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CLINICAL TRIAL

Impact of diet on the efficacy of insulin lispro mix 25 and insulin lispro mix 50 as starter insulin in East Asian patients with type 2 diabetes: Subgroup analysis of the Comparison Between Low Mixed Insulin and Mid Mixed Insulin as Starter Insulin For Patients with Type 2 Diabetes Mellitus (CLASSIFY Study) randomized trial

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ABSTRACT

Aims/Introduction: The pathophysiology of diabetes differs between Asian and Western patients in many ways, and diet is a primary contributor. The present study examined the effect of diet on the efficacy of 25% insulin lispro/75% insulin lispro protamine suspension (LM25) and 50% insulin lispro/50% insulin lispro protamine suspension (LM50) as starter insulin in Chinese and Japanese patients with type 2 diabetes and inadequate glycemic control with oral antidiabetic medication.

Materials and Methods: This was a predefined subgroup analysis of a phase 4, open-label, 26-week, parallel-arm, randomized (computer-generated random sequence) trial (21 January 2013 to 22 August 2014). Nutritional intake was assessed from food records kept by participants before study drug administration. Outcomes assessed were changes from baseline in self-monitored blood glucose, 1,5-anhydroglucitol and glycated hemoglobin.

Results: In total, 328 participants were randomized to receive twice-daily LM25 (n = 168) or LM50 (n = 160). Median daily nutritional intake (by weight and percentage of total energy) was 230.8 g of carbohydrate (54%), 56.5 g of fat (31%) and 66 g of protein (15%). Improvements in self-monitored blood glucose were significantly greater ($P \leq 0.028$) in the LM50 group than in the LM25 group, regardless of nutritional intake. When carbohydrate (by weight or percentage energy) or fat (by weight) intake exceeded median levels, LM50 was significantly more efficacious than LM25 ($P \leq 0.026$) in improving 1,5-anhydroglucitol and glycated hemoglobin.

Conclusions: Glycemic control improved in both LM25 and LM50 groups, but LM50 was significantly more efficacious under certain dietary conditions, particularly with increased carbohydrate intake.

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INTRODUCTION

Diabetes is one of the major causes of morbidity and early death in Asia. The prevalence of diabetes, especially type 2 diabetes mellitus, in China and Japan is amongst the highest in the world and is increasing dramatically[1–3]. More effective management and treatment of this debilitating and increasingly common disease is urgently required in Asia.

There are substantial differences in the pathophysiology of diabetes between Asian and Caucasian patients, many of which might be related to differences in diet. Greater insulin resistance and reduced β-cell function leading to impaired insulin secretion are characteristic of diabetes in Chinese and Japanese patients[4]. The increased intake of carbohydrates, which is characteristic of the traditional Asian diet, has also been implicated in playing a major role in the pathogenesis of diabetes[5]. Asians also have a substantially higher glycemic response to carbohydrate intake compared with Europeans, resulting in postprandial hyperglycemia[6]. Management of postprandial hyperglycemia is vital for slowing disease progression and vascular complications, and for preserving β-cell function[7]. Currently, treatments targeting postprandial hyperglycemia, such as acarbose and premixed insulins, are widely used in East Asia[8–11]. For example, in China, acarbose is positioned as a first-line, oral antihyperglycemic medication with metformin, and premixed insulins are recommended for use as starter insulin after the failure of oral antihyperglycemic medication[12].

For optimal efficacy, the choice of starter insulin should account not only for disease characteristics, but also for lifestyle factors, such as diet. Premixed insulins, such as 25% insulin lispro/75% insulin lispro protamine suspension (LM25; Humalog® Mix 25™; Eli Lilly and Company, Indianapolis, IN, USA) or 50% insulin lispro/50% insulin lispro protamine suspension (LM50; Humalog® Mix 50™; Eli Lilly and Company), are commonly used treatments in both China and Japan[8–10], where they are also used as starter insulin[13]. However, few studies have considered the impact of diet and nutrition on the efficacy of LM25 and LM50 in patients with type 2 diabetes mellitus, despite the general belief that insulin treatment should be adjusted according to nutritional intake and the fact that calculating insulin dose based on carbohydrate intake is a well-established practice for patients with type 1 diabetes mellitus[14,15]. Personalization of insulin treatment according to nutritional intake is of growing importance, because of the increased diversification of diets beyond what has traditionally been consumed in Asian countries[11]. Over the past two decades, the increased consumption of calories and fat in Asian countries has helped drive the rapid rise of diabetes in Asia[16].

