Co-Stimulation Modulation with Abatacept in Patients with Recent-Onset Type 1 Diabetes: Follow-Up One Year After Cessation of Treatment

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Abstract

Objective. We previously reported that two years of co-stimulation modulation with abatacept slowed decline of beta-cell function in recent-onset type 1 diabetes mellitus (T1DM). Subsequently, abatacept was discontinued, and subjects followed to determine whether there was persistence of effect.

Research Design and Methods. In 112 subjects (ages 6-36) with T1DM, 77 received abatacept and 35 received placebo infusions intravenously for 27 infusions over two years. The primary outcome – baseline-adjusted geometric mean 2-hour area under the curve (AUC) serum C-peptide during a mixed meal tolerance test (MMTT) at two years – showed higher C-peptide with abatacept versus placebo. Subjects were followed an additional year, off treatment, with MMTTs performed at 30 and 36 months.

Results. C-peptide AUC means, adjusted for age and baseline C-peptide, at 36 months were 0.217 (95% CI: 0.168, 0.268) and 0.141 (95% CI: 0.071, 0.215) nmol/L for abatacept and placebo groups, respectively (p=0.046). The C-peptide decline from baseline remained parallel with an estimated 9.5 months' delay with abatacept. Moreover, HbA1c levels remainded lower in the abatacept group than in the placebo group. The slightly lower (non-significant) mean total insulin dose among the abatacept group reported at 2 years was the same as the placebo group by 3 years.

Conclusions. Co-stimulation modulation with abatacept slowed decline of beta-cell function and improved HbA1c in recent-onset T1DM. The beneficial effect was sustained for at least one year after cessation of abatacept infusions, or three years from T1DM diagnosis.

Type 1 diabetes mellitus (T1DM) is an immune-mediated disease in which insulin-producing beta-cells are destroyed [1]. A number of studies have used various forms of immune intervention in recent-onset T1DM, usually initiated within three months of diagnosis, in an attempt to preserve residual beta-cell function. We have previously reported that co-stimulation modulation with abatacept administered for two years slowed decline of beta-cell function over this period in patients with recent-onset type 1 diabetes mellitus (T1DM) [2]. Longer term, chronic therapy designed to alter the immune response may carry untoward effects that outweigh the benefits of therapy. Moreover, the therapeutic window for effect of such approaches may be limited to the peri-diagnosis period. In addition, transient alteration of the rate of beta-cell dysfunction early in diagnosis may have long term clinical benefits [3,4]. Thus, this trial was designed for two years of therapy, with continued follow-up to evaluate risks and benefits after the pre-specified primary study outcome at two years. Herein, we report the effect of abatacept in T1DM one year after discontinuation of study drug.

Research Design and Methods:

This Phase 2 clinical trial was registered with ClinicalTrials.gov (NCT00505375). In our earlier report [2], we described the study design and patient characteristics. Figure 1 depicts the CONSORT diagram, showing randomization/enrollment and retention of subjects during the study through 36 months of follow-up. The baseline characteristics of the two groups are summarized in Table S1 . A total of 112 patients were enrolled in a double-masked parallel group design, and were randomized in a 2:1 ratio, with 77 subjects receiving abatacept and 35 subjects receiving placebo. Abatacept (CTLA4-Ig, Orencia®, Bristol-Myers Squibb) was given as a 30 minute intravenous infusion at a dose of 10 mg/kg (maximum 1000 mg/dose) in a 100 ml 0.9% sodium chloride, on days 1, 14, 28, and then every 28 days with the last dose on day 700 (total 27 doses). Normal saline infusion was used as placebo. Patients did not receive any premedication. Beta-cell function was evaluated by stimulated C-peptide secretion. The pre-specified primary outcome of this trial was a comparison of the area under the curve (AUC) of stimulated C-peptide response over the first 2 hours of a 4-hour MMTT conducted at the 24 month visit. Four-hour MMTTs were performed at baseline and at 24 months; 2-hour MMTTs were performed at 3, 6, 12 and 18 months. After completion of the 2-year treatment phase, subjects entered a follow-up phase to continue to assess safety and efficacy, including the performance of 2-hour MMTTs at 30 and 36 months.

The study protocol is available at the Type 1 Diabetes TrialNet public website www.diabetestrialnet.org.

Statistical Analyses:

Details of the statistical plan are included in our earlier report [2]. In summary, all analyses were based on the pre-specified intention-to-treat (ITT) cohort with known measurements. Missing values were assumed to be missing at random. The p-values associated with the ITT treatment comparisons of the primary and secondary endpoints are one-sided. The pre-specified analysis method for C-peptide mean AUC, HbA1c, and total daily insulin dose was an analysis of

covariance model adjusting for baseline age, gender, baseline value of the dependent variable, and treatment assignment. In the protocol design, a normalizing transformation of $\log(X_{C-Pep}+1)$ was pre-specified for C-peptide AUC mean and normal plots of the residuals indicated that it was adequate transformation in order to fulfill the assumptions of the linear model employed in the analysis. The C-peptide mean AUC equals the AUC divided by the two-hour interval (i.e. AUC/120). The AUC was computed using the trapezoidal rule from the timed measurements of C-peptide during the MMTT. Means that are calculated on this normalizing scale then inverse transformed back are referred to geometric-like means. The time to peak C-peptide falling below 0.2 nmol/L was analyzed using the Cox proportional hazards model, which assumes a constant hazard ratio for treatment group. The data would suggest that this ratio is not constant and the estimate provides an approximate average over the follow-up period. Note that 95% confidence intervals are more akin to 2-sided tests while all p-values reported are one-sided in accordance with the design which is based on a one-sided hypothesis test.

Results:

In the primary analysis at two years, those subjects assigned to abatacept had a population mean stimulated C-peptide 2-hour AUC, adjusted for age, gender, and baseline C-peptide, of 0.378 nmol/L (95% CI: 0.328, 0.431), versus 0.238 nmol/L (95% CI: 0.167, 0.312) for those assigned to placebo (p=0.0014). At three years, one year after discontinuation of treatment, population mean stimulated C-peptide 2-hour AUC, adjusted for age, gender, and baseline C-peptide, was 0.217 (95% CI: 0.168, 0.268) nmol/L in the abatacept group, versus 0.141 (95% CI: 0.071, 0.215) nmol/L in the placebo group (p=0.046). Figure 2A displays the adjusted population C-peptide mean 2-hour AUC over three years. Subjects who received abatacept had a significantly higher mean AUC of 28%, 30%, 38%, 59%, 48%, and 54% compared to placebo subjects at 6, 12, 18, 24, 30, and 36 months, respectively. The the geometric-like means of the unadjusted values for mean stimulated C-peptide 2-hour AUC at 2 years were 0.375 nmol/L in the abatacept group and 0.266 nmol/L in the placebo group, and at 3 years were 0.214 nmol/L in the abatacept group and 0.156 nmol/L in the placebo group.

The predicted population mean of C-peptide AUC by treatment group over time was calculated, to display the impact of treatment on delaying the decline of C-peptide (Figure 2B). Considering the entire three year observation period, the estimated lag time in the means of the abatacept group to drop to the same level as the placebo group is 9.5 months (95% confidence interval [3.44, 15.7]), p=0.0011. At two years, this was 9.6 months, indicating a consistent parallel separation when including the third year data.

Following the 36 month assessment, 35% of subjects in the abatacept group continued to have a peak stimulated C-peptide > 0.2 nmol/L compared to 30% among placebo subjects (Figure 2C); the difference (5%) is considerably smaller than 13% observed at 2 years. Thus the rate of the peak C-peptide falling below 0.2 nmol/L for the abatacept group was initially less but increased after year 2 and is close to that in the placebo group. However, the adjusted relative risk estimate of the peak C-peptide falling below 0.2 nmol/L (based on proportional hazards

model and adjusting for age, gender, and baseline C-peptide) was 0.60 (abatacept to placebo group; 95% confidence interval [0.34, 1.1]; p=0.043).

