Initiation and Gradual Intensification of Premixed Insulin Lispro Therapy vs. Basal ± Mealtime Insulin in Patients with Type 2 Diabetes Eating Light Breakasts

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Abstract

Objective: Compared two strategies initiating, intensifying insulin treatment and tested for noninferiority of premixed insulin to basal ± mealtime insulin analogue in patients eating light breakfasts.

Research Design and Methods: This randomized, open-label, 48-week study compared 2 algorithms. Up to 3 injections of insulin lispro mix 25 and/or insulin lispro mix 50 (Premix: premixed insulin lispro) or basal insulin glargine plus up to 3 injections of insulin lispro (Basal+: glargine + insulin lispro) were used in T2DM patients uncontrolled with oral antihyperglycemic medication, consuming <15% daily calories at breakfast. The hypothesis was to test noninferiority of Premix to Basal+ for glycemic control measured by HbA1c after 48 weeks, assessed using ANCOVA with a 0.4% margin.

Results: Patients (n=344: 176 [51%] females, mean [standard deviation (SD)] age 54.3 [8.8] years, BMI 29.4 [4.6] kg/m², baseline HbA1c 9.02 [0.97] %) were randomized to Premix (n=171) or Basal+ (n=173). In the per-protocol analysis (n=230) LSmeans (95%CI) endpoint HbA1c were 7.40% (7.15%-7.65%) and 7.55% (7.27%-7.82%) in respective arms. Between-treatment difference was -0.14% (-0.42, 0.13); noninferiority met. Significantly more patients in Premix achieved HbA1c targets of <7.0% compared to Basal+ (48.2% vs. 36.2%; P=0.024). Self-monitored blood glucose profiles, body weight changes, total insulin doses, and overall hypoglycemia (65% vs. 60%) were similar in Premix and Basal+ (P=0.494) except nocturnal episodes (34.3% vs. 23.7%; P=0.018) were more common in Premix.

Conclusions: Both intensive insulin strategies improved glycemic control, however, final HbA1c levels were seen above those achieved in previous treat-to-target trials,
likely due to the inadequate insulin titrations and probably due to the complexity of tested insulin regimens. A higher percentage of patients achieved target HbA1c <7% with multiple premixed insulins but this treatment resulted in more nocturnal hypoglycemia than a basal-bolus regimen.

3 Keywords: light breakfasts, premix insulin lispro, glargine

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Eating light breakfast or even skipping it altogether is an increasingly common dietary habit among children and adults in the United States, Europe, Middle East Asia, the Persian Gulf, and Japan (1-5). It has been demonstrated in various ethnic groups that skipping breakfast may be associated with obesity (4-7), increased visceral fat, and increased prevalence of diabetes mellitus (5).

Limited data are available about the dietary habits in patients with type 2 diabetes mellitus initiating insulin treatment. Studies in patients with Type 1 diabetes report that eating practices are remarkably resistant to change, even in younger patients who initiate insulin therapy (8). Most people choose the same kinds of food because of their preferences and meal routines developed during childhood (9,10). Many patients with type 2 diabetes may therefore continue to consume light breakfasts or skip breakfasts which could have considerable metabolic consequences. In patients with diabetes skipping breakfast is associated with poorer metabolic control (11,12) and may increase the risk of hypoglycemia in the morning hours if conventional insulin therapy is applied. There is also evidence that patients who skip breakfast altogether increase food intake with other meals and snacks which may contribute to poorer glycemic control (13, 14), but consequences of eating light breakfasts in patients with diabetes are not well studied. The individual needs of these patients should be considered in treatment decisions leading to individualized therapy models to achieve glycemic targets safely.

So far, no studies have been reported that evaluate insulin treatment strategies in type 2 diabetes patients routinely consuming light breakfasts. We report the results of a noninferiority trial comparing two strategies of initiating and gradually intensifying insulin therapy in this group of patients: premixed insulin lispro (Premix arm) versus basal insulin glargine therapy ± mealtime insulin lispro (Basal+ arm).
Research Design and Methods

This was a multi country, multicenter, randomized, open-label, active-controlled, parallel 48-week trial. The study was conducted in accordance with the ethical principles that originated in the Declaration of Helsinki and consistent with Good Clinical Practices and applicable laws and regulations of participating countries. All patients gave written informed consent.

Patients

Patients with type 2 diabetes aged 30-74 years with HbA1c of ≥7% (≥53 mmol/mol) and <11.0% (<97 mmol/mol) who had BMIs of ≤40 kg/m$^2$ and were treated with metformin and at least one other oral antihyperglycemic medication (OAM; sulfonylureas and/or thiazolidinedione) for at least 3 months before the study were enrolled if they routinely consumed <15% of their daily caloric intake at breakfast (5-10 am) based on their routine practice (15), confirmed by 1-day dietary recall.

Exclusion criteria were treatment with other glucose-lowering medications or with pioglitazone at doses higher than approved for combination with insulin, having more than 1 episode of severe hypoglycemia within 6 months, use of systemic glucocorticoids, advanced cardiac disease, history of renal transplantation, liver disease, active malignancy, or conditions affecting reliability of HbA1c assessment. Patients were also excluded if during screening they had a self-monitored blood glucose (SMBG) reading ≤70 mg/dL (3.9 mmol/L) without a diet- or activity-related cause, or both a fasting glucose and a before dinner SMBG ≤130 mg/dL (7.2 mmol/L) for 3 nonconsecutive days.

