Office of Clinical Pharmacology Review

NDA or BLA Number	020450-0069 (SUPPL-3, Efficacy)
Link to EDR	\\CDSESUB1\evsprod\NDA020450\020450.enx
Submission Date	09/01/2016
Submission Type	Resubmission of Prior Approval Pediatric Labeling Supplement (Standard priority)
Brand Name	Cerebyx
Generic Name	Fosphenytoin Sodium
Dosage Form and Strength	Solution for injection, (b) (4) mg/mL *fos*phenytoin solution (50 mg *phenytoin equivalent*/mL)
Route of Administration	Intravenous, Intramuscular
Proposed Indication	Control of generalized tonic-clonic status epilepticus and prevention of and treatment of seizures occurring during neurosurgery.
Applicant	Parke Davis, A Division of Pfizer Inc
Associated IND	040588
OCP Review Team	Michael Bewernitz, Ph.D. Kevin Krudys, Ph.D. Angela Men, M.D., Ph.D.

Table of Contents

1. EXECUTIVE SUMMARY

Fosphenytoin is a pro-drug of phenytoin. Fosphenytoin, which is available as a solution for intravenous (IV) and intramuscular (IM) injection, is typically used when oral phenytoin cannot be administered. Fosphenytoin and phenytoin are both approved for the treatment of status epilepticus in adults. Phenytoin is approved for status epilepticus in adults and pediatric patients age 6 years and older. Fosphenytoin is administered in terms of "mg phenytoin equivalent" (mg PE) since 1 mole of fosphenytoin is metabolized into 1 mole of phenytoin. The current submission is an efficacy supplement intended to support fosphenytoin labeling for the status epilepticus indication as well as non-emergent use in pediatric patients age birth to 16 years.

Sponsor assessed the safety and pharmacokinetics of IV and IM fosphenytoin in pediatric patients that required a phenytoin loading dose for seizure prophylaxis (Phase 3 Study 982-028). In addition, Sponsor assessed the safety and PK of IV fosphenytoin for the acute treatment of generalized convulsive status epilepticus in pediatric patients (Phase 2/3 trial 982-016). Using data from these two pediatric PK studies as well as phenytoin PK data provided by the author of a literature study (Ogutu et al., 2003), the Sponsor developed a combined fosphenytoin and phenytoin population pharmacokinetic model.

Using the pediatric population PK model, Sponsor assessed various dose regimens via pharmacokinetic simulations. In order to evaluate the simulated pediatric fosphenytoin loading doses, Sponsor derived a "reference range" of unbound phenytoin C_{max} values based on observed unbound phenytoin concentrations in adults receiving IV fosphenytoin in one of their clinical trials. Sponsor proposed a pediatric loading dose that provided a best match with the adult exposure "reference range".

(b) (4) a therapeutic range of 1-2 µg/mL unbound phenytoin. Sponsor utilized this therapeutic unbound phenytoin concentration target range for assessing appropriateness of simulated pediatric maintenance dose regimens.

Key review issues include selection of an appropriate "reference range" in adults for assessing loading dose selection for status epilepticus as well as non-emergent situations, selection of initial maintenance dose, and directions for dose adjustment during maintenance.

1.1 Recommendations

The Office of Clinical Pharmacology Divisions of Clinical Pharmacology 1 and Pharmacometrics have reviewed the information contained in NDA 020,450 (SUPPL-005). This NDA is approvable from a clinical pharmacology perspective. The key review issues with specific recommendations/comments are summarized below:

Table 1: Key Review Issues and Recommendations

Review Issue	Recommendations and Comments
Pivotal or supportive evidence of effectiveness	2 pediatric clinical trials combined with PK modeling and simulation.
General dosing instructions	CEREBYX should ordinarily not be given intramuscularly. Loading Dose: • *Status epilepticus*: 15-20 mg PE/kg loading dose • *Non-emergent situations*: 10-15 mg PE/kg loading dose • If IV administration, recommended infusion rate is 2 mg PE/kg/min (max 150 mg PE/kg/min) Maintenance Dose: • *Initial dose*: 2-4 mg PE/kg to be given 12 hours after loading dose • *Subsequent doses*: Therapeutic drug monitoring is recommended in order to guide subsequent maintenance doses (as is the case for adult fosphenytoin therapy and phenytoin therapy). Dosing interval is 12 hours. • If IV administration, recommended infusion rate is 1-2 mg PE/kg/min (max 100 mg PE/kg/min)
Dosing in patient subgroups (intrinsic and extrinsic factors)	Similar to adults, doses are to be administered on a weight basis and monitoring is recommended for renal and/or hepatic impairment or hypoalbuminemia.

1.2 Post-Marketing Requirements and Commitments

None.

2. SUMMARY OF CLINICAL PHARMACOLOGY ASSESSMENT

2.1 Pharmacology and Clinical Pharmacokinetics

Fosphenytoin is a pro-drug of phenytoin. Modulation of sodium channels may be a primary anticonvulsant mechanism because this property is shared with several other anticonvulsants in addition to phenytoin. Fosphenytoin is administered in mg Phenytoin Equivalent (mg PE).

Pharmacokinetics of fosphenytoin listed in the current label (11/04/2016 version)
http://www.accessdata.fda.gov/drugsatfda_docs/label/2016/020450s033lbl.pdf

Absorption:
Intravenous: T_{max} occurs at infusion completion. Fosphenytoin half-life is approximately 15 minutes.
Intramuscular: Approximately 100% Fosphenytoin bioavailability. T_{max} occurs 30 minutes post-dose.

Distribution: Protein binding is 95% to 99, primarily albumin. Binding to plasma proteins is saturable. Fosphenytoin displaces phenytoin from protein binding sites. The volume of distribution ranges from 4.3 to 10.8 liters.

Metabolism and Elimination: Half-life is 15 minutes for fosphenytoin conversion to phenytoin. Phosphatases probably play a major role. Fosphenytoin is not excreted in urine.

2.2 Dosing and Therapeutic Individualization

2.2.1 General dosing

CEREBYX should ordinarily not be given intramuscularly.

Loading Dose:

For Status Epilepticus:

- Pediatric loading dose is 15 mg PE/kg – 20 mg PE/kg at a rate of 2 mg PE/kg/min.
- Because of the risk of hypotension, Cerebyx should be administered no faster than 150 mg PE/min in adults and children. Continuous monitoring of the electrocardiogram, blood pressure, and respiratory function is essential.

For Non-emergent Loading:

- Pediatric loading dose is 10 mg PE/kg -15 mg PE/kg at a rate of 1mg PE/kg/min -2 mg PE/kg/min.
- The rate of IV administration of the loading dose in adults and children should be no greater than 150 mg PE/min. Continuous monitoring of the electrocardiogram, blood pressure, and respiratory function is essential.

Maintenance Regimen:

The initial maintenance dose in pediatric patients is 2 mg/PE/kg - 4 mg PE/kg every 12 hours (4 mg PE/kg/day - 8 mg PE/kg/day) at a rate of 1mg/PE/kg/min -2 mg PE/kg/min (no faster than 100 mg PE/min). After the initial maintenance dose, subsequent doses should be guided by therapeutic drug monitoring (as is the practice approved for adult maintenance dosing).

2.2.2 Therapeutic individualization

Unbound phenytoin concentration should be monitored in patients with renal and/or hepatic impairment or hypoalbuminemia.

After the initial maintenance dose, subsequent maintenance doses should be individualized by monitoring serum phenytoin concentrations to achieve a target therapeutic concentration of phenytoin (1-2 µg/mL unbound phenytoin).

2.3 Outstanding Issues

None.

2.4 Summary of Labeling Recommendations

Section 2.2 (Status Epilepticus): Provided dose recommendation for status epilepticus loading dose for pediatric patients.

Section 2.3 (Non-Emergent Loading and Maintenance Dosing): Provided dose recommendation for non-emergent loading dose as well as maintenance dosing for pediatric patients.

Sections 7.1 and 7.2: A sentence is added to both of these sections (b) (4) Other than adding a statement clarifying that phenytoin is the active metabolite of the pro-drug fosphenytoin, there are no edits to the drug interactions sections in 7.1 and 7.2 from an OCP perspective

3. COMPREHENSIVE CLINICAL PHARMACOLOGY REVIEW

3.1 Overview of the Product and Regulatory Background

The clinical development program consists of 2 pediatric clinical studies and pharmacokinetic modeling and simulation. Sponsor utilized published information from the literature (Ogutu et al., 2003) to supplement the population pharmacokinetic model. Sponsor engaged in numerous rounds of discussion regarding pharmacokinetic modeling and simulation. The regulatory history regarding these communications is summarized below (PHT = phenytoin):

Table 2: Summary of Regulatory Interactions

Dates	Interaction Type	Key Communication Points
01/11/2011 (OCP review of NDA 020450 signed on 06/10/2011)	Type C	Focus on free PHT levels (instead of total PHT), compare free PHT variability after Cerebyx versus Dilantin, consider the appropriateness of age in PK development, try to obtain raw PK data from authors of publications such as Ogutu et al.
09/28/2011 (OCP review of NDA 020450 signed on 08/10/2011)	General Advice Letter	Sponsor should evaluate the distribution of free PHT concentration after IV Dilantin administration under the approved regimen. Non-linear PK should be accounted for in the population PK model. Adjust for gestational age in modeling and simulation plan.
02/29/2012	Sponsor responded to General Advice Letter	1. 90% PI for reference range will be used to assess effect of dosing regimens on pediatric exposure. Acceptable to FDA. 2. Sponsor obtained PHT concentration data after IV Dilantin administration to children from Ogutu et al. (2003), study. 3. Sponsor agreed to account for nonlinear PK of PHT and fosphenytoin in population PK model. 4. FDA accepted Sponsor's plan to use bootstrap replication to obtain reliable prediction intervals. 5. FDA accepted Sponsor's plan to address extensive PK variability in newborns by estimating 90% PI interval for free PHT exposure in newborns. 6. FDA accepted Sponsor's plan to exhaustively search the literature for information on phenytoin PK in the pediatric ICU.
03/27/2012	Emailed responses to 02/29/2012 submission	
01/08/2014 email (NDA 020450, communication signed on 01/15/2014)	Email comments	1. Pharmacometrics group determined that the final phenytoin and fosphenytoin models generally describe the observed and published data well. 2. C_{max} is the driving factor in resolution of seizures. C_{max} is crucially important to derive fosphenytoin dosing. The model is adequate for the simulation of C_{max} distributions. C_{max} prediction for the combined fosphenytoin-PHT model is sufficient to inform dosing. 3. Targeting the 1-2 µg/mL free PHT concentration may be acceptable for non-emergency maintenance dosing, but not for status epilepticus.
03/2014, 04/10/2014 emails (NDA 020450, communication signed on 04/24/2014)	Email comments	Address role of age-related and disease-related changes in PHT CL and protein binding, including the role of bilirubin and age-related changes in CYP enzymes involved in PHT metabolism.
12/11/2015 meeting (OCP review of NDA 020450, signed on 03/01/2016)	Type B, pre-sNDA	To support loading dose selection in children, include comparison of simulated unbound PHT C_{max} values following Fosphenytoin loading dose to in children to unbound PHT C_{max} values following approved Dilantin loading dose in children. If observed unbound PHT C_{max} data following pediatric Dilantin administration are not available, the population PK model should be used to simulate this data.

3.2 General Pharmacology and Pharmacokinetic Characteristics

Fosphenytoin sodium salt has a molecular weight of 406.24 grams per mole (362.28 grams per mole for the free acid) and is a pro-drug for phenytoin. The active metabolite, phenytoin, has a molecular weight of 252.26 grams per mole (molecular weight 274.25 grams per mole for the sodium salt). The cellular mechanisms of phenytoin thought to be responsible for its anticonvulsant actions include modulation of voltage-dependent sodium channels of neurons, inhibition of calcium flux across neuronal membranes, modulation of voltage-dependent calcium channels of neurons, and enhancement of the sodium-potassium ATPase activity of neurons and glial cells. The modulation of sodium channels may be a primary anticonvulsant mechanism because this property is shared with several other anticonvulsants in addition to phenytoin.

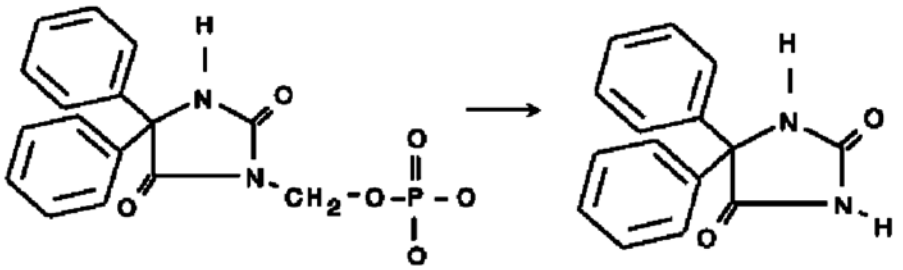
Fosphenytoin is administered in mg Phenytoin Equivalence (mg PE). The following is a summary of the clinical pharmacokinetics of Fosphenytoin from the current Fosphenytoin label.

Absorption:
Intravenous: When CEREBYX is administered by IV infusion, maximum plasma fosphenytoin concentrations are achieved at the end of the infusion. Fosphenytoin has a half-life of approximately 15 minutes.
Intramuscular: Fosphenytoin is completely bioavailable following IM administration of CEREBYX. Peak concentrations occur at approximately 30 minutes post dose. Plasma fosphenytoin concentrations following IM administration are lower but more sustained than those following IV administration due to the time required for absorption of fosphenytoin from the injection site.

Distribution: Fosphenytoin is extensively bound (95% to 99%) to human plasma proteins, primarily albumin. Binding to plasma proteins is saturable with the result that the percent bound decreases as total fosphenytoin concentrations increase. Fosphenytoin displaces phenytoin from protein binding sites. The volume of distribution of fosphenytoin increases with CEREBYX dose and rate. Volume of distribution ranges from 4.3 to 10.8 liters.

Metabolism and Elimination: The conversion half-life of fosphenytoin to phenytoin is approximately 15 minutes. The mechanism of fosphenytoin conversion has not been determined, but phosphatases probably play a major role. Fosphenytoin is not excreted in urine. Each mole of fosphenytoin is metabolized to 1 mole of phenytoin, phosphate, and formate.

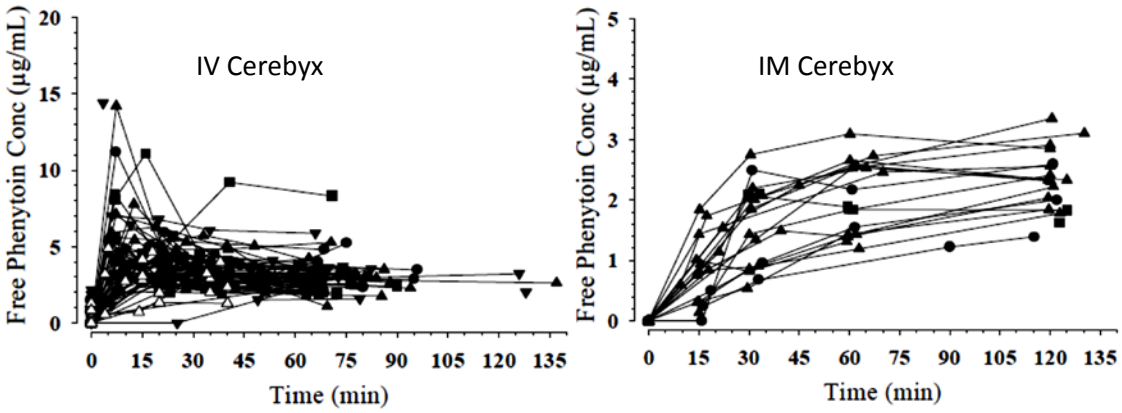
Figure 1: Chemical Structure of Fosphenytoin and Phenytoin



Source: clinical-overview.pdf, page 9 of 63

The follow tables show plots of unbound phenytoin concentration profiles in pediatric patients in trial 982-028.

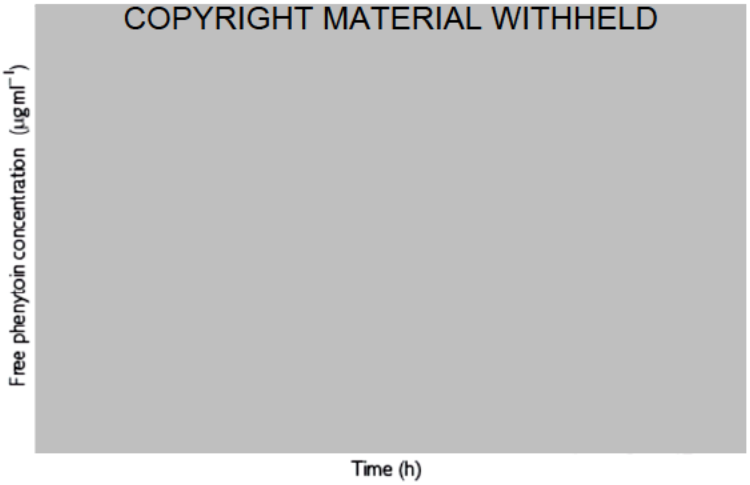
Figure 2: Individual Free (Unbound) Phenytoin PK Profiles in Pediatric Patients Following IV and IM Cerebyx Loading Dose Administration in Study 982-028.



Study 982-28: Neonates (▼), Infants (■), Children (▲), and Adolescents (●).

Source: study-982-028.pdf, page 315 of 337

Figure 3: Mean (± SD) Phenytoin PK Profile Following IV Dilantin, IV Cerebyx, and IM Cerebyx Administration (Ogutu et al., 2003 Study)

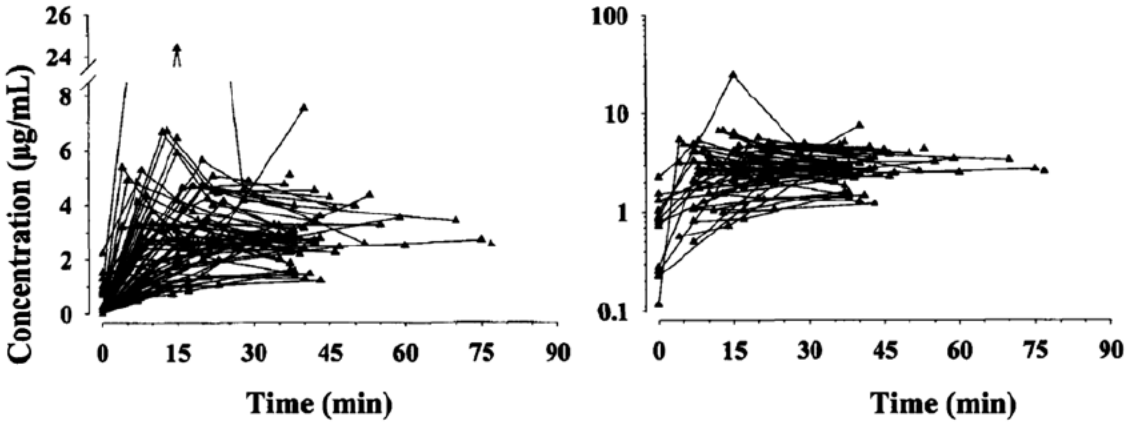


Maintenance doses were given at 12, 24, 36, and 48 hours.

I.V. Dilantin (▲, n = 6), I.V. Cerebyx (□, n = 7), I.M Cerebyx (●, n = 7)

Source: summary-clin-pharm.pdf, page 23 of 46

Figure 4: Individual PK Profile for Free Phenytoin on a Linear Scale (Left Panel) and Log Scale (Right Panel) Following IV Fosphenytoin administration to n=58 Patients in Pediatric Study 982-016.



Source: study-982-016.pdf, page 31 of 282

Table 3: Comparison of Mean (%CV) Free Phenytoin PK Parameters Following a Single IV Infusion of 1200 mg Dilantin (50 mg/min), 1200 mg PE Fosphenytoin (100 mg PE/min) or 1200 mg PE Fosphenytoin (150 mg PE/min)to n=12 Adults in Study 982-024

PK Parameter	Fosphenytoin 1200 mg PE	Dilantin (Phenytoin) 1200 mg	Ratio	90% CI
Fosphenytoin Infusion rate 100 mg PE / min				
ln(C_{max}) (µg/mL)	2.72	3.21	84.7%	**72.7** – 98.8%
ln($AUC_{0\text{-last}}$) (µg*hr/mL)	78.8	85.5	92.2%	88.4 – 96.2%
C_{max} (µg/mL)	2.78 (22%)	3.30 (26%)	84.2%	N/a
T_{max} (hr)	0.524 (37%)	0.526 (17%)	99.9%	
$AUC_{0\text{-last}}$ (µg*hr/mL)	79.5 (14%)	87.1 (22%)	91.3%	
Fosphenytoin Infusion rate 150 mg PE / min				
ln(C_{max}) (µg/mL)	3.08	3.21	96.0%	82.1 – 111.7%
ln($AUC_{0\text{-last}}$) (µg*hr/mL)	84.5	85.5	98.8%	94.8 – 103.2%
C_{max} (µg/mL)	3.18 (28%)	3.30 (26%)	96.4%	N/a
T_{max} (hr)	0.576 (59%)	0.526 (17%)	109.5%	
$AUC_{0\text{-last}}$ (µg*hr/mL)	85.5 (17%)	87.1 (22%)	98.2%	

Source: study-982-024.pdf, page 27 of 212

3.3 Clinical Pharmacology Review Questions

3.3.1 To what extent does the available clinical pharmacology information provide pivotal or supportive evidence of effectiveness?

Sponsor conducted extensive pharmacokinetic modeling and simulation to support pediatric dosing of fosphenytoin. As there is limited information regarding pediatric unbound phenytoin PK in this patient population, Sponsor integrated PK data from pediatric Cerebyx administration, pediatric Dilantin administration, and adult Cerebyx administration to generate a comprehensive model of pediatric unbound phenytoin concentration following Cerebyx administration.

The Sponsor's general approach for designing pediatric dose recommendations was to select pediatric dosing to match simulated unbound phenytoin exposure in virtual pediatric patients with an appropriate reference range.

For assessing the loading dose for status epilepticus, the Division notified the Sponsor that unbound phenytoin C_{max} is the driving factor in resolution of seizures and thus C_{max} is crucially important for deriving fosphenytoin dosing. Sponsor created a "reference range" of unbound phenytoin C_{max} values based on observed PK data from adults that were treated with IV Cerebyx. Sponsor conducted PK simulations for various loading dose levels administered to virtual pediatric patients. Sponsor assessed the performance of each potential loading dose in terms of the proportion of virtual pediatric patients with unbound phenytoin C_{max} values that fell within the unbound phenytoin C_{max} reference range derived from adults.

For the loading dose for non-emergent situations, Sponsor did not conduct PK simulations. Sponsor states that the medical need in non-emergent situations is different than with status epilepticus and that a lower loading dose compared to status epilepticus is appropriate. Sponsor proposed a pediatric loading dose range for the non-emergent indications based solely on this rationale.

For assessing the maintenance dose regimen, Sponsor utilized the therapeutic concentration range listed in the current Dilantin® and Cerebyx® labels of 1-2 µg/mL unbound phenytoin as a target. Sponsor conducted PK simulations for various combinations of loading doses followed by various maintenance dose levels to virtual pediatric patients. Sponsor assessed the performance of each potential loading + maintenance dose regimen in terms of the proportion of virtual patients with unbound phenytoin C_{trough} values on Day 2 after loading dose administration that fell within the therapeutic range. While Sponsor simulated unbound phenytoin values for up to 5 days after the loading dose, the Day 2 C_{trough} was selected for assessing the dose regimens since the common practice for both Dilantin and Cerebyx maintenance dosing is to adjust the maintenance dose using therapeutic drug monitoring. Thus, as Sponsor anticipated that pediatric patients will also undergo therapeutic drug monitoring for adjusting the maintenance dose, and the maintenance dose may be adjusted based on PK measurements acquired as early as on Day 2, then it is reasonable to use the Day 2 C_{trough} as the time point for assessing the maintenance dosing regimens.

Please refer to sections 3.3.2, 3.3.3, and 4.4 for additional details regarding the loading and maintenance dose.

3.3.2 Is the proposed dosing regimen appropriate for the general patient population for which the indication is being sought?

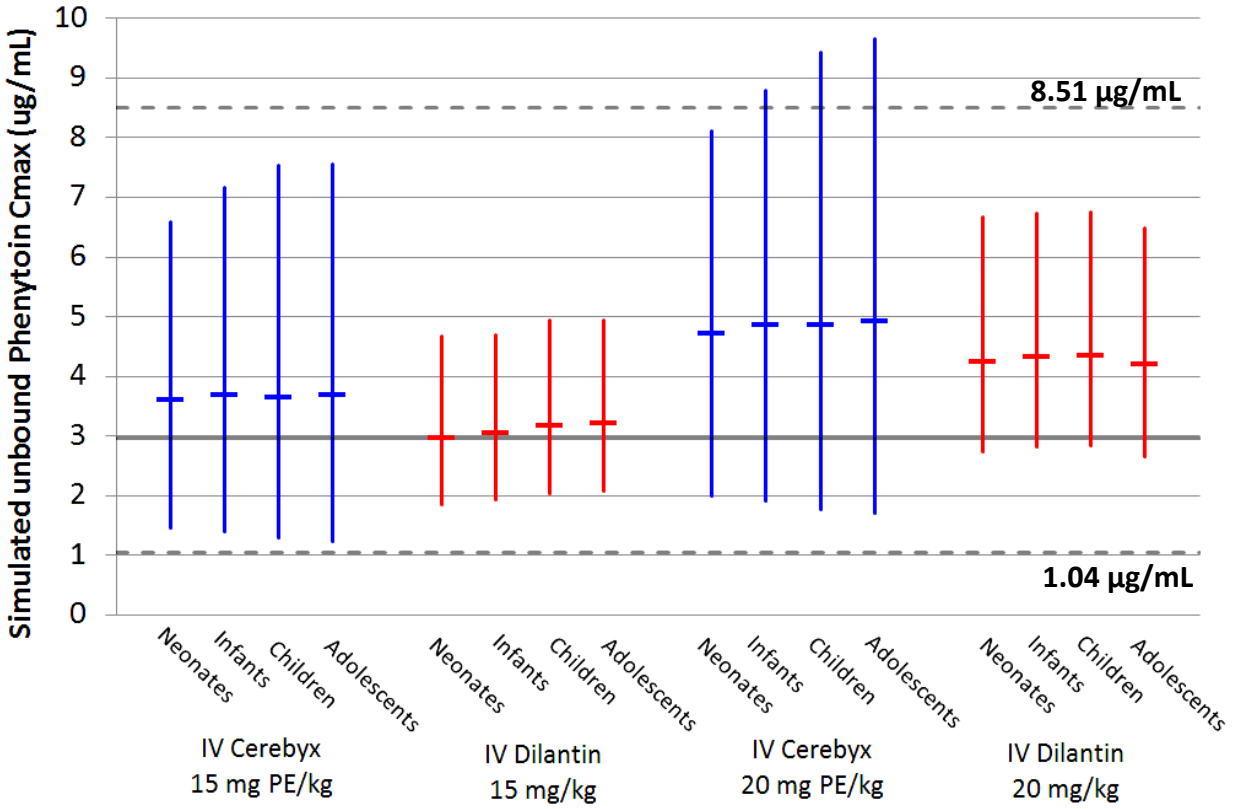
Loading Dose – Status Epilepticus: Achieving a desired unbound phenytoin C_{max} is crucial for treating patients with status epilepticus. In order to select a status epilepticus loading dose for pediatric patients, Sponsor estimated a "reference range" of unbound phenytoin C_{max} values (90% prediction interval [PI]; predicted 5^{th} percentile and predicted 95^{th} percentile based on a log-normal distribution) based on observed PK data acquired from adults receiving IV Cerebyx in study 982-016. The Sponsor's reference range is 0.95 to 7.47 µg/mL. Sponsor conducted PK simulations to estimate the unbound phenytoin C_{max} values for various fosphenytoin loading doses in virtual pediatric patients across a range of ages from birth to adolescence. Based on this analysis, Sponsor proposed a 15 mg PE/kg loading dose pediatric loading dose for status epilepticus. Sponsor believes this dose provides an acceptable balance of maximizing the chance that children achieve unbound phenytoin C_{max} within the C_{max} reference range and minimizes the chance of being below or above that range.

