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ORIGINAL RESEARCH

Predicted Efficacy of Once-Daily Extended-Release Oxcarbazepine (Oxtellar XR®) Monotherapy in Adults and Children with Partial-Onset Seizures: Exposure-Response Modeling and Simulation

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Purpose: We conducted exposure-response modeling and simulations to compare the predicted efficacy of extended-release oxcarbazepine (OXC-XR), an oral once-daily (qd) antiepileptic drug, with that of immediate-release (IR) OXC twice-daily (bid) when the agents are used as monotherapy or adjunctive therapy in patients with epilepsy characterized by partial-onset seizures (POS).

Methods: Modeling assessed percent change from baseline 28-day seizure frequency (PCH) as a function of minimum concentration (C_{min}) of monohydroxy derivative (MHD), the clinically relevant metabolite of OXC. For OXC-IR, the model used historical data; values for OXC-XR were derived from observed data. The model was simulated (N=100) to predict PCH at MHD C_{min} concentrations achieved with 1200 and 2400 mg/day in adults and children receiving OXC-XR qd or OXC-IR bid. Mean PCH and 95% confidence intervals (CIs) were generated and compared.

Results: Predicted efficacy was not different (ie, 95% CI of mean PCH overlapped) for OXC-XR qd vs OXC-IR bid at mean MHD C_{min} concentrations achieved with 1200 and 2400 mg/day adjunctive OXC-XR (47.4 and 76.4 µmol/L) and at target MHD C_{min} concentrations for OXC-IR monotherapy (59.1 and 112 µmol/L) in adults. Predicted efficacy in adults vs children was not different between formulations. Depending on MHD C_{min}, the predicted mean PCH in adults ranged from −51.4% to −73.4% with OXC-XR qd and −53.2% to −78.5% with OXC-IR bid. In children, the predicted mean PCH ranged from −48.4% to −58.1% (OXC-XR qd) and −32.5% to −70.4% (OXC-IR bid).

Conclusion: This model-based analysis predicted comparable efficacy for OXC-XR qd vs OXC-IR bid at MHD C_{min} concentrations corresponding to 1200 and 2400 mg/day as monotherapy or adjunctive therapy. Based on this analysis, the US Food & Drug Administration approved OXC-XR for use as monotherapy in adults and children ≥6 years of age with POS.

Keywords: oxcarbazepine, monotherapy, Oxtellar, monohydroxy derivative, adjunctive therapy

Introduction

Epilepsy is characterized by recurrent unprovoked seizures with life-altering neurobiological, cognitive, psychological, and social consequences.[1] Epilepsy is one of the most common neurologic disorders in adults and children[2–4] and ranks fifth among such disorders in terms of disability.[3] Moreover, the risk of premature death

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is more than two-fold higher in persons with epilepsy vs those without.[5] The predominant seizure types in adults and children with epilepsy are focal or partial-onset seizures (POS) (seizures originating in one hemisphere of the brain) that cause impairment or loss of consciousness.[2,4,6] Although epilepsy surgery can be effective in controlling or reducing POS frequency/severity,[7] antiepileptic drugs (AEDs) are the primary therapy in POS.[8] Over the past two decades, more than a dozen new AEDs have been approved to treat POS.[8]

Historically, clinical trials of new drugs, including AEDs, were typically conducted in children only after the drugs had been approved for use in adults, resulting in prescribers treating children off-label without guidance on dosing and an understanding of the safety and efficacy in pediatric populations.[9,10] To take advantage of adequate, well-controlled studies in adults as potentially rich sources of data to inform pediatric labeling, the Food and Drug Administration (FDA) established rules for extrapolating these data to the pediatric population when 1) the medical condition/disease follows a similar progression in adults and children and 2) the populations respond similarly to intervention.[9,10]

The Pediatric Epilepsy Academic Consortium for Extrapolation (PEACE), in collaboration with the FDA-funded Center of Excellence in Regulatory Science and Innovation (University of Maryland), determined that, in the absence of epileptic encephalopathies, the pathophysiology of POS is similar in adults and children and that AED efficacy in adults predicts efficacy in pediatric patients ≥4 years of age.[10–12] The FDA subsequently defined a path by which AEDs could be approved for use in children with POS on the basis of adequate efficacy data from randomized controlled trials (RCTs) in adults, adequate pediatric pharmacokinetic (PK) and tolerability data, and simulations identifying doses achieving drug exposures known to be effective in adults.[13]

The FDA took a similar position with regard to extrapolating AED efficacy as adjunctive therapy to monotherapy use.[8,14] Beginning in the 1980s, adjunctive therapy and monotherapy had been separate indications for AEDs, requiring that each indication be supported by RCT(s) demonstrating a statistically significant difference favoring study drug over a control.[15] Because epilepsy is a potentially life-threatening disorder, placebo monotherapy is generally considered unethical.[15] While RCTs that did not involve placebo monotherapy allowed some AEDs to gain a monotherapy indication, the study designs were not without ethical concerns.[15]

As with indications for children vs adults, AED monotherapy as an FDA-approved indication generally lagged years behind the drug's initial approval as adjunctive therapy,[15] even though monotherapy has been the preferred mode of AED therapy in epilepsy for decades.[16–18] Approximately 80% of individuals with epilepsy can be successfully maintained long term on AED monotherapy, with more than half achieving seizure freedom.[19] Labeling limited to adjunctive use therefore excluded information relevant to the most common use of AEDs. Based on cumulative evidence that AEDs proven effective as adjunctive therapy in POS are also effective as monotherapy,[15] the FDA has adopted a policy eliminating monotherapy as a separate indication for AEDs provided PK data show that exposure–response relationships and recommended dosages with AED monotherapy would be similar to those demonstrated to be safe and effective in RCTs of adjunctive therapy.[8,14] For AEDs with adjunctive-only indications that were approved before the policy change, the FDA proposed that sponsors submit, for FDA review, PK data and exposure-response analyses that would support inclusion of monotherapy-related information in labeling.[20–22] To date, labeling for three AEDs has been expanded to include monotherapy use via this approach – perampanel (Fycompa®, Eisai Inc., Woodcliff, NJ, USA), brivaracetam (Briviact®, UCB, Inc., Smyrna, GA, USA) and extended-release oxcarbazepine (Oxtellar XR®, Supernus Pharmaceuticals, Inc., Rockville, MD, USA).[20–22] Here, we summarize the exposure-response and modeling studies that supported FDA approval of extended-release oxcarbazepine (OXC-XR) monotherapy in adults and children ≥6 years of age with POS.

