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Lack of effect of perampanel on QT interval duration: Results from a thorough QT analysis and pooled partial seizure Phase III clinical trials

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ABSTRACT

Introduction: Perampanel is a selective, noncompetitive AMPA receptor antagonist approved as adjunctive treatment for partial seizures. To assess potential for delayed cardiac repolarization, a Phase I thorough QT study was performed, supplemented by plasma concentration–QT data modeled from 3 pooled Phase III studies.

Methods: The Phase I thorough QT study (double-blind, combined fixed-sequence, parallel-group) quantified the effect of perampanel (6 mg once daily for 7 days, followed by dose escalation to a single 8-mg dose, a single 10-mg dose, then 12 mg once daily for 7 days), moxifloxacin positive control (single 400-mg dose on Day 16), and placebo on QT interval duration in healthy subjects ($N = 261$). Electrocardiograms were recorded at baseline, Day 7 (post 6 mg dose), and Day 16 (post 12 mg dose). Statistical comparisons were between the highest approved perampanel dose (12 mg) versus placebo, a "mid-therapeutic" dose (6 mg) versus placebo, and moxifloxacin versus placebo. Acknowledging that the Phase I thorough QT study could not incorporate a true "supratherapeutic" dose due to length of titration and tolerability concerns in healthy subjects, Phase III studies of perampanel included expanded electrocardiogram safety evaluations specifically intended to support concentration–QT response modeling. The lack of effect of perampanel on the QT interval is shown from pooled analysis of 3 double-blind, placebo-controlled, 19-week, Phase III studies with perampanel doses ≤12 mg ($N = 1038$, total perampanel; and $N = 442$, placebo) in patients with partial seizures. QT measures were corrected for heart rate using Fridericia's (QTcF; the primary endpoint) and Bazett's (QTcB) formulas.

Results: In the Phase I thorough QT study, the positive control moxifloxacin caused peak time-matched, baseline-adjusted, placebo-corrected (ΔΔ) QTcF of 12.15 ms at 4 h postdose, confirming a drug effect on QTc interval and study assessment sensitivity. Mean baseline-adjusted (Δ) QTcF versus nominal time curves were comparable between perampanel 12 mg and placebo, with most ΔQTcF values being slightly negative. Healthy subjects receiving perampanel 6 and 12 mg doses for 7 days showed no evidence of effects on cardiac repolarization. Peak ΔΔQTcF was 2.34 ms at 1.5 h postdose for perampanel 6 mg and 3.92 ms at 0.5 h postdose for perampanel 12 mg. At every time point, the upper 95% confidence limit of ΔΔQTcF for perampanel 6 and 12 mg was <10 ms. Phase III studies revealed no clinically significant

Abbreviations: AE, adverse event; AED, antiepileptic drug; ANOVA, analysis of variance; AUC, area under the concentration–time curve; BMI, body mass index; CI, confidence interval; C_{max}, maximum plasma concentration; ECG, electrocardiogram; hERG, human ether-à-go-go-related gene; IC_{50}, 50% inhibitory concentration; ICH, International Conference on Harmonisation of Technical Requirements for Registration of Pharmaceuticals for Human Use; MTD, maximum tolerated dose; QTcB, Bazett's formula for QT interval corrected for heart rate; QTcF, Fridericia's formula for QT interval corrected for heart rate; QTci, individual formula for QT interval corrected for heart rate; SUDEP, sudden unexpected death in epilepsy; TdP, torsade de pointes; t_{max}, time to maximum plasma concentration relative to time of dosing.

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difference between patients with partial seizures treated with perampanel or placebo in QTcF and QTcB values >450 ms, with no dose-dependent increases or large incremental changes from baseline of >60 ms. Regression analysis of individual plasma perampanel concentrations versus corresponding QTc interval values in Phase I thorough QT and Phase III studies demonstrated no relationship between perampanel concentrations and QT interval duration.

Conclusion: Treatment with perampanel 6 mg and 12 mg for 7 days did not delay cardiac repolarization in healthy volunteers. In a population analysis of 1480 patients with partial seizures treated with perampanel doses ≤12 mg or placebo, no clinically significant trends in QT interval data were noted. Based on the thorough QT study and evaluations from pooled Phase III studies, there is no evidence of prolonged QT interval duration with perampanel treatment.

