctive treatment of partial-onset seizures in adults who have responded inadequately to other treatments and for whom the benefits outweigh the risk of retinal abnormalities [1].

Retigabine/ezogabine has a unique primary pharmacologic action among the current AEDs, mediated through facilitation of the opening of specific neuronal voltage-gated potassium channels (potassium central nervous system Q [KCNQ] channels), which causes a hyperpolarizing shift in the potassium current and reduces the excitability of the neuronal cell [2]. In addition to its primary activity at KCNQ channels, RTG/EZG augments γ-aminobutyric acid-mediated inhibitory currents, which may also confer a stabilizing effect on neuronal excitability [3].

Retigabine/ezogabine was shown to be efficacious as adjunctive therapy in three double-blind, randomized, placebo-controlled studies in adults with refractory partial-onset seizures [4–6]. Based on the results from these pivotal studies, RTG/EZG was initially approved in 2011 in the USA and the European Union for the adjunctive treatment of partial-onset seizures in adults.

Ethnic differences in host and environmental factors may adversely affect safety and efficacy of medications, including AEDs. For instance, the incidence of carbamazepine-induced Stevens–Johnson syndrome

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is substantially higher in Asian patients than in Caucasian patients, possibly because the former have a higher carrier rate of HLA-B*15:02, which is strongly predictive of this adverse drug reaction [7]. In the trials on which EU and US approvals of RTG/EZG were based, only 10 Asian patients, of whom 5 received RTG/EZG, were included in the 1240 patients who received study medication [4–6]. The present study was initiated in 2012 to evaluate the efficacy, safety, and tolerability of RTG/EZG in adult Asian patients with drug-resistant partial-onset seizures. However, with the emergence of data concerning the risk of retinal pigmentation and possible visual impairment associated with RTG/EZG treatment, the indicated patient population was revised in May 2013 such that patients could be treated with RTG/EZG only when other appropriate drug combinations had proved inadequate or intolerable. As a result of this development, the enrolled patients were unblinded, and the study was terminated early. Here, we report the descriptive efficacy results and safety outcomes for the intent-to-treat (ITT) population.

2. Methods

2.1. Study design

This was a randomized, double-blind, placebo-controlled, parallel-group, multicenter, Phase III study, NCT01777139, to compare the efficacy, safety, and tolerability of RTG/EZG at doses of 600 mg/day and 900 mg/day versus placebo as adjunctive therapy in adult Asian patients with drug-resistant partial-onset seizures. The study was conducted at 26 centers in Hong Kong, the Republic of Korea, Malaysia, Singapore, Taiwan, and Thailand. Of these, 19 centers enrolled patients; the other centers screened patients who did not enroll in the study. The first patient was screened on August 29, 2012, and the first patient was randomized to treatment on October 25, 2012. The study was terminated early, and the date of the last patient's last visit was December 23, 2013.

Eligible patients were randomized in a 1:1:1 ratio to receive RTG/EZG 600 mg/day (200 mg 3 times daily [TID]), RTG/EZG 900 mg/day (300 mg TID), or placebo in a double-blind fashion. The study consisted of an 8-week screening/baseline phase, a 16-week treatment phase (consisting of titration and maintenance phases), and a 4-week transition or taper/follow-up phase. Randomization followed the screening/baseline phase (Fig. 1). At the end of the maintenance phase, eligible patients were given the opportunity to enroll in an open-label extension (OLE) study (Study RTG114873).

After due consideration of new safety information, the study was terminated. Ongoing patients who were randomized to placebo at the time of study closure were to be withdrawn from the study at the next visit or, if in transition to the OLE study, withdrawn as soon as possible after being tapered off the study drug. Ongoing patients randomized to RTG/EZG were to undergo a benefit–risk assessment. Patients with a favorable benefit–risk assessment were to continue treatment and would be permitted to continue into the OLE study. Otherwise, they were to be tapered from the study medication.

2.1.1. Ethics

Study protocols, consent forms, and other relevant information were reviewed and approved by the relevant Institutional Review Board/Institutional Ethics Committee. The study was conducted in accordance with the International Conference on Harmonisation of Technical Requirements for Registration of Pharmaceuticals for Human Use, Good Clinical Practice, and all applicable local regulatory requirements, as well as with the guiding principles of the Declaration of Helsinki. Written informed consent was obtained from all patients prior to participation in the study.