When generating the "reference range", Sponsor included doses that were outside of the approved adult Cerebyx loading dose range in study 982-016. In addition, Sponsor included pediatric patients in the development of the "adult reference range". The reviewer computed a "revised reference range" by including only adult patients and including only doses within the approved dose range from the Cerebyx label (15-20 mg PE/kg). The "revised reference range" had a higher value for both the 5^{th} percentile and 95^{th} percentile predicted unbound phenytoin C_{max}. The reviewer's revised reference range is 1.04 to 8.51 µg/mL.

Though the "revised reference range" seems more appropriate than the Sponsor's reference range, the overall difference between two ranges is not likely to be clinically significant. In other words, the same conclusion would be arrived at whether using the Sponsor's reference range (0.95 – 7.47 µg/mL) or the FDA's revised reference range (1.04 – 8.51 µg/mL).

When compared with the reviewer reference range for unbound phenytoin C_{max} in adults, the Sponsor's simulations for 15 mg PE/kg Cerebyx and 20 mg PE/kg Cerebyx administered to virtual pediatric patients appear to produce comparable unbound phenytoin exposures for all pediatric age groups (please see the figure below).

Figure 5: Simulated Unbound Phenytoin C_{max} Distribution for Pediatric Patients Versus Adults at Proposed Status Epilepticus Loading Dose (15-20 mg PE/kg)



The horizontal grey solid and dashed lines represent the 90% PI (1.04 to 8.51 µg/mL) and median prediction (2.97 µg/mL) for unbound phenytoin C_{max} based on PK data from adults receiving IV Cerebyx doses in the range of 15-20 mg PE/kg in study 982-016. The vertical lines with intersecting horizontal lines represent the 90% PI and median prediction for pediatric patients grouped by age group, dose, and drug (Cerebyx or Dilantin). Blue represents simulated unbound C_{max} values following IV Cerebyx administration to virtual pediatric patients and red represents simulated unbound phenytoin C_{max} values following IV Dilantin administration to virtual pediatric patients.

In addition, the predicted unbound phenytoin C_{max} values resulting from Cerebyx administration (blue lines in Figure 5) appear to be not less than the unbound phenytoin C_{max} values resulting from Dilantin administration (red lines in Figure 5).

Available safety information was also considered in order to assess the appropriateness of the loading dose for pediatric status epilepticus. As safety cannot be extrapolated from adult patients to pediatric patients, safety data from adult patients receiving Cerebyx doses ≥ 15 mg PE/kg cannot be directly used to inform the safety of pediatric dose selection. However, Sponsor reports some pediatric patients that were exposed to Cerebyx doses from 15 – 20 mg PE/kg in the clinical program.

In study 982-028, clinicians had the flexibility to adjust the dose as was clinically necessary. While the target dose was 15 me PE/kg, some pediatric patients were exposed to doses higher than the target (please refer to the table below).

Table 10: Number of Pediatric Patients Exposed to Fosphenytoin Loading Doses ≥ 15 mg PE/kg in Study 982-028

		Neonates	Infants	Children	Adolescents	**Total**
IM Loading Dose	15 to < 20 mg PE/kg	--	1	5	0	**6**
	≥ 20 mg PE/kg	--	2	9	1	**12**
IV Loading Dose	15 to < 20 mg PE/kg	7	12	15	5	**39**
	≥ 20 mg PE/kg	9	10	11	2	**32**

Source: rr-959-00048.pdf, page 19 of 38

As the table above shows, n=12 patients were exposed to IM loading doses ≥ 20 mg PE/kg and n=32 patients were exposed to IV loading doses ≥ 20 mg PE/kg.

In addition, the medical officer provided this statement regarding the severity of the status epilepticus condition:

> "The significant morbidity and mortality from delayed control of status epilepticus makes the risk to benefit ratio different from routine loading for seizure prophylaxis".

In addition, in regards to the subset of pediatric patients predicted to exceed the "revised reference range" of unbound phenytoin C_{max} values at the 20 mg PE/kg loading dose, the medical officer states:

> "… attaining these higher levels does not pose a significant risk for serious cardiovascular adverse effects."

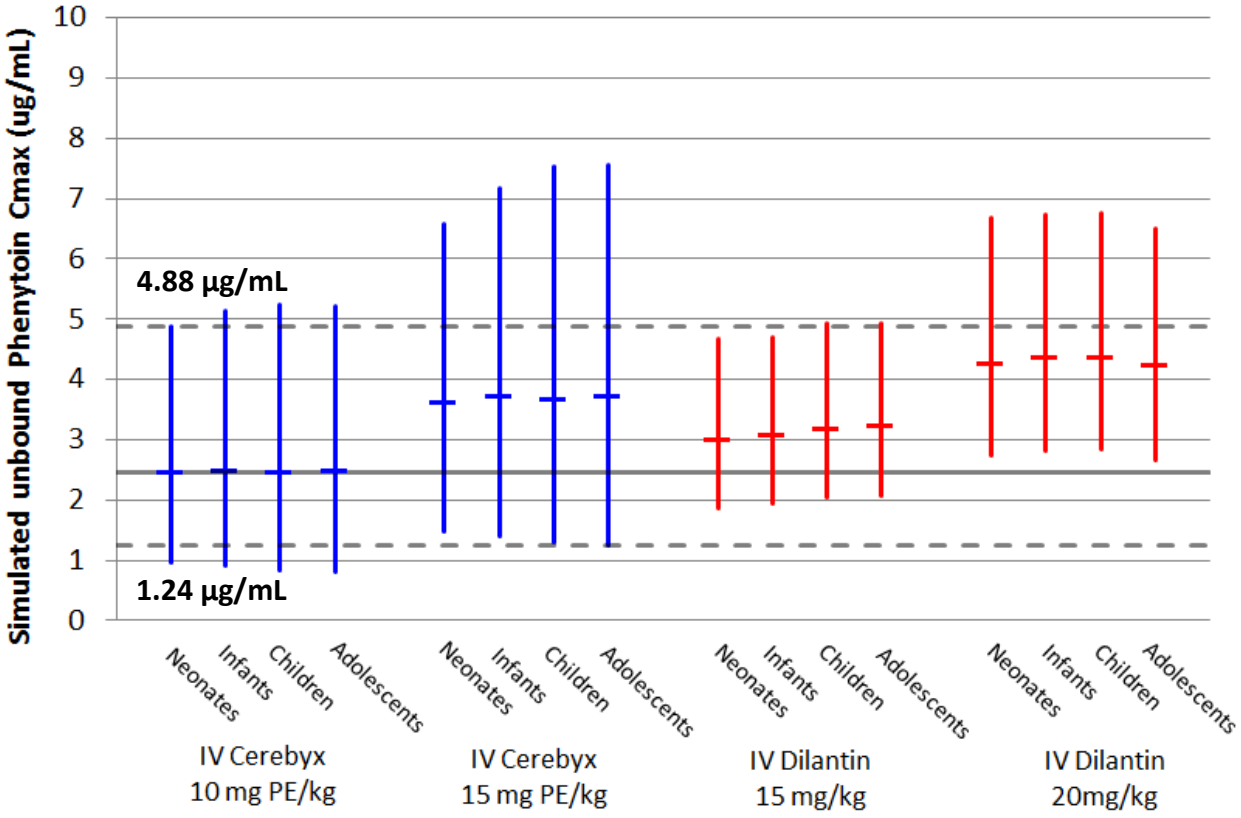
Please refer to the medical officer's review for addition details regarding safety.

Based on this analysis and discussions with the medical officer regarding the severity of the status epilepticus condition and the importance of halting seizure progression quickly, and in light of the safety profile in Study 982-028, **the final recommended loading dose for status epilepticus is 15-20 mg PE/kg**. This dose range is the same as the Cerebyx loading dose range approved for adult status epilepticus.

Loading Dose – Non-emergent: The current Cerebyx label allows for a "non-emergent" Cerebyx loading dose of 10-20 mg PE/kg in adults. The Sponsor proposed a 10-15 mg PE/kg non-emergent Cerebyx loading dose for pediatric patients. Sponsor believes that allowing a lower dose is appropriate for the non-emergent scenario which is a different situation than treating status epilepticus patients. Sponsor did not conduct analyses regarding the non-emergent loading dose.

The reviewer conducted an independent analysis to assess the non-emergent pediatric Cerebyx loading dose using the same methodology that was used for assessing the status epilepticus loading dose. Based on discussions with the medical officer, unlike the scenario for status epilepticus, the benefits of the 20 mg PE/kg loading dose in a non-emergent situation do not outweigh the risks. OCP agrees with the medical officer that the range 10-15 mg PE/kg, as the Sponsor proposed, was a reasonable range to assess for the potential non-emergent loading dose (and that doses above 15 mg PE/kg and/or doses below 10 mg PE/kg were not worth assessing). As such, a "revised reference range" of unbound phenytoin C_{max} values (90% PI 1.24 – 4.88 µg/mL) was determined based on PK data acquired from adults that received the labelled Cerebyx non-emergent loading dose for Cerebyx (10 – 15 mg PE/kg). The simulated unbound phenytoin C_{max} values resulting from 10 mg PE/kg as well as 15 mg PE/kg Cerebyx loading doses were computed in virtual pediatric patients across a range of ages from birth to adolescence (please see the figure below).

Figure 6: Simulated Unbound Phenytoin C_{max} Distribution for Pediatric Patients Versus Adults at Proposed Cerebyx Loading Dose for Non-emergent Indications



The horizontal grey solid and dashed lines represent the 90% PI (1.24 – 4.88 µg/mL) and median prediction (2.46 µg/mL) based on PK data from adults receiving IV Cerebyx doses in the range of 10-15 mg PE/kg in study 982-016. The vertical lines with intersecting horizontal lines represent the 90% PI and median prediction for pediatric patients grouped by age group, dose, and drug (Cerebyx or Dilantin). Blue represents simulated unbound C_{max} values following IV Cerebyx administration to virtual pediatric patients and red represents simulated unbound phenytoin C_{max} values following IV Dilantin administration to virtual pediatric patients.

The simulated unbound phenytoin C_{max} values from a 10 mg PE/kg Cerebyx loading dose were comparable to the FDA's "revised reference range" (1.24 – 4.88 µg/mL) for the approved adult non-emergent loading dose range of 10-15 mg PE/kg. As such, 10 mg PE/kg is a reasonable lower limit for the pediatric Cerebyx non-emergent loading dose.

Though there is a subset of virtual pediatric patients receiving Cerebyx 15 mg/kg administration with simulated unbound phenytoin C_{max} values higher than the FDA's "revised adult reference range", the majority of the virtual pediatric patient unbound phenytoin C_{max} distribution appears to overlap with the FDA's "revised reference range". Furthermore, based on these simulations, the predicted unbound phenytoin C_{max} distribution for the 15 mg PE/kg Cerebyx administration to virtual pediatric patients appears to have substantial overlap with the 20 mg/kg Dilantin administration (where 15-20 mg/kg is the approved pediatric loading dose range

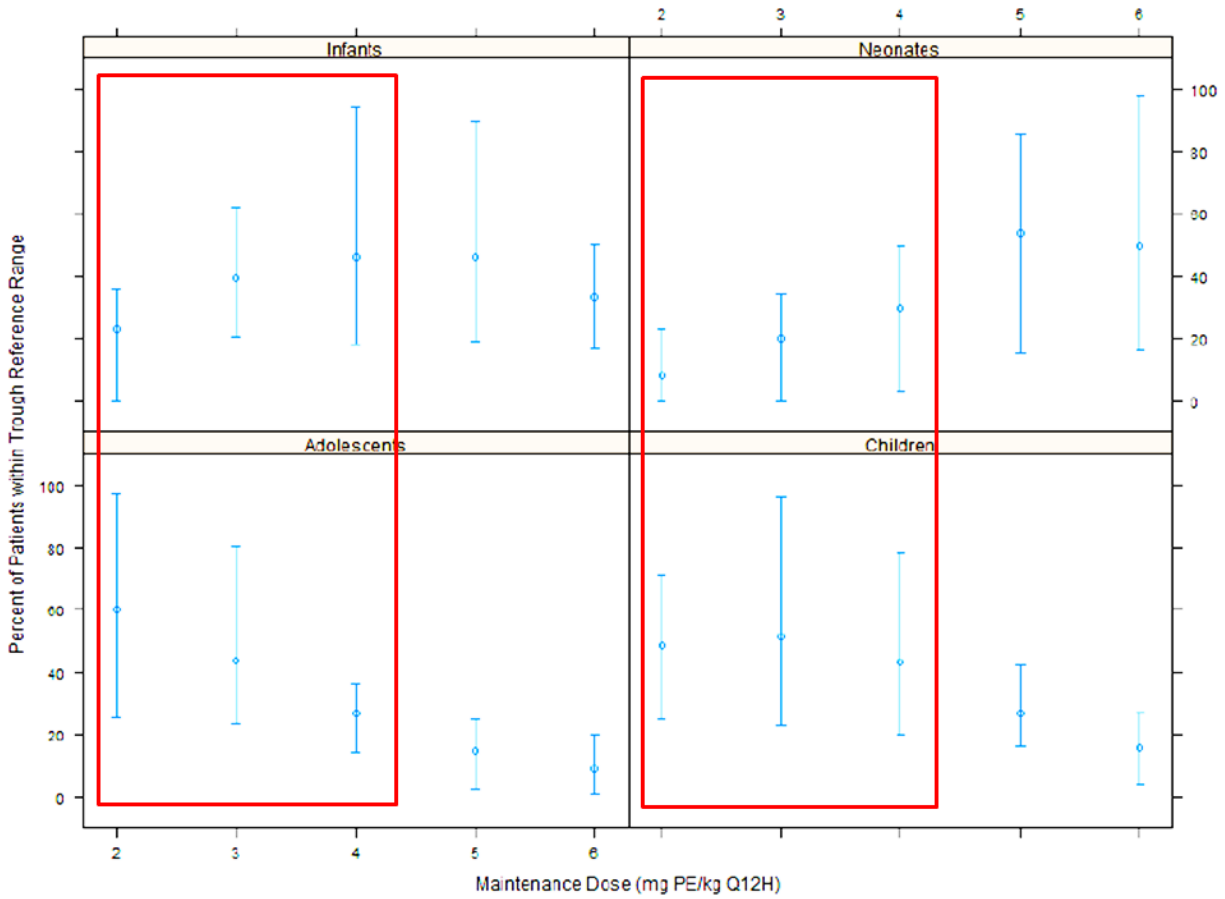
for non-emergent use in the current Dilantin label). **Overall, OCP agrees with the Sponsor regarding non-emergent loading dose values and recommends the range of 10-15 mg PE/kg**.

Maintenance Dose: The current Cerebyx label states that 1-2 µg/mL unbound phenytoin is a therapeutic concentration range. Sponsor utilized this therapeutic exposure range as a target for assessing pediatric maintenance dose regimens. Sponsor utilized PK simulations for various loading doses (10, 15, and 20 mg PE/kg) followed by 5 days of maintenance dosing at 2, 3, 4, 5, and 6 mg PE/kg/12 hours. These dose levels and dose intervals are based on adult labeled Cerebyx doses (2 and 3 mg PE/kg/12 hours; listed in Cerebyx label as 4-6 mg PE/kg/day) and doses achieved in pediatric Cerebyx trials (2, 3, 4 mg PE/kg/12 hours). Sponsor also assessed 5 and 6 mg PE/kg/12 hours maintenance dose regimens in their simulations. Sponsor assessed the proportion of patients with unbound phenytoin C_{trough} values that were within the labelled therapeutic range (1-2 µg/mL) for each of the dosing regimens.

Originally Sponsor intended to assess the C_{trough} values throughout the entire 5 days of simulated maintenance dosing. However, the current Dilantin and Cerebyx labels recommend drug monitoring to guide maintenance dosing. Therefore, the Sponsor, anticipating that drug monitoring would be applied to children as it is in adults, proposed to utilize the Day 2 simulated unbound phenytoin C_{trough} concentration for comparison with the therapeutic range of 1-2 µg/mL for assessing the performance of pediatric maintenance dosing regimens.

Sponsor's analyses demonstrate that for all 15 dosing regimens assessed, at best, no more than 60% of the virtual pediatric patients could be expected to have a Day 2 C_{trough} within the labelled 1-2 µg/mL therapeutic range of unbound phenytoin. Overall, the regimens performed similarly despite the different loading doses. The figure below shows the performance of the regimens which utilized 15 mg PE/kg loading dose and maintenance doses of 2-6 mg PE/kg/12 hours.

Figure 7: Proportion of Patients Predicted to have Day 2 trough in 1-2 µg/mL free phenytoin range by Age, Dose: IV Cerebyx



The x-axis represents the maintenance dose (mg PE/kg/12 hours) received subsequent to the 15 mg PE/kg loading dose, the y-axis represents the proportion of patients that are expected to have a unbound phenytoin trough concentration on Day 2 that falls within the target therapeutic range of 1-2 µg/mL. The blue dots represent point estimates and the blue vertical bars represent the 95% CI of the proportion estimate. The 4 panels represent the 4 pediatric age groups. The red boxes highlight the Sponsor's recommendations for the initial maintenance dose.

Source: summary-clin-pharm, page 38 of 46

In addition, Sponsor points out that the certainty in the proportion estimates is low (e.g. the 60% point estimate has a 95% CI of 25.5% to 97.5%). Sponsor concludes that increasing the maintenance dose beyond what was already assessed in the PK simulations is not likely to result in an increased proportion of patients with unbound phenytoin C_{trough} within the target range. As such, Sponsor did not conduct additional simulations at higher doses.

Overall, Sponsor concludes that a fixed maintenance dose is not suitable for children and that drug monitoring is necessary for guiding maintenance dosing. **Sponsor recommended an initial maintenance dose level of 2-4 mg PE/kg/12 hours. Sponsor also recommended using therapeutic drug monitoring (TDM) to guide all subsequent maintenance dosing. This recommendation is acceptable from an OCP perspective**.

Please refer to section 4.4 for additional details.

Infusion Rate: Sponsor is recommending an infusion rate of 2 mg PE/kg/minute (max 150 mg PE/minute) for treatment of SE as well as treatment of non-emergent situations.

Study 982-024 demonstrates that unbound phenytoin C_{max} is comparable between the 100 – 150 mg PE/kg/min range (14% greater following 150 mg PE/min than 100 mg PE/min; mean C_{max} of 3.18 µg/mL versus 2.78 µg/mL, respectively).

Infusion rates within this range have been utilized in clinical trials and are listed within the approved labels for Cerebyx and Dilantin. The infusion rates of 1-3 mg PE/kg/minute Cerebyx (maximum 150 mg PE/minute) were used in pediatric studies 982-028 and 982-016. In the PK simulations, the infusion rate of 2 mg PE/kg/minute (maximum 150 mg PE/minute) was applied. The 150 mg PE/minute rate is the upper limit for adults in the current approved Cerebyx label. The current Cerebyx label states that a 100-150 mg PE/min IV Cerebyx infusion rate can yield plasma free phenytoin concentrations over time that approximate those achieved when an equivalent dose of phenytoin sodium (e.g. parenteral Dilantin®) is administered at 50 mg/min. Also, the current Dilantin label indicates that IV pediatric phenytoin loading doses should be administered at a rate of 1-3 mg/kg/min, no faster than 50 mg/min, whichever is slower. The rate is not to exceed 50 mg/min for adults receiving Dilantin IV infusion.

The current Cerebyx label indicates that ECG, blood pressure, and respiratory function monitoring are essential during infusion and the period where maximum serum phenytoin concentrations may occur (up to 10 – 20 minutes post-infusion). Sponsor is recommending these monitoring assessments for pediatric patients as well.

[*Reviewer comment: Since the proposed infusion rate has been utilized in trial 982-028, there are no safety signals of concern according to the medical officer regarding this infusion rate, and since the PK analyses are based on the mean of the infusion rate range, 2 mg PE/kg/min, the* ***proposed infusion rate of 2 mg PE/kg/minute (max 150 mg PE/minute) during loading dose infusion is acceptable***.]

Maintenance Dose: Sponsor is recommending 1-2 mg PE/kg/minute (max 100 mg PE/minute) for all maintenance dosing. This infusion rate is slower than was assessed in clinical studies in pediatric patients (1-3 mg PE/kg; max 150 mg PE/minute). Sponsor indicates that adverse events such as vomiting (n=6) and nystagmus (n=5) occurred in patients with infusion rates > 3 mg/kg/min and/or doses > 20 mg/kg. Sponsor also indicates that the pediatric maintenance infusion rate in numerous European counties is 1-3 mg PE/kg/minute (max 100 mg PE/minute).

[*Reviewer comment: AUC is comparable between the 100 and 150 mg PE/min infusion rates in study 024. The 150 mg PE/minute infusion rate is expected to produce a 14% higher unbound*

C_{max} than the 100 mg PE/kg infusion rate. However, as the clinical scenario is not as urgent during maintenance, achieving a higher C_{max} is not as high of a priority during maintenance.

Overall, as the clinical situation during maintenance does not require achieving C_{max} values as high as for the loading dose administered during status epilepticus, and as the lower infusion rate may help minimize the chance of vomiting and/or nystagmus during maintenance therapy, then ***the Sponsor's proposal of 1-2 mg PE/kg/minute (max 100 mg PE/min) during maintenance is acceptable****.*]

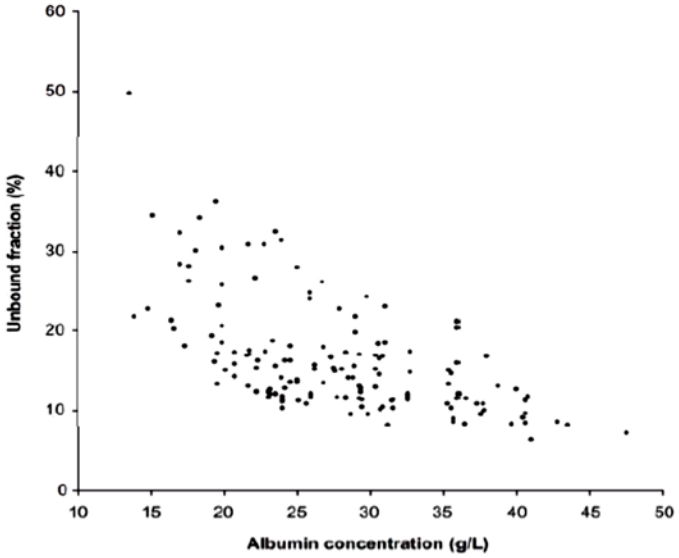
3.3.3 Is an alternative dosing regimen and/or management strategy required for subpopulations based on intrinsic factors?

Changes in protein binding are known to affect the unbound phenytoin exposure in adults. Sponsor attempted to assess what factors may affect the phenytoin protein binding in children. Both albumin and bilirubin are known to bind to phenytoin. The influence of albumin and bilirubin are relevant to children and were explored by the Sponsor.

Albumin: The current Dilantin label (11/30/2016 version) indicates that because the fraction of unbound phenytoin is increased in patients with hypoalbuminemia, the monitoring of phenytoin serum levels should be based on the unbound fraction in those patients. In addition, the current Cerebyx label (11/04/2016 version) indicates that unbound phenytoin concentrations may be more useful than total phenytoin plasma concentrations in patients with hypoalbuminemia.

Sponsor cited clinical studies published in the literature which assessed the relationship between albumin concentration and unbound phenytoin concentration. One relevant study was published by Heine et al. (2014) which identified and quantified covariates of protein binding on phenytoin pharmacokinetics in n=186 children. Serum albumin was one of the covariates found to significantly influence unbound phenytoin concentration. The following plot presents the observed relationship between serum albumin concentration and unbound phenytoin concentration in children (from the publication by Heine et al., 2014).

Figure 8: Relationship between Serum Albumin Levels and Unbound Fraction (as a Percentage of Total Phenytoin Concentration) in Children



Source: summary-clin-pharm.pdf, page 13 of 46

In a study Hennig et al. (2015), results of a population PK analysis of bound and unbound phenytoin concentration in n=32 critically ill children (age 0.08 to 17 years) suggested that albumin concentration was found to be a significant covariate for protein binding of phenytoin. In a study by Wolf et. al. (2006), a retrospective review of n=60 critically ill pediatric patients receiving phenytoin for treatment of seizures in the ICU, the authors observed an increase in free phenytoin fraction with increasing albumin concentration (though the relationship was non-linear).

