The Swedish GAD-vaccination Trial: Outcomes of a Phase II Safety and Efficacy Trial with Diamyd™ for Preservation of Beta Cell Function in Children with Type 1 Diabetes.

Background

- Immune interventions at onset of diabetes in children so far have given
  - no or limited effect
  - too serious side effects
- GAD can prevent diabetes in experimental animals
- GAD vaccination (20 microgram) in LADA patients saved beta cell function (Agardh et al 2005)
Design of the Study

- Randomized, double blind, placebo-controlled clinical trial.
- Either placebo or 20 microg GAD (Diamyd™) sc at Days 1 and 30.
- Sustacal loads with determination of C-peptide (Delphia)
  - 0,30,60,90,120 minutes
  - day 1 and at 3 months, 9 months, 15 months
  - will continue at 21 and 30 months
Subjects and Inclusion Criteria

- 70 patients, male and female, with Type 1 diabetes
- 10 - 18 years at diagnosis of Type 1 diabetes and at first Diamyd vaccination. Disease duration 0-18 months at intervention.
- Fasting-C-peptide 0.1 nmol/l or more at screening.
- Positive for GAD65 auto-antibodies at screening.
- Written informed consent both from patients and both parents.
## Baseline Data

<table>
<thead>
<tr>
<th></th>
<th>GAD (Diamyd™)</th>
<th>Placebo</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Fasting s/C-peptide at screening, pmol/ml</strong></td>
<td>0.337 ± 0.158</td>
<td>0.336 ± 0.178</td>
</tr>
<tr>
<td><strong>C-peptide AUC Day 1, pmol/ml*2hour</strong></td>
<td>1.239 ± 0.569</td>
<td>1.414 ± 0.867</td>
</tr>
<tr>
<td><strong>Age, years</strong></td>
<td>13.8 ± 2.3</td>
<td>12.8 ± 1.9</td>
</tr>
<tr>
<td><strong>Duration of diabetes, (months) at intervention</strong></td>
<td>9.9 ± 5.3</td>
<td>8.8 ± 5.4</td>
</tr>
<tr>
<td><strong>GADA, Units (median)</strong></td>
<td>500</td>
<td>500</td>
</tr>
<tr>
<td><strong>GADA Day 1, % &lt;500 U</strong></td>
<td>42.9</td>
<td>32.4</td>
</tr>
<tr>
<td><strong>GADA Day 1, % &gt; 500 U</strong></td>
<td>57.1</td>
<td>67.6</td>
</tr>
</tbody>
</table>

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Change from Day 1 in C-Peptide after Sustacal Challenge; 9 Months

**Conclusion:** Over a 2 hour period after a meal, Diamyd™ treatment group’s C-peptide production declined less than placebo group when compared to measurements obtained at day 1.

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Change from Day 1 in C-Peptide after Sustacal Challenge; 15 Months

Conclusion: Over a 2 hour period after a meal, Diamyd™ treatment group’s C-Peptide production declined less than placebo group when compared to measurements obtained at day 1.
Change in C-Peptide, AUC

Change in C-peptide, AUC, Month 3 to 15

-0.8  -0.7  -0.6  -0.5  -0.4  -0.3  -0.2  -0.1  0
pmol/ml*2hour

Month 3  Month 9  Month 15

Diamyd  Placebo

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No decline of Max C-Peptide when GAD given to patients with <3 months disease duration

Change from Day 1, Maximum C-peptide, Disease duration at intervention 0-<3 months
No decline of C-Peptide AUC when GAD given to patients with <3 months disease duration
Less C-peptide decline also in patients treated with 3-6 months disease duration

Change from Day 1, Maximum C-peptide, Disease duration at intervention 3-<6 mon

- Diamyd
- Placebo

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Less increase of insulin dose in the GAD intervention group
## Adverse Events

<table>
<thead>
<tr>
<th></th>
<th>Diamyd™</th>
<th>Placebo</th>
</tr>
</thead>
<tbody>
<tr>
<td>Connective tissue</td>
<td>3</td>
<td>6</td>
</tr>
<tr>
<td>Nervous system</td>
<td>3</td>
<td>3</td>
</tr>
<tr>
<td>Immune System</td>
<td>2</td>
<td>1</td>
</tr>
<tr>
<td>Blood</td>
<td>1</td>
<td>1</td>
</tr>
<tr>
<td>Serious AE</td>
<td>1</td>
<td>3</td>
</tr>
</tbody>
</table>

*There were no treatment-related Serious Adverse Events.*
Conclusions

- GAD 65 has demonstrated efficacy in slowing the decline of C-peptide Levels after sustacal load.
- GAD 65 therapy proposes a novel, first-in-class therapy for slowing the progression of autoimmune Type 1 diabetes.
- GAD 65 offers a compelling therapeutic option for type 1 diabetes due to ease of use and patient acceptance.