Randomization and interventions
After a 2-week screening period patients were randomized (stratified by baseline HbA1c ≤8.5% [≤69 mmol/mol] and >8.5%[>69 mmol/mol]) to either premixed insulin lispro (Premix: 1, 2 or 3 injections of insulin lispro mix 25 (25% insulin lispro, 75% insulin lispro protamine suspension [ILPS] [LM25]) and/or insulin lispro mix 50 (50% insulin, 50% ILPS [LM50] in one arm or basal insulin glargine ± 1, 2 or 3 mealtime injections of insulin lispro (Basal+) in another arm in a 1:1 ratio, using an interactive voice response system. In both arms, patients continued their prestudy OAM regimens except for rosiglitazone (discontinued at Visit 1) and sulfonylurea (reduced or discontinued in the presence of hypoglycemia and stopped when the second injection of insulin was added). Dietary and lifestyle counseling and interventions were at the discretion of investigators.

After randomization, visits were scheduled at 2, 6, 10, 16, 20, 26, 32, 36, 42, and 48 weeks, and additional weekly contacts by telephone occurred between the visits for the first 12 weeks and then every second week to help patients adjust and optimize their insulin regimens.

Insulin dosing algorithm

Patients in both arms started treatment with a single insulin injection of 10 IU of glargine in the morning or at bedtime (Basal+ arm) or 10 IU of either LM50 before lunch or LM25 before dinner (Premix arm), depending on the higher 2-hour postprandial blood glucose (BG) measures. Insulin doses were titrated according to the dosing algorithm (Table 1). In the Premix arm treatment could start with LM25 dose before dinner despite higher postlunch BG levels if fasting BG levels were ≥144 mg/dL (8.0 mmol/L). If the target of HbA1c <7% (<53 mmol/mol) was not achieved
after 16 or 32 weeks and/or 2-hour postprandial BG target of <144 mg/dL (8.0 mmol/L) despite effective titration of existing doses, subsequent injections of insulin lispro or LM50/LM25 were added. In the Basal+ arm, the initial insulin lispro dose equal to approximately 10% of the daily dose of glargine was added before either lunch or dinner depending on higher 2-hour postprandial BG. In the Premix arm, the previous total insulin lispro LM50/LM25 dose was split equally into 2 doses. Half of the dose was administered as LM50 before lunch and half as LM25 before dinner. Additional injections of insulin lispro (in Basal+ arm) or LM25 (5 U in the Premix arm) before breakfast could be added as a last step in the intensification process. LM25 before breakfast was replaced with LM50 if prelunch BG was high (although maintaining small breakfast) despite normal/low predinner BG values or hypoglycemia due to the protracted action of insulin developed. No additional insulin doses were to be introduced within 4 weeks after the last dose adjustment or in the last 12 weeks before study end, even if previous insulin dose was still unstable.

Efficacy and safety measures

The primary objective was to test the hypothesis that the Premix treatment provides noninferior glycemic control compared to the Basal+ regimen based on the HbA1c at Week 48 (adjusted on baseline HbA1c, noninferiority margin of 0.4%). Secondary objectives included efficacy endpoints such as change in HbA1c; proportions of patients achieving HbA1c ≤6.5% (≤48 mmol/mol) and <7% (<53 mmol/mol); 7-point SMBG profiles; 1.5 anhydroglucitol levels reflecting postprandial blood glucose levels over the period of 1-2 weeks (16); insulin dose; body weight change; and proportions of caloric intake consumed at breakfast, lunch, and dinner.
Safety endpoints included treatment-emergent adverse events (TEAEs) and self-reported hypoglycemic episodes (all, nonnocturnal, and nocturnal) defined as signs or symptoms associated with hypoglycemia, or blood glucose level of ≤75 mg/dL (4.2 mmol/L) International Federation of Clinical Chemistry (IFCC) plasma values corresponding to ≤70 mg/dL (3.9 mmol/L) Roche plasma glucose irrespective of signs and symptoms (17). A severe hypoglycemic episode was defined as an episode requiring third-party assistance and associated with a blood glucose level of <55 mg/dL (3.0 mmol/L), IFCC plasma values corresponding to <50 mg/dL (2.8 mmol/L), Roche plasma glucose, or prompt recovery after oral carbohydrate, glucagon, or intravenous glucose. We report in this manuscript IFCC measures.

Health Outcome measures were assessed by the EuroQol instrument (EQ-5D) (18) and the Diabetes Treatment Satisfaction Questionnaire (DTSQs) (19).

Statistical analysis

The primary efficacy analysis was performed on the per protocol (PP) population, which is defined as those patients completing the study with no major protocol violations. A linear regression model was fitted that included treatment, country, baseline HbA1c (continuous), and a variable indicating whether Ramadan occurred between Visits 10 and 12 as independent variables. The CI for the difference of HbA1c between the 2 treatment arms (least square [LS] means of Premix arm – Basal+ arm) was based on a t distribution using the mean square error from the model. The noninferiority margin was defined as 0.4%. If the upper limit of the CI was below 0.4%, the Premix arm was concluded to be noninferior to the Basal+ arm.
Secondary efficacy analyses were performed on the full analysis set (FAS; all randomized patients with postbaseline HbA1c measurements). For handling incomplete data, mixed-model-repeated-measures (MMRM) for continuous and generalized linear mixed models for discrete variables were used. CIs and $P$ values at the visits were obtained from contrast analysis between treatment regimens. The continuous variables were analyzed using MMRM analysis similar to the one used for the HbA1c changes. Least square means for the 2 treatment regimens, differences, and the $P$ values for the difference were reported at visits from contrast analysis between the treatment regimens. For subgroup analysis the same MMRM model was calculated by subgroup.

