Potential for Preservation of Residual Insulin Secretion in Individuals with Presymptomatic T1D

Emily K. Sims

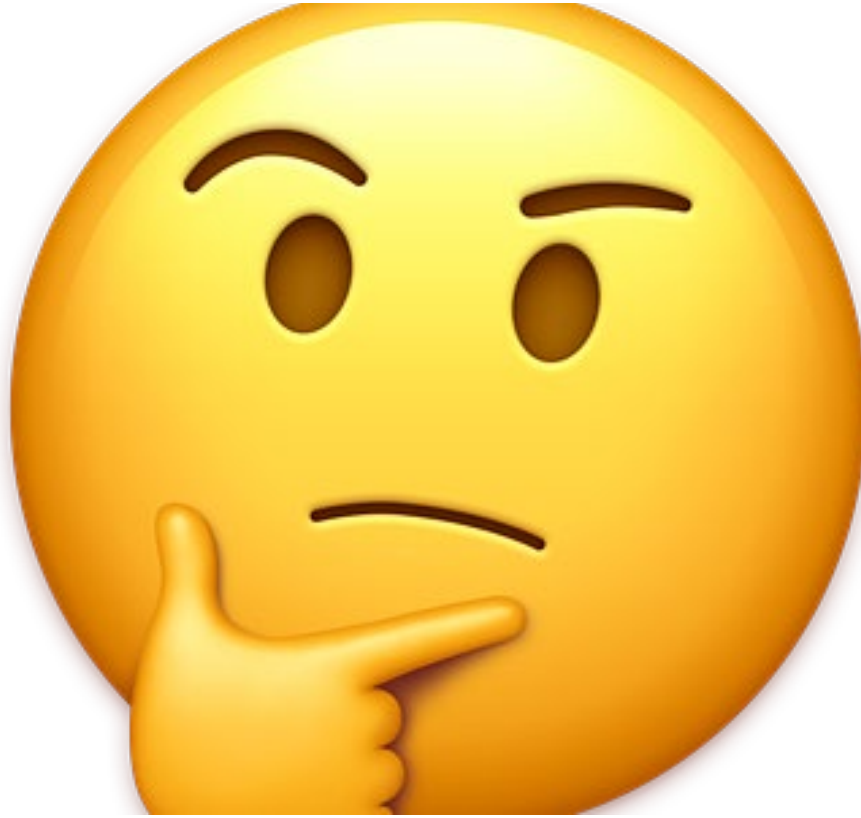
Associate Professor of Pediatrics, IU School of Medicine

Conflicts

- Emily Sims is a consultant and has been a speaker for Sanofi

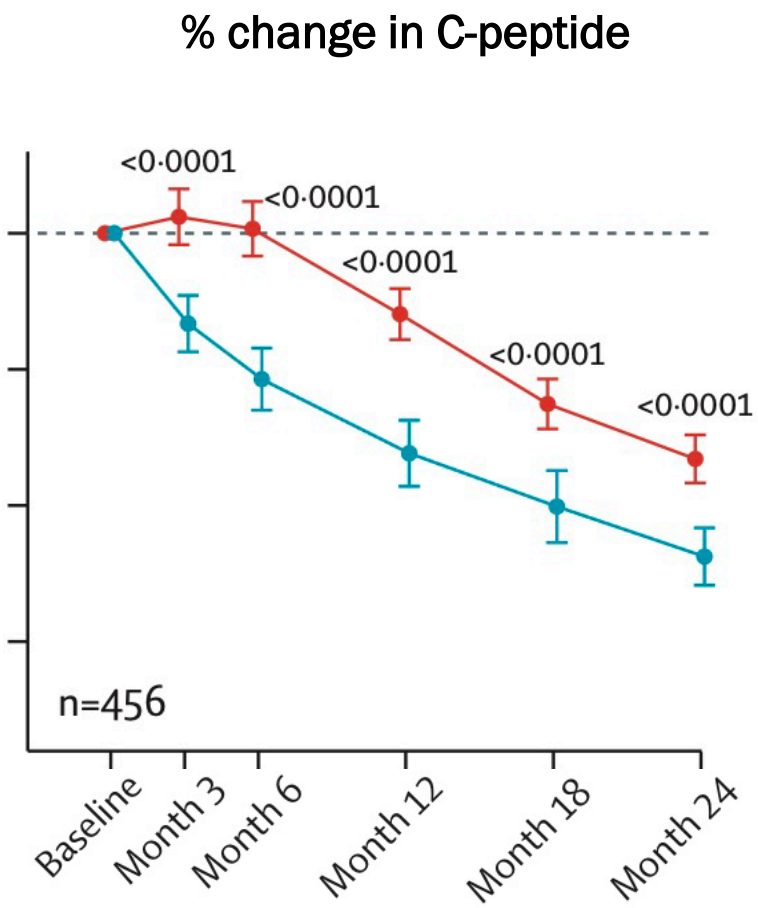
Why should we care about impacts on residual insulin secretion?

