

## ORIGINAL ARTICLE

# Effect of prandial treatment timing adjustment, based on continuous glucose monitoring, in patients with type 2 diabetes uncontrolled with once-daily basal insulin: A randomized, phase IV study

Jacob Ilany MD<sup>1</sup> | Hamad Bhandari MD<sup>2</sup> | Dan Nabriski MD<sup>3</sup> | Yoel Toledano MD<sup>4</sup> |  
Noa Konvalina RD<sup>1</sup> | Ohad Cohen MD<sup>1\*</sup>

<sup>1</sup>Institute of Endocrinology, Sheba MC, Ramat-Gann, Israel

<sup>2</sup>Clalit Health Fund, Tel-Aviv, Israel

<sup>3</sup>Endocrine Unit, Meir MC, Clalit Health Fund, Kfar-Saba, Israel

<sup>4</sup>Diabetes Clinic, Maccabi Health Fund, Netanya, Israel

## Correspondence

Dr Jacob Ilany, Sheba MC, Ramat-Gann, Israel 5265601.

Email: jacob.ilany2@sheba.health.gov.il

## Funding information

This study was funded by Sanofi, who monitored clinical sites, collected and managed the data and performed statistical analyses.

**Aims:** To evaluate the glycaemic control achieved by prandial once-daily insulin glulisine injection timing adjustment, based on a continuous glucose monitoring sensor, in comparison to once-daily insulin glulisine injection before breakfast in patients with type 2 diabetes who are uncontrolled with once-daily basal insulin glargine.

**Materials and Methods:** This was a 24-week open-label, randomized, controlled, multicentre trial. At the end of an 8-week period of basal insulin optimization, patients with HbA1c  $\geq$  7.5% and FPG  $<$  130 mg/dL were randomized (1:1) to either arm A (no sensor) or arm B (sensor) to receive 16-week intensified prandial glulisine treatment. Patients in arm A received pre-breakfast glulisine, and patients in arm B received glulisine before the meal with the highest glucose elevation based on sensor data. The primary outcome was mean HbA1c at week 24 and secondary outcomes included rates of hypoglycaemic events and insulin dosage.

**Results:** A total of 121 patients were randomized to arm A ( $n = 61$ ) or arm B ( $n = 60$ ). There was no difference in mean HbA1c at week 24 between arms A and B ( $8.5\% \pm 1.2\%$  vs  $8.4\% \pm 1.0\%$ ;  $P = .66$ ). The prandial insulin glulisine dosage for arm A and arm B was 9.3 and 10.1 units, respectively ( $P = .39$ ). The frequency of hypoglycaemic events did not differ between study arms ( $36.1\%$  vs  $51.7\%$ ;  $P = .08$ ).

**Conclusion:** Using a CGM sensor to identify the meal with the highest glucose excursion and adjusting the timing of prandial insulin treatment did not show any advantage in terms of glycaemic control or safety in our patients.

## KEYWORDS

basal insulin, clinical trial, continuous glucose monitoring (CGM), insulin therapy

## 1 | INTRODUCTION

Type 2 diabetes is increasing, both in incidence and prevalence.<sup>1</sup> According to the International Diabetes Federation (IDF), in 2015, the global prevalence reached approximately 415 million, with the highest prevalence (22%) in the age group of 70–75 years.<sup>1,2</sup>

\*Complete list of study investigators is available online (Table S3, Appendix S1).

The persistent advancing nature of type 2 diabetes, with progressive deterioration of pancreatic  $\beta$ -cell function, eventually requires insulin supplementation and intensification in an attempt to tackle a worsening glycaemic profile.<sup>3,4</sup> Basal insulin, targeting elevated fasting plasma glucose (FPG), is often initiated in patients who fail to achieve target glycaemic control with oral anti-hyperglycaemic agents (OADs) and GLP-1 agonists; however, despite the addition of basal insulin, nearly 40% of such patients fail to achieve the recommended

goal of HbA1c < 7%.<sup>5,6</sup> For these patients, there has been growing acceptance of a strategy that progressively adds “bolus” rapid insulin to the basal insulin treatment, focusing on both FPG and postprandial plasma glucose (PPG).<sup>7–9</sup> The addition of bolus insulin is based on self-monitoring of blood glucose (SMBG) measurements and takes into account the patients' habits as they pertain to meal timing and composition and to their level of activity.

