5-19-2021

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Recommended Citation

Bergenstal RM, Johnson ML, Aroda VR, Brazg RL, Dreon DM, Frias JP, Kruger DF, Molitch ME, Mullen DM, Peyrot M, Richter S, Rosenstock J, Serusclat P, Vance C, Weinstock RS, and Levy BL. Comparing Patch vs Pen Bolus Insulin Delivery in Type 2 Diabetes Using Continuous Glucose Monitoring Metrics and Profiles. J Diabetes Sci Technol 2021.

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Original Article

Journal of Diabetes Science and Technology
1–7

DOI: 10.1177/19322968211016513
journals.sagepub.com/home/dst
SAGE

Comparing Patch vs Pen Bolus Insulin Delivery in Type 2 Diabetes Using Continuous Glucose Monitoring Metrics and Profiles

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Abstract

Objective: CeQur Simplicity™ (CeQur, Marlborough, MA) is a 3-day insulin delivery patch designed to meet mealtime insulin requirements. A recently reported 48-week, randomized, multicenter, interventional trial compared efficacy, safety and self-reported outcomes in 278 adults with type 2 diabetes (T2D) on basal insulin therapy who initiated and managed mealtime insulin therapy with a patch pump versus insulin pen. We assessed changes in key glycemic metrics among a subset of patients who wore a continuous glucose monitoring (CGM) device.

Methods: Study participants (patch, $n = 49$; pen, $n = 48$) wore a CGM device in masked setting during the baseline period and prior to week 24. Glycemic control was assessed using international consensus guidelines for percentage of Time In Range (%TIR: >70% at 70-180 mg/dL), Time Below Range (%TBR: <4% at <70 mg/dL; <1% at <54 mg/dL), and Time Above Range (%TAR: <25% at >180 mg/dL; <5% at >250 mg/dL).

Results: Both the patch and pen groups achieved recommended targets in %TIR (74.1% ± 18.7%, 75.2 ± 16.1%, respectively) and marked reductions in %TAR >180 mg/dL (21.1% ± 19.9%, 19.7% ± 17.5%, respectively) but with increased %TBR <70 mg/dL (4.7% ± 5.2%, 5.1 ± 5.8, respectively), all $P < .0001$. No significant between-group differences in glycemic improvements or adverse events were observed.

Conclusions: CGM confirmed that the patch or pen can be used to safely initiate and optimize basal-bolus therapy using a simple insulin adjustment algorithm with SMBG. Preference data suggest that use of the patch vs pen may enhance treatment adherence.

Keywords
mealtime insulin, patch, CGM, time in range, TIR, type 2 diabetes, T2D, SMBG, algorithm

Introduction

Basal-bolus insulin regimens, utilizing long-acting basal insulin in combination with rapid-acting insulin analogs, provide a physiological approach to achieve optimal glycemic control in individuals with type 2 diabetes (T2D) who require insulin therapy.[1,2] Studies have shown that intervention with basal-bolus therapy in newly diagnosed T2D patients facilitates rapid improvement in glycemic control and may help to preserve beta-cell function.[3,4]

Despite the demonstrated benefits of basal-bolus regimens, intensification of insulin therapy is often delayed.[5-7] A recent retrospective claims-based U.S. study found that less

than one third of basal insulin users achieved target glycated hemoglobin (HbA1c) at 6 months and that mealtime insulin was prescribed to only 37.7% of these patients.[8] This reflects hesitance on the part of many clinicians to initiate and intensify insulin therapy due to time constraints, lack of knowledge, potential risks of hypoglycemia, variations in guideline recommendations, and misconceptions about patient fears.[9,10]

People with T2D often resist insulin initiation/intensification due to fear of injection pain, fear of hypoglycemia, interference with daily activities, embarrassment, concerns about weight gain and reduced quality of life, as well as clinician concerns about treatment adherence.[10-15] Even when insulin therapy is initiated or intensified, adherence to therapy is often inadequate,[11,15,16] leading to suboptimal glycemic control. CeQur Simplicity™ (CeQur, Marlborough, MA), a 3-day insulin delivery patch designed to meet mealtime insulin requirements, may address many of these barriers by simplifying insulin delivery.[17]

We recently reported findings from a 48-week, randomized, multicenter, multi-national open-label, parallel, 2-arm interventional trial that compared efficacy, safety and self-reported outcomes in 278 T2D adults on basal insulin therapy who initiated and managed mealtime insulin therapy with the patch versus insulin pen (NCT02542631).[18] Participants utilized a pattern-control logbook, which included data from self-monitoring of blood glucose (SMBG) and a simple insulin adjustment algorithm to adjust basal and bolus insulin weekly based on fasting and premeal glucose targets. At study end, both the patch and insulin pen groups showed significant improvements from baseline in glycated hemoglobin (HbA1c) change ($P < .0001$) with no differences in adverse events between patch and pen. Importantly, participant-reported data at week 48 significantly favored the patch over the pen.