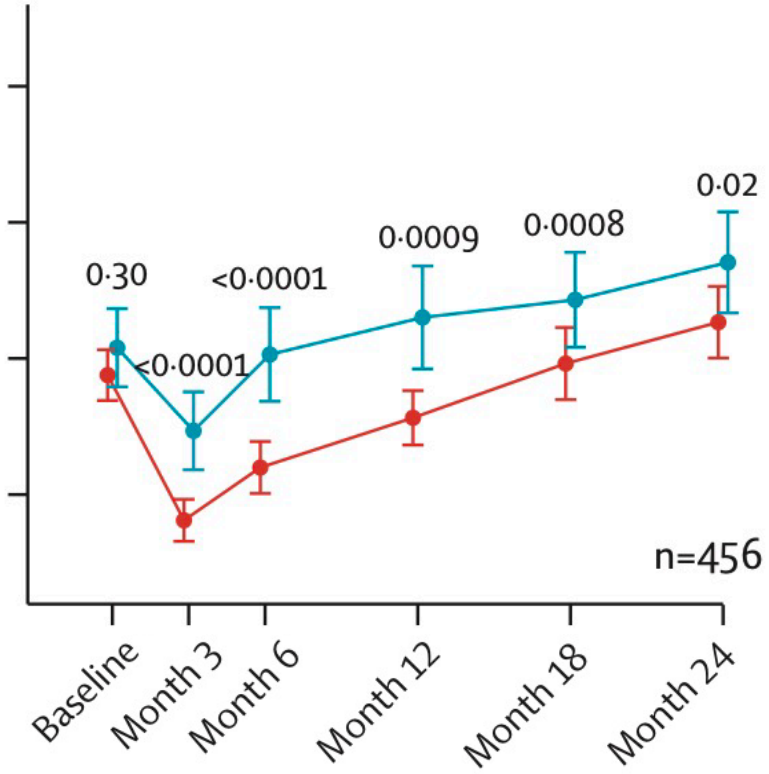
- Delay of stage 3 T1D
- Higher residual insulin secretion in stage 3 T1D
  - Lowers HbA1c
  - Reduces Hypoglycemia
  - Reduces microvascular and macrovascular complications

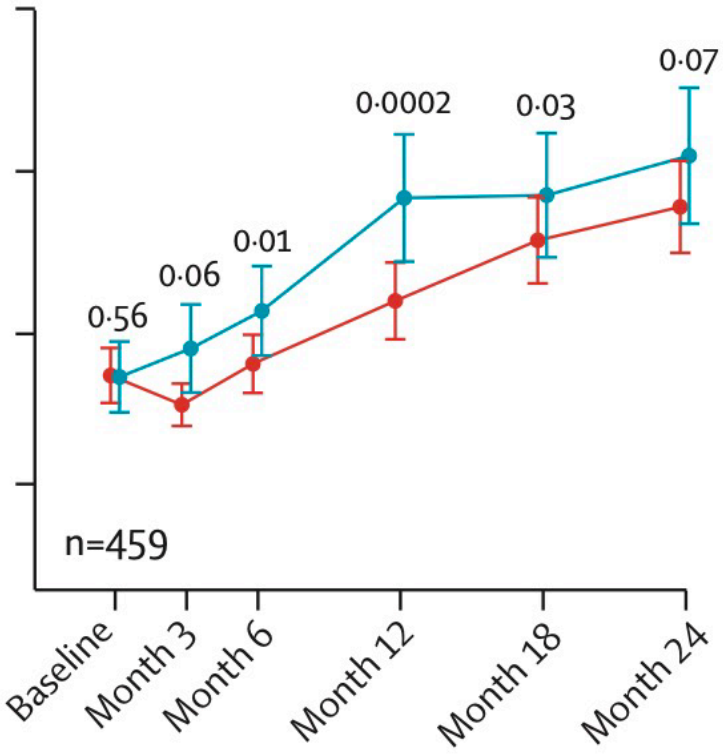


Lachin et al. Diabetes. 2014 Feb;63(2):739-48.; Gubitosi-Klug et al. J Clin Invest. 2021 Feb 1;131(3):e143011. Harsunen et al. Lancet Diabetes Endocrinol. 2023 Jul;11(7):465-473.

Improvements in C-peptide from Disease Modification are Linked to Improved Clinical Endpoints Post-Diagnosis







Taylor et al. Lancet Diabetes Endocrinol 2023; 11: 915–25

Can Screening for Presymptomatic T1D Improve C-peptide?

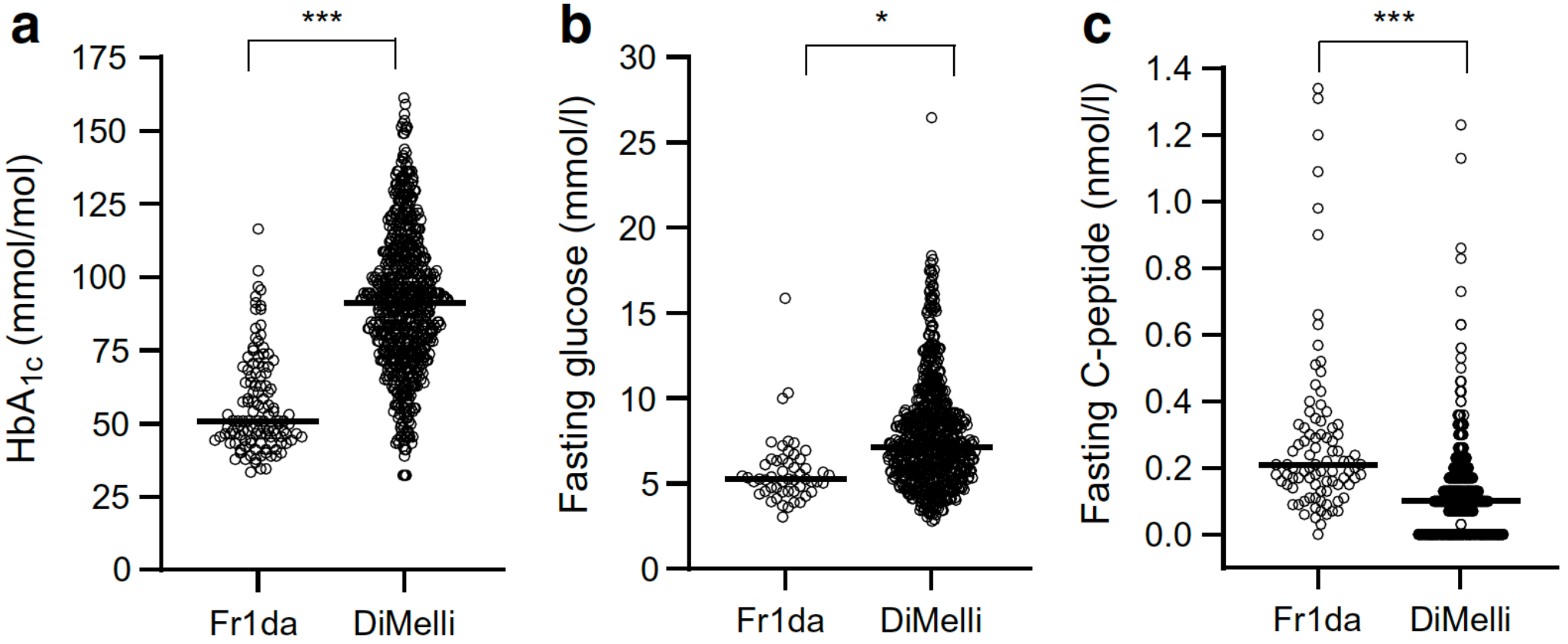
- Identifies T1D earlier in the natural history and reduces rates DKA at diagnosis
- Impact of disease modification in presymptomatic disease

