STUDY TITLE: A Randomized Pilot Study of Nuedexta® for the Prevention and Modification of Disease Progression in Episodic Migraine

STATISTICAL ANALAYSIS PLAN

PROTOCOL NO: **14-001AV**

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DATA ANALYSIS

The statistical analysis of the data obtained from this study will be the responsibility of Clinvest. For the purpose of the final analysis, the database will not be unblended until medical/scientific review has been completed and data has been declared "clean".

PRIMARY ENDPOINT

Change in the average number of headache days at treatment period months 1, 2, and 3 (28 day period for each month) compared to baseline (28 day run-in period) in the Nuedexta® arm vs. the placebo arm.

SECONDARY ENDPOINTS

1. Change in the number of headache days reported in baseline compared to the end of treatment period, month 3 (28 day period), in the Nuedexta® arm vs. the placebo arm.
2. Change in the average number of migraine days at treatment period months 1, 2, and 3 (28 day period for each month) compared to baseline in the Nuedexta® arm vs. the placebo arm.
3. Change in average headache severity per month comparing baseline to each treatment period month: 1, 2, and 3 (28 day period for each month) in the Nuedexta® arm vs. the placebo.
4. Change in mean headache duration (time of onset to pain free) comparing baseline to each treatment period months 1, 2, and 3 (28 day period for each month) in the Nuedexta® arm vs. the placebo.
5. The number of subjects with at least a 50% reduction in number of headache days comparing baseline to each visit (treatment period months 1, 2, and 3: 28 day for each month) in the Nuedexta® arm vs. the placebo arm.
6. Change in the total number of doses of acute medication taken per month comparing baseline to treatment period months 1, 2, and 3 (28 day period for each month).
7. Compare the number of adverse events in the Nuedexta® arm vs. the placebo arm.
8. MIDAS scores at Visit 2 vs. Visit 5 (end of treatment period month 3).
9. Changes in the Headache Health Score at baseline, month 1, month 2, and month 3 (28 day period for each month) post treatment for the Nuedexta® arm vs. the placebo arm.

APPROACHES TO ANALYSIS

The primary analysis will use a full data set. This analysis will include all randomized subjects who have at least one assessment in the treatment period. In cases where the daily diary are not completed, it will be assumed no migraine headache pain was experienced by the subject that day.

An exploratory per-protocol analysis may be performed to establish the robustness of conclusions from the primary efficacy analysis by excluding subjects whose violations of the protocol would significantly impact the outcome of the study due to the violation and not in direct relation to the study medication.

All subjects treated will be included in the safety and demographic analysis.

STATISTICAL METHODS

Descriptive statistics will establish baseline characteristics and adverse event frequency. A mixed factorial repeated measures ANOVA will be performed to detect differences among each time point for the primary and secondary endpoints. Post hoc analyses will be conducted as appropriate. Chi-Square and two-tailed t-tests will also be used to measure the significance of the differences in response rate between group A and B for the primary and secondary endpoints. Subgroup analysis of the type and frequency of rescue medication on primary and secondary endpoints will also be performed. All analyses will be considered statistically significant $p \leq .05$. All data assumptions will be verified and nonparametric methods may be employed if deemed appropriate.