SMBG measurements can provide only intermittent snapshots of blood glucose levels, often missing hyperglycaemic or hypoglycaemic excursions; in contrast, a continuous glucose-monitoring (CGM) system provides information on day-to-day change in blood glucose levels and highlights the diverse contributions of FPG and PPG values at different HbA1c levels. Indeed, the optimal timing of PPG measurement varies according to the composition of each meal; hence, single postprandial measurement can miss the highest peak values, which are detectable only with CGM. Therefore, CGM devices may increase the timeliness and safety of insulin initiation and up-titration among patients with type 2 diabetes, particularly by identifying asymptomatic nocturnal hypoglycaemia and unrecognized PPG elevations. Although the impact of CGM on the achievement of metabolic control in type 1 diabetes has been evaluated in numerous trials and recognized by recent guidelines,<sup>10</sup> the impact has not been extensively studied in type 2 diabetes. However, several recent meta-analyses suggest better glycaemic control with CGM than with SMBG in adults with type 2 diabetes.<sup>11,12</sup>

In patients with type 2 diabetes who are uncontrolled with basal insulin plus OADs, a single bolus of rapid-acting insulin glulisine added to glargine demonstrates significant improvement in HbA1c levels and superior glycaemic control without an increase in the rates of hypoglycaemia, irrespective of the time of administration.<sup>8,9,13</sup> However, the impact of CGM on glycaemic control, when used to guide the timing of glulisine administration, is not well delineated in patients with type 2 diabetes. Therefore, we aimed to evaluate the effect of once-daily prandial glulisine treatment timing adjustment, based on CGM, in comparison to pre-breakfast once-daily prandial glulisine on glucose control in patients with type 2 diabetes who are uncontrolled with once-daily basal insulin. We designed a pilot study, assuming a difference of 0.5% in mean HbA1c in favour of the group of patients using CGM to determine the timing of insulin glulisine injection.

## 2 | RESEARCH DESIGN AND METHODS

### 2.1 | Study design and patient population

This was a 24-week, randomized, open-label, controlled, phase IV study, conducted at 11 sites across Israel. The study included an 8-week run-in period, followed by a 16-week period of intensified treatment. The study design and patient visits are provided online (Figure S1, Appendix S1).

The study (registered at [clinicaltrials.gov](http://clinicaltrials.gov): NCT01234597) was conducted in accordance with the ethical principles of the Declaration of Helsinki. Study protocol approval was obtained for each participating centre, and all patients provided written informed consent.

Patients with type 2 diabetes, aged >21 years, with inadequate glycaemic control (HbA1c  $\geq$  8%), who had been treated with basal insulin or mixed insulin once daily for at least 6 months before visit 1, who had been deemed eligible according to the physician's decision, and who were capable of complying with the study requirements were included in the study. Exclusion criteria included patients with type 1 diabetes, pregnant or breastfeeding women, patients under continuous treatment with short-acting insulin or mixed insulin more than once daily for 3 weeks during the 6-month period before visit 1, patients allergic to insulin, patients with severe diseases characterized by recurrent hospitalizations (renal insufficiency, cardiac insufficiency and oncological disease), and patients participating in any other clinical trial involving the use of an investigational product.

## 2.2 | Study procedures and data collection

### 2.2.1 | Run-in period

Eligible patients entered an 8-week run-in period where optimization of basal insulin glargine was attempted, with the goal of reaching fasting glucose below 130 mg/dL without hypoglycaemia. During the run-in period, all earlier anti-diabetes medications were discontinued, with the exception of metformin and dipeptidyl peptidase-4 inhibitors, and patients were put on a basal insulin (insulin glargine) regimen, which was further titrated to achieve an FPG target of >70 to <100 mg/dL. Patients with HbA1c levels  $\geq$ 7.5% and FPG < 130 mg/dL at the end of the run-in period entered the randomization phase.

At the end of the run-in period, patients were screened according to randomization criteria (HbA1c and FPG). Generation of the random allocation sequence and actual randomization were performed by a statistical company (MediStat Ltd., Tel-Aviv, Israel). All eligible patients were randomized (1:1) at week 10 into 1 of the 2 study arms: Arm A patients were not connected to the CGM sensor, while arm B patients were connected to a blinded CGM sensor for 6 consecutive days and they returned 1 week after randomization. The insulin glargine dose was maintained constant from this time point.

Patients were reminded to examine their 7-point blood glucose profile on a particular day of the week before week 10 and record it in the diary.

### 2.2.2 | Intensified treatment period

From week 12 to week 24 (end of study), insulin glulisine was added to the fixed glargine dose. Patients in arm A received insulin glulisine 0 to 15 minutes before the first meal of the day, while patients in arm B received glulisine 0 to 15 minutes before the meal with the highest elevation in glucose level based on CGM data collected during the 6 days of monitoring. Patients in both groups were required to contact their physician before any dose adjustment. In both study arms, the initial dose of insulin glulisine was 6 units and the titration upwards or downwards was carried out to reach the target 2-hour postprandial blood glucose value of  $\leq$ 135 mg/dL or to resolve recurrent hypoglycaemic events.

All patients were provided with diaries to record blood glucose levels, insulin doses, information related to hypoglycaemia and the 7-point blood glucose profile during the study period. Other

information, such as demographic data, medical history, hypoglycaemic events and full diabetes-specific clinical history, was also collected.

