ORIGINAL ARTICLE

doi: 10.1111/j.1463-1326.2009.01088.x

# Effects of insulin glulisine as mono- or add-on therapy in patients with type 2 diabetes mellitus

**R. Kawamori,[1] Y. Iwamoto,[2] T. Kadowaki,[3] M. Iwasaki,[4] S.-W. Kim,[5] J.-T. Woo,[6] S.-H. Baik[7] and K.-H. Yoon[8]**

[1]Department of Medicine, Metabolism and Endocrinology, School of Medicine, Juntendo University, Tokyo, Japan
[2]Diabetes Center, Tokyo Women's Medical University, Tokyo, Japan
[3]Department of Metabolic Diseases, Graduate School of Medicine, The University of Tokyo, Tokyo, Japan
[4]Department of Information Sciences, Seikei University, Japan
[5]Division of Endocrinology and Metabolism, Department of Internal Medicine, Kangbuk Samsung Hospital, Seoul, Korea
[6]Department of Endocrinology and Metabolism, Kyung Hee University Medical Center, Seoul, Korea
[7]Department of Endocrinology and Metabolism, Department of Internal Medicine, Korea University Guro Hospital, Seoul, Korea
[8]Department of Endocrinology and Metabolism, Kangnam Saint Mary's Hospital, Seoul, Korea

**Aim:** To evaluate the safety and efficacy of insulin glulisine (glulisine) with and without oral antidiabetic drugs (OAD; sulphonylurea or sulphonylurea + biguanide) relative to that of OAD alone in Japanese and Korean patients with inadequately controlled type 2 diabetes mellitus (T2DM).

**Methods:** In an open, randomized, parallel-group, comparative, controlled trial, 387 patients were randomized and treated with glulisine + OAD (n = 130), glulisine monotherapy (n = 127) or OAD only (n = 130) for 16 weeks. Glulisine was self-injected subcutaneously three times daily (0–15 minutes before meals) at a starting dose of ⩾0.2 U/kg/day. Patients titrated the glulisine dose to achieve a 2-h postprandial plasma glucose (2h-PPG) level of 7.1–9.5 mmol/l (128–172 mg/dl) by administering at least one additional unit at each appropriate meal time if the 2h-PPG level was >9.5 and <11.1 mmol/l (>172 and <200 mg/dl) and by administering at least two additional units if the 2h-PPG level was ⩾11.1 mmol/l (⩾200 mg/dl). Therapy with OAD was continued at the stable baseline regimen. The primary efficacy endpoint was change in haemoglobin $A_{1c}$ ($HbA_{1c}$) from baseline to endpoint in the intention-to-treat population.

**Results:** At baseline, therapy with OAD was a sulphonylurea only and a sulphonylurea + a biguanide in approximately 24 and 76% of patients respectively. Both glulisine groups had larger reductions in adjusted mean $HbA_{1c}$ than the OAD-only group (glulisine + OAD, −2.07%; glulisine monotherapy, −1.25%; OAD only, −0.61%). Superiority of glulisine + OAD and glulisine monotherapy vs. OAD only was shown by differences in adjusted mean $HbA_{1c}$ change from baseline values of −1.46% ($p < 0.0001$) and −0.64% ($p < 0.0001$) respectively. Both glulisine groups had better 2h-PPG control than the OAD-only group. Mean daily glulisine doses increased from baseline to endpoint (glulisine + OAD, 13.3–22.5 U; glulisine monotherapy, 14.2–38.0 U). The rate of all symptomatic hypoglycaemia events per patient-year in the entire treatment phase was 11.9 in the glulisine + OAD group, 8.8 in the glulisine monotherapy group and 1.7 in the OAD-only group. There was only one event of severe hypoglycaemia, which occurred in the glulisine + OAD group. Efficacy and safety were similar in Japanese and Korean subpopulations.

**Conclusions:** Both glulisine + OAD and glulisine monotherapy were well tolerated and effective for Japanese and Korean patients with T2DM mellitus inadequately controlled by OAD therapy alone.

Keywords: glycated haemoglobin $A_{1c}$, insulin glulisine, type 2 diabetes

**Received 4 March 2009; returned for revision 20 April 2009; revised version accepted 21 April 2009**

**Correspondence:**
Professor Ryuzo Kawamori, MD, PhD, Department of Medicine, Metabolism and Endocrinology, School of Medicine, Juntendo University, 2-1-1 Hongo, Bunkyo-ku, Tokyo, 113-8421, Japan.
**E-mail:**
kawamori@med.juntendo.ac.jp

## Introduction

The main objective of treating patients with diabetes mellitus is to safely normalize blood glucose levels in order to avoid the complications associated with chronic hyperglycaemia [1,2]. For patients with type 2 diabetes mellitus (T2DM), the current practice is to introduce one or more oral antidiabetic drugs (OADs) when diet and exercise fail to achieve good glycaemic control [3,4]. As T2DM is a progressive disease [5,6], most patients will ultimately require adjunctive insulin therapy [7,8].

Use of regular human insulin (RHI) has not been wholly effective in preventing postprandial hyperglycaemia, as its slow time to peak action requires administration 30–45 min before meals [9]. The rapid-acting insulin analogues were designed to overcome the limitations of RHI by providing a rapid onset of peak action and therefore tight glycaemic control, particularly at mealtimes.

Insulin glulisine (glulisine) is a new recombinant human insulin analogue in which asparagine at position B3 has been replaced by lysine, and lysine at position B29 has been replaced by glutamic acid. Glulisine can be administered 15 minutes before or immediately after a meal [10], because of its twofold faster onset of action than RHI [11–13]. Relative to RHI, glulisine has been associated with statistically significant improvements in glycaemic control and a comparable safety profile [14].