Changes of body weight from baseline to 48 weeks were analyzed by MMRM, including treatment, country, and baseline weight as independent variables. Safety analyses were performed on the safety population (patients treated with at least 1 dose) including hypoglycemic episodes, TEAEs, and body weight. Unless otherwise specified, statistical analyses to compare treatments for continuous and discrete data were performed using similar random-effects models as for secondary efficacy variables.

Incidence of hypoglycemia was analyzed by logistic regression and the rate of hypoglycemia per patient/year by ANCOVA with baseline value, treatment, country, and Ramadan as explanatory factors.

EQ-5D scores were analyzed using MMRM. Patients’ satisfaction with their diabetes therapy was evaluated by the DTSQs and summarized at Week 48.
The planned overall sample size of 300 patients in the PP population had 80% power to confirm noninferiority at a 1-sided significance level of 2.5% with a noninferiority limit of 0.4% (Premix – Basal+), using the upper limit of a 2-sided 95% CI.

Results

The trial was conducted in 9 countries from April 2008 to November 2010. From 553 screened patients 344 patients were recruited (n, %) from Brazil (13, 3.8%), Canada (7, 2.0%), Egypt (64, 18.6%), India (58, 16.9%), Mexico (71, 20.6%), Portugal (15, 4.4%), Romania (50, 14.5%), Spain (40, 11.6%), and Turkey (26, 7.6%).

Patients were randomized to the Premix (n=171) or to the Basal+ (n=173) treatment arm (Figure 1: Patient flow, online appendix). Altogether, 342 treated patients were included in the safety set (Premix 169, Basal+ 173), 321 patients (Premix 158, Basal+ 163) in the FAS, and 230 patients (Premix 119, Basal+ 111) in the PP set. Overall, 74 patients (22%) discontinued the study (Premix 33 [19%], Basal+ 41 [24%]). No relevant differences in patient demographics and baseline characteristics were observed between treatment groups (Table 2).

Treatment Regimen

At the visit after initiation, the majority of patients (105, 66.5%) in Premix arm followed the LM25 injection before dinner scheme and 45 patients (28.5%) with the LM50 injection before lunch scheme. Eight patients (5%) could not be classified into one of the treatment arms. At study end, mean (standard deviation [SD]) number of insulin injections was 1.96 (0.829) and 1.99 (1.060) in the Premix and Basal+ arms,
respectively. The number of insulin injections is shown in online appendix Table 1. In the Premix arm all patients needed LM50 at lunch and LM25 at dinner, and fewer patients needed some insulin at breakfast (online appendix Table 2). Mean (SD) total daily insulin dose for the Premix and Basal+ arms at Week 48 was 0.56 [0.32] IU/kg and 0.57 [0.39] IU/kg, \( P=0.774 \). Basal insulin dose was 0.37 (0.21) IU/kg and 0.39 (0.21) IU/kg; \( P=0.235 \), and the rapid-acting insulin analogue dose was 0.20 (0.12) IU/kg and 0.18 (0.23) IU/kg; \( P=0.414 \), respectively. Treatment compliance as observed by the investigator throughout the study was Premix 82.3%, Basal+ 86.5%, \( P=0.580 \).

Glycemic Control

LS mean HbA1c at endpoint was 7.40% (95% CI: 7.15-7.65) in the Premix arm (n=119) and 7.55% (95% CI: 7.27-7.82) in the Basal+ arm (n=111); the between-treatment difference was -0.14% (95% CI: -0.42%, 0.13%), thus confirming the primary hypothesis of noninferiority of Premix versus Basal+. These results were confirmed in the FAS population. The mean (SD) HbA1c at baseline was 8.93% (0.94%) in the Premix arm and 9.08% (0.99%) in the Basal+ arm, and the values at endpoint were 7.27% (1.16%) in the Premix arm and 7.49% (1.18%) in the Basal+ arm (FAS with last observation carried forward). The baseline adjusted LSmean HbA1c at endpoint was 7.40% (95% CI: 7.20-7.60) in the Premix arm and 7.58% (95% CI: 7.38-7.78) in the Basal+ arm; the between-treatment difference was -0.18% (95% CI: -0.42, 0.07; \( P=0.155 \)). The LSmean (SEM) HbA1c change from baseline to Week 48 was not significantly different between both arms (Premix -1.65% [0.10%] and Basal+ -1.57% [0.10%] HbA1c; \( P=0.556 \); Figure 2, online appendix). The mean change within the groups was statistically significant different with \( P<0.001 \). Significantly more patients in the Premix arm achieved HbA1c targets of <7.0%
compared to the Basal+ arm (48.2% vs. 36.2%; Odds ratio = 1.87, \( P=0.024 \)), and 24.8% patients in the Premix arm achieved target HbA1c \( \leq 6.5\% \) compared to 18.5% patients in the Basal+ arm (Odds ratio = 1.59, \( P=0.138 \); Figure 1A). No difference was seen in HbA1c change from baseline between both treatment arms for patients’ with a baseline HbA1c level below or above 8.5%. Proportions of patients achieving HbA1c targets with different final treatment regimens are presented in Figure 1B. At Week 48, the mean (SD) daily blood glucose level from SMBG was Premix 7.26 mmol/L (1.34) and Basal+ 7.30 mmol/L (1.24); \( P=0.579 \). Mean (SD) 7-point SMBG values were presented in Figure 1C, with the only statistically significant difference between arms at post dinner SMBG readings \( P=0.001 \). Levels of 1.5 anhydroglucitol at 48 weeks were 11.4 \( \mu \)g/mL and 10.9 \( \mu \)g/mL in the PLMP and Basal+ arms, respectively \( P=0.104 \).