The Comparison Between Low Mixed Insulin and Mid Mixed Insulin as Starter Insulin For Patients with Type 2 Diabetes Mellitus (CLASSIFY Study) randomized trial recently showed that after 26 weeks of treatment, more participants treated with LM50 achieved glycated hemoglobin (HbA1c) targets compared with LM25[17]. Furthermore, participants who had carbohydrate intake (as a percentage of total energy consumed) above median levels had a significantly greater decrease in HbA1c when treated with LM50 than when treated with LM25[17]. The aim of the current subgroup analysis of the CLASSIFY trial was to characterize the effect of diet on the efficacy of LM25 and LM50 in participants from China and Japan. Efficacy was assessed based on the changes in self-monitored blood glucose (SMBG) measurements and in the concentrations of 1,5-anhydroglucitol (1,5-AG) and HbA1c.

MATERIALS AND METHODS

Study design

The present study was a subgroup analysis of the CLASSIFY study (clinicaltrials.gov NCT 01773473), a phase 4, open-label, 26-week, parallel-arm, multinational, randomized trial comparing LM25 and LM50 primarily in East Asian participants[17]. Participants were assigned to treatment groups using a computer-generated random sequence and an interactive voice-response system. The CLASSIFY study was carried out between 21 January 2013 and 22 August 2014 at 38 sites in China, Japan, Korea, and Turkey, in accordance with the Declaration of Helsinki and the International Conference of Harmonisation – Good Clinical Practice. The study was approved by Ethical Review Boards at each participating site.

Study population

The main inclusion criteria for entry into the CLASSIFY study were as follows: diagnosis of type 2 diabetes mellitus for at least 6 months; currently taking oral antidiabetic medications; and HbaA1c levels ≥7.0% and ≤11.0% at screening. Participants in the CLASSIFY study were randomly assigned (1:1) to receive twice-daily subcutaneous LM25 or LM50 for 26 weeks. The dose was adjusted based on the blood glucose concentration of each participant[17]. Only participants from China and Japan were included in this predefined subgroup analysis, which included dietary evaluation.

Dietary intake

Participants in China and Japan were required to complete a 24-h food record for two separate, non-consecutive days during the week before week 0 (before study drug administration), and during the 2 week period before week 26 or at the early termination visit. Food records were compiled for the same meals for which SMBG measurements were recorded. Participants in China recorded dietary information about their meals by completing a questionnaire[11]. Participants in Japan kept written records and photographs of their meals (with a measurement scale for reference), including between-meal snacks, for nutritional evaluation. Food records and photographs (where used) were then transferred to a central external evaluator who calculated the nutritional value of each meal in terms of total energy (kilocalories), carbohydrates (grams), protein (grams), fat

(grams), and percentage of energy derived from carbohydrates, protein and fat.

Outcome measures

The efficacy outcomes assessed in this subgroup analysis were the changes from baseline to end-point (week 26) in the levels of SMBG, 1,5-AG and HbA1c. Participants carried out seven-point SMBG measurements on two separate, non-consecutive days during the week before week 0 (before study drug administration) and during the week before week 26 or at the early termination visit. The concentration of 1,5-AG was measured at weeks –2, 0, 12 and 26, or at the early termination visit. The concentration of HbA1c was measured at weeks –2, 0, 4, 8, 12 and 26 or at the early termination visit. To evaluate safety, the incidence of total, severe, and nocturnal hypoglycemic episodes and the change in bodyweight from baseline were recorded.

Statistical analysis

The effects of energy, carbohydrate, protein, and fat intake on the change from baseline in SMBG, 1,5-AG and HbA1c levels after treatment with either LM25 or LM50 were analyzed. Treatment differences were assessed by least squares mean change from baseline using a mixed-effects model with repeated measures for HbA1c and 1,5-AG, and an analysis of covariance model for SMBG. In the mixed-effects model with repeated measures analyses, the fixed effects were treatment (LM25 or LM50), country, baseline blood glucose excursion, visit and treatment-by-visit interaction. The random effect was the participant, and the covariates were baseline 1,5-AG or HbA1c values, depending on the analysis carried out. In the analysis of covariance model, the fixed effects were treatment (LM25 or LM50), country and baseline blood glucose excursion, and the covariate was baseline SMBG. All *P*-values were two-sided and were not adjusted for multiplicity. Analyses were carried out using SAS version 9.2 (SAS Institute, Cary, NC, USA).

