Supplemental Material

Supplemental Table 1. Participant Characteristics at Baseline

	All N=76	**Placebo N=32**	**Teplizumab N=44**
Sex			
Female	34 (44.74%)	15 (46.88%)	19 (43.18%)
Male	42 (55.26%)	17 (53.13%)	25 (56.82%)
Race			
Asian	2 (2.63%)	2 (6.25%)	0 (0.00%)
Hispanic	2 (2.63%)	1 (3.13%)	1 (2.27%)
White	72 (94.74%)	29 (90.63%)	43 (97.73%)
Age, mean (SD)	18.52 (11.51)	17.53 (11.10)	19.24 (11.87)
BMI at baseline, mean (SD)	22.01 (5.60)	22.08 (4.39)	21.95 (6.39)
Log BMI at baseline, mean (SD)	3.06 (0.23)	3.08 (0.19)	3.05 (0.26)
BMI-for-age z-score, mean (SD)	0.74 (1.23)	0.98 (0.75)	0.55 (1.47)
Mean Glucose AUC, mean (SD)	159.46 (22.69)	155.31 (22.94)	162.47 (22.28)
Mean C-peptide AUC, mean (SD)	1.94 (0.79)	1.89 (0.72)	1.97 (0.84)
Peak C-peptide, mean (SD)	2.68 (1.09)	2.58 (0.99)	2.75 (1.16)
Index60, mean (SD)	1.95 (0.58)	1.85 (0.64)	2.02 (0.53)
DPTRS, mean (SD)	8.17 (1.02)	8.10 (1.06)	8.22 (1.01)
C-peptide AUC/Glucose AUC (x1000)	12.14 (4.71)	12.08 (4.34)	12.18 (5.01)
log(C-peptide AUC/Glucose AUC)	-4.48 (0.36)	-4.47 (0.34)	-4.48 (0.38)
30 - 0 min C-peptide	1.07 (0.61)	1.11 (0.61)	1.04 (0.62)
60 - 0 min C-peptide	1.56 (0.80)	1.50 (0.69)	1.60 (0.87)
120 - 60 min C-peptide	0.29 (0.69)	0.18 (0.84)	0.37 (0.56)
30 - 0 min glucose	70.07 (27.63)	69.88 (22.47)	70.20 (31.10)
60 - 0 min glucose	83.92 (35.75)	77.53 (37.21)	88.57 (34.33)
120 - 60 min glucose	-26.66 (36.51)	-25.81 (38.26)	-27.27 (35.62)
Glucose, mean (SD)			
0 minutes	95.32 (10.71)	94.94 (13.69)	95.59 (8.05)
30 minutes	165.38 (28.55)	164.81 (24.17)	165.80 (31.62)
60 minutes	179.24 (35.86)	172.47 (38.50)	184.16 (33.40)
90 minutes	169.26 (38.96)	163.16 (44.27)	173.70 (34.44)
120 minutes	152.58 (32.12)	146.66 (34.89)	156.89 (29.62)
C-peptide, mean (SD)			
0 minutes	0.61 (0.29)	0.61 (0.31)	0.61 (0.27)
30 minutes	1.67 (0.76)	1.71 (0.79)	1.65 (0.75)
60 minutes	2.16 (0.97)	2.11 (0.89)	2.21 (1.02)
90 minutes	2.38 (1.10)	2.28 (0.98)	2.45 (1.19)
120 minutes	2.46 (1.06)	2.29 (0.97)	2.58 (1.11)

Supplemental Table 2. Comparison between Placebo and Oral Insulin Arms of Endpoints Utilizing Changes in Metabolic Parameters from Baseline to 1-year Visit*

