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A Model Based Approach to Sample Size Estimation in Recent Onset Type 1 Diabetes

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Abstract

The area under the curve C-peptide following a 2-hour mixed meal tolerance test from 481 individuals enrolled on 5 prior TrialNet studies of recent onset type 1 diabetes from baseline to 12 months after enrollment were modelled to produce estimates of its rate of loss and variance. Age at diagnosis and baseline C-peptide were found to be significant predictors and adjusting for these in an ANCOVA resulted in estimates with lower variance. Using these results as planning parameters for new studies results in a nearly 50% reduction in the target sample size. The modelling also produces an expected C-peptide that can be used in Observed vs. Expected calculations to estimate the presumption of benefit in ongoing trials.

Keywords

C-peptide; Clinical trial; Type 1 diabetes

Introduction

Type 1 diabetes is characterized by the loss of insulin production secondary to the autoimmune destruction of insulin secreting β-cells in the pancreas. Studies of potential therapeutic agents have generally accepted C-peptide, in response to a standardized stimulus, as a measure of treatment response [1]. It has been observed that the amount of C-peptide within 100 days of diagnosis, and its rate of loss over the next two years, varies with the age of the individual at diagnosis [2–3]. Therefore, the evaluation of studies of therapeutic interventions in recent onset type 1 diabetes need to be adjusted for the effects of these baseline characteristics. We reasoned that since analysis of trial results required this statistical adjustment, that the planning parameters for these trials also should incorporate these adjustments. In this paper, we establish new planning parameters for recent onset type

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[*]A complete list of the TrialNet Study Group can be found in the Supplementary Data online.

Author Contributions

Brian Bundy and JP Krischer researched data, contributed to discussion, wrote manuscript, and reviewed/edited manuscript.

Conflict of Interest

The authors declare that they have no conflicts of interest. Drs. Bundy and Krischer work at the TrialNet Coordinating Center funded by the NIDDK of the NIH.

Supporting information

Additional supporting information may be found in the online version of this article at the publisher's web site.

1 diabetes trials. The primary hypothesis test remains the treatment effect on C-peptide within the ANCOVA model adjusting for baseline c-peptide, treatment and age at diagnosis. We derive these parameters from the retrospective analysis of 5 TrialNet recent onset studies. Type 1 Diabetes TrialNet is a multi-institutional, multi-national study group focused on prevention of type 1 diabetes through prospective clinical trials, and obtaining a better understanding of the progression of autoimmunity to diabetes diagnosis. Evaluation of promising new prevention therapies is done, in part, by conducting trials in recent onset individuals with stimulated C-peptide as their end point.

There are 6 parameters that need to be set when determining the sample size: 1. statistical power, 2. the type I error, 3. sidedness of the test, 4. the minimum increase in the experimentally treated group mean over that of the placebo treated group that we desire to detect (minimal detectable difference), 5. the variation in c-peptide levels in the study population (i.e., standard deviation) and 6. the study group mean of c-peptide under the null (i.e., control group mean). The first three are essentially dictated by convention and/or the specific trial under development. The fourth has varied over the TrialNet studies and may be influenced by the agent being evaluated (Table 1). The last two parameters (5 and 6) are dependent on the subjects enrolled and should be aligned with the TrialNet experience. We evaluated the five completed TrialNet studies to determine the appropriateness, and potential improvement into the design and analytical plan of future recent onset trials.

Materials and Methods

Subjects

Baseline and one-year follow-up data from five completed TrialNet studies of recent onset type 1 diabetes subjects [4–8] were included in this analysis. A written informed consent and/or assent was obtained from all participants prior to participation in these studies. The eligibility for these studies was quite similar in that all had to meet the definition with respect to the diagnosis of type 1 diabetes and enrollment within 100 days of diagnosis. The studies did vary at the younger age range by design with an upper limit of 45 years.

