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Insulin glulisine imparts effective glycaemic control in patients with Type 2 diabetes☆

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Abstract

Introduction: Insulin glulisine (glulisine) was evaluated versus regular human insulin (RHI) in Type 2 diabetes (T2DM) patients.
Methods: Patients previously on >6 months' continuous insulin treatment aged ≥18 years in a randomized, multinational, controlled, open-label, parallel group, 26-week study received twice-daily NPH insulin and either glulisine (0–15 min before breakfast and dinner; $n = 448$) or RHI (30–45 min before breakfast and dinner; $n = 442$) at least twice daily.
Results: Mean baseline characteristics were similar between groups. There were no differences in baseline to endpoint HbA_{1c} reductions (glulisine: −0.32%; RHI: −0.35%; $p = 0.5726$), and the non-inferiority of glulisine versus RHI was demonstrated (difference in adjusted mean change 0.03%; 95% CI: −0.07, 0.13). Postprandially, glulisine lowered plasma glucose significantly more versus RHI at 2 h (14.14 mmol/L versus 15.28 mmol/L; $p = 0.0025$) and excursions at 1 h (3.99 versus 4.59; $p = 0.0151$) and 2 h (4.87 versus 6.03; $p = 0.0002$). No between-group differences occurred in the frequencies and monthly rates of all symptomatic hypoglycaemia; nocturnal hypoglycaemia from Month 4 to treatment end was less frequent with glulisine versus RHI (9.1% versus 14.5%; $p = 0.029$).
Conclusion: Glulisine was non-inferior to RHI in reducing HbA_{1c} in T2DM. Glulisine demonstrated superior postprandial glucose control and was associated with fewer nocturnal hypoglycaemic episodes, indicating clinical benefits.

Keywords: Insulin glulisine; Type 2 diabetes (T2DM); Glycaemic

1. Introduction

Glycaemic control is the ultimate goal of therapy prescribed for patients with diabetes [1,2]. Oral hypoglycaemic agents (OHAs) are required by most patients with Type 2 diabetes (T2DM) to improve glycaemic control; however, these may not provide adequate long-term control due to the progressive nature of diabetes. Thus, the introduction of basal insulin is required to help control fasting hyperglycaemia; this can provide a simplified initiation for insulin therapy [3]. In addition, postprandial glycaemic excursions may be important therapy targets in patients who are close to glycaemic control, as they have been shown to make a significant contribution to glycated haemoglobin (HbA_{1c}) levels in T2DM

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patients whose overall hyperglycaemia is mild-to-moderate [4,5].

Insulin glulisine is a novel, rapid-acting insulin analogue, differing from human insulin by the replacement of the amino acid asparagine with lysine at position 3, and lysine with glutamic acid at position 29 of the B-chain ([LysB3, GluB29]-insulin). This analogue has a faster onset and shorter duration of action than regular human insulin (RHI), with a time–action profile that more closely resembles the physiological insulin response to a meal [6–11]. As a consequence, insulin glulisine may be administered immediately pre- or post-meal, providing patients with more treatment flexibility compared with RHI, which must be injected 30–45 min before meals [12–14].

The purpose of this study was to evaluate the efficacy and safety of insulin glulisine (with NPH insulin as basal therapy) in patients with T2DM who had received continuous insulin therapy for >6 months at baseline.

2. Materials and methods

2.1. Study design

This was a Phase 3, multinational ($n = 22$), multi-centre ($n = 90$), controlled, open-label, parallel group, 1:1 randomized study with a 4-week run-in (five visits) and a 26-week treatment phase (10 visits), beginning with Day 1, followed by weekly visits from Weeks 1 to 4, and thereafter at Weeks 6, 8, 12, 18 and 26 of treatment (Fig. 1). All patients received intensive training during the run-in phase to educate them on the necessity of achieving good glycaemic control, with information provided about the different time of action of insulin glulisine versus RHI. The follow-up period lasted for up to 24 h after the last injection of study medication, during which patients reported any symptomatic hypoglycaemia or adverse events (AEs).

The study was conducted in accordance with Good Clinical Practice and conformed to the ethical principles of the Declaration of Helsinki. All study materials were reviewed and approved by an Independent Ethics Committee or Institutional Review Board.