[*Reviewer comment: These studies indicate that children demonstrate a trend of reduced unbound phenytoin concentration accompanying an increase in albumin concentration. This observation is expected in children as labeling language regarding hypoalbuminemia exists in the current Dilantin for adults and children as well as the Cerebyx label for adults. The current approved Cerebyx label is not in PLR format. However, the albumin label statements from the current approved Cerebyx label are proposed by the Sponsor for addition to sections 2.1, 2.5, 5.13, 7, 8.6, and 12.3.* ***The label statements proposed in sections 2.1, 2.5, 5.13, 7, 8.6, and 12.3 of the label adequately address the effect of hypoalbuminemia on phenytoin pharmacokinetics in children***.]

Bilirubin: The effect of bilirubin levels on unbound phenytoin concentration has been previously discussed in the clinical pharmacology review of NDA 020,450 signed on 09/16/2016. The clinical pharmacology reviewer concluded that the evidence presented in the literature reports (b) (4) not robust enough to draw a conclusion that there is a significant effect of total bilirubin concentrations on the unbound fraction of phenytoin. Sponsor has not provided any new information in the current submission (b) (4) . As such, the conclusion from the clinical pharmacology review of NDA 020450 signed on 09/16/2016 remains relevant. **The available information do not support a dose adjustment based bilirubin levels**.

Weight: Phenytoin pharmacokinetics are known to vary with body weight. The current approved Cerebyx loading dose for status epilepticus is 15-20 mg PE/kg for adults. The current Dilantin label recommends a loading dose of 10-15 mg/kg for adults and 15-20 mg/kg for children.

Sponsor conducted PK simulations to assess the appropriateness of weight-based Cerebyx loading doses in pediatric patients. The simulated unbound phenytoin concentration profiles following administration of Cerebyx loading doses to virtual pediatric patients were compared with a reference range predicted from adults in trial 982-016. The reference range was determined by extracting the 90% prediction interval (5^{th} percentile and 95^{th} percentile predicted based on a log-normal distribution) based on observed unbound phenytoin concentrations in adults after receiving Cerebyx loading doses (Study 982-016). Based on the results of these simulations, a weight-based dosing approach for pediatric loading doses (as is the current approach for adults) is reasonable.

Please refer to Section 3.3.2 and Appendix 4.4 for additional details regarding the modeling and simulation efforts that helped inform to these decisions.

3.3.4 Are there clinically relevant food-drug or drug-drug interactions and what is the appropriate management strategy?

As Cerebyx is to be administered intravenously, there is no concern regarding food-drug interactions with Cerebyx. The drug-drug interaction statements for adults are applicable to pediatric patients. There are no apparent drug-drug interaction concerns that are unique to pediatric patients at this time.

4. APPENDICES

4.1 Summary of Bioanalytical Method Validation and Performance

Fosphenytoin, total phenytoin, and free phenytoin were measured using high performance liquid chromatography (HPLC). Linear over the 0.25 – 250 µg/mL for fosphenytoin, 0.1 – 100 µg/mL total phenytoin, and 0.10 – 100 µg/mL free phenytoin. Assay precision is < 15% and accuracy is -4.6% to 6.4% for all three measurements.

The assays are acceptable.

4.2 Clinical PK and/or PD Assessments

The following table summarizes all the clinical trials which enrolled pediatric patients and collected pediatric PK data.

Table 4: Clinical Studies That Included Pediatric Patients Who Received Cerebyx

Study Number	Study Description	Subjects[a] ≤ 16 Years (N)	Age Range (years)	Pediatric PK Data
982-014	IM loading/maintenance in neurosurgery patients	2	16	No
982-015	IV loading/maintenance in neurosurgery patients	1	16	No
982-016	IV loading in patients with status epilepticus	10	5-14	Yes
982-021	IV loading dose	1	16	No
982-022	IM loading dose	1	16	No
982-028	Multiple dose PK study in pediatric patients; IM and IV loading/maintenance doses	115	1 day- 16.7	Yes
982-038	Single IV dose for treatment of status epilepticus	4	1-8	No

Source: CSRs 982-014, 982-015, 982-016, 982-021, 982-022, 982-028, and 982-038.
CSR = Clinical Study Report; IM = intramuscular; IV = intravenous; N = number of treated subjects; PK = pharmacokinetics.
a. Pediatric subjects were defined in these studies as ≤ 16 years of age.

Source: summary-clin-pharm.pdf, page 15 of 46

[*Reviewer comment: Studies 016 and 028 were the dedicated pediatric studies in the development program. The other studies had inclusion criteria to enroll adults and by chance happened to enroll some children. For example, studies 014, 015, 021, and 022 all enrolled 1 or 2 pediatric patients age 16 or older. In addition, though study 038 enrolled patients age 1-8 years old, PK data were not collected in the n=4 pediatric patients.*

Studies 982-016 and 982-028 are the main studies of interest for this submission as they have pediatric PK data collected from neonates, infants, children, and adolescents.]

4.3 Population PK and/or PD Analyses

Sponsor developed a population PK model to characterize the pharmacokinetics of fosphenytoin and its active metabolite phenytoin in adults and pediatric patients to assess the relationship of fosphenytoin PK and phenytoin PK with demographics and other covariates, and to conduct PK simulations for assessing potential fosphenytoin loading doses and maintenance doses.

The following is an overview of studies from which PK data were used to build the population PK model. Please refer to section 4.6 for additional details on these studies.

Study 982-028: Open-label, multi-center, non-comparative, study to assess PK and safety of IV and IM fosphenytoin administered as loading and maintenance doses in n=115 pediatric patients. Sponsor enrolled adolescents (n = 14; age 12 to 16 years), children (n = 45; age 2 to < 12 years), infants (n = 33; age 29 days to < 2 years), and neonates (n = 21; ages of birth to < 29 days).

PK samples were acquired according to 2 schedules: A) pre-dose, 0 (end of infusion), 15, 30, 60, and 120 minutes post-infusion or B) 0 (end of infusion), 30, and 60 minutes post-infusion. Unbound phenytoin was measured during the loading dose phase. Total phenytoin was measured during the loading and maintenance phases.

Age range was birth to 16.7 years. Mean body weight was 17.2 kg (range: 0.7 to 71 kg).

Mean IV fosphenytoin loading doses were 18.1, 17.9, 16.9, and 15.4 mg PE/kg, for neonates, infants, children, adolescents, respectively. The overall mean dose was 17.3 mg/kg. Mean IV fosphenytoin infusion rates were 2.08, 2.43, 2.20, 1.60 mg/kg/min for neonates, infants, children, adolescents. Overall mean infusion rate was 2.18 mg/kg/min, respectively.

Ogutu et al. (2003): Study to assess PK of IV phenytoin and IV fosphenytoin in n=38 pediatric subjects with a median age of 29 months (range 13 to 156 months). Subjects randomized to the phenytoin arm received an IV phenytoin 18 mg/kg loading dose administered over 20 minutes and a maintenance dose 2.5 mg/kg maintenance dose administered over 5 minutes, every 12 hours for 48 hours total. Patients in the IM fosphenytoin arm or IV fosphenytoin arm received the same dose, but in phenytoin equivalent (PE). Patients in the IV fosphenytoin arm received doses at a rate of 50 mg/min.

- The IV phenytoin arm had n=11 subjects (7 male, 4 female).
- The IV fosphenytoin arm had n=16 subjects (8 male, 8 female),
- The IM fosphenytoin arm had n=11 subjects (6 male, 5 female).

PK samples of total and free phenytoin were obtained 5, 10, 15, 20, 25, 30, 40, 60 min, and 2, 4, 6, 8, 12, 24, 36, 48, 54, 60 and 72 h post-dose. Sponsor requested PK data from Ogutu. The only PK data provided by the author to the Sponsor were from n=10 subjects (out of the n=11 subjects enrolled) in the IV phenytoin arm. This study is also referred to as "Study 1" in the Sponsor's submission.

Study 982-024: Randomized, open-label, 3-way crossover study to assess the PK of loading doses of IV fosphenytoin 1200 mg PE infused at 100 mg PE/min, IV fosphenytoin 1200 mg PE infused at 150 mg PE/min, and IV phenytoin 1200 mg infused at 50 mg/min to n=12 healthy adult men. Infusions were separated by a 1-week washout.

PK samples were collected at pre-dose, and at 2, 4, 8, 12, 18, 24, 30, 35, and 40 minutes and 1, 1.5, 2, 4, 6, 8, 12, 24, 36, 48, 60, 72, and 96 hours following the start of each infusion. Sponsor measured total fosphenytoin, total phenytoin, and unbound phenytoin.

Summary of PK Data:

In total, there were 591 measureable fosphenytoin concentrations and 225 BLQ fosphenytoin concentration measurements for the combined phenytoin and fosphenytoin model. There were 772 measureable free phenytoin concentration measurements and 109 BLQ free phenytoin concentration measurements available for the combined phenytoin and fosphenytoin PK model.

Population PK Model:

Sponsor utilized a two-compartment model with linear elimination for fosphenytoin linked to a two-compartment model with nonlinear elimination for free phenytoin as the structural model.

Fosphenytoin Parameters: fosphenytoin clearance (CL_f), fosphenytoin central compartment volume (V_{1f}), fosphenytoin intercompartmental clearance (Q_f), fosphenytoin peripheral volume of distribution (V_{2f}), and the fosphenytoin intramuscular absorption rate constant of (K_{51}).

Free Phenytoin Parameters: nonlinear free phenytoin clearance modeled via a Michaelis-Menten model (maximum rate of elimination [V_m], and concentration at which half-maximum rate is achieved [K_m]), phenytoin volume of distribution (V_3), phenytoin intercompartmental clearance (Q), and phenytoin peripheral volume of distribution (V_4).

Allometric scaling: CL_f, V_{1f}, Q_f, V_{2f}, V_M, V_3, Q, and V_4 had allometric scaling applied.

Interindividual variability: additive variance in log domain

Residual variability: additive + proportional, separate terms for each analyte. Covariance terms to account for potential correlation between fosphenytoin and free phenytoin within a sample.

Final model parameters are shown in Table 5.

Table 5: Parameters Estimates from Combined Fosphenytoin and Free Phenytoin Population Pharmacokinetics (Final Model; Model 700)

parameter	estimate	bootstrap 95% CI
$CL_f(exp(\theta_1))$ $\cdot(WT/70)^{0.75}$	33.1 L/h	(29.2,36.7)
$V1_f(exp(\theta_2))$ $\cdot(WT/70)^{1}$	6.5 L	(5.07,7.73)
$Q_f(exp(\theta_3))$ $\cdot(WT/70)^{0.75}$	3.8 L/h	(2.45,5.5)
$V2_f(exp(\theta_4))$ $\cdot(WT/70)^{1}$	1.69 L	(1.46,2.1)
$VM(exp(\theta_5))$ $\cdot(WT/70)^{0.75}$	483 mg/day	(438,524)
$V3(exp(\theta_6))$ $\cdot(WT/70)^{1}$ $\cdot exp(\theta_{10})^{pediatric}$	197 L 0.486	(134,270) (0.332,0.623)
$Km(exp(\theta_7))$	0.729 mcg/mL FIX	NA
$Q(exp(\theta_8))$ $\cdot(WT/70)^{0.75}$	474 L/h	(317,748)
$V4(exp(\theta_9))$ $\cdot(WT/70)^{1}$	293 L	(243,344)
$K51(exp(\theta_{11}))$	1.52 hr^{-1} FIX	NA
SharedETAscale(θ_{12})	0.231	(-0.378,1.03)
$\Omega^{1.1} CL_f$	0.26 (%CV=54.6)	(0.163,0.381)
$\Omega^{2.1} COV_{CL_f - V1_f}$	0.143 (r=0.0485)	(-0.00819,0.312)
$\Omega^{2.2} V1_f$	0.374 (%CV=67.4)	(0.0113,0.704)
$\Omega^{3.3} V3$	0.75 (%CV=106)	(0.417,1.22)
$\sigma^{1.1} prop_{Upht24}$	0.0306 (%CV=17.5)	(0.0203,0.0423)
$\sigma^{2.2} prop_{Fos24}$	0.0688 (%CV=26.2)	(0.0429,0.0985)
$\sigma^{3.3} add_{Upht24}$	0.335 (SD=0.579)	(0.0458,0.515)
$\sigma^{4.4} add_{Fos24}$	0.123 (SD=0.351)	(3.09e-06,0.161)
$\sigma^{5.5} prop_{Upht28}$	0.151 (%CV=38.8)	(0.0643,0.335)
$\sigma^{6.5} COV_{Upht28-Fos28}$	-0.0261 (r=0.365)	(-0.0599,0.0163)
$\sigma^{6.6} prop_{Fos28}$	0.0959 (%CV=31)	(0.0585,0.144)
$\sigma^{8.8} add_{Fos28}$	0.586 (SD=0.766)	(8.26e-06,3.85)

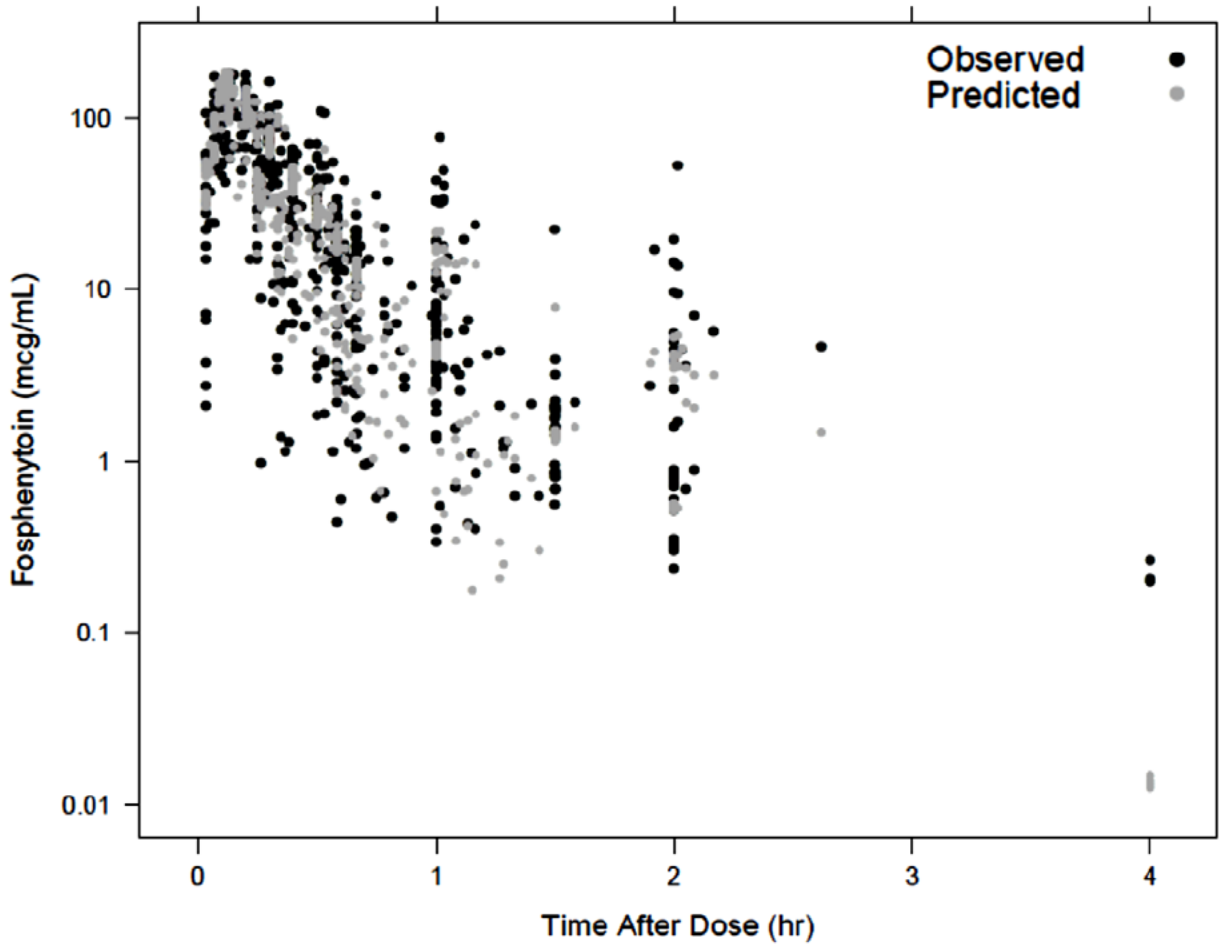
CL*f* = clearance fosphenytoin, V1*f* = central volume fosphenytoin, Q*f* = intercompartmental clearance fosphenytoin, V2*f* = peripheral volume fosphenytoin, VM = maximum elimination rate, V3 = central volume free phenytoin, Km = concentration at half-maximal elimination rate, Q = intercompartmental clearance free phenytoin, V4 = peripheral volume free phenytoin, K51 = IM absorption rate constant, pediatric = 0 if adult, pediatric=1 if pediatric, Ω*VM* = sharedETAscale*$\Omega^{3.3}$*V3* (**ETA3 is shared between V3 and VM**), WT=weight, Ω = interindividual variance (%CV), *σ* = residual variance (proportional (prop) or additive (add)), r = correlation, COV = covariance, SD = standard deviation (µmole/L), %CV = percent coefficient of variation, CI=confidence interval, Upht = unbound ("free") phenytoin, Fos = fosphenytoin, 24 = Study 982-24, 28 = Study 982-28.

Source: summary-ped-analysis-25jun2013.pdf, page 42 of 225

Initially, K_m estimates were too large and not consistent with the K_m value reported in the Deleu et al. (2005) study. In order to establish the model and allow for estimates of V_M for free phenytoin (abbreviated $V_{m,fp}$ in Sponsor's report), Sponsor fixed the value of K_m to 0.73 µg/mL in order to stabilize the model and allow an estimate of $V_{m,fp}$.

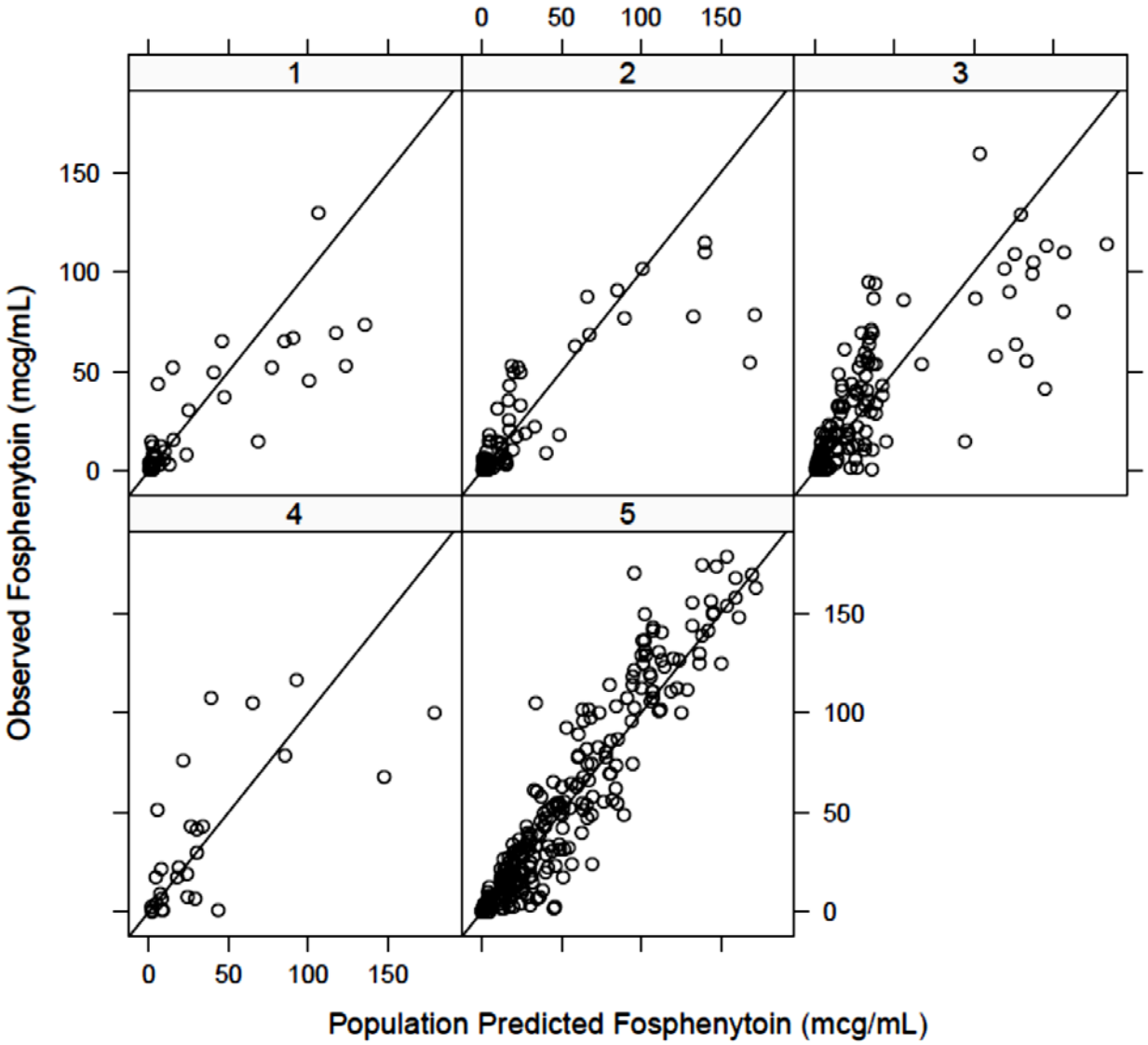
Model diagnostics will be presented for the total fosphenytoin component of the model first. Modeling diagnostics for the unbound phenytoin model will be presented subsequent to the diagnostics for total fosphenytoin.

Figure 9: Observed and Population Predicted Total Fosphenytoin vs. Time (Final Combined fosphenytoin / phenytoin PK model; Model 700)



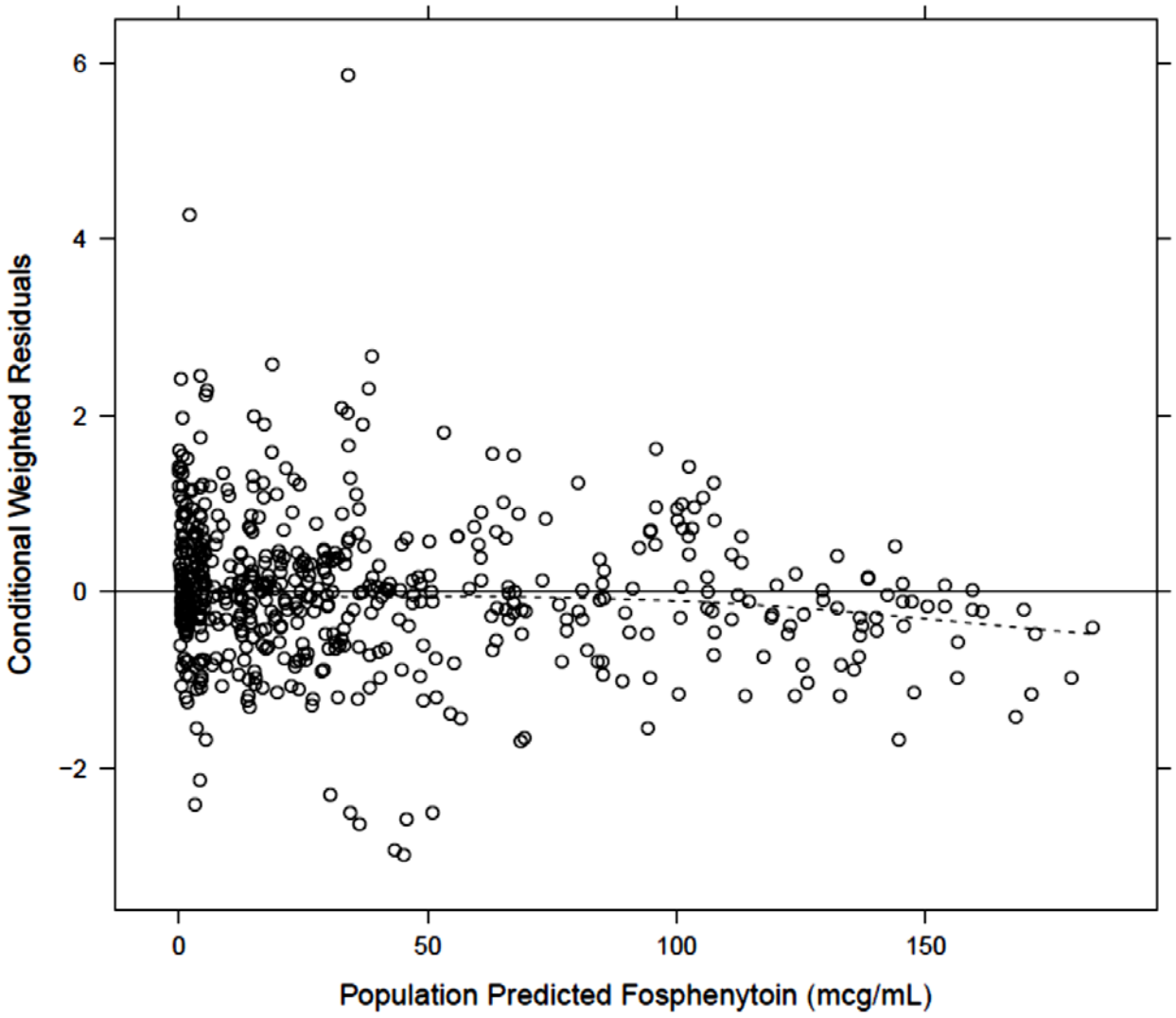
Source: summary-ped-analysis-25jun2013.pdf, page 102 of 225

Figure 10: Observed vs. *Population* Predicted Total Fosphenytoin by Age Category (Final Combined fosphenytoin / phenytoin PK model; Model 700)



