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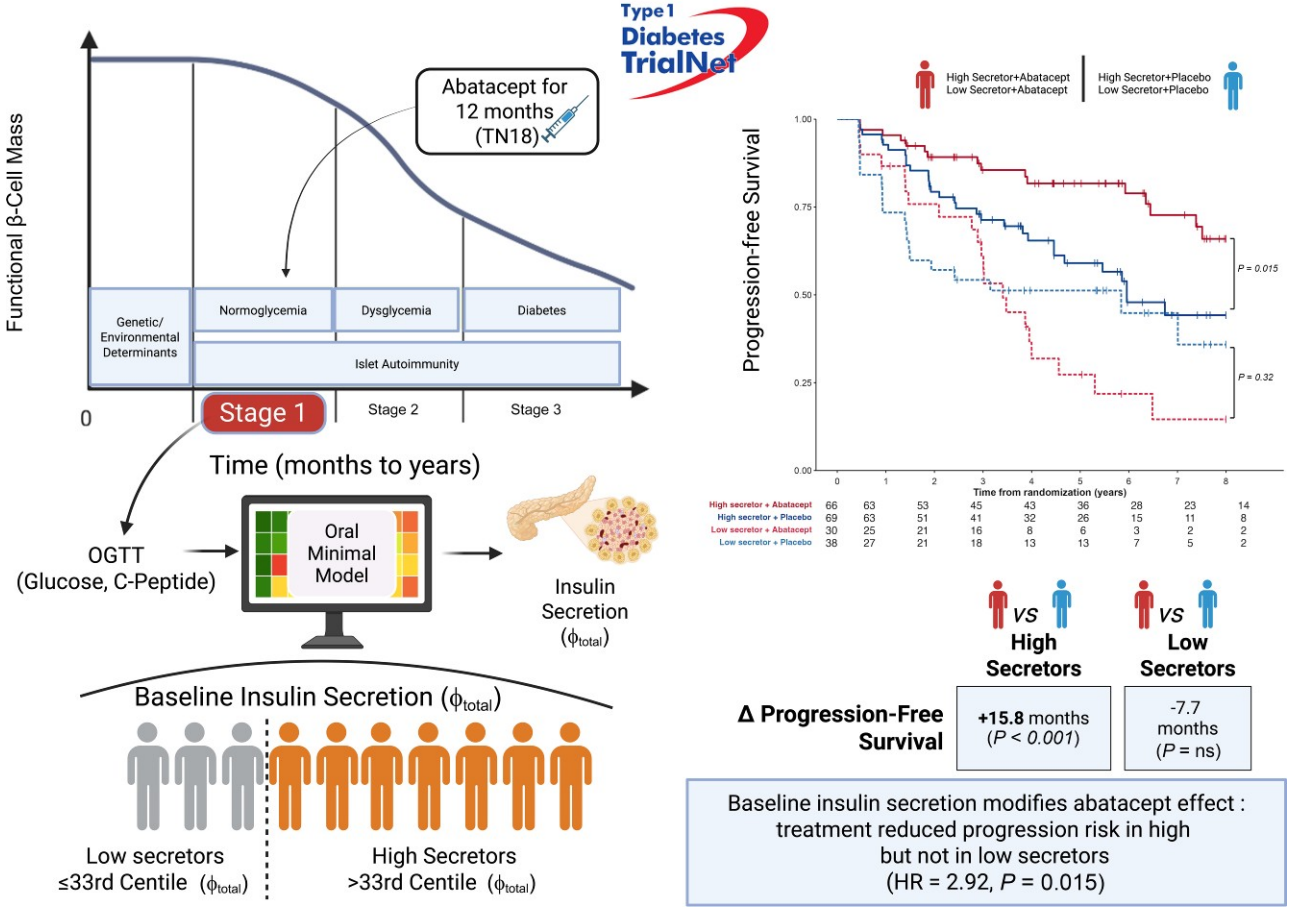

Baseline Insulin Secretion Determines Response to Abatacept in Stage 1 Type 1 Diabetes

Alfonso Galderisi,[1] Alice L.J. Carr,[2] Peter Taylor,[3] Jacopo Bonet,[4] David Cuthbertson,[5] Jay Sosenko,[6] Emily K. Sims,[7] Carmella Evans-Molina,[7] Chiara Dalla Man,[4] Heba M. Ismail,[7] Brandon Nathan,[8] Alessandra Petrelli,[9,10] Peter Senior,[2] Jennifer L. Sherr,[1] Kevan C. Herold,[11,12] William E. Russell,[13] Antoinette Moran,[8] and Colin Dayan[3]

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Abatacept, a cytotoxic T lymphocyte–associated protein 4 immunoglobulin that inhibits T-cell costimulation, was evaluated for 12 months in stage 1 type 1 diabetes (T1D) to delay disease progression. Despite modest preservation of area under the curve C-peptide at 12 months, the primary end point was not met. We adopted the oral minimal model (OMM) to assess β-cell function over 48 months and explored how baseline insulin secretion (φ_{total}) modified treatment response. Using the OMM, φ_{total} was computed from oral glucose tolerance tests conducted at baseline and every 6 months. Participants were stratified into high- and low-secretor groups depending on baseline φ_{total} ≥33rd or <33rd centile, respectively. A sensitivity analysis was performed to validate threshold choice. Among 203 participants (abatacept *n* = 96; 107 placebo *n* = 107), 39% receiving abatacept and 47% receiving placebo experienced progression to stage 2 or 3 within 96 months. High secretors receiving abatacept gained 15.8 progression-free months (95% CI 4.85, 26.68; *P* = 0.005) and had a 54% lower hazard of progression versus those receiving placebo (hazard ratio [HR] 0.46; 95% CI 0.25, 0.84; *P* = 0.012). Treatment effect differed significantly by secretor status (interaction HR 2.92; 95% CI 1.23, 6.96; *P* = 0.015). A subgroup of responders to 12 months of abatacept was identified by φ_{total}, providing the first evidence that an immune intervention in stage 1 T1D may delay disease progression.

ARTICLE HIGHLIGHTS

- We sought to investigate whether baseline insulin secretion (φ_{total}), quantified using the oral minimal model assessing β-cell function, could identify a subgroup of responders to abatacept (a cytotoxic T lymphocyte–associated protein 4 immunoglobulin that inhibits T-cell costimulation) among those with stage 1 type 1 diabetes (T1D).
- Abatacept preserved φ_{total} during and up to 1 year after treatment cessation; high baseline secretors treated with abatacept gained ∼16 months of progression-free survival and had a 54% lower hazard of progression versus those receiving placebo, whereas no benefit was observed in low secretors.
- This is the first evidence of an immune intervention delaying disease progression in those with stage 1 T1D. Continued treatment may result in a greater delay in progression.