RESULTS

Demographic and baseline clinical characteristics

A total of 403 participants were randomized in the CLASSIFY study; of these, 328 were Chinese or Japanese (LM25, $n = 168$; LM50, $n = 160$) and were included in this subgroup analysis (Figure 1). The number of participants from China and Japan within each treatment group and overall were approximately equal (Table 1). Demographic and baseline characteristics were similar between both treatment groups (Table 1). Almost two-thirds of the participants were men, with a mean age of 56.4 years. Participants had had diabetes for a mean duration of almost 9 years, with elevated HbA1c levels (≥8.4%), indicating inadequate glycemic control.

Dietary profile

Dietary intake was very similar between treatment groups (Table 1). Dietary intake by weight consisted mostly of carbohydrates (median 230.8 g/day), followed by protein (median 66.0 g/day) and fat (median 56.5 g/day). Approximately half of

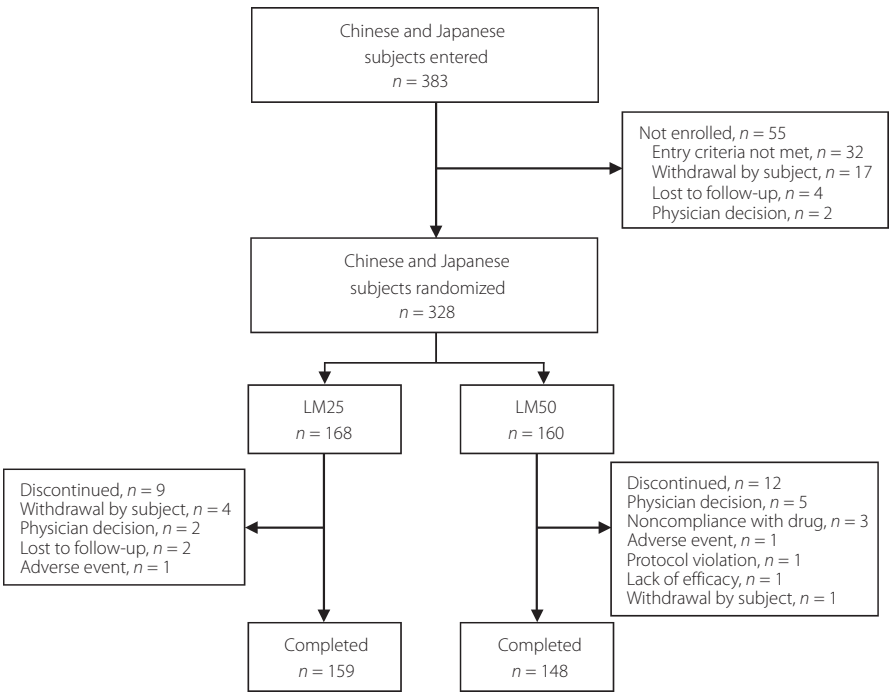

Figure 1 | Participant flow diagram. LM25, 25% insulin lispro/75% insulin lispro protamine suspension; LM50, 50% insulin lispro/50% insulin lispro protamine suspension.

Table 1 | Baseline and dietary characteristics

Variable	LM25 (n = 168)	LM50 (n = 160)	Total
Mean age, years (SD)	55.4 (10.16)	57.4 (9.82)	56.4 (10.03)
Female, *n* (%)	58 (34.5)	60 (37.5)	118 (36.0)
Mean height, cm (SD)	164.8 (9.32)	163.8 (8.59)	164.3 (8.97)
Mean weight, kg (SD)	69.8 (12.44)	68.9 (12.15)	69.4 (12.29)
Mean BMI, kg/m^2 (SD)	25.6 (3.20)	25.6 (3.53)	25.6 (3.36)
Mean HbA1c, % (SD)	8.55 (1.04)	8.41 (1.12)	8.48 (1.08)
Mean duration of T2DM, years (SD)	9.0 (5.49)	8.6 (5.97)	8.8 (5.72)
Country/region, *n* (%)			
China	80 (47.6)	76 (47.5)	156 (47.6)
Japan	88 (52.4)	84 (52.5)	172 (52.4)
Carbohydrate, g/day			
Mean (SD)	235.2 (59.6)	231.7 (67.1)	233.5 (63.3)
Median	236.0	229.3	230.8
Carbohydrate (% of total energy/day)			
Mean (SD)	54 (9)	53 (1)	54 (1)
Median	54	53	54
Fat (g/day)			
Mean (SD)	60.0 (24.3)	60.4 (22.5)	60.2 (23.4)
Median	55.5	58.5	56.5
Fat (% of total energy/day)			
Mean (SD)	30 (7)	31 (8)	31 (8)
Median	31	31	31
Protein (g/day)			
Mean (SD)	68.0 (24.4)	69.0 (23.3)	68.5 (23.9)
Median	66.0	65.75	66.0
Protein (% of total energy/day)			
Mean (SD)	16 (4)	16 (4)	16 (4)
Median	15	16	15
Energy (kcal/day)			
Mean (SD)	1752.3 (402.4)	1746.5 (417.8)	1749.5 (409.3)
Median	1711.3	1722.3	1714.5