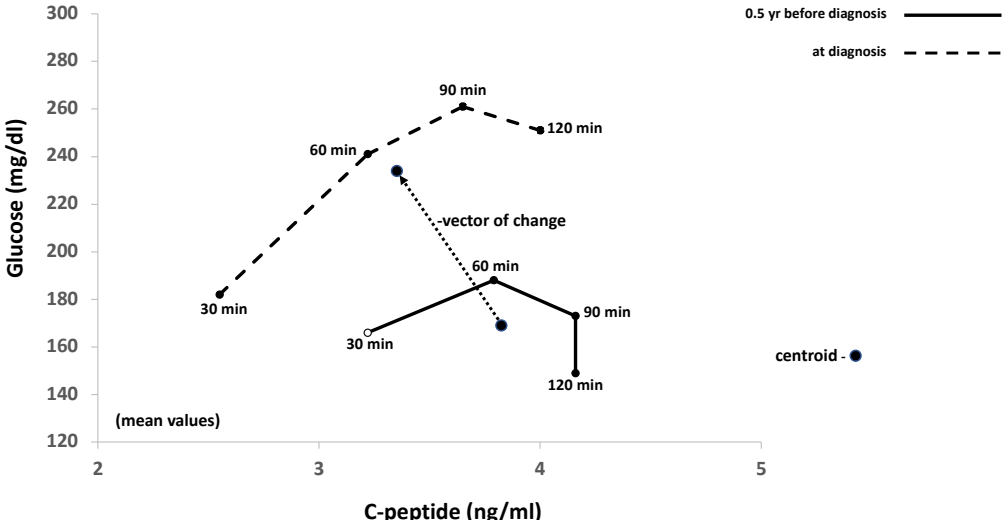
Change from Baseline Visit to 3-month visit (n=97 for placebo arm, n=110 for oral insulin arm)				
Endpoint	**Placebo Arm**	**Oral Insulin Arm**	**Unadjusted p-value**	**Adjusted p-value[+]**
ODE	205 (85)	170 (81)	0.003	0.005
WQE	0.66 (0.66)	0.36 (0.50)	<0.001	<0.001

[+]Adjusted for age, BMI, baseline AUC C-peptide, and AUC glucose values

*1-year visit used to assess endpoints since oral insulin peak effect was at that time point in prior study (22)

Supplemental Figure 1

A



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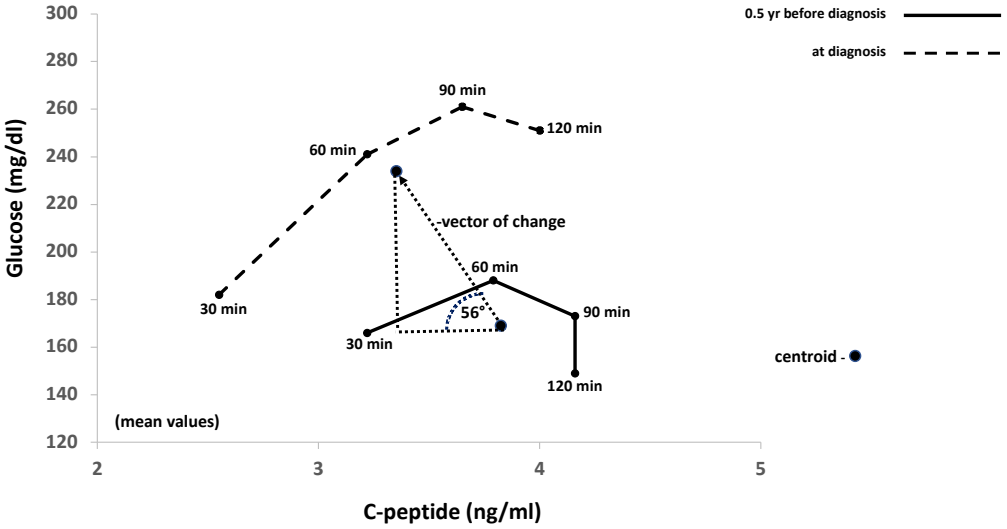