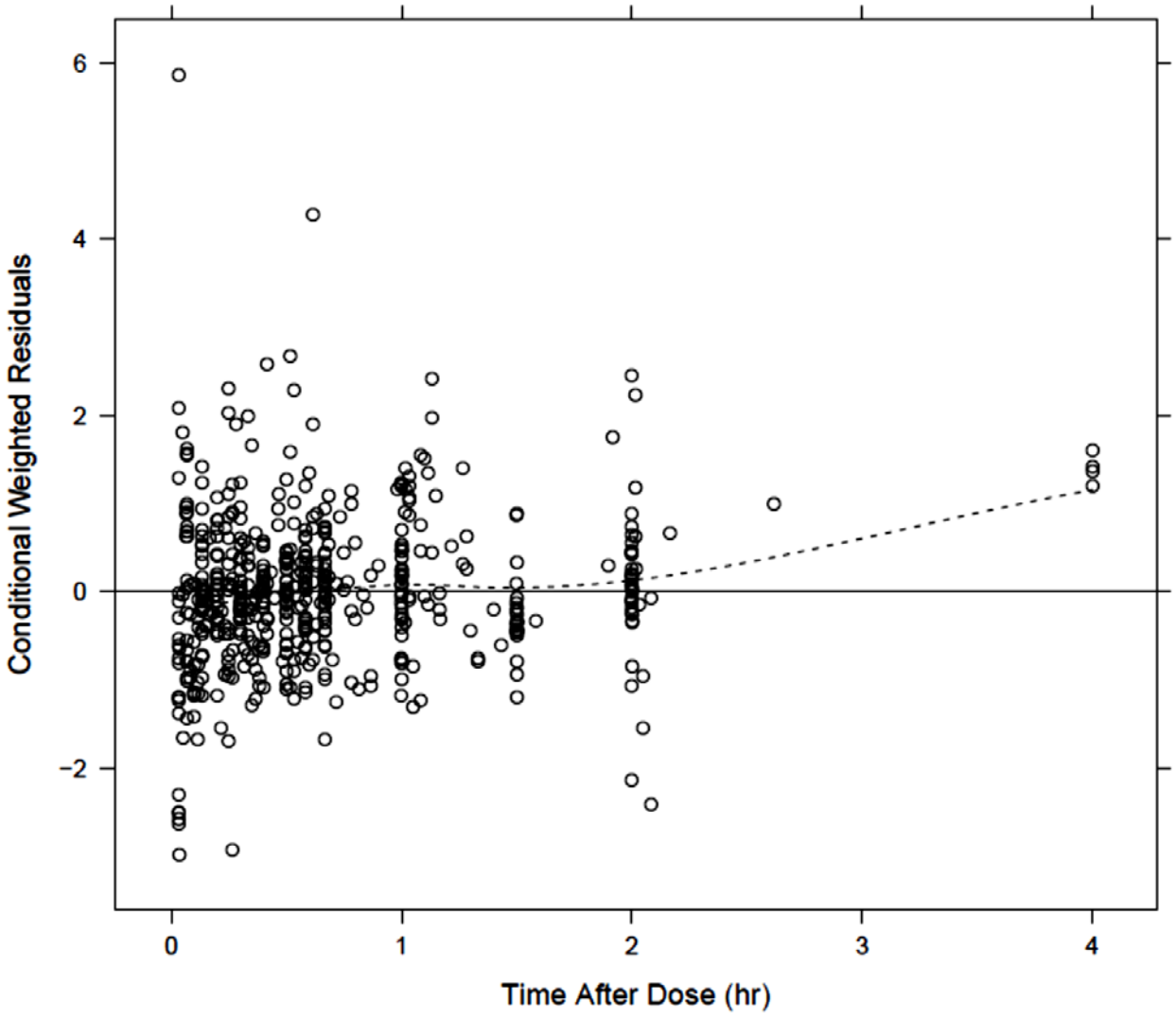
**(1=neonate, 2=infant, 3=child, 4=adolescent, 5=adult)*
Source: summary-ped-analysis-25jun2013.pdf, page 95 of 225

Figure 11: Conditional Weighted Residuals vs. Population Predicted Total Fosphenytoin (Final Combined fosphenytoin / phenytoin PK model; Model 700)



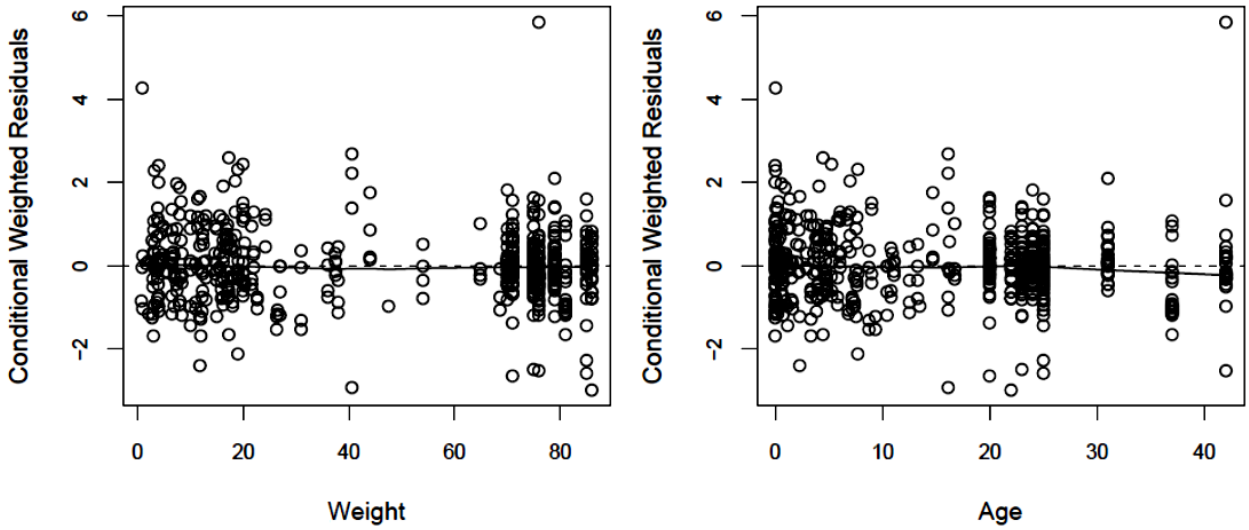
Source: summary-ped-analysis-25jun2013.pdf, page 99 of 225

Figure 12: Conditional Weighted Residuals vs. Time for Total Fosphenytoin (Final Combined fosphenytoin / phenytoin PK model; Model 700)



Source: summary-ped-analysis-25jun2013.pdf, page 101 of 225

Figure 13: Conditional Weighted Residuals vs. Covariate Factors For Total Fosphenytoin (Final Combined fosphenytoin / phenytoin PK model; Model 700)

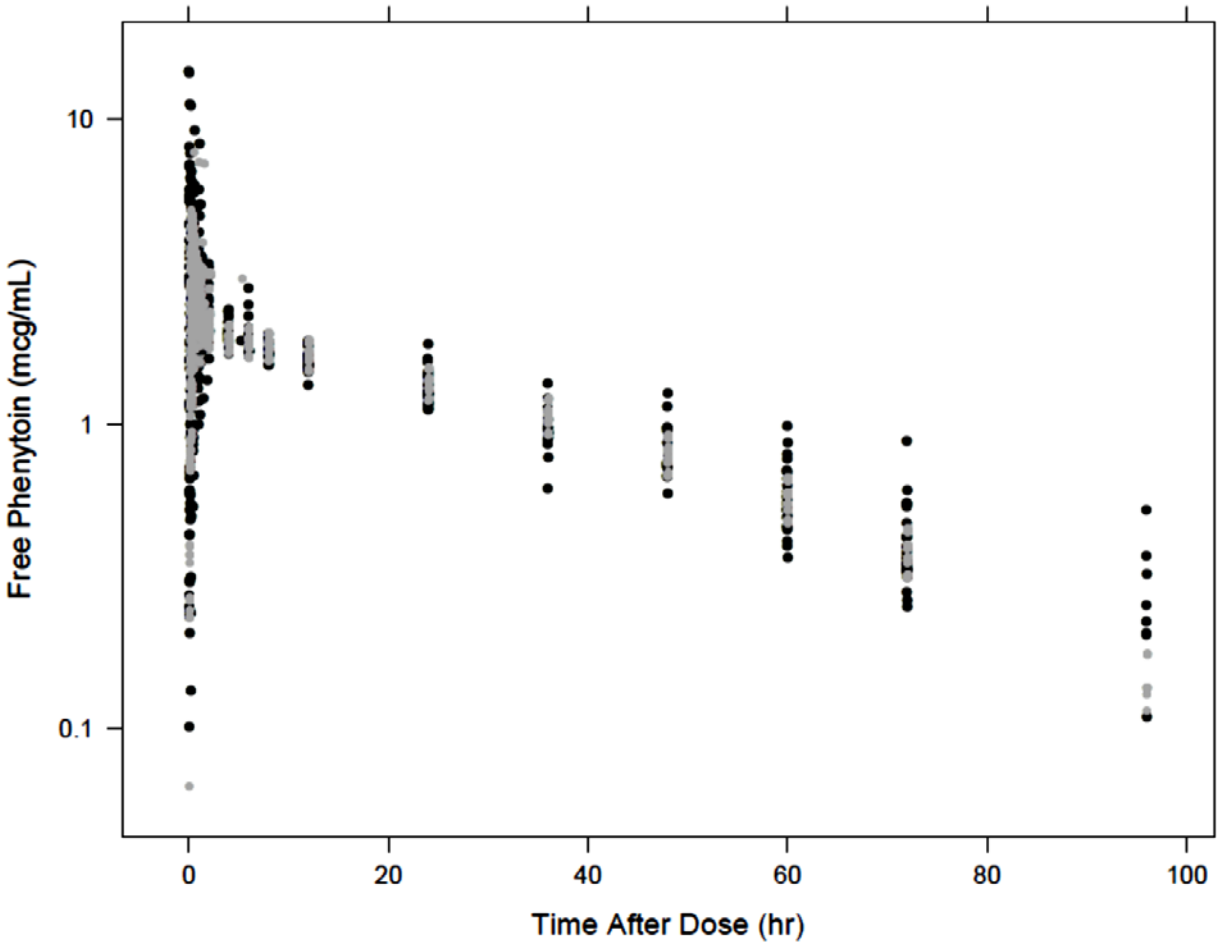


Source: summary-ped-analysis-25jun2013.pdf, page 116 of 225

[*Reviewer comment: The model adequately describes fosphenytoin pharmacokinetics. The results of these analyses indicate that there are no apparent covariates for conversion of fosphenytoin into phenytoin.*]

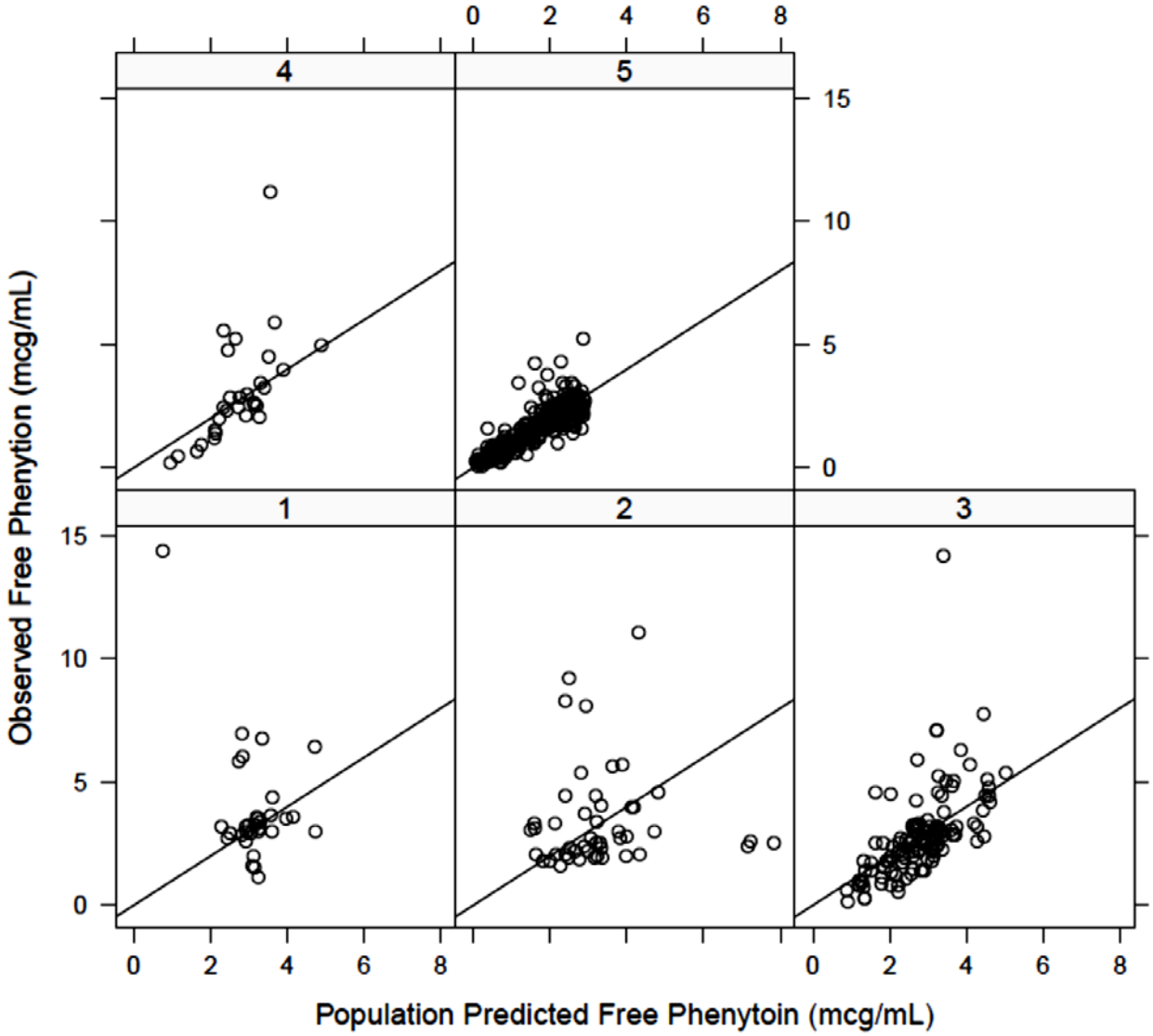
The following section covers the diagnostics for the free phenytoin section of the model. As FDA had requested during previous correspondence, Sponsor modelled the unbound phenytoin concentration and expressed diagnostic plots in terms of unbound phenytoin concentrations.

Figure 14: Observed and *Population* Predicted Free Phenytoin vs. Time (Final Combined fosphenytoin / phenytoin PK model; Model 700)



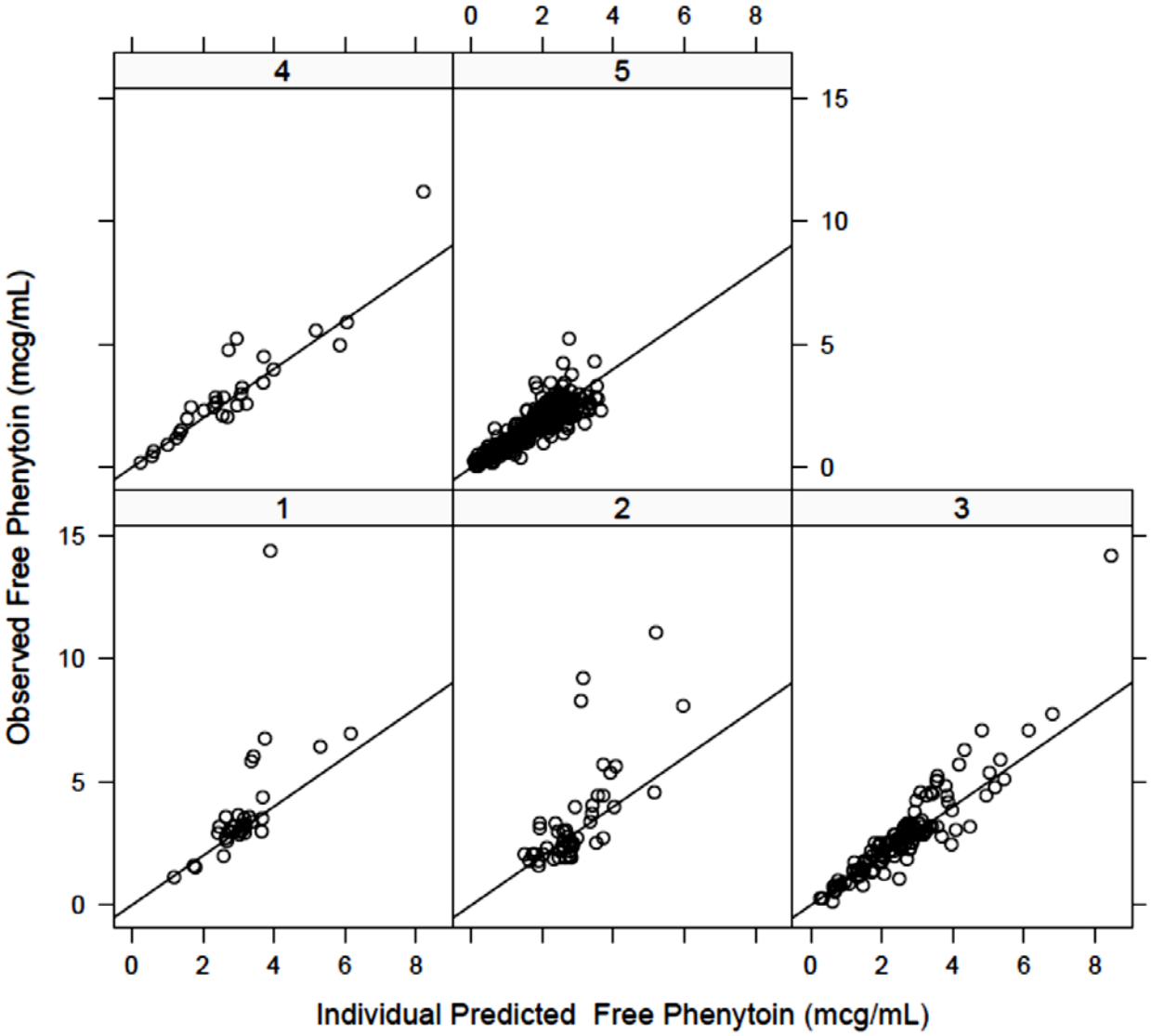
Source: summary-ped-analysis-25jun2013.pdf, page 112 of 225

Figure 15: Observed vs. *Population* Predicted Free Phenytoin by Age Category (Final Combined fosphenytoin / phenytoin PK model; Model 700)



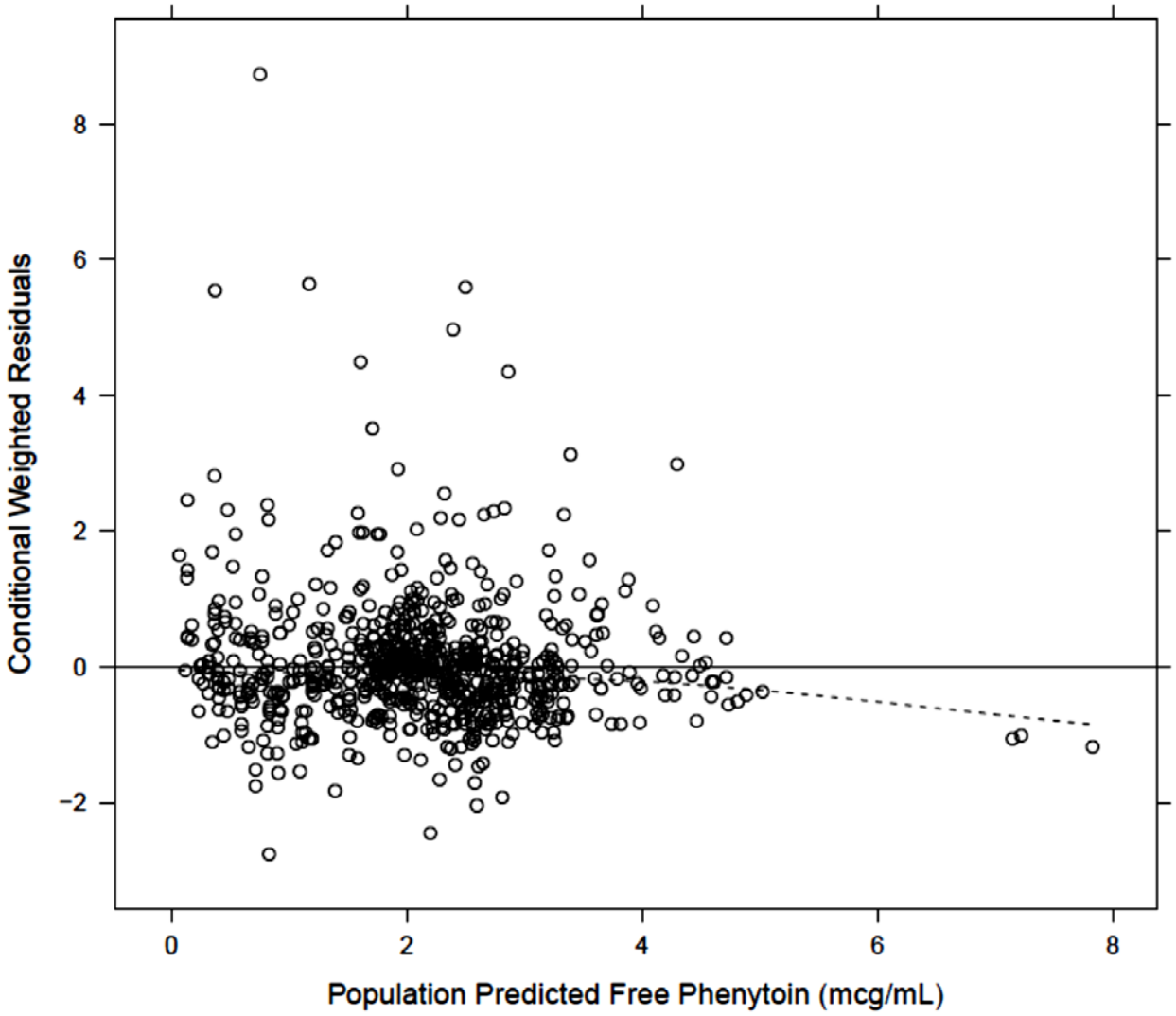
The label on each panel defines the age category
(1=neonate, 2=infant, 3=child, 4=adolescent, 5=adult)
Source: summary-ped-analysis-25jun2013.pdf, page 105 of 225

Figure 16: Observed vs. *Individual* Predicted Free Phenytoin by Age Category (Final Combined fosphenytoin / phenytoin PK model; Model 700)



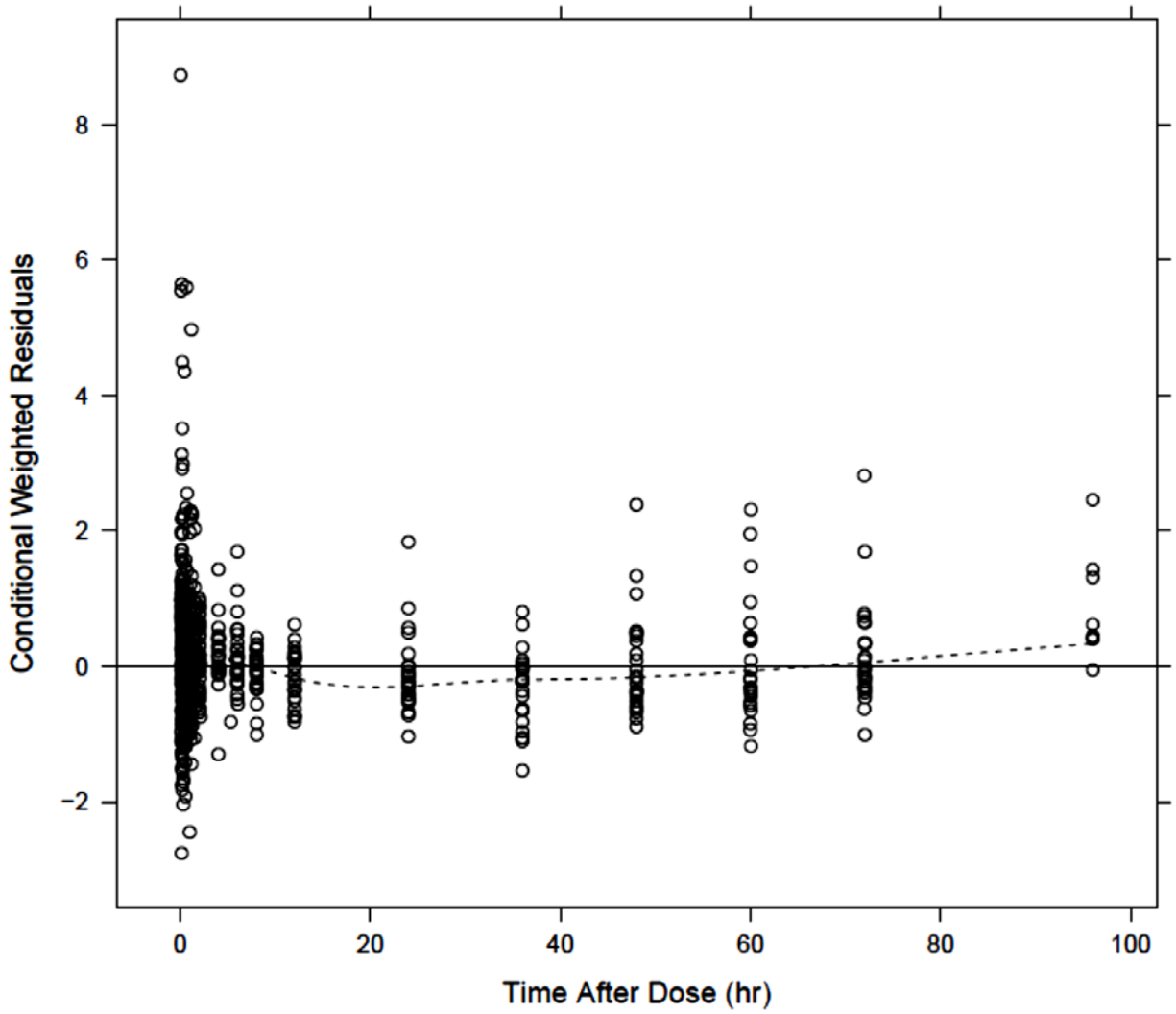
The label on each panel defines the age category
(1=neonate, 2=infant, 3=child, 4=adolescent, 5=adult)
Source: summary-ped-analysis-25jun2013.pdf, page 107 of 225

Figure 17: Conditional Weighted Residuals vs. *Population* Predicted Free Phenytoin (Final Combined fosphenytoin / phenytoin PK model; Model 700)