At two years, the adjusted mean HbA1c was lower in the abatacept group (7.21, 95% CI: [6.96 to 7.46]) than in the placebo group (7.87, 95% CI: [7.48 to 8.26]) in the placebo group and in the abatacept group. During the extended follow-up, the abatacept group continued to have a lower adjusted mean HbA1c than the placebo group, with the values at three years being 7.64, 95% CI: [7.28, 7.99] in the abatacept group and 8.55, 95% CI: [8.00, 9.11] in the placebo group; (see Figure 3A). Noteworthy for HbA1c is that the significance levels are < 0.005 for all 6 month interval group differences. However, insulin doses in the two groups were nearly the same at 3 years (difference: 1%) with a non-significant difference of 4% at 2 years and only significantly less use in the abatacept group at 6 and 12 months (Figure 3B).

Further analyses of the pre-defined subgroups are shown in Figure 4. The homogeneity test of treatment effect was significant for DR3 allele status (p = 0.025) and race (p < 0.001). The significance level of the qualitative interaction between DR3 allele and treatment was adjusted for multiple comparisons and remained significant (p = 0.014). The significance level of the homogeneity test for race may be spurious stemming from the small sample non-whites assigned placebo (N=3) and the potential lack of normally distributed C-peptide values required for a valid model-based test.

No new safety issues emerged during the extended follow-up (On-Line Appendix Table S1).

Discussion:

We previously reported the primary outcome of this clinical trial [2]. Those results demonstrated that two years of co-stimulation modulation with abatacept slows the decline of beta-cell function, measured by C-peptide as an index of endogenous insulin production, in recent-onset T1DM. The current report, which extended follow-up of subjects for an additional year without further abatacept therapy, shows that the difference between the abatacept and placebo groups is maintained, with the delay in decline of beta-cell function estimated to be 9.5 months, virtually identical to the estimated delay of 9.6 months seen after two years of abatacept therapy. Thus, it would appear that post-cessation the autoimmune response did not rebound to a more aggressive state, but rather the subjects previously treated with abatacept experienced a gradual and continued loss of beta-cell function at a rate similar to that seen in the placebo group. These data suggest that co-stimulation blockade initiated within three months of diabetes onset transiently alters the natural history of disease progression. At the time of onset of diabetes, when there is an ongoing autoimmune response, co-stimulation blockade appears to arrest or diminsh T-lymphocyte-mediated effects on beta-cell function. Subsequent monthly treatment may maintain this effect but does not appear to extend or amplify it. At a mechanistic level, such an outcome could be ascribed to modulation of co-stimulation-dependent autoreactive T-lymphocytes that are specifically recruited in the peri-diagnosis period, perhaps as a component of epitope spreading. There is evidence to

indicate that at the doses used in the present study, abatacept is highly effective in limiting priming of T-lymphocyte and B-lymphocyte responses to newly encountered antigens [5,6]. However, after the initial post-diagnosis response abatacept treatment does not alter further the tempo of the underlying, progressive loss of beta-cell function. This may imply that this later component of the autoimmune process is co-stimulation-independent. This would also be consistent with the observation that cessation of co-stimulation blockade does not result in acceleration of decline in beta-cell function.

It is not known how late after diagnosis abatacept treatment could be used. Also, an unanswerable question, from the current data alone, is whether a shorter treatment protocol would be sufficient to maintain the slowed decline of beta-cell function. This is a particularly important issue, since abatacept is a potential candidate to be tested in a trial for prevention of T1DM in individuals determine to be at high risk for the disease. Abatacept also is a candidate to be a component of a combination therapy protocol in recent-onset T1DM. The apparent lack of effect of abatacept in HLA-DR3 negative subjects needs further study. It is not related to age, as the mean age in HLA-DR3 positive subjects was 14.5 years and the mean mean age in HLA-DR3 negative subjects was 14.9 years, with no statistically significant shift in age distribution.

Four recent randomised trials with adequate sample size that have demonstrated some preservation of beta-cell function in T1DM as evidenced by stimulated C-peptide secretion, including the earlier report from this trial using abatacept for co-stimulation modulation. The other trials have used anti-CD3 [7,8], and anti-CD20 [9]. Interestingly, in all of these trials, the treatment effect diminished with time, such that after an initial effect, C-peptide secretion subsequently declined parallel to the control group in all of these studies. Yet, continued effects on insulin dose were seen after four years in one of the anti-CD3 trials [10].

Whether a transient change in the natural course of the disease will have long term clinical benefit is unknown. In this regard, it is important to reflect upon the results from the DCCT study. In that trial, after the primary endpoint was met and all individuals were offered intensive therapy, there were no longer differences between the two groups with regard to HbA1c [11-13]. Yet, the previously intensively treated group had less retinopathy and nephropathy even after the HbA1c levels converged [11-12], and less macrovascular disease more than 15 years later [13]. These observations suggest that a short term treatment close to diagnosis had a clinically important effect many years later [11-13]. Remarkably, in our trial the significantly improved HbA1c persisted in the abatacept treated group even after discontinuation of the therapy. In the light of the DCCT trial results, this may translate into reduction of micro and macrovascular complication at later stage.

In the current study, we demonstrate that treated subjects as a group maintain better HbA1c and still have more insulin secretion three years after diagnosis than the placebo treated subjects, although the number maintaining C-peptide >0.2 nmol/L has diminished. Even if the eventual course of beta-cell destruction in these individuals results in essentially absent beta-cell function over time, this early preservation may, like the DCCT treatment, have long term

benefits. Continued long term follow-up of these cohorts will be needed to address this important question. Moreover, the optimal duration of treatment is unknown. Further studies are indicated to clarify the role of co-stimulaton blockade in altering the course of recent-onset diabetes, and in preventing the disease in individuals at risk thereof. To that end, a prevention study is currently underway (www.clinicaltrials.gov, NCT01773707).

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Bristol-Myers Squibb (Princeton, NJ) provided abatacept (Orencia®), but had no involvement with study design, conduct, or management; data collection, analysis or interpretation; or manuscript preparation. There are no agreements concerning confidentiality of the data between the sponsor and the authors or the institutions named in the credit lines. The authors provided Bristol-Myers Squibb a copy of the original manuscript prior to submission.

Lifescan Division of Johnson and Johnson provided blood glucose monitoring meters and strips to research subjects.

Author Contributions: The trial was proposed to TrialNet by Tihamer Orban, who served as study chair. Jay S. Skyler wrote the first draft of this manuscript. Other members of the manuscript writing group included Tihamer Orban, Brian Bundy, Carla J. Greenbaum, Mark Peakman, and Jeffrey P. Krischer. All of the authors (DB, LAD, SEG, RG, PAG, JBM, RM, AM, PR, WER, DS, DKW, DMW) were involved in the conduct of the study and the collection and review of study data. The writing group (TO, BB, CJG, MP, JPK, JSS) had full access to all of the data and made the decision to publish the paper. The other authors (DB, LAD, SEG, RG, PAG, JBM, RM, AM, PR, WER, DS, DKW, DMW) reviewed and commented on various versions of the paper, and suggested revisions. Jay S. Skyler is the guarantor of this work and, along with the writing group (TO, BB, CJG, MP, JPK), had full access to all the data in the study and takes responsibility for the integrity of the data and the accuracy of the data analysis.

