STATISTIC

The results obtained from clinical, instrumental and subjective evaluations will be compared between experimental timepoints and later between treatments.
The hypothesis tests used in the study will have a 95% significance level and the statistical power of these tests will be above 80%.

➢ Study Variables

Primary Variables

- To evaluate the treatment superiority with the Exímia Probiac® product associated with the Epiduo® product use versus placebo use and Epiduo® on the success rate of the participants percentage with a reduction in the total number of inflammatory and non-inflammatory lesions in the facial region.
- To evaluate the treatment superiority with the Exímia Probiac® product associated with the Epiduo® product use versus placebo use and Epiduo® on the success rate of the participants percentage with regression of the IGA scale score to grade 1 or zero.

Secondary Variables

- To compare the treatment with the Exímia Probiac® product associated with the Epiduo® product use versus placebo use and Epiduo® on the response rate of the individuals percentage who had regression of the IGA scale score.
- To compare the treatment with the Exímia Probiac® product associated with the Epiduo® product use versus placebo use and Epiduo® on the perceived efficacy of the volunteer, evaluated through subjective questionnaires.
- To compare the treatment with the Exímia Probiac® product associated with the Epiduo® product use versus placebo use and Epiduo® on the evaluation of dilated pores and inflammatory lesions through photographic records and analysis of the Visia® equipment software.

➢ Statistical Methodology

- Primary Variables data analysis

First, we will perform descriptive analyses of the study variables through frequency tables and descriptive statistics (means, standard deviation, minimum, maximum and quartiles).

The percentage of participants with a reduction in the total number of inflammatory and non-inflammatory lesions, the percentage of participants with regression of the IGA scale score to cured (zero score) or almost cured (score one) will be evaluated through the *z test* for comparison of two proportions. The tested hypotheses will be:

Ho: Perci(P + E) ≤ Perci(E)

Ha: Perci(P + E) > Perci(E)

Where Percc is the percentage of participants for each study variable.

- Secondary Variables data analysis

In order to evaluate the individuals percentage who presented regression of the IGA scale score, primarily a data descriptive analysis will be performed and subsequently the evaluation through the z test for two proportions.

Ho: Perci(P + E) ≤ Perci(E)

Ha: Perci(P + E) > Perci(E)

Where Percc is the percentage of participants for each study variable.

The comparison between treatments of perceived efficacy evaluated through a subjective questionnaire and counting the number of inflammatory lesions and dilated pores will be carried out using the Mann Whitney test, which is the most suitable for evaluating ordinal data from independent samples. The tested hypotheses will be:

Ho: Medj(P + E) = Medj(E)

Ha: Medj(P + E) ≠ Medj(E)

Where Medj is the median of the results of each study variable.

The results will be considered statistically significant at a significance level of 5% (P value ≤0.05). The significance level will be controlled by rejecting the null hypotheses if the p Value is less than or equal to 5%.

For the analysis of pores and inflammatory lesions through the Visia® equipment, the equipment's raw data will be exported regarding the parameters quantification of each participant in their respective experimental time. The Anderson-Darling normality test will be applied to identify the data normality. According to the samples distribution result, it will be checked whether there is a difference between the experimental timepoints:

• Parametric tests - *t-student* for paired data to compare experimental timepoints if the normality hypothesis is not rejected;

• Nonparametric tests - *Wilcoxon* for paired data to compare experimental timepoints and *Mann-Whitney*, in case normality is rejected.

Subsequently, the results will be compared between experimental timepoints and later between treatments.

The results will be considered statistically significant at a 5% significance level (P value≤0.05). The significance level will be controlled by rejecting the null hypotheses if the p Value is less than or equal to 5%.

The data collected in the studies will be evaluated according to the statistical methodology described and primary and secondary study variables, after the participants return from D60, D90 visits and the final visit D180.

➢ Sample Design

The study primary hypothesis is the superiority of the Exímia Probiac® and Epiduo® (P + E) combination in relation to Epiduo (E) in the mean percentage change in the number of inflammatory lesions and in the mean percentage change in non-inflammatory lesions. Below is a sample size calculation for the superiority hypotheses: The hypotheses tested for the superiority study will be:

$$H_0: p_t - p_c \leq \delta$$

$$H_A: p_t - p_c > \delta$$

The sample size in each group was calculated considering the following formula:

$$n = \frac{(p_t(1-p_t) + p_c\,(1-p_c))\;(z_{1-\frac{\alpha}{2}} + z_\beta)^2}{(p_t - p_c - \delta)^2}$$

Where:

For a 5% significance level

$z_\beta = 0,864$ → for 80% test power

p_t is the expected proportion of the test group, 69.23%

p_c is the expected proportion of the control group, 52.50%

δ is the margin of superiority, where we will use 1%

Considering the parameters, the sample size considered in the study will be of 200 participants in each group, totaling 400 participants.

- **Randomization of treatments**

The participant determination who will be part of each treatment is performed randomly.

The codes of the 400 participants were arranged in a column in the MINITAB statistical program, then a random sample of 200 participants was selected. Selected participants will use the Probiac and Epiduo combination and the remaining participants will use Placebo and Epiduo.

To ensure that the study is double-blind, the identification that the participant will receive each product sample will be performed by the sponsor according to the study randomization. The collaborators/research assistants who have contact with the participants, during the execution and dispensing of the products to the participants, do not have access to the type of product being used.