Statistical Considerations

The primary data of interest are the timed C-peptide levels from the first 2 hours of a mixed-meal tolerance test (MMTT). These timed values are combined using the trapezoidal rule to approximate the area under the curve (AUC) then divided by the time interval (hereafter: AUC mean). These AUC means were log transformed (after adding 1) in keeping with the primary analysis of each study: analysis of covariance (ANCOVA) of the AUC mean regressing on age, log transformed (after adding 1) baseline C-peptide AUC mean, gender, and study treatment assignment. The model is expressed algebraically as:

$$\log(Cp_{12}+1)=\beta_0+\beta_{Cp}\cdot\log(Cp_0+1)+\beta_{\text{Age}}\cdot\text{Age}+\beta\cdot I\begin{bmatrix}\text{male}&=1\\\text{female}&=0\end{bmatrix}+\beta_{Rx,i}+\varepsilon$$

where Cp's represent the pertinent C-peptide AUC means, $I_{[\ ]}$ is an indicator function for gender, β's are the unknown coefficients to be estimated, and ε is the random variable expressing the unexplained variation. The ε is assumed to be normally distributed with mean zero and unknown but constant variance. A linear model using the QR decomposition method was employed to estimate the coefficients. A predicted C-peptide level for specific covariate values was determined by substituting both the estimated coefficients for the β's and the covariate values for their corresponding variables in the model. A predicted population mean of C-peptide was determined in a similar fashion except covariate means were substituted and treatment coefficient was set to zero i.e., placebo (henceforth predicted control group mean).

The analytical cohort included all subjects from both the placebo and experimental treatment groups. Each experimental treatment had its own coefficient allowing the possibility of partially activity or even an unfavorable effect (all placebo groups were considered as one and was the implicit category in the output). Adjusting for treatment rather than excluding such subjects increased the analytical cohort by approximately four times (521 vs. 128); consequently increasing the precision of the β coefficients and the variance of ε estimates (i.e., residual mean squared error). By including the experimental treatment groups, the modeling mimics an actual primary analysis that would be conducted on a future trial and thus producing a more appropriate estimate of residual mean squared error.

The necessary statistical characteristics of ε were assessed using the Bartlett's test [9], Shapiro-Wilk W-statistic test [10] and modified White's test [11]. Bartlett's test was employed to assess the variance of each treatment group for each trial (N=12). White's test was modified by focusing exclusively on the relationship of the continuous covariates (i.e., baseline c-peptide and age) to the squared deviations. A simple linear model adequately captured the change in the residual mean squared error over the range of baseline c-peptide (Cp_0). The expected value of the root mean squared error (RMSE) is expressed algebraically as:

$$E(\mathrm{RMSE}|Cp_0)=\sqrt{-0.000648+0.044\cdot\log(Cp_0+1)}$$

The Monte Carlo simulation addressed the drift in the RMSE as a function of baseline c-peptide. Using our estimates for RMSE and the control group mean from the five study fitted model, we calculated the sample size (15+29, assuming a 1:2 randomization) to detect a 50% increase in the treated group c-peptide AUC mean that would produce a statistical power of 0.85 when setting the Type I error at 0.05 (1-sided test). Each simulation sampled 44 baseline c-peptide and age pairs at random with replacement. The standard deviation of the unexplained error was determined from the equation above based on the baseline c-peptide levels sampled. We set the simulations at 20,000 which provided a 95% confidence interval for the statistical power and Type I error of ±0.0049 and ±0.0030, respectively. All analyses were conducted in TIBCO Spotfire S+™ 8.2.

Results

Table 1 provides some pertinent details of the five recent onset Type I Diabetes Trials. Together they represent 521 subjects of which 498 had their 12 month MMTT assessment representing 95.6% retention. The sample size calculation for each study used the same standard deviation estimate and the same control group mean; only the design effect size and the α-level of the primary hypothesis test(s) varied across trials.

Table 2 displays the results of modeling the transformed 12 month C-peptide AUC means regressing on the covariates listed. The GAD study did not have a placebo control group, rather three injections of aluminum hydroxide served as the control treatment. The coefficient estimate for this control was indistinguishable from the other placebo groups, and therefore, it was combined with the other control groups as a single control group in the model. An extension of this model was fitted that included a variable for trial in order to determine if there were any systematic differences among the five studies beyond any distributional differences of the covariates; the F-test was not significant ($p = 0.26$). Although the F-test suggests very little evidence for a systematic trial difference over-all, the Canakinumab Trial was associated with the largest positive coefficient (0.0411), indicating the 12 month C-peptide levels were higher, on average, than the other studies, even after adjusting for the covariates in table 2. This explains the significance of Canakinumab treatment indicator for the model presented in Table 2 when not adjusting for trial. The Canakinumab group does not have a significantly higher c-peptide mean when compared to its randomized control group [3]. Gender was not statistically significant and contributed nothing to reducing the unexplained variance. The square-root of the residual mean squared error (RMSE) was 0.152 and the R-squared value was 0.593. The R-squared value is the proportion of variance of the C-peptide values explained by the covariates.

