Original research

Safety and effectiveness of biphasic insulin aspart 30 in people with type 2 diabetes switching from basal-bolus insulin regimens in the A\textsubscript{1}chieve study

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Aims: Biphasic insulin aspart 30 allows fewer daily injections versus basal-bolus insulin regimens, which may improve adherence and treatment outcome. This sub-analysis of the observational \textsubscript{A}chieve study assessed clinical safety and effectiveness of biphasic insulin aspart 30 in people with type 2 diabetes previously receiving basal-bolus insulin regimens.

Methods: \textsubscript{A}chieve was an international, open-label, 24-week study in people with type 2 diabetes starting/switching to biphasic insulin aspart 30, insulin detemir or insulin aspart. This sub-analysis assessed patients switching from insulin glargine- or neutral protamine Hagedorn insulin-based basal-bolus insulin regimens to biphasic insulin aspart 30.

Results: 1024 patients were included. At 24 weeks, glycated haemoglobin and fasting plasma glucose were significantly reduced from baseline in both cohorts (all \(p<0.001\)). The proportion reporting any hypoglycaemia, major hypoglycaemia or nocturnal hypoglycaemia was significantly reduced after 24 weeks (all \(p<0.05\)). No serious adverse drug reactions were reported. Both cohorts had significantly improved health-related quality of life (HRQoL; \(p<0.001\)).

Conclusions: 24 weeks after switching from basal-bolus insulin regimens to biphasic insulin aspart 30, glycaemic control and HRQoL were significantly improved, and hypoglycaemia was significantly reduced. This suggests that people with type 2 diabetes inadequately controlled on basal-bolus insulin regimens can consider biphasic insulin aspart 30.

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1. **Introduction**

Achieving and maintaining glycated haemoglobin (HbA1c) target is an important treatment goal in diabetes, in order to reduce the long-term risk of diabetes-associated complications, as demonstrated by the Diabetes Control and Complications Trial (DCCT) [1] and the United Kingdom Prospective Diabetes Study (UKPDS) [2].

For people with type 2 diabetes who do not achieve glycaemic target with oral medications alone, the American Diabetes Association (ADA)/European Association for the Study of Diabetes (EASD) position statement [3] recommends initiating insulin therapy with basal insulin. However, additional bolus insulin may be required for patients who do not achieve adequate glycaemic control with basal insulin as the sole insulin. A disadvantage with basal-bolus insulin regimens is that four to five insulin injections per day are needed [4,5].

Premixed insulin analogue formulations, which combine rapid-acting and intermediate-acting insulin analogues, were developed to provide basal and prandial glycaemic control with fewer insulin injections. In a real-world clinical setting, people with diabetes who find a basal-bolus regimen to be too complex for their lifestyle may benefit from a change to a premixed insulin regimen.

Biphasic insulin aspart 30 (NovoMix® 30; Novo Nordisk A/S, Bagsvaerd, Denmark) effectively controls HbA1c levels when used once- or thrice-daily [6,7], and thrice-daily biphasic insulin aspart 30 was shown to provide similar glycaemic control to a four-times-daily basal-bolus regimen of neutral protamine Hagedorn (NPH) insulin and insulin aspart, with no difference in the frequency of hypoglycaemia [4]. In addition, a multinational, randomised study comparing biphasic insulin aspart 30 and insulin analogue basal-bolus regimens in insulin-naïve people with type 2 diabetes showed that the two treatments resulted in similar HbA1c reductions and similarly low rates of hypoglycaemia [8].

A1chieve was an international study assessing the safety and effectiveness of insulin analogues in people with type 2 diabetes in routine clinical practice [9,10]. The objective of this sub-analysis of the A1chieve study was to evaluate the safety and effectiveness of biphasic insulin aspart 30 in patients switching from basal-bolus insulin regimens that included insulin glargine or NPH insulin.

2. **Methods**

A1chieve was an international, multi-centre, open-label, prospective, non-interventional, 24-week study in people with type 2 diabetes who had been using anti-diabetes medication before starting, or switching to, insulin therapy with biphasic insulin aspart 30, insulin aspart (NovoRapid®; Novo Nordisk A/S, Bagsvaerd, Denmark) or insulin detemir (Levemir®; Novo Nordisk A/S, Bagsvaerd, Denmark) without or without oral glucose-lowering drugs (OGLDs) in routine clinical practice [9].

