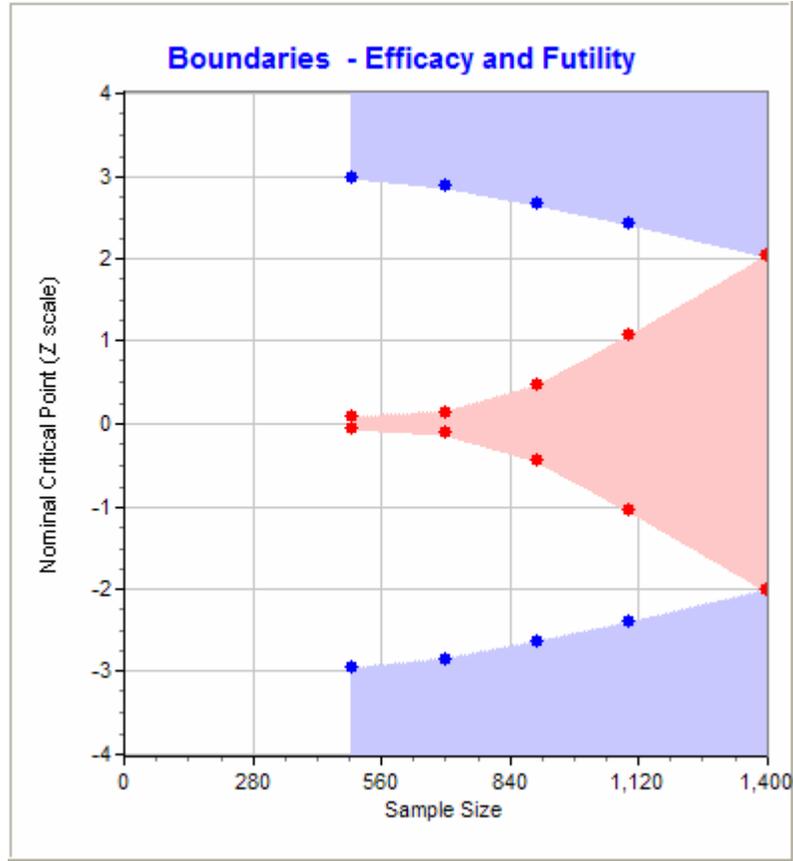


SHINE Interim Statistical Analysis Plan:

The study is designed using four interim looks for both efficacy and futility of the primary outcome and one final look for a total of 5 planned analyses of the primary outcome. The interim analysis plan uses the error spending function method with O'Brien and Fleming (OBF) type stopping guidelines. The error spending function distributes the type I and II error rates across the interim monitoring points giving the flexibility of changing the intervals of monitoring while still preserving the overall type I and II error rates. The OBF-type boundary is considered conservative as its boundaries make it difficult to terminate a study early on by requiring extreme early evidence of efficacy or futility. It spends smaller amounts of alpha at the first look and gradually increases the spending as more information is acquired. The trial may be stopped for overwhelming efficacy of one treatment group over the other or for futility at the planned interim analyses if the test statistic crosses the respective boundaries.

The current plan is to conduct the first interim analysis after approximately 500 randomized subjects complete the primary outcome assessment (90-day mRS). Assuming an accrual rate of 33.3 patients per month, it is anticipated that the 1st look will occur roughly 2.5yrs from the start of enrollment. Subsequent analyses will occur after every additional 200 subjects complete the 90-day mRS (i.e., 700, 900, and 1100). The interval may be altered if requested by the DSMB. The stopping boundaries are defined using the gamma family spending functions with a gamma value of -4 (closely resembles OBF boundaries). Specific to the futility boundaries, they are derived as non-binding meaning that if a futility boundary is crossed there is the ability for it to be overruled without inflation of the type 1 error rate. If the crossing of an efficacy boundary is overruled, then this decision can impact the type II error rate but not the type I error rate. EAST[®] 5 software (Cytel Corporation) was used for the boundary calculations.

The below graph depicts the stopping boundaries based on the test statistic at each planned look. The inner wedge represents rejection of the alternative (futility) and the outer boundaries represent rejection of the null (overwhelming efficacy). The boundaries have the property that under the null hypothesis of no difference the overall probability of crossing either outer boundary does not exceed the overall type I error rate and under the alternative hypothesis the overall probability of crossing the inner boundary does not exceed the type II error rate.



The following table lists the test statistics (shown in the above graph) and the corresponding p value at each look.

Analysis	Approximate Sample Size	Minimum Test Statistic Z value (p value) to reject H_0	Minimum Test Statistic Z value (p value) to reject H_a
1	500	2.97 (0.003)	0.06 (0.949)
2	700	2.86 (0.004)	0.13 (0.896)
3	900	2.65 (0.008)	0.45 (0.652)
4	1100	2.42 (0.016)	1.05 (0.293)
Final	1400	2.02 (0.043)	2.02 (0.043)

The SDMC will be responsible for conducting these analyses and compiling the reports for the DSMB. Since several factors need to be taken into consideration before stopping a study, safety and study progress also will be taken into consideration by the DSMB and Executive Committee in the decision to stop the study if an efficacy or futility boundary is crossed.