Although HbA1c remains the key surrogate marker for the development of long-term diabetes complications, this measure is limited in its ability to identify the frequency, magnitude and duration of acute glycemic events.[19,20] To address this limitation, the study included a subset of participants who wore a continuous glucose monitoring (CGM) system (in masked setting) for 1-2 weeks during the baseline period and prior to week 24. Glycemic control in these participants was assessed using recently published international consensus guidelines for the standardization of key CGM metrics and clinical targets for percentage of Time In Range (%TIR: >70% at 70-180 mg/dL), Time Below Range (%TBR: <4% at <70 mg/dL; <1% at <54 mg/dL) and Time Above Range (%TAR: <25% at >180 mg/dL; <5% at >250 mg/dL). In this report, we present findings from our analyses of changes in these metrics within the subset of participants who wore the CGM device during the study.

Methods

Design and Participants

Details of the full cohort study design, inclusion/exclusion criteria and interventions have been presented elsewhere (NCT02542631; EudraCT 2015-003761-28).[18] In this predefined analysis, a goal of 50 participants in each treatment arm at a subset of sites who met inclusion/exclusion criteria for the full cohort study were recruited for this subset analysis if they were willing to wear a CGM device and abstain from acetaminophen and paracetamol medications for at least 4 hours prior to CGM and during CGM.

Study Devices

The patch is a small, wearable device (65 × 35 × 8 mm) that can be worn on the abdomen for up to 3 days.[21] The patch holds up to 200 units of mealtime insulin and delivers a 2-unit dose via a subcutaneous cannula with each simultaneous click of the 2 buttons on either side of the device. The patch can be worn under clothing and the 2 buttons can be accessed either directly or through clothing. In the United States, the patch is approved for use with rapid-acting insulins lispro (Humalog®; Eli Lilly and Co., Indianapolis, IN) and aspart (NovoLog®/NovoRapid®; Novo Nordisk, Inc., Plainsboro, NJ). Insulin aspart (Novo Nordisk, Inc., Plainsboro, NJ) was used in the patch during the study. The comparator device was a NovoLog/NovoRapid FlexPen®

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(insulin aspart) (Novo Nordisk Pharmaceuticals, Inc., Princeton, NJ). All participants were provided with Verio IQ blood glucose meters and test strips (LifeScan, Inc., Wayne, PA). Participants in the subgroup analysis were provided Dexcom G4 CGM system (Dexcom, Inc., San Diego, CA) set in the "masked" mode.

Procedures

Following a 4-week screening and baseline period, all participants were randomized (1:1 to patch or pen) and followed for 44 weeks to evaluate glycemic control, safety, and treatment experience. Investigators instructed participants to continue taking their basal insulin either before their evening meal or at bedtime and use their insulin delivery device (either Patch or Pen, as randomized) for mealtime insulin administration.

Insulin dosages were initially determined by dividing the total daily insulin dose between basal and mealtime insulin. Half the total daily insulin dose was given as basal insulin and half as mealtime insulin (split evenly between usual daily meals). In subjects with HbA1c <9.0% at screening, the daily basal insulin dose was reduced by 10% before splitting into basal and mealtime insulins to decrease the potential for hypoglycemia. Participants were taught how to adjust their basal and mealtime insulin doses weekly, using a pattern-based logbook combining SMBG values with a simple insulin adjustment algorithm.[22,23]

Participants in the CGM subset analysis wore their CGM devices in masked mode for one week between week −2 to 0 and week 22 to 24. CGM was repeated for a second week during those periods only if data collection from the first week was inadequate (eg, <70% data utilization).CGM participants were asked to record 3-day, 7-point glucose values, insulin doses, hypoglycemic events and other adverse events in a diary. Throughout the study, participants were asked to perform SMBG every day before morning, midday, and evening meals, at bedtime, and when hypoglycemia was suspected based on symptoms.