A1chieve was conducted in 28 countries in seven geographical regions: China; South Asia (Bangladesh, India, Pakistan); East Asia (Indonesia, Korea, Malaysia, Philippines, Singapore, Taiwan); North Africa (Algeria, Morocco, Tunisia, Libya); Middle East/Gulf (Egypt, Iran, Jordan, Turkey, Bahrain, Kuwait, Oman, Qatar, Saudi Arabia, United Arab Emirates, Yemen); Latin America (Argentina, Mexico); and Russia. Participants were recruited to the study between January 2009 and June 2010. Further details on inclusion and exclusion criteria, and study design have previously been reported [9].

Trial visits were defined as baseline, interim (around 12 weeks after baseline [results not reported here]), and final (around 24 weeks after baseline) visit. The participants were patients attending diabetes care clinics where insulin therapy was initiated or modified at the discretion of the treating physician, based on their clinical judgement.

Insulin analogues were used in accordance with the label approved by the regulatory authority. The study was conducted in accordance with the Guidelines for Good Pharmacoepidemiology Practice [11] and Declaration of Helsinki [12]. All local requirements for Health Authorities or Ethics Committee approvals, if applicable, were acquired. All participants signed informed consent forms and were free to withdraw from the study at any time.

2.1. **Assessments and outcome measures**

The primary endpoint was to assess the clinical safety of the insulin analogue regimens by measuring the incidence of serious adverse drug reactions (SADRs), including major hypoglycaemia events, deemed related to the study insulin during the study period (from baseline to 24 weeks). Secondary safety assessments included the change in the proportion of participants experiencing hypoglycaemia events (overall, major, nocturnal) in the 4 weeks preceding the final visit, compared with the 4 weeks preceding the baseline visit. Major hypoglycaemia events were defined as events with severe central nervous system symptoms consistent with hypoglycaemia in which the patient was not able to self-treat and with one of the following characteristics: plasma glucose <3.1 mmol/l, or reversal of symptoms after either food intake, glucagon or intravenous glucose administration. Nocturnal hypoglycaemia was defined as a symptomatic event consistent with hypoglycaemia that occurred during sleep, after the evening insulin injection and before getting up in the morning; and if relevant, before morning determination of fasting plasma glucose (FPG) and the morning insulin injection.

The secondary endpoints included effectiveness and other measures: change in HbA1c, FPG levels before breakfast, post-prandial glucose (PPG) levels after breakfast, lunch and dinner, body weight, health-related quality of life (HRQoL), systolic blood pressure (SBP), and triglyceride, creatinine, cholesterol (total, high-density lipoprotein [HDL] and low-density lipoprotein [LDL]) levels between baseline and 24 weeks. HRQoL was evaluated by self-reporting using the EQ-5D questionnaire, which assesses five domains of patient health/lifestyle (mobility, self-care, usual activities, pain/discomfort, and anxiety/depression). The scores were on a visual analogue scale (VAS) of 0 (worst imaginable health) to 100 (best imaginable health). The dosage of insulin pre-study, at baseline after switching to biphasic insulin aspart 30, and at subsequent visits were also recorded, as were the number of SADRs deemed to be related to biphasic insulin aspart 30.
2.2. Statistical analysis

All analyses were performed on the full analysis set, defined as all patients with a baseline visit and who used biphasic insulin aspart 30 at least once. For hypoglycaemia, the proportions of patients reporting at least one event were statistically compared between baseline and 24 weeks using McNemar’s test. Changes from baseline in HbA1c, FPG, PPG, blood lipids, body weight, and HRQoL were analysed using paired t-test. All statistical tests were two-tailed, using a pre-specified 5% significance level, and were conducted by Novo Nordisk A/S using SAS (Version 9.1.3). Statistical analyses were not conducted where patient numbers were less than 100.

3. Results

3.1. Study participants

A total of 1024 people with type 2 diabetes were switched from basal-bolus insulin therapy to receive biphasic insulin aspart 30 on entering the study; 240 and 784 participants received insulin glargine-based (BB-GLA group) and NPH insulin-based basal-bolus insulin regimens (BB-NPH group) before the switch, respectively (Table 1). The mean duration of diabetes appeared to be similar in the two groups (BB-GLA 9.4 ± 8.0 years, BB-NPH 10.3 ± 7.6 years; Table 1). The mean body weight appeared to be higher in the BB-NPH group than in the BB-GLA group (75.7 kg versus 68.2 kg, respectively), and body mass index (BMI) appeared to be higher in the BB-NPH group than in the BB-GLA group (28.1 kg/m² versus 25.3 kg/m², respectively; Table 1).

