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DEVELOPMENT OF INTRAVENOUS TOPIRAMATE FOR NEONATAL SEIZURES

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Neonatal seizures are a very rare, but significant medical problem with a high mortality rate, serious neurological sequelae including impaired cognition, developmental delay, and subsequent onset of epilepsy. An estimated 10,000-20,000 newborn babies (0.1-0.4% of live births) per year develop seizures, primarily due to birth hypoxia. The current drugs of choice, phenobarbital and phenytoin, have never been subjected to adequately controlled clinical trials. In open-labeled studies without a placebo arm, fewer than 50% of babies respond to therapy. Compounding their questionable efficacy, these drugs have serious acute and long-term adverse effects including further brain injury. The latter problem is supported by several reports suggesting both phenobarbital and phenytoin cause accelerated apoptosis in laboratory animal pups that are comparable in developmental age to human neonates. The proapoptotic doses found in these studies are similar to doses used to control seizures in rodent models of epilepsy and likely result in plasma concentrations, which are attained in human neonates when given standard therapy.

This project is directed at the development of intravenous topiramate (TPM), an approved oral product for migraines and epilepsy, as an FDA-designated orphan drug for the treatment of neonatal seizures. TPM is highly effective in treating epilepsy and is neuroprotective in newborn laboratory animal models of status epilepticus and cerebral ischemia. The proven safety and effectiveness of oral TPM together with substantial laboratory evidence showing benefit in models of hypoxic-ischemic encephalopathy strongly suggests that it would be useful in newborn babies for neuroprotection and seizure control.

We have made a 10 mg/ml solution of TPM dissolved in 10% sulfobutyl cyclodextrin (Captisol®), which improves both the solubility and stability of the drug (see attachment). This formulation is sufficiently concentrated to limit injection volume in neonates, but does not require amounts of Captisol® larger than those in currently approved products. We have developed an assay to measure TPM in plasma using a liquid chromatograph mass spectrometry. Sample preparation is minimal, the sensitivity and specificity are high, and the plasma volume needed is small (200 µl). The latter feature is particularly important when conducting studies in newborn animals and human neonates where blood collection must be limited. In 2007 the FDA approved an IND (#78993) allowing us to conduct a Phase I study in adults taking oral TPM for epilepsy or migraine. We initiated the study in the fall of 2008 and completed it with the 20 planned patients in early 2010. The study was funded by an FDA Orphan Drug Grant. A subsequent Phase I study, funded by the Epilepsy Research Foundation New Therapy Grant Program, involved 12 healthy volunteers in a dose ranging, pharmacokinetic, and safety study. Results from these studies show that the same dose IV and orally results in similar plasma TPM concentrations. The studies also revealed an extended elimination half-life indicating that TPM can be given once or twice daily in some patients while maintaining targeted plasma concentrations. There were no moderate or severe adverse effects with intravenous doses of 25 mg to 100 mg given over 10 to 15 minutes. Importantly, all healthy volunteers receiving the 100 mg IV dose exhibited mild CNS side effects at the end of the infusion, indicating rapid diffusion into the brain. These studies provide pharmacokinetic and safety data needed to begin studies in younger patients.