OXC was initially approved in 2000 as an immediate-release (IR) formulation (Trileptal®, Novartis Pharmaceuticals, Corp., East Hanover, NJ, USA) dosed twice daily (bid) as adjunctive therapy in adults and children with POS and as monotherapy in adults.[23] Consistent with FDA policy at the time, adjunctive and monotherapy indications were based on RCTs showing significant treatment effects favoring OXC-IR bid over placebo or pseudo-placebo.[23] In 2003, OXC-IR bid was approved for use as monotherapy in children ≥4 years of age based on exposure-response analyses incorporating efficacy and PK data from RCTs in adults and PK data in children.[23] In these analyses, the analyte of interest was the clinically relevant

moiety monohydroxy derivative (MHD) 10,11-dihydro -10-hydroxycarbazepine.[24]

Compared with the IR formulation, the matrix tablet formulation of OXC-XR slows OXC release/absorption to produce a more favorable MHD plasma concentration-time profile that allows once-daily (qd) dosing.[25] The plasma concentration-time profile may also improve tolerability vs OXC-IR since rising and peak MHD concentrations reportedly influence OXC-related side effects such as dizziness, diplopia, nystagmus, and ataxia.[26] The FDA approved OXC-XR qd in 2012 with an indication for adjunctive therapy in adults and children ≥6 years of age with POS.[27] To validate the extrapolation of adjunctive OXC-XR efficacy in adults to its use as monotherapy, we used exposure-response modeling and simulation to compare the predicted efficacy of OXC-XR qd and OXC-IR bid in adult and pediatric populations. As described in Methods, we used the MHD exposure-response model described by FDA statisticians in the agency's review of OXC-IR as monotherapy in children.[23]

Methods

Studies providing data for these analyses were conducted in accordance with Good Clinical Practice guidelines, International Council on Harmonization, the Declaration of Helsinki, and the United States Code of Federal Regulation. The study protocols were approved by each study site's institutional review board. Written, informed consent was obtained from all adult study subjects. In the case of pediatric subjects, consent was obtained from the parent or legally authorized representative; pediatric subjects provided informed assent. Key eligibility criteria for OXC-IR efficacy studies have been previously described,[28,29] and eligibility criteria for OXC-XR studies (804P103, 804P107, and 804P301[30]) are described in the Supplemental Material.

OXC-IR bid: MHD Exposure-Response Model

The methodology for MHD exposure-response modeling was developed for the FDA review of OXC-IR bid as monotherapy in children with POS.[23] The first step in demonstrating that PK bridging was appropriate for extrapolating efficacy from adults to children was to demonstrate that exposure–response relationships were similar for the two populations when receiving adjunctive OXC-IR.

The adjunctive OXC-IR efficacy study in adults[28] comprised an 8-week baseline phase of stable AED therapy followed by double-blind treatment with placebo or 600, 1200, or 2400 mg/day OXC-IR (2-week titration from 600 mg/day starting dose, 24-week maintenance, optional 2-week tapering phase). Samples for MHD concentrations were collected approximately 12 hours post-dose to determine the minimum concentration (C_{min}) at up to six visits per patient during the maintenance phase. In the adjunctive efficacy study in pediatric subjects,[29] the 8-week baseline with stable AED therapy was followed by a 16-week double-blind treatment period (2-week titration from 10 mg/kg/day as starting dosage to weight-based target dosages of 900, 1200, 1800 mg/day; 14-week maintenance phase) with OXC-IR bid. Dosages could be adjusted during the maintenance phase due to poor tolerability or inadequate seizure control. Blood samples were drawn at random points during the maintenance phase. The average steady-state MHD C_{min} was inferred from population PK modeling that estimated each patient's 12-hour post-dose MHD concentration using a one-compartment PK model with first-order absorption and elimination.[31]

The efficacy measure of interest in both OXC-IR studies was percent change from baseline 28-day seizure frequency (PCH).[28,29] Post-hoc linear regression models were fitted to log-transformed PCH as a function of C_{min} to characterize the exposure–response relationship.[23,31] The final model used by FDA statisticians[23] was:

$$\log(\%\ \text{change from baseline 28-day seizure frequency} + 110) = \beta 0 + \beta 1 * \text{MHD } C_{min}$$

Parameters β0 and β1 were, respectively, y-intercept (placebo response) and slope from the log-linear regression model; C_{min} was MHD exposure in μmol/L (transformed from original values expressed in mg/L using 254.3 as MHD molecular weight).[23] Due to large variability and skewed distribution of observed PCH vs C_{min} values, log-transformed PCH values were used in the analysis.[23] A normalization value of 110 was selected to ensure that the log-transformed PCH value was positive.[31] Error terms were assumed to be independently, normally distributed with zero means and variance equal to σ^2. The estimated parameter values for OXC-IR generated by FDA statisticians (Table 1) were used in our comparison of OXC-XR and OXC-IR.

