OpT2mise: A Randomized Controlled Trial to Compare Insulin Pump Therapy with Multiple Daily Injections in the Treatment of Type 2 Diabetes—Research Design and Methods

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Abstract

Background: In insulin-requiring type 2 diabetes patients, current insulin therapy approaches such as basal-alone or basal-bolus multiple daily injections (MDI) have not consistently provided achievement of optimal glycemic control. Previous studies have suggested a potential benefit of continuous subcutaneous insulin infusion (CSII) in these patients. The OpT2mise study is a multicenter, randomized, trial comparing CSII with MDI in a large cohort of subjects with evidence of persistent hyperglycemia despite previous MDI therapy.

Subjects and Methods: Subjects were enrolled into a run-in period for optimization of their MDI insulin regimen. Subjects showing persistent hyperglycemia (glycated hemoglobin [HbA1c] ≥8% and ≤12%) were then randomly assigned to CSII or continuing an MDI regimen for a 6-month phase followed by a single crossover of the MDI arm, switching to CSII. The primary end point is the between-group difference in mean change in HbA1c from baseline to 6 months. Secondary end points include change in mean 24-h glucose values, area under the curve and time spent in hypoglycemia and hyperglycemia, measures of glycemic excursions, change in postprandial hyperglycemia, and evaluation of treatment satisfaction. Safety end points include hypoglycemia, hospital admissions, and emergency room visits.

Results: When subject enrollment was completed in May 2013, 495 subjects had been enrolled in the study. The study completion for the primary end point is expected in January 2014.

Conclusions: OpT2mise will represent the largest studied homogeneous cohort of type 2 diabetes patients with persistent hyperglycemia despite optimized MDI therapy. OpT2mise will help define the role of CSII in insulin intensification and define its safety, rate of hypoglycemia, patient adherence, and patient satisfaction.

Introduction

In type 2 diabetes, when oral therapy does not maintain acceptable glycemic control, the addition of basal insulin improves glycemic control and achieves the target glycated hemoglobin (HbA1c) level in over 50–60% of patients.1,2 For patients who are refractory to basal insulin therapy alone, treatment intensification requires the addition of prandial insulin therapy to target the control of postprandial hyperglycemia.3 The resulting regimen of multiple injections of rapid-acting insulin with basal insulin achieves target glycemia in >70% of patients but carries an increased risk of hypoglycemia and weight gain. Full compliance with insulin therapy regimens remains challenging, and injection anxiety, quality of

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life disruption, and discomfort are all well-documented obstacles.\textsuperscript{4}

For insulin-requiring type 2 diabetes patients, continuous subcutaneous insulin infusion (CSII) is an available alternative to multiple daily injections (MDI) regimens. Although the use of CSII has been well documented in type 1 diabetes,\textsuperscript{5} relatively few studies of CSII, using U100 insulin, in type 2 diabetes mellitus have been published to date. Studies that used U500 regular insulin were not included in this review.

In the case of extreme insulin resistance and poor glycemic control, transient intravenous insulin infusion alone\textsuperscript{6}\textsuperscript{7} or transient intravenous insulin infusion followed by CSII\textsuperscript{2} has shown improved glycemia with significantly reduced insulin requirements. In a small cohort of patients with poor glycemia, 40 weeks of CSII utilization reduced HbA1c by 2%, with a 20% reduction in insulin requirement.\textsuperscript{8}

Recent interventional studies have emphasized the potential benefit provided by CSII on glycemic control in type 2 diabetes. Edelman et al.\textsuperscript{9} conducted a 16-week study in 58 patients with uncontrolled glucose levels (mean HbA1c, 8.4±1.3%) despite oral antidiabetes agents (OADs) in combination with basal insulin or MDI and observed a 1.2% HbA1c lowering attributable to CSII. Kesavade et al.\textsuperscript{10} conducted a 24-week study in 46 patients on a prior basal-bolus regimen and observed a 0.5% HbA1c reduction with CSII. A retrospective study on the largest cohort to date included 102 poorly controlled patients and found that CSII sustainably decreased HbA1c by 1.5% at 1 year, regardless of the prior insulin regimen.\textsuperscript{11} Despite their limitations, these open-label, uncontrolled or retrospective reports are suggestive of glycemic control benefits with CSII in the treatment of type 2 diabetes patients.\textsuperscript{12}

