

Use of an exposure-response model for lacosamide in adults with partial onset seizures to analyze preliminary data from a pediatric trial

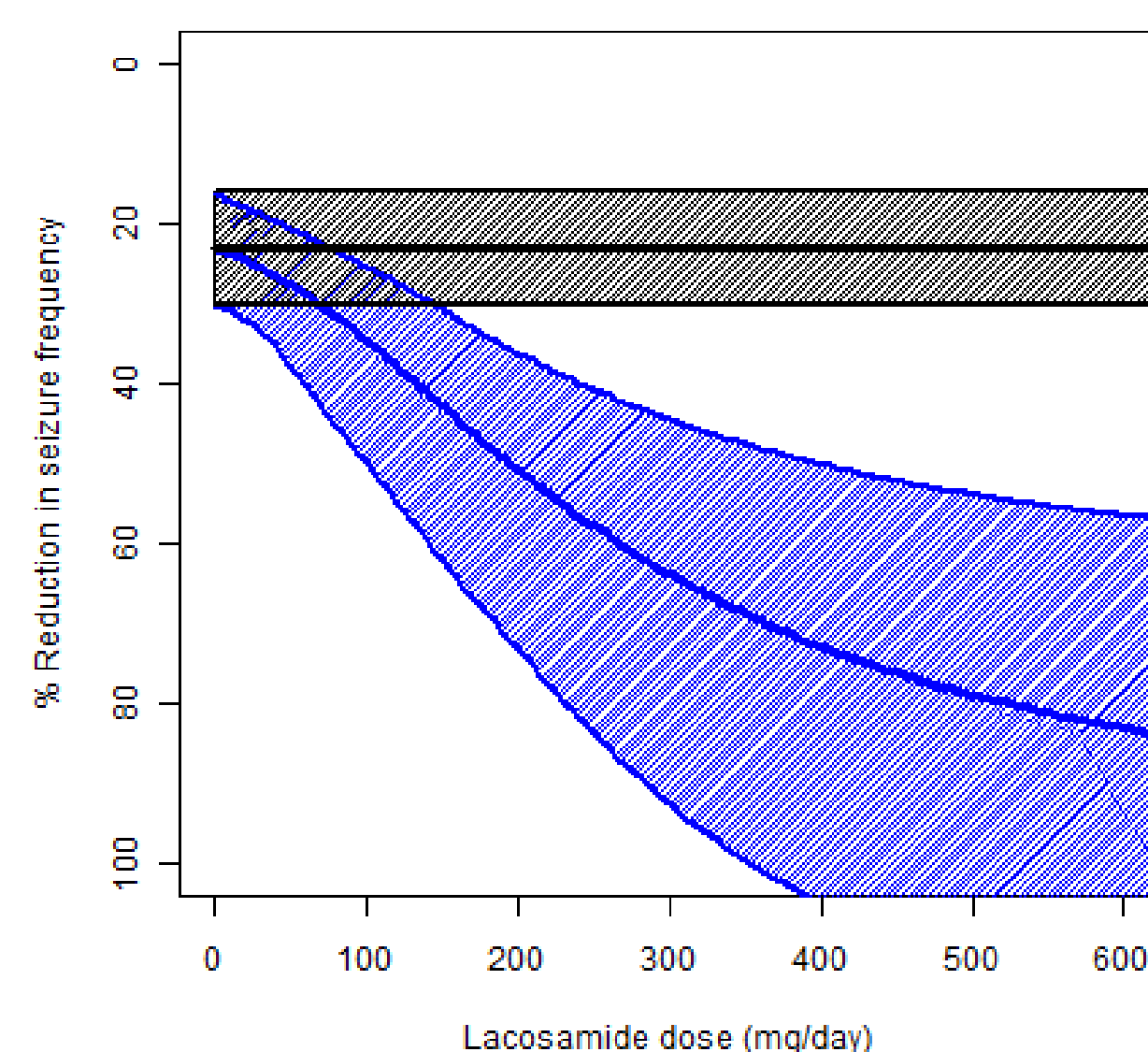
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Introduction

- A retrospective exposure-response model was built for lacosamide (LCM) based on daily seizure counts (n=210,234) of 1308 adult patients who participated in three double-blind placebo-controlled clinical trials in adjunctive treatment of partial onset seizures (POS) (studies SP667, SP754, SP755) [1-3].
- A negative binomial distribution with zero-inflation (ZINB [4]) and Markovian element, associated with a mixture model stratifying patients according to reduced or increased seizure frequency (SF), provided the best fit.

Figure 1: Median (95%CI) SF reduction from baseline for LCM (blue) and placebo (black) in improving adult patients not taking sodium channel blockers. The horizontal axis is daily dose but the Emax model is driven by plasma concentration



- The model developed for adults was applied to interim seizure count data obtained in 28 children with POS in order to assess the relevance of the exposure-response relationship in children.