OXC-XR Once-Daily Population PK Modeling

The population PK model used to estimate individual MHD C_{min} values in the OXC-XR exposure-response

Table 1 Estimated Parameters for MHD Exposure–Response Relationships with OXC-IR bid and OXC-XR qd in Adult and Pediatric Populations

Treatment	Population	N	β0 (SE)	β1 (SE)	σ
OXC-IR bid[23]	Adult Pediatric	480 230	4.55036 (0.04169) 4.54554 (0.06259)	−0.01028 (0.00114) −0.007164 (0.001513)	0.68698 0.74166
OXC-XR qd	Adult Pediatric*	283 18	4.36203 (0.06211) 4.36203 (0.0932)	−0.00613 (0.0012) −0.00427 (0.00159)	0.75104 0.81082

Note: *Parameters derived from adult population.
Abbreviations: β0, y-intercept (placebo response); β1, slope; OXC-IR bid, immediate-release oxcarbazepine twice-daily; OXC-XR qd, extended-release oxcarbazepine once-daily; SE, standard error; σ, residual error standard deviation.

analysis was based on data generated in two studies in adults (804P103; 804P301[30]) and one in pediatric subjects (804P107).

Study 804P103 was a Phase I randomized, two-drug crossover study in healthy adults that compared steady-state bioavailability of 600-mg bid OXC-IR and 1200 mg qd OXC-XR. Study drug was administered in increasing dosages (Days 1–3, 600 mg/day; Days 4–6, 900 mg/day; Days 7–13, 1200 mg/day). PK samples were drawn before the morning dose on Days 1, 4, 7, 11, 12, and 13 of each period; serial post-dose samples were collected on Day 13. To accommodate the extended-release profile of OXC-XR, the population PK model (see Supplemental Material) described OXC release/absorption as a hybrid zero-order and first-order process, with disposition into two compartments and first-order elimination from the central compartment. In the MHD model, MHD was formed by a first-order process, driven by the central compartment concentration of OXC, with a small fraction formed during OXC absorption, presumably due to first-pass metabolism. The MHD model described a single systemic compartment for MHD, with first-order elimination.

Study 804P301 (NCT00772603) was a Phase III multicenter, double-blind, randomized, parallel-group 16-week study in patients ages 18 to 65 years with inadequately controlled POS despite stable treatment with one to three AEDs.[30] Patients were randomized to qd placebo, 1200 mg OXC-XR, or 2400 mg OXC-XR. The starting dose (600 mg qd) was increased in 600-mg increments at weekly intervals. Blood samples were collected during the maintenance and post-maintenance period to measure MHD concentrations at five different time points (0, 1, 2, 4, and 7 hours post-dose). Each sample was obtained at a separate visit when possible. The structural population PK model initially developed in healthy adults (804P103) was applied to the patient PK data. The model fit the observed data well. Covariates incorporated into the final model for MHD included an effect of weight on apparent clearance and a factor to describe the effect of co-administered AEDs (ie, carbamazepine, phenytoin, phenobarbital, or valproate) on apparent clearance (see Supplemental Material). For each subject receiving OXC-XR, PK variables were derived from simulated data at each visit for which there was a valid PK observation based on the individual predicted concentration vs time profile at that visit. MHD C_{min} values were derived by direct inspection. Median MHD C_{min} was the median of values across visits for that subject.

Study 804P107 (NCT00918047) was a Phase I multicenter, open-label study of 8–10 mg/kg/day OXC-XR added to one to three AEDs in children 4 to 16 years of age with inadequately controlled POS. Patients were assigned to receive 150, 300, 450, or 600 mg qd, based on weight, for 7 consecutive days. Blood samples for PK analysis were collected pre-dose (0 hours) and at 1, 4, and 7 hours post-dose on Day 7. The structural population PK model developed in healthy adults and refined in adult patients was applied to pediatric patient data, using the typical adult values for systemic parameters scaled for body size. The weight-normalized model for MHD did not require additional scaling and fit the data. These findings supported OXC-XR dosing based on body weight in pediatric patients to produce MHD exposures comparable to those in typical adults.

Parameter estimates for the final population PK models in adult and pediatric populations are summarized in Supplemental Material.

OXC-XR Once-Daily: MHD Exposure-Response Analysis

Efficacy data for the OXC-XR qd MHD exposure-response analysis were generated in Study 804P301 in adults.[30] Study

subjects maintained daily diaries to record seizure occurrence during the 8-week baseline phase of stable AED therapy and the 16-week double-blind treatment phase. The primary efficacy variable was PCH. Individual MHD C_{min} values were estimated from the population PK model. Using observed data in adults, log-linear regression analysis characterized the relationship of log-transformed response vs median MHD C_{min} with OXC-XR qd as adjunctive therapy.

Predicted clinical responses based on the MHD exposure-response model described above were compared for OXC-XR qd and OXC-IR bid and for adult and pediatric populations at MHD C_{min} concentrations considered to be effective or target concentrations with 1200 mg/day and 2400 mg/day administered adjunctively or as monotherapy. MHD C_{min} values used in simulations of OXC adjunctive therapy were 47.4 µmol/L and 76.4 µmol/L (mean MHD C_{min} with adjunctive 1200 mg/day and 2400 mg/day OXC-XR qd). Concentrations in simulations of OXC monotherapy were 59.1 µmol/L and 112 µmol/L considered effective targets for seizure control based on data from adult monotherapy trials of 1200 and 2400 mg/day OXC-IR. To compare adult and pediatric populations, simulations used exposure levels of 40–80 µmol/L MHD C_{min} – the concentration range achieved with 1200 mg/day and 2400 mg/day OXC-XR qd in adults. In each exposure analysis, the clinical response of OXC-IR bid and OXC-XR qd was simulated using estimated parameters in a typical trial with 100 hypothetical subjects per treatment arm.

For OXC-XR qd, estimated parameters for the MHD exposure–response relationship in adults were based on observed data. Parameters for the pediatric population were derived from the observed adult data and assumed that the proportionality ratio between adult and pediatric populations was the same as for OXC-IR. Parameter values for OXC-IR in adult and pediatric populations were extracted from the FDA review and were based on observed data in clinical studies of adjunctive OXC-IR bid in adult and pediatric populations.[23]

All data preparation, summary statistics, and graphical display presentations were performed using R (3.2.2 version, www.r-project.org). The population PK analysis and exposure-response analyses were conducted with NONMEM software, Version 7.4 (Icon Development Solutions, Ellicott City, MD, USA).