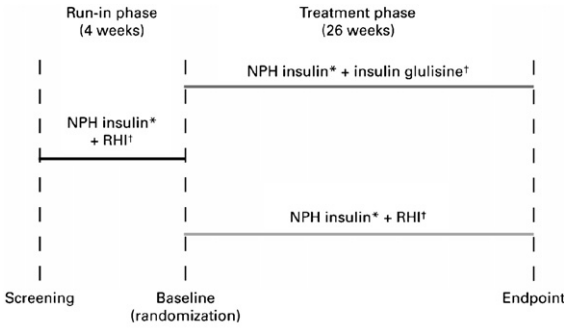

Fig. 1. Study design.

2.2. Patients

Inclusion criteria included: men or women aged ≥18 years with established T2DM (with no initial need for insulin therapy at diagnosis); >6 months of continuous insulin treatment (short-acting, rapid-acting and/or basal insulin) prior to study entry; HbA_{1c} levels 6.0–11.0%; the ability and willingness to perform blood glucose monitoring using the study meter, and to keep a patient diary. Exclusion criteria: active proliferative or unstable diabetic retinopathy; any diabetes other than T2DM; treatment with repaglinide, nateglinide, glitazones or any investigational drug in the 4 weeks prior to the baseline visit; a history of seizure disorders or hypersensitivity to insulin or its analogues; impaired renal/hepatic function or clinically relevant major systemic disease.

2.3. Study treatments

Insulin glulisine and RHI were titrated to achieve a 2 h postprandial (defined here as 2 h after the start of the meal) blood glucose target of 6.7–8.9 mmol/L (120–160 mg/dL), while avoiding hypoglycaemia. NPH insulin was titrated to achieve average preprandial blood glucose levels of 5.0–6.7 mmol/L (90–120 mg/dL). Dose-adjustment of the treatments was permitted during the study as required, to meet predefined glycaemic targets, while avoiding hypoglycaemia. Randomization was stratified according to whether or not patients were treated with OHAs at the time of randomization (Visit 6); patients were allowed to continue stable doses of OHA therapy (except repaglinide, nateglinide or glitazones) during the treatment phase to mimic clinical practice.

2.4. Study objectives

This study aimed to demonstrate the non-inferiority of insulin glulisine with RHI in terms of changes in HbA_{1c} levels from baseline to endpoint (Week 26 or patients' last available value during treatment), and the safety of insulin glulisine (in terms of AEs, clinical chemistry, lipids and haematology). Secondary objectives were to compare insulin glulisine with RHI, in terms of HbA_{1c} levels at Weeks 12 and 26, blood glucose parameters measured by self-monitoring and plasma glucose after a test meal, symptomatic hypoglycaemia and insulin doses.

2.5. Glycaemic control parameters

2.5.1. HbA_{1c} levels

HbA_{1c} levels in whole blood were analysed in a single central laboratory (Diabetes Diagnostic Laboratory, Columbia, MS, USA), which has been certified by the National Glycohemoglobin Standardization Program.

2.5.2. Self-monitored blood glucose profiles

During the run-in phase, patients were trained to measure and record their blood glucose profiles using the blood glucose meter provided by the sponsor (the Accucheck Sensor). Seven-point blood glucose profiles (before and 2 h after breakfast, lunch and dinner, and at bedtime) were measured on three different days during the 7 days preceding clinic visits at Day 1 (baseline), Week 12 and Week 26.

2.5.3. Standardized in-clinic test meal

The standardized in-clinic test meal was given to patients on Day 1 of the study treatment (baseline) and Week 26; patients fasted from the evening before the test meal was administered. Blood was collected for the measurement of fasting plasma glucose (FPG) before the test meal, which was followed by an injection of 0.15 U/kg of insulin glulisine or RHI along with the usual dose of basal NPH insulin. The test meal (400 mL ENSURE Plus® Drink, Abbott), comprising of carbohydrate (54%), protein (17%) and fat (30%), contained 600 kcal and was consumed within 15 min. Blood glucose measurements were taken before the meal and 1–2 h post-meal.