Table 3 provides the observed and model predicted transformed C-peptide means of the control group, and the RMSE for each of the five recent onset trials. The observed standard deviation estimates represent unadjusted estimates of the variation and vary more among the trials than the corresponding RMSE's. The last row includes estimates when analyzing all five studies combined. When modeling each treatment group separately, the RMSE (not shown) ranged from 0.134 to 0.162 for the experimental groups and ranged from 0.145 to 0.171 for the placebo groups suggesting no systematic differences in variation among the treatment-study groups. This observation was substantiated with a non-significant ($p = 0.77$) Bartlett's Test (homogeneity of variance test).

The statistical behavior of the unexplained error term was explored further. The Shapiro-Wilk W-statistic, tests for departures from normality and was applied to the residuals from the five study fitted model; the statistic was 0.997 with a significance level of 0.58 supporting that the residuals are normally distributed. A more subtle assumption but requires adherence is whether the variance of the explained error is constant (referred to as homoscedasticity); specifically to assess the evidence that the variance is constant throughout the range of the predicted values. This was explored using two tests. The Bartlett test was used to check for departure from homoscedasticity across the 9 treatment groups represented in these five studies; the statistic was 6.25 with a significance level of 0.86. The

other test was a modification of White's test which is designed to detect a linear drift in the variance across the continuous covariates, specifically baseline c-peptide and age. This test was found to be significant: F-test = 4.04 ($p < 0.0001$). Further exploration indicated the heteroscedasticity was not due to outliers, extreme values, or age, but only the baseline c-peptide level. We fit a linear model to the squared deviations and found that the RMSE estimate range was 0.0964 – 0.195; the associated 5^{th} and 95^{th} percentile of the baseline c-peptide, respectively. We explored the deleterious effect this heteroscedasticity might have on our hypothesis testing, specifically the Type I error and power. The results of a Monte Carlo simulation study yielded probability estimates of 0.8548 and 0.0497 for the statistical power and Type I error, respectively. Consequently, the five study RMSE estimate, which turns out to be an average due to the varying C-Peptide levels, is a satisfactory choice to use in the sample size calculation.

The RMSE used in the design of the five trials was 0.179 based upon an earlier publication [5]. This is larger than any of the modelled estimates from the five studies, although less than the observed unbiased unadjusted estimate of the standard deviation (Table 3). To preserve the sensitivity of the ANCOVA treatment coefficient test, the standard deviation value used in the sample size calculation must be greater than or equal to the actual RMSE. With substantial evidence from the five trials, an RMSE of 0.152 would seem to be a good choice for determining sample size for future trials. However, for the sake of protecting the sensitivity of the trial and recognizing that the RMSE estimate is subject to random variation, the 90% upper bound of RMSE estimate of 0.158 may be a better choice.

The minimal detectable difference on the transformed scale is invariant to the control group mean. Unfortunately, the minimal detectable difference on the original C-peptide scale, even as a percent is not, due to the transformation employed i.e., $\log [Cp + 1]$ (this is in contrast to the simple log transform where the minimal detectable difference expressed in percent is invariant to the control group mean). A specific control group mean must be selected as a reference point to quantify the minimal detectable difference on the original scale. The predicted control group mean derived from the ANCOVA model serves this purpose. The combined predicted estimate of 0.334 (or 0.397 on the original scale) would serve as a good choice for the control group mean of any future trial (Table 3). An alternative choice might be the 90% lower bound of 0.319 (or 0.376 on the original scale) which would increase the confidence that the realized control group mean is greater than the predicted and thus the realized minimal detectable difference on the original scale is less than advertised in the design. Figure 1 illustrates this inverse relationship and quantifies the diminishing minimal detectable difference in percent on the original scale as a function of the control group mean for three specified minimal detectable differences defined using 0.376 as the reference control group mean.

Table 4 provides the sample size for two and three arm trials, two minimal detectable differences (50% and 65%) and for various combinations of RMSE's and predicted control group means estimated from the five studies combined. One-sided and two-sided calculations are given for the 2 arm studies for completeness and to demonstrate comparability with the TrialNet completed studies. In most TrialNet studies it is customary to increase the target sample size by 10% as an allowance for study subjects who drop out or

otherwise are missing the endpoint. Included in Table 4 is the sample size required if the trial design is based on a simple two-sample t-test in order underscore the reduction in size by exploiting the relationship the 12 month c-peptide AUC means have with the subject's baseline age and C-peptide.