Compared with their Western counterparts, Japanese and Korean patients with T2DM tend to be non-obese, with relatively more insulin secretory defects and less insulin resistance [15–19]. Sulphonylureas are the most commonly used OAD in both Japanese and Korean patients. Insulin therapy is recommended for patients with T2DM inadequately controlled by OAD, although the optimal method of providing insulin replacement has yet to be determined in the Asian population. Therefore, the present study sought to compare the efficacy and safety of 16-weeks' administration of glulisine by bolus injection alone or concomitantly with OAD therapy vs. OAD therapy alone in Japanese and Korean patients with T2DM who had not achieved optimal glycaemic control on a sulphonylurea-based regimen.

## Methods

This randomized, open-label, parallel-group, multicentre clinical study was conducted in patients with inadequately controlled T2DM from 2003 to 2005 at 43 medical institutions in Japan and Korea. The study was approved by the appropriate institutional review boards and was undertaken in full compliance with the principles of the Declaration of Helsinki (and its amendments). Written informed consent was obtained from all patients before participation in the study, according to the guidelines at each institution.

Eligible patients were outpatients aged $\geqslant$20 and $\leqslant$75 years with T2DM diagnosed $\geqslant$1 year before study entry. Additional inclusion criteria included: body mass index (BMI) $<$30 kg/m$^2$; glycosylated haemoglobin A1c ($HbA_{1c}$) $\geqslant$8.0 and $\leqslant$11.0%; fasting serum C-peptide $\geqslant$0.7 ng/ml; and stable sulphonylurea-based regimen (glibenclamide $\geqslant$5 mg/day, glimepiride $\geqslant$3 mg/day or gliclazide $\geqslant$80 mg/day) with possible adjunctive biguanide therapy for $\geqslant$8 weeks before written informed consent. Exclusion criteria included: an inability or unwillingness to receive a starting dose of $\geqslant$0.2 U/kg/day of glulisine; previous treatment with another investigational product within 12 weeks (including glulisine); treatment with systemic corticosteroids within 4 weeks; a high likelihood of requiring concomitant treatment during the study period with drugs not permitted by the study protocol; clinically relevant cardiovascular, hepatic, neurological or endocrine diseases, active cancer, or other major systemic disease that could have created difficulties with implementation of the protocol or interpretation of the study results; pancreatectomy, pancreas/islet cell transplant or gastrectomy; diabetic retinopathy requiring surgical treatment (laser photocoagulation or vitrectomy) or proliferative diabetic retinopathy diagnosed within 12 weeks before written informed consent; a history of alcohol abuse; a history of serious allergy or hypersensitivity to insulin preparations; impaired hepatic or renal function; two or more episodes of severe hypoglycaemia or hospitalization for the treatment of hyperglycaemia within 24 weeks before written informed consent; and treatment with OAD such as thiazolidinediones, α-glucosidase inhibitors and D-phenylalanine derivatives. Women who were pregnant, breast-feeding or attempting to become pregnant during the study period were also ineligible.

### Treatment Regimens

The study consisted of a 4-week screening phase and a 16-week treatment phase (figure 1). Eligible patients were randomly assigned in a 1:1:1 ratio (minimization method) to glulisine plus OAD therapy (glulisine + OAD group), glulisine monotherapy or continued fixed-dose OAD therapy alone (OAD-only group; the active control group). Glulisine was self-injected subcutaneously three times daily (0–15 min before each meal) using the insulin injection device (OptiPen® Pro1, sanofi-aventis,

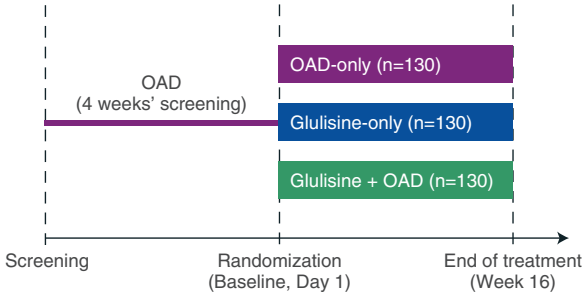


**Fig. 1** Study design.

Frankfurt, Germany). Glulisine could be injected into the abdomen, thigh region or upper arm, although the abdominal area was strongly encouraged as the preferred injection site. In the glulisine + OAD and glulisine monotherapy groups, the initial glulisine dose was ⩾0.2 U/kg/day, with subsequent doses adjusted on an individual basis according to a predefined titration algorithm based on blood glucose values, symptoms and laboratory findings. The titration goal was a 2-h postprandial plasma glucose (2h-PPG) level of 7.1–9.5 mmol/l (128–172 mg/dl), as measured by self-monitoring of blood glucose (SMBG), while avoiding hypoglycaemia. The glulisine dose was increased by ⩾1 unit at each mealtime if the 2h-PPG level was >9.5 and <11.1 mmol/l (>172 and <200 mg/dl) and was increased by ⩾2 units at each mealtime if the 2h-PPG level was ⩾11.1 mmol/l (⩾200 mg/dl). All SMBG values were measured using a plasma-referenced blood glucose meter. In the OAD-only group, patients were maintained on their stable dose and administration schedule unless hypoglycaemia or other safety concerns necessitated a dose reduction. All patients received adjunctive diet and exercise instruction at screening, which was to be continued without change throughout the study period.

### Analysis Populations

Patients, who provided written informed consent, met the inclusion criteria and were not subsequently found to meet any exclusion criteria, were included in the randomized intention-to-treat (ITT) population and safety population, regardless of the quantity of treatment received.