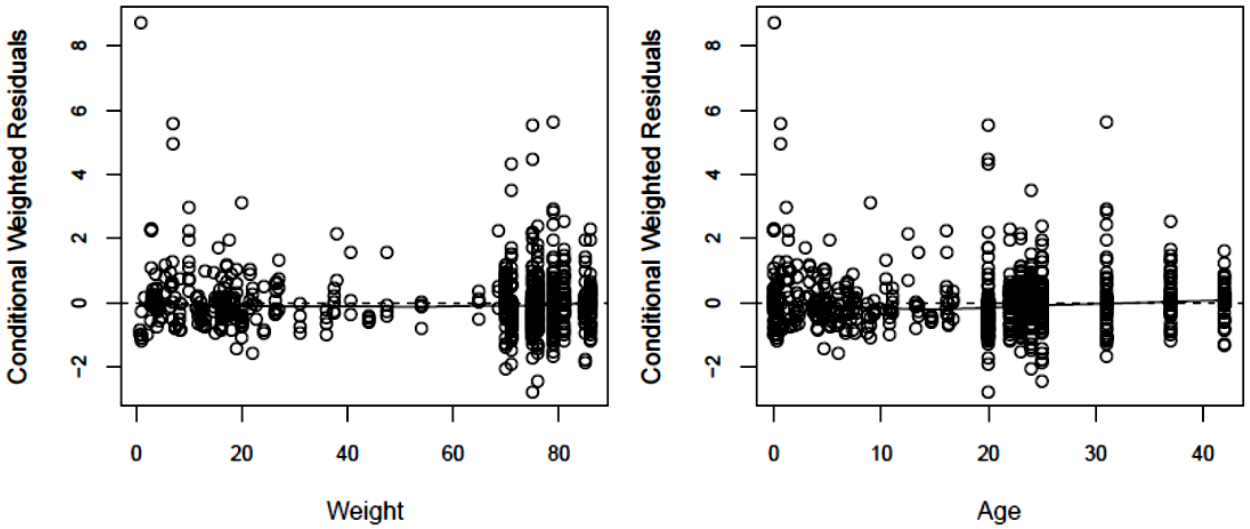
Source: summary-ped-analysis-25jun2013.pdf, page 109 of 225

Figure 18: Conditional Weighted Residuals vs. Time for Free Phenytoin (Final Combined fosphenytoin / phenytoin PK model; Model 700)



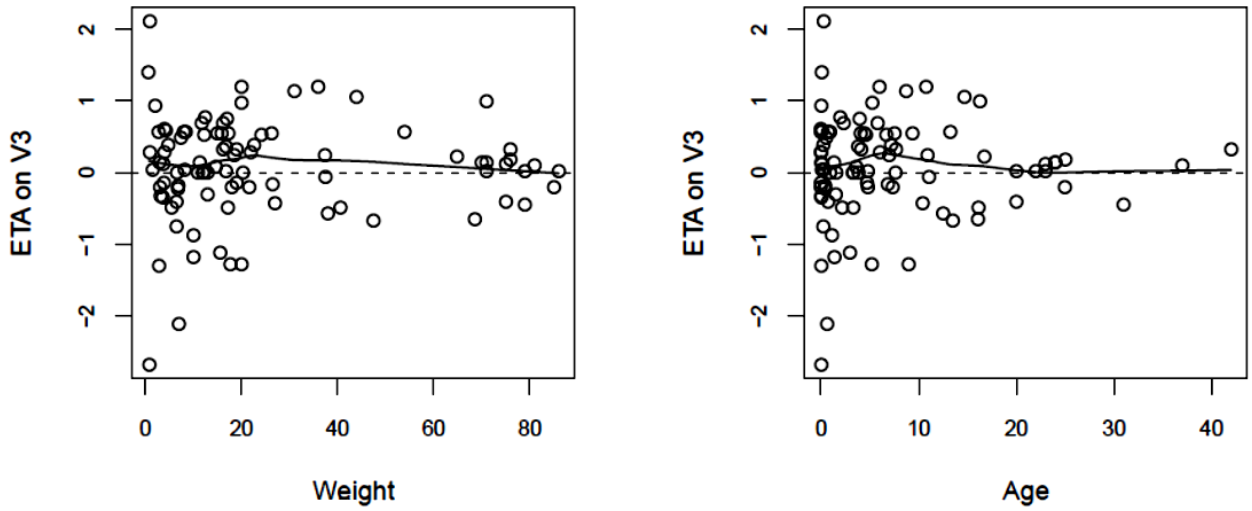
Source: summary-ped-analysis-25jun2013.pdf, page 111 of 225

Figure 19: Conditional Weighted Residuals vs. Covariate Factors For Free Phenytoin (Final Combined fosphenytoin / phenytoin PK model; Model 700)



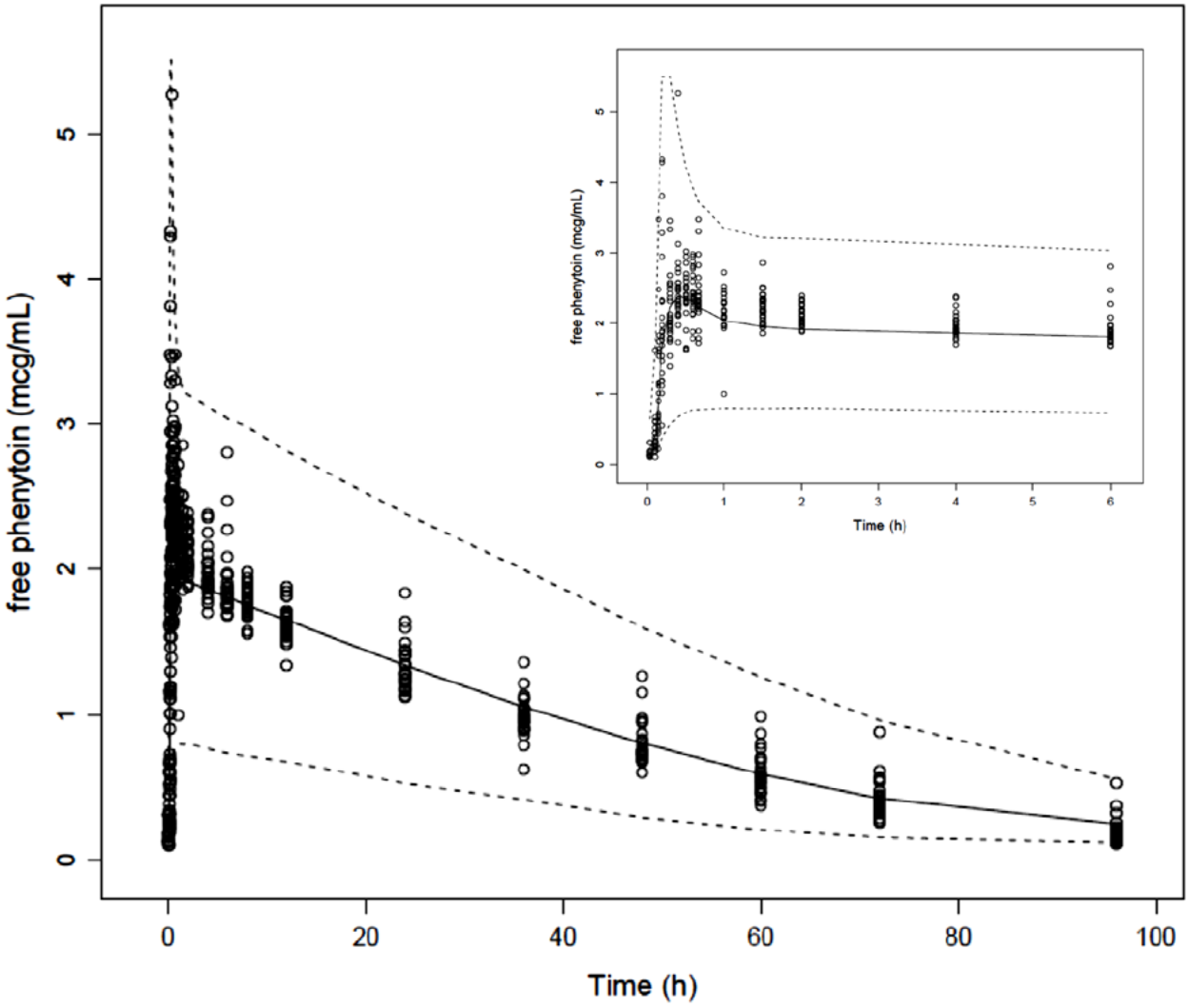
Source: summary-ped-analysis-25jun2013.pdf, page 117 of 225

Figure 20: ETA on V3 (ETA3) vs. Covariate Factors For Free Phenytoin (Final Combined fosphenytoin / phenytoin PK model; Model 700)



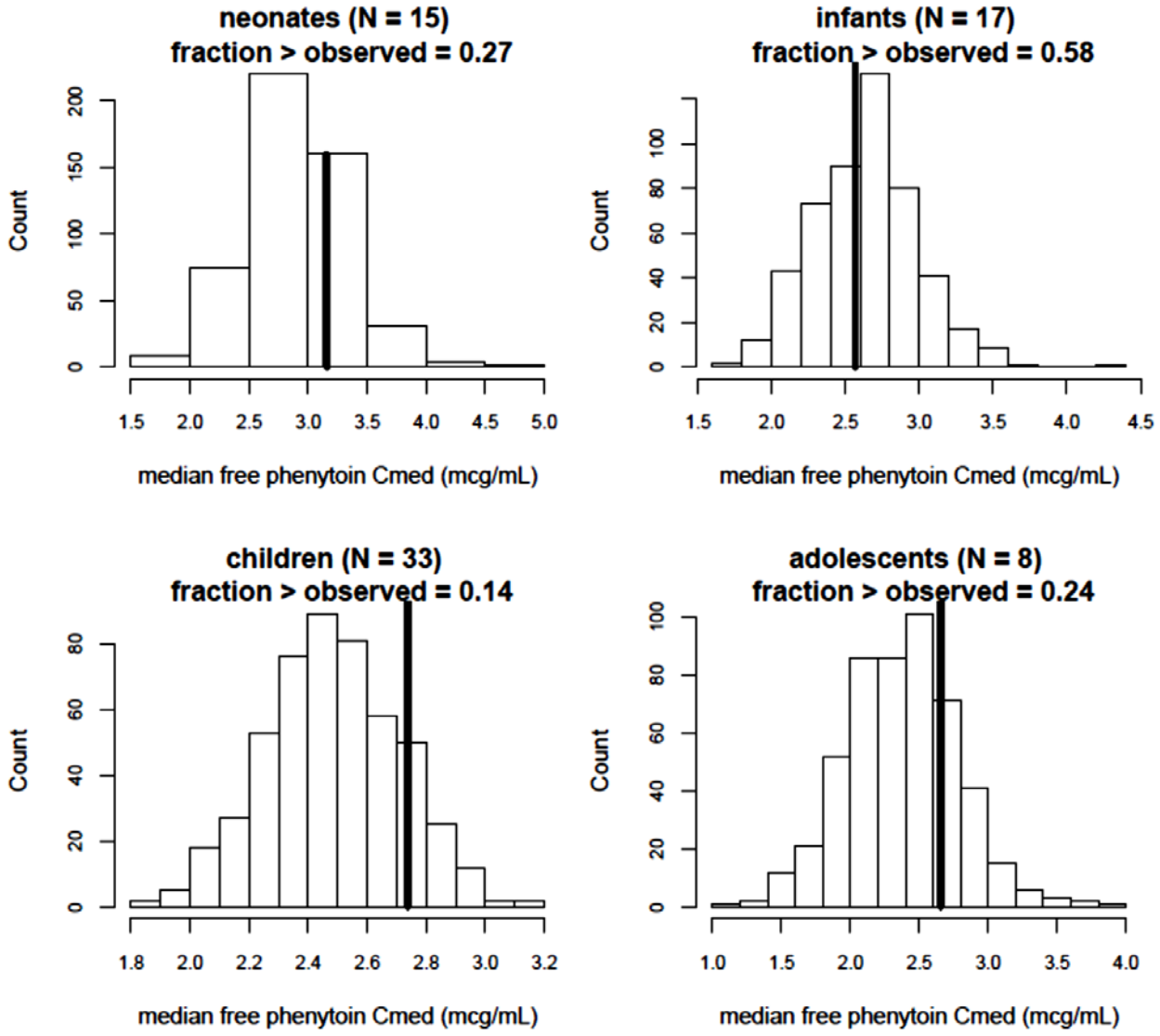
Source: summary-ped-analysis-25jun2013.pdf, page 120 of 225

Figure 21: Visual Predictive Check Plot for Free Phenytoin Study 982–24 in n=12 Adults (Final Combined fosphenytoin / phenytoin PK model; Model 700)



The inset figure is same PK profile with a focus the first 6 hours after infusion onset.
Source: summary-ped-analysis-25jun2013.pdf, pages 123,124 of 225

Figure 22: Histogram Predictive Check for Free Phenytoin in Study 982–28 in n=73 Pediatric Patients (Final Combined fosphenytoin / phenytoin PK model; Model 700)



100 trials were simulated with each trial containing 400 subjects (100 for each pediatric category, neonates, infants, children, and adolescents). Sponsor used the median concentration during a dosing interval (C_{med}) as the PK metric to assess in this predictive check. Simulated C_{med} values within each individual were summarized across 500 simulation replicates and expressed as histograms. The observed median C_{med} is indicated by a solid black line.

Source: summary-ped-analysis-25jun2013.pdf, pages 121 of 225

[*Reviewer comment: The Division of Pharmacometrics previously provided preliminary feedback on the Sponsor's population PK model. In a communication regarding modeling and simulation (archived under NDA 020450, signed on 01/15/2014), the Pharmacometrics reviewer stated:*

> *"An independent assessment by the pharmacometrics reviewer concludes the final phenytoin and fosphenytoin PK models general describe the observed and published data well. Specifically, the models were consistent with the observed data and no systematic bias was present. The models provided an adequate description of central tendency and variability of the free phenytoin concentrations".*

Upon more extensive review of the Sponsor's population PK model, this reviewer agrees with the previous assessment from the Pharmacometrics reviewer from the 01/15/2014 letter. ***Overall, the Sponsor's model adequately describes the unbound phenytoin concentration data and the total fosphenytoin concentration data****.*

Sponsor conducted reasonable assessments of covariates for both total fosphenytoin and unbound phenytoin. The Sponsor's analyses suggest that there are no covariates that are able to explain variability of total fosphenytoin in pediatric patients. The Sponsor implemented allometric scaling in order to account for changes in unbound phenytoin clearance due to maturation of organ systems involved in unbound phenytoin clearance.

The predictive check histograms indicate that model is able to reasonably approximate the observed central tendency most accurately in infants (e.g. in the histogram predictive check, 58% of the simulated unbound phenytoin C_{med} values are greater than the observed median unbound phenytoin C_{med} value).

In neonates, children, and adolescents, the model appears to under predict unbound phenytoin C_{med} (e.g. 27%, 14%, 24% of the simulated C_{med} values are greater than the observed unbound C_{med}, when ideally, ~50% of the simulated C_{med} values should be greater than the observed unbound C_{med}). However, in light of the overall observed variability in unbound phenytoin levels in adults receiving the approved Cerebyx dose (reviewer's revised 90% PI of ***1.04 to 8.51 µg/mL*** *in Study 982-16; see section 3.3.2 and section 4.4 for details), as well as the predicted variability in unbound phenytoin levels based on simulated administration of approved doses (15. 17.5, and 20 mg/kg) of Dilantin to virtual pediatric patients (90% PI range from 1.86 – 6.68 µg/mL for neonates, 1.94 - 6.73 µg/mL for infants, 2.04 – 6.75 µg/mL for children, and 2.07 – 6.49 µg/mL for adolescents [see section 4.4 for details]),* ***the model performs adequately for the PK simulations to inform pediatric Cerebyx dosing****.*

Please refer to section 4.4 for details regarding PK simulations used to inform pediatric Cerebyx dosing.]

4.4 Pharmacokinetic Simulation Analyses

Sponsor conducted pharmacokinetic simulations to inform the selection of the fosphenytoin loading and maintenance doses in pediatric patients. Sponsor utilized the combined population PK model for fosphenytoin and phenytoin described in section 4.3.

PK Simulations to Support Loading Dose Selection for Status Epilepticus: Sponsor engaged in several rounds of discussion with the Division of Neurology Products as well as OCP regarding the proposed modeling and simulation approach for determining a loading dose and maintenance dose. In regards to pharmacokinetic simulations for selecting the loading dose, the DNP told the Sponsor: "*… to immediately control status epilepticus… C_{max} is crucially important to derive fosphenytoin dosing*" (discussion archived in DARRTs under NDA 020,450 on 01/15/2014). In addition, the Sponsor was also advised to create a "reference range" of unbound phenytoin C_{max} values based approved Dilantin phenytoin IV dosing in adults. Sponsor followed this approach but instead of approved Dilantin doses, Sponsor used approved Cerebyx doses, which is acceptable. Sponsor generated a "reference range" based on observed unbound phenytoin C_{max} values measured after administering IV Cerebyx loading doses to adults in Study 982-016. Sponsor estimated the 90% PI by predicting the 5^{th} percentile and 95^{th} percentile of unbound observed phenytoin C_{max} (assuming log-normal C_{max} distribution) after administration of single doses of 10 to 20 mg PE/kg (target dose 18 mg PE/kg) to n=47 subjects (which includes n=5 pediatric patients). The reference range the Sponsor derived based on this method is **0.95 to 7.47 µg/mL**.

[*Reviewer comment: Please refer to the discussion at the end the status epilepticus loading dose section regarding the Sponsor's 90% PI for the 982-016 PK data.*]

IV Cerebyx Simulations: Sponsor conducted 100 simulated loading dose administrations to n=400 subjects (n=100 in each pediatric group; neonates, infants, children, and adolescents). Sponsor simulated unbound phenytoin concentration profiles following IV Cerebyx loading doses of 10, 15, and 20 mg PE/kg administered at 2 mg PE/kg/min (max 150 mg PE/infusion), respectively. Unbound phenytoin concentrations were simulated at each minute after infusion onset and for up to 15 minutes post-infusion. The maximum concentration within that interval was selected as C_{max}.

Sponsor computed the proportion of virtual patients which fell below, within, and above the aforementioned "reference range" of unbound phenytoin C_{max} values (see table below).

Table 6: Proportion of Patients Predicted to have unbound Phenytoin C_{max} fall within the Sponsor's Reference Range Following Simulated IV Cerebyx Loading Dose Administration by Age and Dose

Age Category	Loading Dose (mg PE/kg)	Below Reference Range (<0.95 µg/mL) N = 400[a]	Within Reference Range (0.95-7.47 µg/mL) N = 400[a]	Above Reference Range (>7.47 µg/mL) N = 400[a]
		% of Patients (95% CI)[b]		
Neonates	10	11.0 (3.75, 19.5)	89.0 (80.5, 96.2)	0.00 (0.00, 0.250)
	15	3.38 (0.500, 8.01)	95.8 (90.2, 99.5)	0.500 (0.00, 3.26)
	20	1.25 (0.00, 4.76)	94.9 (87.7, 99.4)	3.38 (0.120, 9.38)
Infants	10	12.6 (4.48, 24.4)	87.2 (75.6, 95.5)	0.00 (0.00, 0.750)
	15	4.25 (0.750, 11.2)	94.5 (86.5, 99.2)	1.25 (0.00, 4.89)
	20	1.25 (0.00, 5.91)	92.5 (84.0, 98.9)	5.50 (1.00, 13.0)
Children	10	16.8 (6.69, 26.7)	82.8 (73.1, 92.7)	0.250 (0.00, 1.50)
	15	6.50 (1.50, 13.5)	91.4 (81.4, 97.8)	2.25 (0.250, 6.75)
	20	2.75 (0.00, 8.38)	89.4 (79.4, 96.8)	8.00 (1.87, 16.4)
Adolescents	10	19.5 (9.36, 28.9)	80.2 (71.0, 90.4)	0.250 (0.00, 2.38)
	15	7.25 (1.62, 13.9)	89.8 (80.1, 97.5)	3.00 (0.00, 9.75)
	20	2.75 (0.250, 8.38)	86.9 (74.1, 95.5)	10.0 (2.25, 22.0)

Source: summary-simulations-27-aug2015.pdf, pages 9 of 30

IV Dilantin Simulations: Sponsor conducted 100 simulated loading dose administrations to n=400 subjects (n=100 in each pediatric group; neonates, infants, children, and adolescents). Sponsor simulated IV Dilantin loading doses of 15, 17.5, and 20 mg /kg at 1, 2, and 3 mg/kg/min (max 50 mg/min). Concentrations were simulated at each minute for up to 15 minutes post-infusion. The maximum concentration within this time interval was selected as C_{max}.

Sponsor computed the proportion of virtual patients which fell below, within, and above the aforementioned "reference range" of unbound phenytoin C_{max} values when administered IV Dilantin loading doses (see the table below).

Table 7: Proportion of Predicted Unbound phenytoin C_{max} Values Within the Sponsor's Reference Range Following Simulated IV Dilantin Loading Dose Administration By Age Group and Dose

Age Category	Dose	Below Reference Range (<0.95 mcg/mL)	Within Reference Range (0.95-7.47 mcg/mL)	Above Reference Range (>7.47 mcg/mL)
Neonates	15 mg/kg	0.00 (0.00, 1.52)	100 (98.0, 100)	0.00 (0.00, 1.00)
	17.5 mg/kg	0.00 (0.00, 0.525)	100 (97.0, 100)	0.00 (0.00, 3.00)
	20 mg/kg	0.00 (0.00, 0.00)	98.0 (92.5, 100)	2.00 (0.00, 7.52)
Infants	15 mg/kg	0.00 (0.00, 1.00)	100 (98.5, 100)	0.00 (0.00, 1.00)
	17.5 mg/kg	0.00 (0.00, 0.525)	100 (96.0, 100)	0.00 (0.00, 4.00)
	20 mg/kg	0.00 (0.00, 0.00)	98.0 (91.0, 100)	2.00 (0.00, 9.00)
Children	15 mg/kg	0.00 (0.00, 0.525)	100 (98.0, 100)	0.00 (0.00, 1.52)
	17.5 mg/kg	0.00 (0.00, 0.00)	99.0 (96.0, 100)	1.00 (0.00, 4.00)
	20 mg/kg	0.00 (0.00, 0.00)	97.0 (92.5, 100)	3.00 (0.00, 7.52)
Adolescents	15 mg/kg	0.00 (0.00, 1.00)	100 (98.0, 100)	0.00 (0.00, 1.52)
	17.5 mg/kg	0.00 (0.00, 0.525)	99.5 (97.0, 100)	0.00 (0.00, 3.00)
	20 mg/kg	0.00 (0.00, 0.00)	98.0 (93.5, 100)	2.00 (0.00, 6.52)

Source: summary-simulations-1mar2016.pdf, page 7 of 10

The following two tables summarize the distribution of simulated unbound phenytoin C_{max} values following IV Cerebyx and IV Dilantin administration to virtual pediatric patients.