Impact on DKA at diagnosis on residual insulin secretion

- DKA at diagnosis linked to reduced residual insulin secretion
- Reduced DKA from screening, education, and monitoring could have long-term impacts on insulin secretion

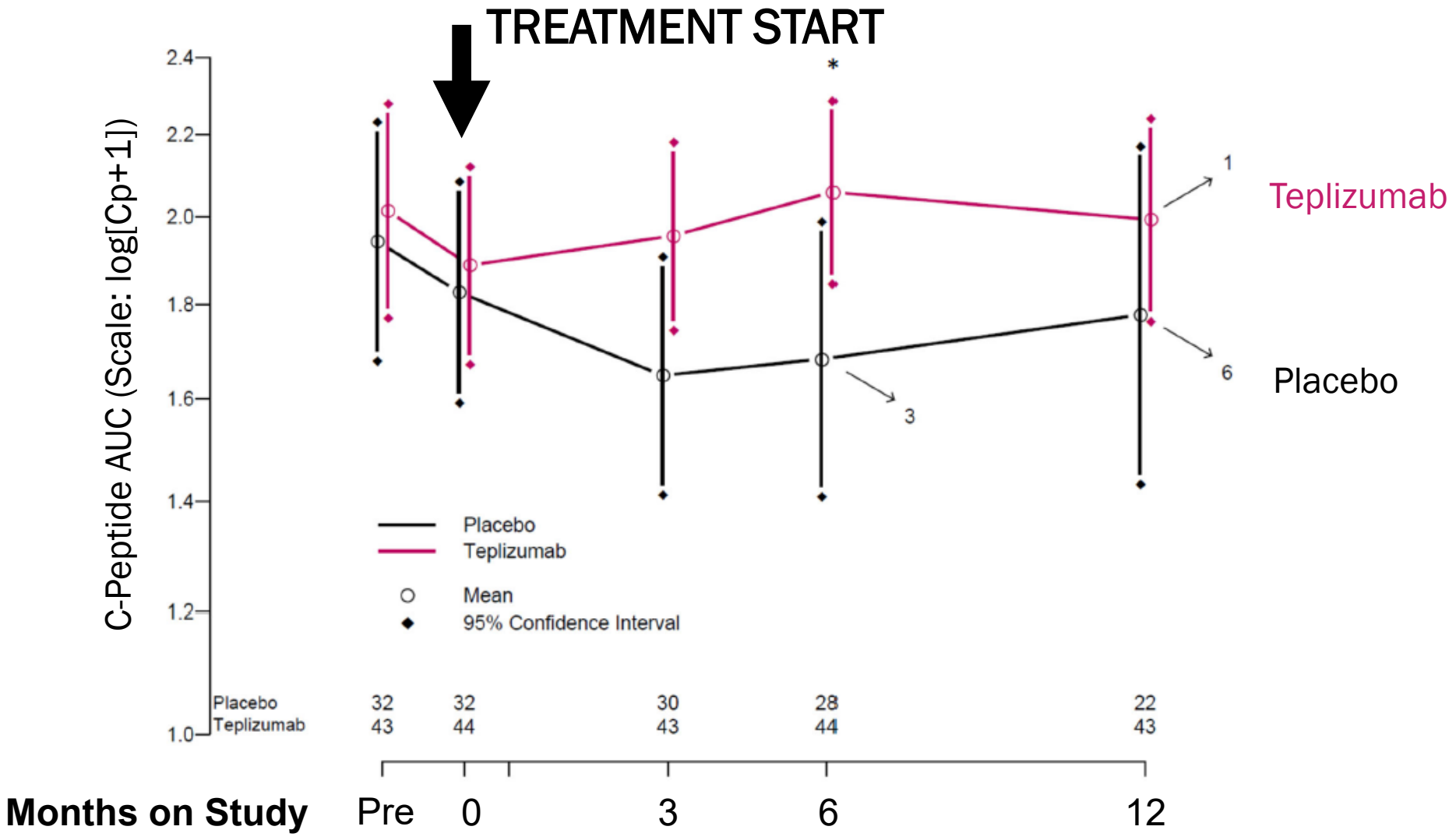
Castaner et al. *Diabetes Metab*. 1996 Oct;22(5):349-55. Fredheim et al. *Diabetologia*. 2013 May;56(5):995-1003. nejm.org

C-peptide at diagnosis is higher in the Fr1da cohort compared to background controls with incident stage 3 diagnoses



Hummel et al. *Diabetologia*. 2023. 66:16331642.

