

Supplemental Information

The supplemental information contains the following items: (1) the original protocol, final protocol, summary of changes to the protocol, and details of pharmacy preparation of study drugs and (2) the original statistical analysis plan, final statistical analysis plan, and summary of changes.

NEOLEV2 SUMMARY OF PROTOCOL CHANGES

Over the course of the study, our inclusion criteria were widened slightly to include the following: infants with a gestational age ≥ 36 weeks (initially 37 weeks); serum creatinine levels ≤ 1.6 mg/dL at time of enrollment (initially 1.2 mg/dL); infants with birth weight > 2200 g (initially 2440 g); and although initially we excluded any infant pretreated with an anticonvulsant medication, we changed that so that we could include infants who had received treatment with short-acting benzodiazepines > 24 hours before recruitment time. We began the study with 6 study sites but closed 1 study site (Loma Linda) because of poor recruitment.

NEOLEV2 SUMMARY OF STATISTICAL ANALYSIS PLAN CHANGES

An amendment was made to the study protocol, replacing the initial planned primary outcome measure of seizure freedom to 48 hours with a planned secondary end point of seizure freedom to 24 hours. The amendment was made because it was often clinically indicated to stop EEG

monitoring after 24 hours of seizure freedom to allow for MRI imaging, handling and breastfeeding of the infant, and even transfer or discharge of patients in some cases. Clinical care decisions overrode our research preferences. Twenty-four hours of seizure freedom was deemed by many clinicians to be adequate reassurance that seizures were well controlled. As a result, although all treated subjects completed 24 hours of EEG monitoring, only 70% of the treated infants were continued on EEG monitoring to 48 hours. No bias was introduced by the change in the primary outcome measure. The statistical plan was finalized before database lock and unblinding. Forty-eight hours of seizure freedom was retained as a reported secondary end point.