3.2. Insulin dose and injection frequency

In the BB-GLA group, the mean (sd) baseline total biphasic insulin aspart 30 dose was 0.62 (0.26) U/IU per kg (n = 228), and after 24 weeks the total biphasic insulin aspart 30 dose was 0.60 (0.29) U/IU per kg (n = 155). In the BB-NPH group, baseline total biphasic insulin aspart 30 dose was 0.61 (0.25) U/IU per kg (n = 762), and after 24 weeks the total biphasic insulin aspart 30 dose was 0.70 (0.28) U/IU per kg (n = 570). Most patients in the BB-GLA group received twice daily biphasic insulin aspart 30 at baseline (76.3%) and at 24 weeks (67.6%). In this cohort, the other injection frequencies at baseline and week 24, respectively, were: once daily (4.2% and 6.5%), three times daily (19.2% and 23.2%), and more than three times daily (0.4% and 2.7%). In the BB-NPH group, most patients received twice daily biphasic insulin aspart 30 at baseline (82.5%) and at 24 weeks (71.0%). Other injection frequencies at baseline and week 24, respectively, were: once daily (3.7% and 2.9%), three times daily (13.8% and 22.8%), and more than three times daily (0% and 3.3%).

3.3. Safety measures

3.3.1. Hypoglycaemia and SADRs

The proportion of participants experiencing any hypoglycaemia was significantly reduced from baseline at 24 weeks in both the BB-GLA group (17.1% versus 8.1% at baseline and 24 weeks, respectively, p < 0.01) and the BB-NPH group (23.2% versus 11.1% at baseline and 24 weeks, respectively, p < 0.001; Table 2). There was a significant reduction from baseline at 24 weeks in the proportion of participants in the BB-NPH group reporting nocturnal hypoglycaemia (13.1% versus 3.9% at baseline and 24 weeks, respectively, p < 0.001; Table 2) and major hypoglycaemia (4.6% versus 0.2% at baseline and 24 weeks, respectively, p < 0.001; Table 2). There were no reports of nocturnal hypoglycaemia and major hypoglycaemia at 24 weeks in the BB-GLA group (Table 2). No SADRs were reported.

3.3.2. Body weight

Body weight was significantly increased in the BB-GLA group at 24 weeks (1.1 kg, p < 0.001) and significantly reduced in the BB-NPH group (−0.4 kg, p < 0.05; Table 2).

3.3.3. Systolic blood pressure

Systolic blood pressure was not significantly different between baseline and 24 weeks in the BB-GLA group, but was significantly reduced in the BB-NPH group (p < 0.001; Table 2).

3.4. Clinical laboratory test results

Creatinine levels were significantly reduced in the BB-NPH group between baseline and 24 weeks (p < 0.01; Table 2). At 24 weeks, blood triglyceride levels, total cholesterol levels and LDL levels were significantly reduced, and HDL levels were significantly increased in the BB-NPH group (p < 0.001; Table 2). No statistical testing was carried out for these measurements in the BB-GLA group as data were available for <100 participants who completed the study.

3.5. Effectiveness measures

3.5.1. Glycaemic measures

Glycaemic control was significantly improved after 24 weeks’ treatment with biphasic insulin aspart 30 in both cohorts. HbA1c was significantly reduced in both cohorts at 24 weeks (p < 0.001; Table 3 and Fig. 1); mean (sd) change in HbA1c between baseline and 24 weeks was −2.5% (2.4%) and −1.9% (1.8%) in the BB-GLA and BB-NPH groups, respectively. Pre-breakfast FPG was also significantly reduced in both cohorts (p < 0.001; Table 3); mean change in FPG between baseline and 24 weeks was −4.1 mmol/l and −2.9 mmol/l in the BB-GLA and BB-NPH groups, respectively. Mean (sd) post-breakfast, post-lunch, and post-dinner FPG levels were significantly reduced in the BB-NPH group (p < 0.001; Table 3) by −4.5 mmol/l (4.7 mmol/l), −3.0 mmol/l (4.2 mmol/l), and −3.6 mmol/l (4.1 mmol/l), respectively. Reductions in FPG levels were not statistically analysed in the BB-GLA group as these data were available for <100 participants who completed the study (Table 3). In addition, the percentage of participants with HbA1c <7.0% appeared to be increased at 24 weeks in both cohorts. The proportion of patients with HbA1c <7.0% at baseline and 24 weeks was 3.3% (n = 211) and 37.6% (n = 157) in the BB-GLA group, respectively, and 7.6% (n = 684) and 28.1% (n = 531) in the BB-NPH group, respectively.

