Retapamulin for Reducing MRSA Nasal Carriage
Statistical Analysis Plan
October 28, 2011
ClinicalTrials.gov ID: NCT01461668

Statistical Analysis Plan for Randomized Placebo Controlled Trial of Retapamulin in Mupirocin Resistant Patients

D. L. Gillen

October 28, 2011

Statistical Analysis Plan

The current study seeks to demonstrate the superiority of Retapamulin to Placebo with respect to the probability of virus clearance at 6 weeks following hospital discharge. In making the decision to terminate the study, investigators shall be guided by a formal stopping rule based on the primary endpoint of the probability of clearance at 6 weeks following hospital discharge. The test statistic shall be the normal approximation to the difference in binomial proportions between the treatment and control group. In the event that testing is performed at lower than expected sample sizes, a more conservative Fisher's Exact test will also be performed to assess sensitivity to the normal approximation under small sample sizes. Additional secondary analyses that adjust for covariates will be performed using generalized estimating equations and logistic regression.

The clinical trial may be stopped early either for reasons of demonstrated efficacy (the Retapamulin treatment arm has significantly higher probability of clearance at 6 weeks when compared to the placebo arm) or for reasons of futility (the probability of clearance at 6 weeks on the Retapamulin arm is not sufficiently higher than that on the placebo arm to warrant continuation of the trial).

The formal stopping boundaries will be determined by a symmetric one-sided design (Emerson and Fleming, *Biometrics*, 1989), a family also included in the unified family of group sequential stopping rules (Kittelson and Emerson, *Biometrics*, 1999). In the notation of the latter paper, the stopping rule will be based on a one-sided group sequential design testing a upper alternative hypothesis at a level of significance α =.025 with β =.975, an upper (efficacy) stopping boundary relationship specified by P_d = 1.0 (an O'Brien-Fleming (1979) type boundary), and a lower (futility) stopping boundary relationship specified by P_a =1.0 (an O'Brien-Fleming type boundary). It is envisioned that one formal interim analysis will be performed during the monitoring of the study, occurring at 50% of the maximal sample size. Under such a monitoring schedule and assuming a baseline probability of spontaneous clearance of 40% at 6 weeks in the placebo arm, a maximal sample size of 116 patients (58 patients on the Retapamulin arm and 58 patients on the placebo arm) will provide approximately 90.2% power to detect a 30% absolute difference in the probability of clearance at 6 weeks. The following table provides a more detailed description of the power provided by such a sample size for a range of baseline 6 week spontaneous clearance rates in the placebo arm.

Table 1: Alternatives for which a maximal sample size of 116 subjects provides the specified power as a function of the 6 week clearance rate on the placebo arm.

Power	30% Probability of Clearance at 6 weeks in the Placebo Arm		40% Probability of Clearance at 6 weeks in the Placebo Arm		50% Probability of Clearance at 6 weeks in the Placebo Arm	
	Retapamulin Probability	Diff From Placebo	Retapamulin Probability	Diff From Placebo	Retapamulin Probability	Diff From Placebo
50%	47.57%	17.57%	58.08%	18.08%	68.13%	18.13%
80%	55.10%	25.10%	65.84%	25.84%	75.91%	25.91%
90%	59.04%	29.04%	69.90%	29.90%	79.98%	29.98%
95%	62.30%	32.30%	73.25%	33.25%	83.34%	33.34%
97.5%	65.13%	35.13%	76.17%	36.17%	86.26%	36.26%

Under the planned schedule of one interim analysis at 50% of the maximal sample size and assuming a baseline probability of spontaneous clearance at 6 weeks in the placebo arm, Table 2 presents the stopping boundaries at the interim and final analysis for the specified stopping rule expressed as the absolute difference 6 week clearance rates (Retapamulin – Placebo). Also presented are the Z statistics and fixed sample upper one-sided P values that correspond to those stopping boundaries.