### Assessments and Outcome Definitions

The primary efficacy endpoint was change in $HbA_{1c}$ from baseline to study endpoint in the ITT population. The study endpoint was defined as the patient's last available value measured during the treatment phase. Secondary objectives were: changes in $HbA_{1c}$ every 4 weeks from baseline to week 16; consecutive changes in fasting morning plasma glucose (FPG) and 2h-PPG values from baseline to week 8, week 16 and endpoint; extent of blood glucose excursion (computed as the difference between 2h-PPG and the corresponding FPG values at baseline, week 8, week 16 and endpoint); and incidence of symptomatic hypoglycaemia. Plasma levels of $HbA_{1c}$ were measured using the Japanese Diabetes Society Lot 2 $HbA_{1c}$ standard at a central laboratory (SRL Medisearch Inc., Tokyo, Japan).

Safety was assessed by recording adverse events (including severe symptomatic hypoglycaemia), routine laboratory values (haematology and biochemistry), antibody levels, body weight, sedentary blood pressure, standard 12-lead electrocardiogram and funduscopic examination. Severe hypoglycaemia was defined as an event associated with either a blood glucose value 1.9 mmol/l (<35 mg/dl) or an event characterized by prompt recovery after oral carbohydrate, intravenous glucose or glucagon administration. In both cases, the patient must have required the assistance of another person.

Blood samples were taken for the measurement of insulin antibodies (human insulin-specific, glulisine-specific and cross-reactive antibodies) and *Escherichia coli* protein antibodies at baseline and at week 16 (or at study withdrawal). Quantitative analysis of plasma insulin antibodies was conducted by MDS Pharma Services (Fehraltorf, Switzerland) and *E. coli* protein antibody analysis was conducted by CEPHAC (Saint-Benoit Cedex, France).

### Statistical Analyses

All efficacy and safety variables were analysed using data from the ITT population. The ITT population was defined as all patients randomized and treated with at least one dose of the study medication during the treatment phase. The primary efficacy endpoint, change in $HbA_{1c}$ from baseline to endpoint, was conducted using an analysis of covariance (ANCOVA) model, with treatment and country as fixed effects and baseline $HbA_{1c}$ as the covariate.

The protocol planned for enrolment of 130 patients per treatment arm, assuming 86% of patients would be clinically evaluable, and that the differences in $HbA_{1c}$ change between the glulisine + OAD group and the OAD-only group would be 0.7%, and between the glulisine monotherapy group and the OAD-only group would be 0.5%. If these assumptions were met, then a one-sided,

 

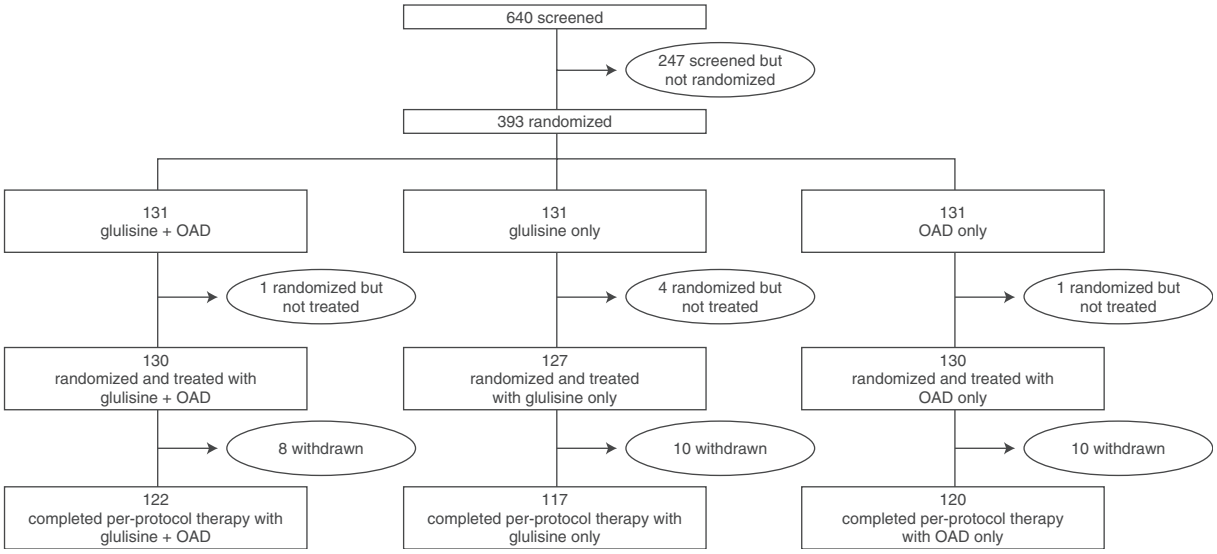


**Fig. 2** Flow of patients through the study.

0.025 α-level test for superiority would have ⩾90% power. If superiority was shown, the same statistical comparison between the glulisine monotherapy group and the OAD-only group was performed.

The ANCOVA model was also used to evaluate between-group efficacy by country. Statistical tests were two-sided and p-values less than 0.05 were considered to be statistically significant. It was anticipated that an equal number of patients would be randomized in Japan and Korea.

## Results

### Patient Disposition and Analysis Populations

Of 640 patients screened for study participation, 247 were not randomized to treatment, primarily because of $HbA_{1c}$ levels outside the specified range (figure 2). Six of the remaining 393 randomized patients were withdrawn before the start of treatment in accordance with their desire not to continue. Thus, 387 patients were randomized, received at least one dose of study medication, and were included in the ITT population. The three treatment groups shared similar baseline demographics and clinical characteristics (table 1). Slightly more than half of the study population were women (51–54% across the treatment groups). The means ± s.d. of the key characteristics in the ITT population were: age, 57.4 ± 9.6 years; BMI, 24.3 ± 2.9 kg/m$^2$; $HbA_{1c}$, 9.02 ± 0.86%; age at diagnosis, 47.3 ± 10.1; duration of previous OAD therapy, 5.73 ± 5.1 years. The proportion of patients with a BMI ⩾25 kg/m$^2$ was 39.5%. Three times as many patients were receiving OAD therapy with a sulphonylurea plus a biguanide than with a sulphonylurea alone (76 vs. 24%).

