Cholinesterase Inhibitor Discontinuation

Statistical Analysis Plan (5/8/2014)

NCT002248636

Analytic Plan:

The study is designed to test two hypotheses: that the Sham Taper arm will have a higher successful discontinuation rate than the Real Taper arm, and that the rate of negative outcomes will be lower in the Sham Taper arm compared to the Real Taper arm. This is a non-inferiority design. The null hypothesis is that Real Taper is better than Sham Taper by a non-inferiority (or equivalence) limit. This limit can be defined in a number of ways, but the most straightforward in this setting is as the "smallest value that would represent a clinically meaningful difference". {Wiens, 2002 #75} In the setting of dementia, we propose that a non-inferiority limit of 25% is appropriate. This is somewhat smaller than the limit used in other non-inferiority studies.

The main threat of this design is a Type II error (falsely accepting that there is no difference between groups), which could happen if the sample was inadequate. As described further below, the sample size has been selected in order to ensure that the study would be adequately powered to detect a meaningful difference between groups. For the main analyses, we will use a threshold of $p < 0.05$ to define statistical significance for the main analysis, and $p < 0.025$ for the secondary analyses. The more stringent threshold is selected for the latter because of multiple comparisons.

Discontinuation Rates: The primary outcome is the fraction of participants who completed a successful 6-week taper (either real or sham). For instance, if half of the Real Taper and 65% of the Sham Taper group successfully discontinued the medication, then p(Real) = 0.5, and p(Sham) = 0.25. The statistical significance of the difference between these proportions can be computed manually. The variance of the estimate is $\frac{p*(1-p)}{n}$, where p is the proportion and n is the total number of observations. The difference between groups is p(Real) – p(Sham). The pooled variance is var(Real) + var(Sham), and the standard deviation is the square root of this sum. The z-score of the group difference is established using the mean variance relationship, as $\frac{Mean\ Difference}{Standard\ Deviation}$, and the z-score can be converted into a p-value assuming a normal distribution. This method will be used to assess both the primary study endpoint and the group differences at the interim analyses. For instance, in the example of p(Real) = 0.5 and p(Sham) = 0.65, if there were 100 in each group, the z-score of the difference would be 2.17, and a two-sided p-value for the difference would be 0.038.

Change in Cognitive, Functional, Behavioral, and Caregiver Outcomes: For the four domains assessed at baseline and follow-up (cognition, functioning, behaviors, and caregiver burden), we will compare Real Taper and Sham Taper groups, using T-tests. This will be an intent-to-treat analysis, including those who did or did not discontinue successfully. If analysis of the sample suggests that the groups are unequally distributed based on patient or disease characteristics, then regression models controlling for these factors will be produced, examining the same outcomes.

Unblinding and Post-Study Treatment Decision: The treatment received will be unblinded for the caregiver and Veteran at the Completion Visit, and written information will be provided about what this means (i.e. exactly what medication the Veteran received). This will be provided to both arms, since it is possible that even participants in the Sham Taper arm would desire to stop the CI medication. The unblinding will not be shared with the Study Coordinator, Research Assistant, or Investigators. At week 12, study staff will contact the caregiver to ascertain what CI medication, if any, the Veteran is taking. Because there is no comparison group, this will be a descriptive result rather than a group comparison.

	Sham taper	Real taper	p-value of difference
% with successful discontinuation			
Change in Cognition (SCIP)			
Change in Functioning (ADCS-ADL)			
Change in Behaviors (BEHAVE-AD)			
Change in Caregiver burden (ZBI)			
Return to pre-study CI medication		[Not applicable]	

Patient Factors Associated with Negative Outcomes: For the 100 participants in the Sham Taper arm, we will explore which patient factors were associated with negative outcomes. The main patient and disease variables (age, sex, race, duration of AD, duration of treatment, current or historical use of memantine, use of antipsychotic medication, use of other psychotropic medication) will be analyzed as predictors. Each of the main outcomes described above (successful discontinuation; cognition; functioning; behavior; and caregiver burden) will be analyzed as outcomes, separately, using regression models.

Interim Analyses: There is the possibility that one of the arms could experience a greatly increased risk of negative outcomes. Continuing the trial in this setting would be ethically unwarranted, by the principles of beneficence and nonmaleficence, since harm to Veterans could be prevented by either stopping or continuing the CI medication. We therefore propose to conduct interim analyses every 6 months, starting 2 years after study initiation. We will aggregate all the completed cases to date, and calculate differences between Real Taper and Sham Taper in (1) successful discontinuation, and (2) adverse events. The Biostatistician will apply formal statistical methods to control for overall significance level and power of the trial, and will present summary results to the Principal Investigators if there is concern about excess harm in one treatment arm.{Pignon, 1994 #67} If the interim analyses show a large relative risk reduction (>25%) in one arm, then the Biostatistician and Principal Investigators will weight the totality of the evidence and consider stopping the trial.