Discussion

The TrialNet experience represented by five studies in recently diagnosed patients with type 1 diabetes provides a wealth of data to use for estimating a target sample size for a new study using C-peptide as its primary end point at 12 months from randomization. The model produces a greatly reduced RMSE which is consistent across all five trials. Using the RMSE estimate as the standard deviation in the sample size formula leads to a much smaller sample size, on the order of 50% or more when compared to a simple t-test. The use of the upper bound for the standard deviation and a lower bound of the estimate for the control group mean provide a conservative sample size goal to increase the likelihood of maintaining the advertised power and minimal detectable difference (expressed as a percent) in the design.

The modelled approach has other benefits as well. The data set and model can be configured to fit a planned study within a specific age range to provide more tailored estimates. This is important when planned trials are restricted to adolescents or adults or when older individuals are to be excluded based upon the expected benefit of the trial agent. Another potential benefit is to use the fitted model for calculating predicted C-peptide values as if treated with placebo and contrasting these values with the observed values of treated subjects in an ongoing trial. This Observed-minus-Expected analysis might allow for early termination of such a trial due to the lack of evidence of greater than predicted c-peptide levels (futility analysis). Alternatively, observed levels larger than or similar to predicted values might be considered no evidence of harm and allow an imposed age restriction to be removed in an ongoing trial. We are currently exploring the use of the Observed-minus-Expected value as a continuous measure of response. Specifying a certain threshold might provide an effective definition of a dichotomous response.

The ANCOVA model of all five trials (Table 2) uncovered the danger of historical comparison analysis where it appeared that Canakinumab was active when compared with all five control groups together but was inferred to be inactive in the randomized comparison. The confounding issue is the greater than average 12-month c-peptide levels in both treatment groups for that trial unexplained by the covariates.

The transformation $\log [Cp + 1]$ is critical in maintaining normally distributed residuals a critical assumption in the ANCOVA model. Unfortunately this transformation leads to difficulties in expressing the minimal detectable difference on the original c-peptide scale. Although expressing it as a percent increase of the treated group mean to the control group mean provides some sense of the precision of the trial it only holds for the predicted control group mean stipulated in the statistical design.

The probability of retention in TrialNet over the five studies is remarkable at 95.6%. Such a consistently low percentage of missing values considerably reduces any challenge to the

integrity of such trials. There is no universally accepted statistical method that can correct for a large percentage of missing values, and therefore, the results of such a trial, are open to question.