[1]Department of Pediatrics, Yale University, New Haven, CT
[2]Alberta Diabetes Institute, University of Alberta, Edmonton, Alberta, Canada
[3]Department of Infection and Immunity, Cardiff University School of Medicine, Cardiff, U.K.
[4]Department of Information Engineering, University of Padova, Padova, Italy
[5]Health Informatics Institute, University of South Florida, Tampa, FL
[6]University of Miami Miller School of Medicine, Miami, FL
[7]Herman B. Wells Center for Pediatric Research, Department of Pediatrics, and Center for Diabetes and Metabolic Diseases, Indiana University School of Medicine, Indianapolis, IN
[8]Department of Pediatrics, University of Minnesota, Minneapolis, MN
[9]Department of Clinical Sciences and Community Health, University of Milan, Milan, Italy
[10]Pio Albergo Trivulzio, Milan, Italy
[11]Department of Immunobiology, Yale University, New Haven, CT
[12]Department of Internal Medicine, Yale University, New Haven, CT
[13]Departments of Pediatrics and Cell and Developmental Biology, Vanderbilt University Medical Center, Nashville, TN

Corresponding author: Alfonso Galderisi, alfonso.galderisi@yale.edu

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Clinically symptomatic type 1 diabetes (T1D) is preceded by a presymptomatic phase, characterized by progressive loss of functional β-cell mass after the onset of islet autoimmunity. Presence of multiple autoantibodies without (stage 1) or with dysglycemia (stage 2) during an oral glucose tolerance test (OGTT) defines disease stage, which is the main inclusion criterion for clinical trials of immunotherapy (1). Staging provides an estimate of the rate of progression to clinical disease (stage 3) (2). However, metabolic and immunological heterogeneity within stages have been described (3–5) and shown to affect time to clinical progression (3), as well as response to disease-modifying treatments (5).

Metrics combining both glucose and C-peptide (6) have been shown to outperform metrics based only on C-peptide in predicting disease progression and describing within-stage heterogeneity (5,7). Recently, by applying the oral minimal model (OMM) over OGTT data to estimate insulin secretion and sensitivity (8), we demonstrated that changes in insulin secretion allow early identification of individuals with rapid or slow disease progression within stage 2 disease and after 3 months of treatment with teplizumab (5).

We expand on those results and use OMM-derived insulin secretion (φ_{total}) to quantify response to a 12-month course of the cytotoxic T lymphocyte–associated protein 4 (CTLA-4) immunoglobulin abatacept (9) in individuals with stage 1 T1D enrolled in the TrialNet Abatacept Prevention Study (TN18) conducted by the TrialNet consortium. As an inhibitor of T-cell costimulatory signals through the CD80/86 pathway, Abatacept can prevent T-cell activation and β-cell attack (10,11). Insulin preservation with a 2-year course of abatacept in individuals with new-onset stage 3 T1D was initially described in the TN09 study conducted by TrialNet (12). However, in those with stage 1 disease, the TN18 trial was unable to demonstrate a delay in disease progression (time to either abnormal glucose tolerance [stage 2] or stage 3 disease) (9). In this trial, a measurable difference in area under the curve (AUC) C-peptide at 12 months from randomization was reported, suggesting preserved insulin secretion with respect to the placebo group. This, however, was in the absence of measurable differences at 6 months from randomization or after treatment cessation (9). Exploratory analysis in the original trial report, using a range of baseline measures, including AUC C-peptide, did not identify a responder subgroup (9).

Here, we describe insulin secretion, computed using the OMM as φ_{total}, over a 48-month follow-up of the TN18 trial in those receiving either placebo or abatacept, in comparison with AUC C-peptide, along with risk indices (Index60 and Diabetes Prevention Trial Type 1 Risk Score [DPTRS]) computed over the same time frame. We stratified analyses by OMM-derived insulin secretion at study entry to investigate differential treatment responses and describe the effect of baseline secretion on time to disease progression in the placebo and abatacept arms.

RESEARCH DESIGN AND METHODS

Study Design

The TN18 trial included individuals with stage 1 T1D (defined as two or more diabetes-related autoantibodies, excluding those with insulin autoantibodies without dysglycemia) who were randomly assigned to receive intravenous infusions of either placebo or abatacept (at 0, 2, and 4 weeks and then every 4 weeks) for 12 months. Participants underwent a 2-h OGTT before randomization and approximately every 6 months until the primary study end point (i.e., confirmed transition to stage 2 or clinical onset of T1D [stage 3], whichever event was detected first) (9). This post hoc analysis included all participants with a baseline OGTT and at least one OGTT after randomization, with participants with clinical onset of T1D within 30 days from randomization excluded from the analysis. OMM metrics and other OGTT-derived metrics were calculated at baseline and each follow-up point every 6 months, as per the parent trial design. We described β-cell function and risk index trajectories using longitudinal data from the first 48 months after randomization (extending the original report, which described 30 months), and survival analyses were conducted with administrative censoring at 96 months, consistent with the original report (9).

To investigate differential effects of treatment by metabolic phenotype, participants were stratified into two groups according to the baseline φ_{total} as derived by the OMM. The low-secretor group included those with a baseline φ_{total} <33rd centile of the φ_{total} distribution throughout the entire cohort ($\varphi_{total} = 54.69 * 10^{-9}$ min^{-1} or 4.001 when naturally log transformed), whereas those with φ_{total} ≥33rd centile (i.e., upper two tertiles) were assigned to the high-secretor group.

φ_{total}, SI, insulin clearance, disposition index (DI), AUC C-peptide, and risk indices (Index60 and DPTRS) were assessed at prespecified discretized visits every 6 months per treatment arm (i.e., abatacept vs. placebo). The overall trajectories over 48 months of OMM φ_{total}, AUC C-peptide, Index60, and DPTRS were assessed per treatment arm (i.e., abatacept vs. placebo) and per treatment arm within low- and high-secretor groups (i.e., high secretor [abatacept vs. placebo] and low secretor [abatacept vs. placebo]). These overall trajectories were identified as nonlinear through locally

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A.G. and A.L.J.C. contributed equally to the work.

estimated scatterplot smoothing (LOESS) regression. Segmented regression was henceforth chosen to describe the trajectories of these metrics within the time periods of 0–24 and 24–48 months from randomization. These time periods were selected to reflect distinct phases of trajectory behavior based on visual assessment of the LOESS regression, with a noticeable change in slope observed at ∼24 months in the treated group. In addition, early effects of treatment on the trajectories were assessed by restricting to a 0- to 6-month segment. Because of the longitudinal nature, repeated measures, and interindividual variation of this cohort, mixed-effects regression models with random effects (intercept and slope) at the participant level were used in each segment to control for the effect of individual-level differences in each metric and their change over time. In addition, survival and risk regression analyses were performed to compare times to progression, with administrative censoring at 96 months, to stage 2 or 3 diabetes between treatment arms, stratified by low- and high-secretor groups.

OGTT-Derived Metrics

Participants underwent a 2-h OGTT, with glucose, C-peptide, and insulin measured at −10, 0, 30, 60, 90, and 120 min before randomization and every 6 months. The OMM metrics included insulin secretion (φ_{total}), SI, and DI.

