Title: Double-bllind, double-dummy, randomized clinical trial comparative between oral nicotinamide versus topical nicotinamide in the management of actinic keratosis of the face.

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Protocol

A questionnaire with the following information was completed by each participant: sex, age, skin type, profession, current or previous history of smoking and sun exposure history. Sun exposure was assessed, both current and past, as little, occasional or frequent, as well as the use of sunscreen. All participants were examined and evaluated for the number and location of facial actinic keratoses and the presence of NMSC on the entire skin by a blinded dermatologist.

At all visits participants were evaluated by the same blinded dermatologist regarding number and location of facial actinic keratoses, and presence of NMSC on the entire skin. In follow-up assessments (2, 4, and 6 months), the presence of potential adverse effects of topical and systemic medications was assessed. Photographs of the participants' faces were also taken at the initial assessment and at 6 months.

Statistical analyses plan

Continuous variables were tested for normal distribution using the Shapiro-Wilks test and visual assessment of the Q-Q graph. Continuous variables were described using mean and standard deviation when they had normal distribution (age) and median and interquartile range when asymmetric (number of basal actinic keratoses). Absolute and relative frequencies were used for categorical variables (sex, photoprotection, phototype). The comparison of

characteristics between groups was performed using the chi-square test for heterogeneity of categorical variables and Student's t-test for age. To compare the number of facial actinic keratoses between groups throughout the evaluations, the generalized estimating equations (GEE) model was used with adjustment by the Bonferroni test, considering the Tweedie distribution and log link function, due to the asymmetry of these variables. The following factors were considered for the model: group, time, and the interaction between them.

Back-transformed estimates were performed using a paired Student's t-test in each group based on the logarithm data for actinic keratosis counts at each study time point compared to the baseline.

The absolute difference between time points in the logarithm of actinic keratosis counts corresponds to the relative percentage difference between time points in the count of these lesions.

The analyses were performed by intention to treat, using the last observation carried forward (LOCF) method. All participants who completed at least the 60-day assessment were included in the analyses. Exploratory analyses were also performed including the total number of study participants.

Data were processed using IBM SPSS 25.0 version for statistical analysis and a 5% significance level was considered for all analyses.