## 2.3 | Primary and secondary outcome measures

The primary outcome was mean HbA1c at week 24 in both treatment arms. Secondary outcome measures included comparison of the rate of hypoglycaemic events and insulin glargine/insulin glulisine dose between the randomized groups. Hypoglycaemic events were defined as symptomatic (without measuring BG values) or moderate (symptoms of hypoglycaemia confirmed by BG values 55-70 mg/dL). Severe hypoglycaemia was defined as measurable hypoglycaemia with glucose values <55 mg/dL and/or the necessity of involvement of a third party in the treatment.

Other analyses included change in HbA1c and FPG levels from Week 8 to Week 24, glycaemic response rate (proportion of patients achieving HbA1c < 7%), 7-point blood glucose profile (fasting before breakfast, 2 hours after breakfast, before lunch, 2 hours after lunch, before dinner, 2 hours after dinner and at bedtime) at 24 weeks, and change in 7-point glucose profile from Week 10 to Week 24 in both treatment arms.

## 2.4 | Statistical methods

### 2.4.1 | Determination of sample size

The rationale for sample size calculation is based on demonstration of a difference of at least 0.5% in HbA1c change from baseline between the treatments, with 80% power and 5% statistical significance. A sample size of 52 in each group would have 80% power to detect a difference in means of 0.50, assuming that the common standard deviation is 0.90 using a 2-group T-test with a 0.05 2-sided significance level. Analyses of efficacy data were performed using the intention-to-treat (ITT) population, which included all randomized patients. Additional analyses were performed using the per-protocol (PP) population, which included all patients who completed the study without major protocol violations. Safety evaluations were performed using the safety population that included all patients who had at least 1 dose of study medication. The T-test or Wilcoxon test (U-test) (as applicable) was used for evaluating the statistical significance of the difference in HbA1c levels and insulin dose between the 2 study arms at Week 24. The chi-square test or Fisher's exact test (as applicable) was used for evaluating the statistical significance of the difference in percentage of patients experiencing hypoglycaemic events between the 2 study arms. Logistic regression was used for evaluating the statistical significance of the difference in proportion of patients with hypoglycaemic events, with adjustments for the following variables: age, sex, disease duration, insulin dose, FPG level and HbA1c level. The T-test and chi-square tests were applied for analysing the differences in 7-point blood glucose values at Week 10 and Week 24, and the change from Week 10 to Week 24 between the study arms. All tests were 2-tailed, and a *P* value of 5% or less was considered statistically significant.

## 3 | RESULTS

### 3.1 | Patient disposition and baseline characteristics

Between December 2012 and April 2015, 219 patients were screened for inclusion in the run-in phase. Of 219 patients screened, 121 patients were randomly assigned to the study treatments arms (arm A, *n* = 61; arm B, *n* = 60). Patient disposition is presented in Figure 1. Baseline characteristics and demographics were similar between the study arms (Table 1). Patients were predominantly men (>55%) with a mean age of 63 years. The average duration of diabetes was 13.7 years and baseline weight was >80 kg. A majority of the randomized patients (>65%) in both arms were receiving insulin glargine at baseline.