BMI, body mass index; HbA1c, glycated hemoglobin; LM25, 25% insulin lispro/75% insulin lispro protamine suspension; LM50, 50% insulin lispro/50% insulin lispro protamine suspension; SD, standard deviation; T2DM, type 2 diabetes mellitus.

the energy intake was from carbohydrates (median 54%), followed by fat (median 31%) and protein (median 15%).

Efficacy

Compared with the LM25 group, the LM50 group showed greater improvement in all three glycemic markers (SMBG, 1,5-AG and HbA1c), regardless of dietary intake, although not all improvements between the two treatment groups were statistically significant.

Participants in both treatment groups achieved a reduction in SMBG, regardless of dietary intake (Figure 2, Table S1). The least squares mean change from baseline in SMBG at 26 weeks was significantly greater in the LM50 group than in the LM25 group, irrespective of carbohydrate, fat, protein or energy intake (Figure 2, Table S1). The largest between-treatment difference in SMBG reduction was observed in participants whose carbohydrate intake as a percentage of energy was greater than the median (54%). In terms of timing, SMBG was significantly lower in the LM50 group compared with the LM25 group after the morning and evening meals, and at bedtime (Table S4, Figure S1).

Participants in both treatment groups achieved an increase in 1,5-AG levels, regardless of dietary intake, but LM50 showed significantly greater efficacy under certain dietary conditions (Figure 3, Table S2). In participants consuming greater than median levels of carbohydrates (by weight and as a percentage of total energy), LM50 treatment was associated with significantly greater increases in 1,5-AG compared with LM25 treatment. This between-treatment difference was not observed in participants whose carbohydrate intake was below median levels. Greater efficacy of LM50 was also observed in participants whose dietary intake of fat (by weight) or energy was above median levels, but not in participants whose intake of fat or energy was below median levels. However, compared with LM25, LM50 was associated with significantly greater increases in 1,5-AG, regardless of whether fat intake as a percentage of total energy was above or below median levels. Similarly, compared with LM25, LM50 was associated with significantly greater increases in 1,5-AG, regardless of protein intake.

Participants in both treatment groups achieved a reduction in HbA1c levels, regardless of dietary intake, but LM50 showed significantly greater efficacy under certain dietary conditions (Figure 4, Table S3). In participants consuming greater than median levels of carbohydrates, fat or protein, LM50 treatment was associated with a significantly greater reduction in HbA1c compared with LM25 treatment. This between-treatment difference was not significant in participants whose intake of these macronutrients was below median levels. In contrast to SMBG and 1,5-AG, LM50 showed significantly greater efficacy than LM25 in reducing HbA1c for participants whose dietary intake of energy was lower than the median, but not for participants whose intake was higher than the median.

In terms of safety, the number of participants who experienced total and nocturnal episodes of hypoglycemia was similar between treatment groups (Table S5). No episodes of severe hypoglycemia were observed for any participant, regardless of treatment assigned (Table S5). Although there was an increase in the mean bodyweight of participants in both treatment groups, the least squares mean change in bodyweight was not significantly different between groups (Table S6).

