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Pharmacokinetics, exposure–cognition, and exposure–efficacy relationships of perampanel in adolescents with inadequately controlled partial-onset seizures

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ABSTRACT

Objective: To characterize, in adolescents aged 12–17, the pharmacokinetic (PK) profile of perampanel, the impact of intrinsic and extrinsic factors on PK, and the relationships between perampanel exposure and cognitive function, seizure frequency, and responder status.
Methods: Population PK analysis used plasma concentration data from Phase II study 235 (NCT01161524), in which adolescents with inadequately controlled POS despite treatment with 1–3 antiepileptic drugs (AEDs) were randomized to receive once daily oral placebo or perampanel (8–12 mg/day) for 19 weeks, pooled with data from adolescent patients in perampanel Phase III studies 304, 305, 306. Exposure–cognition and exposure–efficacy relationships were modelled using data from study 235.
Results: Population PK results from 152 adolescent patients revealed a perampanel apparent clearance of 0.729 L/h, consistent with previous analyses in adolescents and adults. Clearance was increased with coadministration of inducing AEDs (carbamazepine, oxcarbazepine and phenytoin), and was slightly higher in females. The PK/pharmacodynamics (PD) analysis for cognition (n = 110) showed that increasing perampanel exposure had no significant effect on overall cognition, measured by the Cognitive Drug Research global cognition score. The PK/PD analysis for efficacy (n = 123) showed a significant decrease in seizure frequency and significant increased probability of being a responder, as perampanel concentration increased – both in the presence and absence of inducing AEDs. Carbamazepine, oxcarbazepine and phenytoin reduced perampanel exposure in adolescents, but reduced the magnitude of seizure frequency reduction and responder probability to a lesser extent.
Significance: Pharmacokinetics of perampanel are similar in adolescents to adults. Increasing perampanel exposure reduces seizure frequency and increases probability of being a responder regardless of concomitant inducers. The lack of relationship between perampanel exposure and cognitive function suggests a benign cognitive profile for this AED in adolescents. We await results from long-term exposure.
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1. Introduction

Perampanel is a highly selective AMPA receptor antagonist approved for adjunctive treatment of partial-onset seizures in adolescents and adults aged ≥12 years. Because the AMPA receptor has many crucial roles in central nervous system (CNS) function and development, it is important to establish any impact of perampanel on cognition and development. This is especially important in adolescents, as neurologically and socially they are at a sensitive time of change. Phase II, randomized, placebo-controlled study 235 in ado-

Abbreviations: AED, antiepileptic drug; AMPA, α-amino-3-hydroxyl-5-methyl-4-isoxazole-propionate; $C_{av,ss}$, average steady-state plasma concentration at; CDR, Cognitive Drug Research system; CNS, central nervous system; CL/F, apparent clearance; CYP, cytochrome P450; IIV, inter-individual variability; PD, pharmacodynamics; PK, pharmacokinetic; POS, partial-onset seizures; UGT, uridine 5′-diphospho-glucuronosyltransferase; V/F, apparent volume of distribution.

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lescents (12–17 years) demonstrated no overall treatment effect of perampanel vs. placebo on cognition, as measured with the Cognitive Drug Research (CDR) system global cognition score, and small but statistically significant changes vs. placebo in three subdomains (improvement in Quality of Episodic Memory; worsening in Continuity of Attention and Speed of Memory) (Meador et al., 2015). Detailed exploration of antiepileptic drug (AED) cognitive impact of this kind is rare (Wesnes et al., 2009), especially for children and adolescents with epilepsy (Aldenkamp et al., 1993; Guerrini et al., 2014; Loring and Meador, 2004; Nordli, 2004). Furthermore, blood sampling was conducted in the study, to allow exposure–response analysis of perampanel on cognition and on seizure responses.

The pharmacokinetic (PK) profile of perampanel has been characterised in healthy volunteers (Patsalos, 2015), and population PK and PK/pharmacodynamics (PD) characteristics have been reported in the Phase III clinical trial population (Gidal et al., 2013; Laurenza et al., 2012; Patsalos, 2015). Perampanel is not a potent inhibitor or inducer of any major cytochrome P450 (CYP) or UDP-glucuronosyltransferase (UGT) enzymes, but because perampanel is extensively metabolised by CYP3A4, drugs that inhibit or induce CYP3A4 can impact perampanel clearance. In the Phase III population PK analyses, perampanel clearance was increased by carbamazepine, oxcarbazepine and phenytoin, but without affecting the slope of the exposure–efficacy relationship (Gidal et al., 2013). Hence, patients taking concomitant CYP3A4 inducers will have a lower exposure to perampanel and may require higher doses of perampanel to achieve comparable efficacy to patients not taking concomitant CYP3A4 inducers (Fycompa SPC, 2015; Gidal et al., 2013; Patsalos, 2015).