Impact of disease modification on insulin secretion

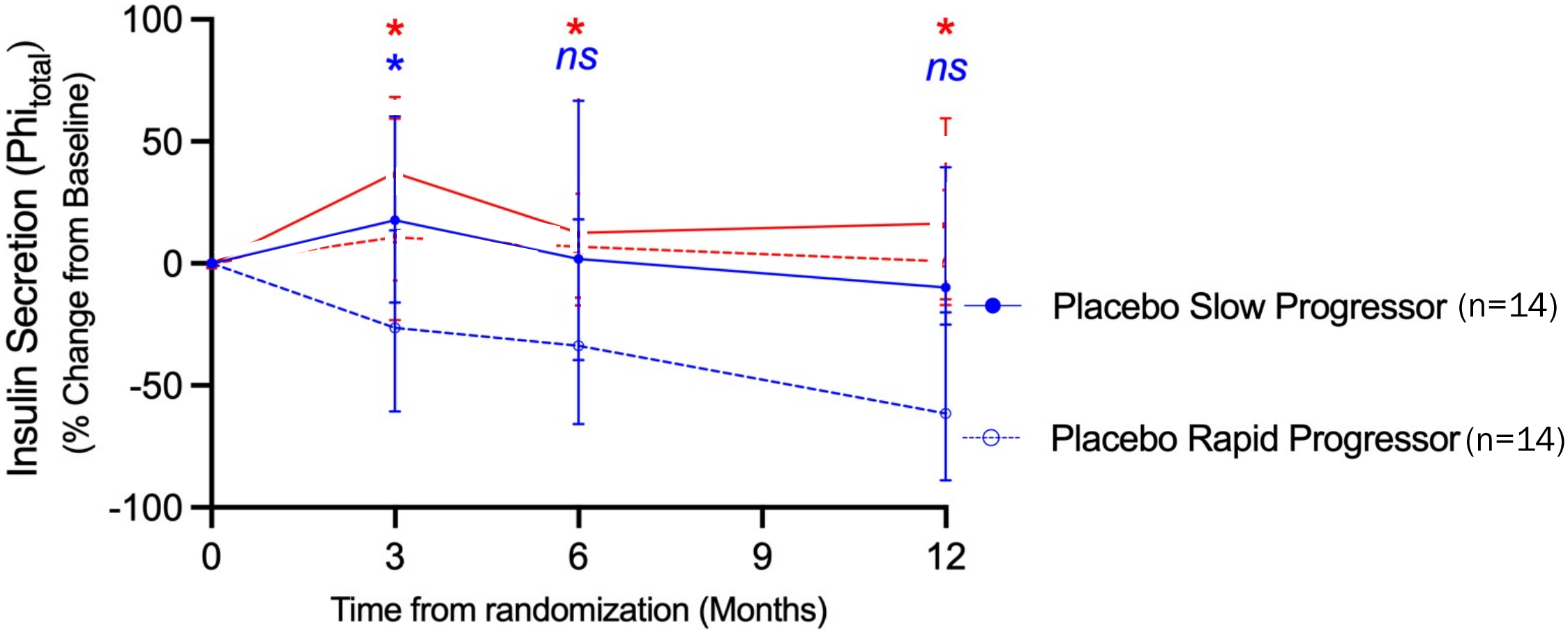


Teplizumab

Placebo

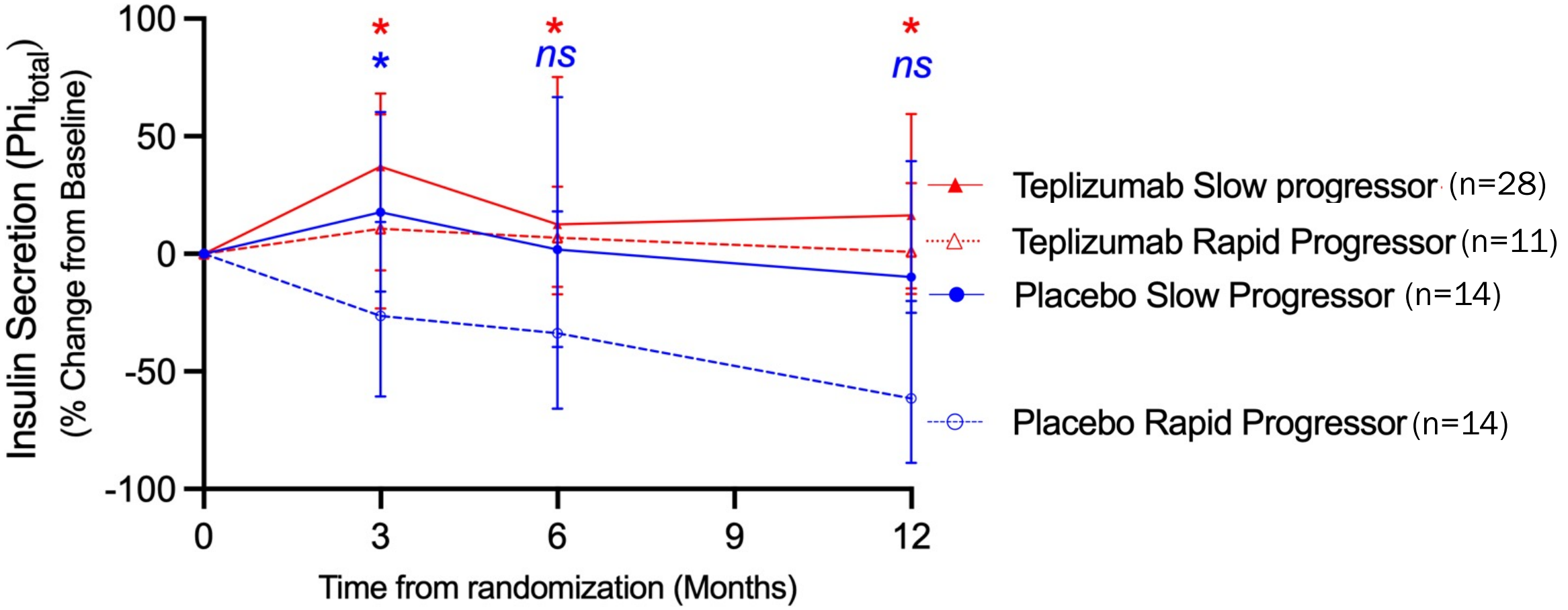
Sims et al. *Sci Transl Med*. 2021 Mar 3;13(583):eabc8980.

Impact of Disease Modification on Insulin Secretion within Treatment "Responders" and "Nonresponders"



Galderisi et al. accepted at *Diabetologia*.

Impact of Disease Modification on Insulin Secretion within Treatment "Responders" and "Nonresponders"



Galderisi et al. accepted at *Diabetologia*.