Dualities:

Dr. Orban reports serving on the Data Safety Monitoring Board for Osiris Therapeutics, and being a founder of Orban Biotech LLC; Dr. Becker reports receiving a grant from Diamyd; Dr. Gitelman reports serving on an advisory board for Genentech; Dr. Goland reports receiving grants from Diamyd and Tolerx; Dr. Gottlieb reports serving on advisory boards for Genentech, Eli Lilly, Sanofi-Aventis, and Tolerx, and reports receiving grants from Bayhill Therapeutics, Diamyd, Macrogenics, Omni BioTherapeutics, and Tolerx; Dr. Greenbaum reports receiving grants from Bayhill Therapeutics, Diamyd, and Tolerx; Dr. Marks reports serving on an advisory board for Amgen; Dr. Moran reports serving on an advisory board for Pfizer, and receiving grants from Tolerx, Merck, and Osiris Therapeutics; Dr. Raskin reports serving on advisory boards for Amgen, AstraZeneca, MannKind, and Novo-Nordisk, serving on speakers bureaus for Merck and Novo-Nordisk, and receiving grants from Aegera,

Andromeda Biotech, Bayhill Therapeutics, Biodel, Boehringer Ingelheim, Calibra, CPEX, Generex, Hoffman-LaRoche, MannKind, Novo-Nordisk, Osiris Therapeutics, and Reata; Dr. Schatz reports serving on advisory boards for Eli Lilly and GlaxoSmithKline, and receiving a grant from Diamyd; Dr. Wherrett reports receiving lecture fees from Eli Lilly and Medtronic; Dr. Wilson reports serving on an advisory boards for DexCom and Genentech, and receiving grants support from Genentech, Diamyd, and Osiris Therapeutics; Dr. Skyler reports serving on boards for Amylin Pharmaceuticals, DexCom, Moerae Matrix, Sanofi Diabetes, and Viacyte, and reports receiving grants from Bayhill Therapeutics, Halozyme, Intuity, Mesoblast, and Osiris Therapeutics. No other potential conflict of interest relevant to this article was reported. Specifically, Drs. Bundy, Monzavi, Peakman, Russell, and Krischer report having no conflicts.

Figure Legends.

Figure 1. Enrollment, Randomization, and Follow-up of Study Participants.

Figure 2. **(A)** Population mean of stimulated C-peptide 2-hour AUC mean over time for each treatment group. The estimates are from the analysis of covariance model adjusting for age, gender, baseline value of C-peptide, and treatment assignment. Y-axis is on a log(y + 1) scale. The significance level at 36 months is 0.046. **(B)** Predicted population mean of stimulated C-peptide 2-hour AUC mean over time for each treatment group. Estimates are from the analysis of mixed effects model adjusting for age, gender, baseline value of C-peptide and treatment assignment, and including a fixed effect for time as a linear line on the log(y + 1) scale. The significance level of the difference between the two parallel lines is 0.0011. **(C)** The proportion of participants with 2-h peak C-peptide remaining at or above 0·2 nmol/L over time for each treatment group.

Figure 3. The population mean of **(A)** HbA1c (significance levels are < 0.005 for all 6 month interval group differences) and **(B)** insulin use over time for each treatment group (only statistical significance for less use in the abatacept group was at 6 and 12 months). The estimates are from the analysis of covariance model adjusting for age, gender, baseline value of HbA1c, and treatment assignment. Insulin use is per kg of bodyweight, at 3-month intervals. Error bars show 95% CIs. HbA1c = glycated hemoglobin A1c.

Figure 4. The ratio (abatacept to placebo) of treatment effect on 3 year stimulated C-peptide AUC mean within categories of pre-specified baseline factors. The estimates are from the analysis of covariance modeling log of C-peptide adjusting for age, gender, baseline value of C-peptide, the indicated categorized factor, treatment assignment, and treatment interaction terms.

Figure 1

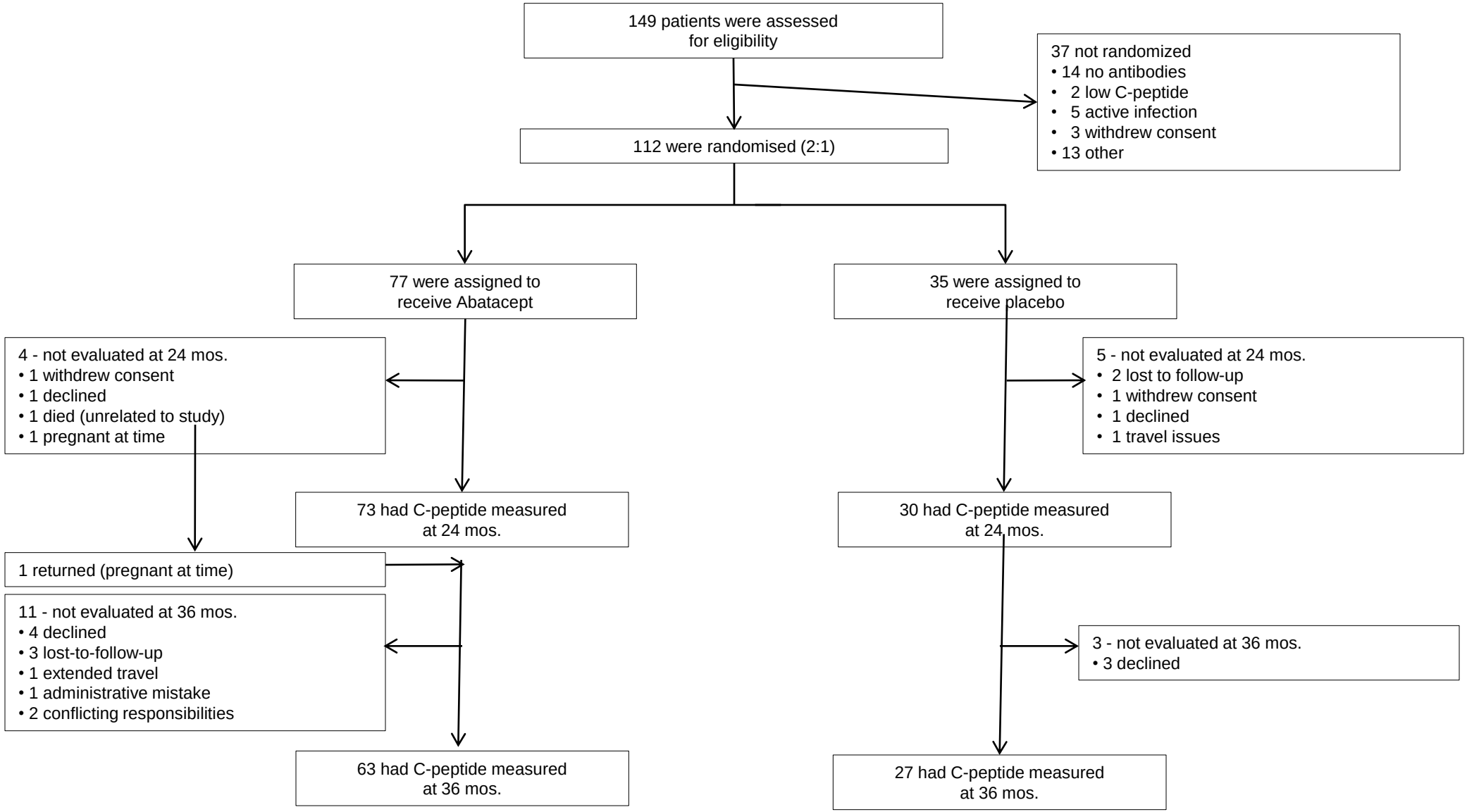

149 patients were assessed for eligibility
37 not randomized
• 14 no antibodies
• 2 low C-peptide
• 5 active infection
• 3 withdrew consent
• 13 other
112 were randomised (2:1)
77 were assigned to receive Abatacept
35 were assigned to receive placebo
4 - not evaluated at 24 mos.
• 1 withdrew consent
• 1 declined
• 1 died (unrelated to study)
• 1 pregnant at time
5 - not evaluated at 24 mos.
• 2 lost to follow-up
• 1 withdrew consent
• 1 declined
• 1 travel issues
73 had C-peptide measured at 24 mos.
30 had C-peptide measured at 24 mos.
1 returned (pregnant at time)
11 - not evaluated at 36 mos.
• 4 declined
• 3 lost-to-follow-up
• 1 extended travel
• 1 administrative mistake
• 2 conflicting responsibilities
3 - not evaluated at 36 mos.
• 3 declined
63 had C-peptide measured at 36 mos.
27 had C-peptide measured at 36 mos.