The model has been validated across different age groups (13–15), and the accuracy of φ_{total} and SI estimates with this study protocol has been previously described (16). The method of calculation of the minimal model metrics has been previously described (13–15). Briefly, φ_{total} was computed using C-peptide and glucose concentrations and referred to β-cell responsiveness to glucose, with higher φ_{total} describing higher insulin secretion during the 2-h OGTT. For simplicity, we use the term insulin secretion throughout this report to refer to β-cell responsiveness to glucose (17).

SI was derived from insulin and glucose concentrations during the 2-h OGTT, with lower SI indicating reduced SI. DI represented the relationship between insulin secretion and sensitivity and was computed as the product of φ_{total} and SI. Insulin clearance was calculated as the ratio of the AUC of the insulin secretion rate over AUC insulin during the OGTT. Insulin secretion rate was computed using glucose and C-peptide, as described by Van Cauter et al. (18,19).

AUC C-peptide was computed using the Simpson rule by integrating a cubic spline interpolation of C-peptide concentrations over time during the OGTT, as previously calculated in the original TN18 study. DPTRS and Index60 were calculated as previously described (20–23).

Statistical Analysis

Normality was assessed visually using density distributions and Q–Q plots. φ_{total}, SI, DI, and insulin clearance were identified as having nonnormal distributions. These variables were natural log transformed, and all subsequent analyses were performed using the natural log–transformed values. At prespecified discretized visits, age-adjusted ANCOVA was conducted to compare between treatment arms each of the OMM metrics, AUC C-peptide, Index60, and DPTRS, where the average age was substituted as the covariate value to isolate and express the treatment group effect. In these calculations, the model assumed that all individuals had the same average age to ensure that the comparison between treatment groups reflected only the effect of the treatment, without being influenced by differences in age.

Adjusted means and CIs were tabulated, calculated for each treatment group based on the fitted model. Mixed-effects models were computed to compare trajectories within each preidentified temporal segment (0–6, 0–24, and 24–48 months) for φ_{total}, AUC C-peptide, Index60, and DPTRS.

For the purpose of survival analysis, progression to confirmed stage 2 disease was defined as the presence of at least two sequential OGTTs meeting dysglycemia thresholds within a 12-month period (presence of impaired fasting glucose [fasting glucose 110–125 mg/dL], impaired glucose tolerance [2-h glucose 140–199 mg/dL], or both or presence of any intermediate glucose during OGTT >200 mg/dL). Progression to stage 3 diabetes was defined as at least two sequential OGTTs within a 12-month period meeting American Diabetes Association diagnostic criteria for diabetes (i.e., fasting glucose ≥126 mg/dL or 2-h glucose ≥200 mg/dL). Timing of progression was defined as the time of the first OGTT meeting the respective criteria. Cumulative incidence of disease progression, defined as progression to either stage 2 or 3 disease as described above, was assessed using Kaplan-Meier curves, stratified by baseline low- and high-secretor groups for each treatment group, censored at 96 months. Log-rank tests were used to compare the cumulative incidence of disease progression over 96 months between treatment arms within the high- and low-secretor subgroups. Cox proportional hazards models were used to calculate hazard ratios (HRs) to estimate the relative risk of progression associated with treatment for each secretor group. Because <50% of participants in the high-secretor subgroup experienced an event, median survival times could not be estimated. Instead, we report restricted mean survival time (RMST) to summarize progression-free survival up to 96 months. RMST was recently recommended as an alternative or complement to the HR, providing an interpretable measure of average time gained under treatment within a fixed follow-up horizon (24–27). Between-group RMST differences (treatment vs. placebo) were estimated within high- and low-secretor subgroups, and *P* values were obtained from Wald tests of the difference in RMST means.

Continuous variables are summarized as median (25th, 75th centile) and compared by Wilcoxon rank sum test or as age-adjusted mean ± CI and compared by age-adjusted ANCOVA, where specified and appropriate. Categorical

variables were compared by the Pearson χ^2 test. Significance level was tested at α of 0.05.

Sensitivity Analysis Using a Decision Analytic Framework to Identify Secretor Groups

To test whether an empirically derived threshold might alter secretor group conclusions, we performed a sensitivity analysis using a formal decision analytic framework based on RMST. This allowed us to evaluate treatment heterogeneity across the continuous spectrum of baseline insulin secretion and derive an optimal threshold that maximized clinical benefit. The analytic framework behind RMST has been described elsewhere (24,26,27). Briefly, RMST was calculated as the area under the predicted survival curve, based on a Cox model that allowed for baseline φ_{total} to vary nonlinearly (spline) with treatment up to a prespecified time horizon (τ) (27), with τ set to 120 months to ensure that RMST estimates captured the range of available data in the study (maximum follow-up 122.3 months). For each individual, we then predicted two counterfactual survival curves (one assuming treatment and one assuming placebo) and integrated the area under each curve up to 120 months, with the difference taken as the treatment benefit in months of progression-free survival gained (28). Next, we considered a grid of candidate thresholds across the distribution of φ_{total} (5th–95th percentiles, in 1% increments, to avoid sparse extremes). For each candidate cutoff, patients above the threshold were classified as eligible for treatment, and we calculated the mean net benefit: the average RMST gain in this subgroup minus a prespecified minimum worthwhile gain of 6 months. The cutoff that maximized mean net benefit was selected as the optimal threshold. The optimal threshold was defined as the point that maximized net benefit (Supplementary Fig. 1*A*), corresponding to φ_{total} of 4.11 on the natural log scale (back transformed 60.95), which was similar to the threshold identified using the simple 33rd centile method. Plotting RMST gain as a continuous function of baseline secretion confirmed that benefit increased with higher φ_{total} and plateaued at higher levels (Supplementary Fig. 1*B*). We applied this definition of secretor status to explore if Kaplan-Meier survival estimates would be altered.

Analyses were performed using R statistical analysis software (version 4.4.0).

Data and Resource Availability

The data sets generated during and/or analyzed in the current study are available from the corresponding author on reasonable request.

RESULTS

Participants

We included 203 participants (abatacept n = 96; placebo n = 107) in this analysis. Five participants were excluded because they withdrew before follow-up assessment, and four participants were excluded because of missing data for OMM metric computation. After randomization, 50 (47%) individuals receiving placebo and 37 (39%) receiving abatacept experienced progression to either stage 2 or 3 disease within 96 months. No significant differences in baseline characteristics or metabolic indices were identified between treatment arms when comparing characteristics within low- or high-secretor groups (Table 1). None of the participants experienced progression to clinical diabetes <30 days from randomization.