2.2. Study population

Eligible patients were Asian men and women at least 18 years of age who had a confirmed diagnosis of epilepsy with partial-onset seizures with or without secondary generalization for at least 2 years and who were currently taking 1, 2, or 3 AEDs with or without vagus nerve stimulator (VNS). Patients were eligible if they were having partial-onset seizures despite prior treatment with at least 2 approved AEDs, either alone or together, at adequate doses for a sufficient length of time, in the opinion of the investigator. Additionally, patients were required to have a documented 28-day partial-onset seizure frequency rate of at least 4 seizures over the 8 weeks preceding the screening visit and could not have been seizure-free for 21 or more consecutive days. In patients with simple partial seizures, only seizures with motor signs were counted towards meeting the inclusion criteria.

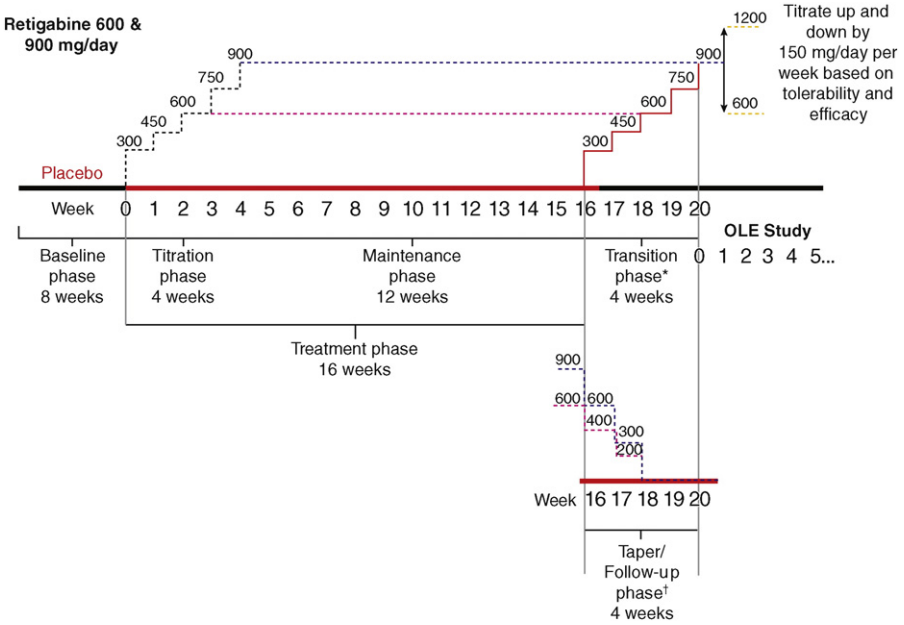

Fig. 1. Study design. *Patients who successfully completed the maintenance phase and were eligible to enter the open-label extension (OLE) study were to enter the titration phase at Week 16. †Patients who were not eligible to enter the OLE study or who withdrew from the study during the maintenance phase were to enter the taper/follow-up phase.

Key exclusion criteria included being seizure free for ≥21 consecutive days; presence of any of the prespecified disqualifying conditions; previous exposure to retigabine; or treatment with felbamate or vigabatrin ≤6 months prior to screening.

Other eligibility criteria, detailed key exclusion criteria, and randomization criteria are described in the Supplemental Materials.

The ITT population was the primary efficacy population and included all patients in the safety population who had baseline seizure data and ≥1 postbaseline seizure record (whether or not they had a seizure) between the start of the titration phase and the end of the maintenance phase. The safety population was the primary population for evaluation of safety parameters and included all patients who received ≥1 dose of study medication.

2.3. Efficacy assessments

Primary and secondary efficacy assessments were based on seizure frequency, which was recorded by patients or their primary caregivers in a daily calendar by seizure type, duration of episodes of innumerable seizure activity, and occurrence of status epilepticus as recorded in the calendar during each study phase.

The primary efficacy endpoint was the proportion of responders, defined as patients with ≥50% reduction in 28-day total partial-onset seizure frequency, from the baseline phase to the maintenance phase, in patients randomized to RTG/EZG 900 mg/day compared with those randomized to placebo. Secondary efficacy endpoints included the proportion of responders in the RTG/EZG 600-mg/day group compared with the placebo group, the proportion of responders in the entire treatment phase, the percent change from baseline in 28-day total partial-onset seizure frequency and the proportion of patients who were seizure-free during the maintenance and treatment phases, and the incidence of new seizure types. Patients who dropped out during the titration phase were classified as nonresponders during the maintenance phase. For patients who dropped out during the titration phase, percent change from baseline in 28-day total partial-onset seizure frequency during the maintenance phase was calculated based on titration phase data. For all others, only maintenance phase data were used to calculate percent change from baseline.

