AIM 2- Prevention of Neonatal Abstinence Syndrome

Statistical Analysis Plan

NCT01965704

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Only infants who received at least one dose of study medication and met the inclusion criteria were included in the efficacy analysis. All infants and mothers who were allocated and received at least one dose of study medication were included in the safety analysis. Power analysis effect size was based upon NPOW response data that was obtained from the healthy opioid-naïve adult volunteers under controlled conditions. In that study, there was a difference of 2.38 between the means of the control and ondansetron-treated withdrawal responses, with standard deviations of 2.23 and 0.89, respectively. Based upon these numbers, 13 patients per treatment arm would have 90% power to ensure that a treatment difference (ondansetron vs. control) could be detected at the p=0.05 level. However, because of the very large of differences between opioid-naive adults analyzed under experimentally controlled conditions and infants that are exposed *in utero* to opioids, the actual relative effect size of ondansetron treatment was assumed to be 25-33% of that estimated from the pilot data in normal subjects. This revised effect size estimate provided 45 infants in each arm to provide the same statistical power. For the categorical outcomes in the primary and secondary endpoints (the fraction of infants requiring pharmacologic therapy with morphine and the need for adjunctive phenobarbital or clonidine therapy), Fisher's Exact test was used to perform the analysis of independence. Because the need for morphine was not impacted by the sex of the neonates or by the race/ethnicity of the mother, these stratification factors were not corrected for in the analysis of primary outcome.

The null hypothesis for the Fisher's Exact test was that the need for morphine treatment and study drug allocation were independent. The continuous outcomes of secondary endpoints were examined using the two-sided Wilcoxon Rank-Sum test (equivalent to the Mann-Whitney test), where the null hypothesis is stated as the outcomes in the ondansetron and placebo arms are equal. Inclusion of neonates in the safety population was based upon receipt of ondansetron in any form (study drug administered to infant or exposure through maternal transfer). QTc values in the safety population were analyzed by two sample t-test to determine if the mean QTc of two groups were equal. All tests were two-sided, and the p-values obtained from statistical tests were compared with the significance level (α =0.05) to determine whether null hypothesis could be rejected or retained. Statistical analyses were performed using R software (version 3.6.1).