Results

Descriptive statistics for data used in the log-linear regression analysis to characterize the MHD exposure–response relationship with OXC-XR qd are presented in Table 2. Figure 1 depicts plots of observed data for individual subjects with the model-predicted regression line and 90% prediction level.

Estimated parameters of the exposure–response relationship derived from regression analyses were similar for OXC-XR qd and OXC-IR bid as adjunctive therapy in adults (Table 1). The numerical difference in the slope (β1) for OXC-XR exposure-response (−0.006) vs OXC-IR (−0.010) was explained by the lower placebo response observed in OXC-IR clinical studies in adults. In model simulations, predicted seizure reduction (mean PCH) in the placebo arm (MHD C_{min} = 0) was −15.3% (OXC-IR) vs −31.6% (OXC-XR). In a subset analysis of OXC-XR patients with placebo response similar to that observed in OXC-IR studies, the shape of the OXC-XR exposure–response relationship more closely mirrored that of OXC-IR (β0, 4.583 vs 4.550; β1, −0.009 vs −0.010). The β1 value for OXC-XR in the pediatric population (Table 1) was derived from the β1 value in the adult population by assuming that the ratio for adult vs pediatric populations was the same as the adult–pediatric ratio observed with

Table 2 OXC-XR as Adjunctive Therapy in Adults with Inadequately Controlled Seizures (Study 804P301): Percent Change from Baseline 28-Day Seizure Frequency (PCH) and MHD C_{min} Values by Treatment Arm

Study Arm	N	Variable	Mean	Std Dev	Median	Minimum	Maximum
Placebo	117	PCH MHD C_{min}, µmol/L	−15.43 0	67.34 0	−28.70 0	−100.00 0	333.60 0
OXC-XR 1200 mg	85	PCH MHD C_{min}, µmol/L	−26.05 47.36	76.29 16.93	−36.20 46.01	−100.00 17.07	556.10 89.26
OXC-XR 2400 mg	81	PCH MHD C_{min}, µmol/L	−48.33 76.40	41.72 30.66	−49.60 76.29	−100.00 18.84	103.60 147.86

Abbreviations: MHD C_{min}, monohydroxy derivative minimum concentration; OXC-XR, extended-release oxcarbazepine; PCH, percent change from baseline 28-day seizure frequency; Std Dev, standard deviation.

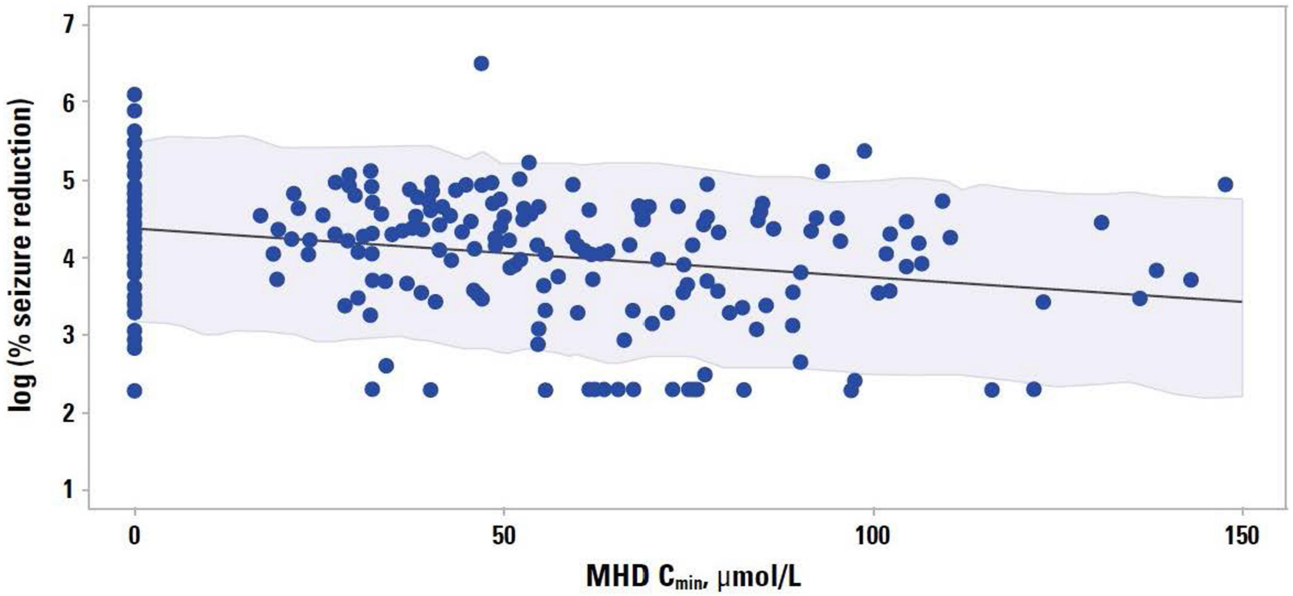

Figure 1 Exposure-response model applied to observed data from double-blind, placebo-controlled trial of 1200 mg and 2400 mg OXC-XR qd as adjunctive therapy in adults with POS.
Notes: log(% seizure reduction) = log(% change from baseline 28-day seizure frequency + 110). Dots are observed data; line depicts model-predicted curve and shaded area shows 90% prediction level. MHD C_{min} value of 0 represents placebo arm.
Abbreviations: MHD C_{min}, monohydroxy derivative minimum concentration; OXC-XR qd, extended-release oxcarbazepine once-daily.