DISCUSSION

To our knowledge, this is the first randomized clinical trial to examine the impact of the Asian diet on the efficacy of different premixed insulin regimens in East Asian patients with type 2 diabetes mellitus. In the present study, both LM25 and LM50 improved glycemic control in East Asian participants irrespective of dietary intake, as judged by improvements in SMBG, 1,5-AG and HbA1c levels. However, LM50 treatment resulted in

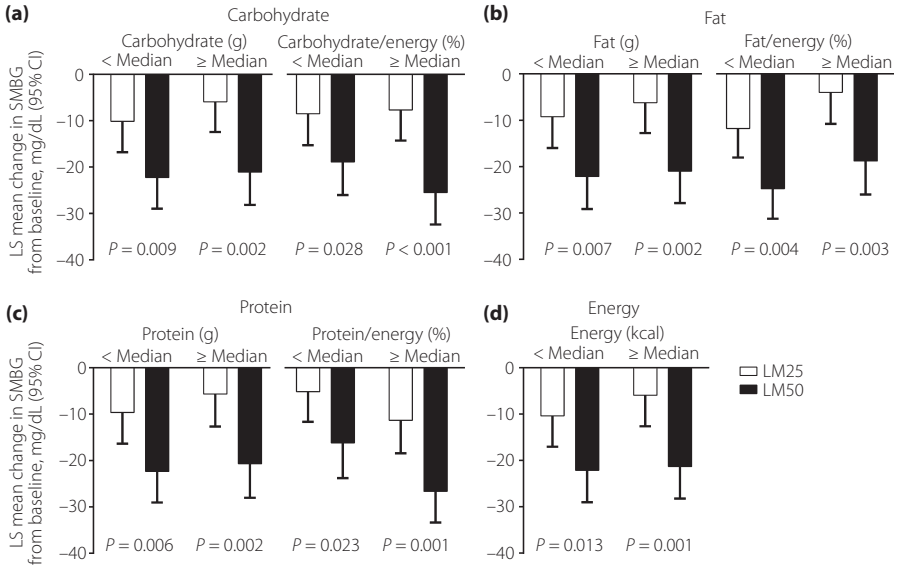

Figure 2 | Least squares mean change from baseline in self-monitored blood glucose (SMBG) levels in East Asian participants with type 2 diabetes mellitus treated with 25% insulin lispro/75% insulin lispro protamine suspension (LM25) or 50% insulin lispro/50% insulin lispro protamine suspension (LM50), stratified according to dietary intake of (a) carbohydrate, (b) fat, (c) protein and (d) energy. CI, confidence interval.

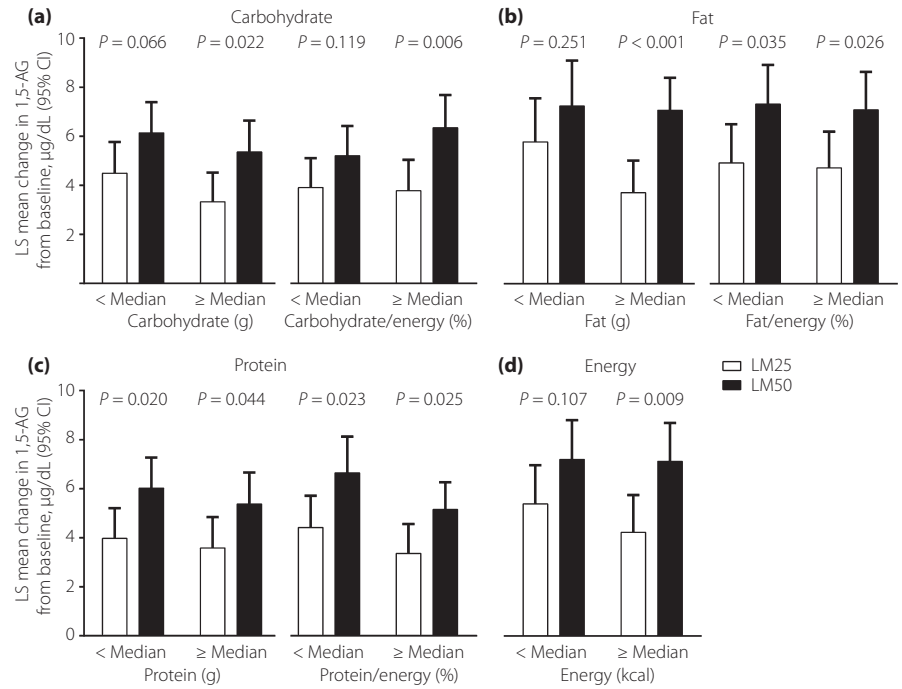

Figure 3 | Least squares (LS) mean change from baseline in 1,5-anhydroglucitol (1,5-AG) levels in East Asian participants with type 2 diabetes mellitus treated with 25% insulin lispro/75% insulin lispro protamine suspension (LM25) or 50% insulin lispro/50% insulin lispro protamine suspension (LM50), stratified according to dietary intake of carbohydrate, fat, protein, and energy. CI, confidence interval.

significantly greater improvements in a number of glycemic markers compared with LM25, particularly in participants who consumed greater than median levels of carbohydrates or fat. In order to ensure optimal glycemic control when using premixed insulins, LM50 might be preferable to LM25 in patients with high carbohydrate intake, as is common in East Asian patients.