Table 8: Predicted Unbound phenytoin C_{max} Values Following Simulated IV Cerebyx Loading Dose Administration By Age Group and Dose

Age Category	Fosphenytoin Loading Dose	Median (95%CI) of Simulated C_{max} Values of Free Phenytoin (µg/mL)		
		5th percentile	50th percentile	95th percentile
Neonates	10 mg PE/kg	0.970 (0.640, 1.33)	2.42 (2.03, 2.86)	4.88 (3.83, 6.27)
	15 mg PE/kg	1.47 (0.970, 2.05)	3.60 (3.05, 4.22)	6.58 (5.31, 8.50)
	20 mg PE/kg	1.99 (1.31, 2.82)	4.71 (4.05, 5.58)	8.11 (6.52, 10.1)
Infants	10 mg PE/kg	0.910 (0.580, 1.34)	2.45 (2.02, 2.90)	5.14 (3.91, 6.31)
	15 mg PE/kg	1.40 (0.880, 2.02)	3.68 (3.04, 4.30)	7.16 (5.64, 8.66)
	20 mg PE/kg	1.91 (1.21, 2.74)	4.85 (4.05, 5.71)	8.80 (7.05, 10.6)
Children	10 mg PE/kg	0.840 (0.530, 1.30)	2.42 (1.99, 2.88)	5.23 (4.00, 6.81)
	15 mg PE/kg	1.29 (0.810, 1.95)	3.64 (3.01, 4.35)	7.53 (5.85, 9.66)
	20 mg PE/kg	1.76 (1.12, 2.67)	4.86 (4.05, 5.70)	9.44 (7.38, 11.7)
Adolescents	10 mg PE/kg	0.800 (0.480, 1.24)	2.45 (1.77, 2.92)	5.20 (3.89, 7.60)
	15 mg PE/kg	1.24 (0.760, 1.93)	3.68 (2.70, 4.41)	7.56 (5.68, 11.0)
	20 mg PE/kg	1.70 (1.05, 2.59)	4.92 (3.62, 5.93)	9.65 (7.44, 13.8)

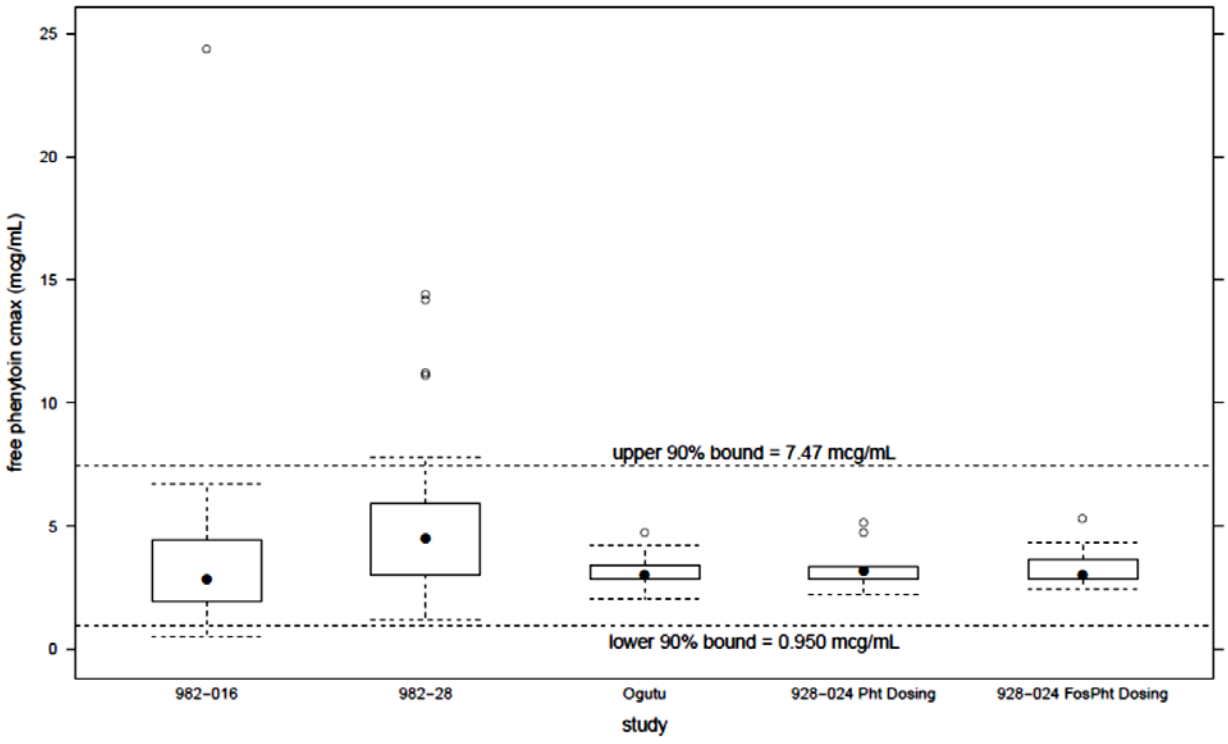
Source: summary-simulations-27-aug2015.pdf, pages 18 of 30

Table 9: Predicted Unbound phenytoin C_{max} Values Following Simulated IV Dilantin Loading Dose Administration By Age Group and Dose

Age Category	Phenytoin Loading Dose	Median (95%CI) of Simulated C_{max} Values of Free Phenytoin (µg/mL)		
		5th percentile	50th percentile	95th percentile
Neonates	15 mg/kg	1.86 (1.51, 2.26)	2.97 (2.66, 3.33)	4.67 (4.06, 5.54)
	17.5 mg/kg	2.34 (1.85, 2.77)	3.64 (3.27, 4.10)	5.73 (4.89, 6.78)
	20 mg/kg	2.73 (2.18, 3.22)	4.24 (3.81, 4.77)	6.68 (5.66, 7.88)
Infants	15 mg/kg	1.94 (1.51, 2.25)	3.04 (2.73, 3.38)	4.70 (4.09, 5.66)
	17.5 mg/kg	2.41 (1.95, 2.76)	3.68 (3.31, 4.15)	5.80 (4.88, 6.98)
	20 mg/kg	2.82 (2.31, 3.22)	4.33 (3.81, 4.83)	6.73 (5.66, 8.21)
Children	15 mg/kg	2.04 (1.58, 2.37)	3.16 (2.83, 3.53)	4.94 (4.14, 5.73)
	17.5 mg/kg	2.47 (1.90, 2.86)	3.80 (3.38, 4.22)	5.91 (4.93, 7.03)
	20 mg/kg	2.83 (2.19, 3.27)	4.34 (3.86, 4.84)	6.75 (5.63, 8.08)
Adolescents	15 mg/kg	2.07 (1.61, 2.39)	3.21 (2.83, 3.55)	4.94 (4.22, 5.86)
	17.5 mg/kg	2.36 (1.85, 2.76)	3.71 (3.28, 4.13)	5.73 (4.89, 6.78)
	20 mg/kg	2.65 (2.09, 3.11)	4.20 (3.73, 4.64)	6.49 (5.53, 7.63)

Source: summary-simulations-1mar2016.pdf, page 8 of 10

Figure 23: Distribution of Free Phenytoin C_{max} Following Cerebyx Administration in All Available Studies (Ogutu, 982-016 and 982-028 are Pediatric Studies; 982-024 is in Adults)



Dashed lines are Sponsor's 90% prediction interval (5th percentile and 95th percentile predicted based on a log-normal distribution) derived from observed unbound phenytoin concentrations in adults after receiving Cerebyx loading doses (Study 982-016).

Source: summary-clin-pharm.pdf, page 32/46

Overall, Sponsor concludes that a the 15 mg PE/kg loading dose is appropriate as Sponsor believes this dose provides an acceptable balance of maximizing the chance that children will be exposed to unbound phenytoin concentration within the desired C_{max} range and minimize the chance of being below or above that range.

[*Reviewer comment: The approved Cerebyx loading dose range for status epilepticus in adults is 15-20 mg PE/kg. The Sponsor's "reference range" for unbound phenytoin C_{max} from Study 982-016 included doses that were outside of the approved dosing range (e.g. < 15 mg PE/kg in some patients and > 20 mg PE/kg in other patients). When including observed unbound phenytoin C_{max} values in the dataset only for the approved Cerebyx status epilepticus dose range of 15-20 mg PE/kg, and for adults only (n=25), the revised 5^{th} and 95^{th} percentiles become* ***1.04 to 8.51 µg/mL****. This range has an increased lower bound and increased upper bound in comparison to the Sponsor's reference range of 0.95 to 7.47 µg/mL. Though the reviewer's "revised reference range" seems more appropriate for assessing the pediatric dose regimens, the difference between the two reference ranges is not expected to be clinically significant.*

Comparison of the Sponsor's simulated unbound phenytoin C_{max} distributions following IV Cerebyx administration to virtual pediatric patients with the "revised reference range" can be found in Figure 5 in section 3.3.2. When comparing the reviewer's "revised reference range" to the predicted unbound phenytoin C_{max} values after administration of IV Cerebyx and IV Dilantin to virtual pediatric patients, at both 15 and 20 mg PE/kg, unbound phenytoin exposures in pediatric patients can be expected to be comparable to those in adults receiving Cerebyx 15-20 mg PE/kg. Use of the Sponsor's reference range also supports this conclusion.

Sponsor also conducted PK simulations to predict unbound phenytoin C_{max} values following Dilantin administration. Based on these simulations, 15 and 20 mg/kg IV Dilantin can also be expected to produce unbound phenytoin C_{max} values in pediatric patients that fall within the reviewer's "revised reference range". The distribution of unbound phenytoin C_{max} values measured in the Ogutu et al. (2003) study (see Figure 3 in section 3.2 as well as Figure 23 in section 4.4) also fall within the "revised reference range" of 1.04 – 8.51 µg/mL.

The simulations suggest that a subset of pediatric patients receiving the 20 mg PE/kg Cerebyx dose may experience elevated unbound phenytoin C_{max} values above the adult unbound phenytoin C_{max} reference range (e.g. a subset of infants, children, and adolescents receiving IV 20 mg PE/kg Cerebyx are predicted to have unbound phenytoin C_{max} values greater than 8.51 µg/mL; See Figure 5 in section 3.3.2). However, the medical officer has expressed the view that status epilepticus is a life-threatening emergency and that successful treatment demands an adequate unbound phenytoin C_{max} be attained within a short time period. In addition, pediatric patients were exposed to doses greater than 15 mg PE/kg. For example, in trial 982-028, neonates, infants, children, and adolescents received mean (± SD) fosphenytoin loading doses of

18.1 (± 3.8), 17.9 (± 6.3), 16.9 (± 3.1), and 15.4 (± 3.4) mg PE/kg, respectively. The overall mean (± SD) loading dose was 17.3 (± 4.5) mg PE/kg in pediatric study 982-028. There were no significant safety concerns associated with these doses according to the medical officer (please refer to the "Safety Information" text in section 3.3.2). Also, please refer to the review written by the medical officer for additional details.

As such, rather than the Sponsor's proposed 15 mg PE/kg loading dose, ***the recommended Cerebyx loading dose for status epilepticus will be 15-20 mg PE/kg****.*]

PK Simulations to Support Non-emergent Indications:

Sponsor is proposing 10 to 15 mg PE/kg as a loading dose for non-emergent Cerebyx use. Sponsor provides the following rationale for the proposed non-emergent loading dose:

> "The medical need for treatment of patients in non-emergent situations is different than those with SE. In non-emergent situations, a provision to allow for a lower loading dose seems appropriate, which is consistent with that in adults in the USPI. Therefore, for non-emergent situations, a loading dose of fosphenytoin of 10 to 15 mg PE/kg is recommended in pediatric patients."

Sponsor has not conducted any PK simulations to support the proposed loading dose for non-emergent indications.

[*Reviewer comment: This reviewer conducted an independent analysis to assess the non-emergent indication loading dose using the same approach as was employed to assess the loading dose for status epilepticus. In terms of a reference range of unbound phenytoin C_{max} values for the loading dose for non-emergent indications, the current approved Cerebyx loading dose for non-emergent indications is 10-20 mg PE/kg in adults. However, the Sponsor has proposed a lower range, from 10-15 mg PE/kg. In the opinion of the medical officer, unlike the status epilepticus indication, the benefits of the 20 mg PE/kg dose do not outweigh the risks in the context of a non-emergent indication. As such, the 20 mg PE/kg dose was not explored in these analyses. Thus, and the doses of 10-15 mg PE/kg was utilized for developing a reference range of unbound C_{max} values in adults following a Cerebyx loading dose for non-emergent indications.*

Using the observed unbound C_{max} values observed in adults that received 10-15 mg PE/kg (n=10) in study 982-016, assuming a log-normal distribution of unbound phenytoin C_{max} values, the 90% PI for unbound phenytoin C_{max} is ***1.24 to 4.88 µg/mL****. This unbound phenytoin C_{max} reference range for the 10-15 mg PE/kg adult dose range was compared with the simulated*

pediatric exposures for 10 and 15 mg PE/kg in neonates, infants, children, and adolescents (see Figure 6 in section 3.3.2). Overall, IV Cerebyx 10 mg PE/kg dose is predicted to produce a distribution of unbound phenytoin C_{max} values in all pediatric age groups that is comparable to the adult reference range for 10-15 mg PE/kg Cerebyx (and IV Dilantin 15 mg/kg).

Though the majority of pediatric patients receiving the 15 mg PE/kg Cerebyx loading dose are predicted to have unbound phenytoin C_{max} within the adult reference range, the simulations suggest that a subset of pediatric patients receiving the 15 mg PE/kg IV Cerebyx dose may experience higher unbound phenytoin C_{max} values than adults receiving 10-15 mg PE/kg Cerebyx. However, the unbound phenytoin C_{max} distribution predicted for pediatric patients receiving 15 mg PE/kg Cerebyx has substantial overlap with distribution of unbound phenytoin C_{max} values predicted in pediatric patients receiving the approved 20 mg/kg Dilantin non-emergent loading dose ((see Figure 6 in section 3.3.2).

Overall, the Sponsor's proposed loading dose range of 10 to 15 mg PE/kg for non-emergent indications in pediatric patients is acceptable.]

PK Simulations to Support Maintenance Dose Selection: The current approved Cerebyx label states the following regarding therapeutic unbound phenytoin levels: "*Phenytoin doses are usually selected to attain therapeutic plasma total phenytoin concentrations of 10-20 µg/mL, (unbound phenytoin concentrations of 1 to 2 µg/mL)*". In previous discussions with the Sponsor, OCP approved of the Sponsor's approach to utilize the labeled 1 to 2 µg/mL free phenytoin concentration range as a target for selecting maintenance dosing for pediatric patients (review of NDA 020,450 signed on 08/10/2011). Sponsor conducted PK simulations to predict the unbound phenytoin trough concentration (C_{trough}) for 15 Cerebyx regimens: 3 loading doses (10, 15, and 20 mg PE/kg) combined with 5 maintenance doses (2, 3, 4 mg PE/kg/12 hours based on dosing rates administered in Study 982-08 , and two additional dose levels, 5 and 6 mg PE/kg/12 hours). Infusion rates were 2 mg PE/kg/minute (≤ 150 mg PE/minute).

Sponsor's original plan was to compare the unbound phenytoin C_{trough} at days 2, 3, 4, and 5 with the therapeutic range of 1-2 µg/mL from the current approved Cerebyx label. However, Sponsor ultimately used only the C_{trough} at Day 2 in order to assessed maintenance regimens.

[*Reviewer comment: Sponsor has suggested that, in line with current Phenytoin and Fosphenytoin treatment practice of performing therapeutic drug monitoring, pediatric maintenance doses will be guided by therapeutic drug monitoring as well. This recommendation is acceptable to OCP and to the medical officer. As such, the Sponsor has proposed to provide labeling recommendations for the initial pediatric maintenance dose, and recommend that subsequent maintenance doses be guided by TDM.* ***This is acceptable to OCP****.*]

For these reasons, the assessment of the maintenance dose will focus on the "early" unbound phenytoin trough concentrations achieved (those predicted to occur on Day 2) and less emphasis will be placed on later predicted unbound phenytoin trough concentrations (as by Day 5, the dose will likely be adjusted due to TDM, and thus the Day 5 predictions at the constant dose regimen are not likely to be relevant).]

Sponsor provided a plot that shows the proportion of patients with Day 2 trough unbound phenytoin concentrations that fall within the 1-2 µg/mL target concentration range for the 15 mg PE/kg loading dose followed by maintenance doses of 2, 3, 4, 5, and 6 mg PE/kg/12 hours (please refer to Figure 7 in section 3.3.2).

Sponsor points out that by Day 2, regardless of loading dose or maintenance dose selection, no more than 60.0% of patients in any pediatric group can be expected to achieve a C_{trough} in the target range of 1-2 µg/mL. Furthermore, the estimate of 60.0% (in reference to the adolescent patients receiving a 2 mg PE/kg/12 hours in Figure 7 in section 3.3.2) and many other proportion point estimates have low certainty (in other words, a wide 95% CI; e.g. the 95% CI is 25.5% to 97.5% for the aforementioned 60.0% point estimate). In addition, Sponsor points out that incremental dose increases beyond 4 mg PE/kg/12 hours did not appear to result in an increased percentage of subjects that achieve trough unbound phenytoin concentrations in the 1-2 µg/mL target range. As such, Sponsor did not explore doses greater than 6 mg PE/kg/12 hours.

Overall, the Sponsor concludes that fixed maintenance doses will not be suitable and there is a need for individualization of therapy based on monitoring of trough phenytoin levels and adjusting doses to target the 1-2 µg/mL unbound phenytoin trough concentration.

Therefore, Sponsor is **recommending an initial maintenance dose of 2-4 mg PE/kg/12 hours (4-8 mg PE/kg/day) at an infusion rate of 1-2 mg PE/kg/minute (≤ 100 mg PE/minute). Sponsor is recommending TDM to guide all subsequent maintenance doses**.

[*Reviewer comment: OCP agrees with the Sponsor that doses greater than 6 mg PE/kg/12 hours are unlikely to result in a greater proportion of patients falling within the target therapeutic concentration range of 1-2 µg/mL unbound phenytoin.*

In trial 982-028, neonates, infants, children, and adolescents received mean (± SD) fosphenytoin maintenance doses of 5.5 (± 2.3), 8.1 (± 4.6), 6.5 (± 3.1), and 5.5 (± 2.1) mg PE/kg/24 hours, respectively. The overall mean (± SD) maintenance dose was 6.7 (± 3.6) mg PE/kg/24 hours. There were no significant safety concerns during the maintenance period identified by the medical officer. The proposed initial maintenance dose range (e.g. 2-4 mg PE/kg/12 hours = 4-8 mg PE/kg/24 hours) overlaps with (e.g. neonates, children, and adolescents) or is less than (e.g.

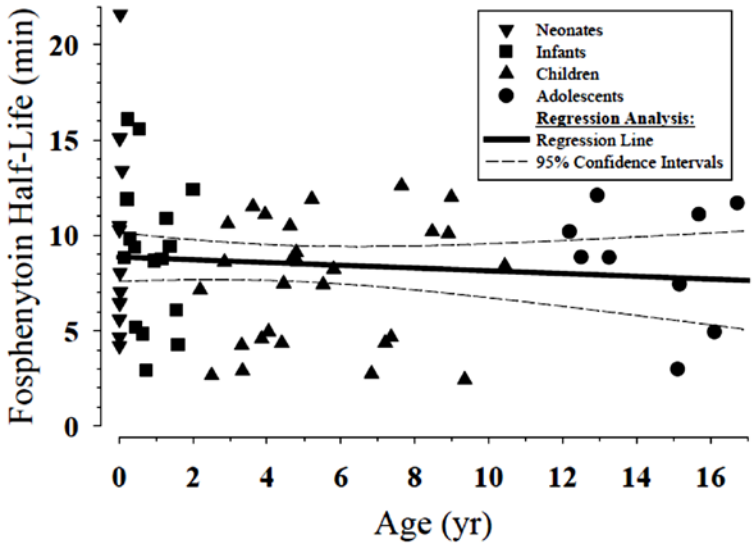
infants) the mean maintenance dose administered to each pediatric patient group in trial 982-028.

Considering the variability and uncertainty in achieving the target concentration at the various maintenance dose regimens, it is not clear that there is justification to make more specific dose recommendations. As such, ***the Sponsor's proposal for the initial maintenance dose of 2-4 mg PE/kg/12 hours as well as the recommendation for TDM to guide subsequent doses is acceptable***.]

4.6 Individual Study Summaries

4.6.1 Study 982-028 (Phase 3)

<table>
<tr><td>Study Report#</td><td>RR 720-03794</td></tr>
<tr><td>Title</td><td>An Open-Label, Safety, Tolerance, and Pharmacokinetic Study of Intravenous and Intramuscular Fosphenytoin (Cerebyx®) in Children (Protocol 982-28)</td></tr>
<tr><td>Objectives</td><td>Primary: Assess PK of IV and IM fosphenytoin in pediatric epilepsy patients.
Secondary: Assess safety</td></tr>
<tr><td>Study Design</td><td>Open-label, single-arm study</td></tr>
<tr><td>Duration</td><td>Loading dose, 14 days of maintenance dosing, follow-up 12-24 hours after last dose</td></tr>
<tr><td>Dosage and Administration</td><td>Loading dose: 10 to 20 mg PE/kg fosphenytoin IV or fosphenytoin IM.
Maintenance dose and regimen: individualized to maintain desired plasma total phenytoin concentrations (≥ 10 µg/mL total phenytoin) for up to 14 days.
IV Infusion Rates: 1 to 3 mg PE/kg/min (maximum 150 mg PE/min)
IM Injections: Single or multiple injections</td></tr>
<tr><td>PK Assessment</td><td>Plasma PK Samples: pre-dose, 15, 30, and 60 minutes following loading dose (except in patients < 6 years old, or weighing < 3 kg who had samples only at 30 and 60 minutes post-infusion). In patients who received IM fosphenytoin, an additional sample was collected at 120 minutes following IM administration.</td></tr>
<tr><td>Bioanalytical Methods</td><td>HPLC-MS/MS Analytical Methods for Fosphenytoin Plasma Concentrations
<table>
<tr><td>Analyte Name</td><td>Total fosphenytoin</td></tr>
<tr><td>Linear Range</td><td>0.403 – 466 µg/mL</td></tr>
<tr><td>QC Accuracy</td><td>-0.277% to 0.334%</td></tr>
<tr><td>QC Precision, Standards precision</td><td>0.940% to 13.6%.</td></tr>
<tr><td>LLOQ (total fosphenytoin)</td><td>0.403 µg/mL</td></tr>
<tr><td>Analyte Name</td><td>free fosphenytoin</td></tr>
<tr><td>LLOQ (free fosphenytoin)*</td><td>0.240 µg/mL</td></tr>
</table>
* Equilibrium dialysis performed prior to HPLC analysis
HPLC-MS/MS Analytical Methods for Phenytoin Plasma Concentrations
<table>
<tr><td>Analyte Name</td><td>Total phenytoin</td></tr>
<tr><td>Linear Range</td><td>0.0795 to 40.2 µg/mL</td></tr>
<tr><td>QC Accuracy</td><td>-7.21% to 5.09%</td></tr>
<tr><td>QC Precision, Standards precision</td><td>0.990% to 5.67%.</td></tr>
<tr><td>LLOQ</td><td>0.0795 µg/mL</td></tr>
<tr><td>Analyte Name</td><td>free phenytoin</td></tr>
<tr><td>LLOQ (free phenytoin)*</td><td>0.121 µg/mL</td></tr>
</table>
* Equilibrium dialysis performed prior to HPLC analysis
[Reviewer comment: The assays are acceptable.]</td></tr>
</table>

Population/ Demographics	**N= 113 subjects** (63 male, 50 female). Two subjects entered the study twice and were each counted as two separate people (thus, n=115 is number reported). 90 subjects received IV fosphenytoin, 19 received fosphenytoin IM, and 6 received both IV and IM fosphenytoin. **Age groups**: n=21 neonates (birth to < 29 days), n=33 infants (29 days to < 2 years), n=45 children (2 years to < 12 years), n=14 adolescents (12 years to < 17 years) Inclusion criteria: 1. Males and female age ≤ 16 years 2. Require a parenteral loading dose of phenytoin for the treatment or prophylaxis of seizures Exclusion criteria: 1. Hypersensitivity to hydantoins 2. Serious medical condition likely to interfere with the study or expose the patient to increased risk
Concomitant Medication	No medications were specifically excluded, although concurrent medications beyond those necessary for the routine care and well-being of the patients were discouraged. Although not prohibited, investigators were provided with a list of drugs that alter phenytoin concentrations or that phenytoin could affect. At the discretion of the investigator, medications considered necessary for the patients' welfare were allowed.
PK Results	Mean half-life of fosphenytoin conversion was 8.54 minutes following IV Cerebyx loading doses. Sponsor conducted a regression analysis to assess the relationship between age and fosphenytoin conversion half-life (see the figure below). **Figure 982-028-1: Individual Patient Fosphenytoin Half-Life Values Versus Age Following IV Cerebyx Loading Dose Administration to Neonates, Infants, Children, and Adolescents**  *Thick line depicts the linear regression. Dashed lines depict upper and lower 95% CI of the regression line.*

Mean apparent half-life of fosphenytoin conversion was 38.9 minutes following IM Cerebyx loading doses

Figure 982-028-2: Infusion Rate Versus Dose Following IV Cerebyx Loading Dose Administration to Neonates, Infants, Children, and Adolescents

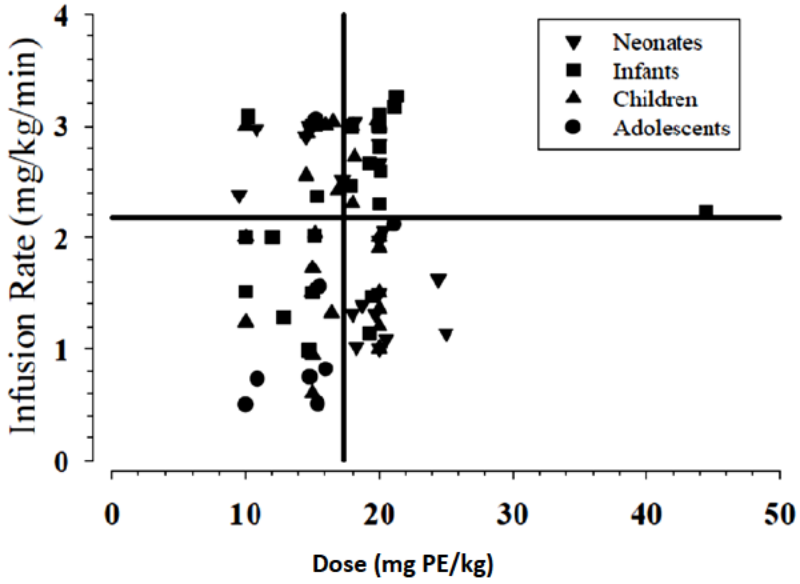


Figure 982-028-3: Fosphenytoin PK Profile Following IV Cerebyx Loading Dose Administration to Neonates, Infants, Children, and Adolescents

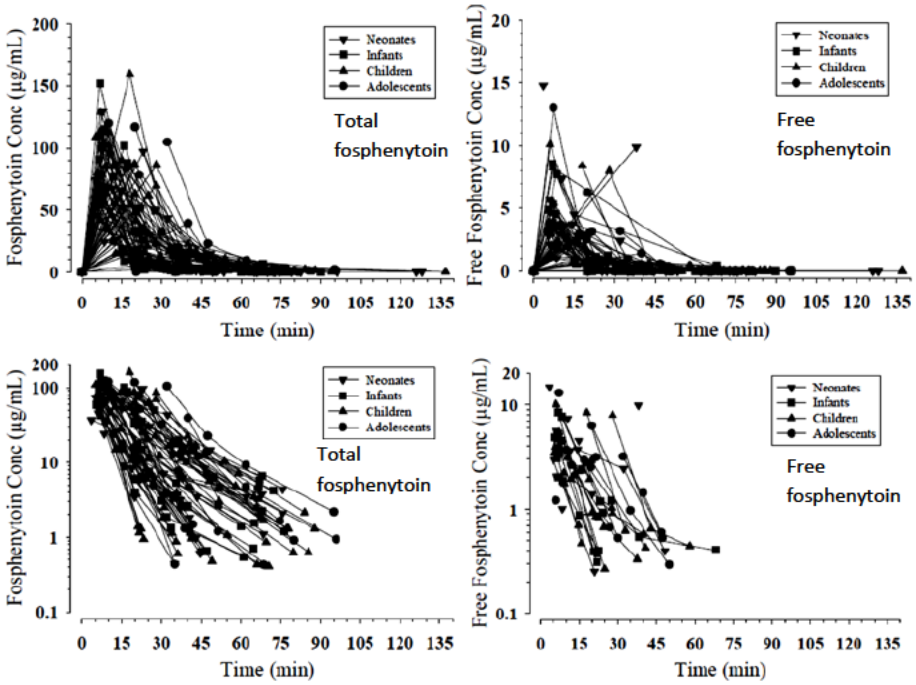


Figure 982-028-4: Total and Unbound Phenytoin PK Profile Following IV Cerebyx Loading Dose Administration to Neonates, Infants, Children, and Adolescents