2.4. Pharmacokinetic (PK) assessments

The PK endpoint was systemic exposure to RTG/EZG. Blood samples were collected during the titration and maintenance phases at every scheduled clinic visit together with details of the last dose of investigational product and time of sample collection.

2.5. Safety assessments

Safety and tolerability endpoints included the following: incidence and severity of adverse events (AEs); proportion of patients with AEs leading to discontinuation; changes from baseline in vital sign measurements, body weight, electrocardiogram, hematology, chemistry, and urinalysis parameters; changes from baseline in American Urological Association Symptom Index and postvoid residual bladder ultrasound volumes; and assessment of suicidality via use of the summary of the Columbia-Suicide Severity Rating Scale.

After reports of retinal pigmentation and skin/mucosal discoloration in patients taking RTG/EZG in long-term studies, comprehensive ophthalmic and dermatologic examinations were performed to assess retinal and nonretinal pigmentary abnormalities, pigmentation of nonretinal ocular tissues, and changes in visual acuity and the confrontation visual field from the initial examination. Details of these comprehensive eye and dermatologic examinations are provided in Supplementary Information.

2.6. Statistical analyses

Sample size calculation was based on detecting the difference in the responder rate between RTG/EZG 900 mg/day and placebo. On the assumption that the allocation ratio of RTG/EZG 900 mg/day and placebo is 1:1, at least 112 patients per treatment group in the ITT population were required to detect a difference of 20% in the responder rate between RTG/EZG 900 mg/day and placebo with 90% power. Sample size was based on an assumed placebo responder rate of 17% and an RTG/EZG 900-mg/day responder rate of 37% [5,6]. A 2-sided significance level of 0.05 was used in this study.

The randomization scheme for the study was 1:1:1 for the 3 treatment groups, which would provide a total of approximately 336 evaluable patients. Assuming that 5% of randomized patients would not have at least 1 postbaseline seizure record, approximately 354 patients were to be randomized to achieve a minimum of 112 patients per treatment group in the ITT population.

Owing to the early termination of the study, abbreviated statistical outputs were generated, which included listings and descriptive summaries of available collected data. No hypothesis testing was performed.

3. Results

3.1. Study population

A total of 132 patients were screened, of whom 12 were rescreened (N = 144; Fig. 2). Of the total, 28 patients did not meet eligibility criteria and a further 40 entering the baseline phase were not randomized. A total of 76 patients were randomized, of whom 75 (placebo, n = 25; RTG/EZG 600 mg/day, n = 26; RTG/EZG 900 mg/day, n = 24) received at least 1 dose of study drug and were included in the safety and ITT populations. Twenty patients in the placebo group, 20 in the RTG/EZG 600-mg/day group, and 12 in the RTG/EZG 900-mg/day group completed the treatment phase. Of the 75 patients in the safety population, 35 completed the study (13 in the placebo group, 14 in the RTG/EZG 600-mg/day group, and 8 in the RTG/EZG 900-mg/day group), and 40 patients withdrew from the study (12 in the placebo group, 12 in the RTG/EZG 600-mg/day group, and 16 in the RTG/EZG 900-mg/day group). Two patients in the placebo group, 3 in the RTG/EZG 600-mg/day group, and 6 in the RTG/EZG 900-mg/day group withdrew during the titration phase. A greater proportion of patients discontinued in the RTG/EZG 900-mg/day group compared with those in the placebo and RTG/EZG 600-mg/day groups. The primary reason for discontinuation was an AE. After the decision to terminate the study, treatment blind was broken for 7 patients (3 in the placebo group, 3 in the RTG/EZG 600-mg/day group, and 1 in the 900-mg/day group).

Demographic and baseline characteristics were well balanced across treatment groups (Table 1). Similar percentages of patients had a history of secondarily generalized seizures in the placebo (64%), RTG/EZG 600-mg/day (69%), and RTG/EZG 900-mg/day (63%) groups. Across all treatment groups, more patients received 3 background AEDs at baseline, the largest proportion of whom were in the RTG/EZG 900-mg/day group (75%). One patient in the RTG/EZG 900-mg/day group had implanted VNS. Background AEDs during the treatment phase were generally similar across treatment groups. Most patients received more than 1 concomitant AED during the study, commonly carbamazepine, levetiracetam, and valproate sodium. A greater proportion of patients in the RTG/EZG 900-mg/day group (63%) received levetiracetam compared with those in the placebo (24%) and RTG/EZG 600-mg/day (35%) groups.

