**STATISTICAL ANALYSIS PLAN:**

The main outcome of this test will be described as follows:

- the proportion of patients who agreed to enter the trial,
- the differences between those who entered and those who refused,
- the characteristics of the sample,
- adherence to treatment, and
- the number and characteristics of dropouts during follow-up.
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A preliminary statistical analysis of the primary outcomes will be carried out in order to report on the estimates for a more definitive trial:

- The characteristics of the participants in each arm of the trial will be compared, but will not be subjected to statistical tests. The variables to be compared will be sex, age, comorbidity, PBC consumption time, severity of CBP use disorder and baseline CBP craving to verify homogeneity between groups.
- Primary outcomes will be compared at four-week follow-up, as follows: percentage of abstinence from adverse drug reaction (ADR) treatment, percentage of ADR patients, and mean duration of CBP abstinence days.
- After verifying the distribution of the mean duration of CBP abstinence days in both groups, a model will be analyzed by adjusting according to the severity of the CBP use disorder in the baseline, since this is the most relevant variable reported in the literature that could influence abstinence.
- Differences in primary outcome by group (with severity adjustment) will be reported along with their 95% confidence intervals.
- The results will be analyzed using the statistical program SPSS and R. According to the variables of result to be evaluated, the analyzes will be:
- For tolerability assessment: Proportion comparison test (normal approximation, sample sizes allow) for ADR for each of the 7 post-basal measurement instances.
- For safety assessment: proportion of patients with mild, moderate and severe ADR per group analyzed with the Brunner-Munsel test, extension of the Mann-Whitney U for ordinal data with many repetitions.
- To assess CBP abstinence time: Abstinence days will be compared using a Kaplan-Mier estimator. In the case of finding a siginifcant increase in CBP abstinence days in the NAC treatment group, a correlation study (Pearson, if there is normality, Spearman otherwise) will be made between the quantitative variables measured to the individuals and days of abstinence.
- To evaluate the rate of falls in CBP consumption: Fall rates in CBP consumption will be compared using a generalized linear mixed model, with Poisson response and

times between exponential relapses. In case of over-dispersion, a model with Negative Binomial response will be considered.

- For Craving evaluation: it will be analyzed by means of test comparisons of means (Student T, under normality verified with Kolmogorov Smirnov, or U Mann Whitney, otherwise) for independent samples, considering the initial measurements (before there is much desertion ).

A comparison of means between experimental and control groups will be performed using repeated measures ANOVA (if normality is verified with Kolmogorov Smirnov and Fisher homoskedasticity) or non-parametric ANOVA analysis for repeated measures (otherwise).

It is also important to mention that incomplete data due to abandonment of the study, whether or not there is a return, should be considered for the analysis.