Longitudinal Trajectory of the Metabolic Phenotype by Treatment Arm

Figure 1*A* describes the LOESS trajectory of φ_{total} over 48 months, demonstrating two distinct phases: a prevailing effect of treatment with abatacept for ∼1 year during the first 24 months and the waning of the treatment effect afterward. There was a significant increase in φ_{total} over 24 months in those receiving abatacept versus a declining trend in the placebo group (P = 0.005) (Fig. 1*B* and Table 2). From 24 to 48 months, φ_{total} trajectory demonstrated the waning of the abatacept treatment effect, with a decline in insulin secretion in the abatacept arm that paralleled the trajectory in the placebo group (P = 0.90) (Fig. 1*C* and Table 2). φ_{total} demonstrated an effect of abatacept as early as 6 months, with a significantly increasing trajectory apparent in those receiving abatacept versus placebo (P = 0.0094) (Table 2).

Although the LOESS trajectory of AUC C-peptide similarly suggested two distinct phases (Fig. 1*D*), the trajectories did not differ between the two treatment arms in either 0- to 24-month or 24- to 48-month segments (P = 0.62 and P = 0.9, respectively) (Fig. 1*E* and *F*), nor were there any early (0–6 months) differences in AUC C-peptide trajectory (P = 0.73) (Table 2).

Index60 and DPTRS displayed similar divergent trends to that demonstrated by φ_{total} over 24 months of follow-up, with a stable risk profile for the abatacept group during the first 24 months from randomization versus placebo (P = 0.003 and P = 0.022, respectively) (Fig. 1*G*–*L* and Table 2) that increased after 24 months. When assessing early (0–6 months) trajectories, Index60 did not distinguish differences between groups (P = 0.14), whereas a stable DPTRS was observed in the abatacept arm compared with an increase in the placebo group (P = 0.022) (Table 2).

Consistent with the LOESS trajectories, the individual time point comparisons between abatacept and placebo groups demonstrated that φ_{total} was higher in those who received abatacept compared with placebo starting 6 months after treatment was initiated (P = 0.03). Levels remained persistently higher at 18 (P = 0.033) and 24 months postrandomization (P = 0.017), with the latter time point being 12 months after completion of drug treatment. This resulted in a higher φ_{total} at 48 months in the abatacept versus placebo group (P = 0.049) (Supplementary Table 1).

Abatacept did not significantly affect SI or insulin clearance at any time point (Supplementary Table 1), whereas DI trended higher at 6 and 24 months in the abatacept

Table 1—Baseline characteristics of placebo and abatacept recipients in high- and low-secretor subgroups

	High secretor			Low secretor		
Characteristic	Placebo (n = 69)	Abatacept (n = 66)	P	Placebo (n = 38)	Abatacept (n = 30)	P
Age, years*	16 (12, 22)	16 (13, 31)	0.57	12 (9, 19)	14 (10, 18)	0.55
BMI, kg/m^2*	23.2 (19.2, 26.0)	23.1 (20.4, 28.4)	0.54	19.0 (15.7, 23.8)	20.5 (16.9, 22.9)	0.67
BMI z score	0.40 (–0.05, 0.88)	0.43 (–0.19, 0.96)	0.32	0.32 (–0.38, 1.10)	0.43 (–0.19, 0.97)	0.30
Sex (male)*	32 (46)	32 (48)	0.81	19 (50)	17 (57)	0.58
Fasting glucose, mg/dL*	90 (87, 96)	90 (88, 96)	0.56	90 (84, 95)	91 (86, 94)	0.73
2-h glucose, mg/dL*	108 (87, 118)	104 (91, 116)	0.76	116 (103, 124)	114 (107, 124)	0.95
Fasting C-peptide, ng/mL*	2.01 (1.67, 2.33)	2.00 (1.58, 2.58)	0.86	1.34 (1.02, 1.67)	1.41 (0.93, 1.92)	0.40
2-h C-peptide, ng/mL*	7.19 (5.90, 9.53)	6.87 (5.38, 8.06)	0.25	5.18 (3.93, 6.20)	5.42 (4.43, 6.43)	0.42
Total follow-up, months*	64 (41, 89)	70 (44, 98)	0.31	48 (29, 74)	56 (31, 69)	0.93
Insulin secretion (φ_{total}), 10^{-9} min^{-1}†	99.48 (90.02, 121.51)	90.02 (81.45, 109.95)	0.18	40.45 (36.60, 44.70)	36.60 (33.12, 44.70)	0.64
Insulin sensitivity, dL/kg/min/ μU/mL × 10^{-4}†	18.17 (14.88, 22.20)	20.09 (16.44, 27.11)	0.47	36.60 (29.96, 49.40)	36.60 (27.11, 49.40)	0.78
DI, dL/kg/min^2/μU/mL × 10^{-13}†	1,998.20 (1,480.30, 2,440.60)	1,998.20 (1,480.30, 2,440.60)	0.98	1,480.30 (1,211.97, 1,998.20)	1,339.43 (992.27, 1,808.04)	0.64
Insulin clearance, AUC $ISR_{C\text{-}peptide}/AUC_{insulin}$†	0.41 (0.41, 0.45)	0.41 (0.37, 0.41)	0.12	0.45 (0.41, 0.50)	0.50 (0.45, 0.55)	0.12
AUC C-peptide, ng/mL/min†	915.4 (852.7, 978)	877.7 (813.7, 941.8)	0.41	587.7 (530.5, 645)	628.2 (563.8, 692.7)	0.35
Index60†	–1.1 (–1.3, –0.9)	–0.9 (–1.1, –0.6)	0.16	0.4 (0.2, 0.6)	0.5 (0.3, 0.7)	0.43
DPTRS†	5.8 (5.6, 5.9)	5.9 (5.7, 6)	0.45	6.8 (6.6, 7.1)	7.1 (6.8, 7.3)	0.16

*Data presented as median (interquartile range) or n (%) with comparison P value derived by Wilcoxon rank sum test or Pearson χ^2 test. †Data presented as age-adjusted mean and 95% CI from ANCOVA, with comparison P value derived by age-adjusted ANCOVA. Values of OMM metrics (φ_{total}, insulin sensitivity, disposition index, and insulin clearance have been back transformed [exponential]).

arm, mainly driven by higher β-cell responsiveness over time when compared with the placebo arm (Supplementary Table 1). AUC C-peptide was not significantly different at any time point between the abatacept compared with placebo arm (Supplementary Table 1).

A lower DPTRS was measured at 24 and 36 months in the abatacept arm, whereas Index60 was not different between the two treatment arms at any time point (Supplementary Table 1).