3.2. Exposure

Patients in the RTG/EZG 900-mg/day group had a shorter duration of exposure to the study drug (79.8 days) compared with those in the placebo (97.7 days) and RTG/EZG 600-mg/day (95.7 days) groups. The

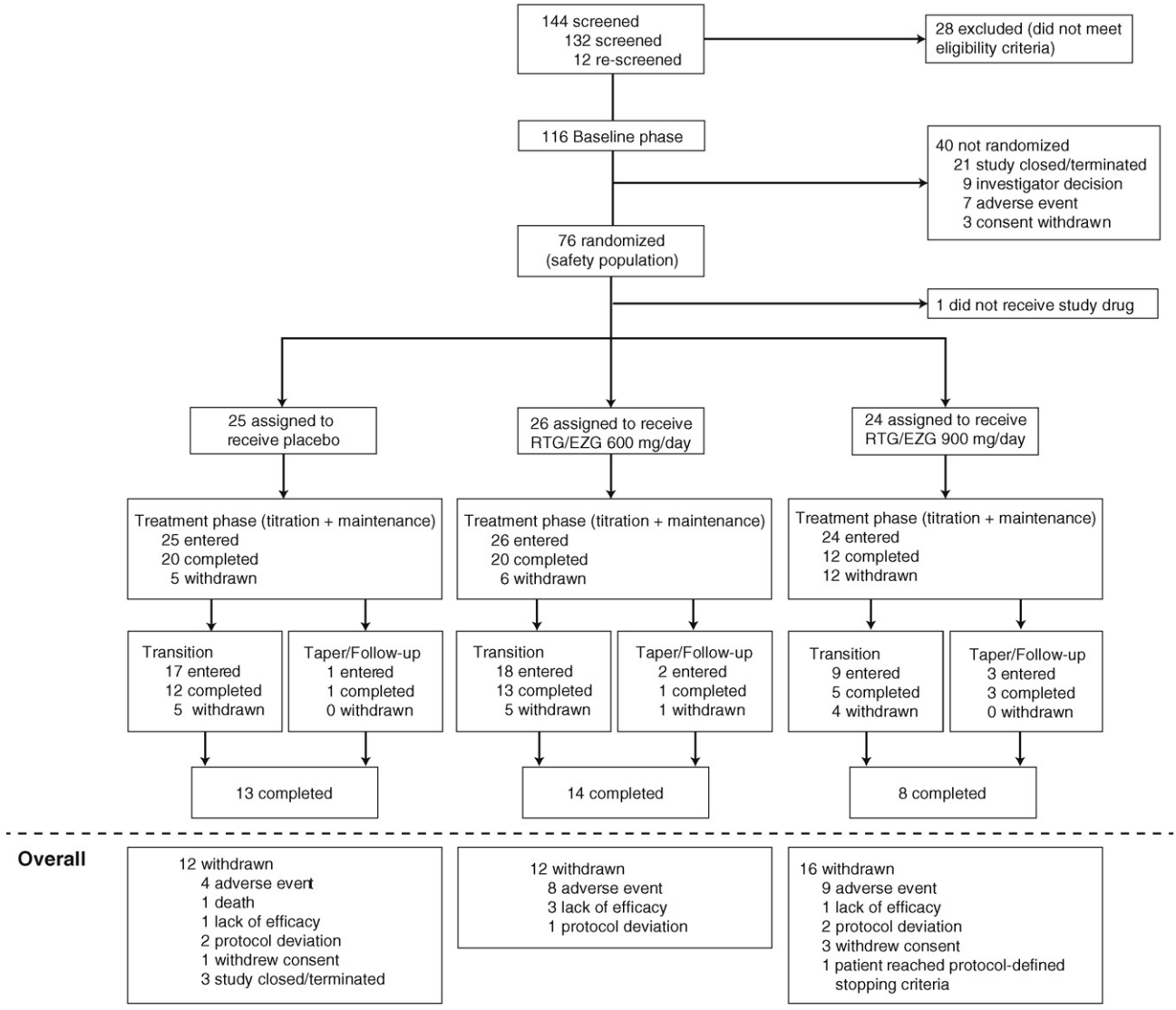

Fig. 2. Patient flow diagram. Note: 2 patients in the placebo group completed the maintenance phase but did not enter the transition phase or taper/follow-up phase. RTG/EZG = retigabine/ezogabine.

mean average actual dose was 532.7 mg/day in the RTG/EZG 600-mg/day group and 684.0 mg/day in the RTG/EZG 900-mg/day group.

3.3. Efficacy results

As the study was terminated early, summaries of efficacy data are presented for descriptive purposes only, and results should be interpreted with caution. No hypothesis testing was performed.