Summary

- Insulin secretion is improved by teplizumab treatment in most individuals in stage 2 disease
- When compared to those who progress most rapidly in the placebo group, treatment also had an impact on “rapid progressors” in the teplizumab group
  - The median time to stage 3 clinical disease was 5.8 (3.1, 12.0) and 18.6 (12.2, 22.3) months for placebo and teplizumab rapid-progressors

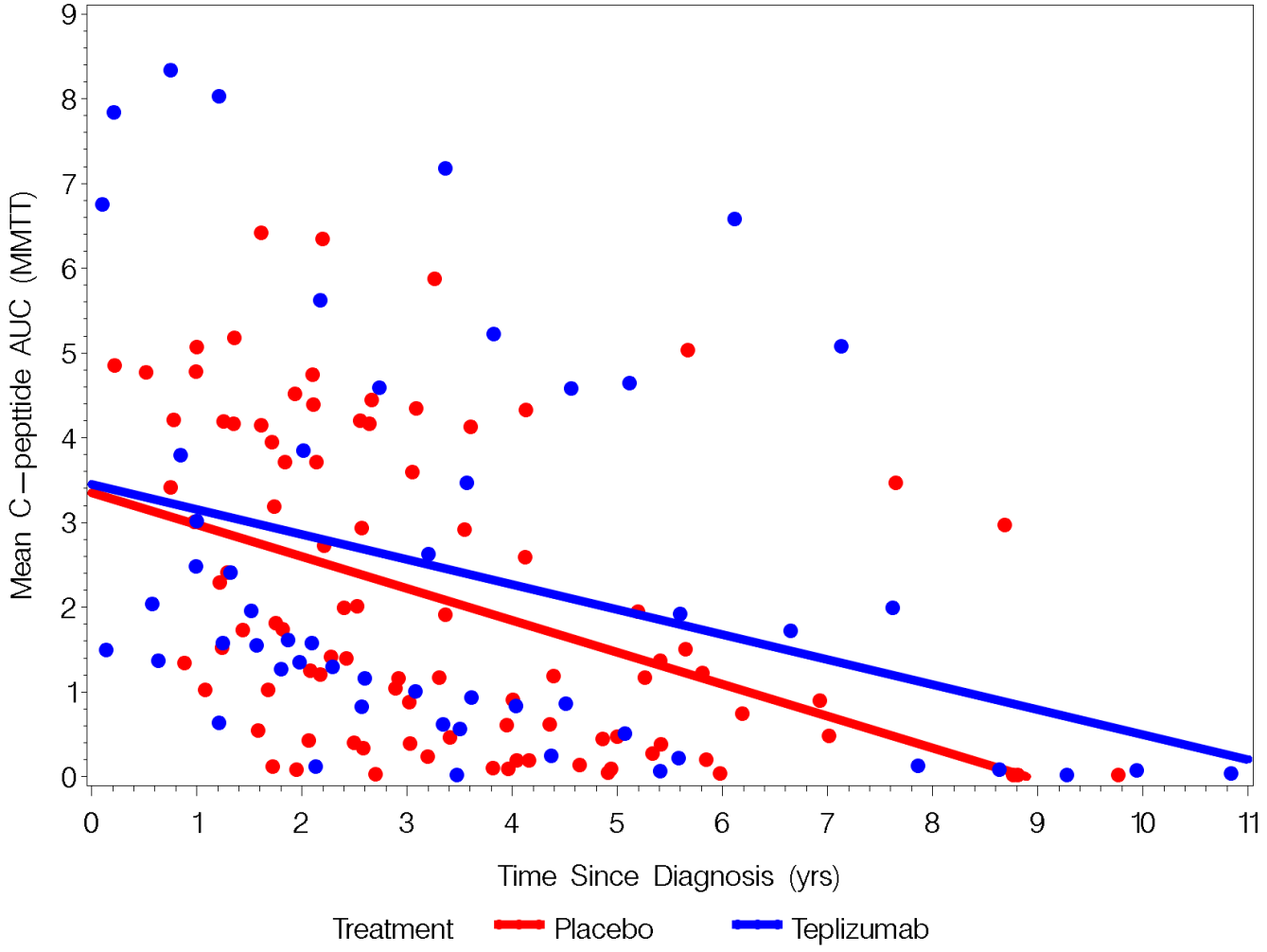
Is there a residual impact on insulin secretion after stage 3 diagnosis?

- Insulin secretion is improved by teplizumab treatment in stage 2 disease
- At the time of stage 3 conversion, C-peptide AUC values were similar between treatment groups
- What about trajectories after diagnosis?
- Mixed-meal tolerance test (MMTT) c-peptide and glucose data were analyzed for participants from the TrialNet Anti-CD3 (teplizumab) Prevention Study who also participated in follow-up monitoring via the TrialNet Long-term Investigative (LIFT) Follow-Up Study
- Slopes of area under the curve (AUC) values were calculated and a mixed generalized linear model using all available MMTT data was generated with adjustments for age and time from stage 3 diagnosis