Participants in the LM50 group were able to achieve significantly greater reductions in SMBG when compared with the

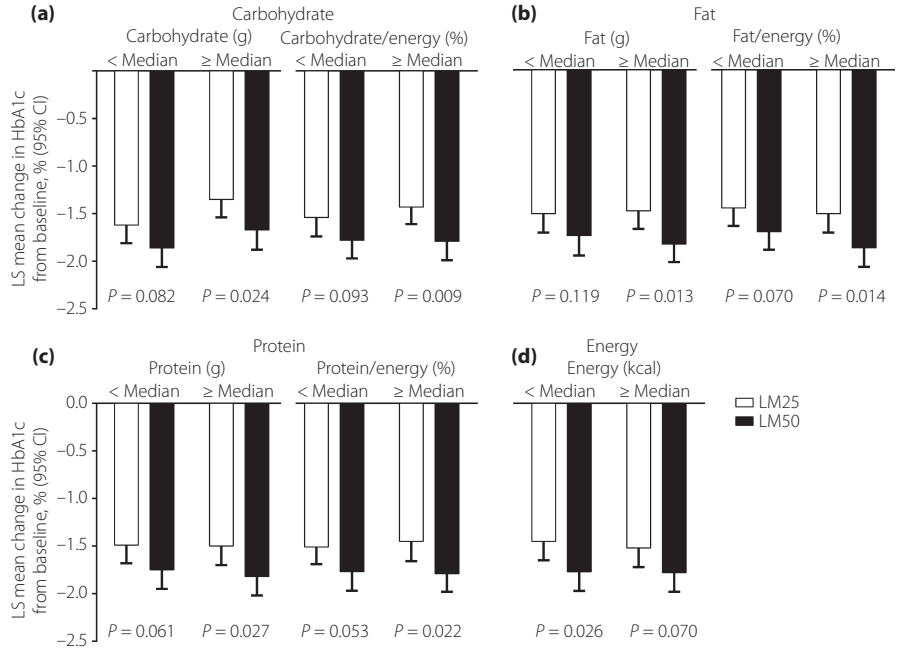

Figure 4 | Least squares (LS) mean change from baseline in glycated hemoglobin (HbA1c) levels in East Asian participants with type 2 diabetes mellitus treated with 25% insulin lispro/75% insulin lispro protamine suspension (LM25) or 50% insulin lispro/50% insulin lispro protamine suspension (LM50), stratified according to dietary intake of carbohydrate, fat, protein, and energy. CI, confidence interval.

LM25 group, regardless of nutritional intake. Asian patients with type 2 diabetes mellitus are known to have increased postprandial hyperglycemia, and excursions in postprandial glucose (PPG) contribute markedly to the cardiovascular complications in diabetes[18]. The importance of monitoring SMBG levels is underscored by the fact that SMBG provides information on daily fluctuations in PPG, which are not necessarily reflected by HbA1c levels[19]. Results from the CLASSIFY study[17] and the work of others[20] show that LM50 is significantly better at controlling PPG than LM25, particularly after the morning and evening meals; the same trend was also observed in our subgroup analysis. In addition to supporting the findings of these other studies, the results of our subgroup analysis also showed that LM50 was more efficacious than LM25 at reducing SMBG in East Asian participants regardless of diet.

In contrast to SMBG levels, only participants whose intake of carbohydrate, fat (by weight) or energy was greater than median levels showed significantly greater increases in 1,5-AG when treated with LM50 compared with LM25. The concentration of 1,5-AG has been proposed as a useful marker of short-term glycemic control and PPG[21], and is expected to be sensitive to dietary carbohydrate intake, hence changes in this parameter were monitored as an outcome in the present study. Our findings further support the idea that patients with higher than median levels of carbohydrate intake might be able to improve glycemic control using mid-mixture insulins, such as LM50. As higher carbohydrate consumption has been shown to increase PPG, especially in Asian patients[6], a premixed insulin that enables enhanced control of PPG is likely to be of greater benefit to this population.