**Table 1** Baseline demographics and clinical characteristics

| Characteristic | Glulisine + OAD | Glulisine monotherapy | OAD only |
|---|---|---|---|
| ITT patients, n (%) | 130 (100.0) | 127 (100.0) | 130 (100.0) |
| Male, n (%) | 60 (46.2) | 62 (48.8) | 61 (46.9) |
| Mean age ± s.d., years | 57.9 ± 9.27 | 57.8 ± 8.73 | 56.4 ± 10.78 |
| Mean BMI ± s.d., kg/m$^2$ | 24.44 ± 2.73 | 24.14 ± 2.92 | 24.17 ± 3.02* |
| Mean $HbA_{1c}$ ± s.d., % | 8.99 ± 0.80 | 9.03 ± 0.94 | 9.04 ± 0.85 |
| Treatment with sulphonylurea, n (%) | 31 (23.8) | 30 (23.6) | 30 (23.1) |
| Treatment with sulphonylurea + biguanide, n (%) | 99 (76.2) | 97 (76.4) | 100 (76.9) |

BMI, body mass index; $HbA_{1c}$, glycosylated haemoglobin A1c; ITT, intention-to-treat; OAD, oral antidiabetic drugs; s.d., standard deviation. Percentages were calculated using the ITT population as the denominator.
*n = 129

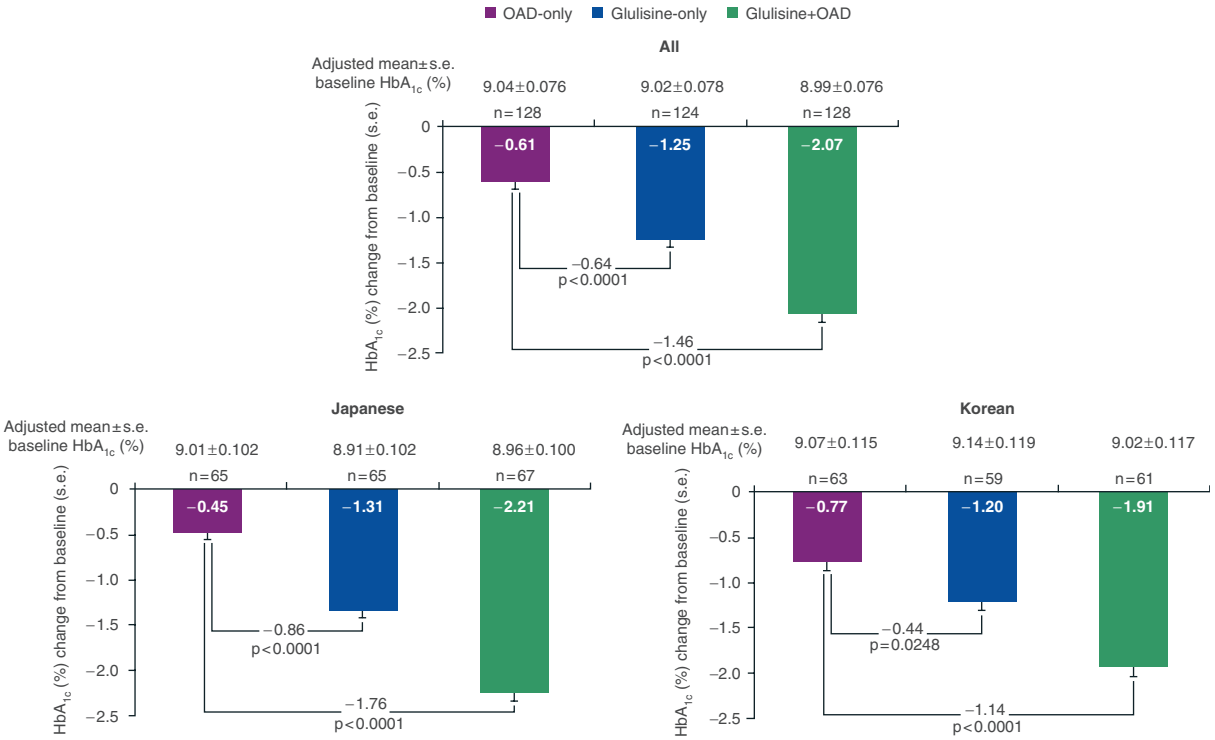


**Fig. 3** Change in $HbA_{1c}$ from baseline to study endpoint (intention-to-treat population). $HbA_{1c}$, glycosylated haemoglobin A1c; OAD; oral antidiabetic drugs; s.e., standard error.

At least one ongoing disease was reported in 348 of 387 patients (89.9%), the two most common being metabolic disorders and hypertension. Approximately 51% of patients in each group were enrolled in Japan. There were no discernible differences between Japanese and Korean patients regarding baseline demographics or clinical status.

The mean doses of glulisine were similar in the glulisine treatment groups at baseline (glulisine + OAD, 13.3 U; glulisine monotherapy, 14.2 U). Adherence to treatment was similar across study groups and the mean durations of the treatment phase were similar (glulisine groups, 107 days; OAD group, 110 days). At baseline, 96% of patients in the glulisine treatment groups were receiving three injections daily, 3% were receiving two injections daily and 1% was receiving one injection daily. By study endpoint, all glulisine monotherapy patients were receiving three injections daily compared with 98% of patients in the glulisine + OAD group (the remaining 2% of patients in this group received two injections daily). The total daily OAD dose was essentially unchanged in the OAD-only group and the glulisine + OAD group throughout the course of the study.

## Clinical Outcomes

### *$HbA_{1c}$ and Blood Glucose*

The adjusted mean reduction in $HbA_{1c}$ from baseline to endpoint was significantly lower in both glulisine groups than the OAD-only group (figure 3). The glulisine + OAD group was superior to the OAD-only group for this measure, with an adjusted mean change difference in $HbA_{1c}$ of −1.46% ($p < 0.0001$). Furthermore, glulisine monotherapy was found to be superior to OAD-only therapy, with an adjusted mean change difference in $HbA_{1c}$ of −0.64% ($p < 0.0001$). Similar trends were observed in subgroup analyses of Japanese or Korean patients (figure 3).