Participant Characteristics

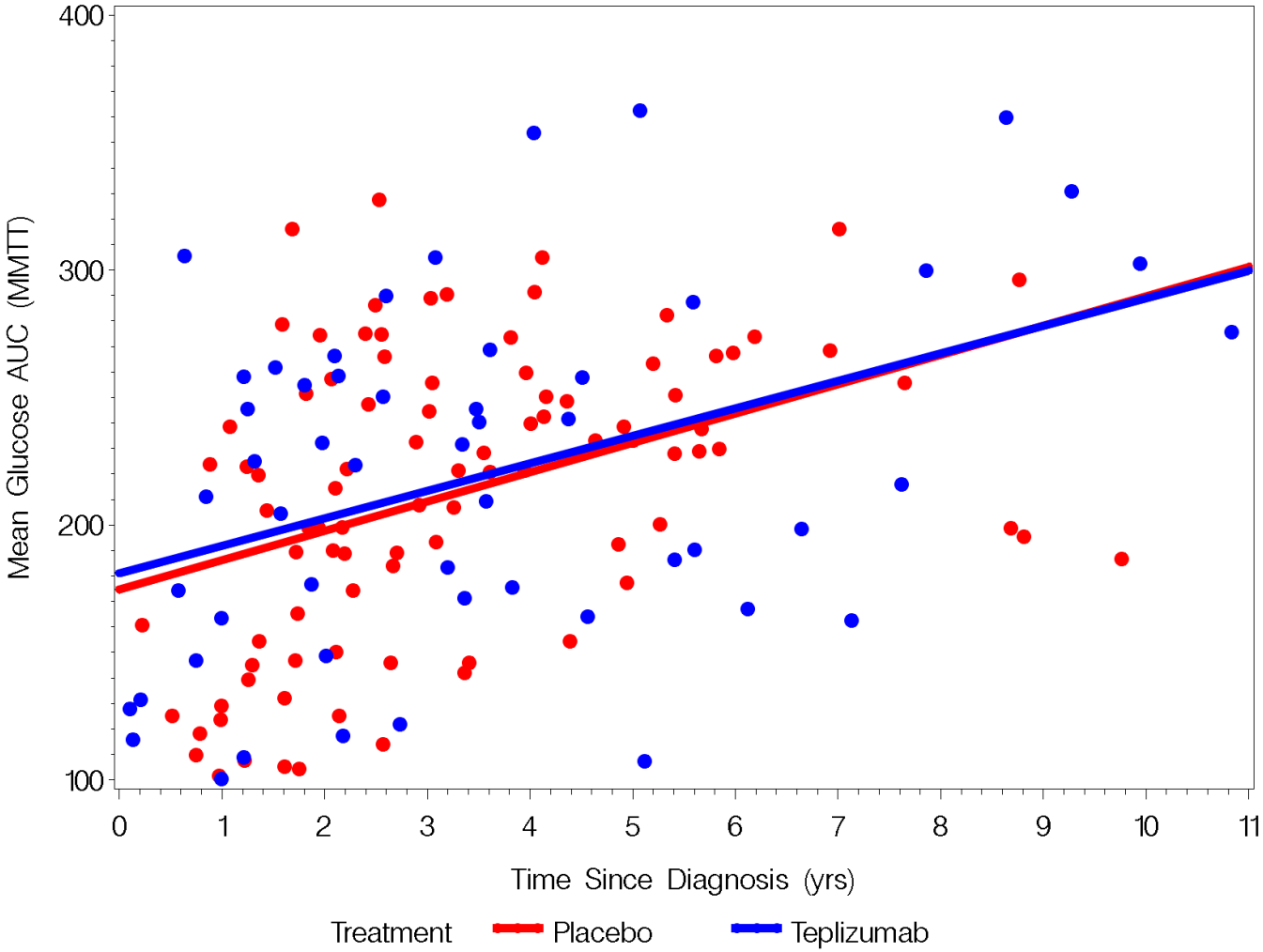
- 34 (17 placebo-treated, 17 teplizumab-treated) prevention study participants had multiple available MMTT results for analysis
- Mean±SD post-diagnosis follow-up was : 5.6±2.3 yrs (Placebo) and 4.7±3.4 yrs (Teplizumab)
- Groups were similar in age, sex, race and ethnicity
  - Placebo mean±SD: 22 ±12 yrs, 47% female, 100% white, 88% non-Hispanic
  - Teplizumab: 20±10 yrs, 41% female, 100% white, 94% non-Hispanic.

C-peptide AUC slopes in teplizumab-treated participants tended to be higher compared to placebo



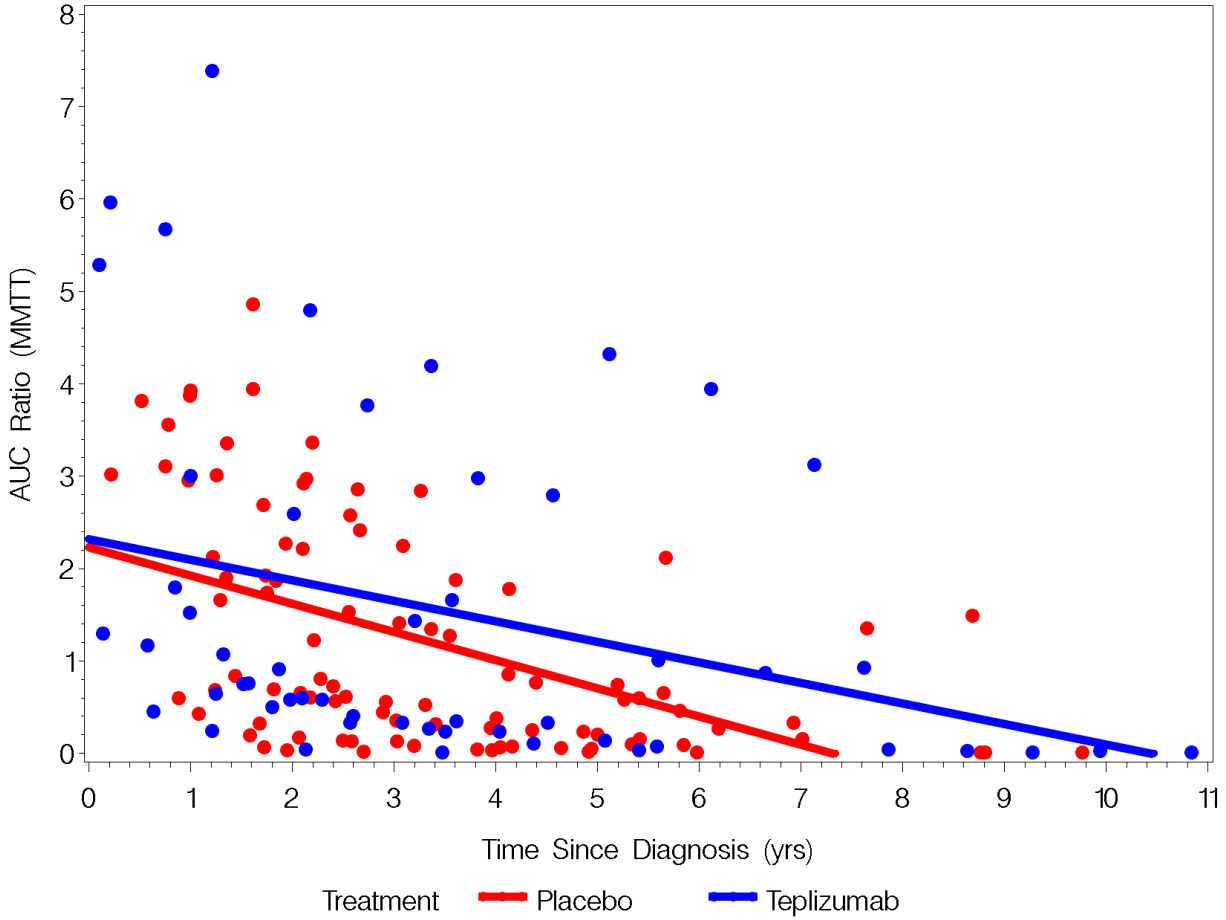
Mean teplizumab slope difference (SE): +0.13 (0.069); p=0.069