2.6. Hypoglycaemia

Symptomatic hypoglycaemia was defined as an event with clinical symptoms considered to have resulted from hypoglycaemia; a severe case was defined as an episode of symptomatic hypoglycaemia requiring assistance from another person and confirmed by blood glucose < 2.0 mmol/L ($<$36 mg/dL), or associated with a prompt recovery following oral carbohydrate, intravenous glucose or glucagon administration. Nocturnal hypoglycaemia was defined as symptomatic hypoglycaemia, which occurred while the patient was asleep, between bedtime and before rising in the morning. For the purpose of this study, all episodes of severe symptomatic hypoglycaemia were reported as possibly related serious treatment-emergent AEs (TEAEs).

2.7. Safety

2.7.1. Adverse events

The study investigator observed patients for local or systemic AEs and patients were instructed to report any such events over the study period. TEAEs included all AEs reported during the study except if they started and ended in the screening/run-in phase or began >1 day after the treatment phase (i.e. >1 day after the last dose of study medication and were not related to study medication, as assessed by the investigator).

2.7.2. Laboratory and clinical safety variables

Laboratory safety data were collected from blood samples from fasting patients. Serum/whole blood samples from patients were sent to the central coordinating laboratory (or to its regional partner laboratories), to determine lipid levels and to perform haematology and clinical chemistry tests. Vital signs including body weight, heart rate and systolic/diastolic blood pressure were monitored in each patient. Each patient underwent a full physical examination.

2.8. Statistical methods

The primary analysis assessed non-inferiority using the upper bound of the 95% confidence interval (CI) for the between-treatment difference in the adjusted mean HbA_{1c} baseline-to-endpoint change. Non-inferiority was demonstrated if the upper bound of the CI was $\leq$0.4%. If this occurred, a corresponding check of statistical superiority (i.e. that the upper bound of the CI $< 0.0\%$) was performed without a α penalty, since this was a closed procedure.

Statistical tests of non-inferiority and superiority related to the primary efficacy analysis of change in HbA_{1c} from baseline to study endpoint were one-sided and performed at a significance level of $\alpha = 2.5\%$; all other statistical tests, including secondary efficacy analyses, were two-sided and performed at a significance level of $\alpha = 5\%$. Continuous variables were analysed by an analysis of covariance (ANCOVA) with treatment and (pooled) centre as fixed effects and the baseline value as covariate. The baseline between-treatment comparisons were analysed by an analysis of variance (ANOVA) with treatment and (pooled) centre as fixed effects. Categorical variables were assessed by frequency distributions and between-treatment comparisons were conducted using the Cochran–Mantel–Haenszel test stratified by (pooled) centre. Statistical analyses were performed by the Biometrics Department of Covidence GmbH, Eschborn, Germany and Quintiles Inc., Kansas City, USA, using SAS™ version 6.12.

2.9. Sample size justification

A sample size of 676 patients (338 patients per group) was needed to ensure that the upper bound of the two-sided 95% CI for the adjusted mean difference between groups would not exceed HbA_{1c} 0.4% with 90% power and with an expected treatment difference of HbA_{1c} 0.1%. Taking into account a non-evaluable rate of 20%, a total of 846 patients were required to obtain a sample size of 676 patients evaluable for the primary analysis.

3. Results

3.1. Patients

Patient disposition throughout the trial is shown in Fig. 2.

3.2. Baseline characteristics

Baseline characteristics were similar between the two groups (Table 1); however, there was a significantly higher proportion of patients of Hispanic origin in the RHI