$HbA_{1c}$ values decreased steadily over the entire 16-week treatment period in the glulisine + OAD and glulisine monotherapy groups, but $HbA_{1c}$ decrements were only observed over the first 8 weeks in the OAD-only group (figure 4). The greatest decrease occurred in the glulisine + OAD group. There was a slight decrease in 2h-PPG levels in the OAD-only group during the first 8 weeks of treatment, which was maintained until week 16 and endpoint (figure 4). In contrast, in the two glulisine treatment groups, 2h-PPG levels decreased dramatically

 

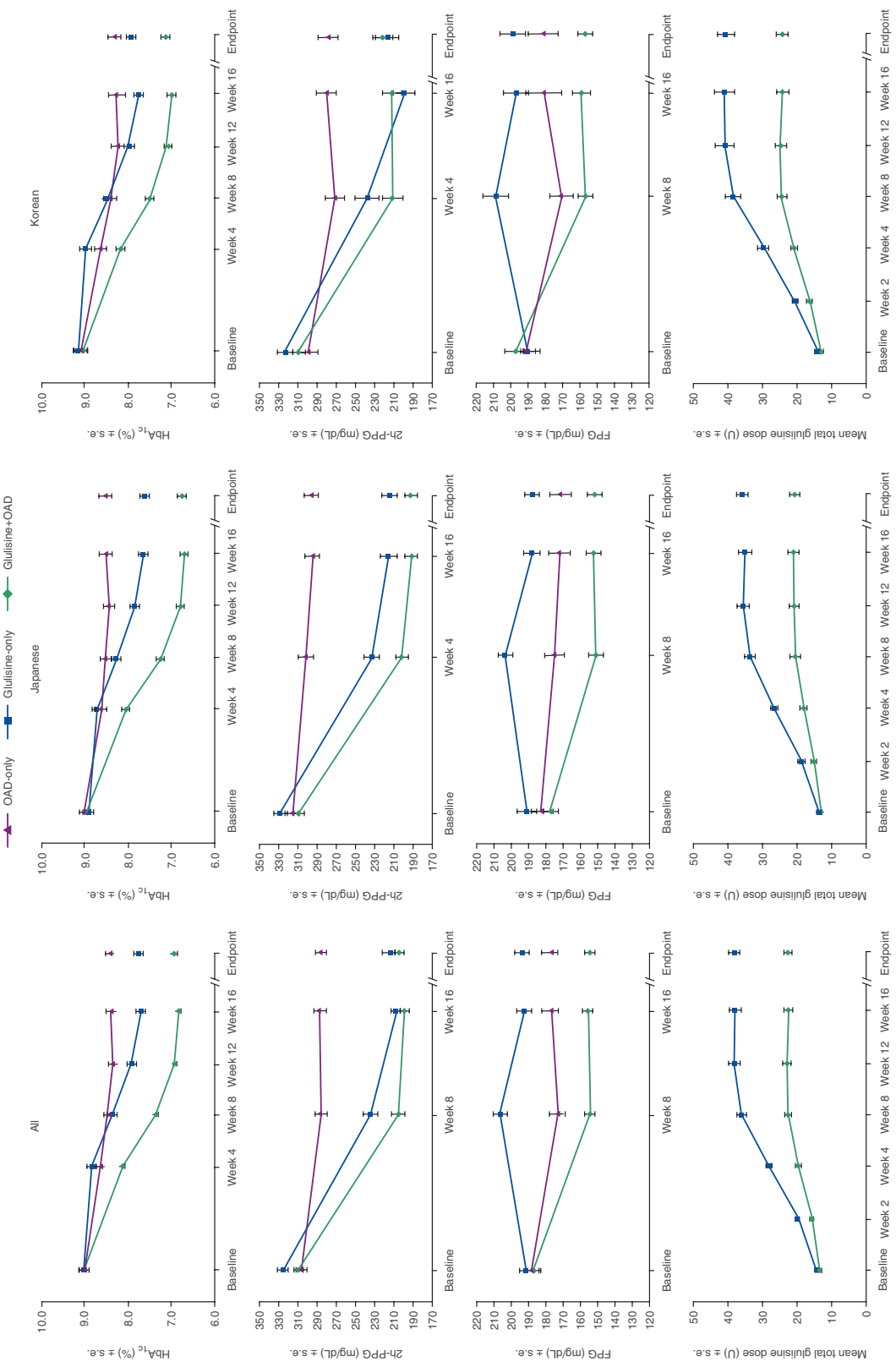


**Fig. 4** Mean ± s.e. $HbA_{1c}$ levels, FPG levels, 2h-PPG levels and total daily glulisine dose in ITT population. 2h-PPG, 2-hour postprandial plasma glucose; FPG, fasting morning plasma glucose; $HbA_{1c}$, glycosylated haemoglobin A1c, OAD, oral antidiabetic drugs, s.e., standard error.

