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Efficacy and safety of ezogabine/retigabine as adjunctive therapy to specified single antiepileptic medications in an open-label study of adults with partial-onset seizures

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ABSTRACT

Purpose: To assess efficacy/tolerability of ezogabine (EZG)/retigabine (RTG) in combination with specified monotherapy antiepileptic drug (AED) treatments in adults with uncontrolled partial-onset seizures using a flexible dosing regimen.
Methods: NCT01227902 was an open-label, uncontrolled study of flexibly dosed EZG/RTG. Adults with partial-onset seizures must have been taking either carbamazepine/oxcarbazepine (CBZ/OXC), lamotrigine (LTG), levetiracetam (LEV), or valproic acid (VPA). The study comprised a screening/baseline phase, a 4-week titration phase (initiation on 150 mg/day [50 mg three times daily (TID)] with weekly increases of 150 mg/day [50 mg TID] over 4 weeks to 600 mg/day), and a flexible dose evaluation (FDE) phase (optional weekly dose changes of 50–150 mg/day, to an optimal daily dosage [300–1200 mg/day]). The primary efficacy endpoint was percentage of patients experiencing a ≥50% reduction from baseline in partial seizure frequency (responder rate) during the treatment phase (titration and FDE phases). Safety and tolerability were also assessed.
Results: Patients ($N = 203$) were enrolled and received ≥1 dose of EZG/RTG. The dose of EZG/RTG prescribed most frequently during the treatment phase was 600 mg/day for all AED groups. Responder rates during the treatment phase were: 40.0% (CBZ/OXC), 32.0% (LTG), 50.0% (LEV), and 56.9% (VPA). Treatment-emergent adverse events occurred in 82% (CBZ/OXC), 76% (LTG), 73% (LEV), and 67% (VPA) of patients; most were of mild-to-moderate intensity.
Conclusions: EZG/RTG was effective as adjunctive therapy to CBZ/OXC, LTG, LEV, and VPA, using a flexible dosing regimen, in adults with partial-onset seizures; safety and tolerability were consistent with that previously observed.

Abbreviations: AED, antiepileptic drug; AUA, American Urological Association; CBZ/OXC, carbamazepine/oxcarbazepine; C-SSRS, Columbia Suicide Severity Rating Scale; ECG, electrocardiogram; EZG/RTG, ezogabine/retigabine; FDE, flexible dose evaluation; ITT, intent-to-treat; LTG, lamotrigine; LEV, levetiracetam; OLE, open-label extension; PGI-C, Patient Global Impression of Change; PVR, post-void residual; SF-36v2, Short Form-36 Health Survey version 2; SOC, system organ class; TEAE, treatment-emergent adverse events; TESAE, treatment-emergent serious adverse event; TID, three times daily; VPA, valproic acid.

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1. Introduction

Ezogabine (EZG; United States adopted name)/retigabine (RTG; international nonproprietary name) is an antiepileptic drug (AED) that reduces neuronal excitability by enhancing the activity of KCNQ (K_V7) potassium channels [1]. In the EU, EZG/RTG is indicated for use as adjunctive therapy for drug-resistant partial-onset seizures in adults for whom other AEDs have proved inadequate or have not been tolerated [2]. In the US, EZG/RTG (600–1200 mg daily) is approved for adjunctive treatment of partial-onset seizures in adults who have responded inadequately to several AEDs and for whom the benefits outweigh the risk of ophthalmic adverse events [3].

Despite the availability of several AEDs, up to 30% of patients remain resistant to treatment [4,5]. Adjunctive therapy is warranted for such patients, but there are limited clinical data on AED combinations for treatment optimization [6]. Results from randomized controlled trials (RCTs), using strict inclusion/exclusion criteria and titration to one of three fixed doses, indicated that EZG/RTG was superior to placebo as an adjunctive therapy in patients with partial-onset seizures [7–9]. In approximately 70% of patients, EZG/RTG was used as an adjunct to ≥2 AEDs [7–9]. EZG/RTG was efficacious and generally well tolerated irrespective of the number of concomitant AED(s) [10]. Analyses by AED combinations were confounded, however, as >75% of patients received ≥2 concomitant AEDs and sample sizes varied [11].