### 3.2 | Glycaemic response

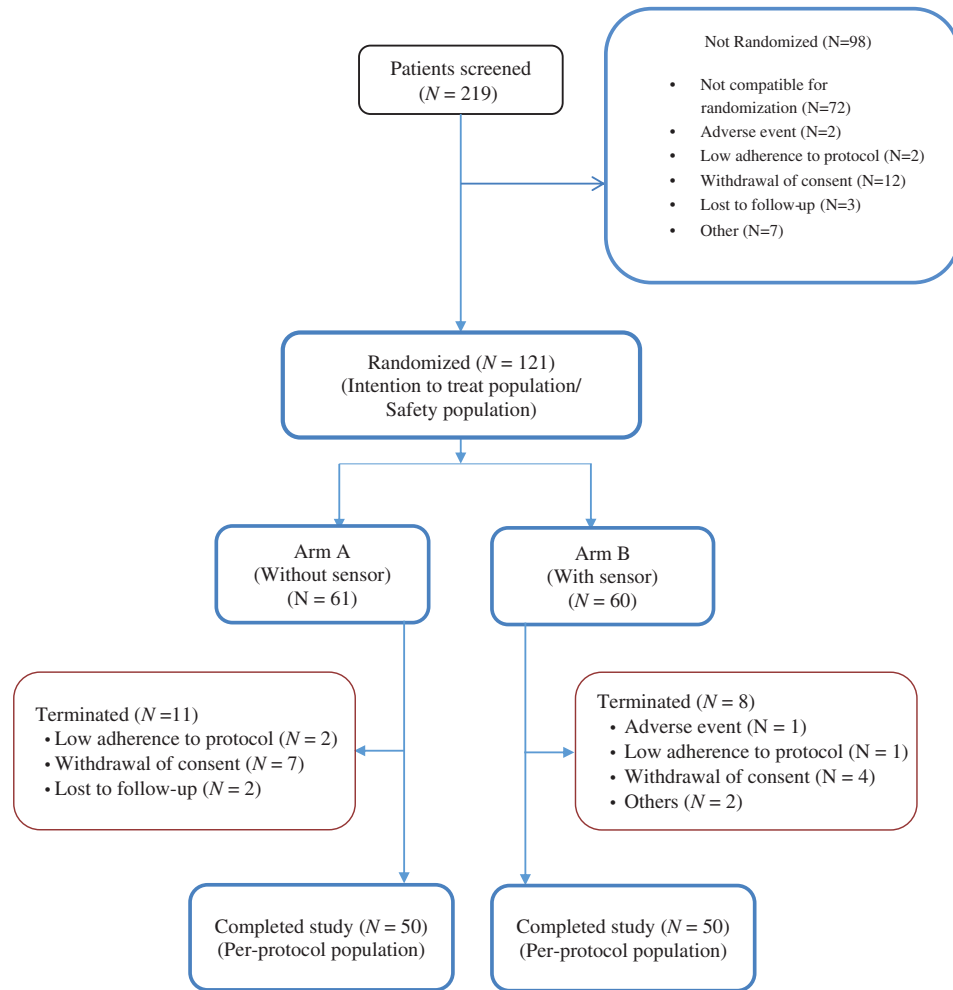
During the run-in phase, treatment with insulin glargine and subsequent dose titration resulted in a reduction of mean (SD) HbA1c from 9.9% (1.3) at baseline to 9% (1.3) at Week 8. Mean HbA1c level at week 24 in arms A and B was  $8.5\% \pm 1.2\%$  (95% CI, 8.1-8.8) and  $8.4\% \pm 1.0\%$  (95% CI, 8.1-8.6), respectively, with no difference between the groups (*P* = .66) (Table 2). Mean difference in HbA1c levels from Week 8 to Week 24 in arm A was  $-0.48\% \pm 0.97\%$  (95% CI, -0.76 to -0.2) and in arm B was  $-0.54\% \pm 0.85\%$  (95% CI, -0.79 to -0.3). The HbA level significantly decreased from Week 8 to Week 24 in both arms (*P* < .0001). However, mean change in HbA1c did not differ between study arms (*P* = .75) (Table 2).

Mean FPG level at Week 24 in arm A was  $132.9 \pm 50.0$  mg/dL (95% CI, 118.3-147.4) and in arm B was  $145.7 \pm 57.3$  mg/dL (95% CI, 128.6-162.9), with no significant difference between treatment arms (*P* = .25) (Table 2). Further, mean change in FPG levels from Week 8 to Week 24 for arm A was  $19.37 \pm 55.1$  mg/dL (95% CI, 3.00-35.73) and for arm B was  $27.41 \pm 60.93$  mg/dL (95% CI, 9.10-45.72). The FPG level significantly increased from Week 8 to Week 24 in both groups (*P* = .021 for arm A and *P* = .004 for arm B). However, the change in FPG level at Week 24 between the 2 study arms was not significantly different (*P* = 0.51) (Table 2).

At the end of the study (Week 24), no significant difference was observed in patients achieving HbA1c < 7% between the study arms (arm A, 8.2% and arm B, 10.2%; *P* = .73). In arm B, 10 patients received glulisine before breakfast, 17 before lunch and 17 before dinner. The timing was not clear for the other 6 patients.

Mean 7-point blood glucose values did not differ between study arms (*P* > .05) at the end of the study (Figure 2). No reduction was observed in 7-point plasma glucose levels in arm A (Figure 3A); however, in arm B, a borderline reduction in plasma glucose levels was observed 2 hours after breakfast (*P* = .05) and a significant reduction in glucose levels was observed 2 hours after dinner (*P* = .04) (Figure 3B).

The change in 7-point blood glucose values from Week 10 to Week 24 for each glulisine injection-time group (morning/afternoon/evening) was also analysed (Table S1, Appendix S1). Glulisine injection before the meal was found to decrease 2-hour post-meal glucose values. Particularly, glulisine injection in the afternoon and evening



**FIGURE 1** Patient disposition

**TABLE 1** Baseline characteristics of randomized patients

	Randomized patients	
	Arm A (n = 61)	Arm B (n = 60)
Demographic data		
Males/females (% male)	35/26 (57.4)	33/27 (55.0)
Age, years	63.1 ± 9.9	63 ± 10.9
BMI, kg/m <sup>2</sup>	30.51 ± 6.07	29.89 ± 5.14
Weight, kg	84.3 ± 13.9	80.8 ± 15.9
Disease history		
Duration, years	12.8 ± 6.2	14.6 ± 8.5
Duration of oral treatment, years	10.6 ± 6.6	11 ± 7.8
Insulin treatment before the study		
Duration, years	2.6 ± 1.8	2.6 ± 1.9
Daily dose, units	36.9 ± 17.7	32.55 ± 14.5
Type of insulin		
Glargine	41 (68.3)	39 (65.0)
Detemir	15 (25.0)	18 (30.0)
Mixed OD	3 (5.0)	0 (0.0)
Glargine + Mixed OD	1 (1.7)	0 (0.0)
Detemir + Mixed OD	0 (0.0)	3 (5.0)

Abbreviation: OD, once daily. Data are presented as n (%) unless otherwise indicated.

showed a significant decrease in glucose values 2 hours after lunch ( $P = 0.02$ ) and 2 hours after dinner ( $P = .04$ ), respectively. However, this decrease was not significant when 3 injection-timing values were combined at each 7-point glucose-measurement timing.

