Beta cell function and metabolic control during two years of follow-up after GAD65 dose-escalation immunomodulation in adult-onset autoimmune diabetes

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Conclusion
Our two-year follow-up of the 47 LADA patients who were given Diamyd™ as an escalating dosages demonstrates that the increase fastening and stimulated c-peptide and decrease in HbA1c previously reported for six months remained during the two year follow-up. As there were no treatment-related SAEs we suggest that further exploration of the immunomodulating effects of 20 μg Diamyd™ is warranted. Two more clinical trials are therefore now under way in Sweden using Diamyd™. The first of these is a double-blind trial in a greater number of patients in order to confirm efficacy in LADA patients, and the second is to investigate therapeutic efficacy in newly diagnosed type 1 diabetic patients. The outcome from these trials will be critical to future Phase III clinical trials for efficacy.

Background
• Autoimmune destruction of pancreatic β-cells is the major cause of Type 1 diabetes.
• Presence of GADA, IAA2A, or IAA predict Type 1 diabetes.
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• Studies in the NOD mouse have shown that destruction of insulinβ-cells was associated with T cells recognizing GAD65.
• GAD65 effectively prevent autoimmune β-cell destruction and reduce and delay the development of spontaneous diabetes.

Purpose
The purpose of this study was to evaluate if alum-formulated recombinant GAD65 (Diamyd™) is safe and does not comprise beta cell function in GAD65-autoantibody positive type 2 diabetes patients.

Methods

Trial design
A phase II randomized, double blind, placebo controlled trial in LADA patients.

Inclusion Criteria
• Diabetic patients of both sexes aged 36-76 years
• Diagnosed with Type 2 diabetes within 5 years
• Presence of GADA
• Diabetes treatment with diet and/or oral agents
• Females of non-child-bearing potential

Test substances
The unmodified recombinant form of human GAD65 (Diamyd™ Bulk Drug) was formulated with Alhydrogel® (aluminium hydroxide). The bulk drug was manufactured using baculovirus/insect cell expression of the cDNA for mGAD65. Both manufacture of the Diamyd™ Bulk Drug and Diamyd™ was performed under strict conditions of current Good Manufacturing Practice. Each vial contained a sterile formulation of either 4, 20, 100, or 500 μg of Diamyd™ Bulk Drug in a constant amount of Alhydrogel®. Coded vials containing an identical amount of Alhydrogel® alone were used as placebo.

Results

Marker of diabetes in placebo and treatment dose groups at baseline

<table>
<thead>
<tr>
<th>Marker of Diabetes</th>
<th>Placebo</th>
<th>100 μg</th>
<th>20 μg</th>
<th>40 μg</th>
</tr>
</thead>
<tbody>
<tr>
<td>% of LADA patients</td>
<td>10%</td>
<td>10%</td>
<td>10%</td>
<td>10%</td>
</tr>
<tr>
<td>HbA1c (months)</td>
<td>8.8</td>
<td>8.8</td>
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<tr>
<td>BMI (kg/m2)</td>
<td>25.0</td>
<td>25.0</td>
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<tr>
<td>S-LDL (mmol/L)</td>
<td>2.7</td>
<td>2.7</td>
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<tr>
<td>Auto-antibodies</td>
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<tr>
<td>GADA (%)</td>
<td>20.0</td>
<td>20.0</td>
<td>20.0</td>
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<tr>
<td>IA2A (%)</td>
<td>10.0</td>
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<tr>
<td>IAA (%)</td>
<td>5.0</td>
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</tr>
</tbody>
</table>

Change in mean HbA1c

In the 20 μg dose group, fasting c-peptide increased by 0.14 (0.06 – 0.21) log mU/mL (p < 0.005), stimulated c-peptide by 0.19 (0.06 – 0.31) log mU/mL (p<0.01), as well as fasting c-peptide/glucose by 0.20 (0.06 – 0.33) log mU/mL (p<0.01) compared to baseline.

Change in mean stimulated c-peptide

In the 20 μg dose group showed an increase compared to the placebo group in fasting c-peptide (p<0.05), stimulated c-peptide (p<0.05) and fasting c-peptide/glucose (p<0.005).

Reference