Title: Low- Dose Propofol Infusion as an Abortive Treatment for Migraine Headaches in Pediatric Patients

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INTRODUCTION

The purpose of this statistical analysis plan (SAP) is to describe the procedures and the statistical methods that will be used to analyze and report results for study STU 042014-002 Low- Dose Propofol Infusion as an Abortive Treatment for Migraine Headaches in Pediatric Patients.

STUDY OVERVIEW

The aim of this prospective study was to evaluate the efficacy and safety of propofol administration in a hospital setting, as an abortive medication for children aged 7-18 with migraines.

We enrolled subjects who were scheduled to undergo DHE infusion for treatment of migraine headaches as part of standard medical care. Subjects were identified from the investigators' patient list, of children presenting to the Headache Clinic in the Pain Management Clinic for treatment of migraine headache or who had been admitted to the hospital for treatment of migraine headache. If the investigator determined that they were eligible, the family was contacted in advance of the visit to discuss possible participation. An investigator was present at the visit to discuss the study in further detail and answer any questions, and informed consent was obtained prior to any study procedures performed.

Prior to initiation of DHE infusion, the subjects received sub-anesthetic doses of propofol infusion:

20 mcg/kg/min for 10 minutes, followed by an increase to 30 mcg/kg/min for 10 minutes and then by an increase to 40 mcg/kg/min for 40 minutes.

If the propofol infusion was effective in resolving headache symptoms, then subjects were monitored for at least 30 minutes after termination of infusion. Outpatient subjects were discharged home.

If propofol infusion was not successful in resolving the headache, then the subjects proceeded with standard of care.

For all subjects who received a propofol infusion, follow-up occurred at 24 and 48 hours via phone call to evaluate headache status and recover information on headache symptoms and side effects.

STUDY OBJECTIVES

<u>Primary Objective</u>

Based on the adult and the limited pediatric data available we hypothesized that propofol infusion in sub anesthetic dose, would result in either complete resolution or improvement in headache pain scores by 50% from the baseline pain scores. Patients were assessed with a 0-10 Numeric Pain Rating Scale.

<u>Secondary Objectives</u>

- Duration of effect (from the end of propofol administration till discharge criteria are meet or if treatment is ineffective, till start of new therapy)
- Total propofol dose based on weight.

<u>Study Endpoints</u>

The propofol infusion was terminated if:

- The patient had no pain, or greater than 50% reduction in pain scores as compared to the pretreatment pain score.
- After completing 40 minutes of propofol infusion at 40 mcg/kg/min irrespective of the pain score
- If the anesthesiologist feels cardio-pulmonary depression, airway obstruction or over sedation (Ramsay Sedation Score greater than 3) had occurred.

STATISTICAL ANALYSIS

Demographic and clinical characteristics for the sample of pediatric patients who received low- dose propofol infusion as an abortive treatment for migraine headaches were described using the sample mean and standard deviation for continuous variables and the frequency and percentage for categorical variables. The mean level of headache pain score at baseline and post-treatment (10-60 minute periods and 24- and 48-hour follow-up) was compared using the dependent samples t-test. Dependent samples t-test was also used to test for differences in the mean percent change in pain severity from baseline to each post-treatment assessment period. Statistical analyses were carried out using SAS software, version 9.4 (SAS Institute, Inc., Cary, NC). The level of significance was set at $\alpha=0.05$ (two-tailed).6.2. Data Analysis General Considerations

Sample Size Considerations

Forty patients were screened, and 38 patients participated in the study.

Handling of Missing Data

Missing data will not be imputed unless otherwise specified elsewhere in this SAP.

Protocol Deviations

Important protocol deviation criteria will be established, and subjects with important protocol. deviations will be identified and documented.
Important protocol deviations will be summarized and listed by category for all subjects.

Safety Analyses

All safety analyses will be performed based on the Safety Analysis Set. Descriptive statistics will be used to analyze all safety data.

Adverse Events

Adverse events will be reported during scheduled follow-up communications and documented.