8-Week Atopic Dermatitis (AD) Treatment Study
NCT03386032
April 27, 2018

The Sponsor's statistician or designee will perform the statistical analyses.

A. Study Measurements

Method/Measurement	Rationale	Data Collection Time Points
SCORAD, PGA, EASI, & SCORAD Lesion Evaluation	Atopic Dermatitis Grading, Physician's Global Assessment & Lesion Evaluation	Baseline Trt Week 2 Trt Week 4 Trt Week 8
Quality of Life (DQLI, POEM & Bother), Self- Assessment and Tolerability Questionnaires	Quality of Life, Self- Assessment & Tolerability	Baseline Trt Week 1 Trt Week 2 Trt Week 4 Trt Week 6 Trt Week 8
Tape Strip	Skin Barrier/Health Biomarkers	Baseline Trt Week 2 Trt Week 6

B. Statistical Analysis

Prior to the breaking of the blind and statistical analysis, all data will be checked for accuracy, completeness, and compliance to the study protocol. Subject evaluations will be checked for compliance to the study protocol regimen and subjects will be assessed for compliance to the protocol inclusion/exclusion criteria. Additionally, investigator comments will be assessed for extraneous factors that could affect the usefulness of the subject's data. Non-evaluable observations and the rationale, along with the method for handling the observations will be documented by the Sponsor prior to unblinding data and subsequent analysis of the results.

The analyses will be performed on the "full analysis set" which is as complete as possible and as close as possible to the intention-to-treat (ITT) ideal of including all randomized subjects. Preservation of the initial randomization in analysis is important in preventing bias and in providing a secure foundation for statistical tests. For those who withdraw prior to Week 8, measurements will be made at the time of treatment discontinuation and this observation will be carried forward in analyses. This provides estimates of treatment effects that are more likely to mirror those observed in actual practice. In addition to the ITT analysis, the analysis will be performed on evaluable subjects only.

1. Analysis Variables

The following variables will be analyzed to assess treatment efficacy:

1.) The primary endpoint, change from baseline in dermatologist Severity Scoring of Atopic Dermatitis (SCORAD),

2.) Change in other visual grades of Atopic Dermatitis severity from baseline (PGA, EASI and SCORAD lesion evaluation (extent and severity)),

3.) Change in skin barrier/health biomarkers from Baseline via tape stripping of the secondary lesion site and an adjacent unaffected skin site

4.) Subject self-perception (DLQI, POEM, Bothersome, SAQ)

Tolerability will be self-assessed and graded by a dermatologist or designee to determine the incidence of treatment emergent AE's.

Product weights will be collected at all visits to monitor consumption.

2. Analysis Methods

Each variable above will be analyzed separately. For the primary endpoint, superiority of treatment will be assessed relative to vehicle control.

For variables that have a continuous distribution, the post treatment evaluations will be analyzed using a mixed model for repeated measures with Subject nested within treatment (random effect), and Treatment, Week, Treatment-by-Week, Age & Baseline (fixed effects). A normal plot of the residuals will be examined to assess the assumptions of the model. Additionally, the standardized residuals will be assessed for outliers (points that lie far beyond the scatter of the remaining residuals, i.e. four or more standard deviations from zero). Transformations and nonparametric methods may be applied to address departures from the distributional assumptions of the mixed model method of analysis and/or for outliers.

For variables that are ordinal categorical, each of the visits will be analyzed separately with a Cochran-Mantel-Haenszel test. Frequency tables will be constructed.

The baseline visit will be analyzed for treatment differences as well.

Summary statistics and/or subgroup analyses will be calculated for each baseline severity (SCORAD), race, age group and gender to understand the impact of these on the overall treatment effect.

3. Significance Level

The type I error rate will be 5% based on a 2-sided test; No adjustments for multiple comparisons will be made for this study.

4. Sample Size

Assuming the most conservative SD=13.2 (Haus study), a sample size of 26 for treatment and 13 for control (2:1 randomization) will provide 80% power to detect a difference in change in SCORAD from baseline of 12.9 (two-sided test with type I error rate of 5%). A sample size of 8 for positive control and 13 for control will provide 80% power to detect a difference of 17.5.

The sample size will be inflated 30% to 62 for dropouts (34 randomized to Treatment, 17 to Control and 11 to Positive Control). Note for perspective, a clinically important difference is 8.7 units.[1]

5. Treatment Randomization

Treatment assignment will be randomized to subject to balance for baseline AD severity (SCORAD Moderate or Severe) and race (Black and Non-black) within each site.

6. Interim Analysis

This study requires rolling enrollment to meet the target base size with 50% severe subjects and may cause a delayed completion. At a certain date, if the study remains ongoing, there may be a business need to conduct an interim analysis. The purpose of this request is to understand the probability of success so that leadership can make the capital investment to meet the scheduled Global Business Plan timeline. Management will initiate the conduct of an interim analysis by signing a memo (separate from the protocol) outlining the risks, timing, principles, process and resources associated with an interim analysis.

The interim analyses will be conducted on available data for completed subjects (including dropouts). Database lock is not required for interim analysis. However, these data will be checked for accuracy and completeness and evaluability for these completed subjects will be determined and incorporated into the interim analysis. The project statistician will be the only person with authority to break the blind for interim analysis of data. The project statistician will no longer be involved in any evaluability discussions after the interim analysis. All other team members will remain blinded. Only the statistical analysis for the primary endpoint of SCORAD will be performed. Only summary results will be shared with the PGV leadership through a written communication (i.e. summary statistics and results). No un-blinded subject level data will be made available to anyone besides the statistician. No information will be shared with the rest of the clinical team supporting this project.

References:

[1] Schram, ME, Spuls, PI, Leeflang, MMG, Lindeboom, R, Bos, JD, Schmitt, J. EASI, (objective) SCORAD and POEM for atopic eczema: responsiveness and minimal clinically important difference. *Allergy* 2012; 67: 99-106.