Only four randomized controlled studies have compared the relative efficacy of CSII and MDI for lowering HbA1c in type 2 diabetes.\textsuperscript{13–16} Two of these studies were parallel-group studies that included 132 and 107 type 2 diabetes patients, respectively, with a mean age range of 55–66 years. Patients were moderately obese, had a baseline HbA1c between 8% and 8.4%, and were previously treated with at least one daily U100 insulin injection, with or without OADs. Study durations were 6 and 12 months, respectively.\textsuperscript{13,14} Raskin et al.\textsuperscript{14} found that treatment intensification resulted in HbA1c lowering in both groups with a 0.46% improvement in MDI users and 0.62% improvement in CSII users. Herman et al.\textsuperscript{15} found an even more pronounced glucose-lowering effect, also consistently in both treatment groups, with a 1.6% benefit in MDI users and a 1.7% benefit among CSII users. Progression in insulin requirement was reported in one article\textsuperscript{14} and remained consistent from baseline (0.7 U/kg/day) to completion (0.7–0.8 U/kg/day). These studies showed a similar impact on HbA1c lowering in both CSII and MDI regimens.

In contrast to these results, two randomized crossover studies have shown superiority of CSII in comparison with MDI. In these two studies, 17 and 29 obese type 2 diabetes patients were successively treated by CSII and MDI for periods of 12 and 18 weeks, respectively.\textsuperscript{15,16} In these studies, intensification was proposed after failure to respond to at least two insulin injections per day of neutral protamine Hagedorn (NPH) or premixed NPH plus rapid insulin analogs, with a mean baseline HbA1c above 9% despite mean insulin requirement of 1 U/kg/day. In the two studies, CSII was more efficacious than MDI for lowering HbA1c. Berthe et al.\textsuperscript{15} found an HbA1c reduction of 1.2% with CSII use versus a significantly smaller drop of 0.45% among MDI users. Similarly, Wainstein et al.\textsuperscript{16} found a similar further HbA1c benefit of 0.8% versus 0.4%, respectively. In both studies, CSII also significantly reduced the area under the curve, measured by a professional continuous glucose monitoring system, in comparison with MDI.

The discrepancy observed between the crossover studies compared with the parallel-group studies may be explained by the greater severity of diabetes in the crossover studies, as evidenced by the higher baseline insulin dose requirement and the higher baseline HbA1c level. Both crossover studies also selected a population of patients who were refractory to insulin therapy, given the entry requirement of failure to respond to two or more insulin injections daily.

No conclusive findings can be drawn from these few reports. The crossover studies were limited owing to the small sample sizes, and the parallel-group studies selected populations that had not been first adequately optimized on simple insulin regimens before randomizing them to the resulting equally effective advanced interventions. To this point, no intervention study in type 2 diabetes patients has included a large and homogeneous sample of patients failing to respond to intensive insulin titration by a basal-bolus regimen and adapted nutritional counseling, in order to evaluate the incremental advantage of CSII over MDI. Randomized controlled trials, comparing CSII with MDI in a large cohort of subjects with evidence of persistent hyperglycemia despite stable MDI therapy and with adequate individual dosing, are therefore needed to draw definitive conclusions about the potential benefit of CSII versus MDI in type 2 diabetes.

**Research Design and Methods**

OpT2mise is a multicenter, randomized, controlled, parallel-group study that includes a single-arm crossover in the continuation phase to evaluate the comparative efficacy of CSII versus MDI regimens in insulin-using patients with type 2 diabetes, suboptimally controlled with advanced basal-bolus therapy. In total, 36 centers are participating: eight in Canada, 23 in Europe and Israel, two in South Africa, and three in the United States.

The device under investigation is the Medtronic MiniMed Paradigm® Veo\textsuperscript{TM} system (Medtronic, Inc., Northridge, CA). The Bayer (Tarrytown, NY) Contour\textsuperscript{®} Link serves as the blood glucose meter in most sites. The pump and blood glucose meter data are uploaded to diabetes management software (CareLink Therapy Management System for Diabetes—Clinical; Medtronic, Tolochenaz, Switzerland) (referred to here as CareLink Clinical) that is used for treatment optimization. Glycemic variability data are obtained with the Medtronic iPro\textsuperscript{TM}2, with glucose data recorded and downloaded in a double-blinded manner.

