

## **Statistical Analysis Plan**

**Study Title: Evaluation of two Riboflavin Dosing Regimens for Corneal Collagen Cross-Linking in Eyes with Progressive Keratoconus or Ectasia**

**Study Number: 2010-0243**

**NCT01143389**

**Version 2, Sept 12, 2017**

### *Main Outcome Measure*

The main efficacy outcome is the change in maximum keratometry (assessed by corneal tomography) from baseline to the 6-month post-treatment examination. This will be assessed for the per-protocol population as well as the intent-to-treat (randomized) population. The last-observation-carried-forward method will be used to impute missing data for participants lost to follow-up in the intent-to-treat analysis.

### *Null and Research Hypotheses*

The null hypothesis is that the 2 riboflavin dosing frequencies do not produce equivalent results and the research hypothesis is that they do produce equivalent results. Equivalence will be assessed with a 2 one-sided test at the 0.05 significance level. A clinically relevant margin of equivalence is considered to be  $\pm 0.75$  D. Enrollment of 510 patients will provide 80% power to determine whether the 2 treatment arms are equivalent within this margin of equivalence, assuming a mean change in maximum keratometry of -1.0 D in each group, a standard deviation of 2.7, and 10% loss to follow up during the 6-month follow up period.

### *Secondary Efficacy Outcomes*

The secondary efficacy outcome measures are the changes from baseline to 6 months after treatment in corrected distance visual acuity, uncorrected distance visual acuity, and minimum corneal thickness assessed by corneal tomography. The visual acuities will be measured with Snellen charts and converted to the logarithm of the minimum angle of resolution (logMAR) for statistical analysis. A 2-sided, 2-sample t test will be run for the per-protocol population at a 0.05 significance level.

### *Safety Analysis*

The safety analysis will tabulate adverse events for all treated eyes (both study eyes and fellow eyes).

### *Exploratory Analysis*

The protocol specifies randomization of one eye per subject to 2- or 5-minute riboflavin dosing. Study subjects may elect to have the fellow eye treated with 5-minute riboflavin dosing. An exploratory analysis will be run to examine the variability and confidence intervals for the mean paired difference between fellow eyes treated with the same or differing riboflavin dosing intervals (paired *t* test) with regard to the main outcome.