The simulation studies conducted evaluated the modest heteroscedasticity that was directly proportional to the baseline C-peptide. The results clearly indicated that no deleterious effect was noticeable on the statistical power and Type I error. We conducted an unsuccessful but exhaustive exploration of other transformations that might eliminate the heteroscedasticity but at the same time maintain the normally distributed residuals.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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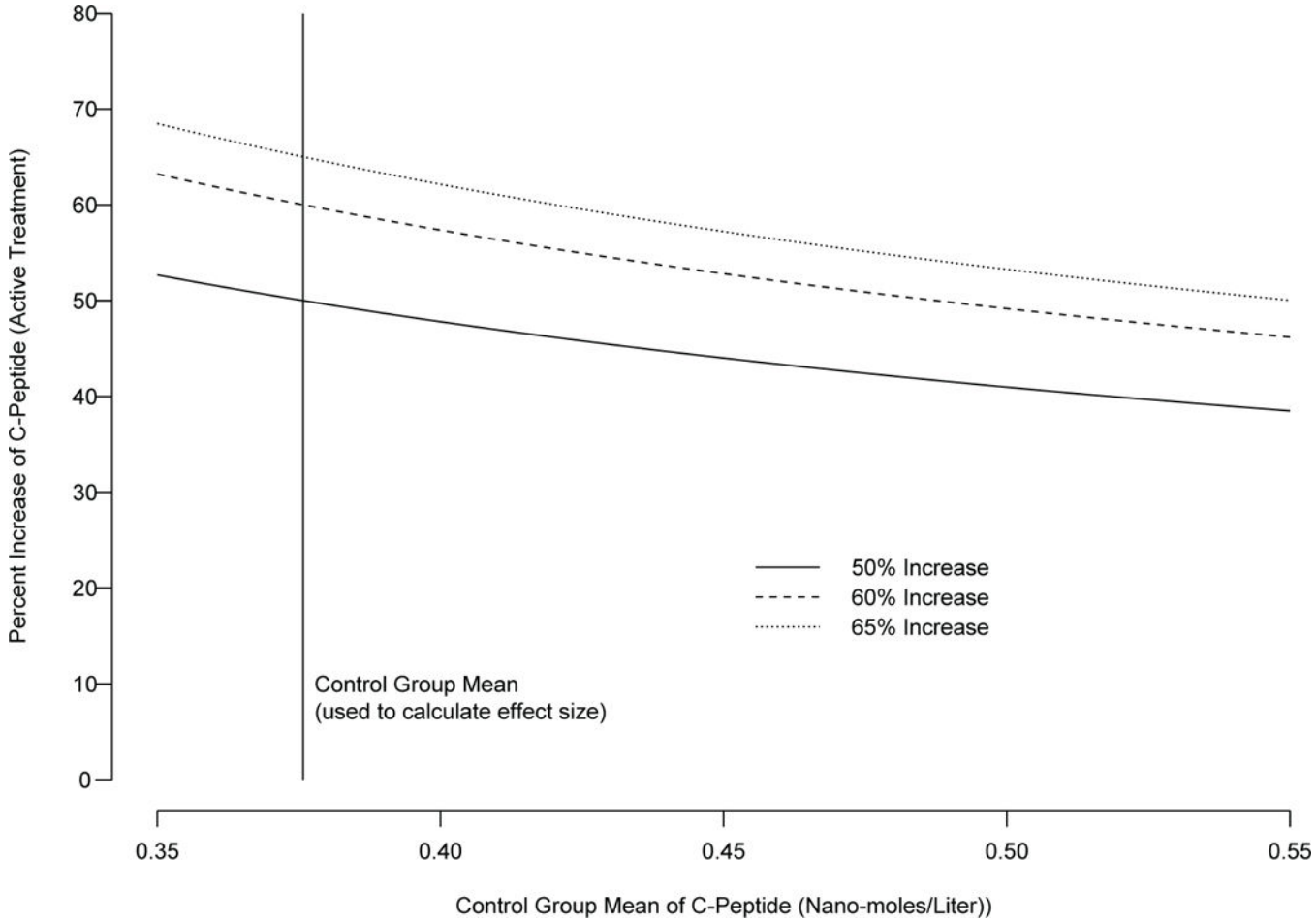

Figure 1.
Percent Increase of C-Peptide in Treatment Group Mean as a Function of Control Group Mean

Table 1

Characteristics of the Five TrialNet Recent Onset Type 1 Diabetes Trials (All studies assumed the same control group mean at the primary on-study time for analysis to be 0.248 with a standard deviation of 0.179 [6]. Both these estimates are on the transformed scale: $f(x) = \log[x_i + 1]$ on which the primary analysis was conducted. The inverse transform $f^{-1}(y) = \exp(y) - 1$ returns values to the more meaningful mole concentration scale e.g., $f^{-1}(0.248) = 0.281$ pmol/ml.

Subject Characteristic/Statistic	MMF ± DZB TN-02*	Rituximab TN-05	GAD TN-08	Abatacept TN-09	Canakinumab TN-14
Number Randomized Control: Experimental(s)	42:31:41	29:52$^{\Delta}$	48:49:48	35:77	22:47
Age					
Median	15.0	16.1	15.2	12.9	11.1
1st & 3rd Quartiles	12.4, 22.9	13.2, 23.4	10.6, 20.6	10.1, 17.3	9.2, 15.7
Range	8.7 – 46.1	8.3 – 40.5	3.6 – 45.8	6.5 – 36.8	6.1 – 31.9
Gender					
Male	68 (59.6%)	50 (61.7%)	81 (55.9%)	66 (58.9%)	38 (55.1%)
Female	46 (40.4%)	31 (38.3%)	64 (44.1%)	46 (41.1%)	31 (44.9%)
C-Peptide AUC Mean†					
Baseline Mean (pmol/ml)	0.660	0.712	0.697	0.706	0.611
12-month Mean (pmol/ml)	0.366	0.522	0.404	0.476	0.388
Minimum Detectable Difference‡ $\frac{\mu^{\text{Expermntl.}}_{C-\text{Pep}}}{\mu^{\text{Placebo}}_{C-\text{Pep}}}$	$\frac{0.464}{0.281}=1.65$	$\frac{0.464}{0.281}=1.65$	$\frac{0.450}{0.281}=1.60$	$\frac{0.422}{0.281}=1.50$	$\frac{0.464}{0.281}=1.65$
Design alpha-level (sidedness of test)	0.0167 (1)	0.05 (1)	0.025 (1)	0.05 (1)	0.05 (1)
Design Allocation	1:1:1	1:2	1:1:1	1:2	1:2
Sample Size Goal$^{\bullet}$	40×3=120	20+39	38×3=114	32+64=96	20+40=60