Figure 2A

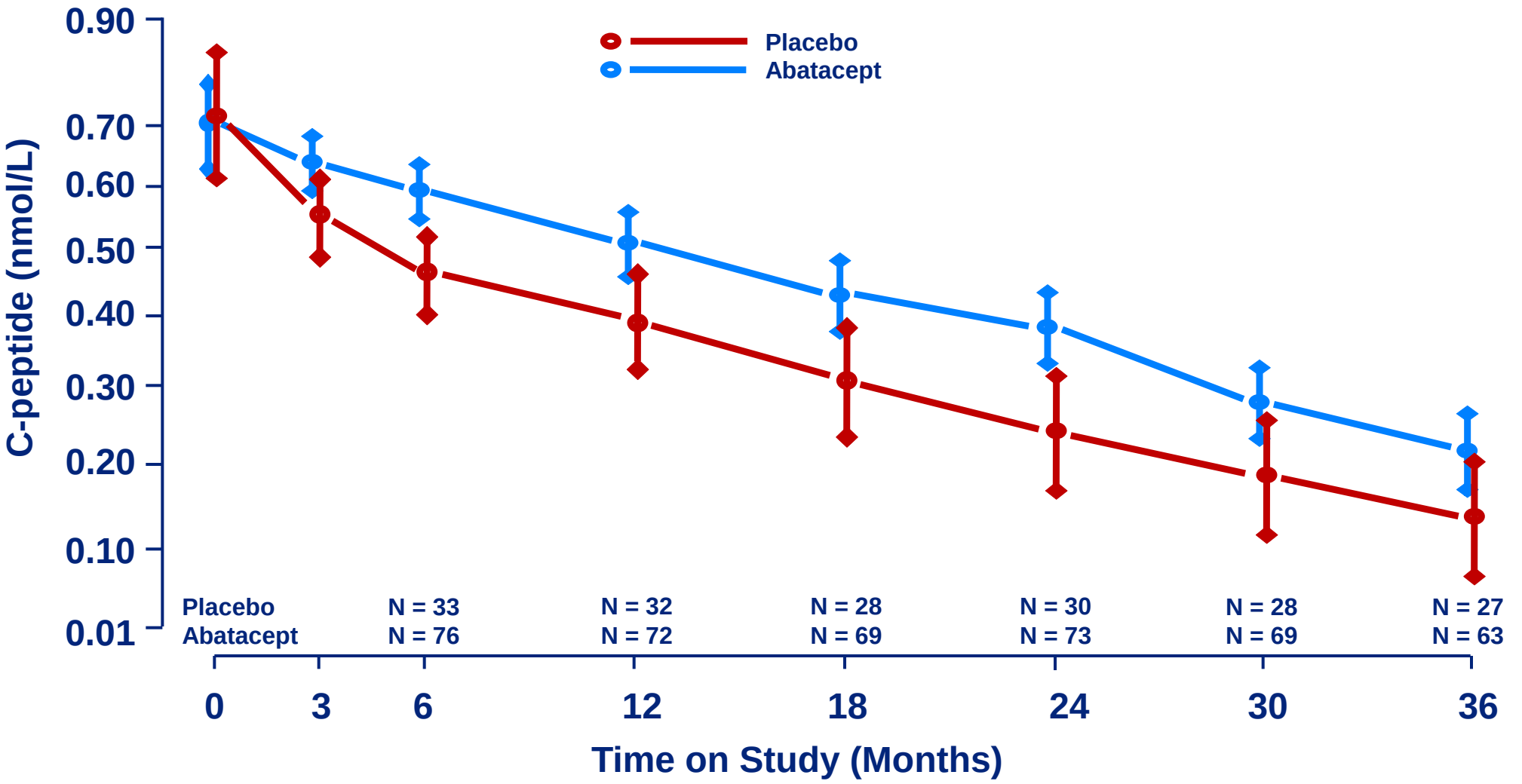

0.90
0.70
0.60
0.50
0.40
0.30
0.20
0.10
0.01
C-peptide (nmol/L)
Placebo
Abatacept
Placebo N = 33 N = 32 N = 28 N = 30 N = 28 N = 27
Abatacept N = 76 N = 72 N = 69 N = 73 N = 69 N = 63
0 3 6 12 18 24 30 36
Time on Study (Months)