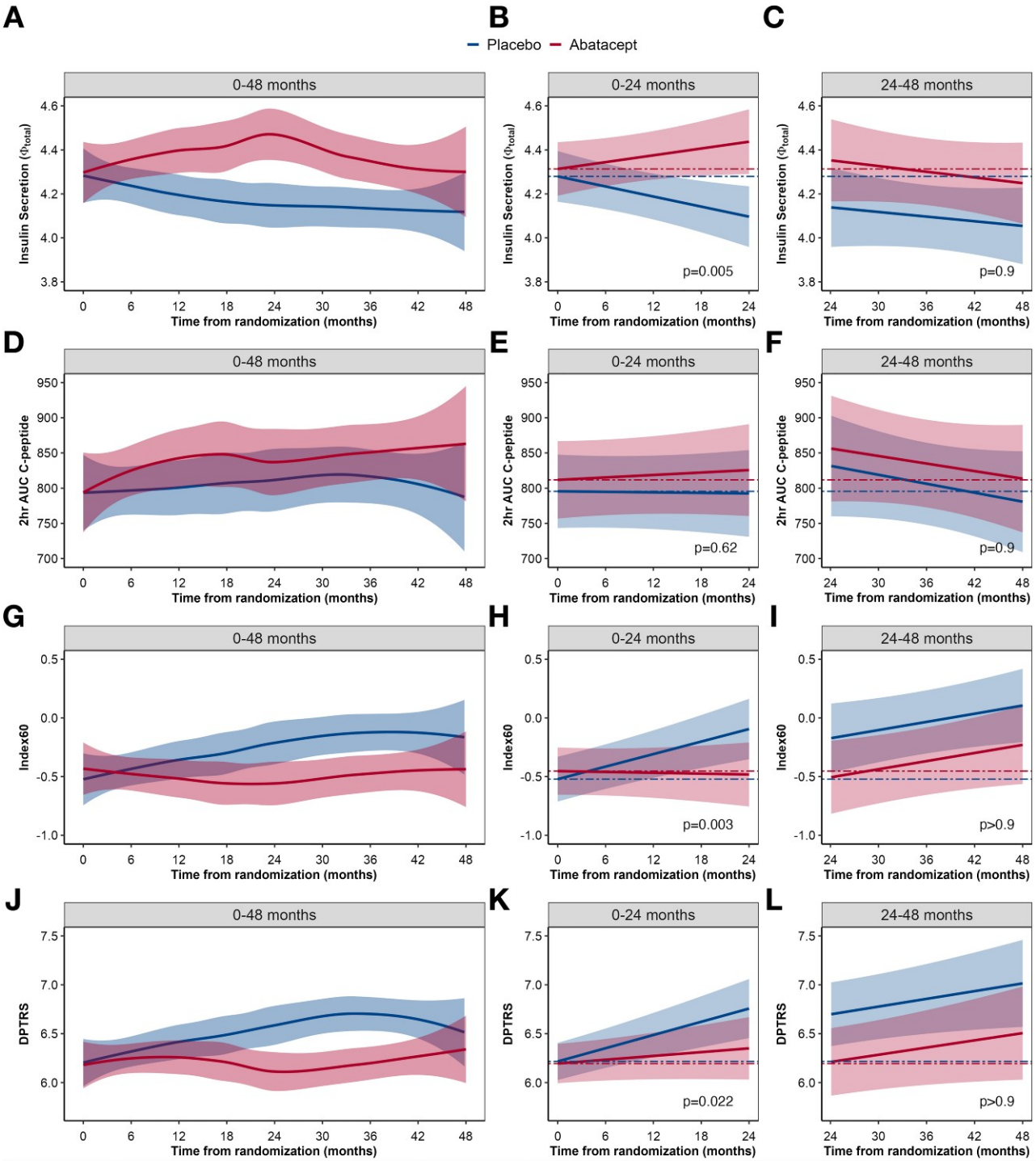
Baseline Insulin Secretion Modifies the Effect of Abatacept in Delaying Time to Disease Progression

Regardless of assigned treatment group (abatacept vs. placebo), metabolic and anthropometric baseline characteristics were similar among those in the high-secretor group and those categorized as low secretors (Table 1).

Overall, however, high secretors were older (median [25th, 75th centile] age 16 [13, 26] vs. 13 [10, 19] years; P = 0.0013) and had a higher BMI (23.2 [19.7, 27.4] vs. 19.3 [16.3, 23.7] kg/m^2; $P < 0.0001$), lower SI ($P < 0.0001$) and clearance (P = 0.0025), and lower risk indices ($P < 0.0001$) than the low secretors (Supplementary Table 2).

As described by the LOESS curves in Fig. 2 (left), baseline high secretors randomly assigned to the abatacept arm had higher insulin secretion during the first 24 months after treatment (P = 0.00035) (Fig. 2*A* and Supplementary Table 3), with a measurable difference between the trajectories of φ_{total} appreciated within the first 6 months (P = 0.039) of treatment (Supplementary Table 3). However, the effect of abatacept waned, with the two trajectories becoming parallel over 24–48 months from randomization (P = 0.73) (Fig. 2*A* and Supplementary Table 3). Despite this convergence over time, the abatacept arm maintained a higher φ_{total} at 48 months. AUC C-peptide trajectories did not differ during the first 24 months or during the 24- to 48-month period (Fig. 2*D–F*).

DPTRS and Index60 LOESS trajectories mirrored φ_{total}, with visible divergence between the treatment arms during the first 24 months; however, only Index60 demonstrated a significantly modified trajectory in the high-secretor subgroup of the abatacept arm (P = 0.005 and P = 0.057, respectively) (Fig. 2*G–L* and Supplementary Table 3). The



	M0	M6	M12	M18	M24	M30	M36	M42	M48
Abatacept	96	95	89	83	80	74	68	60	58
Placebo	107	104	99	94	92	79	75	66	61

Figure 1—*A–L*: LOESS trajectories over 48 months from randomization and segmented regression (0–24 and 24–48 months) of φ_{total} (*A–C*), AUC C-peptide (*D–F*), Index60 (*G–I*), and DPTRS (*J–L*) between treatment arms. Adjoining table summarizes number of individuals within each treatment arm at each 6-month milestone of follow-up. Dot-dash line represents *y*-intercept (i.e., baseline of respective arm).

trajectories over 24–48 months similarly converged (P = 0.54 and P = 0.89, respectively), further suggesting the waning effect of abatacept 24 months after initiation of treatment.

By contrast, for low secretors, there were no differences in the trajectories of φ_{total}, AUC C-peptide, DPTRS, or Index60 between treatment arms during the first 24

Table 2—Mixed-effects model analysis within segments 0–6, 0–24, and 24–48 months for abatacept and placebo arms