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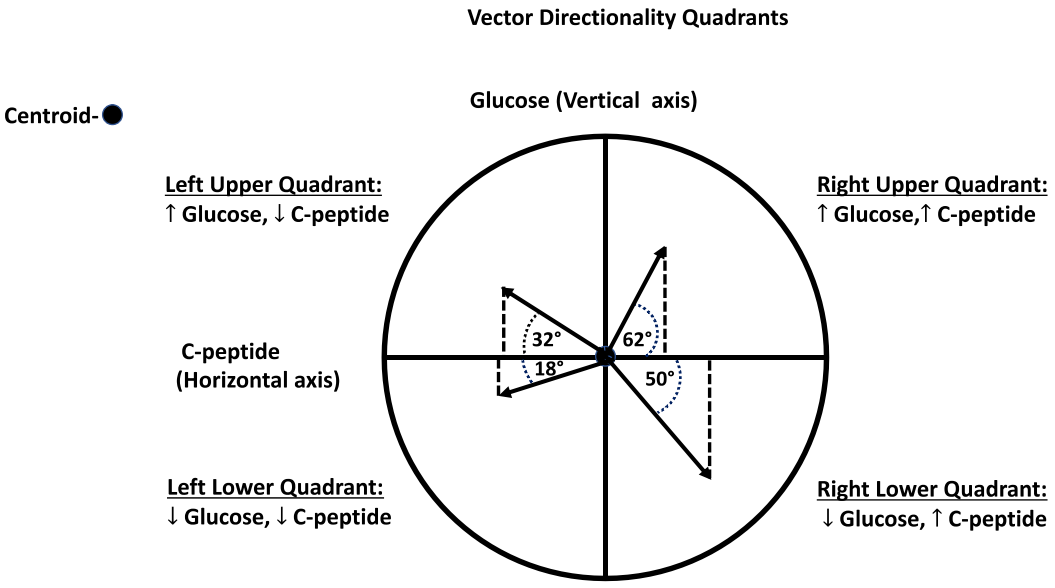
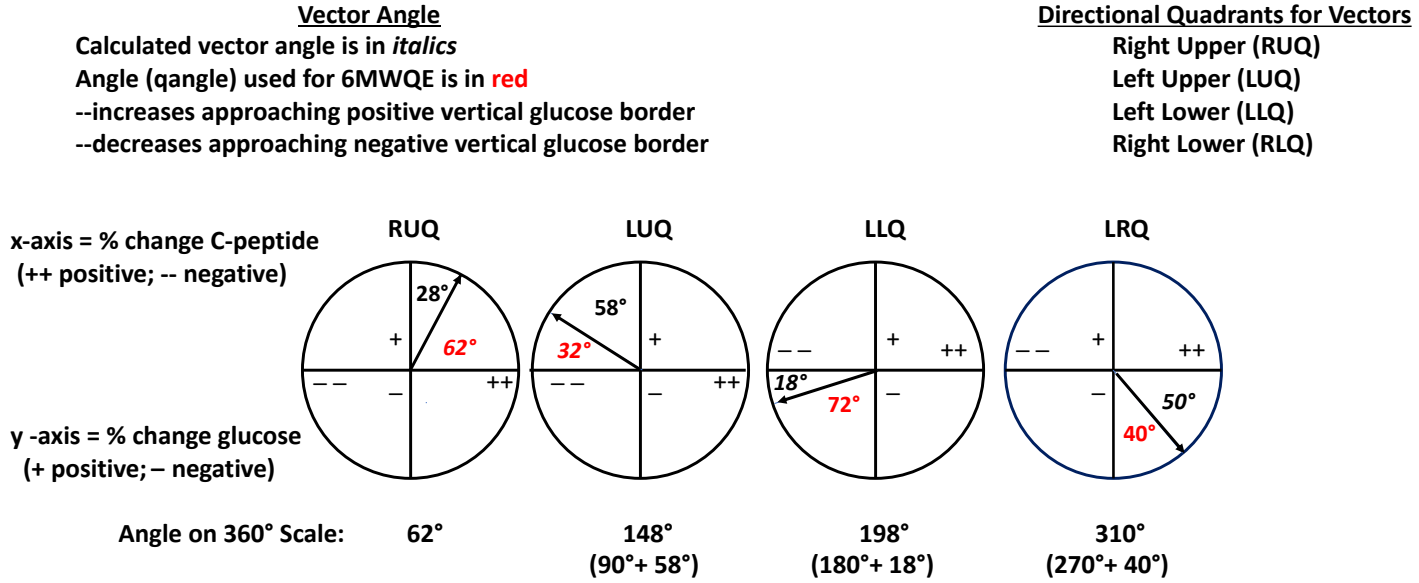