All laboratory values are analyzed by Covance Central Laboratory Services, either in Geneva, Switzerland or in Indianapolis, IN, using the Diabetes Control and Complications Trial standard.

The protocol had received institutional Ethics Committee approval at each of the study centers and has been performed in accordance with ISO 14155 guidelines and with applicable country regulations.

**Inclusion and exclusion criteria**

Patients are eligible to enroll in the run-in phase if they are 30–75 years old, had been diagnosed with type 2 diabetes,
and are using insulin in a total daily dose (TDD) of 0.5–1.8 U/kg, not to exceed 220 U/day. Patients are required to have HbA1c values ≥8.0% and ≤12%. Patients are required to be using an insulin regimen consisting of at least three injections per day of long-acting and rapid-acting insulin analogs, for at least the previous 3 months. Female patients of childbearing potential are required to be using adequate contraception means as assessed by investigators.

Exclusion criteria include a history of two or more hypoglycemia-related seizures or comas within the last 6 months. Patients who are pregnant or planning to become pregnant are also excluded. Patients with proliferative retinopathy or significant maculopathy, a history of macrovascular disease or significant cardiac rhythm disturbances, renal insufficiency, uncontrolled hypertension (>180/110 mm Hg), use of steroids or weight loss medication, abuse of alcohol or drugs, or use of a glucagon-like peptide-1 agonist or pramlintide are also excluded.

Investigators are provided with a guideline questionnaire as an assistive tool to assess patient readiness for CSII therapy, including assessments of independence in self-care, health and device literacy, and reaction to a brief pump demonstration, as well as basic visual and dexterity competence.

To be randomized successfully, subjects must demonstrate willingness to self-monitor at a minimum mean frequency of self-monitoring of blood glucose (SMBG) of ≥2.5 per day during the run-in phase, to be consistent with a realistic degree of anticipated adherence. Although a higher frequency of SMBG is common among patients with type 1 diabetes, this expectation is less common in type 2 diabetes. Patients were asked to do one postprandial SMBG per day. Similarly, the minimum amount of insulin used to determine eligibility is higher than at the start of run-in: TDD between 0.7 and 1.8 U/kg, not to exceed 220 U/day.

Study visit plan

The visit schedule is shown in Figure 1. After the 8-week run-in phase, patients are randomly assigned either to CSII or to continuing an optimized MDI regimen for a 6-month phase (two-arm parallel study phase). This phase is followed by a 6-month continuation phase (single crossover of the MDI arm alone switching to CSII). The total study duration per patient is 15 months.

Run-in phase. The run-in phase consisted of three visits (Fig. 1) and is designed to ensure all subjects had been optimally treated with an MDI regimen. Baseline assessments included HbA1c, general safety laboratory values, and administration of the Diabetes Treatment Satisfaction Questionnaire,17 a patient-reported outcome questionnaire, and the Montreal Cognitive Assessment Test.18

All OAD therapies are standardized to metformin alone at the maximally tolerated dose, with discontinuation of all other OADs. Patients are provided with a Bayer Contour Link or Bayer Contour blood glucose meter and instructed to perform a minimum of 2.5 SMBG determinations per day on average, including one postprandial SMBG. Insulin therapy is then intensified in order to reach at least 0.7 U/kg/day at randomization, but it is not to exceed 1.8 U/kg/day or 220 U/day. An insulin titration protocol was provided to investigators to ensure optimal insulin dosing. The insulin titration regimen targets a preprandial glucose range of 70–130 mg/dL (3.9–7.2 mmol/L) and postprandial glucose readings of <180 mg/dL (<10.0 mmol/L). Investigators are instructed to target an increase in insulin dosing of 20–40% if the initial insulin dose was <0.9 U/kg/day and 10–30% if the initial dose was higher. Guidelines are being provided to assist in assessing subjects’ self-monitored plasma glucose results and responding with either basal dose titration, bolus dose titration, or both. Worksheets are also being provided to encourage consistent and effective dose titrations and adherence to the protocol, and these are regularly reviewed by study site monitors.