Body weight and caloric intake

Body weight increased by a mean (SD) 2.31 (3.3) kg in Premix and by 2.32 (3.7) kg in Basal+ \( P=0.819 \) at 48 weeks. The self-reported mean (SD) total daily caloric consumption at Week 48 was Premix: 1656 (426) kcal and Basal+: 1693 (411) kcal \( P=0.411 \). Breakfast constituted 15% and 13% of the total caloric intake, lunch 48% for both arms, and dinner 33% and 35% of the total for Premix and Basal+, respectively.

Health outcomes measures improved statistically significantly in both arms \( P<0.001 \). The mean baseline DTSQ score was 29 in both arms, and at 48 weeks the scores had increased by mean (SD) 5 (9) in the Premix arm and 5 (7) in the
Basal+ arm; the EQ-5D health state score increased from a mean (SD) baseline value of 73 (17) and 75 (15) by 8 (17) and 6 (15), respectively.

Hypoglycemia

Incidences and rates (episodes/patient/year) of all categories of hypoglycemia studied are shown in Table 3. Patients on glargine +3 injections of insulin lispro had the lowest chance to develop hypoglycemia over time (Figure 3, online appendix). Nocturnal hypoglycemia was reported more frequently in Premix arm. However, proportions of patients in the Premix arm reaching glycemic targets without nocturnal hypoglycemic events were not statistically different compared to the Basal+ arm (40 [29%] patients and 8 [6%] patients reaching HbA1c <7% and ≤6.5%, compared to 26 [20%] and 4 [3%] patients, respectively; P=0.104 and P=0.300). Three patients (2 in the Premix arm and 1 in the Basal+ arm) required hospitalization because of hypoglycemia, and 1 patient in the Premix arm had a hypoglycemic episode treated in the emergency room. No coma associated with hypoglycemia was reported.

Adverse events

A total of 32% of patients in each arm (54 in Premix, 55 in Basal+) reported at least 1 TEAE. Most TEAEs were unrelated to the insulin treatment. Seven (4.1%) and 3 (1.7%) patients in the Premix and Basal+ arms reported serious TEAEs occurring once. No deaths occurred.

Conclusions
This is the first trial to evaluate two strategies of initiating and advancing insulin treatment in patients with type 2 diabetes who have a habit of eating light breakfasts. Both strategies (premixed insulin analogue versus basal insulin with or without mealtime rapid-acting analogue) started with a single injection of insulin and advanced to a more complex regimen if HbA1c and/or postprandial BG targets were not met. The present study showed a significant improvement in glycemic control with both of the 2 strategies. Mean HbA1c decreased significantly in both arms, from 9% (75 mmol/mol) to 7.4% (57 mmol/mol) and 7.6% (60 mmol/mol) in the Premix and Basal+ arms, respectively. Significantly more patients from Premix arm achieved the glycemic target of <7.0% (<53 mmol/mol). In both arms, observed proportions of patients reaching treatment targets were highest among patients using 1 or 2 injections (Fig. 1B). We observed similar proportions of patients meeting the HbA1c target of <7.0% (<53 mmol/mol) with insulin glargine +1 injection of insulin lispro compared to patients with 2 or 3 injections of premixed insulin lispro. Notably, the observed proportions of patients reaching targets appeared to be lower among those who used the highest number of insulin lispro injections at endpoint, and these patients had the lowest chance to develop hypoglycemia over time. This could reflect the difficulty following a more complex treatment regimen, the reluctance to titrate insulin more aggressively or some other factors making successful treatment in this subgroup more difficult.

Incidence and rates of overall and daytime hypoglycemia were similar in both arms; however, the incidence of nocturnal hypoglycemia was higher with premixed insulin analogue treatment.

Treatment options for patients with type 2 diabetes who have a habit of eating light breakfasts and require insulin therapy have not been evaluated in clinical trials so far.
Therapeutic recommendations given to these patients have to be based on results of clinical studies conducted in general populations, which tend to exclude patients with atypical dietary habits. The proposed strategies of gradual intensification of insulin treatment begin with the simplest once-daily injection model and proceed to more complex multiple daily injections treatment if targets are not met.

Starting insulin therapy with a single injection of basal insulin is a common way of initiating insulin therapy in patients with type 2 diabetes, taking into consideration that complexity of the injection regimen and the numbers of injections are a major concern and barrier to insulin therapy (20). A recent European Association for the Study of Diabetes/American Diabetes Association position statement recommends this approach for most patients as the optimal and most convenient option (21). An alternative approach is to initiate insulin therapy with premixed insulin analogues (22). Recent meta-analyses (23-25) comparing basal-only and premixed insulin strategies as first line insulin therapy in type 2 diabetes have indicated that treatment with premixed insulin formulations once-daily results in a greater overall efficacy, but at the cost of increased hypoglycemia risk and weight gain.

There is no consensus on how therapy should be intensified in patients failing on either basal or premixed insulins (21). Targeting post-prandial hyperglycemia with mealtime insulins is a logical choice in these patients as high postmeal BG values significantly contribute to the overall glycemic burden (26). In patients on basal insulin only, addition of mealtime insulin before the main meal (basal plus) is considered the most logical step (21,27). Step-wise escalation of this treatment with additional mealtime insulin doses was applied if target glycemic control was not achieved with the basal-plus treatment regimen (28). In patients not achieving target glycemic control with 1 or 2 injections of premixed insulin, increasing the number of injections
could further improve the glycemic control (29). Premixed insulin analogue formulations with a higher proportion (e.g., 50%) of rapid-acting insulin seem to be particularly useful for the thrice-daily regimen in patients failing twice-daily premixed therapy (30) and in patients failing basal insulin (31).