Figure 2B

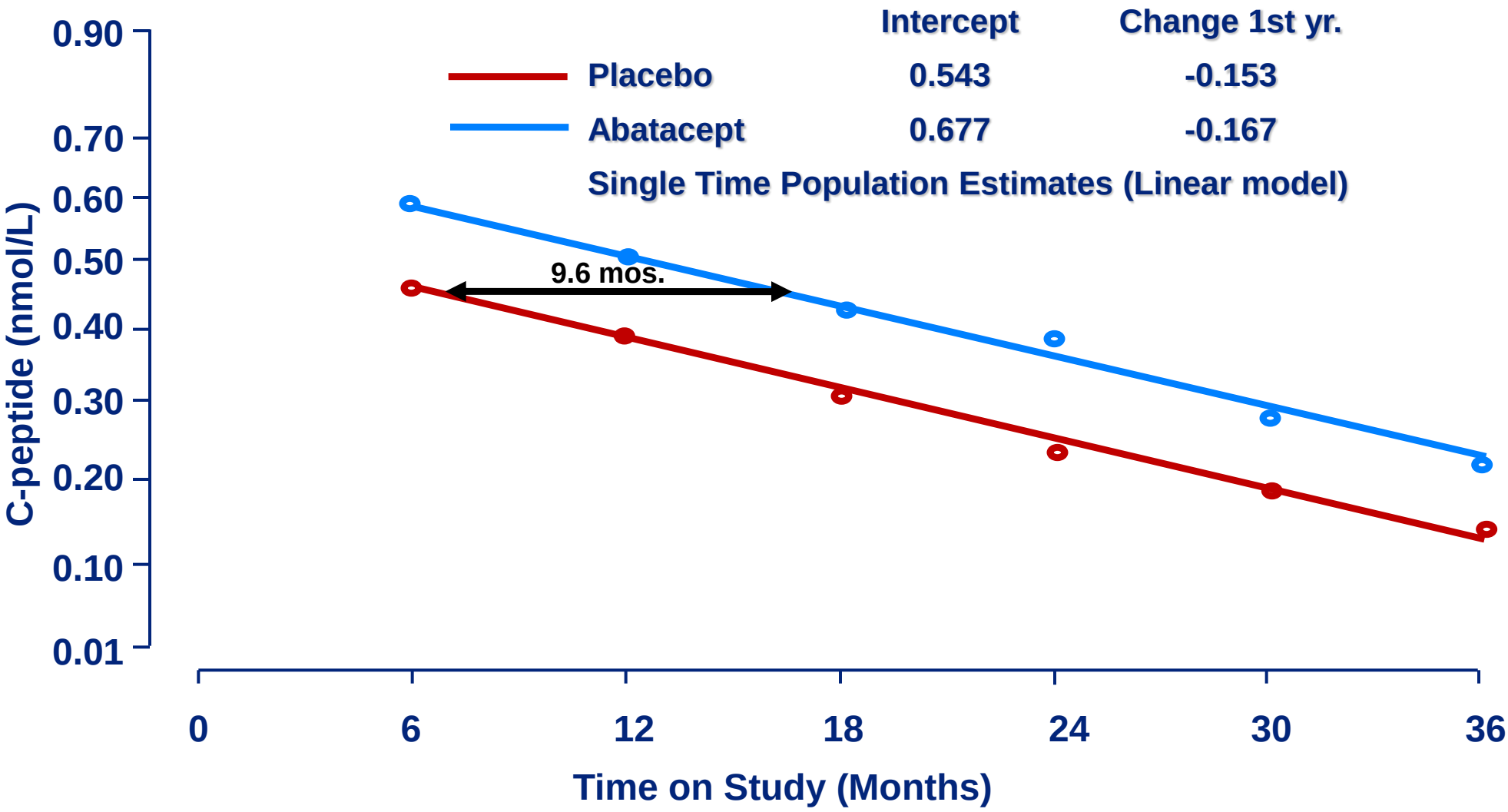

Intercept
Change 1st yr.
Placebo
0.543
-0.153
Abatacept
0.677
-0.167
Single Time Population Estimates (Linear model)
9.6 mos.
C-peptide (nmol/L)
0.90
0.70
0.60
0.50
0.40
0.30
0.20
0.10
0.01
0
6
12
18
24
30
36
Time on Study (Months)

Figure 2C

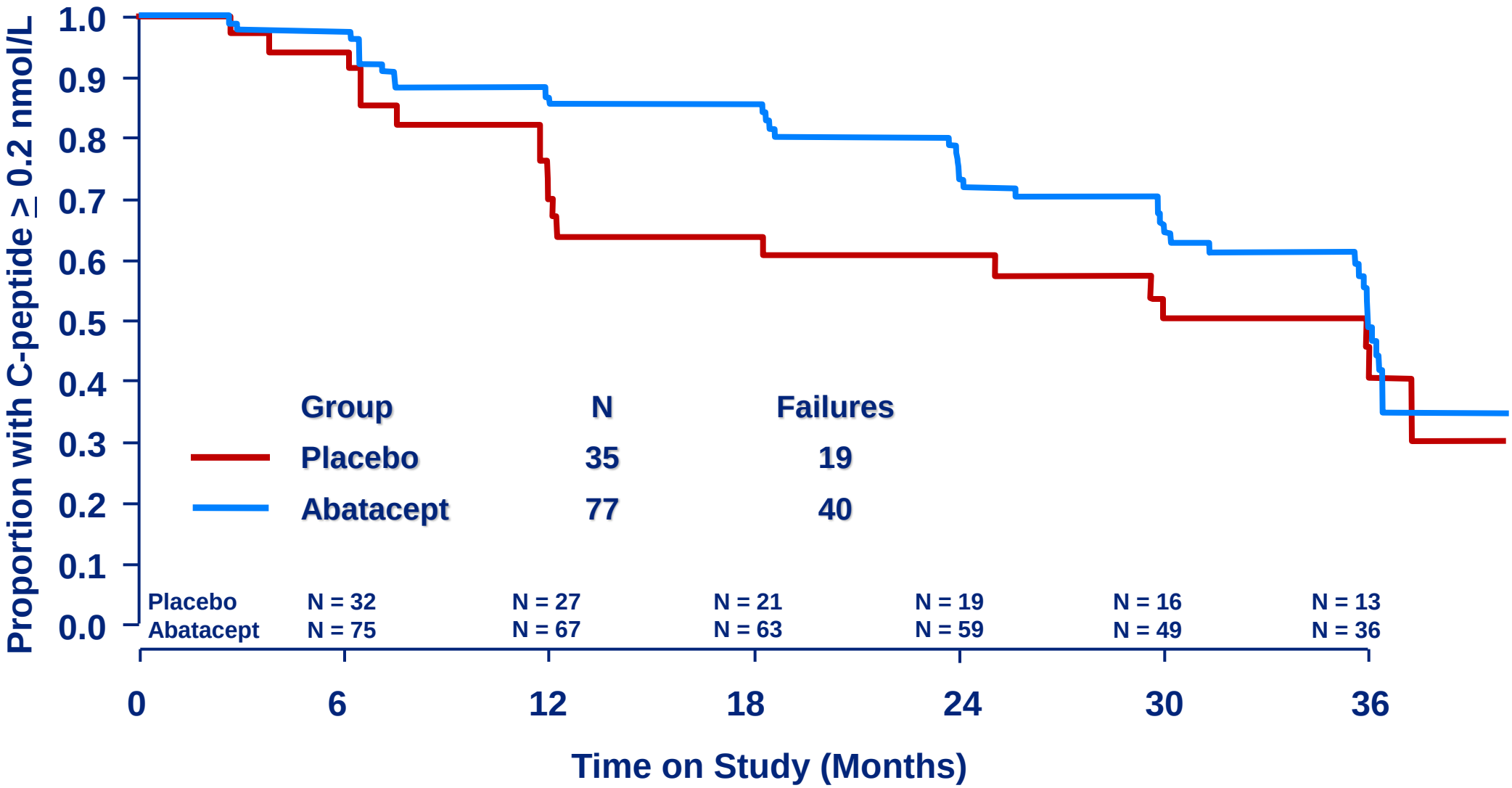

Proportion with C-peptide ≥ 0.2 nmol/L
1.0
0.9
0.8
0.7
0.6
0.5
0.4
0.3
0.2
0.1
0.0
Group
N
Failures
Placebo
35
19
Abatacept
77
40
Placebo
Abatacept
N = 32
N = 75
N = 27
N = 67
N = 21
N = 63
N = 19
N = 59
N = 16
N = 49
N = 13
N = 36
0
6
12
18
24
30
36
Time on Study (Months)

