NUMITOR study (Nummular headache Iberian study on the Treatments and Outcomes in Real-World setting) *statistical analysis plan*

Clinicaltrials number: NCT05475769
Document version 1.0.0 July 11, 2021

A descriptive analysis will be carried out presenting the ordinal qualitative and quantitative variables as frequency and percentage, and quantitative variables as mean and standard deviation, or as median and interquartile range based on the type of distribution. The normality of the distribution will be evaluated using the Kolmogorov-Smirnov test.

Statistical analysis will be performed primarily by intention to treat, but also an analysis per protocol will be carried out.

Response rate:

Primary outcome:

The main study variable will be the 50% response rate evaluated between weeks 8 and 12 of treatment, compared to the baseline. The baseline period will be defined as the month prior to the treatment onset.

For its calculation, the percentage of patients who present a reduction in the number of headache days per month of at least 50%, compared to the month prior to the start of treatment, will be calculated.

Secondary outcomes:

In addition, the 50% response rate will be calculated between weeks 20 and 24, compared to the baseline situation, as well as the 75% and 30% response rates, both between weeks 8 and 12 and 20 and 24.

The proportion of patients experiencing adverse effects and discontinuing treatment because of them will be reported.

As study subgroups, the response and tolerability will be specifically evaluated in women and elderly patients, using the previously defined variables, in women, patients over 65 years of age and over 80 years of age.

All these variables will be presented with their corresponding 95% confidence intervals.

Response predictors:
To assess which variables are associated with a greater probability of response, a logistic regression analysis will be performed in which the dependent variable will be the presence of a 50% response between weeks 8 and 12 of treatment.

First, a univariate logistic regression analysis will be carried out in which all study variables, demographic, clinical, and treatment-related will be evaluated. Those variables with a *P* value lower or equal to 0.2 will be included in a multivariate model.

A statistical significance level of 0.05 will be considered. For the adjustment for multiple comparisons, the adjustment according to False Discovery Rate will be used using the Benjamini-Hochberg method.

Statistical analysis will be performed using SPSS (IBM).