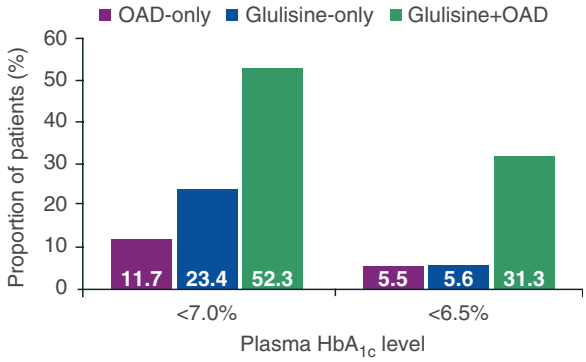


**Fig. 5** Proportion of patients achieving $HbA_{1c}$ levels of <7.0% and <6.5% at study endpoint (intention-to-treat population). $HbA_{1c}$, glycosylated haemoglobin A1c.

in the first 8 weeks of treatment and these low levels were still evident at week 16 and at endpoint. FPG levels decreased slightly in the OAD-only group and increased slightly in the glulisine monotherapy group over the 16-week treatment period (figure 4). In contrast, the glulisine + OAD group was associated with a large decrease in FPG levels from baseline to week 8, and this decrease was maintained through to week 16. Similar temporal trends in $HbA_{1c}$, 2h-PPG and FPG values were observed in the Japanese and Korean subgroups (figure 4). Both glulisine treatment groups had large decreases in mean plasma glucose excursions, which was not evident in the OAD-only group. Blood glucose excursions in the glulisine + OAD group and the glulisine monotherapy group at week 8, week 16 and endpoint were significantly lower than those in the OAD-only group ($p < 0.05$).

At endpoint, 52.3% of patients in the glulisine + OAD group and 23.4% of patients in the glulisine monotherapy group achieved a plasma $HbA_{1c}$ level of <7.0% compared with 11.7% of patients in the OAD-only group (figure 5). An $HbA_{1c}$ level of <6.5% was achieved by 31.3% of patients in the glulisine + OAD group and 5.6% of patients in the glulisine monotherapy group compared with 5.5% of patients in the OAD-only group (figure 5).

*Hypoglycaemia*

More patients in the glulisine + OAD group (64.6%) and glulisine monotherapy group (59.8%) reported at least one episode of symptomatic hypoglycaemia over the entire treatment phase than did patients in the OAD-only group (14.6%). The number of events per patient was also higher in the two glulisine treatment groups. The annual mean ± s.d. rate of all symptomatic hypoglycaemia was 11.9 ± 17.44 in the glulisine + OAD group, 8.8 ± 12.15 in the glulisine monotherapy group and 1.7 ± 10.16 in the OAD-only group. A similar trend was observed for episodes of nocturnal symptomatic hypoglycaemia. One case of severe symptomatic hypoglycaemia was reported in the glulisine + OAD group.

*Insulin dose*

The mean daily dose of glulisine in the two glulisine treatment groups increased from baseline to endpoint (glulisine + OAD, 13.3–22.5 U; glulisine monotherapy, 14.2–38.0 U). The glulisine dose in these groups increased steadily until about week 12 and then remained stable until the study endpoint (figure 4). The mean daily doses of glulisine in Japanese patients (glulisine + OAD, 13.1–20.8 U; glulisine monotherapy, 13.8–35.7 U) were lower than those in Korean patients (glulisine + OAD, 13.6–24.5 U; glulisine monotherapy, 14.5–40.5 U).

## Safety

The type and frequency of treatment-emergent adverse events (TEAEs) were similar across the three treatment groups. The proportion of patients with at least one TEAE was 61.5% (80 of 130 patients) in the glulisine + OAD group, 62.2% (79 of 127 patients) in the glulisine monotherapy group and 62.3% (81 of 130 patients) in the OAD-only group. Overall, 18 patients (7.0%) in the two glulisine treatment groups experienced TEAEs considered possibly related to glulisine, with no apparent difference in incidence between the two glulisine groups. Diabetic retinopathy was the only TEAE possibly related to glulisine use that affected more than one patient in either group. One patient in the glulisine + OAD group, two patients in the glulisine monotherapy group and no patients in the OAD-only group prematurely withdrew from the study because of TEAEs.

Serious TEAEs were reported by nine patients (6.9%) in the glulisine + OAD group, three patients (2.4%) in the glulisine monotherapy group and four patients (3.1%) in the OAD-only group (table 2). Only two patients (1.5%), both of whom received glulisine + OAD in the Korean study, were considered by the investigators to have experienced a serious TEAE that was possibly related to glulisine. One patient developed hypoglycaemic coma lasting 5 min and fully recovered after being treated with oral carbohydrates. No subsequent change in the dosage of antidiabetic therapy was recommended for this patient. The second patient died during a solo hiking trip 4 days after the start of glulisine treatment. As no autopsy

 

**Table 2** Incidence of serious TEAEs in the intention-to-treat population*

| System organ class | Number (%) of patients | | |
|---|---|---|---|
| | Glulisine + OAD (n = 130) | Glulisine monotherapy (n = 127) | OAD only (n = 130) |
| All serious TEAEs | 9 (6.9) | 3 (2.4) | 4 (3.1) |
| Serious TEAEs other than hypoglycaemia* | 8 (6.2) | 3 (2.4) | 4 (3.1) |
| Hypoglycaemia† | 1 (0.8) | 0 | 0 |
| Nervous system disorders | 3 (2.3) | 0 | 0 |
| Cardiac disorders | 2 (1.5) | 0 | 0 |
| Musculoskeletal and connective tissue disorders | 2 (1.5) | 0 | 0 |
| General disorders and administration site conditions | 1 (0.8) | 0 | 0 |
| Renal and urinary disorders | 1 (0.8) | 0 | 1 (0.8) |
| Gastrointestinal disorders | 0 | 1 (0.8) | 1 (0.8) |
| Injury, poisoning and procedural complications | 0 | 1 (0.8) | 0 |
| Metabolism and nutrition disorders | 0 | 0 | 1 (0.8) |
| Neoplasms: benign, malignant and unspecified | 0 | 1 (0.8) | 1 (0.8) |

OAD, oral antidiabetic drug; TEAE, treatment-emergent adverse event.
*A patient may have had more than one serious TEAE.
†Hypoglycaemia reported as serious TEAEs includes hypoglycaemic coma, hypoglycaemic seizure and hypoglycaemia.

was performed, hypoglycaemia could not be excluded as the cause and thus the death was classified as possibly related to glulisine. One other death occurred during the study in a Korean patient (OAD-only group), who died because of a hepatocellular carcinoma that was assessed as not related to study medication.