At Week 44, participants crossed over to the other treatment arm for 4 weeks. An investigator-developed survey was administered to assess participants preference for patch versus pen at 48 weeks.

Measures

Outcomes were changes from baseline in the overall mean glucose and percentage of CGM readings within target range (70-180 mg/dL), below target ranges (Level 1, <70 mg/dL; Level 2, <54 mg/dL) and above target range (Level 1, >180 mg/dL; Level 2, >250 mg/dL) at 24 weeks

Statistical Analyses

The CGM analysis set included all participants who had CGM measurements obtained during the Week −2 to Week 0 and Week 22 to Week 24 periods and who had HbA1c values at baseline and Week 24. Baseline CGM calculations were derived from the measurements obtained during Week −2 to Week 0. Endpoint CGM calculations were derived from the measurements obtained during Week 22 to Week 24. The percentage of time when participants had plasma glucose measurements <54 mg/dL, <70 mg/dL, 70-180 mg/dL, >180 mg/dL), and >250 mg/dL, were calculated. Unless otherwise noted, all tests of device effects were conducted at a two-sided alpha of 0.05, and two-sided confidence intervals (CIs) at 95%. For each item in the patient preference survey (5-points Likert scale), a favorable response was considered a response of 4 or 5.

Results

Participants

Ninety-seven participants (patch, $n = 49$; pen, $n = 48$) had sufficient/adequate CGM sensor data at baseline and week 24. Baseline characteristics of the patch group were: 57.4 ± 1.5 years, 46.9% female, 14.5 ± 0.9 years diabetes duration, 81.6% white, $8.54\% \pm 0.90\%$ HbA1c, 162 ± 5.4 mg/dL fasting glucose, 39.8 ± 2.5 U/day total daily insulin dose and 90.6 ± 2.5 kg body weight. Baseline characteristics of the pen group were: 60.2 ± 1.1 years, 31.3% female, 15.5 ± 1.1 years diabetes duration, 95.8% white, $8.75 \pm 1.03\%$ HbA1c, 167 ± 2.6 mg/dL fasting glucose, 46.0 ± 3.0 U/day total daily insulin dose and 97.8 ± 2.3 kg body weight. All participants were naïve to mealtime insulin therapy.

Outcomes

CGM metrics showed that both study groups achieved statistically and clinically significant increases in percentage of time in range and marked reductions in time spent above target range but with increased time spent below target range. (Table 1)

Reductions in glycemic variability as measured by SD were significant in both study groups. Significant improvements in HbA1c were observed in both groups at week 24 compared with baseline values. No between-group differences in CGM metrics or HbA1c improvements were observed. Ambulatory Glucose Profile (AGP)[24,25] plotting showed notable flattening of glycemic profiles in both groups, particularly during the period from bedtime to morning. (Figure 1)

The majority of participants who wore the patch for 44 weeks reported a preference for using the device for mealtime insulin therapy vs insulin pen. (Table 1) Less constraint and greater freedom in diabetes self-management were considered important advantages by participants in both groups.

Discussion

In this cohort of individuals with T2D who were naïve to basal-bolus insulin therapy, our subset analysis of CGM data

Table 1. Change in HbA1c, Average Glucose, Time in Ranges and Overall Glycemic Variability (SD) from baseline as measured by CGM.