	Placebo		Abatacept		
Metric	*N* of observations and individuals	Coefficient per month over time period (95% CI)	*N* of observations and individuals	Coefficient per month over time period (95% CI)	*P**
φ_{total}					
0–6 months	208 and 107	−0.23 (−0.54, 0.08)	190 and 96	0.37 (0.04, 0.69)	**0.0094**
0–24 months	490 and 107	−0.09 (−0.16, −0.02)	434 and 96	0.06 (−0.02, 0.14)	**0.005**
24–48 months	272 and 90	−0.04 (−0.15, 0.06)	252 and 80	−0.05 (−0.16, 0.06)	0.90
AUC C-peptide					
0–6 months	208 and 107	−30.69 (−123.42, 62.05)	191 and 96	−7.48 (−103.42, 88.46)	0.73
0–24 months	492 and 107	−1.51 (−24.59, 21.56)	438 and 96	6.94 (−17.65, 31.54)	0.62
24–48 months	278 and 92	−25.44 (−67.21, 16.33)	257 and 80	−21.45 (−64.82, 21.92)	0.90
Index60					
0–6 months	208 and 107	0.43 (0.05, 0.81)	191 and 96	0.01 (−0.38, 0.41)	0.14
0–24 months	492 and 107	0.21 (0.11, 0.32)	438 and 96	−0.01 (−0.12, 0.1)	**0.003**
24–48 months	278 and 92	0.14 (0, 0.28)	257 and 80	0.14 (−0.01, 0.28)	0.99
DPTRS					
0–6 months	208 and 107	0.6 (0.28, 0.92)	191 and 96	0.06 (−0.27, 0.39)	**0.022**
0–24 months	492 and 107	0.27 (0.16, 0.38)	438 and 96	0.08 (−0.04, 0.2)	**0.022**
24–48 months	278 and 92	0.16 (0, 0.32)	257 and 80	0.15 (−0.02, 0.31)	0.93

**P* value reflects comparison of slopes between each treatment arm. Bold font indicates significance.

months or during the 24- to 48-month period (Fig. 2*M–X*, right). Over the first 6 months, there was only a marginal suggestion of Index60 having a significantly modified trajectory in the low-secretor subgroup of the abatacept arm ($P = 0.048$) (Supplementary Table 3).

Differences in φ_{total} trajectories were accompanied by different progression-free survival between high secretors in the placebo and abatacept arms. High secretors receiving abatacept exhibited a longer progression-free time over 96 months than their counterparts in the placebo group (log-rank $P = 0.015$) (Fig. 3), with abatacept providing high secretors with 15.8 progression-free months gained (95% CI 4.85, 26.68; $P = 0.005$) as compared with placebo.

Conversely, there was no significant difference in survival probability between treatment arms within the low-secretor group (log-rank $P = 0.31$), with similar progression-free months gained in both treatment arms (−7.88 progression-free months gained; 95% CI −24.79, 9.02; $P = 0.36$). High secretors receiving abatacept had a 54% lower hazard of progression versus placebo (HR 0.46; 95% CI 0.25, 0.84; $P = 0.012$). Treatment effect differed significantly by secretor status (interaction HR 2.92; 95% CI 1.23, 6.96; $P = 0.015$).

Sensitivity Analysis

When secretor status was redefined in the sensitivity analysis using the empirically derived RMST-based threshold ($\varphi_{total} = 4.11$), Kaplan-Meier curves again demonstrated that benefit with abatacept was concentrated in the high-secretor subgroup, mirroring the main analysis (secretor status defined by 33rd centile cutoff). In RMST-based threshold–defined high secretors, abatacept significantly delayed progression compared with placebo (log-rank $P = 0.022$), whereas no significant treatment effect was observed among low secretors (log-rank $P = 0.62$) (Supplementary Fig. 3).

DISCUSSION

In contrast with the primary analysis of the original TN18 trial of abatacept in individuals with stage 1 T1D, this post hoc analysis demonstrates that baseline insulin secretion, quantified as OMM-derived φ_{total}, can identify a subgroup of responders to abatacept in those with greater baseline insulin secretion.

In the overall cohort, treatment with abatacept preserved φ_{total} up to 12 months after treatment cessation, with the effect waning at 24 months after randomization (Fig. 1). Notably, modulation of the φ_{total} trajectory by abatacept, resulting in increased φ_{total}, was observed as early as 6 months into treatment. The waning effect of abatacept on insulin secretion after 24 months parallels the initial trajectory of the placebo-treated group (9), supporting the ability of the drug to delay disease progression. This suggests that continuation of abatacept beyond 12 months may have further delayed the autoimmune destruction of β-cell mass and consequently disease progression. Evidence from individuals at risk of rheumatoid arthritis receiving abatacept to prevent clinical disease progression

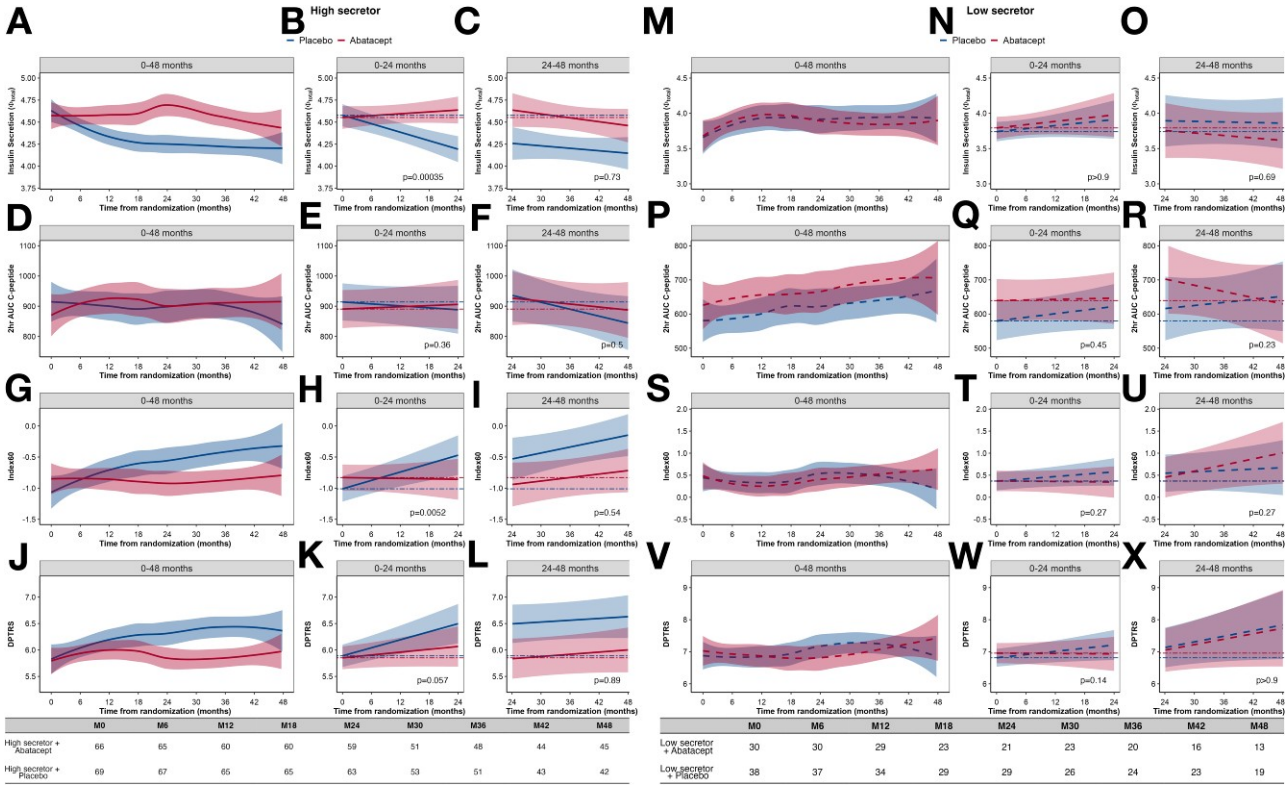


Figure 2—*A–L*: LOESS trajectories (solid lines) over 48 months from randomization and segmented regression (0–24 and 24–48 months) for high secretors in treatment and placebo arms of φ_{total} (*A–C*), AUC C-peptide (*D–F*), Index60 (*G–I*), and DPTRS (*J–L*). *M–X*: LOESS trajectories (dashed lines) over 48 months from randomization and segmented regression (0–24 and 24–48 months) for low secretors in treatment and placebo arms of φ_{total} (*M–O*), AUC C-peptide (*P–R*), Index60 (*S–U*), and DPTRS (*V–X*). Dot-dash line represents *y*-intercept (i.e., baseline of respective arm within each secretor group).

shows sustained efficacy during the treatment phase up to 12 months after treatment cessation, similar to our observations (29).