OXC-IR in RCTs of adjunctive therapy. The β0 for OXC-XR in the pediatric population was assumed equal to the β0 value in adults since these values were almost identical for OXC-IR in RCTs.

Results of simulations with OXC-XR qd and OXC-IR bid as adjunctive therapy (MHD C_{min}, 47.4 and 76.4 µmol/L) are summarized in Table 3 and Figure 2A. Predicted efficacy of adjunctive OXC was not significantly different between the two formulations in both adult and pediatric populations, as demonstrated by overlapping 95% CIs. Based on the back transformation of mean log values, predicted mean seizure frequency reductions at 47.4 µmol/L and 76.4 µmol/L were −51.4% and −54.3%, respectively, with OXC-XR qd and −53.2% and −64.4% with OXC-IR in adults (Table 4). In the pediatric population, the simulation-predicted seizure frequency change with adjunctive therapy was −54.3% and −52.0% with OXC-XR qd, and −32.5% and −60.6% with OXC-IR bid.

Figure 2B and Table 3 compare simulation outputs for OXC-XR qd and OXC-IR bid as monotherapy at the target MHD concentrations considered effective for seizure control (MHD C_{min}, 59.1 and 112 µmol/L). Predicted efficacy responses were similar for OXC-XR vs OXC-IR in both adult and pediatric populations. The 95% CIs overlapped for both MHD C_{min} concentrations in the pediatric population and at 112 µmol/L in adults, indicating no significant differences in predicted efficacy with monotherapy. Back-transformation of mean log values predicted seizure frequency reductions at 59.1 µmol/L and 112 µmol/L of −47.8% and −73.4%, respectively, with OXC-XR qd in adults and −62.5% and −78.5% with OXC-IR bid (Table 4). In children, predicted reductions were −49.1% and −58.1% with OXC-XR qd vs −37.0% and −70.4% with OXC-IR bid.

To compare the clinical response in the pediatric population with that in adults, simulations were performed using the exposure-response model at MHD C_{min} values ranging from 40 to 80 µmol/L, representing the concentration range observed with 1200 mg and 2400 mg OXC-XR as adjunctive therapy in adults. Results (Figure 2C; Table 3) were comparable for pediatric vs adult populations with both formulations. Predicted seizure reductions with OXC-IR bid were −46.6% in children vs −59.1% in adults and −48.4% and −54.3%, respectively, with OXC-XR qd (Table 4).

Discussion

These analyses illustrate the application of exposure-response modeling and simulation to provide evidence-based information for prescribers. As a result of these analyses, labeling for Oxtellar XR was revised to include 1200 to 2400 mg monotherapy as an FDA-approved use in adults and children ≥6 years of age with POS.

Table 3 Predicted Response [Log(% Change from 28-Day Baseline Seizure Frequency + 110)] in Adult and Pediatric Populations at the Range of Reference MHD C_{min} Concentrations Used in Simulations

Reference Exposure	MHD C_{min}, µmol/L	Population	Treatment	Mean Log Value (95% CI)	Std Dev	Median	Min	Max
Mean MHD C_{min} values observed with 1200 and 2400 mg/day adjunctive therapy (OXC-XR qd) in adults	47.4	Adult	OXC-XR qd	4.07 (3.93, 4.22)	0.74	4.11	2.24	5.95
			OXC-IR bid	4.04 (3.90, 4.18)	0.71	4.08	1.55	5.74
		Pediatric	OXC-XR qd	4.02 (3.86, 4.19)	0.84	4.04	1.81	5.88
			OXC-IR bid	4.35 (4.20, 4.49)	0.74	4.26	2.54	6.03
	76.4	Adult	OXC-XR qd	4.02 (3.85, 4.20)	0.88	4.05	2.24	6.18
			OXC-IR bid	3.82 (3.69, 3.96)	0.69	3.76	2.22	5.92
		Pediatric	OXC-XR qd	4.06 (3.92, 4.19)	0.68	4.07	2.17	5.78
			OXC-IR bid	3.90 (3.75, 4.06)	0.80	3.98	2.24	5.46
Target MHD C_{min} values deemed effective for seizure control with 1200 and 2400 mg/day monotherapy (OXC-IR bid) in adults	59.1	Adult	OXC-XR qd	4.13 (3.98, 4.28)	0.73	4.12	2.48	5.77
			OXC-IR bid	3.86 (3.74, 3.97)	0.58	3.85	2.00	5.31
		Pediatric	OXC-XR qd	4.11 (3.94, 4.28)	0.84	4.15	1.70	6.02
			OXC-IR bid	4.29 (4.15, 4.42)	0.68	4.32	2.37	6.20
	112	Adult	OXC-XR qd	3.60 (3.47, 3.73)	0.65	3.65	2.03	4.91
			OXC-IR bid	3.45 (3.30, 3.60)	0.76	3.51	1.52	5.14
		Pediatric	OXC-XR qd	3.95 (3.80, 4.10)	0.74	3.99	2.10	5.71
			OXC-IR bid	3.68 (3.52, 3.84)	0.82	3.58	1.34	6.10
Reference Exposure	**MHD C_{min}, µmol/L**	**Treatment**	**Population**	**Mean log value (95% CI)**	**Std Dev**	**Median**	**Min**	**Max**
MHD C_{min} range observed with 1200 and 2400 mg/day adjunctive therapy (OXC-XR qd)	40–80	OXC-XR qd OXC-IR bid	Adult	4.02 (3.98, 4.06)	0.75	4.03	1.43	6.37
			Pediatric	4.12 (4.08, 4.17)	0.82	4.14	1.42	6.83
			Adult	3.93 (3.89, 3.97)	0.68	3.94	1.47	6.52
			Pediatric	4.15 (4.11, 4.19)	0.76	4.17	1.50	7.15

Abbreviations: CI, confidence interval; Max, maximum value; MHD C_{min}, monohydroxy derivative minimum concentration; Min, minimum value; OXC-IR bid, immediate-release oxcarbazepine twice-daily; OXC-XR qd, extended-release oxcarbazepine once-daily; Std Dev, standard deviation.