	Patch ($n = 49$)			Pen ($n = 48$)		
Metric	Baseline	Week 24	*P* value	Baseline	Week 24	*P* value
Glycemic assessments						
70-180 mg/dL, % time	48.4 ± 25.2	74.1 ± 18.7	<.0001	42.4 ± 23.8	75.2 ± 16.1	<.0001
<70 mg/dL, % time	1.2 ± 2.4	4.7 ± 5.2	<.0001	0.9 ± 3.2	5.1 ± 5.8	<.0001
<54 mg/dL, % time	0.2 ± 0.7	1.1 ± 2.0	<.0001	0.2 ± 1.2	1.2 ± 2.0	<.0001
>180 mg/dL, % time	50.4 ± 26.1	21.1 ± 19.9	<.0001	56.7 ± 24.8	19.7 ± 17.5	<.0001
>250 mg/dL, % time	18.3 ± 18.3	5.6 ± 9.7	<.0001	23.4 ± 21.8	4.6 ± 8.3	<.0001
Glycemic Variability (SD), mg/dL	52.2	46.8	<.0017	54.0	45.0	<.0001
Central lab HbA1c ± SD, %	8.54 ± 0.90	6.82 ± 0.95	<.001	8.75 ± 1.03	6.70 ± 0.79	<.001
Average glucose ± SD, mg/dL	189 ± 41.4	142 ± 30.6	<.0001	199.8 ± 41.4	140.4 ± 28.8	<.0001
Insulin dose	Patch ($n = 49$)			Pen ($n = 48$)		
Mean total Daily dose U/day, ± SE	39.8 ± 2.5	112.4 ± 9.8	<.0001	46.0 ± 3.0	131.3 ± 8.1	<.0001
Mean total insulin dose, U/kg, ± SE	0.43 ± 0.02	1.15 ± 0.09	<.0001	0.47 ± 0.03	1.30 ± 0.09	<.0001
Basal:bolus ratio, %	52:48	44:56	<.0001	52:48	43:57	<.0001

Participant preference (patch vs pen)	Percentage who used patch for 44 weeks, ($n = 45$)	95% CI	*P*-value
More satisfied using the patch vs the pen for mealtime insulin therapy	77.8%	62.9, 88.8	<.0001
Prefer using the patch vs the pen for mealtime insulin therapy	77.8%	62.9, 88.8	<.0001
Had to carry fewer diabetes supplies with me	88.6%	75.4, 96.2	<.0001
Feel less constrained with my diabetes management	84.4%	70.5, 93.5	<.0001
Feel more freedom with my diabetes management	82.2%	67.9, 92.0	<.0001
Would recommend the patch vs the pen to other patients who are on mealtime insulin therapy	80.0%	65.4, 90.4	<.0001
Want to switch from the pen to the patch	77.8%	62.9, 88.8	<.0001

All CGM glucose categories are shown as % time in range ± SD, unless stated otherwise. Difference between patch and pen at baseline or week 24 was nonsignificant for all metrics.
CGM, continuous glucose monitoring; HbA1c, glycated hemoglobin; SE, standard error, SD, standard deviation.

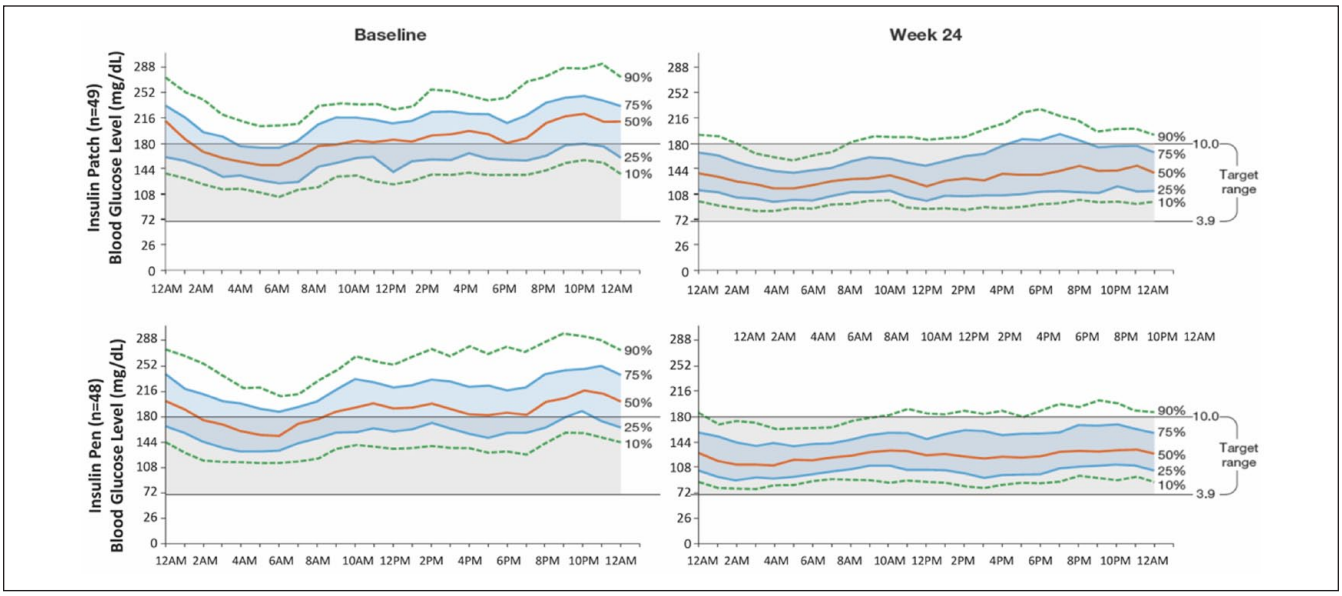

Figure 1. Ambulatory glucose profiles (AGP) at baseline and week 24 for patch and pen groups.