### *Body weight*

The change in body weight from baseline to endpoint was +1.91 kg in the glulisine + OAD group, +1.39 kg in the glulisine monotherapy group and −0.47 kg in the OAD-only group.

### *Antibodies*

Similar plasma levels of cross-reactive insulin antibodies, human insulin-specific antibodies and glulisine-specific antibodies were found in the three treatment groups at baseline. There were no relevant changes in any antibody level across all treatment groups. No correlation was found between plasma levels of cross-reactive antibody and changes in $HbA_{1c}$ levels or incidence of symptomatic hypoglycaemia. No patients had increased plasma levels of *E. coli* protein antibodies between baseline and week 16 or study endpoint.

## Discussion

Around-the-clock normoglycaemic control is increasingly becoming the benchmark of therapy in patients with T2DM. However, supplementing OAD therapy with treat-to-target basal insulin regimens fails to achieve $HbA_{1c}$ <7% in 40% of patients, possibly because of postprandial hyperglycaemia [20]. A large body of evidence has identified postprandial glucose excursions as a risk factor for raised $HbA_{1c}$ levels and cardiovascular mortality, underscoring the need for accurate and flexible mealtime (bolus) insulin therapies [21–24].

The purpose of this study was to compare the efficacy and safety of glulisine with and without OAD therapy against OAD therapy alone, in accordance with standard clinical practice in Japan and Korea. That is, when initiating insulin therapy in patients with T2DM, the Japan Diabetes Association Guidelines recommend either stopping therapy with OAD and then starting insulin the next morning or maintaining and/or reducing the sulphonylurea dose and adding insulin to the regimen [25]. Hence, the glulisine monotherapy arm allows evaluation of glulisine in the absence of any effects induced by OAD co-therapy. Although a long-term comparative study of glulisine would be desirable, the scheduled 16 weeks of treatment in this study was set as an optimal evaluable period from an ethical point of view, because patients in the OAD-only group remained on their baseline fixed-dose regimen despite inadequate glycaemic control.

To our knowledge, this is the first study of glulisine for the treatment of T2DM in an exclusive population of Asian patients. The glulisine + OAD group and glulisine monotherapy group were superior to the OAD-only group in the reduction of $HbA_{1c}$ from baseline to endpoint in the ITT population and also in the Japanese and Korean subpopulations. As a result, ~4.5-fold and twofold more patients in the

glulisine + OAD group and glulisine monotherapy group, respectively, reached the recommended $HbA_{1c}$ target (<7%) than did patients in the OAD-only group. For the secondary efficacy measures, both glulisine treatment groups afforded greater improvements in $HbA_{1c}$ at intermediate timepoints, blood glucose excursions and 2h-PPG relative to the OAD-only group. In addition, the glulisine + OAD group was associated with a large decrease in FPG from baseline to week 8, and this decrease was maintained through to study end, although the treated patients in this study were patients with T2DM not adequately controlled by OAD alone. Findings from a previous study showed that providing insulin glargine to patients with T2DM inadequately controlled by glimepiride reduces glucose toxicity and preserves β-cell function [26]. In contrast, the glulisine monotherapy group was associated with a modest mean increase in FPG to week 8 after which time FPG decreased to the baseline value over the week 8 to week 16 period. This observation may also be explained by recovery of basal insulin secretion and reduced glucose toxicity after week 8, although the FPG-lowering effect of glulisine + OAD was greater than that of glulisine monotherapy. Further studies will determine whether these effects are evident in patients receiving glulisine treatment.

Importantly, the benefit:risk ratios for the glulisine regimens were favourable, as tight blood glucose control was obtained without evidence of greater risk for severe hypoglycaemia: only one event of severe hypoglycaemia was reported (in the glulisine + OAD group) throughout the entire treatment period. Nevertheless, rates of all symptomatic and nocturnal symptomatic hypoglycaemia were higher in the glulisine groups than in the OAD-only group, highlighting the need to educate patients on managing this potential event. Safety analysis showed no notable or consistent differences between patients treated with glulisine and those treated with OAD-only therapy with respect to the incidence or type of adverse events.

In studies of Western patients, OAD therapy can be optimized further by use of adjunctive thiazolidinedione therapy before initiation of insulin. However, thiazolidinediones are not commonly recommended as first-line agents in Japan, and their use was an exclusion criterion in this study.

In conclusion, glulisine is an effective treatment for Japanese and Korean patients with T2DM not adequately controlled by OAD alone (sulphonylureas or sulphonylureas + biguanide). This rapidly acting insulin analogue was well tolerated and no specific safety concerns were raised during the study. Thus, glulisine provides further valuable treatment options as either monotherapy or in combination with OAD for patients with T2DM who have failed to respond adequately to OAD alone.

## Acknowledgements

This study was sponsored by sanofi-aventis K.K. Editorial support was provided by the publications support group of sanofi-aventis K.K.