*MMF = Mycophenolate Mofetil; DZB = Daclizumab; Originally designed as a 3-arm trial: placebo, MMF only, and MMF + DZB, an error in the randomization system allocated 12 subjects to the unintended treatment of MMF only. These 12 were excluded from all analyses conducted in this manuscript.

$^{\Delta}$Not included are 5 subjects that had treatment suspended due to FDA safety alert.

† Values displayed have been referred to as the geometric-like means defined as $\exp\left[\frac{1}{N}\sum_{i=1}^{N}\log(Cp_i+1)\right]-1$ pmol/ml where Cp_i represents the 2-hour MMTT AUC mean of C-Peptide for i^{th} subject.

‡ Expressed as a ratio of the two treatment group means, both in mole concentration units, pmol/ml. Note: the actual effect size used for sample size calculation is the difference in the group means on the transformed scale.

• Includes over sampling to account for up to 10% not having a 12 month 2-hour MMTT and the associated timed values of C-Peptide.

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Table 2

Results of the Analysis of Covariance (ANCOVA) of transformed 12 month C-peptide AUC means regressing on baseline C-Peptide, age at randomization, gender, and treatment group.

Covariate	Coefficient Estimate	Wald Statistic	P-Value
Intercept	−0.196	−7.56	< 0.0001
Baseline C-peptide	0.812	22.3	< 0.0001
Gender	0.00104	0.0736	0.941
Age	0.00648	7.7	< 0.0001
Treatment *: MMF	−0.0294	−0.963	0.336
Treatment *: DZB/MMF	−0.0127	−0.479	0.632
Treatment *: Rituximab	0.073	2.95	0.003
Treatment *: GAD-Al × 2 then Al × 1	−0.0159	−0.634	0.527
Treatment *: GAD-Al × 3	−0.00503	−0.199	0.843
Treatment *: CTLA-4Ig	0.0768	3.56	0.0004
Treatment *: Canakinumab	0.0584	2.26	0.024

* All treatment coefficients are relative to the implicit category of the control treatment

Table 3

Summary Statistics Pertinent for Future Designs of the transformed C-Peptide AUC means at 1 Year for the five Recent Onset Type 1 Diabetes Trials ($f(Cp) = \log[Cp + 1]$)

Trial	Model Based*		Observed	
	RMSE†	Control Group Mean	Standard Deviation$^{\Delta}$	Control Group Mean (N)
MMF ± DZB TN-02*	0.157	0.307	0.200	0.308 (40)
Rituximab TN-05	0.145	0.380	0.250	0.357 (29)
GAD TN-08	0.152	0.345	0.213	0.349 (46)
Abatacept TN-09	0.146	0.328	0. 256	0.325 (32)
Canakinumab TN-14	0.144	0.335	0.250	0.316 (21)
All 5 Studies Combined	0.152◙	0.334•	0.232	0.332 (168)

*The linear model is adjusted for baseline C-peptide, age and gender. The control group estimated mean is calculated using the fitted coefficients from the model and the mean baseline C-peptide level, the mean age and the ratio of males to females of the entire study cohort.

†RMSE is the root mean squared error taken from the fitted model – used as the standard deviation in the sample size formulas

ΔPooled unbiased estimate of the standard deviation (pooled over treatment group)

◙90% upper confidence bound: 0.158

•90% lower confidence bound is 0.319

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Table 4

Planning Parameters and Sample Sizes for Recent Onset Trials (Statistical Power is 85% for all calculations)