Insulin dose titration, nutritional counseling, and diabetes education are continued throughout the run-in period in a comprehensive attempt to improve glycemic control.

![FIG. 1. Study visit schedule. CSII, continuous subcutaneous insulin infusion; d, days; M, months; MDI, multiple daily injections (of insulin); Ta, time for Visit A; V, visit; Vc, Visit C; w, week.](image-url)
Patients who meet the above randomization criteria are then randomly assigned in a 1:1 fashion to either continuing MDI therapy or CSII therapy, using their same rapid-acting insulin analog.

Study phase. At randomization, patients assigned to CSII undergo pump training, whereas MDI therapy is continued, with ongoing titration to target, in the comparator group. Pump initiation procedures had been initially left to the site’s individual routine practice but later were modified through a protocol amendment to ensure a more consistent approach across sites and countries. Pump initiation TDD is matched to the patient’s TDD on MDI. TDD insulin was divided in a 50:50 ratio between basal insulin flow rate and bolus doses. Bolus dosing design are left to investigator judgment and range from set doses to doses based on insulin:carbohydrate ratios.

Further study visits are planned during the study phase after 1, 2, 3, and 6 months and are matched in both treatment groups. The total length of the study phase is 6 months.

Blinded continuous glucose monitoring data obtained using the iPro2 are collected for a 6-day period before randomization (Visit C), at 6 months (Visit 5), and at 12 months (Visit 10a) (see Fig. 1).

The first 6-month study phase is followed by a 6-month continuation phase that allows a single crossover of the MDI-treated subjects to begin CSII therapy. Subsequent visits include those at 6, 7, 8, 9, and 12 months (see Fig. 1).

Outcome measures

Primary end point. The primary end point is the between-group change in mean HbA1c from baseline to 6 months in CSII-treated patients versus MDI-treated patients in the study phase.

Secondary end points. Secondary end points include change from baseline to 6 months in glycemic parameters calculated from sensor glucose data gathered during the iPro2 studies. The end points include the mean 24-h glucose values at baseline and after 6 months of treatment, the area under the curve for hypoglycemia (defined as sensor glucose values of ≤70 mg/dL [3.9 mmol/L]) and hyperglycemia (defined as sensor glucose values of ≥180 mg/dL [10.0 mmol/L]) from baseline to 6 months of treatment, the time spent in hypoglycemia and in hyperglycemia at baseline and after 6 months of treatment, the mean amplitude of glycemic excursions at baseline and at 6 months of treatment, and the SD of glucose values at baseline and at 6 months of treatment. Secondary end points also include the change in 2-h postprandial hyperglycemia, measured as the area under the curve >180 mg/dL (>10 mmol/L) from baseline to 6 months of treatment. Other secondary end points include changes in serum lipids (total cholesterol, high-density lipoprotein, low-density lipoprotein, and triglycerides), body mass index (expressed in kg/m²), and blood pressure, which are determined by comparing measurements at baseline and in 6 months of treatment and treatment satisfaction.

SMBG behaviors are characterized as the mean and SD of measurements per day. Patients are instructed to perform on average ≥2.5 SMBGs per day, as reported in CareLink Clinical, including at least one postprandial SMBG (0–2 h after a meal). Insulin dosage is assessed as changes in insulin TDD from baseline to 6 months of treatment.

Safety end points. Safety end points include the number of severe hypoglycemic events, which are defined as an episode absolutely requiring assistance from another person and preferably accompanied by a confirmatory blood glucose by finger stick of <30 mg/dL (1.7 mmol/L). Safety end points also include the total number of hospital admissions and emergency room visits and the number of diabetic ketoacidosis events expressed as hyperglycemia (blood glucose level of >250 mg/dL [13.9 mmol/L]) with either a low serum bicarbonate level (<15 mEq/L) and/or low pH (<7.3) and either ketonemia or ketouria and requiring treatment within a healthcare facility. Adverse events are expressed as the number and type of adverse event, the severity of the event, and relationship to the device.