Results of one head-to-head clinical trial indicated that both treatment strategies, progressive advancing therapy with premixed insulin lispro or basal plus mealtime insulin, significantly improved glycemic control with similar risk of overall and nocturnal hypoglycemia and similar weight gain (32). However, in contrast to our study, the noninferiority of the premixed insulin strategy to the basal glargine was not demonstrated. The findings from our study, using a step-wise insulin treatment intensification approach in patients with the habit of eating a light breakfast, indicated that patients were able to improve glycemic control comparable to results from other trials. Interestingly, studied patients did not modify their dietary habits and continued to consume light breakfasts.

In this trial, the prebreakfast injection of insulin was the last to be added. We found that at baseline, mean SMBG values after breakfast were actually not much different from the mean SMBG values after lunch and dinner. Whether application of the first injections of premixed insulin or mealtime insulin before any of the 3 main meals, including breakfast, might result in similar improvement of glycemic control remains to be established. As expected for gradual insulin dose escalation strategies, the main drawback of the therapy was hypoglycemia, which was reported by 65% and 60% of patients in the Premix and Basal+ arms, respectively. The incidence of hypoglycemia in our study was comparable to or lower than previously reported from studies evaluating 2 approaches to intensify basal insulin treatment with up to 3 injections of mealtime insulin (28,33,34), gradual intensification of premixed insulin
analogue treatment (29,30,32), or intensification of treatment to basal-bolus therapy (30,32) in patients with type 2 diabetes. Event rates were lower than those reported in the recent meta-analysis by Giugliano et al. (23). The only difference in terms of safety between the two arms was nocturnal hypoglycemia occurring in more patients in Premix arm. Incidence of all categories of hypoglycemia, however, was similar in the 2 arms.

Weight gain is typically associated with insulin therapy, and patients treated according to the algorithms defined in our study were no exception. Mean weight gain of 2.3 kg was observed after 48 weeks, which was higher in patients taking more injections of insulin per day than in patients using simpler treatment schemes. Body weight change seen in our study is comparable to the findings from Meneghini et al. (34) but either lower (23,28,32) or slightly greater (30,33) than in other trials. Final insulin doses exceeding 0.56 U/kg body weight per day are in line with those in other studies evaluating initial insulin therapy algorithms in type 2 diabetes. This dosage was delivered with a similar mean number of injections per day. Interestingly, final proportions of basal and mealtime insulin components were the same in both treatment arms, with approximately 2/3 of insulin delivered as basal and 1/3 delivered as mealtime insulin. This may explain why similar glycemic control was achieved in the 2 arms even though patients in the Basal+ arm received fewer injections of mealtime insulin than patients in the Premix arm.

There were several limitations to this study. Dietary habits were evaluated using a 24-hr recall, which is less objective than a dietary record. Patients could underreport caloric intake. The forced-titration insulin regimens evaluated in this study might not be suitable in some clinical practice settings as healthcare providers and patients may find frequent blood glucose monitoring, frequent dose escalation, and treatment
intensification too complex. Many patients in both study arms eventually used 2
different insulins, which added to the treatment complexity. All these factors might
affect the ability to adhere to the treatment algorithm, explaining why notable
proportions of patients continued treatment with simpler regimens (e.g., single
injection) despite glycemic targets’ not being met. Another limitation of this trial was
the use of fasting/preprandial blood glucose targets higher than those validated in
the treat-to-target trials. The use of these higher targets may have prevented
effective titration of basal insulin glargine and disadvantage the basal-bolus arm. This
could also increase the proportion of patients requiring additional injections of
mealtime insulin in this arm. The results of our study indicate that in patients with type
2 diabetes who have a habit of consuming light breakfast, starting insulin therapy with
either premixed insulin analogue or basal insulin administration and subsequently
advancing the treatment could be used to improve glycemic control. Noninferiority
was confirmed of Premix versus Basal+ in the change of HbA1c. Both intensive
insulin strategies improved glycemic control, however, final HbA1c levels were seen
above those achieved in previous treat-to-target trials, likely due to the inadequate
insulin titrations and probably due to the complexity of tested insulin regimens. The
percentage of patients at HbA1c target <7% (<53 mmol/mol) was higher in the premix
insulin analogue arm, while the incidence of nocturnal hypoglycemia was lower in the
basal arm. This warrants cautious use of premix treatment strategy in patients at high
risk for hypoglycemia. These findings may provide useful guidance to adapt
treatment to individual patient’s needs.

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Conflict of interest: Jacek Kiljański, Alina Jiletcovici, and Simone Wille are employees of Eli Lilly and Company. JK and AJ hold shares and stocks. Jürgen Deinhard is an employee of Accovion, who on behalf of Eli Lilly and Company ran the analyses and also holds stocks from Novo Nordisk. Mariusz Tracz serves as a consultant for Roche Diagnostics and has consultancies with Eli Lilly and Company, serves as a lecturer and speaker bureau for Roche Diagnostics and Sanofi Aventis, and keeps patents for Roche Diagnostics. Sanjiv Shah is in Advisory boards of Eli Lilly, Takeda and USV; Consultancies for Novo Nordisk and Sanofi India; Grants from Astra Zeneca and Eli Lilly and Company for conduct of study; serves as a lecturer for Eli Lilly and Company, Boehringer Ingelheim, and Novartis. Vincent Woo serves as a consultant, lecturer and speakers bureaus for Lilly, Novo Nordisk, Sanofi, Merck, BMS and Astra Zeneca. Rui Duarte served as a lecturer and speaker for Eli Lilly and Company. Dario Giugliano, Alfonso Calle-Pascual, Cristina Mistodie and Ramazan Sari did not report a conflict of interest.