demonstrated that use of a simple insulin adjustment algorithm guided by SMBG improves glycemic control using either the patch or pen. Importantly, participants in both study groups achieved the recommended targets for percentage of TIR (>70% at 70-180 mg/dL) and TAR (<25% at >180 mg/dL) with only slight deviations from time >250 mg/dL (<5%), time <70 mg/dL (<4%) and time <54 mg/dL (<1%).[19]

Many clinicians using a basal only insulin regimen to treat hyperglycemia, continually increase the basal insulin dose in an attempt to optimize the fasting glucose. This minimally improves postprandial glucose excursions, leading to more glycemic variability and potential risk for hypoglycemia.[26] As evidenced by the flattened CGM profile over 24 hours, we were able to increase time in range and decrease glycemic variability through adding prandial insulin to the regimen and then steadily increasing the prandial dose as needed, often while decreasing the basal insulin dose.

Although no significant between-group differences in glycemic measures were observed, participant preference outcomes favored the patch. Overall, participants expressed a higher preference for the patch compared with the pen for administering mealtime insulin. These findings are similar to those reported by patch users in the full study cohort, who expressed significantly higher rates of agreement (vs pen users) that they were able to "dose without attracting attention" (93.8% vs 68.8%, $P < 0.0001$), "felt comfortable using it socially" (89.3% vs 71.0%, $P < .001$) and "mealtime dosing was painless" (90.2% vs 70.4%, <.001). As reported by Peyrot et al., social embarrassment and injection pain are significant contributors to insulin injection omission, particularly among individuals with T2D treated with MDI therapy.[11] Thus, our findings suggest that patch users may be more inclined to bolus for meals as prescribed.

Moreover, our findings confirm that the patch provides a simple and effective alternative to other delivery methods for safely initiating and optimizing basal-bolus therapy using an SMBG-driven simple insulin algorithm without CGM. Although large trials have demonstrated the benefits of CGM in insulin-treated T2D,[27,28] use of this technology may not be preferable or financially feasible for many individuals.

Key strengths of our analysis were the randomized design with a comparator arm and a formal protocol for insulin adjustment/titration. One notable limitation was the potential for enhanced treatment adherence in both groups due to the study effect.

As demonstrated by CGM data, our study showed that it is possible to safely initiate and optimize basal-bolus therapy using a simple insulin adjustment algorithm with SMBG-guided insulin dosing, resulting in increased time in target and minimal hypoglycemia while achieving a flat 24-hour glucose profile using either the patch or pen. Our study showed that CeQur Simplicity offers a safe, preferred alternative to other delivery methods, such as pen.

Conclusions

Use of CGM complemented HbA1c outcome measures in assessing changes in glycemic control, providing further understanding of glycemic control for patients with T2D initiating basal-bolus therapy. Similar studies using CGM in combination with our simplified insulin dosing algorithm would expand our understanding of the clinical utility of this treatment approach.

Abbreviations

AGP, ambulatory glucose profile; CGM, continuous glucose monitoring; %TAR, percentage of time above range; %TBR, percentage of time below range; %TIR, percentage of time in range; T2D, .type 2 diabetes.

Presentation at Scientific Meetings

Presented at the American Diabetes Association (ADA) 78th Scientific Sessions; Orlando, FL, USA; June 22–26, 2018.

Acknowledgments

The authors wish to thank Buddug Rees, PhD, CeQur, and Christopher G. Parkin, MS, for their editorial assistance in developing this manuscript.