3.5.2. HRQoL

Between baseline and 24 weeks, HRQoL was significantly improved in both cohorts (p < 0.001; Table 3).

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Table 1 – Baseline patient and disease characteristics by pre-study insulin regimen and injection frequency.

<table>
<thead>
<tr>
<th></th>
<th>Insulin glargine-based basal-bolus regimen</th>
<th>NPH insulin-based basal-bolus regimen</th>
</tr>
</thead>
<tbody>
<tr>
<td>n (%)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Entire cohort</td>
<td>240 (100)</td>
<td>784 (100)</td>
</tr>
<tr>
<td>One bolus injection</td>
<td>18 (7.5)</td>
<td>54 (6.9)</td>
</tr>
<tr>
<td>Two bolus injections</td>
<td>19 (7.9)</td>
<td>357 (45.5)</td>
</tr>
<tr>
<td>Three bolus injections</td>
<td>203 (84.6)</td>
<td>371 (47.3)</td>
</tr>
<tr>
<td>Analogue bolus</td>
<td>104 (43.3)</td>
<td>14 (1.8)</td>
</tr>
<tr>
<td>Human insulin bolus</td>
<td>136 (56.7)</td>
<td>770 (98.2)</td>
</tr>
<tr>
<td>Mean (sd) age, y</td>
<td>57.1 (13.4)</td>
<td>54.6 (13.0)</td>
</tr>
<tr>
<td>Male, n (%)</td>
<td>134 (55.8)</td>
<td>360 (45.9)</td>
</tr>
<tr>
<td>Mean (sd) weight, kg</td>
<td>68.2 (14.9)</td>
<td>75.7 (15.9)</td>
</tr>
<tr>
<td>Mean (sd) BMI, kg/m²</td>
<td>25.3 (4.5)</td>
<td>28.1 (5.3)</td>
</tr>
<tr>
<td>Mean (sd) pre-study total insulin dose, U/IU per kg</td>
<td>0.75 (0.27)</td>
<td>0.73 (0.30)</td>
</tr>
<tr>
<td>Bolus insulin dose, % total insulin dose</td>
<td>57.3</td>
<td>49.3</td>
</tr>
<tr>
<td>Mean (sd) diabetes duration, y</td>
<td>9.4 (8.0)</td>
<td>10.3 (7.6)</td>
</tr>
<tr>
<td>Mean (sd) duration of insulin therapy, y</td>
<td>1.9 (3.8)</td>
<td>3.1 (4.1)</td>
</tr>
</tbody>
</table>

Note: Due to the non-interventional nature of this study, not all baseline data were recorded and some patients were lost to follow-up.

NPH, neutral protamine Hagedorn; BMI, body mass index

4. Discussion

The results of this sub-analysis of data from the A1tchieve study show in a cohort of people with type 2 diabetes and poor glycaemic control with their basal-bolus insulin regimen that switching to biphasic insulin aspart 30 (±OGLDs) leads to significant improvement in glycaemic control. It is notable that there was no increase in hypoglycaemia, even when HbA1c was significantly lowered after the switch to biphasic insulin aspart 30. Regardless of pre-study insulin regimen, the proportion of participants reporting hypoglycaemia, major hypoglycaemia or nocturnal hypoglycaemia was significantly reduced at 24 weeks after the switch. In addition, there were no reports of SADRs.

In this sub-analysis, the proportion of patients who reached the HbA1c target of <7% after 24-week treatment with biphasic insulin aspart 30 appeared to be increased relative to baseline (BB-GLA group, 3.3% to 37.6%; BB-NPH group, 7.6% to 28.1%). This is notable, given that the total insulin dose at 24 weeks was 0.15 U/IU per kg (BB-GLA group) and 0.03 U/IU per kg (BB-NPH) lower than the pre-study total insulin dose on basal-bolus insulin regimens. There are very few published reports on patients switching from a basal-bolus insulin regimen to a premixed insulin regimen, as this differs from usual clinical practice. The 4-T study compared biphasic insulin with prandial and basal insulins in patients poorly controlled on OGLDs. While the study showed that a significantly lower proportion of patients in the biphasic insulin aspart 30 group had HbA1c ≤7.0% at 3 years compared with the prandial (insulin aspart) and basal (insulin detemir) insulin groups [13], median HbA1c was similar between the treatment arms.