### 3.3 | Insulin dose

At study entry, the mean daily insulin glargine dose for all participants was 35 units (arm A, 37 and arm B, 33;  $P = .26$ ), which increased to a mean of 39 units (arm A, 41 and arm B, 37;  $P = .24$ ) at the end of the run-in phase (Week 8). The prandial insulin glulisine dose for arms A and B was  $9.3 \pm 4.5$  units and  $10.1 \pm 4.6$  units, respectively, at the end of the study (Week 24). There was no significant difference in insulin glulisine dose at week 24 between study arms ( $P = .39$ ) (Table 2).

### 3.4 | Hypoglycaemic events

The frequency of hypoglycaemic events during the study period was not statistically different between study arms (36.1% for arm A vs 51.7% for arm B;  $P = .08$  using chi-Square test and  $P = .11$  using logistic regression) (Table 2). A total of 461 hypoglycaemic events occurred during the study; 197 events occurred in arm A (43%) and 264 events occurred in arm B (51.7%).

**TABLE 2** Clinical outcome at the end of study (week 24)

	Arm A	Arm B	P value
<b>HbA1c (%)</b>			
N	49	49	-
HbA <sub>1c</sub>	8.5 ± 1.2	8.4 ± 1.0	.66
Frequency of HbA <sub>1c</sub> < 7%, n (%)	4 (8.2)	5 (10.2)	.73
Change in HbA <sub>1c</sub> from week 8	-0.48 ± 0.97	-0.54 ± 0.85	.75
<b>FPG (mg/dL)</b>			
N	47	47	-
FPG	132.9 ± 50.0	145.7 ± 57.3	.25
Change in FPG from week 8	19.37 ± 55.1	27.41 ± 60.9	.51
<b>Hypoglycaemic events</b>			
N (Patients)	61	60	
N (Events)	197	264	-
Any hypoglycaemic events, no. of patients (%)	22 (36.1)	31 (51.7)	.08*, .11**
Number of events per patient	9	8.5	.6
<b>Insulin dosage (Units)</b>			
Insulin glargine	40.4 ± 18.4	36.3 ± 16.9	.24
Insulin glulisine	9.3	10.1	.39
Patients with glulisine administration in the morning n (%)	43 (82.7)	21 (40.4)	<.001

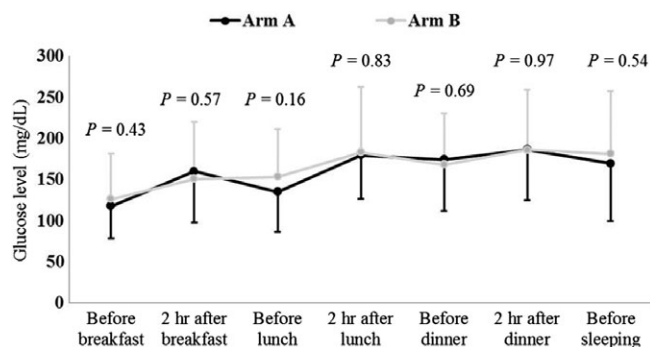
Data are presented as mean ± SD unless otherwise indicated. \* by chi-square test; \*\* by logistic regression.

There were no serious hypoglycaemic events (leading to loss of consciousness or convulsing, hospitalizations, ER visits) reported in either study arm. A majority of patients (arm A, 53.3% and arm B, 50%) experienced hypoglycaemic events in the morning (6:00 AM–12:00 PM). Mean blood glucose levels during hypoglycaemic events were comparable between study arms (arm A, 61 mg/dL and arm B, 62 mg/dL).