Table 2: Stopping boundaries for a level .025 one-sided symmetric design with $P_a = P_d = 1.0$, one interim analysis at 50% maximal information, a maximal sample size of 116 subjects, and a 6 week clearance rate of approximately 55% on both treatment arms combined.

Analysis	Sample Size (R, P)	Futility (lower) stopping boundary			Efficacy (upper) stopping boundary		
		Abs Diff (%)	Z statistic	Fixed P (upper)	Abs Diff	Z statistic	Fixed P (upper)
1	58 (29, 29)	0.000%	0.0000	0.5000	36.17%	2.7897	0.0026
2	116 (58, 58)	18.08%	1.9726	0.0243	18.08%	1.9726	0.0243

Thus, according to the above table, if the 6 week clearance rate on the combined treatment arms is 55%, an absolute difference in the probability of 6 week clearance of 0% or less (e.g., 55% probability of clearance on the placebo arm and the Retapamulin arm) when 58 subjects have been accrued to the study (29 subjects on each arm), the stopping rule would suggest that the study be terminated early with a decision that it was futile to continue the trial because there was not sufficient evidence that any beneficial effect of Retapamulin was clinically important. On the other hand, if at that first analysis there were an absolute difference in the rate of 6 week clearance of 36.17% or more (e.g., 36.92% probability of clearance at 6 weeks on the placebo arm and 73.09% probability of clearance at 6 weeks on the Retapamulin arm), the stopping rule would suggest that the study be terminated early with a decision that treatment with Retapamulin results in a statistically significant improvement in the probability of clearance at 6 weeks.

For the setting presented in Table 2 (i.e., a combined 6 week clearance rate of 55%), Table 3 presents the statistical inference that would be reported if the study were to result in observed treatment effects corresponding to the stopping boundaries. The estimates, P values, and confidence intervals reported in Table 3 have been adjusted for the stopping rule. (Note that the fixed sample P value presented in Table 2 is not appropriate for statistical inference.)

Table 3: Statistical inference regarding the effect of Retapamulin on the probability of clearance at 6 weeks (measured as the absolute difference in 6 week clearance rates between the Retapamulin and placebo arms) which would be reported if observed results corresponded exactly to the stopping boundaries for a level .025 one-sided symmetric design with $P_a = P_d = 1.0$, one interim analysis at 50% maximal information, a maximal sample size of 116 subjects, and a 6 week clearance rate of approximately 55% on both treatment arms combined as presented in Table 2.

		Futility (lower) stopping boundary			Efficacy (upper) stopping boundary		
Analysis	Sample Size (R, P)	Adjusted estimate	95% conf intvl	Adjusted P value	Adjusted estimate	95% conf intvl	Adjusted P value
1	58 (29, 29)	2.5%	(-16.2%, 25.6%)	.375	33.7%	(10.5%, 52.4%)	.003
2	116 (58, 58)	18.1%	(0%, 36.2%)	.025	18.1%	(0%, 36.2%)	.025

The exact stopping boundaries that are appropriate for the group sequential design will depend upon the exact schedule of interim analyses and the best estimate of the variability of the test statistic as computed from the observed 6 week clearance rates. The intended schedule of interim analyses is one analysis at 58 patients and a final analysis at 116 patients. Modifications of the stopping rule to account for any changes in the schedule of interim analyses and estimates of 6 week clearance rates will be made by using the parametric form of the stopping rule as specified above, with constraints imposed for analyses previously performed. Boundaries will be constrained on the scale of the maximum likelihood estimate of the treatment effect, with the current best estimate of the test statistic's variance used at each analysis (Burrington and Emerson, *Biometrics*, 2003). The one-sided type I error will be maintained at .025, and the maximal sample size will be constrained at 116 subjects.

At the formal interim analysis, the study statistician will use the stopping rule computed in the above manner as a guideline in evaluating the trial results with respect to the probability of clearance at 6 weeks. In making a final decision to terminate the study, study investigators will of course also consider information on safety endpoints, as well as consistency of outcomes for secondary endpoints and consistency of outcomes within important subgroups as described in the protocol.