Supplemental Figure 1. Glucose C-peptide Response Curves (GCRCs) Allow for Visualization and Quantification of the Evolving Relationship between Glucose and C-peptide as Type 1 Diabetes Develops. A. Hypothetical GCRC's showing typical glucose and C-peptide values at 30 (open circle), 60, 90, and 120 minute (open square) timepoints of an oral glucose tolerance test are plotted for individuals at the time of diagnosis of type 1 diabetes (dashed line) and 6 months before diagnosis. Mean centroid values for glucose and C-peptide coordinates are indicated as dots within each GCRC. Vector showing the change in mean GCRC centroid values over this period shows directionality toward the upper left portion of the grid, indicating increasing glucose and decreasing C-peptide values. B. Conceptual diagram displaying application of GCRC vector to create a right triangle, allowing for combined application of directional quadrant of change and angles generated by the triangle to quantify changes in metabolic function. The calculated angle is the angle between the vector (hypotenuse) and the horizontal side of the right triangle. C. Hypothetical example of vectors for each of the 4 directional quadrants, which emanate from a baseline centroid which has glucose and C-peptide values fixed at 0. The calculated angles between the horizontal and the vector are also shown.

Supplemental Figure 2



Supplemental Figure 2. Angles Utilized for WQE (qangle, indicated in red) Based on Directional Quadrant of GCRC Vector of Change: The metabolic changes of glucose and C-peptide over the 6- month period would fall into 1 of the 4 directional quadrants indicated. Each quadrant includes calculated vector angles between the vector and the horizontal border as well as the vector and the vertical border. For vectors falling within the upper quadrants, the qangle (the angle used to optimize the model for use as an endpoint, indicated in red) was calculated between the vector and the horizontal border. For vectors falling within the lower quadrants, the qangle was calculated between he vector and the vertical border. In this example, for the RUQ, the vector angle of 62° between the vector and the horizontal axis would be used as the qangle for the development of the WQE. However, for the LRQ, the calculated vector angle of 40° (between the vector and the vertical axis) was utilized for the qangle.

Supplemental Materials for Analytic Components:

Formula for Calculation of Centroid

CPEP Centroid=(1 / 3) * (((CPEP30 + CPEP60) * ((CPEP30 * GLUC60) - (CPEP60 * GLUC30))) + ((CPEP60 + CPEP90) * ((CPEP60 * GLUC90) - (CPEP90 * GLUC60))) + ((CPEP90 + CPEP120) * ((CPEP90 * GLUC120) - (CPEP120 * GLUC90))) + ((CPEP120 + CPEP30) * ((CPEP120 * GLUC30) - (CPEP30 * GLUC120)))) / (((CPEP30 * GLUC60) - (CPEP60 * GLUC30)) + ((CPEP60 * GLUC90) - (CPEP90 * GLUC60)) + ((CPEP90 * GLUC120) - (CPEP120 * GLUC90)) + ((CPEP120 * GLUC30) - (CPEP30 * GLUC120)))

GLUC Centroid =(1 / 3) * (((GLUC30 + GLUC60) * ((CPEP30 * GLUC60) - (CPEP60 * GLUC30))) + ((GLUC60 + GLUC90) * ((CPEP60 * GLUC90) - (CPEP90 * GLUC60))) + ((GLUC90 + GLUC120) * ((CPEP90 * GLUC120) - (CPEP120 * GLUC90))) + ((GLUC120 + GLUC30) * ((CPEP120 * GLUC30) - (CPEP30 * GLUC120)))) / (((CPEP30 * GLUC60) - (CPEP60 * GLUC30)) + ((CPEP60 * GLUC90) - (CPEP90 * GLUC60)) + ((CPEP90 * GLUC120) - (CPEP120 * GLUC90)) + ((CPEP120 * GLUC30) - (CPEP30 * GLUC120)))

Development of 6-Month Within Quadrant Endpoint and 6-month Ordinal Directional Endpoint

The sections below will describe the development of the two novel endpoints used together in the analyses and their formulations. The Supplemental Figures should be used for reference as the endpoints are explained. Please read the Analytic Components section in the Research Design and Methods before reading the content below.