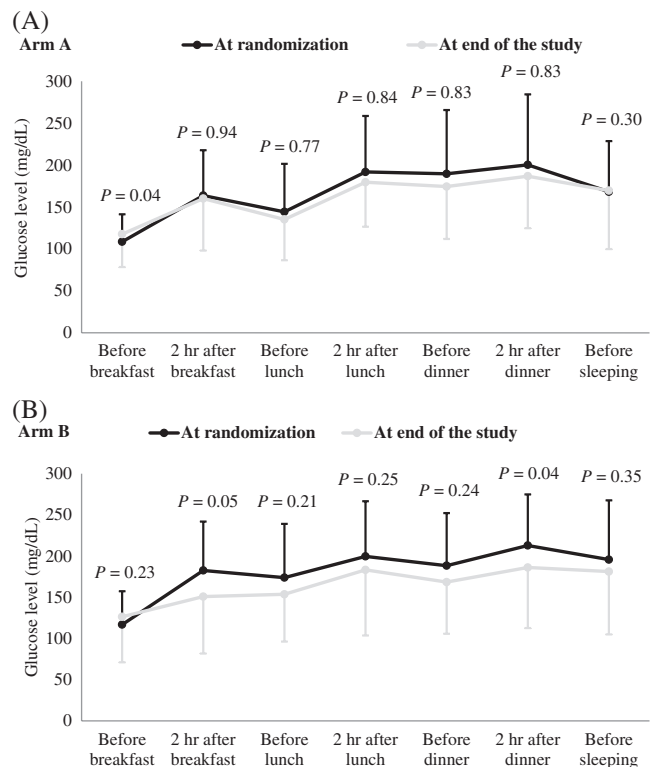
### 3.5 | Safety and tolerability

AEs were equally distributed between the 2 treatment groups. Overall, 40 AEs were reported in arm A and 46 in arm B. The most frequently reported system organ classes were “general disorders and administration site conditions” and “gastrointestinal disorders” in both treatment groups. The most common AEs by preferred term were dyspepsia, chest pain, asthenia, dizziness, headache, diabetic neuropathy, abdominal pain, tooth disorder, hypoglycaemia, back pain, chronic obstructive pulmonary disease and dyspnea. During the

study, no deaths, no severe hypoglycaemic events, and no new safety signals were reported in the study population. Most AEs were mild in intensity and were unrelated to the study drug. A tabulated summary of adverse events can be found online (Table S2, Appendix S1).



**FIGURE 2** Seven point glucose profiles in both treatment arms at end of the study



**FIGURE 3** Seven point glucose profiles. A, Change in 7-point blood glucose levels from randomization (week 10) to end of study (week 24) in arm A. B, Change in 7-point blood glucose levels from randomization (week 10) to end of study (week 24) in arm B



## 4 | CONCLUSIONS

In this multicentre, open-label, randomized, controlled trial, the addition of prandial insulin treatment significantly decreased HbA1c level in patients with and without CGM sensors; however, the difference was not significant between arms. Further, this trial did not show any between-group differences in mean daily dose of insulin glargine and glulisine, in the 7-point blood glucose profile and in proportion of patients experiencing hypoglycaemic events.

Despite the development of numerous new therapies, the glycaemic outcome for a majority of patients with type 2 diabetes remains unsatisfactory and presents a significant challenge. In view of the negative impact of prolonged hyperglycaemia on the development of late microvascular complications,<sup>14</sup> many patients with type 2 diabetes will eventually require insulin therapy when other medications, including GLP 1 agonists and SGLT-2 inhibitors, fail to achieve the target. However, despite technical advances in insulin therapy and favourable long-term safety data,<sup>15,16</sup> many patients and physicians are reluctant to use insulin because of a fear of hypoglycaemia and weight gain.<sup>17,18</sup>

The PPG exhibits a closer association with HbA1c and has a stronger correlation with development of diabetes complications than FPG.<sup>19–21</sup> The primary approach in reducing glycaemic load is addition and up-titrating of long-acting basal insulin injection, which affects both pre- and postprandial glucose. However, PPG control is necessary for patients who are close to, but not at, target (HbA1c < 7%), for those using high doses of basal insulin without success (>0.7 U/kg) or those who are at increased risk of nocturnal hypoglycaemia which prevents further titration of basal insulin doses.<sup>22,23</sup> This can be addressed by administration of a rapid-acting insulin analogue at mealtime, producing a rapid and short insulin spike to control the PPG elevation.

In daily practice, the challenges faced with insulin intensification may benefit from the use of a CGM sensor, which can guide clinicians in optimizing multiple insulin regimens while avoiding hypoglycaemia.<sup>24,25</sup> Use of a CGM sensor has been evident in optimizing insulin therapy in type 1 diabetes.<sup>26–29</sup> In this study, the significance of CGM in optimizing insulin therapy in patients with type 2 diabetes who are uncontrolled with basal insulin and OADs was evaluated. Furthermore, both treatment arms in this study displayed improvement in HbA1c by approximately 0.5%. Hence, regardless of the effect of a CGM system, our results are consistent with those of previous studies wherein addition of prandial insulin injection before breakfast or before the largest meal improved HbA1c by 0.5%, irrespective of what meal was chosen for the injection.<sup>8,30</sup> It should be noted that the baseline HbA1c level was approximately 9%, which improved during the study by 0.5%, and only a small minority of patients reached the target of <7% (8.2% in arm A and 10.2% in arm B), implying that most of these patients required more intensive treatment to attain target HbA1c. In addition, the frequency of patients experiencing hypoglycaemic events during the study period was not statistically different between study arms. Hence, our results indicate that adding 1 pre-meal glulisine injection can be a safe and easy measure in a stepwise treatment regimen, and may reduce fear on the part of both patient and physician of moving from therapy with basal insulin plus OADs to a more intensive insulin regimen.

