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Statistical Considerations and Analysis Plan (Part 9 of Safety and Efficacy of Imatinib for Preserving Beta-Cell Function in New-onset Type 1 Diabetes Mellitus)

In 1 collection

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ABSTRACT

This is Part 9 of "Safety and Efficacy of Imatinib for Preserving Beta-Cell Function in New-Onset Type 1 Diabetes Mellitus".

This clinical study is supported by JDRF. The aim of the collection is to determine whether imatinib will slow the progression of the autoimmune destruction of ß cells and lead to the preservation of C-peptide secretion in T1DM and to assess Diabetes-related objectives and safety of Imatinib in new-onset type 1 diabetes mellitus".

ATTACHMENTS

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COLLECTIONS

Collection of Protocols and Guidelines for Safety and Efficacy of Imatinib for Preserving Beta-cell Function in New-onset Type 1 Diabetes Mellitus

KEYWORDS

Safety, Efficacy, Imatinib, Beta-cell function, New-Onset Type 1 Diabetes Mellitus

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GUIDELINES

Analyses of study data will be conducted to address the primary and secondary objectives of the trial, other stated objectives, and other interrelationships among elements of study data of interest to the investigators and of relevance to the objectives of the study. Such analyses may also entail the use of data from other studies in combination with data from this study. Likewise, data from this study may be used in combination with data from another study to address objectives of that study. Analyses by gender and race/ethnicity, as appropriate, are also planned.

9.1 PRIMARY OUTCOME AND ANALYSES

The primary outcome of each participant is the area under the stimulated C-peptide curve (AUC) over the first 2 hours of a 4-hour mixed meal glucose tolerance test conducted at the one-year visit. The AUC is computed using the trapezoidal rule that is a weighted sum of the C-peptide values over the 120 minutes. By the mean value theorem of integral calculus, the weighted mean C-peptide in pmol/mL is simply AUC/120.

The primary statistical hypothesis to be assessed in the study is whether:

- The mean C-peptide value for study subjects receiving imatinib is significantly higher than the mean value for placebo subjects.

The primary analysis will employ the weighted mean derived from the 2 hour AUC for each participant transformed as log(mean C-peptide+1). The comparison between the two treatment arms will be based on a t-test of treatment effect in an ANCOVA model adjusting for gender, baseline age and baseline log(C-peptide+1)[190].

9.2 SECONDARY OUTCOMES AND ANALYSES

Additional analyses of the primary outcome will include:

- A log rank test of the difference in the hazard function between groups in the incidence of the loss of the 2 hour peak C-peptide < 0.2 pmol/ml on a semi-annual MMTT [191], and
- Longitudinal analyses using mixed effects models with a random intercept and slope of the C-peptide values over the post-treatment period, adjusted for the baseline level of C-peptide. The average intercept and slope will be compared between groups adjusting for age, gender and the baseline log(C-peptide+1).

Additional secondary objectives are to examine how imatinib affects the following:

- Mean area under the stimulated C-peptide curve (AUC) curve at 12 months
- Mean area under the stimulated C-peptide curve (AUC) over 4 hours at 24 months
- HbA1c levels over time

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- Insulin dose (units/kg) over time
- Number of severe hypoglycemic events
- Number and severity of adverse events

The mean levels of quantitative variables (e.g. HbA1c and insulin dose) over all followup values will be compared between groups using a normal errors longitudinal analysis.

The prevalence of a binary characteristic (e.g. yes/no or positive/negative) at a single visit (e.g. a history of hypoglycemia during follow-up) will be assessed using a logistic regression model. The prevalence of a binary characteristic over time will be assessed using generalized estimating equations.

The rates of severe hypoglycemic events and severe adverse events will be computed (total number of events divided by total patient years of follow-up) and the rates compared using a Poisson regression model, allowing for over-dispersion using a quasilikelihood model as appropriate. Tests of significance will employ a robust estimate of the variance.

The above analyses will also be conducted to adjust for age, gender, baseline log(Cpeptide+1) and baseline HbA1c; and by race/ethnicity, as appropriate. Analyses will also be conducted to examine the effect of HLA or other genotype.

Analyses will also be conducted to assess heterogeneity of the effect of treatment group (the group difference) as a function of age, gender, baseline log(C-peptide+1) and baseline HbA1c; and by race/ethnicity and HLA or other genotype. Heterogeneity will be assessed using a test of treatment group by covariate interaction in an appropriate regression model.

9.3 ADDITIONAL OUTCOMES AND ANALYSES

Additional outcomes of interest include

- Change in autoantibody levels and/or B cell function
- Antigen specific and non-specific T and B cell subset enumeration and function
- Responses to vaccination (tetanus and killed flu)

The analyses of each outcome will be conducted using the methods for a quantitative outcome, binary outcome, or rate as described in Section 9.2 above.