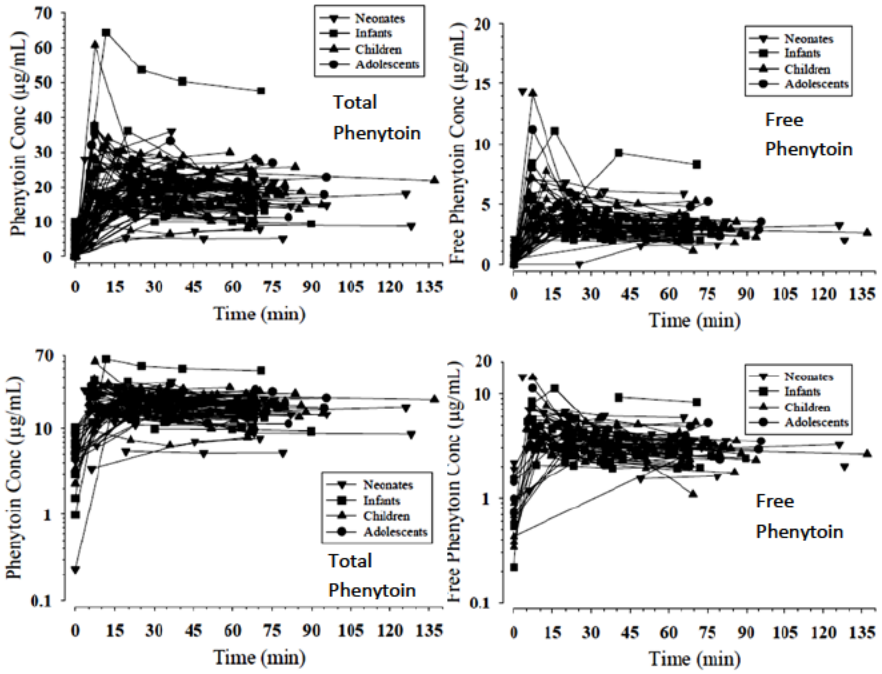


Figure 982-028-5: Total and Unbound Fosphenytoin PK Profile Following IM Cerebyx Loading Dose Administration to Neonates, Infants, Children, and Adolescents

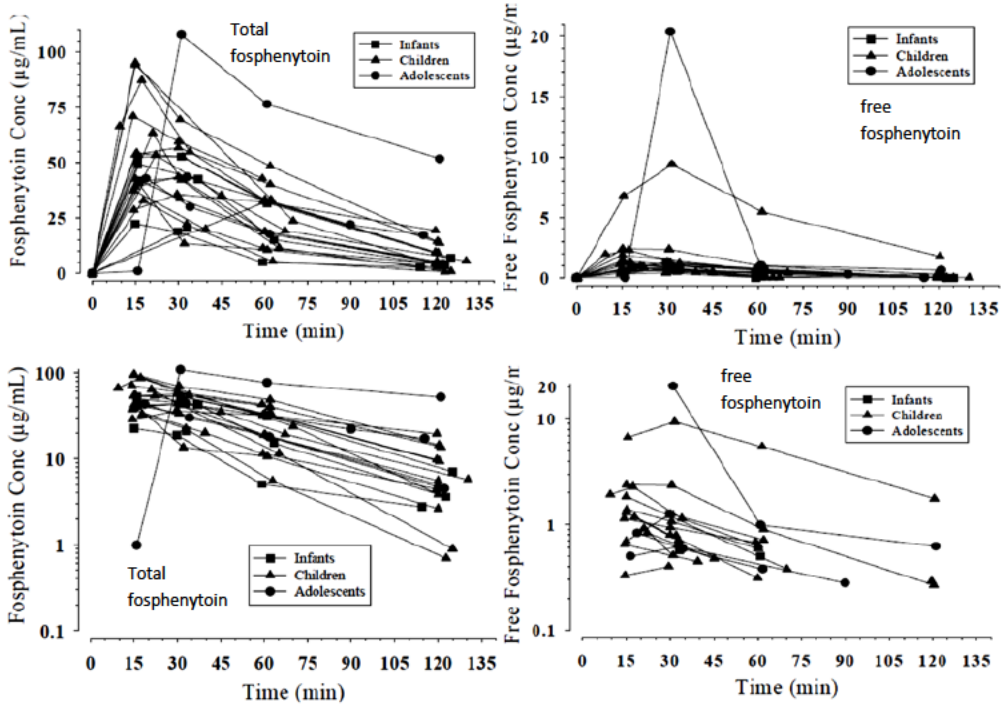


Figure 982-028-6: Total and Unbound Phenytoin PK Profile Following IM Cerebyx Loading Dose Administration to Neonates, Infants, Children, and Adolescents

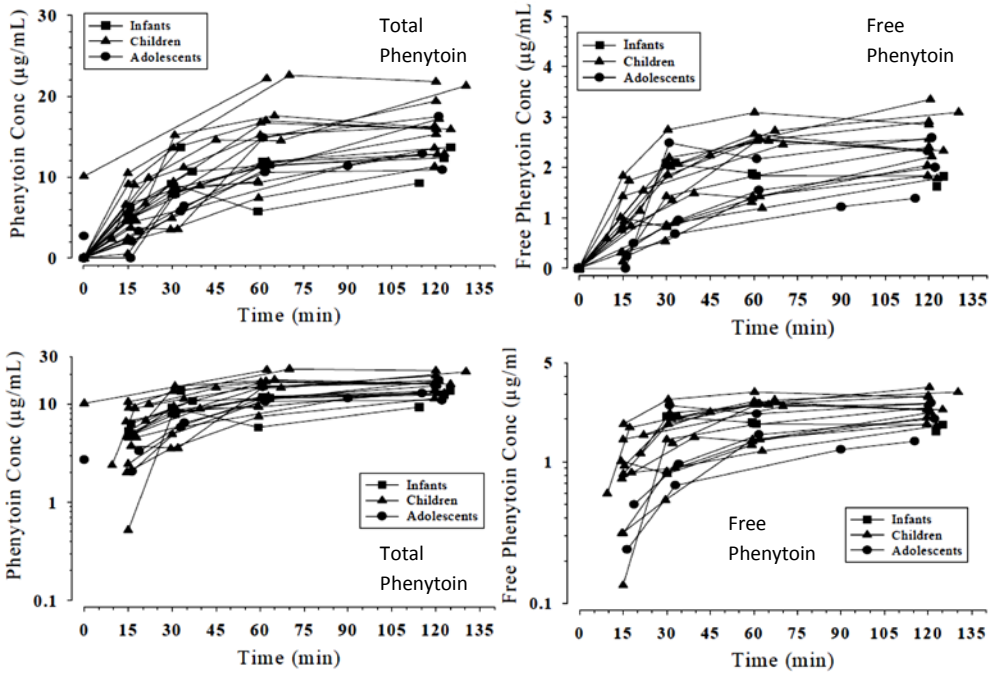
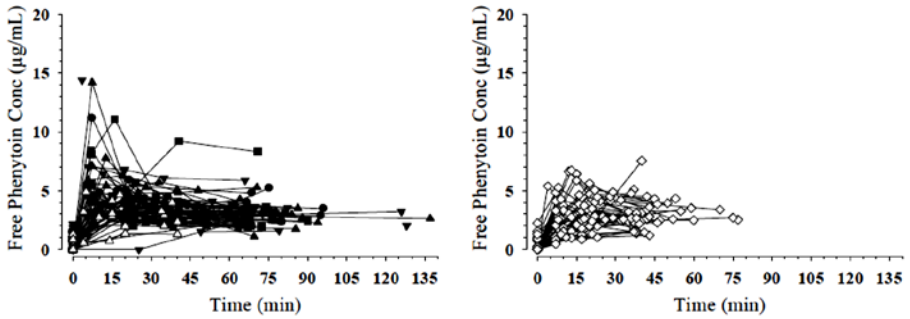
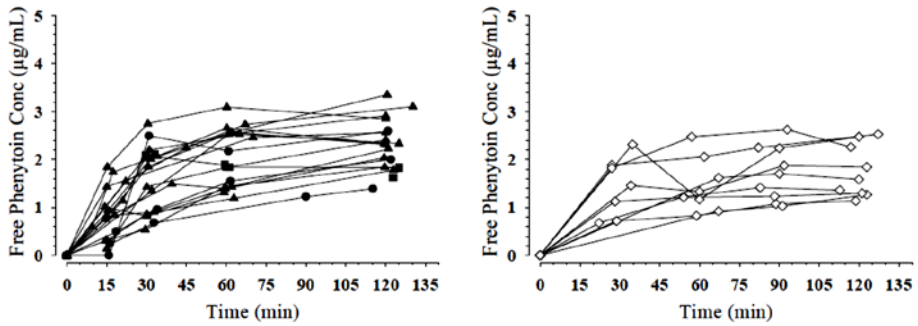


Figure 982-028-7: Comparison of Individual Unbound Phenytoin PK Profiles By Age Category Following IV Cerebyx Loading Dose Administration



Study 982-28: Neonates (▼), Infants (■), Children (▲), and Adolescents (●). Study 982-16: Children (△) and Adults (◇).

Figure 982-028-8: Comparison of Individual Free (Unbound) Phenytoin PK Profiles By Age Category Following IM Cerebyx Loading Dose Administration



Study 982-28: Infants (■), Children (▲), and Adolescents (●). Study 982-14: Adults (◇).

Safety	Nystagmus, vomiting, ataxia, fever, somnolence, nervousness, and pruritus were most common (occurred in ≥ 5% of all pediatric patients treated with fosphenytoin). Majority of events were mild to moderate in severity. AE types were similar to those expected with phenytoin therapy or with the patients' medical condition (e.g. postoperative status).
Sponsor's Conclusions	• The slower conversion of fosphenytoin to phenytoin after IM administration compared to IV administration (38.9 minutes and 8.54 minutes following IM and IV administration, respectively) reflects the overall process of absorption from the muscle and conversion once absorbed, with the rate of absorption being the slower of the 2 processes. • Therapeutic free phenytoin concentrations ≥ 1 µg/mL were generally achieved the by end of an IV infusion and within 30 minutes following IM injection. • Previous studies with IM phenytoin have demonstrated absorption of phenytoin to be slow and unreliable.
Reviewer Comment	• *The Sponsor's conclusions are acceptable.* • *The approved Cerebyx label indicates that, for adults: "IM CEREBYX should ordinarily not be used in the treatment of status epilepticus because therapeutic phenytoin concentrations may not be reached as quickly as with IV administration."* • *The data from this pediatric study support the label claim that for pediatric patients that "Intramuscular administration of CEREBYX should ordinarily not be used in pediatric patients. When IV access has been impossible, loading doses of CEREBYX have been given by the IM route".*

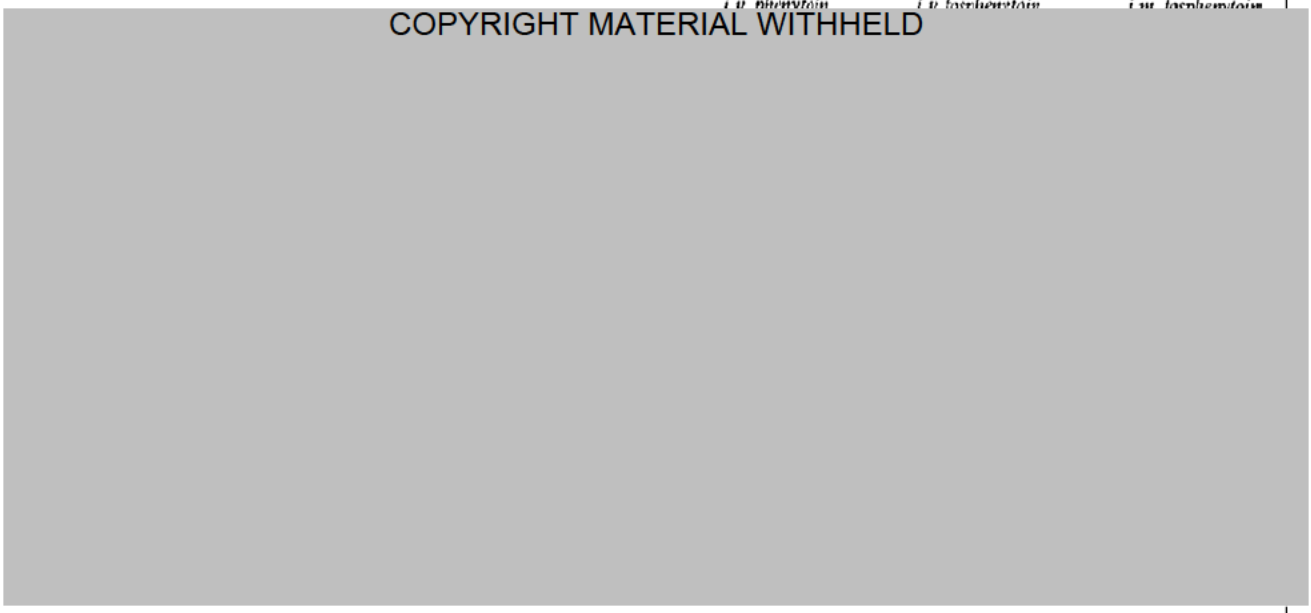
4.6.2 Ogutu et. al. (2003) Study

<table>
<tr><td>Study Citation</td><td>Ogutu BR, Newton CR, Muchohi SN, Otieno GO, Edwards G, Watkins WM, Kokwaro GO. Pharmacokinetics and clinical effects of phenytoin and fosphenytoin in children with severe malaria and status epilepticus. Br J Clin Pharmacol. 2003 Jul;56(1):112-9.</td></tr>
<tr><td>Title</td><td>Pharmacokinetics and clinical effects of phenytoin and fosphenytoin in children with severe malaria and status epilepticus</td></tr>
<tr><td>Objectives</td><td>Assess PK, safety, and effect on status epilepticus of IV Dilantin, IV Cerebyx, and IM Cerebyx</td></tr>
<tr><td>Study Design</td><td>Open-label, randomized, parallel study</td></tr>
<tr><td>Duration</td><td>48 hours of treatment</td></tr>
<tr><td>Dosage and Administration</td><td>Arm 1: Phenytoin IV as an 18 mg/kg loading dose infused over 20 minutes followed by 2.5 mg/kg infused over 5 minutes as maintenance dose twice a day (BID) for 48 hours,
Arm 2: Fosphenytoin IV as a loading dose of 18 mg PE/kg followed by 2.5 mg PE/kg maintenance dose BID for 48 hours, both at a rate of 50 mg/minute, or
Arm 3: Fosphenytoin IM as a 18 mg PE/kg loading dose followed by 2.5 mg/kg maintenance dose BID for 48 hours</td></tr>
<tr><td>PK Assessment</td><td>Analytes: Total phenytoin, unbound phenytoin, total fosphenytoin
Plasma PK Samples: 5, 10, 15, 20, 25, 30, 40, and 60 minutes, and 2, 4, 6, 8, 12, 24, 36, 48, 54, 60, and 72 hours after administration of phenytoin or fosphenytoin.
The author of the Ogutu et. al. provided PK data only from the arm that received IV phenytoin (Arm 1). The PK data from arms that received fosphenytoin IV or fosphenytoin IM (Arm 2 and Arm 3) were not provided to the Sponsor. Also, the author of the Ogutu et al. study only provided PK data from n=10 out of the n=11 subjects enrolled in the IV phenytoin arm (Arm1).</td></tr>
<tr><td>Bioanalytical Methods</td><td>HPLC-UV Analytical Method for Phenytoin Plasma Concentrations
<table>
<tr><td>Analyte Name</td><td>Total phenytoin</td></tr>
<tr><td>Linear Range</td><td>0.08 to 40 µg/mL</td></tr>
<tr><td>QC Concentrations</td><td>3, 9, 17 µg/mL</td></tr>
<tr><td>QC Precision (intra-assay)</td><td>9.9%, 6.0%, and 6.4% (n=6 each)</td></tr>
<tr><td>QC Precision (inter-assay)</td><td>3.4%, 6.8%, and 5.3% (n=5 each)</td></tr>
<tr><td>Analyte Name</td><td>free phenytoin</td></tr>
<tr><td>Linear Range*</td><td>0.02 to 5.0 µg/ml</td></tr>
</table>
* Ultrafiltration dialysis performed prior to HPLC analysis
[Reviewer comment: Though two arms of this study administered Cerebyx to pediatric patients (IV Cerebyx and IM Cerebyx), the author only provided PK data from the IV Dilantin arm to the Sponsor. Therefore, only the phenytoin assay is relevant to the current submission. The phenytoin assay is acceptable.]</td></tr>
</table>

Population/ Demographics	N= 38 (n=11 received IV Dilantin, n=16 received IV Cerebyx, n=11 received IM Cerebyx) Inclusion criteria: 1. Age 6 months to 13 years 2. Severe malaria 3. Status epilepticus Exclusion criteria: 1. History of epilepsy 2. Previous phenytoin exposure
PK Results	**Table 2003-1: Phenytoin PK Parameters Following IV Dilantin and IV Cerebyx Administration** COPYRIGHT MATERIAL WITHHELD Source: Ogutu et al, Table 1[10]; Data presented here for IV route only. AUC (0, 72 h) = area under the time-concentration curve between 0 and 72 hours; C_{max} = maximum drug concentration; C_{ss} = drug concentration at steady state; h = hour(s); IV = intravenous; T_{max} = time of maximum drug concentration. a. Median (range) values. b. Mean (95% confidence interval). **Figure 2003-1: Mean (± SD) Unbound Phenytoin PK Profile Following IV Dilantin, IV Cerebyx, and IM Cerebyx Administration** COPYRIGHT MATERIAL WITHHELD Free phenytoin concentration ($\mu g ml^{-1}$) Time (h) *Maintenance doses were given at 12, 24, 36, and 48 hours. I.V. Dilantin (▲, n = 6), I.V. Cerebyx (□, n = 7), I.M Cerebyx (●, n = 7)*

Safety

Table 2003-2: Clinical Progress and Outcome



Sponsor's Conclusions	• Fosphenytoin was rapidly eliminated from the body • Unbound phenytoin concentrations within the labelled therapeutic range (1-2 µg/mL) were achieved 5 to 20 minutes after the 3 routes of administration.
Reviewer Comment	• *The PK plot suggests that the majority of patients had unbound phenytoin concentrations above the lower therapeutic limit (1 µg/mL) at all time points for all 3 arms. The mean unbound phenytoin concentrations are greater than the upper therapeutic limit (2 µg/mL) for up ~1 hour post-dose for all 3 arms.* • *The PK variability in plot 2003-1 is wide in comparison to the 1-2 µg/mL therapeutic range. Considering the magnitude of this variability, some patients may be above or below the 1-2 µg/mL free phenytoin therapeutic window regardless of dose selected.* • *The individual PK data from the IV Dilantin arm of this study published by Ogutu et al. were used in the population PK model development.*

4.6.3 Study 982-016 (Phase 2/3)

<table>
<tr><td>Study Report#</td><td>RR-720-03776</td></tr>
<tr><td>Title</td><td>An Open-Label, Rate-Escalation, Multicenter Study to Assess Safety, Tolerance, and Pharmacokinetics of Intravenously Administered Fosphenytoin Sodium (CI-982) in the Acute Treatment of Generalized Convulsive Status Epilepticus (Protocol 982-016)</td></tr>
<tr><td>Objectives</td><td>Primary: Assess safety and tolerability
Secondary: Assess pharmacokinetics</td></tr>
<tr><td>Study Design</td><td>Open-label, dose escalation study</td></tr>
<tr><td>Duration</td><td>Following a single fosphenytoin IV dose, subjects were observed for 2 hours or until they were awake and stable. Follow-up visits at 24 hours and 2 or 4 days post-infusion.</td></tr>
<tr><td>Dosage and Administration</td><td>18 mg PE/kg (not to exceed 2000 mg PE total) was the recommended dose to be administered as an IV infusion.
Infusion rate 100 mg PE/min in first n=10 patients, increased to 150 mg PE/min with adjustments in based on response and clinical judgement. In pediatric patients with body weight of 50 kg, infusion rate was 2 mg PE/kg/min, increased to 3 mg PE/kg/min once the initial rate as determined to be safe.</td></tr>
<tr><td>PK Assessment</td><td>Plasma PK Samples: Venous blood samples were obtained from patients immediately before and after infusion, and again approximately 10 and 30 minutes postinfusion</td></tr>
<tr><td>Bioanalytical Methods</td><td>HPLC-UV Analytical Methods for Fosphenytoin Plasma Concentrations
<table>
<tr><th>Analyte Name</th><th>Total fosphenytoin</th></tr>
<tr><td>Linear Range</td><td>0.188 to 188 µg/mL</td></tr>
<tr><td>QC Accuracy</td><td>-3.03% to 3.56%</td></tr>
<tr><td>QC Precision, Standards precision</td><td>1.92% to 7.03%</td></tr>
<tr><td>LLOQ (total fosphenytoin)</td><td>0.188 µg/mL</td></tr>
<tr><th>Analyte Name</th><th>free fosphenytoin</th></tr>
<tr><td>Linear Range</td><td>0.188 to 75.3 µg/mL</td></tr>
<tr><td>QC Accuracy</td><td>4.90 to 8.58%</td></tr>
<tr><td>QC Precision, Standards precision</td><td>0.697% to 5.93%</td></tr>
<tr><td>LLOQ (free fosphenytoin)*</td><td>0.188 µg/mL</td></tr>
</table>
* Ultrafiltration dialysis performed prior to HPLC analysis</td></tr>
</table>

<table>
<tr><td></td><td>

HPLC-UV Analytical Methods for *Phenytoin Plasma* Concentrations

Analyte Name	**Total phenytoin**
Linear Range	0.100 to 100 µg/mL
QC Accuracy	-4.57% to 1.49%
QC Precision, Standards precision	1.60% to 14.8%
LLOQ (total fosphenytoin)	0.100 µg/mL
Analyte Name	**free phenytoin**
Linear Range	0.100 to 10.0 µg/mL
QC Accuracy	5.13% to 11.9%
QC Precision, Standards precision	1.80 to 8.83%
LLOQ (free fosphenytoin)*	0.100 µg/mL

* Ultrafiltration dialysis performed prior to HPLC analysis

[*Reviewer comment: The assays are acceptable.*]
</td></tr>
<tr><td>Population / Demographics</td><td>

N = 85 patients were enrolled

Inclusion criteria:

1. Generalized convulsive status epilepticus
2. Male and female, age ≥ 5 years
3. Not previously enrolled in a fosphenytoin study

Exclusion criteria:

1. Pregnant, nursing females, females who have potential to become pregnant
2. Use of antiepileptic drugs for current status episode

Concomitant Medications: n=16 receive none, n=46 received lorazepam, diazepam in n=41, midazolam in n=3, barbiturates in n=2, phenytoin in n=2, insulin in n=1, other in n=7.
</td></tr>
<tr><td>PK Results</td><td>

PK measured in n=58 (49 adults, 9 pediatric patients)

Table 982-016-1: Fosphenytoin Half-life Values
For Patients Completion the PK Phase of Study 982-016

		Age (yr)	Half-Life (minutes)
Overall	n	45	45
	Mean	39 6	7 76
	SD	19 2	3 30
	%RSD	48 5	42 9
	Minimum	5	2 74
	Maximum	75	17 7
Pediatric	n	7	7
	Mean	7 00	7 12
	SD	1 83	2 33
	%RSD	26 1	32 7
	Minimum	5	3 83
	Maximum	10	9 61
Adult	n	38	38
	Mean	45 6	7 88
	SD	14 1	3 50
	%RSD	31 0	44 4
	Minimum	22	2 74
	Maximum	75	17 7
</td></tr>
</table>

Figure 982-016-1: Individual PK Profile for Total Plasma Fosphenytoin on a(top panel) and Free Fosphenytoin (Bottom Panel) Following IV Fosphenytoin administration to n=58 Patients.

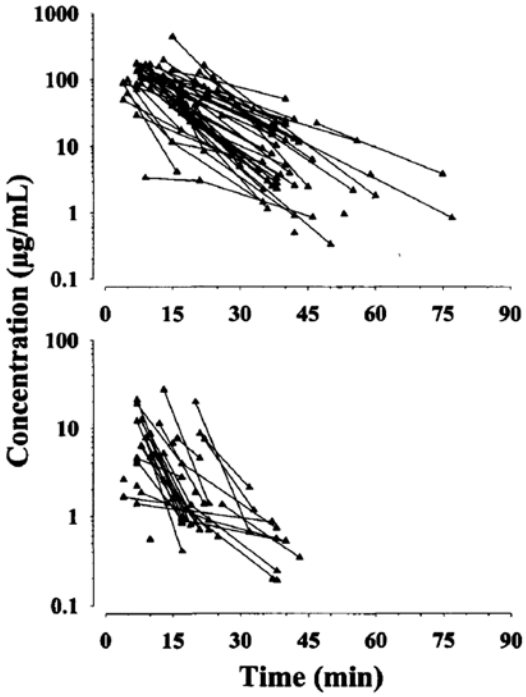


Figure 982-016-2: Individual PK Profile for Total Plasma Phenytoin on a Linear Scale (top panel) and Log Scale (Bottom Panel) Following IV Fosphenytoin administration to n=58 Patients.