The rationale for empiric pre-breakfast bolus injection, as the first step in intensification of a basal insulin regimen, is that, during the morning, the probability of glucose excursions is highest, which may be associated, in part, with the relatively higher levels of insulin resistance driven by the diurnal secretion of cortisol and growth hormone.<sup>31,32</sup> Therefore, glulisine injection just prior to breakfast may be a simple way to improve glycaemic control. The results of the present study are in concordance with those of the OPAL study<sup>8</sup> in which adding the bolus dose at breakfast achieved results similar to those achieved with adding the bolus dose before the largest meal (by anamnesis and not using CGM).

The lack of a control group that received only basal insulin could represent a limitation of our study. However, during the run-in phase, despite receiving basal insulin, many patients did not achieve target HbA1c, but after addition of glulisine in the randomized phase, they exhibited a decrease in HbA1c. Hence, the glycaemic improvement can be attributed to the glulisine injection.

In conclusion, using CGM for identifying the meal with highest glucose excursion and adjusting the timing of prandial insulin glulisine administration accordingly, did not show any advantage in terms of glycaemic outcome or safety in our patients. However, it may be considered for patients in whom a specific meal is suspected to contribute considerably to the HbA1c level.

## ACKNOWLEDGMENTS

Medical writing support was provided by Anahita Gouri from Sanofi (India) and Gali Shani-Maimon from Sanofi (Israel), which was funded by Sanofi. The authors thank Leena Patel, PhD from Jeevan Scientific Technology Limited (Hyderabad, India) for providing writing assistance in the development of this manuscript.

## Conflict of interest

J. I. and O. C. received honoraria from Sanofi. All other authors declare no potential conflict of interest.

## Author contributions

J. I. was the national primary investigator for the study and contributed to the analysis and discussion, and also drafted, reviewed and edited the manuscript. O. H. contributed to the conception and design of the study and reviewed the manuscript. N. K. contributed to the data analysis. All other authors contributed as reviewers of the manuscript.

## REFERENCES

- International Diabetes Federation. *IDF Diabetes Atlas*. 7th ed. 2015. [Internet] <http://www.idf.org/membership/eur/israel>. Accessed January 6 2017.
- Goldberger N, Applbaum Y, Meron J, Haklai Z. High Israeli mortality rates from diabetes and renal failure - can international comparison of multiple causes of death reflect differences in choice of underlying cause? *Isr J Health Policy Res*. 2015;4:31.
- Rosenstock J, Ahmann AJ, Colon G, Scism-Bacon J, Jiang H, Martin S. Advancing insulin therapy in type 2 diabetes previously treated with glargine plus oral agents: prandial premixed (insulin lispro protamine