Author contribution: S.S., A.C.-P., C.M., RD, R.S., and V.W. were involved in the acquisition of data. D.G., M.T., S.S. and J.K. contributed and reviewed critically Introduction, Results and Discussion. J.D. performed the statistical analysis and contributed to the Methods section. J.K. and S.W. drafted the manuscript: All authors were involved in the interpretation of data, critical revision and approval of the manuscript.

Guarantor's name: Jacek Kiljański, as the guarantor, is taking full responsibility for the contents of this article.
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Reference to prior publication of the study in abstract form, where applicable:

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### Tables

#### Table 1. Insulin Dosing Algorithm

<table>
<thead>
<tr>
<th>Fasting/predinner/prelunch BG mg/dL (mmol/L)</th>
<th>Dose change (IU)</th>
<th>Glargine Fasting BG mg/dL (mmol/L)</th>
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<td>&lt;55 (&lt;3.0)</td>
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</tr>
<tr>
<td>&gt;204 (&gt;11.3)†</td>
<td>+6</td>
<td>146-165 (8.1-9.1)</td>
</tr>
<tr>
<td></td>
<td>+8</td>
<td>≥166 (≥9.2)</td>
</tr>
</tbody>
</table>

*Dose adjustments were based on the average of the following SMBG values:

- Fastig BG to adjust doses of glargine and predinner LM25;
- Fasting, bed-time or other lowest BG (at investigator’s discretion) to adjust predinner LP dose;
- Predinner and prelunch BG values to adjust prelunch and prebreakfast doses of LP and LM25, LM50 respectively.

† Applicable to initial dose adjustment for LM25/LM50 in Premix arm.

LM = low mixture (insulin lispro mix 25: 25% insulin lispro and 75% insulin lispro protamine suspension [ILPS]);

LP = insulin lispro; LM = mid mixture (insulin lispro mix 50: 50% insulin lispro and 50% ILPS).
### Table 2: Patient Baseline Demographics (randomized patients)

<table>
<thead>
<tr>
<th></th>
<th>Premix (N=171)</th>
<th>Basal+ (N=173)</th>
<th>Overall (N=344)</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Mean (SD)</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Age, years</td>
<td>54.3 (8.9)</td>
<td>54.2 (8.6)</td>
<td>54.3 (8.8)</td>
</tr>
<tr>
<td>Median (range)</td>
<td>54.9 (31, 75)</td>
<td>54.3 (30, 74)</td>
<td>54.8 (30, 75)</td>
</tr>
<tr>
<td>&gt;65 years, n (%)</td>
<td>24 (14)</td>
<td>17 (10)</td>
<td>41 (12)</td>
</tr>
<tr>
<td><strong>Sex, n (%)</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Female</td>
<td>84 (49)</td>
<td>92 (53)</td>
<td>176 (51)</td>
</tr>
<tr>
<td>Male</td>
<td>87 (51)</td>
<td>81 (47)</td>
<td>168 (49)</td>
</tr>
<tr>
<td><strong>Race, n (%)</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Caucasian</td>
<td>101 (59)</td>
<td>97 (56)</td>
<td>198 (58)</td>
</tr>
<tr>
<td>African</td>
<td>1 (0.6)</td>
<td>2 (1)</td>
<td>3 (1)</td>
</tr>
<tr>
<td>Hispanic</td>
<td>40 (23)</td>
<td>44 (25)</td>
<td>84 (24)</td>
</tr>
<tr>
<td>Asian</td>
<td>29 (17)</td>
<td>30 (17)</td>
<td>59 (17)</td>
</tr>
<tr>
<td><strong>Weight, kg</strong></td>
<td>79.7 (15.6)</td>
<td>78.7 (16.8)</td>
<td>79.2 (16.2)</td>
</tr>
<tr>
<td><strong>BMI, kg/m²</strong></td>
<td>29.6 (4.7)</td>
<td>29.1 (4.5)</td>
<td>29.4 (4.6)</td>
</tr>
<tr>
<td>Median (range)</td>
<td>29.4 (20, 40)</td>
<td>28.9 (20, 40)</td>
<td>29.3 (20, 40)</td>
</tr>
<tr>
<td><strong>HbA₁c, %</strong></td>
<td>8.98 (0.95)</td>
<td>9.07 (0.99)</td>
<td>9.02 (0.97)</td>
</tr>
<tr>
<td><strong>HbA₁c, mmol/mol</strong></td>
<td>75</td>
<td>76</td>
<td>75</td>
</tr>
<tr>
<td>Median (range)</td>
<td>9.00 (7.0, 11.0)</td>
<td>9.20 (7.0, 11.0)</td>
<td>9.10 (7.0, 11.0)</td>
</tr>
<tr>
<td>Median (range), mmol/mol</td>
<td>75 (53, 97)</td>
<td>77 (53, 97)</td>
<td>76 (53, 97)</td>
</tr>
<tr>
<td>HbA₁c &gt;8.5% (&gt;69 mmol/mol), n (%)</td>
<td>109 (63.7)</td>
<td>111 (64.2)</td>
<td>220 (64.0)</td>
</tr>
<tr>
<td>GlycoMark test, µg/ml</td>
<td>5.7 (4.5)</td>
<td>6.3 (5.8)</td>
<td>6.0 (5.2)</td>
</tr>
<tr>
<td>FBG, mmol/L*</td>
<td>9.4 (2.2)</td>
<td>9.6 (2.2)</td>
<td>9.5 (2.2)</td>
</tr>
</tbody>
</table>
### Postprandial BG levels, mmol/L*