3.3.1. Responder rates

Table 2 shows the proportion of responders for all treatment groups. During the maintenance phase, the responder rate was 31% in the RTG/EZG 600-mg/day group and 17% in the RTG/EZG 900-mg/day group, compared with 0% in the placebo group. Results were similar during the treatment phase (titration and maintenance).

3.3.2. Seizure frequency and seizure freedom

The median percent change from baseline in 28-day total partial-onset seizure frequency during the maintenance phase was −33.90% in the RTG/EZG 600-mg/day group, −22.46% in the RTG/EZG 900-mg/day group, and −22.21% in the placebo group (Table 3). The corresponding values during the entire treatment phase were −36.30% and −26.73% in the RTG/EZG 600-mg/day and 900-mg/day groups, respectively, compared with −22.55% in the placebo group (Table 3). One patient (4%) in the RTG/EZG 600-mg/day group was free from seizures during the maintenance phase. One patient (4%) in the RTG/EZG 600-mg/day group and 2 patients (8%) in the RTG/EZG 900-mg/day group were free from seizures during the entire treatment phase. No patients in the placebo group were free from seizures during the study. During the entire treatment phase period, 4 patients experienced a >50% change from baseline in the 28-day partial seizure rate as follows: one patient in the placebo group (increase, 54.81%), none in the RTG/EZG 600-mg treatment group, and 3 patients in the RTG/EZG 900-mg treatment group (increases of 73.04, 105.94, and 176.36%).

3.4. Seizure type

During the treatment phase, a new seizure type was reported by 2 patients (13%) in the placebo group (simple partial seizures with motor signs), 1 patient (5%) in the RTG/EZG 600-mg/day group (complex partial seizures), and 2 patients (10%) in the RTG/EZG 900-mg/day group (secondarily generalized seizures).

Table 1
Summary of demographic characteristics (safety population).

	Placebo (n = 25)	RTG/EZG 600 mg/day (n = 26)	RTG/EZG 900 mg/day (n = 24)	Total (N = 75)
Age (years)				
Median	31.0	36.5	35.0	35.0
Min., Max.	19, 70	19, 56	18, 53	18, 70
Sex, n (%)				
Female	10 (40)	10 (38)	10 (42)	30 (40)
Male	15 (60)	16 (62)	14 (58)	45 (60)
Race, n (%)				
Asian[a]	25 (100)	26 (100)	24 (100)	75 (100)
East Asian heritage	15 (60)	16 (62)	17 (71)	48 (64)
Southeast Asian heritage	10 (40)	10 (38)	7 (29)	27 (36)
BMI (kg/m^2)				
Median	24.1	22.5	23.0	23.1
Min., Max.	17, 33	14, 34	15, 41	14, 41
Partial-onset seizures evolving to secondarily generalized, n (%)				
Yes	16 (64)	18 (69)	15 (63)	49 (65)
No	9 (36)	7 (27)	8 (33)	24 (32)
Unknown	0	1 (4)	1 (4)	2 (3)
Number of AEDs				
1	7 (28)	3 (12)	0	10 (13)
2	6 (24)	10 (38)	6 (25)	22 (29)
3	12 (48)	13 (50)	18 (75)	43 (57)
Implanted VNS				
Yes	0	0	1 (4)	1 (1)
No	25 (100)	26 (100)	23 (96)	74 (99)

AED: antiepileptic drug; BMI: body mass index; RTG/EZG: retigabine/ezogabine; SD: standard deviation; VNS: vagus nerve stimulator.
[a] Patients from Korea, Taiwan, and Hong Kong were classified as East Asian heritage, patients from Thailand and Malaysia were classified as Southeast Asian heritage, and patients from Singapore self-selected either East Asian or Southeast Asian heritage.

3.5. Pharmacokinetics

Concentrations of RTG/EZG observed in this study appear consistent with those observed in the Western studies and in line with the single-dose PK study in Taiwanese patients [8]. These results suggest that the PK profile of RTG/EZG shows no major differences between Asian and Caucasian patients.

3.6. Safety results

A total of 18 patients (72%) in the placebo group, 24 (92%) in the RTG/EZG 600-mg/day group, and 20 (83%) in the RTG/EZG 900-mg/day group reported a treatment-emergent AE (TEAE) during the study (Table 4). Dizziness and somnolence were the most frequently reported TEAEs in the RTG/EZG groups.

Table 2
Proportion of responders[a] (intent-to-treat population).