This report aims to characterize the PK profile of perampanel, and the impact of intrinsic and extrinsic factors on PK, in adolescents. Importantly, we also characterize the relationship between perampanel plasma concentration and cognitive function, seizure frequency, and responder status.

2. Methods

2.1. Design

Study design details, including detailed inclusion and exclusion criteria of this study have been previously published (Meador et al., 2015). Briefly, study 235 (NCT01161524) was a Phase II, double-blind, randomized, placebo-controlled study of adjunctive perampanel in adolescents with inadequately controlled partial-onset seizures (POS) according to ILAE 1981 criteria. The study included a 1-week pre-randomisation phase, a 6-week titration period, and a 13-week maintenance period (total 19-week double-blind phase).

The objectives of the PK analysis were to describe the PK of adjunctive perampanel in patients aged 12–17, and to identify covariates that explain inter-subject variability in perampanel PK. The primary objective of the PK/PD analysis was to explore the relationship between perampanel exposure and CDR global cognition score (change from baseline to Week 19) and domain scores. Secondary objectives included exploring the relationship between perampanel exposure, other covariates, and seizure frequency (mean change from baseline to Week 19), and exploring the relationship between perampanel exposure and responder status (≥50% reduction in seizure frequency relative to baseline).

2.2. Participants

Study 235 recruited male and female patients aged ≥12 and <18, with a diagnosis of POS with or without secondary generalisation. Participants were required to have ≥1 POS in 4 weeks prior to screening, despite stable treatment with 1–3 AEDs (only 1 of which could be an inducing AED). Detailed inclusion/exclusion criteria and study design details have been reported elsewhere (Meador et al., 2015).

Studies 304 (French et al., 2012), 305 (French et al., 2013) and 306 (Krauss et al., 2012) recruited males and females aged ≥12 years with a diagnosis of POS with or without secondary generalisation. Participants were required to have ≥5 POS in the 6-week baseline period, despite stable treatment with 1–3 AEDs (only 1 inducing AED) (French et al., 2013, 2012; Krauss et al., 2012).

The PK analysis population comprised patients in study 235 with PK data, along with the 74 adolescent patients with PK data available from three Phase III studies. The PK/PD cognition analysis population comprised patients in study 235 who had PK data and CDR system cognition score data at Week 19. The PK/PD efficacy population comprised patients in study 235 with PK data and seizure frequency data at baseline and Weeks 10, 14 and 19. (A larger efficacy population was also explored, adding adolescents from the Phase III studies; see Supplemental Information I for details and results).

2.3. Interventions

Patients were instructed to take the study drug once daily, at bedtime, with food. In study 235 perampanel was titrated from 2 mg/day up to a target dose of 8–12 mg/day, in weekly increments of 2 mg. Titration beyond 8 mg/day was based on individual tolerance and the need for better seizure control, at the discretion of the investigator.

Studies 304, 305, and 306 were fixed-dose studies; patients were randomized to placebo, 8 or 12 mg (304 and 305) or placebo, 2, 4 and 8 mg (306). Perampanel (or matched placebo) was titrated from 2 mg to the randomized dose in weekly 2 mg increments.

Blood samples were taken during clinic visits at Weeks 10, 14, and 19 (start, middle, and end of the maintenance period, respectively), and were taken if patients discontinued early. Two samples were taken on each designated day, 1–2 h apart (sparse sampling technique), at any time during the daytime following the bed-time dose the previous evening.

2.4. PK analyses

All PK and PK/PD models were developed in NONMEM version 7.2 interfaced with PDxPop version 5 (ICON Development Solutions, Ellicott City, MD).

2.4.1. PK model development

Details of PK model development are beyond the scope of this report; see Supplemental Information for specifics. A base PK model was developed and the resulting measures of perampanel average exposure at steady state ($C_{av,ss}$) were incorporated into the dataset used for the subsequent population PK/PD analyses. A one-compartment model was used, parameterised for apparent clearance (CL/F) and apparent volume of distribution (V/F). Inter-individual variability (IIV), inter-occasion variability, and residual variability were assessed (see Supplemental Information A for details).

Model acceptability was assessed on a composite of criteria and goodness of fit plots and bootstrapping (see Supplemental Information B for details).

2.4.2. Effect of covariates

The effect of the following patient covariates on PK parameters was explored in a stepwise fashion: demographics (gender, race, age, body weight); renal function (creatinine clearance); liver

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