



## Ezogabine AKA Retigabine: Is More Better? Trying to Find the Right Dose From Clinical Trials

### Randomized, Double-Blind, Placebo-Controlled Trial of Ezogabine (Retigabine) in Partial Epilepsy.

French JA, Abou-Khalil BW, Leroy RF, Yacubian EMT, Shin P, Hall S, Mansbach H, Nohria V, On behalf of the RESTORE 1/Study 301 Investigators. *Neurology* 2011;76:1555–1563.

**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.

### Commentary

Ezogabine, the U.S.-adopted name of the compound formerly known as retigabine, is a first-in-class neuronal potassium channel opener for which two phase 3 pivotal trials have been completed, both of which show significant results in reducing seizure frequency compared with placebo in adults with refractory partial onset epilepsy.

The study discussed herein, the RESTORE 1 trial (1), consists of a forced-titration of ezogabine over 6 weeks to a dose of 1,200 mg per day, after a prospective 8-week baseline, and followed by a 12-week maintenance phase. Twenty-two percent of ezogabine-treated subjects (34/153) did not enter the maintenance phase compared with 10 percent (15/152) of the placebo-treated subjects, discontinuing during the titration phase mostly as a result of adverse effects, the most common of which were dizziness, somnolence, fatigue, confusion, and

urinary tract infection. Another 22 ezogabine-treated subjects discontinued during the maintenance phase (vs 10 in the placebo-treated arm), for a total completion rate of 63 percent in the active arm. Twenty-seven percent of ezogabine subjects discontinued because of adverse effects compared with 9 percent in the placebo arm. One dose reduction to 1,050 mg per day was allowed to manage adverse effects. Because of the low completer rate, the potential for bias is great enough to downgrade this well-designed, adequately masked and blinded study to class 2. The drug also loses points on the 'ease of use' factor: ezogabine is administered three times per day.

Now let's compare this to the results for ezogabine at lower doses. A clinical trial published in 2010, the RESTORE 2 study (2), evaluated ezogabine doses of 600 and 900 mg per day compared with placebo. The study had a similar design but had a forced titration over 4 weeks. Twenty-six percent of 179 subjects in the 900 mg treatment arm, 14 percent of 181 subjects in the 600 mg treatment arm, and 8 percent of placebo subjects discontinued because of adverse effects. Therefore, between 900 mg and 1,200 mg per day, there was no difference in discontinuing because of adverse effects. It should



be stated that discontinuation as a result of adverse effects is probably a reasonable surrogate measure for tolerability outside of the clinical trial setting.

What about efficacy? The efficacy within the narrow characteristics of the clinical trial population was clear and dose-related. For those who were in the maintenance phase (not including the titration phase) of ezogabine at 1,200 mg per day—which numbered 119 and only 97 of them completed—the mean percent seizure frequency reduction was 55 percent, and the responder rate was 56 percent. In the 600-mg-per-day arm during the 12-week maintenance phase, the mean seizure frequency reduction was 35 percent, with a responder rate of 37 percent; for the 900-mg-per-day arm, the findings were 44 percent and 47 percent. Therefore, for every 300 mg increase in total daily dose, another 10 percent in seizure reduction is gained. This is an amazing dose response. The results were a bit less robust but still proportional when the entire treatment period is analyzed, including both titration and maintenance phases. The seizure-free rates were not more impressive than the usual antiepileptic drug (AED) add-on trials, however.

Still, there is the other side of the coin; it is taken three times per day, has a high discontinuation rate because of side effects, and causes increased bladder postvoid residual and urinary tract infections. This adverse effect, which is the result of inhibition of bladder contractility from the effects of ezogabine on KCNQ2–5 channels in bladder muscle (3), will add a new consideration when we receive calls from confused hospital paging operators who are not sure if they are calling “neurology” or “urology.”

The translation of clinical trial data in epilepsy to clinical practice is subject to interpretation from all angles. Sometimes it appears that doses in clinical trials are lower than those that are effective in clinical practice. For example, gabapentin seemed not to be explored adequately at higher doses in clinical trials and was used at much higher doses by neurologists when it was first marketed. Topiramate was systematically evaluated in clinical trials up to 1,600 mg per day, a dose now thought to be outlandish. Many AED trials are analyzed to show at which dose the study drug significantly separates from placebo, and it is declared that at this point in titration, evidence of efficacy is present. For example, for levetiracetam this could be at 1,000 mg per day after 2 weeks of titration and for topiramate at 100 to 150 mg per day after 1 to 2 weeks into titration. Whether this is a clinically meaningful finding or not is debatable, but the analysis provides a bit of insight into AED dosing.

Lamotrigine is approved for epilepsy at a dose of 500 mg per day. It is now well-appreciated that much lower doses

can be effective, and many neurologist use lamotrigine levels and clinical response rather than dose to guide therapy in any case because of the individualized metabolism of lamotrigine. Levels of ezogabine may also prove to be useful.

Most AEDs considered efficacious are associated with a dose response, a reliable sign strongly suggesting that a drug has some action to stop seizures. Ezogabine certainly has this property. The 50 percent responder rates associated with the doses used in RESTORE 1 and 2 are among the highest we have seen in AED trials. But, where will the effective dose be for a partial epilepsy patient who has failed two AEDs? It will likely not be at 900 or 1,200 mg per day but perhaps much lower; the lower dose range certainly has a good chance of meaningfully reducing seizures and will be associated with less risk of side effects. For stalwarts who can tolerate the higher doses of ezogabine, the maximal efficacy was not revealed in these studies. Perhaps more is even better! Adverse effects are not dose-associated above 900 mg per day, according to these data sets. Inexplicably, there is a ceiling dose for adverse effect rates but not for efficacy.

Ezogabine is exciting—it has amazing efficacy and the potential for a completely new set of adverse effects, but perhaps lower doses will be effective in the general epilepsy population, and the adverse effect rate will certainly be less at lower doses. It scores poorly on the ease-of-use scale, though, because of the multiple daily dosing; refractory epilepsy patients are often keyed in to taking medications frequently, so perhaps this will be less of an issue than what it seems at face value. Patients with epilepsy certainly need new treatments that can reduce seizure frequency, and hopefully ezogabine will readily find a niche in the practice of epilepsy.

by Cynthia L. Harden, MD

#### References

1. French JA, Abou-Khalil BW, Leroy RF, Yacubian EM, Shin P, Hall S, Mansbach H, Nohria V; RESTORE 1/Study 301 Investigators. Randomized, double-blind, placebo-controlled trial of ezogabine (retigabine) in partial epilepsy. *Neurology* 2011;76:1555–1563.
2. Brodie MJ, Lerche H, Gil-Nagel A, Elger C, Hall S, Shin P, Nohria V, Mansbach H; RESTORE 2 Study Group. Efficacy and safety of adjunctive ezogabine (retigabine) in refractory partial epilepsy. *Neurology* 2010;75:1817–1824.
3. Streng T, Christoph T, Andersson K-E. Urodynamic effects of the K<sup>+</sup> channel (KCNQ) opener retigabine in freely moving, conscious rats. *J Urol* 2004;172:2054–2058.



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