<table>
<thead>
<tr>
<th></th>
<th>After breakfast</th>
<th>After lunch</th>
<th>After dinner</th>
</tr>
</thead>
<tbody>
<tr>
<td>Postprandial BG levels, mmol/L*</td>
<td>12.0 (2.8)</td>
<td>12.6 (2.8)</td>
<td>12.3 (2.8)</td>
</tr>
<tr>
<td>After breakfast</td>
<td>11.9 (2.8)</td>
<td>12.2 (2.9)</td>
<td>12.0 (2.8)</td>
</tr>
<tr>
<td>After dinner</td>
<td>12.2 (2.7)</td>
<td>12.2 (3.2)</td>
<td>12.2 (2.9)</td>
</tr>
</tbody>
</table>

### Total caloric intake, kcal

<table>
<thead>
<tr>
<th></th>
<th>At breakfast</th>
<th>Proportion at breakfast, %</th>
<th>At lunch</th>
<th>At dinner</th>
</tr>
</thead>
<tbody>
<tr>
<td>Total caloric intake, kcal</td>
<td>1704 (456)</td>
<td>14 (16)</td>
<td>13 (13)</td>
<td>13 (15)</td>
</tr>
<tr>
<td>At breakfast</td>
<td>294 (254)</td>
<td>164 (94.8)</td>
<td>832 (331)</td>
<td>572 (281)</td>
</tr>
<tr>
<td>Proportion at breakfast, %</td>
<td>278 (199)</td>
<td>822 (318)</td>
<td>827 (324)</td>
<td>597 (255)</td>
</tr>
<tr>
<td>At dinner</td>
<td>286 (227)</td>
<td>321 (93.3)</td>
<td>585 (268)</td>
<td>585 (268)</td>
</tr>
</tbody>
</table>

### Concomitant OAM, n (%)

<table>
<thead>
<tr>
<th>OAM</th>
<th>At breakfast</th>
<th>Proportion at breakfast, %</th>
<th>At lunch</th>
<th>At dinner</th>
</tr>
</thead>
<tbody>
<tr>
<td>Metformin</td>
<td>167 (97.7)</td>
<td>171 (98.8)</td>
<td>338 (98.3)</td>
<td></td>
</tr>
<tr>
<td>Sulfonylurea</td>
<td>157 (91.8)</td>
<td>164 (94.8)</td>
<td>321 (93.3)</td>
<td></td>
</tr>
<tr>
<td>Thiazolidinedione</td>
<td>26 (15.2)</td>
<td>24 (13.9)</td>
<td>50 (14.5)</td>
<td></td>
</tr>
<tr>
<td>DPP-IV inhibitor**</td>
<td>1 (0.6)</td>
<td>4 (2.3)</td>
<td>5 (1.5)</td>
<td></td>
</tr>
</tbody>
</table>

### Daily dose of OAM, mg

<table>
<thead>
<tr>
<th>OAM</th>
<th>At breakfast</th>
<th>Proportion at breakfast, %</th>
<th>At lunch</th>
<th>At dinner</th>
</tr>
</thead>
<tbody>
<tr>
<td>Metformin</td>
<td>2011 (448)</td>
<td>1922 (437)</td>
<td>1966 (444)</td>
<td></td>
</tr>
<tr>
<td>Sulfonylurea (Gliclazide)</td>
<td>103 (42)</td>
<td>94 (43)</td>
<td>99 (42)</td>
<td></td>
</tr>
<tr>
<td>Sulfonylurea (Glimepiride)</td>
<td>4.8 (1.4)</td>
<td>4.6 (1.4)</td>
<td>4.7 (1.4)</td>
<td></td>
</tr>
<tr>
<td>Sulfonylurea (Glibenclamide)</td>
<td>13.1 (3.76)</td>
<td>13.2 (3.45)</td>
<td>13.1 (3.57)</td>
<td></td>
</tr>
<tr>
<td>Pioglitazone*</td>
<td>28.8 (7.25)</td>
<td>28.1 (7.49)</td>
<td>28.4 (7.33)</td>
<td></td>
</tr>
</tbody>
</table>

---

* from SMBG reading; ** protocol violation.

BG = blood glucose; Basal+ = basal plus insulin lispro; BMI = body mass index; FBG = fasting blood glucose; HbA1c = hemoglobin A1c; OAM = oral antihyperglycemic medication; Premix = Premixed insulin lispro (LM50/LM25); SD = standard deviation.
Table 3: **Hypoglycemia over the treatment period (safety set*)**

<table>
<thead>
<tr>
<th>Types</th>
<th>Incidence</th>
<th>Rate</th>
<th>Incidence</th>
<th>Rate</th>
<th>Incidence / Rate</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>n (%)</td>
<td>Mean (SD)</td>
<td>n (%)</td>
<td>Mean (SD)</td>
<td></td>
</tr>
<tr>
<td>All hypoglycemia</td>
<td>109 (64.5)</td>
<td>9.63 (19.31)</td>
<td>104 (60.1)</td>
<td>8.13 (13.45)</td>
<td>0.379 / 0.435</td>
</tr>
<tr>
<td>Nocturnal episodes</td>
<td>58 (34.3)</td>
<td>1.91 (5.20)</td>
<td>41 (23.7)</td>
<td>1.09 (3.25)</td>
<td>0.018 / 0.068</td>
</tr>
<tr>
<td>Nonnocturnal episodes</td>
<td>102 (60.4)</td>
<td>7.72 (16.36)</td>
<td>98 (56.6)</td>
<td>7.04 (12.12)</td>
<td>0.472 / 0.733</td>
</tr>
<tr>
<td>Severe episodes</td>
<td>4 (2.4)</td>
<td>0.09 (0.74)</td>
<td>6 (3.5)</td>
<td>0.12 (0.80)</td>
<td>- / 0.852</td>
</tr>
</tbody>
</table>

Incidence = number/percentage of patients with at least one event between baseline and study end; Rate = per episode/patient/1 year.