No. of Treatment Arms	Planning Parameters (from Table 3)			Other Planning Parameters			Total Sample Size	
	Estimates Used*	Standard Deviation (RMSE)	Predicted Control Group Mean	MDDΔ	α level† (sides of test)	Allocation Ratio (C:E)•	Excluding Those with Missing Endpoint	Including Those Missing Endpoint (inflated 10%)
2	RMSE & PCGM	0.152	0.334	50	0.05 (1)	1:2	15+29	16+32
	90% LB of PCGM	0.152	0.319	50	0.05 (1)	1:2	16+31	17+34
	90% UB of RMSE	0.158	0.334	50	0.05 (1)	1:2	16+31	17+34
	Both LB of PCGM & UB RMSE	0.158	0.319	50	0.05 (1)	1:2	17+33	19+37
	Unadjusted Estimates (t-test)	0.232	0.332	50	0.05 (1)	1:2	34+67	37+74
	5 studies combined estimates	0.152	0.334	65	0.05 (1)	1:2	9+18	10+20
	90% LB of control group mean	0.152	0.319	65	0.05 (1)	1:2	10+19	11+21
	90% UB of RMSE	0.158	0.334	65	0.05 (1)	1:2	10+19	11+21
	Both LB mean & UB RMSE	0.158	0.319	65	0.05 (1)	1:2	11+21	12+23
	Unadjusted Estimates (t-test)	0.232	0.332	65	0.05 (1)	1:2	21+41	23+46
	5 studies combined estimates	0.152	0.334	50	0.05 (2)	1:2	18+36	20+40
	90% LB of control group mean	0.152	0.319	50	0.05 (2)	1:2	19+38	22+43
	90% UB of RMSE	0.158	0.334	50	0.05 (2)	1:2	20+39	22+43
	Both LB mean & UB RMSE	0.158	0.319	50	0.05 (2)	1:2	21+42	23+46
	Unadjusted Estimates (t-test)	0.232	0.332	50	0.05 (2)	1:2	42+84	47+93
	5 studies combined estimates	0.152	0.334	65	0.05 (2)	1:2	11+22	13+25
	90% LB of control group mean	0.152	0.319	65	0.05 (2)	1:2	12+24	13+26
	90% UB of RMSE	0.158	0.334	65	0.05 (2)	1:2	12+24	14+27
	Both LB mean & UB RMSE	0.158	0.319	65	0.05 (2)	1:2	13+26	14+28
	Unadjusted Estimates (t-test)	0.232	0.332	65	0.05 (2)	1:2	26+52	29+57
3	RMSE & PCGM	0.152	0.334	50	0.025 (1)	1:1:1	3×24=72	3×27=81
	90% LB of PCGM	0.152	0.319	50	0.025 (1)	1:1:1	3×26=78	3×29=87
	90% UB of RMSE	0.158	0.334	50	0.025 (1)	1:1:1	3×26=78	3×29=87

No. of Treatment Arms	Planning Parameters (from Table 3)			Other Planning Parameters			Total Sample Size	
	Estimates Used*	Standard Deviation (RMSE)	Predicted Control Group Mean	MDD$^{\Delta}$	α level† (sides of test)	Allocation Ratio (C:E)$^{\bullet}$	Excluding Those with Missing Endpoint	Including Those Missing Endpoint (inflated 10%)
	Both LB of PCGM & UB RMSE	0.158	0.319	50	0.025 (1)	1:1:1	3×28=84	3×31=93
	Unadjusted Estimates (t-test)	0.232	0.332	50	0.025 (1)	1:1:1	3×56=168	3×62=186
	5 studies combined estimates	0.152	0.334	65	0.025 (1)	1:1:1	3×15=45	3×17=51
	90% LB of control group mean	0.152	0.319	65	0.025 (1)	1:1:1	3×16=48	3×18=54
	90% UB of RMSE	0.158	0.334	65	0.025 (1)	1:1:1	3×16=48	3×18=54
	Both LB mean & UB RMSE	0.158	0.319	65	0.025 (1)	1:1:1	3×17=51	3×19=57
	Unadjusted Estimates (t-test)	0.232	0.332	65	0.025 (1)	1:1:1	3×35=105	3×38=114

*All estimates are based on the five studies combined. All 4 combinations of the estimate or 90% upper/lower bound of the estimate for both RMSE and the predicted control group mean are listed. Along with, the observed control group mean and the pooled unbiased estimate of the standard deviation (pooled over treatment group).

$^{\Delta}$Minimal Detectable Difference expressed as a percent increase on the original C-Peptide scale of the experimental group mean to the predicted control group mean.

†For the 3 treatment arm trials two-pairwise tests will be performed, thereby controlling the overall type I error at 0.05

$^{\bullet}$C is the Control Group and E is the Experimental Group.