Sample size and statistical analysis

Sample size. The necessary sample size is calculated from the standard formula of a two-sided two-sample t test. For the comparison of two independent means (the mean reduction in HbA1c from baseline to 6 months in each treatment group [CSII and MDI]), with the SD equal to 1.5%, hypothesized difference in population means of 0.5%, 80% power, and a 95% confidence level, the minimally required sample size is 284 patients to be randomized in a 1:1 ratio to either the CSII group or the MDI group.

Because of uncertainty about the magnitude of the SD and the effect of treatment, the study is designed to allow for a sample size reassessment based on an interim analysis to be performed by an independent Data Safety Monitoring Board after at least 100 patients complete the 6-month visit and using the O’Brien and Fleming rule with one interim look protecting the overall type 1 error of 0.05 (two-sided).

Statistical analysis. Efficacy analyses will be performed on an intention-to-treat basis. The intention-to-treat set will be composed of randomized subjects who underwent at least a baseline measurement of HbA1c. Imputation of missing data in the intention-to-treat analysis will be performed using the multiple imputation method.

The primary end point will be analyzed using a two-sided two-sample t test, and the methods of Chen et al.19 will be used to calculate the final P value incorporating a P value penalty for the interim analysis and adaptive design so that the overall type 1 error is maintained. In case of potential outliers, the robust method proposed by Mehrotra et al.20 will be used for analysis. This analysis will be validated by the independent Data Safety Monitoring Board.

For the analysis of binary end points a logistic regression model with treatment group will be applied. For the analysis of continuous end points an analysis of covariance model with treatment group as a factor will be used. Other covariates such as baseline measurements could be included in the analysis of covariance and logistic models and will be explicitly reported in tables for model estimate summaries.

Distribution assessment for continuous end points and model residuals will be done by means of graphical tools such as q-q plots and histograms and preliminarily tested by the Shapiro–Wilk test. If the assumption of normality is not reasonable, the Box–Cox transformation family of functions for transforming data to approximately conform normality will be implemented.
Discussion

Several studies have provided randomized controlled evidence demonstrating that in patients with type 1 diabetes, CSII was associated with significantly improved glycemia in comparison with continued basal-bolus insulin therapy. Evaluations of CSII in patients with type 2 diabetes have been undertaken but with mixed results. The principal challenges have been insufficient study power and the inclusion of a cohort with insufficient time and complexity of the “failing” insulin regimen. Furthermore, no prior study of this population had adequately optimized the dosing and complexity of basal-bolus therapy before randomization.

The OpT2mise protocol design sets out to address each of these issues. Sample size is being determined based on a clinically significant difference in the reduction of HbA1c of at least 0.5%. An adaptive design is being incorporated to allow for further refinement in the sample size based on the unblinded variability and effect size identified in the first 100 patients and carried out by the independent Data Safety Monitoring Board. The study specifically selects for patients with type 2 diabetes who had already had a reasonable trial of advanced basal-bolus therapy, as determined by minimum requirements such as three injections per day over at least a prior 3-month period and use of at least one daily dose of a rapid-acting analog bolus insulin.

To further ensure that the insulin therapy attempt had been adequate before randomization, the study incorporates a run-in period of 8 weeks intended to provide an opportunity to stabilize patients on an optimal pattern and dose of basal-bolus therapy. To standardize the approaches used by the investigators, the protocol actively defines target ranges for fasting glycemia and postprandial glycemia, based on published practice guidelines, and provides both a schedule for dose adjustments and a guide to define the expected extent of those adjustments. Finally, dose escalations are monitored by central study staff, and any titration latency is brought to the investigator’s attention in a timely manner. Patients are expected to progress in dose/kg throughout the run-in period. Sites with a pattern of nonresponsive HbA1c results in the run-in period, while also showing inconsistent dosing escalations, are flagged for further review. The Data Safety Monitoring Board is also instrumental in providing feedback from their monitoring of the patient experience during the run-in period from their perspective of ensuring optimal patient care and protocol adherence.