Teplizumab mean MMTT glucose AUC similar between groups



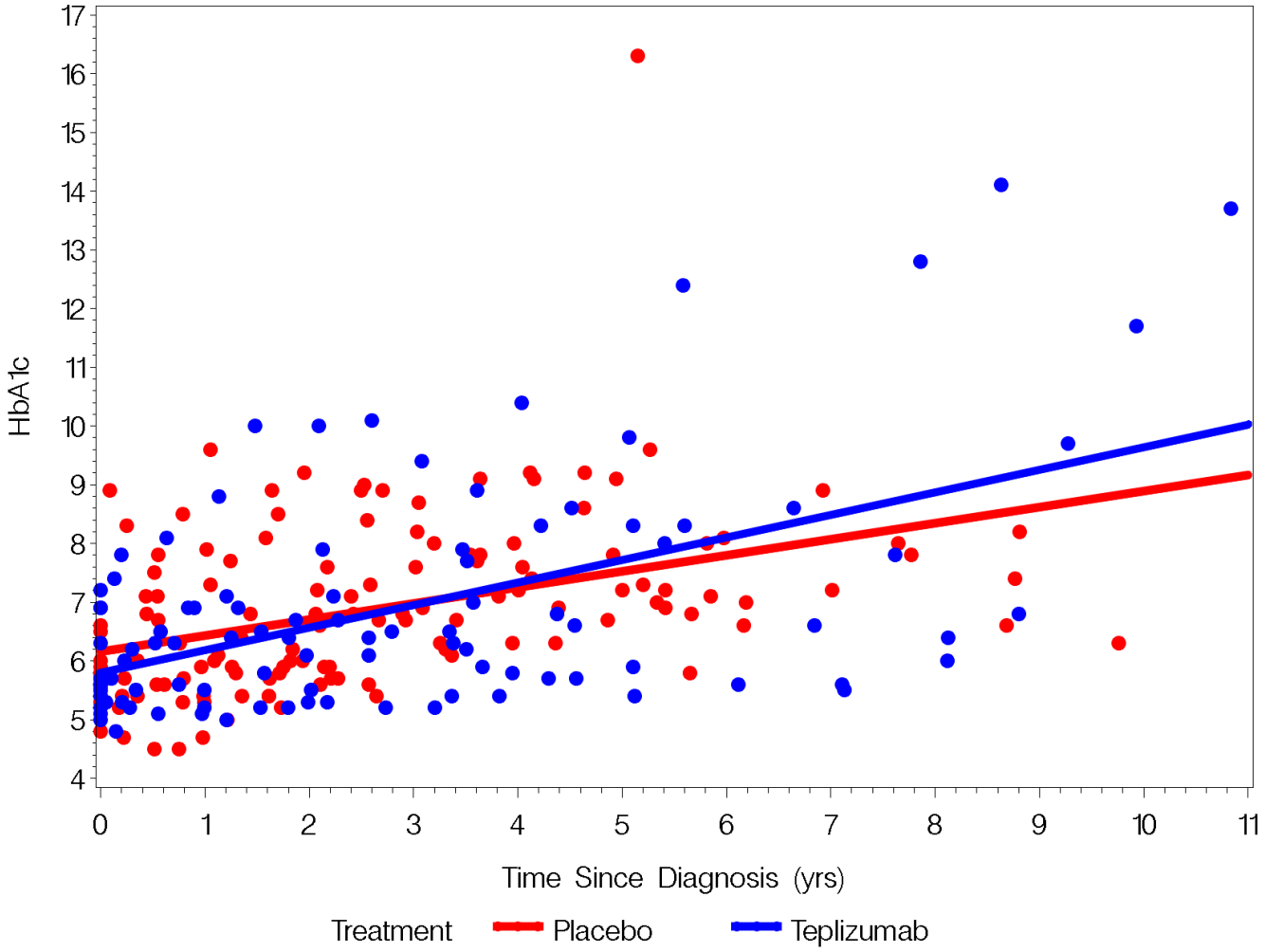
Teplizumab slope difference -4.5 (3.4); p=0.19.