Figure 3A

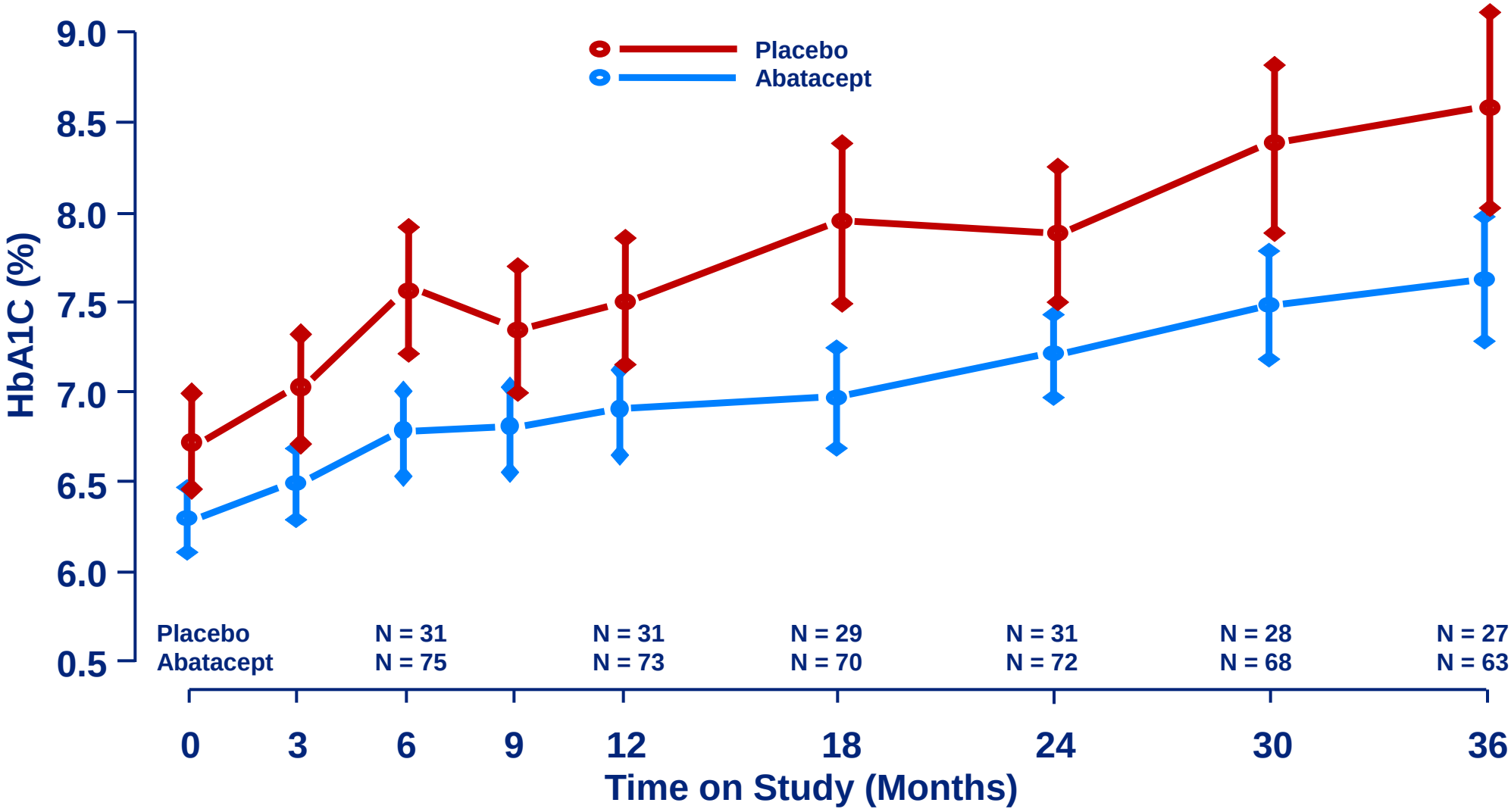

Placebo
Abatacept
HbA1C (%)
9.0
8.5
8.0
7.5
7.0
6.5
6.0
0.5
Placebo N = 31 N = 31 N = 29 N = 31 N = 28 N = 27
Abatacept N = 75 N = 73 N = 70 N = 72 N = 68 N = 63
0 3 6 9 12 18 24 30 36
Time on Study (Months)

Figure 3B

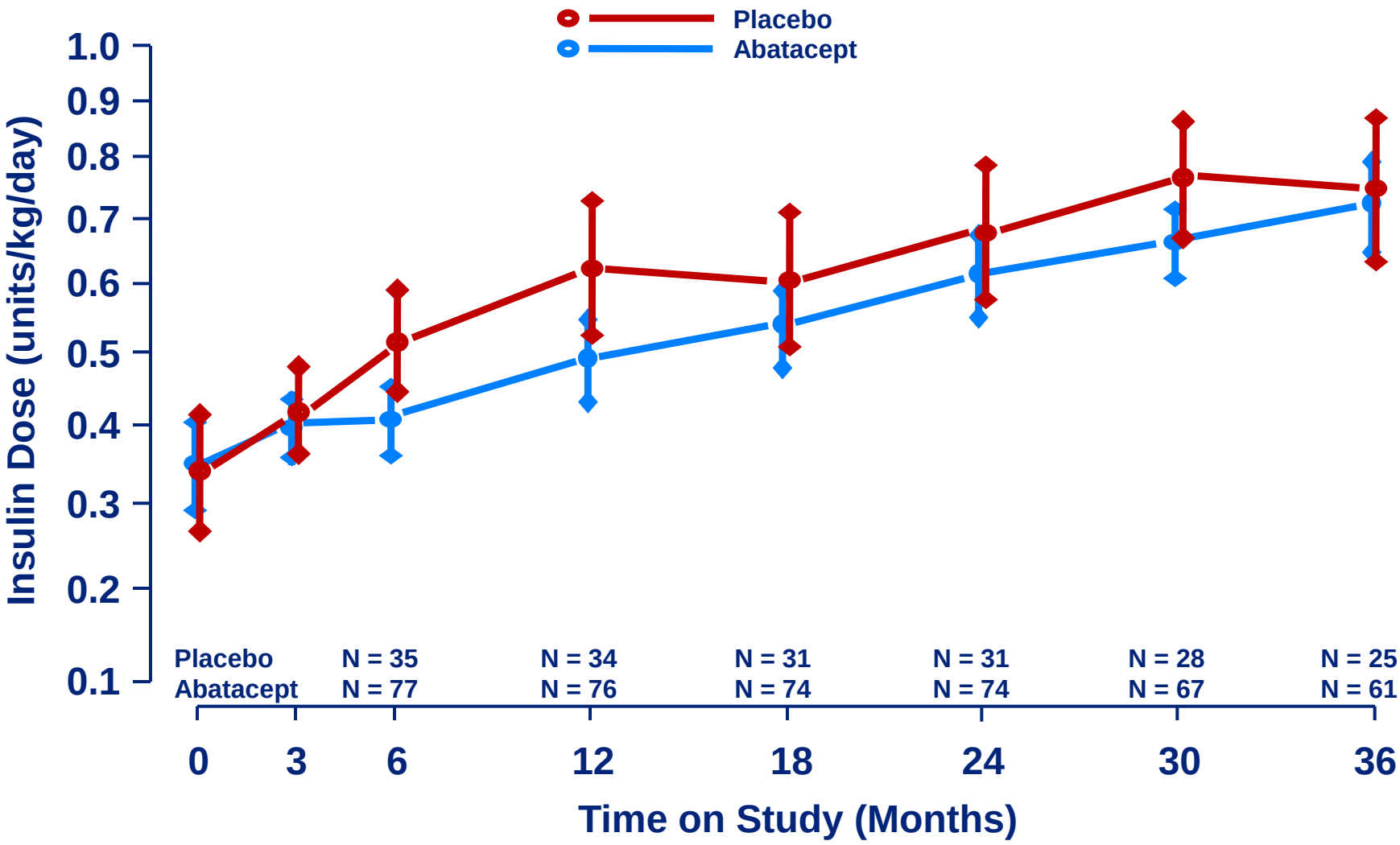
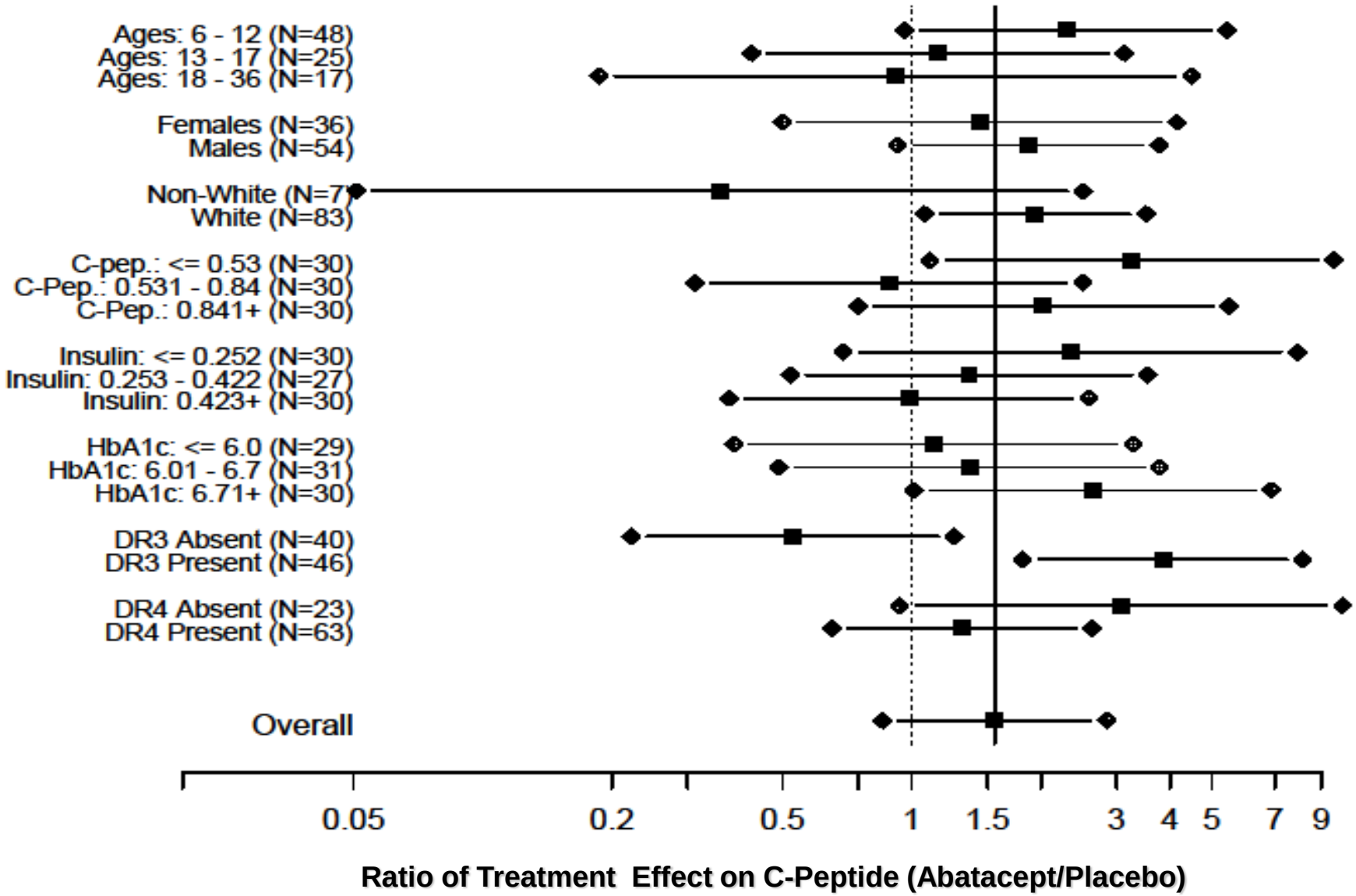