A particularly important benefit after 24-week treatment with biphasic insulin aspart 30 was the significant improvement in HRQoL, which may be related to the observed improvements in glycaemic control and reduction of hypoglycaemia.

Another possible reason for improved HRQoL is reduced insulin injection frequency. Many people with diabetes dislike frequent insulin injections [14], and it has been shown that people with type 2 diabetes significantly value reducing the number of daily insulin injections [15]. Increased injection frequency has been associated with poor adherence in people with type 2 diabetes: adherence was 78.3% in patients requiring one injection per day and 60.8% in patients requiring four injections per day (p < 0.0001) [16]. Compared with basal-bolus insulin regimens, premixed insulins may offer a simpler insulin regimen and in some instances reduce the number of daily insulin injections required [17]. Indeed, in people with inadequately controlled hyperglycaemia, biphasic insulin aspart 30 can be used effectively and safely as an insulin intensification regimen requiring fewer daily injections than a basal-bolus regimen [4]. Biphasic insulin aspart 30 allows simplification of dosing to once or twice per day—most
participants in both cohorts were on twice-daily regimens. This might improve adherence to therapy compared with greater dosing frequency in basal-bolus regimens, and therefore improve patients’ sense of wellbeing when they are receiving their insulin treatment. It would be interesting in a separate study to compare patient adherence to basal-bolus insulin regimens with adherence to biphasic insulin aspart regimens.

Intensification of insulin regimens also need to take into consideration the complexity of the regimen and the likelihood that patients will be able to adhere to the therapy [18]. Patient QoL may be improved through the elimination of unrealistically complex insulin injection regimens [18]. Indeed, patients on basal-bolus regimens that require daily adjustments to their insulin may struggle to maintain adherence and may require extra support from their local clinical practice thus adding to the economic burden of diabetes in the real-world [18–20]. In this respect, biphasic insulin aspart 30 regimens can be optimised through simple self-titration algorithms, which enables easy intensification of insulin therapy and may lead to improved QoL for the patient through better adherence and improved glycaemic control [21,22]. Optimisation of biphasic insulin aspart 30 regimens may also assist when changing from a basal-bolus regimen in clinical practice. Allied to this, a systematic review of biphasic insulin aspart 30 versus other insulin-based therapies showed that biphasic insulin aspart 30 is a cost-effective treatment for many patients with type 2 diabetes who are failing to maintain glycaemic control on other insulin regimens [23]. Moreover, long-term clinical and economic outcomes for several countries have shown that biphasic insulin aspart 30 therapy is also associated with improvements in quality-adjusted life expectancy [23].

Body weight was significantly increased in the BB-GLA group but significantly reduced in the BB-NPH group. Previous studies have also shown significant weight loss in people

Table 2 - Hypoglycaemia, metabolic outcomes and body weight before and after 24 weeks of treatment with biphasic insulin aspart 30 by pre-study insulin regimen.

<table>
<thead>
<tr>
<th>Measurement</th>
<th>Insulin glargine-based basal-bolus regimen</th>
<th>NPH insulin-based basal-bolus regimen</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Baseline (24 weeks)</td>
<td>p-value</td>
</tr>
<tr>
<td>% patients with at least one event (event/person-year)³</td>
<td>17.1 (5.0)</td>
<td>8.1 (1.5)</td>
</tr>
<tr>
<td>Overall hypoglycaemia</td>
<td>1.7 (0.2)</td>
<td>0 (0)</td>
</tr>
<tr>
<td>Major hypoglycaemia</td>
<td>5.4 (0.9)</td>
<td>0 (0)</td>
</tr>
<tr>
<td>Nocturnal hypoglycaemia</td>
<td>240</td>
<td>186</td>
</tr>
<tr>
<td>Mean (sd) systolic blood pressure, mmHg</td>
<td>132.6 (21.8)</td>
<td>129.9 (15.5)</td>
</tr>
<tr>
<td>Mean (sd) triglycerides, mmol/l</td>
<td>2.2 (1.5)</td>
<td>1.8 (0.9)</td>
</tr>
<tr>
<td>Mean (sd) creatinine, μmol/l</td>
<td>73.9 (43.5)</td>
<td>70.4 (33.9)</td>
</tr>
<tr>
<td>Mean (sd) total cholesterol, mmol/l</td>
<td>5.3 (1.2)</td>
<td>4.9 (1.0)</td>
</tr>
<tr>
<td>Mean (sd) high-density lipoprotein, mmol/l</td>
<td>1.1 (0.4)</td>
<td>1.1 (0.4)</td>
</tr>
<tr>
<td>Mean (sd) low-density lipoprotein, mmol/l</td>
<td>3.1 (1.0)</td>
<td>2.9 (0.9)</td>
</tr>
<tr>
<td>Mean (sd) body weight, kg</td>
<td>70.3 (14.2)</td>
<td>71.4 (13.7)</td>
</tr>
</tbody>
</table>