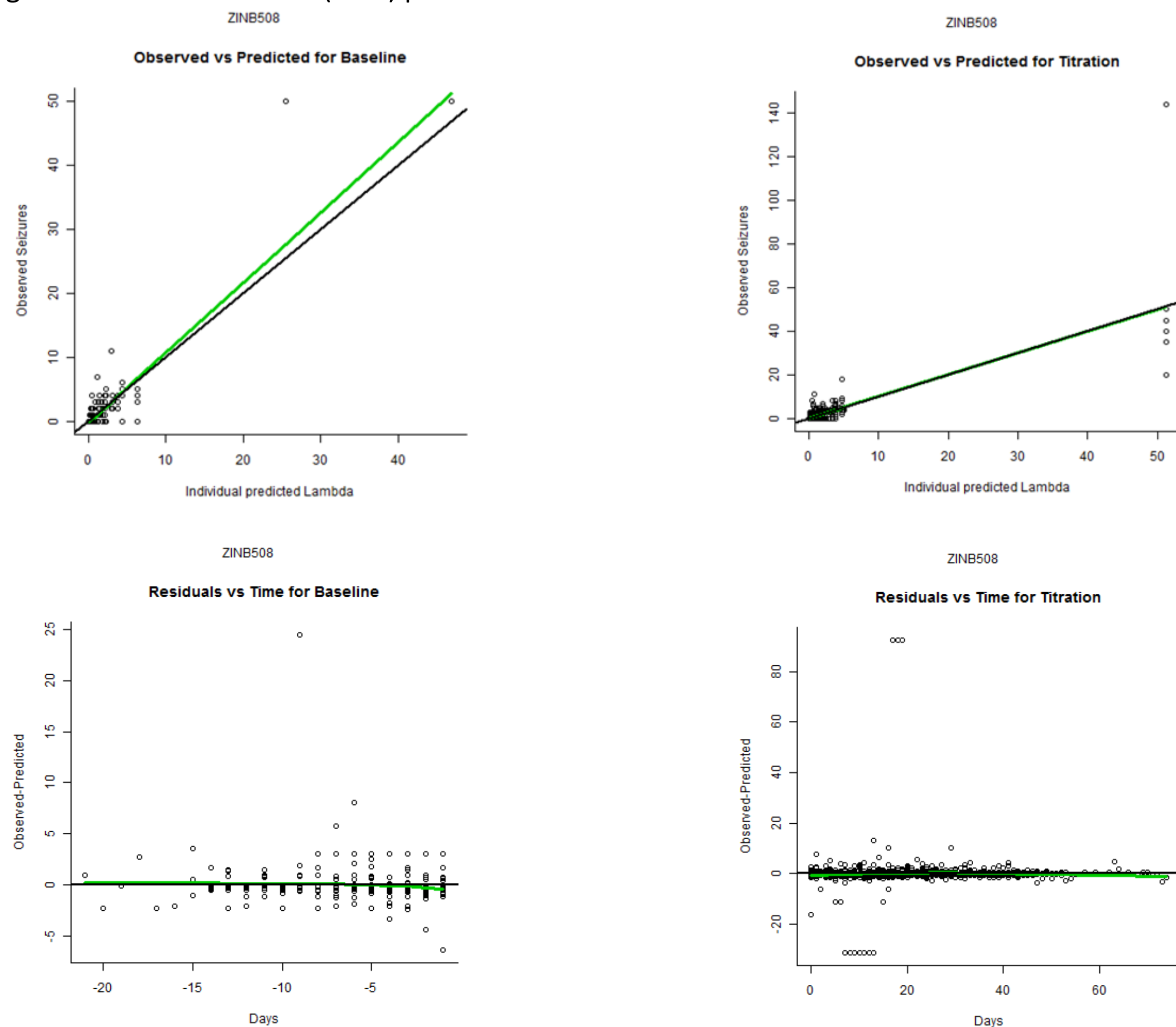
Methods

- Interim SF data from a multicenter, open-label phase-2a trial designed to investigate the safety and pharmacokinetics of lacosamide as adjunctive therapy in children with POS (SP847) were analyzed using the exposure-response model developed in adults.
- Daily seizure counts were available from 28 children aged 3-17 years, having been titrated from 2 to 12 mg/kg/day by weekly increments of 2 mg/kg/day.
- The exposure-response model developed in adults was used to perform an empirical Bayesian feedback and VPC simulations (n=1000 replicates) on percentage of 50% responders ($\geq 50\%$ reduction in SF from baseline) and median percent reduction from baseline in mean daily seizure count.
- Model development and simulations were performed using non-linear mixed-effects modeling implemented in NONMEM V7.1.0 with the Laplacian method.
- Daily trough plasma concentrations were simulated using the individual Empirical Bayesian Estimates from the adult PK model [5] scaled to children, and taking into account the actual individual dosing records.