The inclusion of such information in AED labeling reflects the importance of monotherapy as an option in epilepsy care. Indeed, the consensus approach to AED therapy is to start with a single AED in patients with newly diagnosed epilepsy.[17–19] If the first AED does not achieve the desired outcome, patients are transitioned to monotherapy with a different AED, often with a different mechanism of action.[17–19] Even if the first two trials of AED monotherapy fail and AEDs are used in combination, clinicians will often revert to monotherapy as providing the best outcome for individual patients.[17–19] Following this approach, more than half of patients achieved seizure remission with the first or second AED as monotherapy while the large majority – approximately 80% – of patients were successfully-maintained long term on AED monotherapy.[19]

In a double-blind, placebo-controlled trial, OXC-XR qd was proven to be effective in adults with POS when administered as adjunctive therapy.[30] Median PCH was −28.7% with placebo vs −38.7% with 1200 mg OXC-XR qd (p=0.08 vs placebo) and –42.9% with 2400 mg OXC-XR qd (p=0.003).[30] These data suggested that OXC-XR would be effective as monotherapy in POS since historical RCT data have shown that AEDs effective as adjunctive therapy in POS are also effective as monotherapy.[15] Moreover, OXC-IR bid was approved by FDA for use as monotherapy in adults (2000)[32] and children (2003),[23] giving us a reference product for our analyses.

The foundation for our analytical approach was the methodology that FDA statisticians used when reviewing analyses to justify extrapolation of adjunctive OXC-IR bid efficacy in adults to monotherapy efficacy in children.[23] The equivalence analysis conducted by FDA statisticians compared adult and pediatric populations in terms of predicted efficacy across a range of

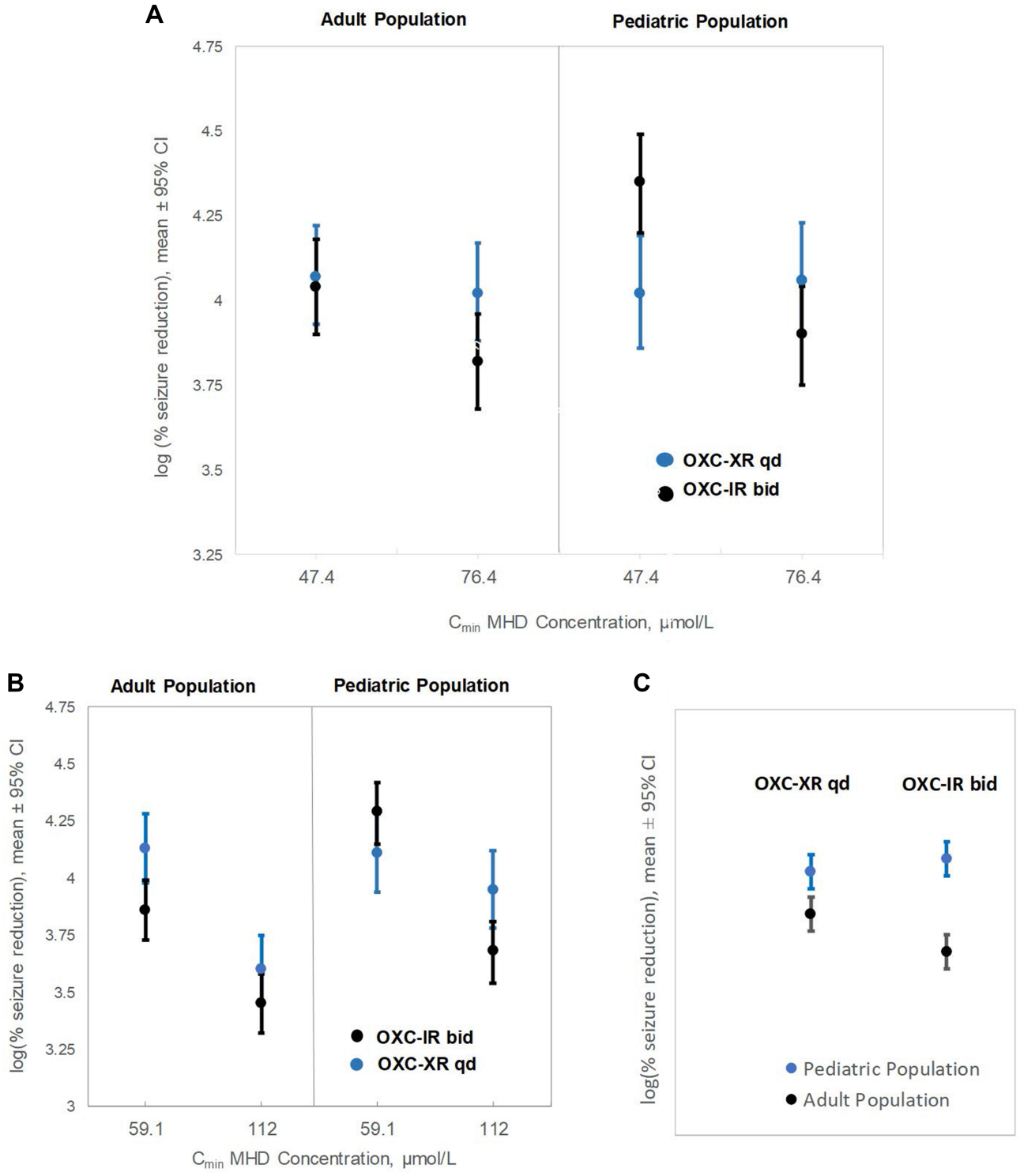

Figure 2 Predicted response (mean ± 95% confidence intervals) in adult and pediatric populations at the range of reference MHD C_{min} concentrations used in simulations. (**A**) Mean MHD C_{min} values observed with 1200 (47.4 µmol/L) and 2400 mg/day (76.4 µmol/L) OXC-XR qd as adjunctive therapy (OXC-XR qd) in adults. (**B**) Target MHD C_{min} exposures (59.1 µmol/L and 112 µmol/L) considered effective for seizure control based on data from adult monotherapy studies with 1200 and 2400 mg/day OXC-IR bid. (**C**) MHD C_{min} values (40–80 µmol/L) observed with 1200 mg/day and 2400 mg/day OXC-XR qd as adjunctive therapy in adults.