Placebo
Abatacept
Insulin Dose (units/kg/day)
1.0
0.9
0.8
0.7
0.6
0.5
0.4
0.3
0.2
0.1
Placebo N = 35 N = 34 N = 31 N = 31 N = 28 N = 25
Abatacept N = 77 N = 76 N = 74 N = 74 N = 67 N = 61
0 3 6 12 18 24 30 36
Time on Study (Months)

Figure 4


Ages: 6 - 12 (N=48)
Ages: 13 - 17 (N=25)
Ages: 18 - 36 (N=17)
Females (N=36)
Males (N=54)
Non-White (N=7)
White (N=83)
C-pep.: <= 0.53 (N=30)
C-Pep.: 0.531 - 0.84 (N=30)
C-Pep.: 0.841+ (N=30)
Insulin: <= 0.252 (N=30)
Insulin: 0.253 - 0.422 (N=27)
Insulin: 0.423+ (N=30)
HbA1c: <= 6.0 (N=29)
HbA1c: 6.01 - 6.7 (N=31)
HbA1c: 6.71+ (N=30)
DR3 Absent (N=40)
DR3 Present (N=46)
DR4 Absent (N=23)
DR4 Present (N=63)
Overall
0.05
0.2
0.5
1
1.5
3
4
5
7
9
Ratio of Treatment Effect on C-Peptide (Abatacept/Placebo)

Co-Stimulation Modulation with Abatacept in Patients with Recent-Onset Type 1 Diabetes: Follow-Up One Year After Cessation of Treatment

ONLINE APPENDIX

Type 1 Diabetes TrialNet Abatacept Study Group

Steering Committee: Jay S. Skyler (University of Miami Diabetes Research Institute), Chairman; Mark Anderson (University of California San Francisco), Mark Atkinson (University of Florida), Katarzyna Bourcier (NIAID), Dorothy Becker (University of Pittsburgh), Penelope Bingley (University of Bristol), Janice Blum (Indiana University), Emanuele Bosi (San Raffaele Hospital), Jane Buckner (Benaroya Research Institute), H. Peter Chase (University of Colorado Barbara Davis Center for Childhood Diabetes), Michael Clare-Salzler (University of Florida), Peter Colman (Walter and Eliza Hall Institute of Medical Research), Linda DiMeglio (Indiana University), George S. Eisenbarth† (University of Colorado Barbara Davis Center for Childhood Diabetes), C. Garrison Fathman (Stanford University), Stephen Gitelman (University of California San Francisco), Robin Goland (Columbia University), Peter Gottlieb (University of Colorado Barbara Davis Center for Childhood Diabetes), Gilman Grave (NICHD), Carla Greenbaum (Benaroya Research Institute), Bernhard Hering (University of Minnesota), Kevan Herold (Yale University), Richard Insel (Juvenile Diabetes Research Foundation), Jeffrey P. Krischer (University of South Florida), Jennifer Marks (University of Miami Diabetes Research Institute), Antoinette Moran (University of Minnesota), Jerry P. Palmer (University of Washington), Mark Peakman (Guy's, King's, and St. Thomas' School of Medicine), Alberto Pugliese (University of Miami Diabetes Research Institute), Philip Raskin (University of Texas Southwestern Medical School), Maria Grazia Roncarolo (San Raffaele Scientific Institute), William Russell (Vanderbilt University), Peter Savage (NIDDK), Desmond Schatz (University of Florida), Robert Sherwin (Yale University), Mark Siegelman (University of Texas Southwestern Medical School), Olli Simell (Hospital District of Southwest Finland), James Thomas (Vanderbilt University), Massimo Trucco (University of Pittsburgh), John Wentworth (Walter and Eliza Hall Institute of Medical Research), Diane Wherrett (University of Toronto), Darrell M. Wilson (Stanford University), William Winter (University of Florida), Judith Fradkin (NIDDK, ex-officio), Ellen Leschek (NIDDK, ex-officio), Lisa Spain (NIDDK, ex-officio).

Past Members: Christophe Benoist (Joslin Diabetes Center), Jeffrey Bluestone (University of California San Francisco), David Brown (University of Minnesota), Catherine Cowie (NIDDK), Leonard Harrison (Walter and Eliza Hall Institute of Medical Research), Stanley Jordan (Cedars-Sinai Medical Center), Francine R. Kaufman (Childrens Hospital Los Angeles), John M. Lachin (George Washington University), Jeffrey Mahon (University of Western Ontario), Kirsti Nanto-Salonen (Hospital District of Southwest Finland), Gerald Nepom (Benaroya Research Institute), Tihamer Orban (Joslin Diabetes Center), Robertson Parkman (Childrens Hospital Los Angeles), Mark Pescovitz† (Indiana University), John Peyman (NIAID), John Ridge (NIAID), Henry Rodriguez (Indiana University), John Wagner (University of Minnesota), Anette Ziegler (Institut für Diabetesforschung).

Executive Committee: Jay S. Skyler, Katarzyna Bourcier, Carla J. Greenbaum, Jeffrey P. Krischer, Ellen Leschek, Lisa Rafkin (University of Miami Diabetes Research Institute), Peter Savage, Lisa Spain.