9.4 SAMPLE SIZE AND POWER CALCULATIONS

The primary analysis will compare the difference between the treated group versus the placebo group in the levels of the 2 hour AUC-mean using the log(mean C-peptide+1) in an ANCOVA model adjusting for gender, baseline age, and baseline log(Cpeptide+1). Estimates of log(mean C-peptide+1) and root mean square error (RMSE) in the placebo group were obtained from prior studies. Among subjects with baseline C-peptide > 0.2 pmol/ml and age <=21 years, the mean log(C-peptide + 1) values is 0.306 with RMSE = 0.185.

The planning parameters for the protocol were based upon the inclusion of adults and children. Unfortunately, the FDA has declined the request to lower the age and, therefore, the study will only enroll adults at this time.

Hence, it is appropriate to revisit the design of the study in light of restricting the eligible population to be age 18 and over. In previous studies, it has shown the older a participant is, the lower the rate of C-peptide loss. This means that the current design of detecting a one-year C-peptide projected level 45% greater than expected on the control arm corresponds to an increase in C-peptide over the baseline value at enrollment, which is not practical. However, analyses completed after this study was initially designed indicate that the appropriate variance estimate to use for the sample size calculation should be smaller than what was used in the current design. This has the net effect of increasing the sensitivity of the trial to detecting an effect size smaller than the advertised value in the current design.

Using standard equations for the comparison of two means, a sample size of 40 Imatinib treated and 20 placebo treated subjects with complete data needed for the primary analysis, would provide power of 85% to detect a 0.35

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increase in the mean log(Cpeptide + 1) (0.306 vs. 0.445, which corresponds to 75% of the RMSE) in the experimental treatment group using a two-sample T- test at the 0.05 level (one-sided).

Assuming that 10% of the subjects will have missing data (one-year MMTT was not done or subject withdrew prior to the one-year assessment), the sample size goal for this study is 66 subjects (46 + 22). Should the number with missing data exceed 10%, the study will enroll additional replacement subjects as needed.

9.5 INTERIM MONITORING PLAN

For purposes of the 6-month analysis, a trend for benefit would be an outcome that does not exclude a significant result being achieved at the end of Phase 2 with a twelve month outcome as specified by the protocol. Changes from baseline in stimulated C-peptide mean AUC in T1D patients on placebo have been reported as approximately 30% at 6 months (Orban et al 2011[39], Raz et al 2007[194]). Sample size calculations were thus based on the assumption of a ~30% treatment effect at around 6 months of treatment and a standard deviation for baseline- and placebo-adjusted stimulated C-peptide mean AUC of 0.39 nmol/liter/2h (Greenbaum et al 2012). In this case, an interim analysis will calculate the conditional power after 21 participants have been evaluated. Based upon the table that follows, should the calculated interim Z value be greater than or equal to 0.8, the conditional power would be estimated to be at least .26 and .74 if the true effect is as assumed under the alternative hypothesis at study conclusion. Therefore, a threshold will be set on the conditional power as the level-of-proof that the difference in stimulated C-peptide mean AUC between gleevec and placebo is of presumed benefit to allow the study to move forward to phase two.

Table of Conditional Power Assuming an Alternate Effect Size (defined as (mu1- mu0)/2(sd) = 0.37, an interim analysis at 21 patients and a final analysis at 66 patients. Two-tailed alpha = 0.05

A	B	C
Interim Z Value	**Conditional Power Under Observed Trend**	**Conditional Power Under Protocol Assumed Effect**
0.0	<0.01	0.54
0.4	0.06	0.65
0.8	0.26	0.74
1.2	0.58	0.82
1.6	0.86	0.89

Additional interim analyses will be conducted when 50% of the targeted number of study subjects have reached the planned end point (i.e., one year of follow up) and will be reviewed by the Data and Safety Monitoring Board (DSMB) for assessment of effectiveness and safety. If a group sequential stopping boundary is crossed, the DSMB may recommend termination of the trial early. The Lan-DeMets[195] spending function with an O'Brien-Fleming boundary will be used to protect the type I error probability for the primary outcome analyses, and to assess the significance of the interim results periodically during the trial. The spending function that approximates the O'BrienFleming boundaries is:

$$\alpha(t^*) = 2 - 2\,\Phi\left[\frac{Z\alpha/2}{\sqrt{t^*}}\right]$$

where t^* is the information fraction ($0 < t^* \leq 1$), α_1 is the α - level of the interim (one-sided) test and α is the over-all type I error.

The DSMB will also consider early termination due to absence of a treatment effect (i.e. futility) based on the method suggested by Ellenberg et al[196]. The stopping rule is: if the t-test (as described in the primary analysis and positive values reflect a higher values among the experimental group) is less than or equal to 0 at $t^* \geq 0.5$, the study should be stopped based on the futility of rejecting the null hypothesis at the completion of the trial. Simulation studies conducted confirmed that this rule combined with the LanDeMets stopping rules have

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negligible effect on the type I and II error probabilities. Additional analysis will assess potential adverse outcomes of treatment and will assess the incidence of all severe adverse events.

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