Declaration of Conflicting Interests

The author(s) declared the following potential conflicts of interest with respect to the research, authorship, and/or publication of this article: RMB has received research support, consulted, or has been on a scientific advisory board for Abbott Diabetes Care, Ascensia, CeCur Corporation, DexCom, Hygieia, Insulet, Johnson & Johnson, Lilly, Medtronic, Novo Nordisk, Onduo, Roche, Sanofi and United Healthcare. His technology research is funded in part by NIH/NIDDK. RMB's employer, non-profit HealthPartners Institute, contracts for his services and no personal income goes to RMB. M.L.J. has received research support from or participated in clinical trials supported by Abbott, Dexcom, Johnson & Johnson, Hygieia, Medtronic, the NIDDK, and Novo Nordisk; her employer (the non-profit Health Partners Institute) contracts for her services; no personal income goes to M.L.J. V.R.A. has had research contracts (clinical trials) within the past 12 months from AstraZeneca/BMS, Calibra Medical, Eisai, Elcelyx, Janssen, Novo Nordisk, Sanofi, and Theracos; and has provided consultant activities within the past 12 months for the ADA, Medscape, Novo Nordisk, Sanofi, and Tufts. R.L.B. (Rainier Clinical Research Center) has received research support from Abbott, Diasome, Eli Lilly and Company, Dexcom, Johnson & Johnson, Medtronic, Novartis, Novo Nordisk, Sanofi, and ViroMed. D.M.D. is a full-time employee of Calibra Medical. J.P.F. has received research support from AbbVie, Allergan, AstraZeneca, Boehringer Ingelheim, BMS, Elcelyx, Eli Lilly and Company, Genentech, IONIS, Janssen, Johnson & Johnson, Lexicon, Ligand, Madrigal, Merck, Mylan, Myovant, Novartis, Novo Nordisk, Ogeda, Pfizer, Sanofi, TaiwanJ, Theracos, and Viking; and is on advisory boards and a consultant for AstraZeneca, BMS, Echosens, Elcelyx, Johnson & Johnson, Ligand, Novo Nordisk, and Sanofi. D.F.K. has served on advisory boards and/or speaker bureaus for Abbott, AstraZeneca, Aventis,

Boehringer Ingelheim, Eli Lilly and Company, Dexcom, Intarcia, Insulet, Janssen, Novo Nordisk, Sanofi, and Valeritas, and her institution has received research support from AstraZeneca, Eli Lilly and Company, Dexcom, Lexicon, and Novo Nordisk. M.E.M. has received research support from Janssen Pharmaceuticals, Bayer, Novartis, NovoNordisk, Strongbridge, Crinetics and consulted for Merck, Pfizer, Sanofi, Janssen. D.M.M.'s nonprofit employer has received research grants from Abbott Diabetes Care and Dexcom for which there was no personal compensation. M.P. has received research support, has acted as a consultant, or has been on the scientific advisory board for Becton-Dickinson, CeQur Corporation, Eli Lilly and Company, Johnson & Johnson, Novo Nordisk, and Valeritas. S.R. has participated in other clinical trials sponsored by the Johnson & Johnson group; her employer contracts for her services and no personal income goes to her. J.R. has served on scientific advisory boards and received honorarium or consulting fees from Boehringer Ingelheim, Eli Lilly and Company, Intarcia, Janssen, Novo Nordisk, and Sanofi. He has received grants/research support from AstraZeneca, Boehringer Ingelheim, Bristol-Myers Squibb, Eli Lilly and Company, GlaxoSmithKline, Genentech, Intarcia, Janssen, Lexicon, Merck, Novo Nordisk, Pfizer, and Sanofi. P.S. has served on advisory boards for Novo Nordisk and has received research support from Eli Lilly and Company, Novo Nordisk, and Sanofi. C.D.V. has received research support from the following: Allergan, Ascensia, AstraZeneca, Boehringer Ingelheim, Glooko, Eli Lilly and Company, Mylan, Novo Nordisk, Oramed, Sanofi, Tolerion and vTv Therapeutics. He serves on no advisory boards. R.S.W. has received research support from or participated in clinical trials supported by Dexcom, Diasome Pharmaceuticals, the Harry B. Helmsley Charitable Trust, the JDRF, the Jaeb Center for Health Research/Leona M. and Medtronic, the Kowa Research Institute, Mylan GmbH, and the NIDDK. B.L.L. is a former full-time employee of LifeScan, Inc. and Calibra Medical and provides consulting services to CeQur Corporation.

Funding

The author(s) disclosed receipt of the following financial support for the research, authorship, and/or publication of this article: The study was funded by Calibra Medical (Wayne, PA), which has since been acquired by CeQur SA (Horw, Switzerland).

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