The trajectories of DPTRS and Index60 similarly reflected φ_{total}, with diverging risk profiles in those receiving placebo compared with abatacept. Over the first 24 months, although individual time points did not demonstrate differences between treatment arms, trajectories demonstrated modulation in risk profiles, with a more favorable risk profile in the high-secretor group receiving abatacept. However, in comparison with φ_{total}, differences between treatment arms over the first 6 and 24 months were less pronounced. This highlights a complementary role for risk indices, such as Index60 and DPTRS, with OMM-derived insulin secretion.

The effect of abatacept on early insulin secretion was not apparent when using AUC C-peptide. The original trial described a measurable difference in AUC C-peptide at 12 months between placebo and abatacept arms. In our comparison of treatment arms at each visit, we did not report a significant difference because of the different statistical approach we selected, which was intentionally applied consistently across the metrics we tested. Although we did adjust for age, because this is well known to affect C-peptide levels, we preferred not to adjust the analysis for baseline values, because the OMM factors in the baseline values, along with other factors, during the computational process, and an additional adjustment might have increased the risk of reporting a false positive difference.

The greater sensitivity of OMM-derived metrics to identify an early treatment effect is consistent with the idea that composite metrics, particularly those that account for both glucose and C-peptide levels, such as OMM-derived φ_{total} or risk indices (30), should be preferred end points in trials involving individuals with preclinical stages of T1D (stage 1 or 2), whereas AUC C-peptide might be a more appropriate end point for studies involving those with stage 3 disease (31). This may allow for smaller sample sizes in trials and earlier detection of treatment effects in stage 1 and 2 disease.

We note that we did not detect a direct effect of abatacept on SI in this cohort at any time point. A relative increase in SI has been described in those with inflammatory arthritis receiving abatacept after a short course of treatment (<24 weeks) but not in those receiving the treatment for longer periods (6 months) (32).

We observed that the clinical response to abatacept (i.e., time to disease progression) was modified by baseline insulin secretion as measured by φ_{total}. Specifically, we identified a responder subgroup with relatively higher baseline φ_{total} who had longer progression-free time over 96 months (Fig. 3), gaining an additional 15.8 months of

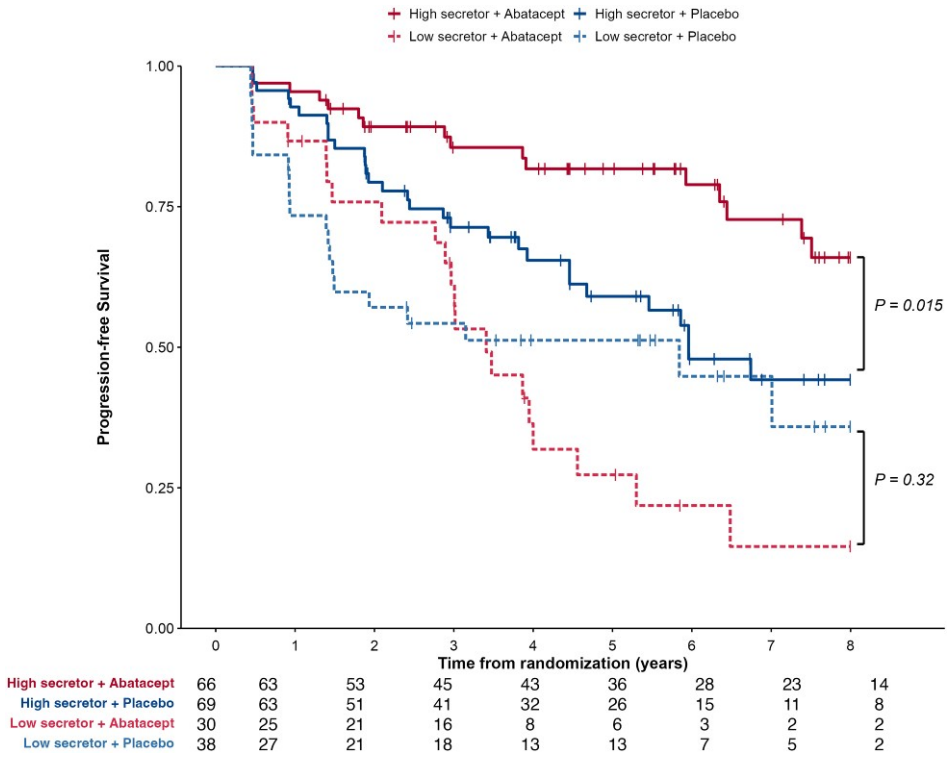


Figure 3—Kaplan-Meier survival curves for high and low secretors in treatment and placebo arms. Log-rank test used to compare curves over 96 months.

progression-free survival over 96 months (95% CI 4.9, 26.7; P = 0.005), and experienced a 54% lower hazard of progression compared with those receiving placebo (HR 0.46; 95% CI 0.25, 0.84; P = 0.012). Importantly, the treatment effect varied significantly by secretor status (interaction HR 2.92; 95% CI 1.23, 6.96; P = 0.015), indicating that benefit was concentrated in the high-secretor subgroup, whereas low secretors exhibited no treatment effect. This clinical response to abatacept was accompanied by increased and preserved insulin secretion both during treatment and after treatment cessation in high secretors treated with abatacept, compared with a declining trend in high secretors receiving placebo. In contrast, insulin secretion was not preserved in low secretors receiving abatacept, with similar trajectories of φ_{total} as compared with the placebo arm, and no clinical response was observed by modulation of progression-free survival (Fig. 3).

The sensitivity analysis using a decision analytic framework based on RMST to empirically derive an optimal threshold of φ_{total} for secretor status closely mirrored the pragmatic centile approach used in the primary analysis, and Kaplan-Meier curves stratified by this threshold again revealed a clear treatment benefit in the high-secretor subgroup. This suggests that the threshold chosen for secretor status in our initial analysis ($\geq$33rd or <33rd centile of φ_{total}) was appropriate and consistent with the totality of the data.