## References

1 The Diabetes Control and Complications Trial Research Group. The effect of intensive treatment of diabetes on the development and progression on long-term complications in insulin-dependent diabetes mellitus. N Engl J Med 1993; **329**: 977–986.
2 UK Prospective Diabetes Study Group. Intensive blood-glucose control with sulphonylureas or insulin compared with conventional treatment and risk of complications in subjects with type 2 diabetes (UKPDS 33). Lancet 1998; **352**: 837–853 (Erratum in: Lancet 1999; **354:** 602).
3 Chehade JM, Mooradian AD. A rational approach to drug therapy of type 2 diabetes mellitus. Drugs 2000; **60**: 95–113.
4 Inzucchi SE. Oral antihyperglycemic therapy for type 2 diabetes: scientific review. JAMA 2002; **287**: 360–372.
5 Turner RC, Cull CA, Frighi V, Holman RR, for the UK Prospective Diabetes Study (UKPDS) Group. Glycemic control with diet, sulfonylurea, metformin, or insulin in patients with type 2 diabetes mellitus: progressive requirement for multiple therapies (UKPDS 49). JAMA 1999; **281**: 2005–2012.
6 Harris MI, Eastman RC, Cowie CC, Flegal KM, Eberhardt MS. Racial and ethnic differences in glycemic control of adults with type 2 diabetes. Diabetes Care 1999; **22**: 403–408.
7 Expert Committee on the Diagnosis and Classification of Diabetes Mellitus. Report of the Expert Committee on the Diagnosis and Classification of Diabetes Mellitus. Diabetes Care 1997; **20**: 1183–1197.
8 Yki-Jarvinen H. Role of insulin resistance in the pathogenesis of NIDDM. Diabetologia 1995; **38**: 1378–1388.
9 Heinemann L, Heise T, Jorgensen LN, Starke AA. Action profile of the rapid acting insulin analogue: human insulin B28Asp. Diabet Med 1993; **10**: 535–539.
10 Rave K, Klein O, Frick AD, Becker RH. Advantage of premeal-injected insulin glulisine compared with regular human insulin in subjects with type 1 diabetes. Diabetes Care 2006; **29**: 1812–1817.
11 Becker RH. Insulin glulisine complementing basal insulins: a review of structure and activity. Diabetes Technol Ther 2007; **9**: 109–121.

 

12 Becker RH, Frick AD. Clinical pharmacokinetics and pharmacodynamics of insulin glulisine. Clin Pharmacokinet 2008; **47**: 7–20.
13 Kapitza C, Becker R, Frick A, Heise T, Rave K. Pharmacodynamics and pharmacokinetics of insulin glulisine compared with insulin lispro and regular human insulin in patients with type 2 diabetes [abstract 733]. Diabetologia 2004; **47**(Suppl. 1): A265.
14 Dailey G, Rosenstock J, Moses, RG, Ways K. Insulin glulisine provides improved glycemic control in patients with type 2 diabetes. Diabetes Care 2004; **27**: 2363–2368.
15 Min HK. Non-insulin-dependent diabetes mellitus (NIDDM) in Korea. Diabet Med 1996; **13**(Suppl. 6): S13–S15.
16 Kim DJ, Song KE, Park JW, Cho HK, Lee KW, Huh KB. Clinical characteristics of Korean type 2 diabetic patients in 2005. Diabetes Res Clin Pract 2007; **77**(Suppl. 1): S252–257.
17 Seino Y. New concept of diabetes mellitus. Med Frontline 1995; **50**: 639–645.
18 Ishida T. Insulin resistance and liver. Nippon Rinsho 2000; **58**: 348–356.
19 Matsumoto K, Miyake S, Yano M *et al*. Glucose tolerance, insulin secretion, and insulin sensitivity in nonobese and obese Japanese subjects. Diabetes Care 1997; **20**: 1562–1568.
20 Riddle MC, Rosenstock J, Gerich J, for the 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.
21 Leiter LA, Ceriello A, Davidson JA *et al*. Postprandial glucose regulation: new data and new implications. Clin Ther 2005; **27**(Suppl. B): S42–S56.
22 Monnier L, Lapinski H, Colette C. Contributions of fasting and postprandial plasma glucose increments to the overall diurnal hyperglycemia of type 2 diabetic patients: variations with increasing levels of $HbA_{1c}$. Diabetes Care 2003; **26**: 881–885.
23 DECODE Study Group, on behalf of the European Diabetes Epidemiology Group. Glucose tolerance and cardiovascular mortality: comparison of fasting and 2-hour diagnostic criteria. Arch Intern Med 2001; **161**: 397–405.
24 Home P. Contributions of basal and post-prandial hyperglycaemia to micro- and macrovascular complications in people with type 2 diabetes. Curr Med Res Opin 2005; **21**: 989–998.
25 Araki E, Iwamoto Y, Kadowaki T *et al*. Treatment Guide for Diabetes. Japanese Diabetes Society, ed. Tokyo, Japan: Bunkodo Co., Ltd; 2008; [in Japanese].
26 Kawamori R, Eliaschewitz FG, Takayama H, Hayashida CY. Efficacy of insulin glargine and glimepiride in controlling blood glucose of ethnic Japanese patients with type 2 diabetes mellitus. Diabetes Res Clin Pract 2008; **79**: 97–102.

## Appendix

### The Investigators of the Study Group

The investigators of the study group were Kazuo Kase, Kenichi Yamada, Fuminobu Okuguchi, Hiroaki Seino, Koichi Kawai, Masayuki Noritake, Takeshi Osonoi, Jun Abe, Taro Maruyama, Nobuichi Kuribayashi, Toru Hiyoshi, Yasushi Tanaka, Yasuhiko Matsuura, Tatsuaki Kurata, Tetsuo Nishikawa, Tasuku Sawa, Kiyokazu Matoba, Mitsuro Niinomi, Shigeo Nakaishi, Tsutomu Kanda, Hideaki Jinnouchi, Hiroshi Kasahara, Yoshiko Funase, Michio Nakagawa, Yasuhisa Yamamoto, Toshiro Negoro, Teruhiko Matsushima, Shuichi Tohyo, Koichi Hirao, Sun Woo Kim, Kyong Soo Park, Bong Soo Cha, Chul Woo Ahn, Jeong Taek Woo, Kun Ho Yoon, Sei Hyun Baik, Moon Kyu Lee, Hyung Joon Yoo, Soon Jib Yoo, Kwan Woo Lee, Yong Seong Kim, Hong Sun Baek, Min Young Chung, Bo Wan Kim, Yong Ki Kim and Cheol Young Park.