Notes: Predicted response = log(% change from 28-day baseline seizure frequency + 110).

Abbreviations: CI, confidence interval; MHD C_{min}, monohydroxy derivative minimum concentration; OXC-IR bid, immediate-release oxcarbazepine twice-daily; OXC-XR qd, extended-release oxcarbazepine once-daily.

Table 4 Predicted Efficacy Expressed as Mean Percent Seizure Change (PCH) Based on Back-Transformation of Log Mean Values and 95% CI at the Range of Reference MHD C_{min} Concentrations Used in Simulations

Reference Exposure	MHD C_{min}, μmol/L	Population	Treatment	Mean PCH (95% CI)
Mean MHD C_{min} values observed with 1200 and 2400 mg/day adjunctive therapy (OXC-XR qd) in adults	47.4	Adult	OXC-XR qd	−51.4 (−42.0, −59.1)
			OXC-IR bid	−53.2 (−44.6, −60.1)
		Pediatric	OXC-XR qd	−54.3 (−44.0, −62.5)
			OXC-IR bid	−32.5 (−20.9, −43.3)
	76.4	Adult	OXC-XR qd	−54.3 (−43.3, −63.0)
			OXC-IR bid	−64.4 (−57.6, −70.0)
		Pediatric	OXC-XR qd	−52.0 (−44.0, −59.6)
			OXC-IR bid	−60.6 (−52.0, −67.5)
Target MHD C_{min} values deemed effective for seizure control with 1200 and 2400 mg/day monotherapy (OXC-IR bid) in adults	59.1	Adult	OXC-XR qd	−47.8 (−37.8, −56.5)
			OXC-IR bid	−62.5 (−57.0, −67.9)
		Pediatric	OXC-XR qd	−49.1 (−37.8, −58.6)
			OXC-IR bid	−37.0 (−26.9, −46.6)
	112	Adult	OXC-XR qd	−73.4 (−68.3, −77.9)
			OXC-IR bid	−78.5 (−73.4, −82.9)
		Pediatric	OXC-XR qd	−58.1 (−49.7, −65.3)
			OXC-IR bid	−70.4 (−63.5, −76,2)
Reference Exposure	**MHD C_{min}, μmol/L**	**Treatment**	**Population**	**Mean PCH (95% CI)**
MHD C_{min} range observed with 1200 and 2400 mg/day adjunctive therapy (OXC-XR qd)	40–80	OXC-XR qd OXC-IR bid	Adult	−54.3 (−52.0, −56.5)
			Pediatric	−48.4 (−45.3, −50.9)
			Adult	−59.1 (−57.0, −61.1)
			Pediatric	−46.6 (−44.0, −49.1)

Abbreviations: CI, confidence interval; MHD C_{min}, monohydroxy derivative minimum concentration; OXC-IR bid, immediate-release oxcarbazepine twice-daily; OXC-XR qd, extended-release oxcarbazepine once-daily; PCH, % change from baseline 28-day seizure frequency.

MHD concentrations observed in RCTs.[23] Importantly, simulations included MHD C_{min} concentrations identified in OXC-IR monotherapy RCTs as effective target exposures for seizure control with OXC monotherapy.[23] We, therefore, used the same model and simulation arguments to provide quantitative and statistical validation for extrapolating the proven effectiveness of adjunctive OXC-XR qd in adults[30] to monotherapy in adults and children by comparing predicted efficacy of OXC-XR qd vs OXC-IR bid.

The key findings of our analyses were: 1) exposure–response relationships for OXC-XR qd vs OXC-IR bid as adjunctive therapy in adults are similar; 2) OXC-XR qd dosages for adjunctive therapy and monotherapy in adults are not different; 3) exposure–response relationships in adult vs pediatric populations are not different; and 4) OXC-XR qd dosages for adjunctive therapy and monotherapy in pediatric populations are not different.

OXC-XR qd vs OXC-IR bid Exposure–Response Relationships with Adjunctive Therapy are Similar in Adults

The shape of the adjunctive exposure–response relationship with OXC-XR qd was similar to that with OXC-IR bid. The efficacy responses over the range of concentrations likely to be experienced, including MHD C_{min} concentrations known to be effective with OXC monotherapy, were also similar.

Adjunctive and Monotherapy OXC-XR qd Dosages are Not Different

The recommended dosages of 1200–2400 mg OXC-XR qd shown to be safe and effective as adjunctive therapy in adults[30] are the same dosages that FDA deemed safe and effective with OXC-IR bid as adjunctive therapy and monotherapy.[33] Therefore, effective monotherapy dosages

for OXC-XR monotherapy should be within the range established with adjunctive OXC-XR qd and OXC-IR bid.

Exposure–Response Relationships are Not Different in Adult vs Pediatric Populations

In light of historical data showing that exposure–response relationships with OXC-IR bid are similar in adult and pediatric patients[23] and our finding that such relationships are similar for OXC-XR qd and OXC-IR bid in adults, the relationship with OXC-XR qd in the pediatric population could be established from the relationship observed in adults. Predicted efficacy in children across the range of MHD C_{min} concentrations, including concentrations known to be effective with OXC monotherapy, was similar to that with OXC-XR qd in adults and with OXC-IR bid in adults and children. Adjunctive and monotherapy OXC-XR qd dosages in children are not different: Because the exposure-responses for OXC-XR qd and OXC-IR bid in adult adjunctive and monotherapy are similar, it can be inferred that the extrapolated effective exposures in the pediatric population would be similar to those in adults. The predicted magnitude of seizure reduction with OXC-XR qd monotherapy in children was clinically meaningful and similar to that predicted with OXC-IR bid monotherapy.