Participants whose intake of carbohydrate, fat or protein was above median levels showed a significantly greater reduction in HbA1c levels when treated with LM50 than when treated with LM25. A previous subanalysis of the CLASSIFY study also reported that participants with carbohydrate intake above median levels experienced greater improvement in their HbA1c levels after treatment with LM50 compared with LM25[17]. Interestingly, LM50 was significantly more efficacious than LM25 at reducing HbA1c in participants whose energy intake was lower than the median, and not in participants whose intake was higher than the median, in contrast to SMBG and 1,5-AG. This inconsistency might be because baseline SMBG was measured on the same day that baseline dietary intake was recorded, whereas 1,5-AG and HbA1c were measured at a later time. Furthermore, as HbA1c likely reflects long-term glycemic control, baseline HbA1c levels are potentially less sensitive to dietary intake at baseline. In fact, the use of HbA1c for monitoring short-term glycemic changes and PPG has been shown to have limitations[22]. However, HbA1c is the current benchmark for the assessment of long-term glycemic control, and thus, current treatments are focused on management of HbA1c levels[19]. Similar to what was observed for SMBG and 1,5-AG, LM50 was significantly more efficacious than LM25 at reducing HbA1c in participants whose intake of carbohydrate, fat and protein (by weight) were above median levels. The effect of insulin on markers for both short-term (1,5-AG) and long-term (HbA1c)

glycemic control appears to be affected by the level of carbohydrate intake, suggesting that the amount of carbohydrate in a patient's diet is an important parameter for clinicians to consider when choosing an optimal insulin treatment. Carbohydrate intake has long been proposed to be the main factor affecting PPG and insulin requirement, given that carbohydrate is converted to blood glucose within 2 h after food intake[15]. Therefore, mid-mix insulins, such as LM50, which have higher proportions of rapid-acting, mealtime insulin, might be more beneficial to patients with increased carbohydrate intake.

Studies have shown that traditional Asian diets include a larger proportion of carbohydrates (55–70% total energy intake) and a smaller proportion of fat compared with typical Western diets[23]. The carbohydrate component of the diets of the participants in the present study (mean 54% daily energy intake) is consistent with a traditional Asian diet, and is well within the limits (<55–65% daily energy intake) recommended for patients with diabetes in China[24]. This is in contrast to the findings from a previous study, which suggested that most newly diagnosed (less than 3 months) patients with type 2 diabetes mellitus in China consumed a much larger proportion (67% of energy intake) of carbohydrates in their diet[11]. This difference might be because the participants in the present study, who had been living with diabetes for years, might have modified their nutritional intake in line with dietary recommendations (reduced carbohydrate intake) for patients with diabetes. The relative intake of carbohydrate and protein (mean 54% and 16%, respectively) by participants in the present study is very similar to the results from a recent survey of Japanese patients with diabetes (mean 53.6% and 15.7%, respectively)[25], suggesting the study findings are relevant to patients with diabetes in Japan.

Notably, the percentage of energy derived from fat by the participants in the present study (31%) is slightly higher than what is recommended for patients with diabetes in China (<30% daily energy intake), and much higher than what is recommended for patients with diabetes in Japan (<25%)[24,26]. This reflects the fact that diets in Asian countries are undergoing a rapid transition in nutrition, resulting in increased intake of total energy and fat[4,27]. Aside from the impact of a high-fat diet on increasing obesity and body mass index (risk factors for diabetes), a low-carbohydrate, high-fat diet has been shown to lead to postprandial hyperglycemia, as a result of decreases in carbohydrate oxidation and insulin sensitivity[28]. Ideally, treatments for diabetes in East Asians should maintain efficacy, even if consumption of energy and fat increase as patients consume a more Western-style diet. The finding that LM50 resulted in significantly improved 1,5-AG levels in participants with elevated intake of energy and fat (by weight) is of particular relevance to clinicians in Asia, who are likely to be treating growing numbers of such patients.

The strengths of the present study include its large study population, which was drawn from two of the top four countries with the largest number of patients with diabetes in East Asia[3]. Unlike many other studies where the participants' diets are controlled, participants in the present study were free to consume their normal diets. As such, the dietary and nutritional information gained from the present study is likely to reflect typical diets for patients with diabetes in China and Japan. The percentage of energy that participants derived from carbohydrate, protein and fat in their diet is also broadly similar to that reported in recently compiled surveys of nutrition in the overall population in both China[29] and Japan[30], further strengthening the relevance of the present study to clinical practice.

