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Safety and tolerability of different titration rates of retigabine (ezogabine) in patients with partial-onset seizures

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Summary Retigabine (RTG; international nonproprietary name)/ezogabine (EZG; US adopted name) is an antiepileptic drug (AED) that prolongs neuronal voltage-gated potassium-channel KCNQ2—5 (K_v 7.2—7.5) opening. This double-blind study evaluated different RTG/EZG dose-titration rates. Patients ($N = 73$) with partial-onset seizures receiving concomitant AEDs were randomized to one of three titration groups, all of which were initiated at RTG/EZG 300 mg/day divided into three equal doses. Fast-, medium-, and slow-titration groups received dose increments of 150 mg/day every 2, 4, and 7 days, respectively, achieving the target dose of 1200 mg/day after 13, 25, and 43 days, respectively. Safety assessments were performed throughout. Discontinuation rates due to treatment-emergent adverse events (TEAEs) were numerically higher in the fast- (10/23) and medium- (7/22) titration groups than in the slow-titration group (3/23) but statistical significance was achieved only for the high-titration group compared with the low-titration group ($p = 0.024$). Stratified analysis, with concomitant AEDs divided into enzyme inducers (carbamazepine, phenytoin, oxcarbazepine) or noninducers, showed that the risk of discontinuation due primarily to TEAEs was significantly higher in the fast- ($p = 0.010$) but not in the medium-titration group ($p = 0.078$) when compared with the slow-titration group. Overall, the slow-titration rate appeared to be best tolerated and was used in further efficacy and safety studies with RTG/EZG.

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Introduction

Retigabine (RTG; international nonproprietary name)/ezogabine (EZG; North American adopted name) (*N*-[2-amino-4(4-fluorobenzylamino)-phenyl] carbamic acid ethyl ester) is an antiepileptic drug (AED) that reduces neuronal excitability by enhancing the activity of the KCNQ2—5 (K_v 7.2—7.5) channels (Gunthorpe et al., 2012; Lange et al., 2009; Rundfeldt and Netzer, 2000; Schenzer et al., 2005; Tatulian et al., 2001; Wuttke et al., 2005). RTG/EZG is not metabolized by cytochrome P450 (CYP) isozymes and does not induce or inhibit CYP isozymes at clinically relevant concentrations (Borlak et al., 2006; Hempel et al., 1999; McNeilly et al., 1997). RTG/EZG is metabolized extensively through the formation of an *N*-acetyl metabolite of RTG/EZG and subsequent *N*-glucuronidation of both RTG/EZG and its *N*-acetyl metabolite (Hempel et al., 1999; Tompson and Crean, 2013). The only potentially significant drug—drug interactions identified with RTG/EZG are that coadministration with carbamazepine or phenytoin may decrease RTG/EZG plasma concentrations and exposure, and increase clearance (GlaxoSmithKline, 2012).

The efficacy and tolerability of RTG/EZG (600, 900, and 1200 mg/day) as adjunctive therapy in patients with partial-onset seizures have been demonstrated in three randomized, double-blind, placebo-controlled trials (Brodie et al., 2010; French et al., 2011; Porter et al., 2007). In these studies, the RTG/EZG dose was initiated at 300 mg/day and increased at the rate of 150 mg/week to the target dose. In common with many other AEDs, the most frequently reported adverse events (AEs) with RTG/EZG involve the central nervous system (CNS), such as dizziness and somnolence (Brodie et al., 2010; French et al., 2011; Porter et al., 2007). RTG/EZG has now been approved, in the EU and USA amongst others, as an adjunctive therapy for adults with partial-onset seizures. RTG/EZG should be administered three times daily without regard to food intake (Tompson and Crean, 2013).

In general, AEDs are titrated to a maintenance dose in order to improve tolerability (Cramer et al., 2010; Ferrendelli, 2001; Gueler and Kramer, 2008). However, there is a paucity of information comparing different rates of dose titration for currently available AEDs and, generally, the information that is available is derived from postmarketing studies (Biton et al., 2001; Fisher et al., 2001). The present study was designed to compare the safety and tolerability of three different rates of dose titration (fast, medium, and slow) for RTG/EZG in patients with partial-onset seizures already taking AEDs in whom seizure control was inadequate. As some AEDs are inducers of hepatic enzymes (e.g. carbamazepine, phenytoin, oxcarbazepine) and can reduce the plasma concentration of concomitant medications (Perucca, 2006), the use of enzyme-inducing or noninducing background AEDs was also assessed. The long-term safety and tolerability of RTG/EZG treatment were also evaluated in an open-label extension (OLE) study.

Methods

Standard protocol approvals and patient consent

This phase II study (Study 3065A1-214) was conducted between December 2000 and September 2001 at 10 centers in the USA and Europe. The study was performed in accordance with the principles of Good Clinical Practice and according to the Declaration of Helsinki and its amendments. Informed consent was obtained from all patients; institutional review board approval was also obtained.

Patients

Men and women aged 16—70 years with a diagnosis of partial epilepsy and a documented seizure frequency of at least two seizures per month in the 4-week period preceding screening were eligible. At the time of study entry, patients could be receiving one or two approved AEDs at a stable dose for at least 1 month. Treatment with vagus nerve stimulation, which was counted as one AED treatment, could be included, providing the stimulation parameters had been kept constant for at least 1 month before the screening. Women of childbearing potential could be included as long as approved methods of contraception (intrauterine device in place for at least 3 months, surgical sterilization, or barrier methods) were in use and pregnancy tests conducted at screening and baseline were negative.

Exclusion criteria included pregnancy; nursing; a history of clinically significant cardiovascular, pulmonary, hepatic, renal, gastrointestinal, hematologic, endocrine, or metabolic disease within the past 2 years; clinically significant abnormalities on pre-study physical examination, vital signs, electrocardiogram (ECG), echocardiogram, or laboratory tests; acute illness within 7 days of screening; a run of three or more beats of nonsustained ventricular tachycardia on the pre-study 24-h Holter recording; history of major psychiatric disorder, other psychotic symptomatology, major depressive disorder, or suicide attempt within the past 5 years; history of alcohol or drug abuse within the past year; history or evidence of progressive CNS disease, lesion, or encephalopathy; history of malignancy within the past 2 years except for basal cell epithelioma and in situ carcinoma; use of any investigational drug or device within 1 month of screening; use of vigabatrin or felbamate within 1 month of screening; and history of status epilepticus within 6 months of screening. Patients who had received prior treatment with vigabatrin for at least 3 months were required to have a visual field assessment within 2 months of screening using Goldman's or Humphrey's perimetry, prior to inclusion.

Patients, who successfully completed Study 214 and were willing to continue treatment, were included in the long-term OLE (Study 3065A1-216).

Study design and treatments

Study 214 consisted of a 1-week screening phase, a 7-week double-blind titration phase, and a 3-week tapering phase