Title Page

April 20, 2017

786680-1

5-fluorouracil Versus Placebo in Periocular Full Thickness Skin Grafts

NCT02705352

10. STATISTICAL METHODS/DATA ANALYSIS

10.1 Primary endpoint or outcome measure

- The primary endpoint will be graft size change. Graft shrinkage will be evaluated by measuring the graft before and after surgery (at each post-operative visit) to estimate the contraction with or without treatment.

10.2 Secondary endpoints or outcome measure(s)

- The secondary endpoints that will be measured during the clinical study are patient and surgeon satisfaction using the scar assessment scale (POSAS) developed and previously published by Draaijers et al., treatment related adverse events, and early post-operative complications.

10.3 Sample Size Determination

- The plan number of subjects to be enrolled into the clinical study is up to 15 for the treatment group and up to 15 for the placebo groupA total sample size of 20 patients is needed to achieve a 80% power to detect a difference of at least 13.2% less than the control in mean changes in graft size from pre-treatment (2-3 weeks post-operative date) to the last follow up with a standard deviation of 10%(common to both groups) and with a significant level (alpha) of 0.050 using a two-sided two-sample equal-variance t-test. If we take into account a 20% dropout rate out of 20 patients, then 12 patients are needed to be enrolled into each arm of the study. For that reason, 15 patients are going to be enrolled but statistical analysis can be done once 10 patients in each arm have completed the study. Determined with the help of Hang Lee, PhD at MGH biostatistics department.

10.4 Analysis Population (if applicable)

- Independent sample t-test will be applied to the primary outcome analysis (i.e., comparison of mean changes in graft size from pre-treatment to the last follow up). In addition, for the secondary outcome we will utilize repeatedly measured POSAS scores over time by using longitudinal linear mixed effects model which can further determine the time dependency of the treatment effect. The model will include treatment group (group 0 for placebo and 1 for treatment), time (0=two-three weeks post-op visit / first injection, 1=second injection, 2=third injection, 3=fourth injection, 4=two to three weeks after last injection), and group x time. Both effects (1. group difference in the pre-treatment measurement 2. time trend of the control) will be considered fixed effects and the individual 2-3 weeks post-operative measurement random. Group x time effect is expected to be an increased slope of the treatment group over time. For the other outcome measurements, we will apply the same methods. Also statistical methods will include intention to treat (ITT) analysis to compare all subjects in the groups randomly assigned. We will exclude anyone who gets partial treatment, exit early or is lost to follow up; in those cases we will replace patient with another subject that meets the criteria. Discussed with Hang Lee, PhD at MGH biostatistics.

10.5 Effectiveness Analysis (if applicable)

- As described above, the population analysis that will be employed in the primary and secondary endpoints is a sample t-test with a level of significance of 0.050.

10.6 Safety Analysis

- The safety analysis of the study drug is our secondary endpoint that will be analyze with a sample t-test using a level of significance of 0.050.

10.7 Interim Analysis

- No interim analysis is planned.