The process of CSII initiation and the pumping goals in cohorts of type 2 diabetes patients manifest a variability not seen in type 1 diabetes. Whereas initial dose reductions are typically used in patients with type 1 diabetes, these are typically not necessary in type 2 diabetes. Similarly, where carbohydrate-based bolus dosing is considered best practice in type 1 diabetes, it is less commonly used in patients with type 2 diabetes. Recent studies have suggested that both fixed-meal bolus dosing and carbohydrate-based bolus dosing are effective in pump therapy in type 2 diabetes patients. Neither appears to be a determinant of success, and so both options are supported in the protocol. Furthermore, to provide a standard experience, a series of pump initiation and titration regimens and worksheets are being provided to all OpT2mise investigators.

Significant proportions of insulin-using type 2 diabetes patients are unable to reach glycemic target despite the initiation of insulin in multiple daily doses. Continued further insulin dose titration has been shown to be of only marginal additional value in these patients and, in some populations with aggressive dose titration regimens, has been shown to be potentially harmful. The option of CSII therapy may provide a more physiological form of insulin replacement therapy, assist this generally older population in dose consistency and accuracy, and potentially have the unique ability to partially overcome the insulin resistance inherent in type 2 diabetes.

The OpT2mise study investigators have completed enrollment, and the cohort under investigation represents the largest studied to date and for the longest duration. Baseline characteristics of the cohort of subjects entering the run-in phase are described in Table 1. Mean age at initiation of run-in is 56.4 ± 9.38 years, with a mean duration of diabetes of 15.2 ± 7.99 years and a mean HbA1c of 9.4% ± 0.98. This group shows a mean body mass index of 33.6 ± 8.00 kg/m² and a mean HbA1c of 9.4% ± 0.98. Using metformin 342 (69.1%) Metformin dosage (mg) 1,781 ± 662.66

Table 1. Baseline Characteristics of the Run-In Cohort (n=495)

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>Value</th>
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<tbody>
<tr>
<td>Age (years)</td>
<td>56.4 ± 9.37</td>
</tr>
<tr>
<td>Gender [n (%)]</td>
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</tr>
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<td>Female</td>
<td>222 (44.8%)</td>
</tr>
<tr>
<td>Male</td>
<td>273 (55.2%)</td>
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<tr>
<td>Duration of diabetes (years)</td>
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<tr>
<td>Body mass index (kg/m²)</td>
<td>33.6 ± 7.43</td>
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<tr>
<td>HbA1c (%)</td>
<td>9.4 ± 0.98</td>
</tr>
<tr>
<td>Therapies</td>
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<tr>
<td>Total daily long-acting insulin dose (units)</td>
<td>52.7 ± 28.33</td>
</tr>
<tr>
<td>Total daily rapid-acting insulin dose (units)</td>
<td>52.2 ± 29.79</td>
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<tr>
<td>Total daily insulin dose (units)</td>
<td>104.9 ± 48.75</td>
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<tr>
<td>Using metformin</td>
<td>342 (69.1%)</td>
</tr>
<tr>
<td>Metformin dosage (mg)</td>
<td>1,781 ± 662.66</td>
</tr>
</tbody>
</table>

Data are mean ± SD values, unless stated otherwise. HbA1c, glycated hemoglobin.

Appendix

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Acknowledgments

This study was sponsored by Medtronic Europe Sàrl, Tolochenaz, Switzerland.

Author Disclosure Statement

Y.R. has carried out clinical trials as a co-investigator for Medtronic, Eli Lilly, and Novo Nordisk, has provided advisory services to Medtronic, Abbott, and Eli Lilly, and has attended conferences organized by Eli Lilly and Medtronic as a contributor. I.C. reports receiving lecture and consulting fees from Medtronic, Bayer AG, GSK, Eli Lilly & Co., Novo Nordisk A/S, Sanofi-Aventis, Novartis, and MSD. R.A. has received speaker and consulting fees from Eli Lilly, Novo Nordisk, Sanofi, and Medtronic and has received investigator fees related to the Opt2mise protocol. O.C. has carried out clinical trials as co-investigator for Medtronic, Eli Lilly, Novo Nordisk, and sanofi-aventis and has provided advisory services and lectures to Medtronic, Eli Lilly, and sanofi-aventis. S.R., J.C., S.deP., and S.L. are full-time employees of Medtronic.

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