Combination of C-peptide and glucose measures (AUC ratio) showed significant benefit of teplizumab



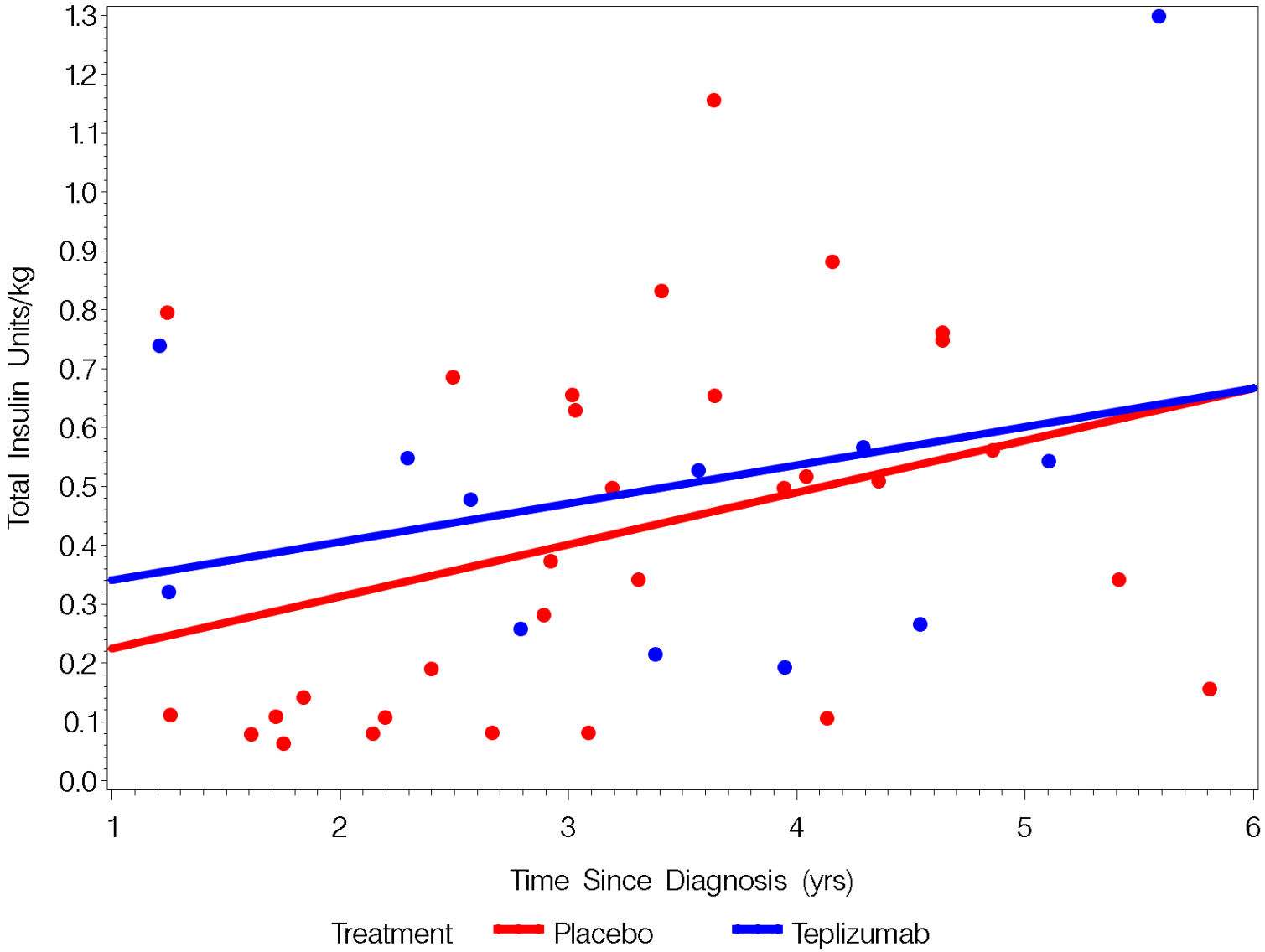
Teplizumab mean AUC ratio slope difference (SE): +0.13 (0.051); p=0.01

HbA1c trajectories did not significantly differ between treatment groups



Teplizumab mean HbA1c slope difference (SE): +0.06 (0.06); p=0.3

Total Insulin dose trajectories were similar between groups



Safety Data

Symptom or Adverse Event	Placebo (n=17)	Teplizumab (n=16)	p-value
Ketoacidosis at Stage 3 Diagnosis- % (n)	0% (0)	0% (0)	N/A
Any Hospitalization - % (n)	41.2% (7)	12.5% (2)	0.12
Any New Chronic - % (n)	11.8% (2)	6.3% (1)	1.0
Any New Chronic (Autoimmune Disease) - % (n)	5.9% (1)	0% (0)	1.0
Any New Chronic (Cancer) - % (n)	0% (0)	0% (0)	N/A
Any New Chronic (Neurological) - % (n)	0% (0)	0% (0)	N/A
Any New Chronic (Other) - % (n)	5.9% (1)	6.3% (1)	1.0
Any Complications - % (n)	0% (0)	6.3% (1)	0.48
Any Complications (Eyes) - % (n)	0% (0)	6.3% (1)	0.48
Any Complications (Kidneys) - % (n)	0% (0)	0% (0)	N/A
Any Complications (Nerves) - % (n)	0% (0)	0% (0)	N/A
Any Complications (Heart) - % (n)	0% (0)	0% (0)	N/A
Any Complications (Other) - % (n)	0% (0)	0% (0)	N/A
Any Episodes of Seizures of Loss of Consciousness from Low Blood Glucose - % (n)	11.8% (2)	0% (0)	0.48
Any Emergency Room Visits or Hospitalizations for High Blood Glucose or DKA - % (n)	0% (0)	6.3% (1)	0.48
Hypertension - % (n)	5.9% (1)	0% (0)	1.0
Rash acneiform - % (n)	5.9% (1)	0% (0)	1.0

Summary

- Long-term follow-up data from this small, underpowered cohort suggest that metabolic trajectories are impacted by disease modification even after clinical diagnosis
- Not surprising that combined c-peptide/glucose measure was most robust to detect impact of drug
- Clinical outcomes not impacted, but data from other studies would suggest that we are going to need bigger numbers to see these kinds of effects
- Safety data highlight benefits of diagnosis during presymptomatic period
- Limitations here highlight need for more comprehensive long-term follow-up of persons participating in positive prevention studies

Conclusions

- Improving residual insulin secretion is a positive outcome in its own right
- Detection of early-stage presymptomatic T1D has potential to impact long-term metabolic trajectories
  - Possibly through impacts on DKA and glucose toxicity at diagnosis
  - Long-term impacts of disease modification, even after a clinical diagnosis

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