Basal+ = basal plus insulin lispro; Premix = premixed insulin lispro (LM50/LM25); SD = standard deviation.*all treated patients with at least 1 dose of study medication
Figure Legends

Figure 1A: Percent of Patients Reaching HbA1c Targets at Week 48 (FAS*)

Basal+ = basal plus insulin lispro; HbA1c = hemoglobin A1c; LP = insulin lispro;
Premix = premixed insulin lispro (LM50/LM25). *only patients attending Visit 48
Weeks were taken into account. **P values derive from the generalized mixed model.

Figure 1B: Proportion of patients reaching target HbA1c <7.0% and ≤6.5% by final
treatment regimen (FAS*)

Basal+ = basal plus insulin lispro; HbA1c = hemoglobin A1c; LP = insulin lispro;
Premix = premixed insulin lispro (LM50/LM25). *only patients attending Visit 48
Weeks were taken into account.

Figure 1C: Mean (SE) 7-point SMBG values at baseline and Week 48 (FAS**) 

* p = 0.0012 between treatment arms at postdinner BG (MMRM analysis).

Basal+ = basal plus insulin lispro; HbA1c = hemoglobin A1c; LP = insulin lispro;
Premix = premixed insulin lispro (LM50/LM25); SMBG = self-monitored blood
glucose. **only patients attending Visit 48 Weeks were taken into account.
**P** values derive from the generalized mixed model.
**Figure 1B**

- **HbA1c <7.0% (<53 mmol/mol):**
  - Premix (n=48)
  - Premix +1 (n=42)
  - Premix +2 (n=43)
  - Basal (n=59)
  - Basal+1 LP (n=27)
  - Basal+2 LP (n=30)
  - Basal+3 LP (n=14)

- **HbA1c ≤6.5% (≤48 mmol/mol):**
  - Premix (n=48)
  - Premix +1 (n=42)
  - Premix +2 (n=43)
  - Basal (n=59)
  - Basal+1 LP (n=27)
  - Basal+2 LP (n=30)
  - Basal+3 LP (n=14)
*P = 0.0012 between treatment arms at postdinner BG (MMRM analysis).
Online appendix

Figure and Tables:

Figure 1: Patient flow

Reasons for discontinuation (n=33, 19%):
- Protocol violation (n=8)
- Patient decision (n=6)
- Sponsor decision (n=6)
- Lost to follow-up (n=10)
- Adverse event (n=3)

Reasons for discontinuation (n=41, 24%):
- Protocol violation (n=10)
- Patient decision (n=7)
- Physician decision (n=8)
- Sponsor decision (n=8)
- Lost to follow-up (n=6)
- Adverse event (n=2)
Figure 2: HbA1c LSmean (SEM) change from baseline at 48 weeks (FAS without LOCF)

FAS = full analysis set, HbA1c = hemoglobin A1c, LOCF = last observation carried forward, LSmean = least square mean, SEM = standard error of the mean
Figure 3: Time to first hypoglycemia for final Premix treatments and final Basal+ treatments (safety set)
Table 1: Number of insulin injections at Week 48 (study end; FAS)

<table>
<thead>
<tr>
<th>No. of insulin injections per patient*</th>
<th>Premix (n=137)</th>
<th>Basal+ (n=130)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>n (%)</td>
<td>n (%)</td>
</tr>
<tr>
<td>1 injection</td>
<td>48 (35)</td>
<td>59 (45)</td>
</tr>
<tr>
<td>2 injections</td>
<td>42 (31)</td>
<td>27 (21)</td>
</tr>
<tr>
<td>3 injections</td>
<td>43 (31)</td>
<td>30 (23)</td>
</tr>
<tr>
<td>4 injections</td>
<td>0</td>
<td>14 (11)</td>
</tr>
</tbody>
</table>

*4 (3%) patients could not be classified.
<table>
<thead>
<tr>
<th>No of insulin injections</th>
<th>Before Breakfast</th>
<th>Before Lunch</th>
<th>Before Dinner</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Premixed insulin</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>analogue arm</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>1 injection (43/13.4%)</td>
<td></td>
<td></td>
<td>LM25</td>
</tr>
<tr>
<td>1 injection (18/5.6%)</td>
<td></td>
<td>LM50</td>
<td></td>
</tr>
<tr>
<td>2 injections (48/15%)</td>
<td></td>
<td>LM50</td>
<td>LM25</td>
</tr>
<tr>
<td>3 injections (36/11%)</td>
<td>LM25</td>
<td>LM50</td>
<td>LM25</td>
</tr>
<tr>
<td>3 injections (7/2%)</td>
<td>LM50</td>
<td>LM50</td>
<td>LM25</td>
</tr>
<tr>
<td><strong>Basal + insulin</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>lispro arm</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Glargine QD (80/25%)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Glargine+ 1Lispro (35/11%)*</td>
<td></td>
<td>X</td>
<td>X</td>
</tr>
<tr>
<td>Glargine+ 2Lispro (31/10%)*</td>
<td></td>
<td>X</td>
<td>X</td>
</tr>
<tr>
<td>Glargine+ 3Lispro (15/5%)*</td>
<td></td>
<td>X</td>
<td>X</td>
</tr>
</tbody>
</table>

* 8 (2.5%) patients could not be classified; **midday or evening.