Type 1 Diabetes TrialNet Oral Insulin Trial
5-IT-SY07

Carla J. Greenbaum
Benaroya Research Institute, Seattle on behalf of
Type 1 Diabetes Oral Insulin Study Group

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Disclosures

- **Carla Greenbaum** has served as advisor for Lilly, NovoNordisk, Bristol Meyers Squib, Pfizer, and has research funding from Janssen and NovoNordisk.

- **Jay Skyler** has acted as an advisor to: Adocia, AstraZeneca, BD Technologies, Boehringer Ingelheim, Dance Biopharm, Diavacs, Elcelyx Therapeutics, Eli Lilly and Company, Ideal Life, Immunomolecular Therapeutics, Intarcia Therapeutics, Intrexon, Merck, Organogenesis, Sanofi, Servier, vTv Therapeutics, Valeritas LLC, and Viacyte. He has had research funding from: Mesoblast, and Viacyte. He is a member of the board of directors of: Dexcom Inc, Moerae Matrix, and VasoPrep Surgical. He has equity in: Dance BioPharma, Dexcom Inc, Ideal Life, Intrexon, Moerae Matrix, and VasoPrep Surgical.

- **Jeff Krischer** has served as advisor for Savara Inc.
T1D Disease Progression

The Stages to Type 1 Diabetes

STAGE 1
- Normal Blood Sugar
- Development of single autoantibody

STAGE 2
- Abnormal Blood Sugar
- ≥ 2Aab

STAGE 3
- Clinical Diagnosis

STAGE 4

Starting Point
- Relatives: 15x greater risk of developing T1D

Genetic Risk

Immune Activation
- Beta cells are attacked

Immune Response

Immune Activation
T1D Disease Progression

**Genetic Risk**

**Starting Point**
Relatives: 15x greater risk of developing T1D

**Immune Activation**
Beta cells are attacked

**Immune Response**
Development of single autoantibody

**STAGE 1**
Normal Blood Sugar ≥ 2 Aab

**STAGE 2**
Abnormal Blood Sugar ≥ 2Aab

**STAGE 3**
Clinical Diagnosis

**ORAL INSULIN**

**STAGE 4**
START OF T1D
Purpose/Objective(s)

• Can Oral Insulin delay or prevent progression to clinical type 1 diabetes (T1D) in those at Stage 1* of T1D? (*2 antibodies, normal blood sugar)

• Background
  – A previous randomized, placebo controlled trial of 7.5 mg oral insulin in antibody positive relatives had no effect in delaying clinical T1D in the group as a whole, but a post-hoc analysis identified a subgroup that suggested benefit
  – Type 1 Diabetes TrialNet thus conducted a new study to explore the role of oral insulin in delaying T1D in relatives with similar characteristics
Method/Materials

- 560 individuals were identified as having at least two antibodies and normal blood sugar through screening in TrialNet’s Pathway to Prevention study.

- Having 2 or more antibodies and normal glucose tolerance is considered “Stage 1 T1D” since essentially all of these individuals will progress to clinical T1D without intervention.

- Eligible individuals were randomized to 7.5 mg Oral Insulin or placebo capsules daily.

- Oral Glucose Tolerance Tests were performed every 6 months to assess whether clinical diabetes had developed.
## Four Groups of Participants Randomized to Oral Insulin or Placebo

<table>
<thead>
<tr>
<th>Antibodies: mIAA and IA2+GAD</th>
<th>Primary Stratum</th>
<th>Secondary Stratum 1</th>
<th>Secondary Stratum 2</th>
<th>Secondary Stratum 3</th>
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<tr>
<th>FPIR (Above or below threshold)</th>
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<table>
<thead>
<tr>
<th>Number of Participants</th>
<th>Primary Stratum</th>
<th>Secondary Stratum 1</th>
<th>Secondary Stratum 2</th>
<th>Secondary Stratum 3</th>
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<tbody>
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<td>389</td>
<td>55</td>
<td>114</td>
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Primary Stratum (N=389)

Results: No effect of Oral Insulin on Time to T1D

No effect of Oral Insulin on time to T1D (data not shown)

- Combined strata (N=560) or Strata 3 and 4 (N=116)
## Four Groups of Participants Randomized to Oral Insulin or Placebo

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| Number of Participants | 389   | 55    | 114   | 2     |

Randomization
Secondary Stratum 1 (N=55): 31 month delay in median time to T1D with Oral Insulin

Annualized rate of diabetes
18.1% oral insulin; 34.1% placebo
Hazard ratio 0.45 (95% CI: 0.22,0.91) p=0.01
Conclusions

• Delaying T1D is important. It means a longer period of time without the day to day burden of living with T1D.
• This is the largest trial ever performed using Oral Insulin
• Oral Insulin did not delay clinical diagnosis of T1D in the main strata of 389 people, or when all the strata were combined
• However, in a secondary analysis of the subgroup of 55 people there was a 31 month delay in median time to clinical T1D
• This further supports our understanding that not everyone develops T1D in the same way and is a step towards targeted therapies
• Type 1 Diabetes TrialNet has three other ongoing studies to determine whether we can delay or stop disease progression
• Since relatives have a 15x increased risk of disease, we urge relatives of those with T1D to join us to stop T1D. TrialNet.org
• Questions? Contact info@trialnet.org
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