Note: Due to the non-interventional nature of this study, not all baseline data were recorded and some patients were lost to follow-up. p-values are for 24 weeks vs. baseline; p-values are not shown where n < 100.
NPH, neutral protamine Hagedorn; NS, not significant.
³ p-values are reported for the proportion of patients with at least one event at baseline vs. 24 weeks.
with type 2 diabetes switching from biphasic human insulin to biphasic insulin aspart 30 [24], and significantly greater weight gain in people with type 2 diabetes initiating insulin therapy with biphasic insulin aspart 30 compared with those initiating insulin therapy with insulin glargine [7]. Thus, a reduction in body weight may be expected in patients switching to biphasic insulin aspart 30 from NPH-based basal-bolus regimens, whereas weight gain may be expected in patients switching from glargine-based basal-bolus regimens. However, it is important to note that the significant but small weight changes have minimal clinical relevance in a real-life situation.

One limitation of this sub-analysis is that it included only 1024 people with type 2 diabetes, as less than 2% of the entire A1chieve population switched from a basal-bolus insulin regimen to a biphasic insulin aspart 30 regimen. This limitation increases the risk of a type II error. The cohort represents a very selected patient group as shifting from a basal-bolus insulin regimen to a premixed insulin regimen goes against usual clinical practice. However, this switch is made when the basal-bolus regimen does not fit with the patient’s lifestyle and behaviour and they would prefer and benefit from a simpler insulin regimen.

This sub-analysis of the A1chieve study shows that selected people with type 2 diabetes inadequately controlled on basal-bolus insulin regimens had significantly improved glycaemic control with reduced hypoglycaemia and improved HRQoL 24 weeks after switching to biphasic insulin aspart 30. These improvements were observed in patients switching from glargine-based and NPH-based basal-bolus insulin regimens, and may be related to better therapy adherence due to the simpler regimen with biphasic insulin aspart 30. These results suggest that patients with poorly controlled type 2 diabetes who have trouble adhering to their basal-bolus insulin regimen might benefit from switching to biphasic insulin aspart 30 therapy.

**Conflict of interest statement**

L-MC and AA did not declare any conflicts. GD worked as a lecturer for Novo Nordisk, Astra Zeneca/BMS, Glaxo Smith Kline and Montpellier, and participated in clinical trials sponsored by Novo Nordisk, Astra Zeneca/BMS and Sanofi. LMC has no conflicts of interest to declare. AZ is working as a lecturer for Abbott, Astra Zeneca/BMS, Bayer, Berlin-Hemi, Novartis, Novo Nordisk, and Sanofi, and participated in clinical trials sponsored by Lilly, Novartis, Novo Nordisk and Sanofi. JC is an employee of Novo Nordisk A/S. FJL-G is on advisory boards for Jannsen-Cilag, Novo Nordisk, Sanofi, Merck Sharp & Dohme, Bristol-Myers Squibb/Astra Zeneca, Bi-Lilly, and Takeda; on the board of speakers for Sanofi, Novo Nordisk, Eli Lilly, Merck Sharp & Dohme, Jannsen-Cilag, Novartis, Glaxo Smith Kline, Bristol-Myers Squibb/Astra Zeneca, Pfizer, Merck Serono, and Silanes. He has received grants for research from or participated in research conducted by Sanofi, Jannsen-Cilag, Boehringer Ingelheim, Pfizer, Novo Nordisk, Merck Sharp & Dohme, Glaxo Smith Kline, and Novartis.

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