The validity of extrapolating OXC-XR qd efficacy as adjunctive therapy to efficacy as monotherapy in adults and children with POS was strengthened by the availability of monotherapy data from OXC-IR bid RCTs showing significant differences favoring OXC-IR over placebo and pseudo-placebo.[34–36] Although ethical concerns now preclude such studies, the OXC-IR monotherapy studies identified target MHD C_{min} concentrations for seizure control with OXC formulations.[28,29] The MHD C_{min} concentrations observed with 1200 and 2400 mg/day OXC-XR as adjunctive therapy (47.4 and 76.4 µmol/L, respectively) were lower than those identified as target concentrations effective for seizure control with OXC monotherapy (59.1 and 112 µmol/L), reflecting the known effects of concomitant AEDs (eg, phenytoin, carbamazepine) on OXC clearance.[24] Simulations, therefore, assessed predicted response across a wide range of MHD C_{min} concentrations likely to occur with recommended dosages of OXC-XR qd and OXC-IR bid.

Efficacy data used to establish exposure-response (MHD C_{min} vs seizure reduction) relationships and predict efficacy were extracted from double-blind RCTs in which placebo or study drug was added to other AEDs in patients with relatively frequent POS. In placebo-controlled RCTs in adults with POS, OXC-IR or OXC-XR was added to ≥2 AEDs in 68–76% of patients; median baseline seizure frequency was 6–10 seizures/28 days.[28,30] These are characteristics of drug-resistant epilepsy and are not broadly representative of patients who are likely candidates for AED monotherapy, whether they are patients being switched from one monotherapy to another due to poor tolerability or breakthrough seizures, or patients in whom AED monotherapy is being initiated or re-started. In these patients, effective AED monotherapy can achieve high rates of seizure freedom, as demonstrated by a pragmatic, randomized, open-label trial of AED monotherapy (carbamazepine, gabapentin, lamotrigine, topiramate, OXC-IR) in patients with newly diagnosed epilepsy, patients who had failed previous monotherapy, and patients who had relapsed after seizure remission and treatment withdrawal.[37] After 4 years of follow-up, 77% of patients randomized to carbamazepine monotherapy had been seizure-free at least 12 months and 65% had been seizure-free at least 24 months.[37] Remission rates were similar for OXC-IR, eg, 75% seizure-free at least 12 months after 4 years of follow-up.[37] At the end of follow-up, seizures were in remission at a mean OXC-IR dosage of 771 mg/day (range, 300–1200 mg/day).[37] These results underscore the likelihood that patients with POS who are candidates for monotherapy in clinical practice would be expected to be more responsive to OXC-XR qd than the prediction of 50–70% seizure frequency reductions that our simulations would suggest and that patients would achieve seizure remission with low to moderate dosages. Thus, results of modeling and simulation using adjunctive efficacy data from patients with drug-resistant epilepsy should be viewed as confirmatory evidence that an AED is effective as monotherapy but not as a measure of the treatment effect's magnitude in patients who are likely candidates for AED monotherapy.

Evidence-based guidelines issued in 2004[38] and updated in 2018[39] recommend OXC as a first-line option for patients with newly diagnosed epilepsy characterized by POS. This recommendation is based on level A evidence from four studies comparing OXC (as OXC-IR bid) with older AEDs (carbamazepine, phenytoin, valproate).[40–43] In these studies, OXC was deemed equivalent to traditional first-line therapies in terms of seizure control but was better tolerated.[40–43] Modeling and

simulation support the extrapolation of these recommendations to OXC-XR qd as monotherapy in newly diagnosed epilepsy.

Conclusion

Based on modeling and simulation analyses, predicted efficacy with OXC-XR qd was not significantly different than with OXC-IR bid in adult and pediatric populations. This model-based analysis provided robust evidence that the efficacy of OXC-XR qd as adjunctive therapy in adults supports the use of OXC-XR qd as monotherapy in adults and children ≥6 years of age with POS. The FDA approved an expanded indication for OXC-XR that includes monotherapy based on exposure-response modeling and analyses described in the present study. The recommended dosages of OXC-XR qd as adjunctive therapy and monotherapy are the same in adults, ie, 1200–2400 mg/day, with weight-based dosing in children.

Abbreviations

AED, antiepileptic drug; bid, twice daily; CI, confidence interval; C_{min}, minimum concentration; FDA, Food and Drug Administration; IR, immediate-release; MHD, monohydroxy derivative; OXC, oxcarbazepine; PCH, percent change from baseline; PEACE, Pediatric Epilepsy Academic Consortium for Extrapolation; PK, pharmacokinetics; POS, partial-onset seizures; qd, once daily; RCT, randomized controlled trial; XR, extended-release.

Data Sharing Statement

Data and models supporting these analyses come from a combination of in-house data owned by Supernus, and published or publicly accessible data. Published data can be found in Barcs et al (2000), Glauser et al (2000), and French et al (2014), and publicly accessible data can be found in the FDA Trileptal Clinical Pharmacology and Biopharmaceutics Review (2003).

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Disclosure

S Mendes, W O'Neal, S Schwabe, and A Nasser are employees of Supernus Pharmaceuticals, Inc. S Faison was an employee of Supernus Pharmaceuticals, Inc. at the time of this work, and is now an employee of Certara Strategic Consulting. R Gomeni is president and founder of PharmacoMetrica and Adjunct Professor, Pharmacotherapy and Experimental Therapeutics, University of North Carolina Eshelman School of Pharmacy, Chapel Hill, NC. The authors report no other conflicts of interest in this work.

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