Results

- There was good agreement between observed and predicted daily seizure counts during Baseline and Titration periods, while few outliers were seen as a function of time:

Figure 2: Goodness Of Fit (GOF) plots



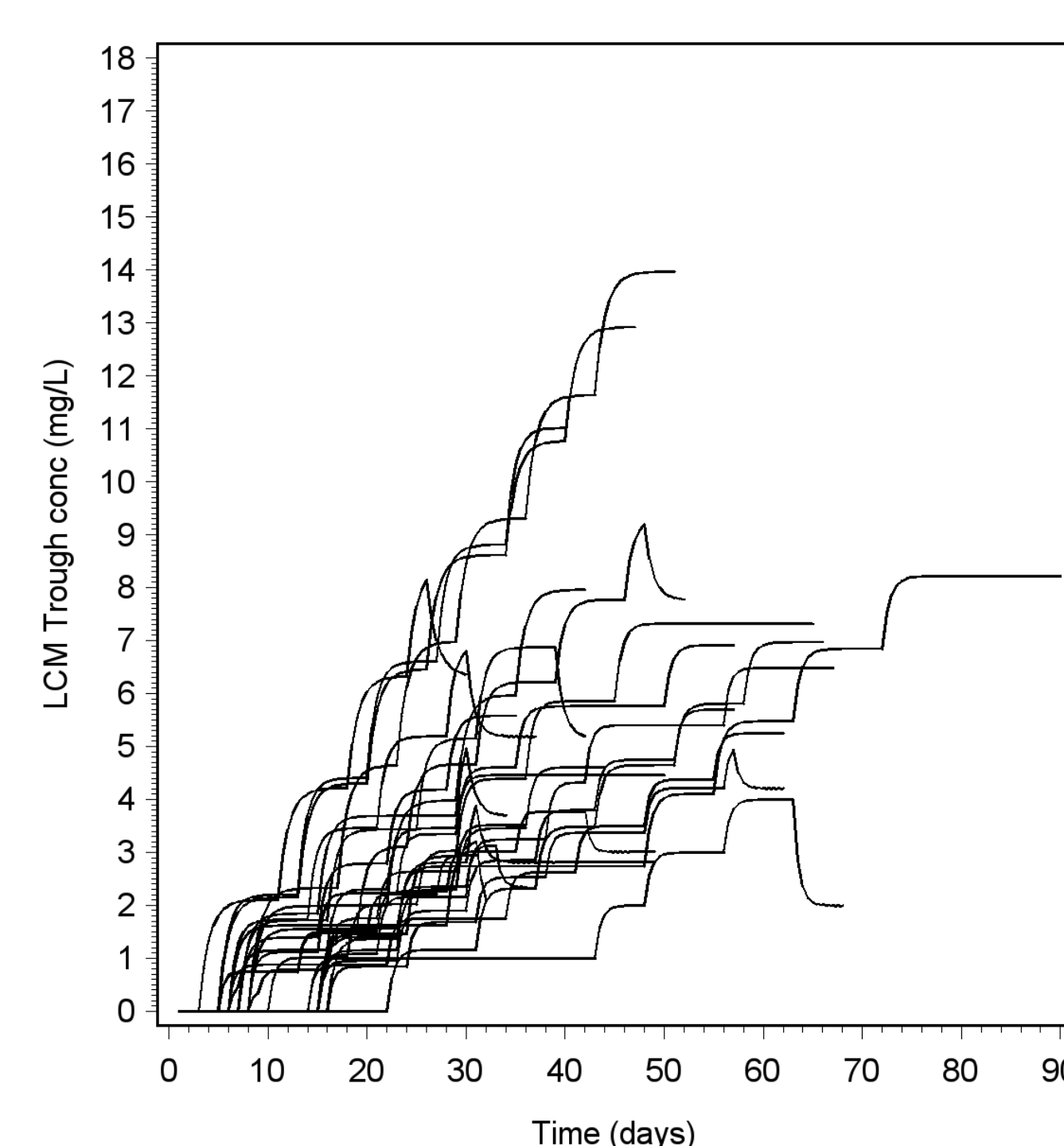
- In order to take into account LCM pharmacokinetics, daily trough concentrations were simulated using the individual Empirical Bayesian Estimates (EBE) from the adult PK model [5] updated in children and using lean body weight (LBW) as the main covariate

