Open Label Study of Subcutaeneous Immunoglobulin (SCIg) in Myasthenia Gravis

NCT02100969

February 22, 2019

Data Analysis Plan and Statistical Considerations:

1. Analysis of Primary Outcome:

At the end of the 9-week IVIg screening phase, baseline QMG scores of all the patients will be recorded. At the end of SCIg experimental treatment phase (Week 12), the QMG score will be captured and compared to Week 0. If the increase in QMG scores from Week 0 to Week 12 in the experimental treatment phase is found to be no more than 3 points, then they will be considered to be a 'success' in terms of their response. We hypothesize that the positive response rate of these patients is at least 70%. Allowing a margin of 5%, our hypotheses are formally stated below:

Null hypothesis H_0: Proportion of patients whose QMG scores are increased by more than 3 points at the end of the SCIg treatment phase ≤ 0.65

Alternate hypothesis H_A: Proportion of patients whose QMG scores are increased by no more than 3 points at the end of the SCIg treatment phase > 0.65

This hypothesis will be tested using a one sided one sample test of proportions with the normal approximation, at the 5% significance level. We will also report a 95% confidence interval for the true proportion of subjects who experience a 'success' as with a sample size of 25 patients, we will have a margin of error of 0.19. In the experimental treatment phase, patients who either experience treatment failure (as previously defined on pg. 22) or clinical deterioration (as defined above on pg. 22) will be withdrawn before Week 12 and we will therefore impute for both non-positive responses at Week 12, a discrete QMG score increase of more than 3 points. For example, if the largest deterioration score observed is 8, then a QMG score ranging between 4 and 8 will be imputed at Week 12. Although we do not expect many missing observations at Week 12 of the SCIg phase, the outcomes recorded at these intermediate time points will allow us the ability to impute data at this endpoint. Specifically, in the case where no outcome is available for a subject at Week 12 due to the subject's perception of a worsened condition, we will impute for this subject a QMG score increase at Week 12 of more than 3 points. In cases where subjects refuse to proceed to Week 12 or are lost to follow-up even though they were responding well on the treatment (as evidenced by the intermediate measurements), we will impute their Week 12 observation using the last observation carried forward (LOCF) approach. We will complement our LOCF approach with sensitivity analyses covering the following alternate approaches: (1) Multiple imputation with 5 replicates per imputation to account for the uncertainty inherent to the imputation (2) Mixed model calculations accounting for the trend in QMG values over time (3) Best case and worst-case scenarios.

2. Additional Exploratory Analysis of Primary Outcomes:

Additional exploratory analysis will be carried out treating QMG scores at baseline, Week 4, Week 8 and Week 12, as a continuous response variable. Descriptive statistics will be reported using means and standard deviations if the distribution of QMG scores is found to be normal and using medians and interquartile range if they are found to be non-normal. One advantage of reporting scores at the intermediate weeks is that it will allow us to assess whether or not some patients on SCIg stabilize early in terms of the QMG scores. It will also allow us to study the trend over time in an exploratory manner. We will further complement our exploratory analysis by conducting a two-sided non-parametric signed rank test in order to assess whether the QMG scores changed significantly after switching from IVIg to SCIg. Also, we will dichotomize the QMG into two groups

(high and low) based on clinically relevant thresholds and compare the differences in proportions at end of study and baseline.

3. Analysis of Secondary Outcomes:

Analysis of secondary outcome measures as listed in the Aims section such as MG-ADL, MG QOL-15, the MG composite score and TSQM will primarily be conducted only for those who complete the study. We will conduct a two-sided signed-rank test to assess whether these scores changed significantly from baseline (Week 0) to Week 12. In case of missing values for the MG-ADL, MG QOL-15, and the MG composite score in cases where subjects refuse to proceed to Week 12 even though they were responding well on the treatment (as evidenced by the intermediate measurements) or are lost to follow-up, we will impute their Week 12 observation using the last observation carried forward (LOCF) approach. We will also report the proportion of subjects enrolled in the subcutaneous experimental treatment study phase (Week 0 to Week 12) fulfilling our definition of improvement (as mentioned on pg. 24) along with a 95% confidence interval. We will compare between the two phases the percent of subjects meeting the definition of deterioration, worsening, stability and improvement. We will analyze the effect of prednisone dosage (Increase vs Not Increased) on clinical improvement (Yes vs No) using a 2x2 Fisher's exact test in the SCIg phase of the study by comparing dose levels at Week 12 to Week 0 for those patients who complete Week 12 of the study. To do this, we will ask the patients at Week 0, Week 4, Week 8 and Week 12 about their prednisone dosage levels. Those patients who exit the study prematurely due to deterioration before Week 12 will be excluded from this Fisher's test calculations. In the event that the Week 12 prednisone dose observation is missing even when patients have completed Week 12 (QMG or MGADL done), we will use the LOCF approach to impute this missing value as long as at the last available assessment, the patient was deemed to be improving (in terms of QMG or MGADL scores as defined under "Subject deterioration, worsening, rescue medication and improvement"). A two-sided signed-rank test will be also conducted to assess whether IgG levels changed significantly between the intravenous screening phase (Week -10 to Week 0) to the subcutaneous experimental treatment study phase (Week 1 to Week 12). All tests will be conducted at the 5% level of significance. For the secondary outcome measures related to monitoring the safety profile of patients between the two study phases, a similar test will be conducted when the safety parameters measured are continuous variables and a one sample test for the difference in proportions will be conducted when they are measured as treatment-related severity rates. The comparison epochs for safety are also between the intravenous screening phase (Week -10 to Week 0) and the subcutaneous experimental treatment study phase (Week 0 [after first SCIg dose] to Week 12). Adverse events occurring in the two phases (mild, moderate/severe) will be summarized using a McNemar's test.