Introduction

The QT interval is the duration of ventricular depolarization and subsequent repolarization as measured on an electrocardiogram (ECG) from the beginning of the QRS complex to the end of the T wave (ICH Expert Working Group, 2005). Prolongation of the QT interval has been identified as a potential risk for cardiac arrhythmias, most commonly torsade de pointes (TdP), during treatment with a variety of drugs (ICH Expert Working Group, 2005; Pollard et al., 2008; Redfern et al., 2003). Delayed repolarization results from suppression of potassium current in cardiac tissues, the rapidly activating delayed rectifier that is mediated by the human ether-à-go-go-related gene (hERG)-encoded voltage-dependent potassium channel (hERG K+ channel) (Pollard et al., 2008; Redfern et al., 2003). Regulatory authorities require most clinical programs to examine the potential for drug-induced QT interval prolongation by conducting a thorough QT study during the course of drug development.

Perampanel is a selective, orally active, noncompetitive AMPA receptor antagonist approved in both Europe and the United States for adjunctive treatment of partial seizures with or without secondarily generalized seizures in patients 12 years of age or older with epilepsy, and in Canada for adult patients 18 years of age or; older with epilepsy (Fycompa Summary of Product Characteristcs, 2012; Fycompa Product Monogrpah, 2013; Fycompa Prescribing Information, 2014). Perampanel has demonstrated efficacy and tolerability in partial seizures in patients ≥12 years of age in 3 multicenter, double-blind, randomized, placebo-controlled Phase III studies (French et al., 2012, 2013; Krauss et al., 2012).

In vitro studies indicate that perampanel blocks the hERG K+ channel in cultured cells in a dose-dependent manner at concentrations ≥10 μmol/L (≥3629 ng/mL), with an estimated 50% inhibitory concentration (IC_{50}) of 15.8 μmol/L (5733.82 ng/mL). No significant inhibition was observed at concentrations of ≤3 μmol/L. In clinical studies, the highest plasma perampanel concentration observed in healthy subjects and patients with epilepsy was approximately 2500 ng/mL, corresponding to a free drug concentration of 0.34 μmol/L. This equates to an approximate 45-fold margin between the hERG IC_{50} and the plasma free drug concentration; published literature suggests that drugs with a >30-fold safety margin are typically not associated with TdP, for which QT interval prolongation is a risk (Pollard et al., 2008; Redfern et al., 2003). Thus, therapeutic doses of perampanel were anticipated to have a low arrhythmogenic or TdP potential.

This report examines a Phase I thorough QT study of the effect of perampanel on QT interval duration and the relationship between plasma perampanel concentrations and QT interval duration in healthy subjects. The International Conference on Harmonisation (ICH) E14 Guidance, *The Clinical Evaluation of QT/QTc Interval Prolongation and Proarrhythmic Potential for Non-Antiarrhythmic Drugs*, provides specific recommendations concerning the design, conduct, analysis, and interpretation of clinical studies to assess the potential of a drug to delay cardiac repolarization (ICH Expert Working Group, 2005). However, due to safety and tolerability concerns in healthy subjects, the Phase I thorough QT study could not include the recommended multiple dosing regimen of perampanel at the maximum therapeutic exposure (ICH Expert Working Group, 2005). Acknowledging that the Phase I thorough QT study could not incorporate a true 'supratherapeutic' dose of perampanel due to the short duration of titration and tolerability concerns in healthy subjects, this report includes plasma concentration–QT data (obtained from expanded ECG safety evaluations) modeled from 3 pooled Phase III studies.

Materials and methods

Standard protocol approvals, registration, and patient consents

This analysis consists of a Phase I thorough QT study of the effect of perampanel treatment on QT interval duration (E2007-A001-013) conducted between September 2007 and March 2008 at a single site in the United States and is supplemented by plasma concentration–QT data modeled from 3 pooled Phase III studies (Study 304, NCT00699972; Study 305, NCT00699582; and Study 306, NCT00700310) conducted between April 2008 and January 2011 in more than 40 countries (French et al., 2012, 2013; Krauss et al., 2012). All studies were conducted in accordance with the Declaration of Helsinki, European Medicines Agency requirements, and the US Code of Federal Regulations, as appropriate. Study protocols, amendments, and informed consents were reviewed by national regulatory authorities in each country and by independent ethics committees or institutional review boards for each site. Prior to participation, all patients provided written informed consent (French et al., 2012, 2013; Krauss et al., 2012).

Patients

Eligible subjects for the Phase I thorough QT study included healthy male and female subjects 18–55 years of age, with a body mass index (BMI) of 18–32 kg/m^2. Of note, subjects who had evidence of any clinically significant disease or abnormality (including hepatic impairment), or who had a clinically significant illness during the 2 months leading up to the start of study drug treatment, were excluded. The concomitant medications taken by subjects were also recorded.

Eligible patients for the three Phase III studies included individuals ≥12 years of age diagnosed with partial seizures with or without secondary generalization in accordance with the 1981 International League Against Epilepsy Classification of Epileptic Seizures (ILAE, 1981) who had experienced ≥2 antiepileptic drug (AED) failures and had ≥5 partial seizures during baseline. Patients