$$CL = 1.89 * (LBW/50)^{0.75} \text{ L/h}$$

$$V = 43.4 * (LBW/50)^1 \text{ L}$$

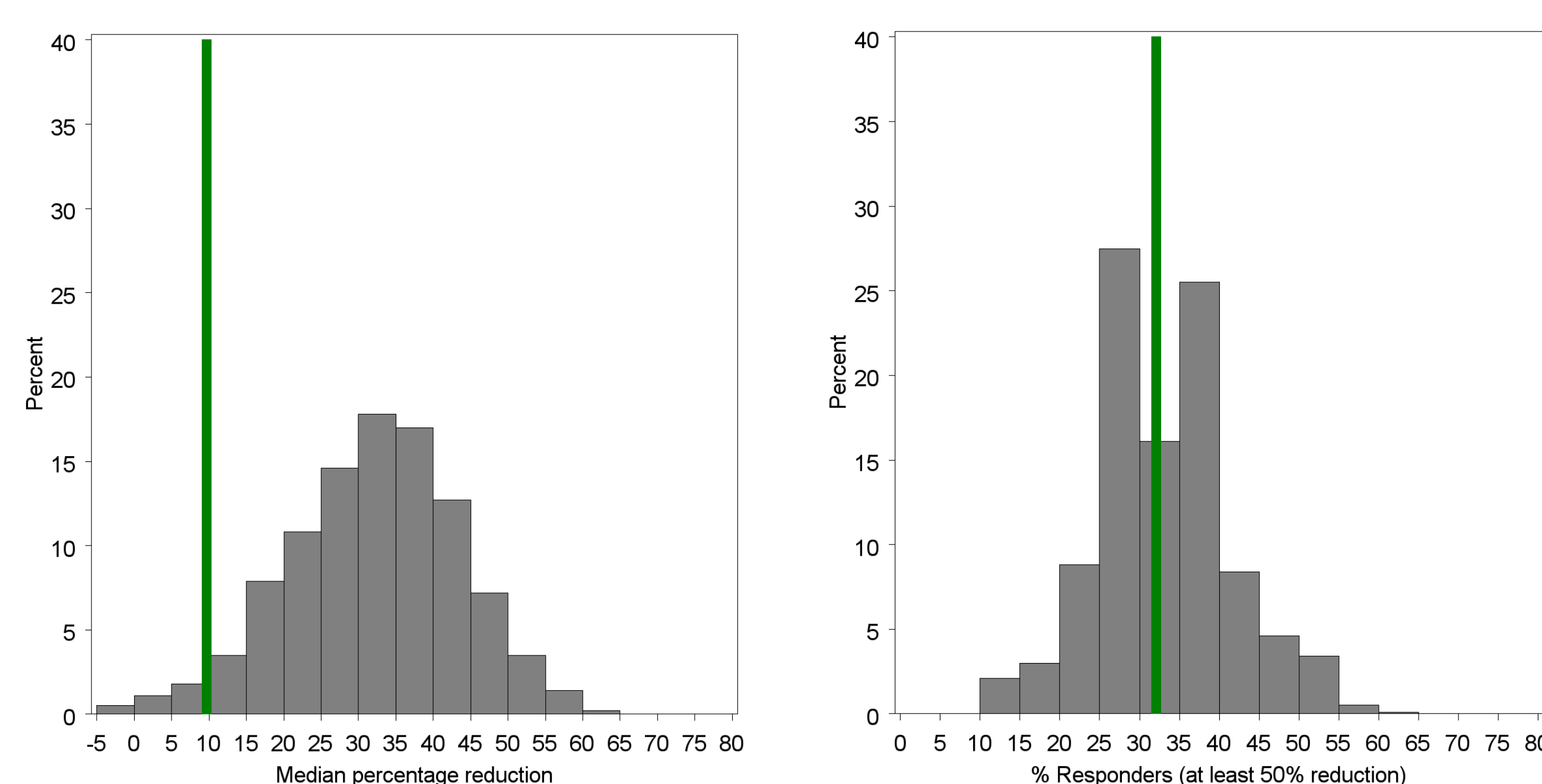
$$Ka = 2.73 \text{ h}^{-1}$$

Figure 3: Simulated Trough concentrations for LCM in 28 children using the post-hoc estimates coming from the scaled adult-pediatric PK model



- There was a good correspondence in the Visual Predictive Checks (VPC) comparing the distribution of simulated median percentage SF reduction from baseline and responder rate in seizure frequency to the observed median values (green lines) for the 28 children:

Figure 4: VPC comparing the distribution of n=1000 simulated replicates and the observed median in the first 28 patients of study SP847.



Conclusions

The exposure-response model developed in adult patients was successfully applied to preliminary data from children. The results did not support an alteration of the exposure-response relationship established in adults. Therefore, the LCM dosing rationale in children may be based on LCM pharmacokinetics.

Reference

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