Basis for Choosing Endpoints for the Analysis

Potential endpoints were first tested for their prediction of type 1 diabetes. Those predictive of type 1 diabetes were then assessed for their performance in detecting an oral insulin treatment effect in the combined DPT-1 and Trial Net oral insulin trial cohorts (n=208; no interaction between trial and treatment). Among the endpoints studied, the within quadrant endpoint (WQE) and ordinal directional endpoint (ODE) were predictive of type 1 diabetes among 281 DPT-1 participants who were in the oral insulin or parenteral insulin control groups ($p<0.001$ for WQE and $p=0.001$ for ODE unadjusted; $p<0.001$ for both after adjustment for AUC glucose AUC, C-peptide AUC, age and BMI). Although other endpoints were also predictive of type 1 diabetes, WQE and ODE were superior to others for detecting an oral insulin effect. Supplemental Table 2 shows the comparisons between the placebo and oral insulin groups for the WQE ($p<0.001$) and the ODE ($p=0.005$) after adjustments for baseline glucose AUC, C-peptide AUC, age and BMI. Based on these findings, we utilized the WQE and ODE to statistically assess an early teplizumab effect.

Within Quadrant Endpoint (WQE)

The full 360° continuum was poorly predictive of type 1 diabetes. Therefore, we explored the possibility that the prediction of risk could be enhanced by dividing the 360° continuum into its 4 directional quadrants from 0° to 90°. Each directional quadrant would be considered to have its own characteristic risk that would be predictive of overall risk when included together in a model. The directional quadrants are designated as:

Right Upper Quadrant (RUQ)

Left Upper Quadrant (LUQ)

Right Lower Quadrant (RLQ)

Left Lower Quadrant (LLQ)

As shown in the Supplemental Figure 2, angles were calculated from right triangles formed according to the directionality quadrant of an individual's vector of change. Since the calculated angles were negative in LUQ and RLQ, they were transformed to positive. The percent change of the centroid glucose from baseline to 6 months on the y-axis and percent change of the centroid C-peptide from baseline to 6 months on the x-axis were used for the calculation of the angle. The hypotenuse of the triangle represents the distance from the baseline GCRC centroid from baseline to 6 months (i.e., vector for change). The formulas for the calculated angle and hypotenuse are shown below:

radian=arc tangent(%change glucose/%change C-peptide)

*angle=radian * 57.296*

*hypotenuse=sqrt ((%change glucose * % change glucose) + (%change C-peptide * %change C-peptide))*

(The formulas use percent change of glucose and C-peptide instead of actual values to standardize the units of the sides of the triangle.)

Using data from the control groups of the DPT-1 and TrialNet parenteral insulin and oral insulin trials (n=281), we developed a Cox regression model which included the calculated angle of change over 6 months within each quadrant as an independent variable for predicting type 1 diabetes. Because an individual's vector of change can only fall into one of the quadrants, the values of the other quadrants were designated as 0. Based on this paradigm we found that the model was significantly predictive of type 1 diabetes. However, we also

found that other models could also be predictive if the calculated angle is subtracted from 90° for certain quadrants.

Supplemental Figure 2 shows how vectors, quadrants and angles were defined. It also shows hypothetically that the angles utilized for the final model included the calculated angles of percent change in the LUQ and RLQ, and the calculated angles of percent change subtracted from 90° in the LLQ and the RLQ. In addition, we observed that by adjusting model coefficients for baseline risk with the DPT-1 risk score (10) (DPTRS), the models were more predictive of type 1 diabetes. Thus, the final model coefficients are based on adjustments for the DPTRS. The equation below shows the coefficients of the directional quadrant angles (qangles) used for the model that detected the greatest difference between the oral insulin and placebo groups ($p<0.001$).