The results of the present study are limited by the fact that *P*-values were not adjusted for multiplicity (which might inflate type I errors), and by the open-label design of the trial. Another limitation was that the methodology used to evaluate the nutritional content of the diets of the participants in China was different to that used for the diets of the participants in Japan, although both methods were considered sufficiently accurate for the purposes of this subgroup analysis. Furthermore, the similarity of the relative nutritional values in the present study to those recorded for the overall population in both China[29] and Japan[30] suggests that the different methodologies used to evaluate nutritional content produced broadly similar estimates.

It should also be noted that given the size of the CLASSIFY trial and the multiple centers involved, it was not feasible to measure endogenous insulin secretion or levels of C-peptide in the participants. As such, we were not able to determine whether the observed superiority of LM50 over LM25 was related to the level of endogenous insulin being secreted. However, as the participants in the present study were no longer able to achieve adequate glycemic control using oral antidiabetic drugs, it is likely that most participants were at similar stages of disease progression, and were therefore likely to have had poor β-cell function and low levels of endogenous insulin. In clinical practice settings worldwide, β-cell function is not a quantitative parameter that is commonly used by physicians when selecting an appropriate insulin regimen for patients. Furthermore, the effect of any potential variations in the levels of endogenous insulin on the study would have been minimized by the randomization of participants and the large sample size. Conversely, it has been suggested that the choice of premixed insulins might affect endogenous insulin secretion; improved glucose control might lead to reduced glucose toxicity, which in turn might allow β-cell function and endogenous insulin secretion to recover[31].

Given the large and increasing number of patients with type 2 diabetes mellitus in Asia, particularly in China and Japan, there is a pressing need for more personalized treatment and management of the disease. In order to be maximally effective, treatments must be tailored to account for the differences in diet and disease pathophysiology in the East Asian population, which include higher carbohydrate consumption and higher glycemic responses to carbohydrates compared with Western populations[5,6]. The present study showed that although both

LM25 and LM50 were associated with improvement in markers of glycemic control, LM50 was significantly more efficacious under certain dietary conditions, particularly in patients with greater dietary intake of carbohydrates.

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DISCLOSURE

LQ and PFL are employees of Lilly Suzhou Pharmaceutical Co. Ltd. NI and MI are employees of Eli Lilly Japan K.K. MI owns stock in Eli Lilly and Company. HW serves as an advisory panel member for and/or has received lecture fees and/or research funds from Astellas Pharma Inc., AstraZeneca, Bayer, Boehringer Ingelheim, Bristol-Myers Squibb, Daiichi Sankyo Inc., Dainippon Sumitomo Pharma, Eli Lilly Japan, Fujifilm, Johnson & Johnson, Kissei Pharmaceutical Co., Kowa Co., Kyowa Hokko Kirin Co., Mitsubishi-Tanabe Pharma, Mochida Pharmaceutical Co., MSD, Novartis Pharmaceuticals, Novo Nordisk Pharma, Ono Pharmaceutical Co., Pfizer Inc., Sanofi, Sanwa Kagaku Kenkyusho Co., Taisho Toyama Pharmaceutical Co., Takeda Pharmaceutical Co., and Teijin Pharma. WYY has received research funding from AstraZeneca, and speaker fees from Eli Lilly, Sanofi and Novo Nordisk. WC declares no conflict of interest.

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SUPPORTING INFORMATION

Additional Supporting Information may be found in the online version of this article:

Figure S1 | Seven-point self-monitored blood glucose levels for participants with type 2 diabetes mellitus treated with 25% insulin lispro/75% insulin lispro protamine suspension or 50% insulin lispro/50% insulin lispro protamine suspension at baseline and at end-point.
Table S1 | Least squares mean change from baseline in self-monitored blood glucose levels.
Table S2 | Least squares mean change from baseline in 1,5-anhydroglucitol.
Table S3 | Least squares mean change from baseline in glycated hemoglobin.
Table S4 | Seven-point self-monitored blood glucose levels for participants treated with 25% insulin lispro/75% insulin lispro protamine suspension or 50% insulin lispro/50% insulin lispro protamine suspension.
Table S5 | Number of participants treated with 25% insulin lispro/75% insulin lispro protamine suspension or 50% insulin lispro/50% insulin lispro protamine suspension that experienced episodes of hypoglycemia.
Table S6 | Changes in bodyweight from baseline in participants treated with 25% insulin lispro/75% insulin lispro protamine suspension and 50% insulin lispro/50% insulin lispro protamine suspension.