Past Members: Catherine Cowie, Mary Foulkes (George Washington University), Heidi Krause- Steinrauf (George Washington University), John M. Lachin, Saul Malozowski (NIDDK), John Peyman, John Ridge, Stephanie J. Zafonte (George Washington University).

For the Abatacept Study, the following individuals were involved:

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Past Staff Members: Monica Bassi, Doug Freeman, Moriah Granger, Michelle Kieffer, Lavanya Nallamshetty, Audrey Shor

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Past Members: Ake Lernmark (Lund University), Bernard Lo (University of California San Francisco), Herman Mitchell (Rho Inc.), Ali Naji (University of Pennsylvania), Jorn Nerup (University of Copenhagen), Trevor Orchard (University of Pittsburgh), Michael Steffes (University of Minnesota), Anastasios Tsiatis (North Carolina State University), Bernard Zinman (University of Toronto).

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Laboratory Directors: Sunanda Babu (University of Colorado Barbara Davis Center for Childhood Diabetes), George S. Eisenbarth†, Santica Marcovina (University of Washington), Jerry P. Palmer, Adriana Weinberg, William Winter, Liping Yu (University of Colorado Barbara Davis Center for Childhood Diabetes)

Protocol Advisory Committee: Tihamer Orban (Chair), Peter Gottlieb, Carla Greenbaum, Ellen Leschek, Brett Loechelt, Robertson Parkman, Lisa Rafkin, Alison Rigby, Jay S. Skyler, Lisa Spain, John Wagner. John M. Lachin, Heidi Krause-Steinrauf, and Paula F. McGee were initial members of this committee involved with the design of the study.

Clinical Center Staff involved in this Protocol:

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Childrens Hospital Los Angeles: Roshanak Monzavi, Mary Halvorson, Meredith Bock, Lynda Fisher, Debra Jeandron, Jamie Wood, Francine R. Kaufman

Columbia University, New York: Robin Goland, Ellen Greenberg, Mary Pat Gallagher, Jeniece Trast, Mary Chan

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University of Pittsburgh, Pennsylvania: Dorothy Becker, Frederico Toledo, Ingrid Libman, Karen Riley, Kelli Delallo, Kym Smith, Diane Gwynn, Gyna Wohlers

University of Texas Southwestern Medical School: Philip Raskin, Perrin White, Bryan Dickson, Soumya Adhikari, Mark Siegelman, Marilyn Alford, Nenita Torres, Tauri Harden, Lourdes Pruneda, Erica Cordova, Renee Davis, Stefani Fernandez, Jamie Arthur, John Richard, Erin Roe, Me'Chelle Hutchins

University of Toronto: Diane Wherrett, Lesley A. Eisel, Brenda Ahenkorah, Natasha Razack, Mithula Sriskandarajah, Mary-Jo Ricci, Jose Cevallos, Roze Kovalakovska, Rachel Steger

Vanderbilt University: William E. Russell, James W. Thomas, Daniel J. Moore, Anne Brown, Margo Black, Eric Pittel, Faith Brendle

† - deceased

Table S1. Baseline demographic and laboratory characteristics of participants

	Abatacept (n=77)	Placebo (n=35)
Age		
Mean (years)	13.9 (6·9)	13.7 (5·3)
Median (years)	12 (6–36)	14 (7–34)
Males	41 (53%)	25 (71%)
Race*		
White	71 (93%)	32 (91%)
Ethnic origin		
Non-hispanic	67 (87%)	31 (89%)
Number of diabetes-related autoantibodies†		
1	9 (12%)	4 (11%)
2	26 (34%)	9 (26%)
3	26 (34%)	15 (43%)
4	16 (21%)	7 (20%)
Number of days from diagnosis to first infusion‡	87.9 (14.1)	83.2 (17.8)
Weight (kg)	52.6 (21.9)	53.0 (19.7)
Body-mass index (kg/m^2)	21.0 (4.5)	20.5 (3.9)
Mean AUC for C-peptide (nmol/L)	0.743 (0.42)	0.745 (0.31)
HbA_{1c} at baseline* (%)	6.31% (0.80)	6.74% (0.94)
Total daily insulin dose at baseline* (U/kg)	0.385 (0.24)	0.339 (0.22)
Ketoacidosis at diagnosis	25 (32%)	8 (23%)
Diabetes-associated HLA alleles present*		
DR3 and DR4	25 (34%)	16 (49%)
DR3 only	11 (15%)	5 (15%)
DR4 only	30 (41%)	10 (30%)
Neither	8 (11%)	2 (6%)

Data are n (%), mean (SD), or median (range). AUC=area under the curve.

*Excludes participants with data missing for indicated variable (number missing: race, 1; HbA1c, 2; insulin use, 1; HLA allele status, 4).

†Islet-cell autoantibodies by immunofluorescence not tested on 16 patients (considered negative for count).

‡Range 51–108 for abatacept group and 38–107 for placebo.

Table S2: The number of subjects by worst grade of adverse effects and number of events and subjects by adverse events type. Worst grade by treatment group was not statistically different using a Wilcoxon Rank Sum Test. Adverse effect category by treatment group was tested using a one-sided (alternative of higher frequency in Abatacept Group) Fisher's Exact Test; only Constitutional Symptoms was significant (p = 0.049).

Grade	Treatment Group			
	Abatacept		Placebo	
	No. of subjects (%*)		No. of subjects (%*)	
0	12(15.6)		7 (20.0)	
1	1 (1.3)		1 (2.9)	
2	45 (58.4)		19 (54.3)	
3	13 (16.9)		6 (17.1)	
4	5 (6.5)		2 (5.7)	
5**	1 (1.3)		0 (0.0)	
Total	77 (100.0)		35 (100.0)	
Adverse Effect Category	No. of events	No. of subjects (%*)	No. of events	No. of subjects (%*)
Allergy/Immunology	4	3 (3.9)	0	0 (0)
Auditory/Ear	5	5 (6.5)	0	0 (0.0)
Blood/Bone Marrow	17	12 (15.6)	18	6 (17.1)
Cardiac Arrhythmia	1	1 (1.3)	1	1 (2.9)
Cardiac General	4	4 (5.2)	0	0 (0.0)
Constitutional Symptoms	19	15 (19.5)	2	2 (5.7)
Death**	1	1 (1.3)	0	0 (0.0)
Dermatology/Skin	17	15 (19.5)	6	5 (14.3)
Endocrine	4	4 (5.2)	2	2 (5.7)
Gastrointestinal	33	20 (26.0)	12	8 (22.9)
Hemorrhage/Bleeding	2	1 (1.3)	0	0 (0)
Infection	67	33 (42.9)	31	15 (42.9)
Hypoglycemia	8	5 (6.5)	2	1 (2.9)
Metabolic/Laboratory♦	8	7 (9.1)	4	2 (5.7)
Musculoskeletal/Soft Tissue	17	13 (16.9)	8	6 (17.1)
Neurology	14	10 (13.0)	3	2 (5.7)
Ocular/Visual	3	3 (3.9)	1	1 (2.9)
Pain	7	6 (7.8)	7	5 (14.3)
Pulmonary/Upper Respiratory	20	10 (13.0)	7	4 (11.4)
Renal/Genitourinary	0	0 (0.0)	2	2 (5.7)
Secondary Malignancy	1	1 (1.3)	0	0 (0.0)
Sexual/Reproductive Function	1	1 (1.3)	0	0 (0.0)
Surgery/Intra-Operative Injury	3	3 (3.9)	0	0 (0.0)
Syndromes	10	9 (11.7)	5	5 (14.3)
Total	266	--	111	--

* Denominator in percent calculation is number in respective treatment groups

** Accidental death, unrelated to study

♦ Other than hypoglycemia