4. Sample Size Considerations:

With a sample size of 25 patients, we have at least 70% power to detect a success rate of 85% or higher using the chi-square test compared to an expected success rate of 65% or lower. We anticipate we will be able to assess efficacy, safety and tolerability of SCIg with the current sample size over 12 weeks and compare that these parameters to the 12-week IVIg phase. The selected sample size will enable us to complete study enrollment with the current number of sites.

MG is a rare disease and MG studies have consistently experienced difficulty enrolling subjects due to a multiplicity of poorly understood reasons.[34] In the Methotrexate study of MG and similar to other previous MG studies, enrollment has been a challenge. However, we managed to complete enrollment of 50 subjects by adding sites. In the current SCIg study protocol, the eligible

study population is narrowed due to the inclusion criterion requiring MG cases to be on stable IVIg doses. While 85 to 90% of MG patients are seropositive for either the AchR or MuSK autoantibodies, some of these cases are treated in clinical practice with IVIg maintenance. Based on the pre-site selection feasibility survey, 25 subjects is a reasonable and achievable goal with the selected five sites. If enrollment is found to be slower than predicted, we are ready to add more sites to complete this study.

5. Study Populations:

Safety population: All patients enrolled at baseline constitute the safety population. The subjects in this population will included in the analysis of adverse events, vital signs, clinical laboratory findings, and other safety data. But for the purpose of statistical analyses, the rates of adverse events experienced by these subjects in the SCIg phase will be compared to the rates experienced during the IVIg phase of the study. Adverse events will be tabulated by treatment group, severity, and perceived relationship to study drug. For each adverse event, the treatment groups will be compared regarding the occurrence of at least one event using the Fisher's exact test. The comparisons will be repeated excluding all mild symptoms. Continuous measures such as vital signs and laboratory test results will be analyzed in a manner similar to that for the primary outcome variable.

Intent to treat population (ITT): Only those patients who receive at least one dose of SCIg are considered to be the primary population which is the same as ITT population. The ITT will be included in the analysis of baseline findings and efficacy results. Only those patients who receive at least one dose of SCIg are considered to be the primary population and the intent-to-treat population.

Unscheduled visits: In the event that there are unscheduled patient visits, we will report the frequency of such visits for the two phases of the study. We will also document the date and reason for such visits and assess if these visits are systematic or random. If occurrence of such visits is due to side effects we will compare the rates of such events across the two phases of the study. Testing at unscheduled visits is done only to check and assess clinical worsening. If no worsening is found, patients will continue to be a part of the study. If a patient experiences a worsening event that does not qualify as clinical deterioration (per pg. 22) and the investigator determines it is safe for that patient to continue, the patient will remain in the study. On the other hand, if a patient experiences a worsening event that qualifies as clinical deterioration the patient will be withdrawn from the study. We will compare the within-person variation to the cross-person variation for the overall data. If the within-person variation is found to be less than the cross-person variation, we will use a LOCF approach to impute the patient's QMG score at the next time point and do a sign rank test on that time point and baseline. On the other hand, if the within-person variation is found to be greater than the cross-person variation, we will impute the observation at the next time point followed by a sign rank test.

SAS 9.4 will be used for all analyses. All data management and statistical analysis will be performed in the Department of Biostatistics at the University of Kansas Medical Center. The Velos Clinical Research Information System (CRIS) will be used at all sites to enter and view data. This will be available to the safety monitors (see below).