	Number (%) of patients		
	Placebo (n = 25)	RTG/EZG 600 mg/day (n = 26)	RTG/EZG 900 mg/day (n = 24)
Maintenance phase[b]			
Responders	0	8 (31)	4 (17)
Nonresponders	25 (100)	18 (69)	20 (83)
Treatment phase (titration + maintenance)			
Responders	1 (4)	8 (31)	6 (25)
Nonresponders	24 (96)	18 (69)	18 (75)

ITT: intent to treat; RTG/EZG: retigabine/ezogabine.
[a] A patient was classified as a responder if there was a ≥50% reduction from baseline in the 28-day total partial-onset seizure frequency.
[b] Patients who dropped out during the titration phase were classified as nonresponders. For all others, only maintenance phase data were used regardless of time in the phase.

Table 3
Percent change from baseline in 28-day total partial-onset seizure frequency in the maintenance and treatment phases (intent-to-treat population).

	Placebo (n = 25)	RTG/EZG 600 mg/day (n = 26)	RTG/EZG 900 mg/day (n = 24)
Maintenance phase[a]			
Baseline			
Median	11.79	9.66	12.53
Min., Max.	4.4, 518.5	3.9, 59.9	4.5, 154.4
Postbaseline			
Median	8.56	7.67	10.07
Min., Max.	3.3, 369.9	0.0, 49.9	0.0, 94.0
Percent change from baseline			
Median	−22.21	−33.90	−22.46
Min., Max.	−48.6, 61.0	−100.0, 16.3	−100.0, 263.6
Treatment phase[b]			
Baseline			
Median	11.79	9.66	12.53
Min., Max.	4.4, 518.5	3.9, 59.9	4.5, 154.4
Postbaseline			
Median	9.08	6.75	8.92
Min., Max.	1.3, 347.5	0.0, 46.5	0.0, 73.3
Percent change from baseline			
Median	−22.55	−36.30	−26.73
Min., Max.	−70.5, 54.8	−100.0, 8.2	−100.0, 176.4

ITT: intent to treat; RTG/EZG: retigabine/ezogabine; SD: standard deviation.
[a] Only patients with baseline and postbaseline seizure measures were included in this table. Patients who dropped out during the titration phase were calculated on the basis of titration phase data. For all others, only maintenance phase data were used.
[b] Only patients with baseline and postbaseline seizure measures were included in this table. Patients who dropped out during the titration phase were calculated based on titration phase data. For all others, only maintenance and treatment phase data were used.

Treatment-emergent AEs in the renal and urinary disorder system organ class were reported by 1 patient (4%) in the placebo group, 3 patients (12%) in the RTG/EZG 600-mg/day group, and 4 patients (17%) in the RTG/EZG 900-mg/day group. One patient (4%) in the RTG/EZG 900-mg/day group developed urinary retention that led to withdrawal from the study. No patients reported suicidal ideation and behavior or cardiac arrhythmias during the study.

3.6.1. Comprehensive eye examinations

A total of 40 patients, comprising 11 patients in the placebo group, 16 in the RTG/EZG 600-mg/day group, and 13 in the RTG/EZG 900-mg/day group, underwent at least 1 comprehensive eye examination after commencing treatment. Of these patients, 5/11 (45%) in the placebo group, 6/16 (38%) in the RTG/EZG 600-mg/day group, and 5/13 (38%) in the RTG/EZG 900-mg/day group had at least 1 abnormal finding. One patient in the RTG/EZG 900-mg/day group had abnormal retinal findings and retinal pigmentary abnormalities, which were a result of previous panretinal photocoagulation by laser. A serious AE (SAE) of retinal pigmentation was originally reported in the GlaxoSmithKline safety database (OCEANS) but was later downgraded to a non-AE by the investigator. However, this was kept as a GlaxoSmithKline serious event in the OCEANS database. No patients discontinued the study owing to abnormal retinal pigmentation.

Abnormal pigmentation of nonretinal ocular tissues, including conjunctiva, corneal epithelium, iris, and lens, was noted equally in the placebo and treatment groups (5 cases in the placebo group, 6 in the RTG/EZG 600-mg/day group, and 4 in the RTG/EZG 900-mg/day group) and was deemed unrelated to the study drug. No patient had a clinically significant decrease in visual acuity from initial examination or decrease in confrontation visual field from initial examination.

3.6.2. Dermatologic examinations

One patient in the RTG/EZG 600-mg/day group and 1 in the RTG/EZG 900-mg/day group reported skin hyperpigmentation TEAEs. One patient in the RTG/EZG 600-mg/day group reported an AE of melanocytic

Table 4
Overview of treatment-emergent adverse events and summary of most common (>1 patient in any treatment group) adverse events (safety population).