The current Phase IIIb trial was a hypothesis-generating study designed to assess the efficacy and tolerability of EZG/RTG combined with specified AED monotherapies in adults with partial-onset seizures using a flexible dosing regimen. This open-label study evaluated the efficacy, safety and tolerability, and health outcomes of EZG/RTG treatment in settings likely to reflect clinical practice. The study used a lower starting dose and a slower titration to a lower target dose of EZG/RTG than in pivotal trials [7–9]. The dose was then managed in the range 300–1200 mg/kg according to individual patient response to assess whether a lower starting dose and individualization of treatment could improve tolerability of EZG/RTG in clinical practice.

2. Methods

2.1. Study design

This was an open-label, multicenter, multinational, Phase IIIb exploratory study (NCT01227902). After a screening period (≤14 days) and a prospective baseline phase (8 weeks), patients receiving a stable dosage of one of four AEDs (carbamazepine [CBZ]/oxcarbazepine [OXC], lamotrigine [LTG], levetiracetam [LEV], or valproic acid [VPA]) from 4 weeks before the start of collection of baseline seizure data initiated EZG/RTG 150 mg/day (50 mg three times daily [TID]). With the sponsor's prior authorization, a maximum of 4 weeks' retrospective seizure data could replace up to the first 4 weeks of the baseline phase provided a daily seizure diary was completed (including number and type of seizures). The dose was up-titrated to 600 mg/day in increments of 150 mg/day (50 mg TID) weekly over 4 weeks (titration phase). Patients then entered a 16-week flexible dose evaluation (FDE) phase, during which the total daily dose could be changed weekly by 50–150 mg/day until the optimal dose for efficacy and tolerability was achieved in the investigator's opinion. The allowable range of total daily doses for the FDE phase was 300–1200 mg/day. After completing the FDE phase, patients who had benefited from the regimen were invited to enroll in an open-label extension (OLE). There was a 3-week taper/follow-up phase for patients who did not enter the OLE or withdrew prematurely from the study (unless safety concerns necessitated immediate withdrawal; for study design, see Fig. 1).

The study protocol, amendments, and consent form were approved by the appropriate national, regional, or investigational center ethics committee or institutional review board in accordance with the International Conference on Harmonisation of Technical Requirements for Registration of Pharmaceuticals for Human Use, Good Clinical Practice and all applicable regulatory requirements, and the principles of the Declaration of Helsinki. All patients provided written informed consent prior to participation.

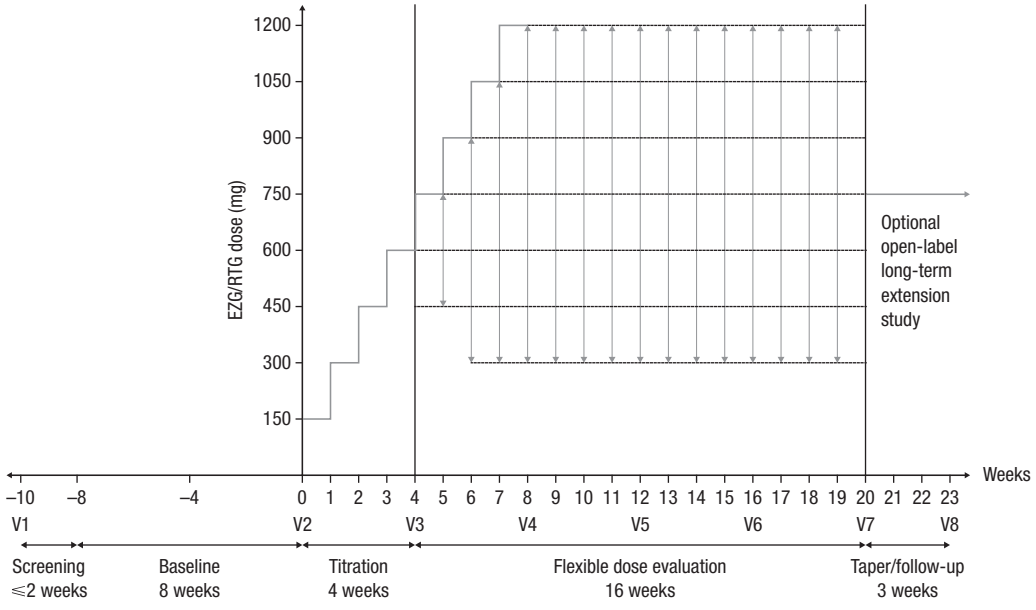

Fig. 1. Study design.
EZG/RTG = ezogabine/retigabine; V = visit.
Titration (start of Week 1 to end of Week 4) – dose increase by 150 mg/day per week.
Flexible dose evaluation (start of Week 5 to end of Week 20) – dose adjustment between 50 and 150 mg/day per week.