- suspension/lispro) versus basal/bolus (glargine/lispro) therapy. *Diabetes Care*. 2008;31:20-25.
4. Owens DR. Stepwise intensification of insulin therapy in type 2 diabetes management--exploring the concept of the basal-plus approach in clinical practice. *Diabet Med*. 2013;30:276-288.
  5. Riddle MC, Rosenstock J, Gerich J, Insulin Glargine 4002 Study Investigators. The treat-to-target trial: randomized addition of glargine or human NPH insulin to oral therapy of type 2 diabetic patients. *Diabetes Care*. 2003;26:3080-3086.
  6. Holman RR, Farmer AJ, Davies MJ, et al. Three-year efficacy of complex insulin regimens in type 2 diabetes. *N Engl J Med*. 2009;361:1736-1747.
  7. Harris SB, Yale JF, Berard L, et al. Does a patient-managed insulin intensification strategy with insulin glargine and insulin Glulisine provide similar glycemic control as a physician-managed strategy? Results of the START (self-titration with Apidra to reach target) study a randomized noninferiority trial. *Diabetes Care*. 2014;37:604-610.
  8. Lankisch MR, Ferlinz KC, Leahy JL, Scherbaum WA. Introducing a simplified approach to insulin therapy in type 2 diabetes: a comparison of two single-dose regimens of insulin glulisine plus insulin glargine and oral antidiabetic drugs. *Diabetes Obes Metab*. 2008;10:1178-1185.
  9. Fritsche A, Larbig M, Owens D, Häring H. Comparison between a basal-bolus and a premixed insulin regimen in individuals with type 2 - diabetes--results of the GINGER study. *Diabetes Obes Metab*. 2010;12:115-123.
  10. American Diabetes Association. Standards of medical care in diabetes--2016. *Diabetes Care*. 2016;39(suppl 1):S1-S106.
  11. Poolsup N, Suksomboon N, Kyaw AM. Systematic review and meta-analysis of the effectiveness of continuous glucose monitoring (CGM) on glucose control in diabetes. *Diabetol Metab Syndr*. 2013;5:39.
  12. Gandhi GY, Kovalaske M, Kudva Y, et al. Efficacy of continuous glucose monitoring in improving glycemic control and reducing hypoglycemia: a systematic review and meta-analysis of randomized trials. *J Diabetes Sci Technol*. 2011;5:952-965.
  13. Riddle MC, Rosenstock J, Vlahjic A, Gao L. Randomized, 1-year comparison of three ways to initiate and advance insulin for type 2 diabetes: twice-daily premixed insulin versus basal insulin with either basal-plus one prandial insulin or basal-bolus up to three prandial injections. *Diabetes Obes Metab*. 2014;16:396-402.
  14. Holman RR, Paul SK, Bethel MA, Matthews DR, Neil HA. 10-year follow-up of intensive glucose control in type 2 diabetes. *N Engl J Med*. 2008;359:1577-1589.
  15. Gerstein HC et al. Basal insulin and cardiovascular and other outcomes in dysglycemia. *N Engl J Med*. 2012;367:319-328.
  16. Caballero AE. Long-term studies of treatments for type 2 diabetes. *Postgrad Med*. 2017;129:352-365.
  17. Peyrot M, Rubin RR, Kruger DF, Travis LB. Correlates of insulin injection omission. *Diabetes Care*. 2010;33:240-245.
  18. Russell-Jones D, Khan R. Insulin-associated weight gain in diabetes - causes, effects and coping strategies. *Diabetes Obes Metab*. 2007;9:799-812.
  19. Ketema EB, Kibret KT. Correlation of fasting and postprandial plasma glucose with HbA1c in assessing glycemic control: systematic review and meta-analysis. *Arch Public Health*. 2015;73:43.
  20. Mannucci E, Monami M, Lamanna C, Johan Adalsteinsson JE. Post-prandial glucose and diabetic complications: systematic review of observational studies. *Acta Diabetol*. 2012;49:307-314.
  21. Peter R, Okoseime OE, Rees A, Owens DR. Postprandial glucose - a potential therapeutic target to reduce cardiovascular mortality. *Curr Vasc Pharmacol*. 2009;7:68-74.
  22. Monnier L, Colette C, Dunseath GJ, Owens DR. The loss of postprandial glycemic control precedes stepwise deterioration of fasting with worsening diabetes. *Diabetes Care*. 2007;30:263-269.
  23. Hedrington MS, Pulliam L, Davis SN. Basal insulin treatment in type 2 diabetes. *Diabetes Technol Ther*. 2011;13((suppl 1)):S33-S42.
  24. De Block C, Manuel-y-Keenoy B, Van Gaal L. A review of current evidence with continuous glucose monitoring in patients with diabetes. *J Diabetes Sci Technol*. 2008;2:718-727.
  25. Vigersky R, Shrivastav M. Role of continuous glucose monitoring for type 2 in diabetes management and research. *J Diabetes Complications*. 2017;31:280-287.
  26. Juvenile Diabetes Research Foundation Continuous Glucose Monitoring Study Group, Tamborlane WV, Beck RW, et al. Continuous glucose monitoring and intensive treatment of type 1 diabetes. *N Engl J Med*. 2008;359:1464-1476.
  27. O'Connell MA, Donath S, O'Neal DN, et al. Glycaemic impact of patient-led use of sensor-guided pump therapy in type 1 diabetes: a randomised controlled trial. *Diabetologia*. 2009;52:1250-1257.
  28. Raccach D, Sulmont V, Reznik Y, et al. Incremental value of continuous glucose monitoring when starting pump therapy in patients with poorly controlled type 1 diabetes: the real trend study. *Diabetes Care*. 2009;32:2245-2250.
  29. Bergenstal RM, Tamborlane WV, Ahmann A, et al. Effectiveness of sensor-augmented insulin-pump therapy in type 1 diabetes. *N Engl J Med*. 2010;363:311-320.
  30. Owens DR, Luzio SD, Sert-Langeron C, Riddle MC. Effects of initiation and titration of a single pre-prandial dose of insulin glulisine while continuing titrated insulin glargine in type 2 diabetes: a 6-month 'proof-of-concept' study. *Diabetes Obes Metab*. 2011;13:1020-1027.
  31. Monnier L, Colette C, Rabasa-Lhoret R, Lapinski H, Caubel C, et al. Morning hyperglycemic excursions: a constant failure in the metabolic control of non-insulin-using patients with type 2 diabetes. *Diabetes Care*. 2002;25:737-741.
  32. Van Cauter E, Blackman JD, Roland D, Spire JP, Refetoff S, Polonsky KS. Modulation of glucose regulation and insulin secretion by circadian rhythmicity and sleep. *J Clin Invest*. 1991;88:934-942.

## SUPPORTING INFORMATION

Additional Supporting Information may be found online in the supporting information tab for this article.

**How to cite this article:** Ilany J, Bhandari H, Nabriski D, Toledano Y, Konvalina N, Cohen O. Effect of prandial treatment timing adjustment, based on continuous glucose monitoring, in patients with type 2 diabetes uncontrolled with once-daily basal insulin: A randomized, phase IV study. *Diabetes Obes Metab*. 2018;20:1186-1192. <https://doi.org/10.1111/dom.13214>