*WQE=0.02455*qangle1+0.01464*qangle2+0.00831*qangle3-0.00465*qangle4*

with qangle1=RUQ, qangle2=LUQ, qangle3=LLQ, and qangle4=RLQ

(Since 3 directional quadrants of the 4 would always be negative for an individual, indicator variables coded as "0" were used.)

The summary below shows the steps necessary for the calculation of the WQE:

--Calculations of glucose and C-peptide coordinates for baseline and 6-month GCRC centroids.

--Conversion of changes of glucose and C-peptide centroid coordinates into percent change.

--Identify directionality quadrant for vector between baseline and 6-month coordinates.

--Calculate within quadrant angle between horizontal and vector using standard formula based on right triangles.

--Convert negative angles in directional quadrants 2 and 4 (qangle2 and qangle4) to positive.

----Use calculated angle for qangle1 and qangle2. Use (90°- calculated angle) for qangle3 and (90 - qangle4) in the model.

The procedures for the angle transformations from negative to positive, and the subtractions of angles from 90° are shown below:

If the vector for centroid change is in the RUQ, then qangle1=calculated angle

If the vector for centroid change is in the LUQ, then qangle2=calculated angle(-1)*

If the vector for centroid change is in the LLQ, then qangle3=90-calculated angle

If the vector for centroid change is in the LLQ, then qangle4=90-calculated angle(-1)*

Example for WQE

An individual's directionality of the baseline GCRC centroid to the 6-month GCRC centroid is in the LLQ with a 32° qangle. The WQE=0.00831*(32) = 0.266

(0.00831 is the regression coefficient for the LLQ directional quadrant)

6-month Ordinal Directional Endpoint (ODE)

Using the 360° scale, we assigned a value for the 4 quadrants as indicated below according to prior evidence of sequential directionality during the longitudinal progression to type 1 diabetes (15).

Lower right quadrant (RLQ): 0°

Lower left quadrant (LLQ): 90°

Upper right quadrant (RUQ): 180°

Upper left quadrant (LUQ): 270°

The value was added to the value of the qangle obtained from the WQE model. The sum is then divided by 360 to create a scale with a maximum value of 1.00.

The summary of steps necessary for the ODE calculation are the same as that for the WQE except that instead of inserting the qangle value into a model, the qangle is added to the designated values indicated above for the directional quadrants.

Example for ODE

An individual's vector directionality for change from the baseline GCRC centroid to the 6-month GCRC centroid is in the LUQ at a qangle of 49^0.

The 6M-ODE for that individual is:

270° + 49° = 319°/360° = 0.87 units

where 270° represents the designated quadrant value for LUQ and 49° the value of the angle within in the LUQ.

Potential endpoints were first tested for their prediction of type 1 diabetes. Those predictive of type 1 diabetes were then assessed for their performance in detecting an oral insulin treatment effect in the combined DPT-1 and Trial Net oral insulin trial cohorts (n=208; no interaction between trial and treatment). Among the endpoints studied, the within quadrant endpoint (WQE) and ordinal directional endpoint (ODE) were predictive of type 1 diabetes among 281 DPT-1 participants who were in the oral insulin or parenteral insulin control groups ($p<0.001$ for WQE and $p=0.001$ for ODE unadjusted; $p<0.001$ for both after adjustment for AUC glucose AUC, C-peptide AUC, age and BMI). Although other endpoints were also predictive of type 1 diabetes, WQE and ODE were superior to others for detecting an oral insulin effect. Supplemental Table 2 shows the comparisons between the placebo and oral insulin groups for the WQE ($p<0.001$) and the ODE ($p=0.005$) after adjustments for baseline glucose AUC, C-peptide AUC, age and BMI. Based on these findings, we utilized the WQE and ODE to statistically assess an early teplizumab effect.