	Number (%) of patients		
	Placebo (n = 25)	RTG/EZG 600 mg/day (n = 26)	RTG/EZG 900 mg/day (n = 24)
Any TEAE	18 (72)	24 (92)	20 (83)
TEAEs by maximum intensity			
Mild	11 (44)	11 (42)	8 (33)
Moderate	5 (20)	11 (42)	9 (38)
Severe	2 (8)	2 (8)	3 (13)
TEAEs related to study treatment (per investigator judgment)	11 (44)	17 (65)	16 (67)
TEAEs leading to permanent discontinuation of study treatment or withdrawal of study	5 (20)	8 (31)	10 (42)
TEAE leading to dose reduction	0	0	0
TEAE leading to dose interruption/delay	1 (4)	0	0
Any TESAE	1 (4)	1 (4)	2 (8)
TESAEs related to study treatment	0	1 (4)	0
Fatal TESAEs	1 (4)	0	0
Most common TEAEs (≥1 patient in any treatment group)			
Dizziness	6 (24)	10 (38)	8 (33)
Somnolence	4 (16)	10 (38)	6 (25)
Headache	2 (8)	5 (19)	1 (4)
Tremor	1 (4)	5 (19)	2 (8)
Dyspepsia	0	0	3 (13)
Memory impairment	0	1 (4)	2 (8)
Confusional state	0	2 (8)	1 (4)
Dysuria	0	2 (8)	1 (4)
Diarrhea	1 (4)	0	2 (8)
Ataxia	0	0	2 (8)
Bradyphrenia	0	0	2 (8)
Muscular weakness	0	0	2 (8)
Vision blurred	0	0	2 (8)
Weight increased	0	2 (8)	0
Hypoesthesia	0	2 (8)	0
Upper respiratory tract infection	2 (8)	1 (4)	0
Skin laceration	2 (8)	0	0
Asthenia	2 (8)	0	0

AE: adverse event; RTG/EZG: retigabine/ezogabine; SAE: serious adverse event; TEAE: treatment-emergent adverse event; TESAE: treatment-emergent serious adverse event. This table includes the TEAEs in the following phases: titration, maintenance, taper/follow-up, and transition.

nevus over the scalp during the study. This event occurred before the initiation of the study drug and was considered unrelated to the study drug by the investigator.

3.7. SAEs and other significant AEs

One death was reported in the placebo group during the study. The patient developed pneumonia 127 days after the first dose of the study drug. Treatment with the study drug was stopped, and the patient was withdrawn from the study. The patient died 5 days after withdrawal, with the cause of death reported as multiple organ failure and pneumonia; the investigator considered that there was no reasonable possibility that the pneumonia might have been caused by the study drug.

Treatment-emergent SAEs (TESAEs) were reported in 1 patient (4%) in the placebo group (pneumonia), 1 (4%) in the RTG/EZG 600-mg/day group (dizziness), and 2 (8%) in the RTG/EZG 900-mg/day group (grand mal convulsion, procedural vomiting, nephrolithiasis). One patient in the RTG/EZG 600-mg/day group had a TESAE (dizziness) that was considered by the investigator to be drug related. A total of 3 patients, including 1 in the placebo group (pneumonia, a fatal SAE), 1 in the RTG/EZG 600-mg/day group (dizziness), and 1 in the RTG/EZG 900-mg/day group (nephrolithiasis) had TESAEs that led to discontinuation of the study drug.

4. Discussion

As the study was terminated prematurely, insufficient data were available to permit a definitive conclusion on the efficacy of RTG/EZG as adjunctive therapy in adult Asian patients with partial-onset seizures. The use of a forced titration design was selected to ensure that efficacy and safety data would be comparable with data reported in the pivotal trials. Responder rates in the RTG/EZG 600-mg/day (31%) and 900-mg/day (17%) treatment groups were numerically higher compared with those in the placebo group (0%). Seizure reduction appeared to be greater in the RTG/EZG 600-mg/day (−33.90%) treatment group compared with that in the placebo (−22.21%) group, whereas the RTG/EZG 900-mg/day (−22.46%) treatment group was comparable with the placebo group.