High secretors were characterized by relatively higher BMI and older age at randomization, as well as lower SI. The relatively higher BMI may be per se associated with greater insulin secretion, although the limited numerosity and the post hoc nature of this analysis prevent any causative inference. In contrast, the older age of the high-secretor group coincides with a physiologically greater β-cell mass in youths, with a peak during adolescence (age ~14 years) as previously described in autoptic samples from healthy donors (33), and is associated to slower disease progression (34).

This is the first evidence of abatacept clinical efficacy in preserving β-cell function in a subgroup of individuals with stage 1 T1D. The use of baseline φ_{total} to identify a responder group suggests the greatest efficacy of abatacept is in those enrolled at an earlier disease phase within stage 1 itself, characterized by higher insulin secretion. The clinical effect of abatacept in the murine model was strictly dependent on drug initiation before hyperglycemia, suggesting its efficacy is limited to early-stage disease (10,11), which indeed was part of the rationale behind selecting this therapy for use in stage 1 T1D (11). Our finding that response to abatacept was greater in higher insulin secretors who were likely to be earlier in the disease process is consistent with the murine model observations.

A differential response to disease-modifying treatments has been observed within stages of disease (5,35,36). We expect that more accurate metrics of β-cell function, such as the OMM-derived φ_{total}, might allow the early identification of responder groups to disease-modifying treatments and inform adaptive trial design for T1D prevention.

The clinical benefit that a higher baseline φ_{total} may convey as a longer progression-free time supports the use

of the OMM to effectively dissect heterogeneity within stage 1 disease and inform inclusion criteria for future clinical trials. Furthermore, φ_{total} seems to provide a tool to identify responders early in treatment, suggesting that φ_{total} could be used as a surrogate metric to detect drug effect as early as 6 months after the beginning of treatment. AUC C-peptide failed to identify early differences, probably because it does not account for the heterogeneity of either insulin secretion in pediatric ages or its effect on glucose excursion. In contrast, the φ_{total} computational process includes both C-peptide and glucose, thus capturing this heterogeneity in a single metric.

Earlier OGTTs were not available, so we cannot exclude that an earlier effect might have been detectable with a 3-month assessment, had that been available (as reported previously in stage 2 disease [5]). Costimulatory inhibition also has an effect on disease progression when initiated at a much later stage in disease, as demonstrated by the TN09 trial in stage 3 disease (new-onset clinical T1D), where those treated with abatacept for 2 years after clinical onset of T1D exhibited higher AUC C-peptide levels of ~50% (12).

The nomenclature adopted in this analysis to describe classification of responder subgroups (high vs. low secretors) reflects relative differences in insulin secretion among a study cohort with islet autoimmunity; however, we acknowledge that all study participants had a relative deficit in insulin secretion with respect to the healthy population without islet autoimmunity (16). Therefore, our subgrouping cannot be interpreted as representing normal versus abnormal insulin secretion in an absolute sense. Moreover, the threshold used to define secretor status was cohort specific and may not directly translate to other populations with stage 1 T1D. Further work will be required to establish a generalizable cutoff for φ_{total} that consistently identifies responders to abatacept across diverse study populations.

The primary limitation of this study is its retrospective post hoc analytic design. Additionally, the stratification of relatively high and low secretors is specific to this cohort, and threshold values used to define these groups may vary according to age, sex, disease stage, and other characteristics of the studied population. Although the treatment effect (interaction term of the Cox model) did indeed demonstrate the heterogeneity of treatment effect within this data set, the exact cutoff for defining responder subgroups requires external validation. The reduced number of participants during the last 24 months of follow-up limits our ability to identify minimal differences in insulin secretion that might have been clinically relevant but nonmeasurable with the sample size. In addition, although our stratification approach, based on the 33rd centile of baseline φ_{total}, resulted in an imbalance in group sizes (with a smaller low-secretor subgroup and a larger high-secretor subgroup) that may have limited statistical power to detect subtle treatment effects in low secretors, both the Cox model demonstrating a significant treatment effect and our sensitivity analysis using the RMST-based decision framework provided consistent evidence that treatment benefit was concentrated in high secretors.

In summary, these results suggest that abatacept may effectively delay progression to stage 2 or 3 disease in a large subpopulation of individuals with stage 1 T1D, characterized by relatively well-preserved baseline β-cell function. Our analysis suggests that this effect of abatacept is mediated by the preservation of insulin secretion, which was notably reduced over time in the placebo group. However, this protective effect diminished 12 months after therapy cessation, suggesting that extended treatment duration may be required to deliver a more durable delay in disease progression. Although these findings are exploratory and require further validation, they contribute valuable insights that could guide the design of future clinical trials targeting early-stage T1D with abatacept. Our data suggest φ_{total} could be an efficient, adaptive, and more sensitive outcome measure in clinical trials of stage 1 T1D to stratify risk of progression and identify the likelihood of treatment response.

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DK085453, U01 DK085461, U01 DK085463, U01 DK085465, UC4 DK085466, U01 DK085476, U01 DK085499, U01 DK085504, U01 DK085505, U01 DK085509, U01 DK097835, U01 DK103153, U01 DK103180, U01 DK103266, U01 DK103282, U01 DK106984, U01 DK106993, U01 DK106994, U01 DK107013, and U01 DK107014 and contract HHSN267200800019C; the National Center for Research Resources through Clinical Translational Science Awards UL1 RR024131, UL1 RR024139, UL1 RR024153, UL1 RR024975, UL1 RR024982, UL1 RR025744, UL1 RR025761, UL1 RR025780, UL1 RR029890, UL1 RR031986, and UL1 TR001872; and General Clinical Research Center Award M01 RR00400. The Immune Tolerance Network–funded portion of the research came from NIAID under award UM1AI109565. Breakthrough T1D (formerly JDRF) supported this study through grants 3-SRA-2015-27-Q-R, 2-SRA-2018-609-Q-R, 2-SRA-2020-900-S-B, 82-2013-652, and 1-SRA-2020-900-M-X. P.S. is supported by the Charles A. Allard Chair in Diabetes Research and the Academic Medicine and Health Services Program.

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Author Contributions. A.G. and A.L.J.C. researched data, performed analyses, interpreted results, and wrote the first draft of the manuscript. A.G., A.L.J.C., D.C., and C.D. had full access to the data. A.G., A.L.J.C., and C.D. planned the analyses. P.T., J.S., J.L.S., P.S., E.K.S., C.E.-M., H.M.I., B.N., and A.P. interpreted results and reviewed and edited the manuscript. J.B. and C.D.M. ran the minimal model analysis. D.C. obtained data, performed analyses, and reviewed and edited the manuscript. J.S., J.L.S., P.S., C.D.M., K.H., A.M., and C.D. contributed to discussion and reviewed and edited the manuscript. W.E.R. led the initial study and critically revised the analyses and the manuscript. All authors revised and approved the final version of the manuscript. A.G. is the guarantor of this work and, as such, 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.

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