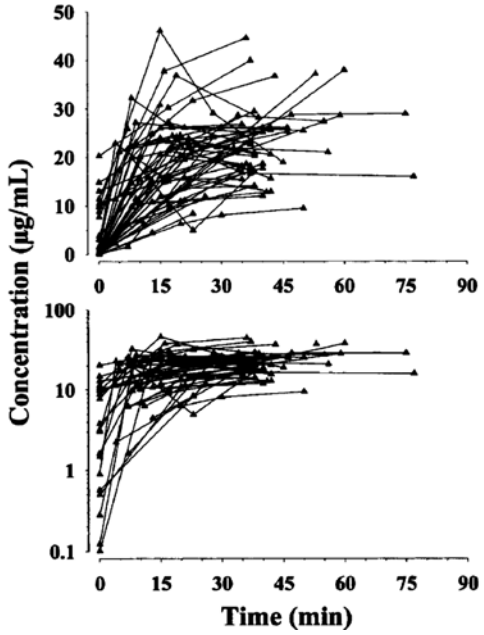
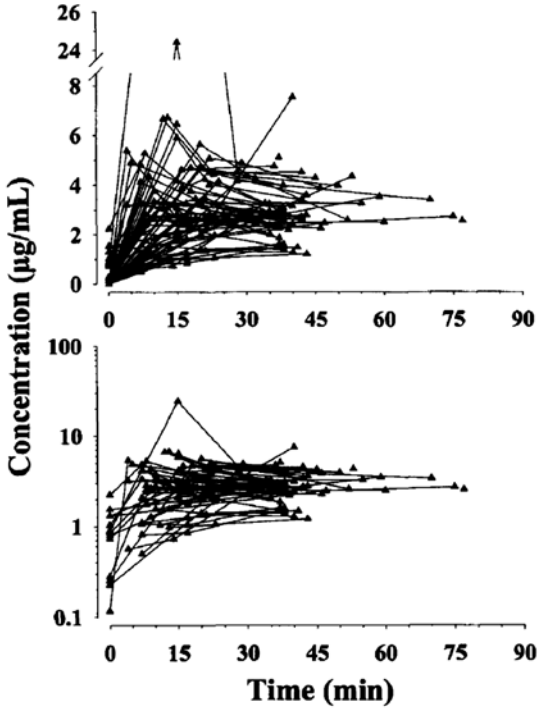
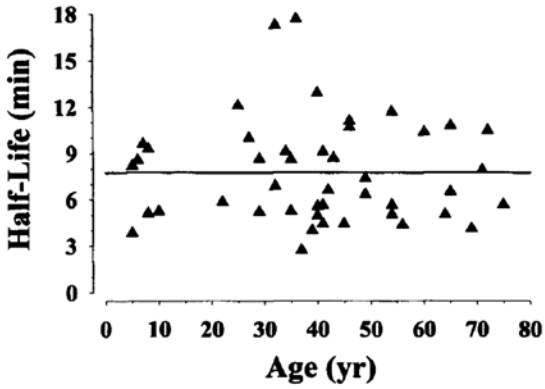


	Figure 982-016-3: Individual PK Profile for <u>Free Phenytoin</u> on a Linear Scale (top panel) and Log Scale (Bottom Panel) Following IV Fosphenytoin administration to n=58 Patients.  **Figure 982-016-4: Individual <u>Fosphenytoin</u> Half-life Following IV Fosphenytoin administration to n=58 Patients.** 
Safety	**3 SAEs probably related to drug**: nystagmus, ataxia, psychosis (other SAEs considered attributable to the underlying disorder)
Sponsor's Conclusions	IV fosphenytoin loading doses of 17.1 mg PE/kg infused at 100 to 150 mg PE/min were safe and well-tolerated in the treatment of patients with generalized convulsive status epilepticus.
Reviewer Comment	• *The Sponsor's conclusions are acceptable* • *Other than computing half-lives, Sponsor did not provide numerical analyses of PK data in this CSR. However, Sponsor utilized this data in the population PK model. In addition, Sponsor utilized data from this trial to compute the 90% PI for adult exposures. The Sponsor computed the geometric mean C_{max} and geometric*

	*standard deviation for C_{max} based on observed C_{max} values. Under the assumption of a log-normal distribution of C_{max} values, Sponsor estimated the 90% PI by estimating the 5th and 95th percentile using the estimated geometric mean and geometric standard deviation. Sponsor arrived at a range of values from **0.95 to 7.47 µg/mL** unbound phenytoin as the 90% PI. However, after looking into the Sponsor's methodology, it was apparent that the Sponsor included all doses from trial 016 as well as all age groups in the reference range estimation.* *This reviewer re-estimated the 90% PI using only IV Cerebyx loading doses that are in the labelled range for status epilepticus (15 to 20 mg/kg) and included only adults. This revised reference range is **1.04 to 8.51 µg/mL**. Overall, while the revised reference range is the appropriate range for assessing pediatric dosing, the difference between the revised reference range and Sponsor's original reference range does not affect the dosing recommendations.* • *Please refer to the medical officer's review for details regarding safety*

4.6.2 Study 982-024

<table>
<tr><td>Study Report#</td><td>982-024 / 744-00152</td></tr>
<tr><td>Title</td><td>A Randomized, Nonblind, Dilantin®-Controlled, Single-Dose Study of the Pharmacokinetic Profile and Tolerance of Intravenous Fosphenytoin Sodium (CI-982) Subjects (Protocol 982-24-0)</td></tr>
<tr><td>Objectives</td><td><u>Primary</u>: Assess phenytoin PK following single doses of IV fosphenytoin and IV Dilantin
<u>Secondary</u>: Assess safety</td></tr>
<tr><td>Study Design</td><td>Non-blind, randomized, 3-way crossover study</td></tr>
<tr><td>Duration</td><td>3 single doses separated by a 1 week washout period</td></tr>
<tr><td>Dosage and Administration</td><td>Randomized to receive 3 single treatments, separated by a 1-week washout:
A) Dilantin, 1200 mg, IV infusion, 50 mg/min (24 minutes)
B) Fosphenytoin, 1200 mg PE*, IV infusion, 100 mg PE/min (12 minutes)
C) Fosphenytoin, 1200 mg PE*, IV infusion, 150 mg PE/min (8 minutes)
PE = phenytoin equivalent, 1200 mg PE = 1800 mg fosphenytoin
Dilantin is a 10 mg phenytoin / mL solution injection. Fosphenytoin was supplied as a solution containing 15 mg/mL fosphenytoin (10 mg PE/mL).</td></tr>
<tr><td>PK Assessment</td><td><u>Plasma PK Samples</u>: 2, 4, 8, 12, 18, 24, 30, 35, and 40 minutes, and 1, 1.5, 2, 4, 6, 8, 12, 24, 36, 48, 60, 72, and 96 hours following infusion start.
<u>Urine PK Samples</u>: pre-dose, 0-1, 1-2, 2-4, 4-8, 8-24, 24-36, 36-48, 48-72, and 72-96 hours postdose.</td></tr>
<tr><td>Bioanalytical Methods</td><td>HPLC-MS/MS Analytical Methods for Fosphenytoin Concentrations
<table>
<tr><td>Analyte Name</td><td colspan="2">Fosphenytoin</td></tr>
<tr><td>Matrix</td><td>Plasma</td><td>Urine</td></tr>
<tr><td>Linear Range</td><td>0.25 to 250 µg/mL</td><td>1.00 to 50.0 µg/mL</td></tr>
<tr><td>QC Precision</td><td>1.92 to 7.03 %</td><td>1.97 to 2.72 %</td></tr>
<tr><td>QC Accuracy</td><td>-3.03 o 3.56 %</td><td>-3.33 to 6.50 %</td></tr>
</table>
HPLC-MS/MS Analytical Methods for Total Phenytoin Concentrations
<table>
<tr><td>Analyte Name</td><td colspan="2">Total Fosphenytoin</td></tr>
<tr><td>Matrix</td><td>Plasma</td><td>Urine</td></tr>
<tr><td>Linear Range</td><td>0.100 to 100 µg/mL</td><td>0.100 to 20.0 µg/mL</td></tr>
<tr><td>QC Precision</td><td>1.60 to 14.8%</td><td>2.99 to 5.14 %</td></tr>
<tr><td>QC Accuracy</td><td>-4.57 to 1.49 %</td><td>-16.0 to 1.50 %</td></tr>
</table>
HPLC-MS/MS Analytical Methods for Free Phenytoin Concentrations
<table>
<tr><td>Analyte Name</td><td>Free Fosphenytoin</td></tr>
<tr><td>Matrix</td><td>Plasma</td></tr>
<tr><td>Linear Range</td><td>0.100 to 100 µg/mL</td></tr>
<tr><td>QC Precision</td><td>2.00 to 7.27 %</td></tr>
<tr><td>QC Accuracy</td><td>.0.606 to 6.43 %</td></tr>
</table></td></tr>
</table>

HPLC-MS/MS Analytical Methods for *p-HPPH*

Analyte Name	Free Fosphenytoin
Matrix	Urine
Linear Range	1.00 to 100 µg/mL
QC Precision	1.96 to 3.65 %
QC Accuracy	-6.25 to 4.50 %

[*Reviewer comment: The assays for are acceptable for each analyte.*]

Population / Demographics

N= 12 were recruited, age 20 to 42 years (median 24 years).

Key Inclusion Criteria:

1. Male subjects age 18 to 50 years
2. Healthy based on medical history, physical examination, ECG, 48-hour Holter monitor, and clinical laboratory measurements
3. Do not have significant concentration of any drug in the urine that could interfere with the study

Key Exclusion Criteria:

1. Significant renal, hepatic , gastrointestinal, neurologic, or other disorder
2. Significant adverse reactions to study medications or other anticonvulsants
3. Use of any medication (prescription or non-prescription) within 2 weeks prior to or during study

PK Results

Table 982-024-1: Mean (%CV) Total Fosphenytoin PK Parameters Following Single IV Infusion of 1200 mg PE Fosphenytoin (100 mg PE/min) or 1200 mg PE Fosphenytoin (150 mg PE/min) (n=12)

PK Parameter	Infusion Rate 100 mg PE / min	Infusion Rate 150 mg PE /min
C_{max} (µg/mL)	184 (13%)	207 (11%)
T_{max} (hr)	0.186 (18%)	0.130 (12%)
$AUC_{0\text{-}last}$ (µg*hr/mL)	64.7 (17%)	60.3 (22%)
$AUC_{0\text{-}\infty}$ (µg*hr/mL)	65.0 (17%)	60.6 (21%)
λ_z (hr^{-1})	2.358 (37%)	2.152 (30%)
$t_{½}$ (hr)	0.315 (20%)	0.341 (21%)
CL (mL/min)	319 (22%)	347 (26%)
V_d (L)	8.46 (21%)	10.1 (31%)

Table 982-024-2: Mean (%CV) Total Phenytoin PK Parameters Following a Single IV Infusion of 1200 mg Dilantin (50 mg/min), 1200 mg PE Fosphenytoin (100 mg PE/min) or 1200 mg PE Fosphenytoin (150 mg PE/min) (n=12)

PK Parameter	Fosphenytoin 1200 mg PE		Dilantin (Phenytoin) 1200 mg
	Infusion rate 100 mg PE / min	Infusion Rate 150 mg PE /min	Infusion rate 50 mg/min
C_{max} (µg/mL)	26.9 (8%)	28.2 (12%)	35.3 (18%)
T_{max} (hr)	1.18 (45%)	0.975 (37%)	0.631 (51%)
$AUC_{0\text{-last}}$ (µg*hr/mL)	1010 (11%)	1070 (13%)	1120 (14%)

Comparison of phenytoin exposures between fosphenytoin and Dilantin was assessed using a bioequivalence approach with standard no-effect boundaries of 80-125%.

Table 982-024-3: Comparison of Mean (%CV) Free Phenytoin PK Parameters Following a Single IV Infusion of 1200 mg Dilantin (50 mg/min), 1200 mg PE Fosphenytoin (100 mg PE/min) or 1200 mg PE Fosphenytoin (150 mg PE/min) (n=12)

PK Parameter	Fosphenytoin 1200 mg PE	Dilantin (Phenytoin) 1200 mg	Ratio	90% CI
Fosphenytoin Infusion rate 100 mg PE / min				
$ln(C_{max})$ (µg/mL)	2.72	3.21	84.7%	**72.7** – 98.8%
$ln(AUC_{0\text{-last}})$ (µg*hr/mL)	78.8	85.5	92.2%	88.4 – 96.2%
C_{max} (µg/mL)	2.78 (22%)	3.30 (26%)	84.2%	N/a
T_{max} (hr)	0.524 (37%)	0.526 (17%)	99.9%	
$AUC_{0\text{-last}}$ (µg*hr/mL)	79.5 (14%)	87.1 (22%)	91.3%	
Fosphenytoin Infusion rate 150 mg PE / min				
$ln(C_{max})$ (µg/mL)	3.08	3.21	96.0%	82.1 – 111.7%
$ln(AUC_{0\text{-last}})$ (µg*hr/mL)	84.5	85.5	98.8%	94.8 – 103.2%
C_{max} (µg/mL)	3.18 (28%)	3.30 (26%)	96.4%	N/a
T_{max} (hr)	0.576 (59%)	0.526 (17%)	109.5%	
$AUC_{0\text{-last}}$ (µg*hr/mL)	85.5 (17%)	87.1 (22%)	98.2%	

Figure 982-024-1: Mean PK Profile of Total Fosphenytoin, Total Phenytoin, and Free Phenytoin (with Free Fraction) Following a Single IV Infusion of 1200 mg Dilantin (50 mg/min), 1200 mg PE Fosphenytoin (100 mg PE/min) or 1200 mg PE Fosphenytoin (150 mg PE/min) (n=12)

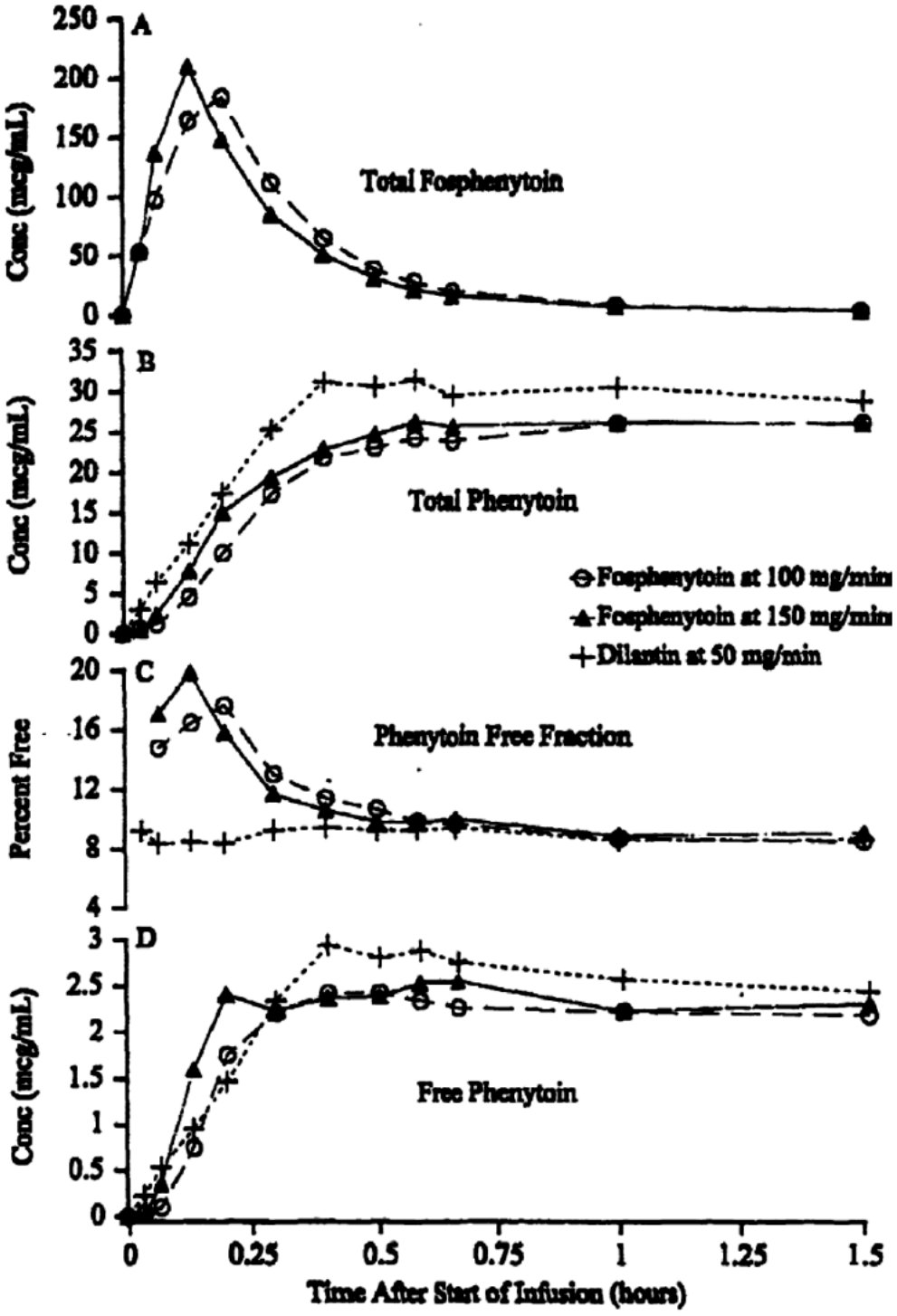


Figure 982-024-2: Mean PK Profiles of Total Phenytoin and Free Phenytoin after a Single IV Dose of 1200 mg Dilantin (50 mg/min), 1200 mg PE Fosphenytoin (100 mg PE/min) or 1200 mg PE Fosphenytoin (150 mg PE/min) (n=12)

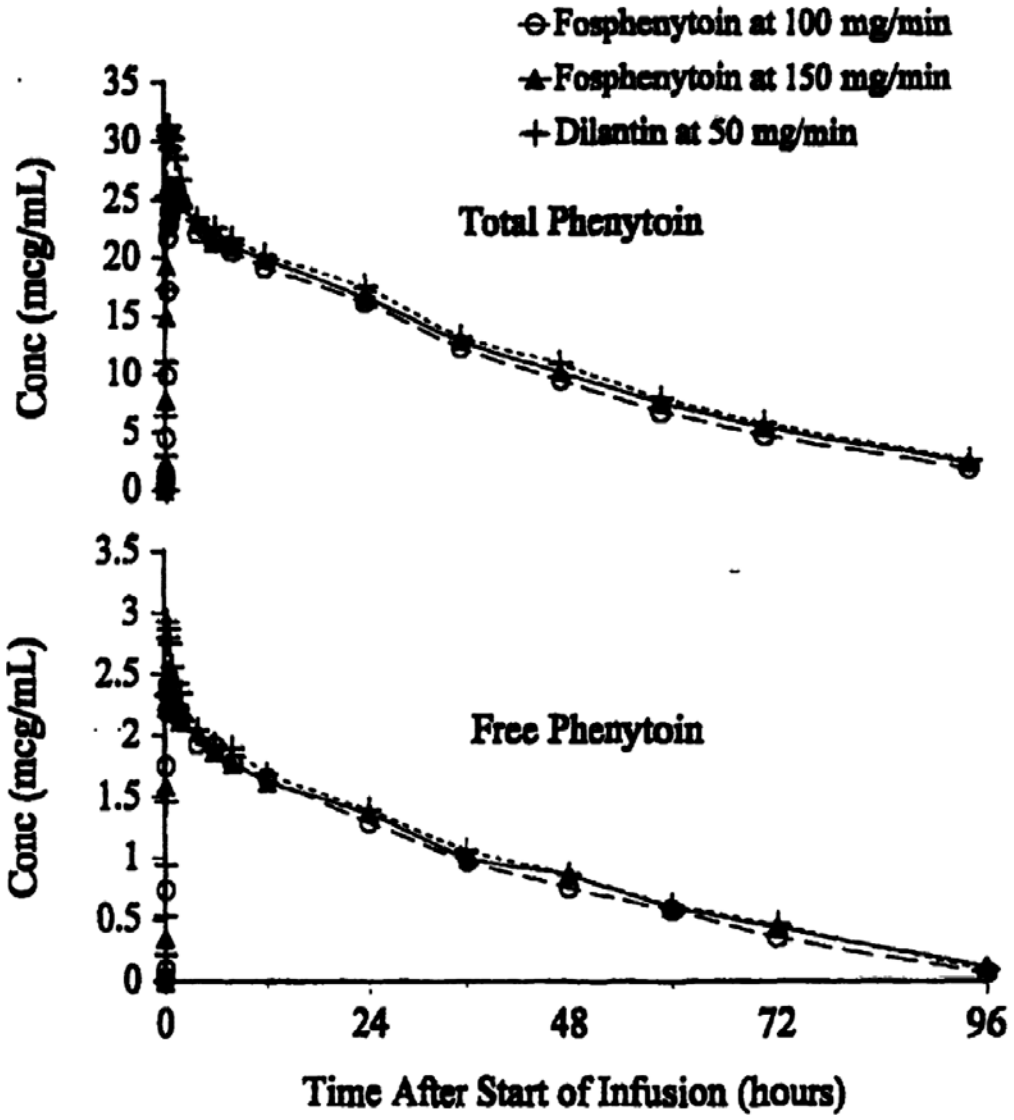
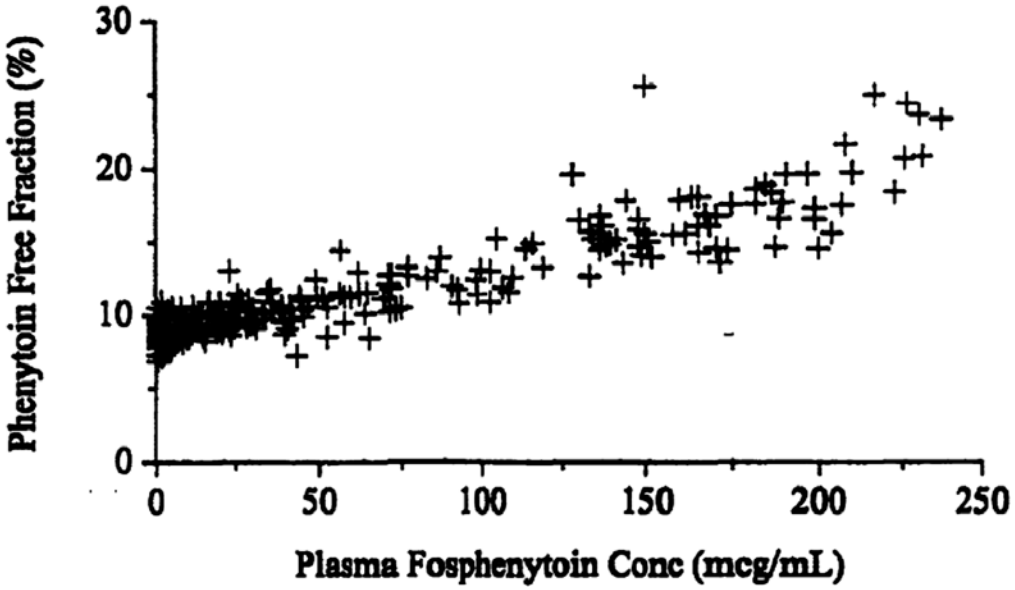


	Figure 982-024-3: Free Phenytoin Fraction versus Total Fosphenytoin Concentration after a Single IV Dose of 1200 mg Dilantin (50 mg/min), 1200 mg PE Fosphenytoin (100 mg PE/min) or 1200 mg PE Fosphenytoin (150 mg PE/min) (n=12) 
Safety	• Similar AE types between Dilantin and Cerebyx • Nystagmus occurred with similar frequency between both treatments • Injection sites inflammation, pain, reaction, hypersensitivity more common for Dilantin (100%) than fosphenytoin (42%) • Cerebyx had higher frequency of paresthesia and pruritus than Dilantin • Dilantin had higher frequency of dizziness than Cerebyx
Sponsor's Conclusions	• **Total Plasma Fosphenytoin**: Increases with increasing infusion rate, peaks near the end of infusion, shows $t_{½}$ of 0.3 hours (independent of infusion rate). When increasing from 100 to 150 mg PE/min infusion rate, C_{max} increased 12% (184 to 207 µg/mL and $AUC_{0-\infty}$ decreased by 7% (from 65 to 60.6 µg*hr/mL). • **Total Plasma Phenytoin**: Total phenytoin concentration following Cerebyx administration lagged behind total phenytoin concentration following Dilantin administration for ~1 hour (likely due to time for conversion of fosphenytoin to phenytoin). Tmax for total phenytoin was 0.5 hour later and 0.3 hour later for Cerebyx compared to Dilantin at 100 mg PE/min infusion rate and 150 mg PE/min infusion rates, respectively. Total phenytoin $AUC_{0\text{-last}}$ was comparable between Cerebyx and Dilantin and total phenytoin C_{max} was 20% lower following Cerebyx administration. • **Free Plasma Phenytoin**: Natural log-transformed free phenytoin C_{max} values met standard no-effect boundaries (90% CI of GMR contained in 80-125% interval) following administration of fosphenytoin at 150 mg PE/min, but not 100 mg PE/min. Despite not achieving "strict" BE for C_{max} at 100 mg PE/min, the overall similarity in free phenytoin PK Profiles suggests that fosphenytoin may be administered at 100 mg PE/min. • **Comparison of Free phenytoin between Fosphenytoin and Dilantin in Plasma**:

	Free phenytoin exposures resulting from 1200 mg PE fosphenytoin (150 mg PE/min) showed comparable bioavailability to 1200 mg Dilantin for both C_{max} (GMR 90% CI was 82.1% – 111.7%) and $AUC_{0\text{-last}}$ (GMR 90% CI was 94.8 – 103.2%). When comparing the 100 mg PE/min fosphenytoin infusion rate, fosphenytoin produced a lower phenytoin C_{max} (GMR 90% CI was 72.7 – 98.8%) and a comparable $AUC_{0\text{-last}}$ (GMR 90% CI was 88.4 – 96.2%). • **Urine** PK: Phenytoin and p-HPPH in urine accounted for 1.5% and 6% of the dose, respectively, and did not depend on treatment. These results are similar to Study 982-018. Fosphenytoin was not detected in the urine.
Reviewer Comment	• *According to Table 982-024-1, 1200 mg IV Cerebyx is administered at 100 mg PE/min or 150 mg PE/min results in unbound phenytoin mean (%CV) C_{max} of 2.78 (22%) µg/mL versus 3.18 (28%) µg/mL. Mean unbound phenytoin C_{max} is 14% higher following 150 mg PE/minute infusion rate vs 100 mg PE/min infusion rate.* • *A 1200 mg IV Dilantin infusion at 50 mg/min produced a mean C_{max} of 3.30 (26%).* • *As the goal during a loading dose for status epilepticus is to rapidly achieve a C_{max} in order to quickly halt progression of this condition, the data from this study support the selection of the 150 mg PE/min infusion rate for status epilepticus.* • *Since maintenance dosing occurs when the clinical condition is less severe, and achieving a rapid C_{max} is not a priority, then the data from this study support the use of the 100 mg PE/min infusion rate. The slower infusion rate is likely to result in a lower C_{max}, which is suggests a lower chance of adverse events in the vicinity of C_{max}. However, the 100 mg PE/min infusion rate is expected to produce a comparable AUC to the 150 mg PE/min infusion rate, which is desirable.*

4.7 References

1. Deleu D, Aarons L, Ahmed IA. Estimation of population pharmacokinetic parameters of free-phenytoin in adult epileptic patients. Arch Med Res. 2005 Jan-Feb;36(1):49-53.

2. Hennig S, Norris R, Tu Q, van Breda K, Riney K, Foster K, Lister B, Charles B. Population pharmacokinetics of phenytoin in critically ill children. J Clin Pharmacol. 2015 Mar;55(3):355-64

3. Ogutu BR, Newton CR, Muchohi SN, Otieno GO, Edwards G, Watkins WM, Kokwaro GO. Pharmacokinetics and clinical effects of phenytoin and fosphenytoin in children with severe malaria and status epilepticus. Br J Clin Pharmacol. 2003 Jul;56(1):112-9.

4. Wolf GK, McClain CD, Zurakowski D, Dodson B, McManus ML. Total phenytoin concentrations do not accurately predict free phenytoin concentrations in critically ill children. Pediatr Crit Care Med. 2006 Sep;7(5):434-9.

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/s/

MICHAEL A BEWERNITZ
02/16/2017

KEVIN M KRUDYS
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