Efficacy results were similar to previous RTG/EZG studies, which included primarily Caucasian subjects. In 2007, for example, Porter et al. reported the results of a 16-week double-blind trial to evaluate adjunctive RTG/EZG 600, 900, and 1200 mg/day in patients with partial-onset seizures [4]. Median percent change in monthly total partial-onset seizure frequency from baseline was −23% for RTG/EZG 600 mg/day, −29% for RTG/EZG 900 mg/day, and −35% for RTG/EZG 1200 mg/day versus −13% for placebo ($p < 0.001$ for overall difference across all treatment arms). Responder rates were 23% for RTG/EZG 600 mg/day, 32% for RTG/EZG 900 mg/day ($p = 0.021$), and 33% for RTG/EZG 1200 mg/day ($p = 0.016$) versus 16% for placebo [4]. Similarly, in RESTORE 1, a multicenter, randomized, double-blind, parallel-group study, the median percent reduction in total partial-onset seizure frequency was 44.3% with RTG/EZG 1200 mg/day versus 17.5% with placebo ($p < 0.001$) during the 18-week double-blind period [6]. Responder rates (≥50% reduction in total partial-onset seizure frequency from baseline) were 44.4% versus 17.8%, respectively ($p < 0.001$). In patients who entered the 12-week open-label maintenance phase, median percent reductions in seizure frequency were 54.5% with RTG/EZG versus 18.9% with placebo ($p < 0.001$); responder rates were 55.5% versus 22.6%, respectively ($p < 0.001$) [6]. The number of patients in the current study was too small to allow meaningful comparisons with these earlier studies. In the current study, although greater seizure reduction was seen in the 600-mg/day group compared with that in the placebo group, seizure reduction in the 900-mg/day group was similar to that in the placebo group. The comparable efficacy in the 900-mg/day group may be due to the higher dropout rate during titration; however, the premature termination of the study and the small sample sizes do not provide sufficient data to explore further.

Safety results were similar to those of previous studies in the clinical development program, and no new safety concerns or findings were identified. A greater proportion of patients in the RTG/EZG groups than in the placebo group reported TEAEs. The proportion of patients who discontinued the study drug owing to TEAEs increased with both of the RTG/EZG doses. Consistent with the pivotal RTG/EZG studies, dizziness and somnolence were the most common TEAEs in the RTG/EZG groups, and there was an RTG/EZG dose relationship for TEAEs leading to withdrawal.

As a potassium channel opener, RTG/EZG affects the function of the smooth muscle of the bladder. The AE profile of RTG/EZG therefore includes a risk of effects on the urinary system [9]. In clinical studies investigating the efficacy and safety of RTG/EZG, an increased risk of urinary retention was reported in patients receiving RTG/EZG compared with those receiving placebo. In this study, 1 patient in the RTG/EZG 900-mg/day group had a TEAE of urinary retention leading to withdrawal.

Treatment-related retinal pigmentation was not reported in any patients who underwent an eye examination. This is likely to have been due to the brief exposure to treatment, as retinal pigmentation has been observed generally after an extended course of treatment [10]. No patients discontinued owing to abnormal retinal pigmentation. In June 2015, an FDA Drug Safety Communication stated that the potential risks of vision loss due to pigment changes in the retina, as well as risks of skin discoloration, could be adequately managed by following the

recommendations in the label update of October 2013 [11]. However, the FDA considers that retigabine safety requires additional study, and, at the time of writing, the manufacturer continues to monitor safety with long-term observational studies.

This study was severely limited by the small sample size because of early termination. Nevertheless, this is the largest study to date of Asian patients treated with RTG/EZG in a double-blind, randomized controlled trial design. The results suggest that the efficacy and safety of adjunctive RTG/EZG in Asian adults are broadly in line with those reported in previous studies and add to the limited data on RTG/EZG in this population.

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This study was funded by GlaxoSmithKline. All authors met the International Committee for Medical Journal Editors criteria for authorship, were fully involved in manuscript development, and assume responsibility for the direction and content of the manuscript. K-SL had a major role in the acquisition, analysis, and interpretation of data; PK was involved in concept and study design, and acquisition, analysis, and interpretation of data; and NL and RW were involved in data analysis and interpretation.

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Conflicts of interest

K-SL: Sponsorship to international conference by GlaxoSmithKline.
NL: GlaxoSmithKline employee and shareholder.
RW: Former GlaxoSmithKline employee. Shareholder in GlaxoSmithKline; currently employed by PAREXEL International GlaxoSmithKline business unit.
PK: Received speaker's honoraria from GlaxoSmithKline and UCB Pharma and has served on scientific advisory boards for Eisai and GlaxoSmithKline; his institution has received research funding from Eisai, GlaxoSmithKline, and UCB Pharma.

Appendix A. Supplementary data

Supplementary data to this article can be found online at http://dx.doi.org/10.1016/j.yebeh.2016.05.018.

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