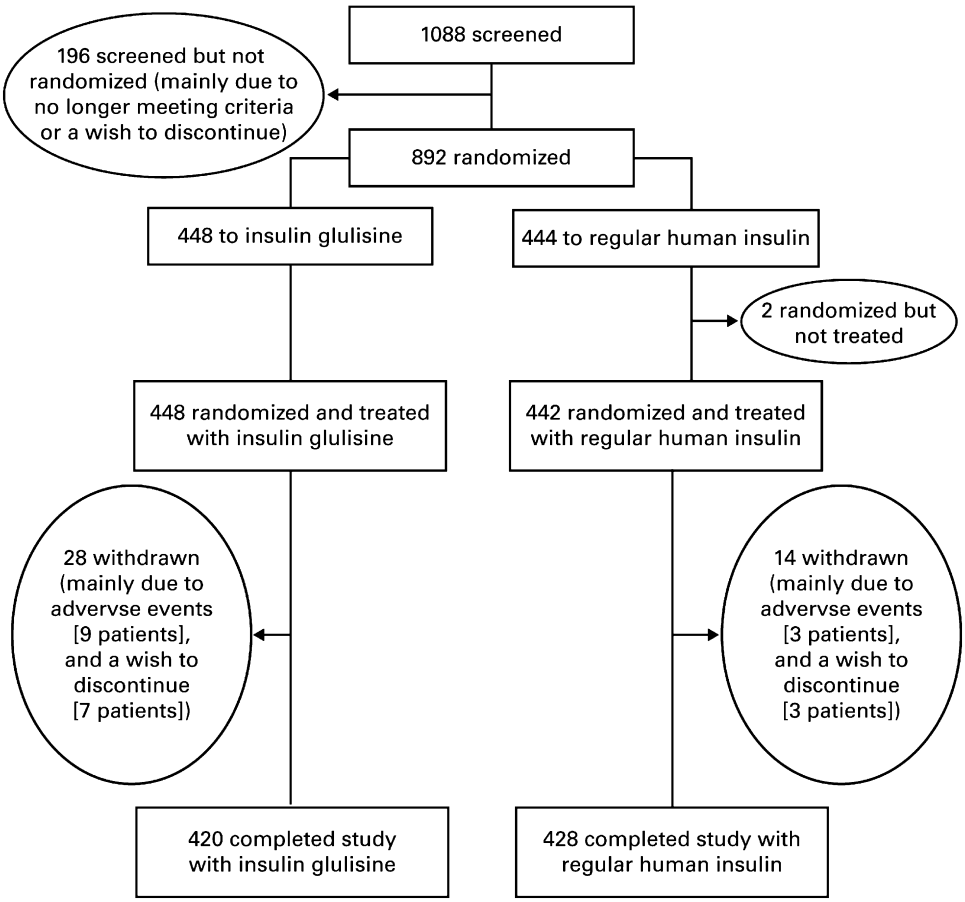

Fig. 2. Patient disposition throughout the trial.

versus insulin glulisine groups (10% versus 7.6%; $p = 0.016$).

3.3. HbA_{1c} change

There was no between-treatment difference in baseline-to-endpoint change in HbA_{1c} for insulin glulisine and RHI (Table 2). The adjusted mean change was −0.32% versus −0.35%, respectively (95% CI = −0.07, 0.13; $p = 0.5726$). The non-inferiority of insulin glulisine compared with RHI was demonstrated by the fact that the upper bound of the 95% CI was 0.13% (difference in adjusted mean change 0.03%; 95% CI: −0.07, 0.13). There was no difference between the two groups in terms of the proportion of patients achieving HbA_{1c} levels ≤7% (Table 2).

3.4. Insulin dose

At baseline, the two groups had similar daily short-acting, basal and total insulin doses. At endpoint, both groups had a similar increase in basal insulin dose, but there was a larger increase in the short-acting insulin dose with RHI (adjusted mean change: 4.47 U) than with insulin glulisine (adjusted mean change: 2.95 U; $p = 0.0645$; Fig. 3). Overall, the total daily insulin dose increased somewhat more with RHI (adjusted mean change: 9.36 U) versus insulin glulisine at endpoint, but the difference was not significant (adjusted mean change: 7.56 U; $p = 0.1727$).

3.5. Oral hypoglycaemic agents

At endpoint, 297 (33.4%) patients were still using OHAs (insulin glulisine versus RHI: 148 [33.0%] versus 149 [33.7%], respectively). While this study was not designed to formally evaluate the differences in the efficacy of insulin glulisine in combination with OHAs, the results of these exploratory analyses showed no difference between the two groups in the two OHA subgroups. As in the total population, the decrease in HbA_{1c} was similar in both groups regardless of whether

Table 1
Demographics and baseline characteristics of patients with Type 2 diabetes receiving insulin glulisine and regular human insulin (RHI; intention-to-treat population)

Variable	Insulin glulisine ($n = 448$)	RHI ($n = 442$)
Gender, *n* (%)		
Male	216 (48.2)	226 (51.1)
Female	232 (51.8)	216 (48.9)
Age (years)	59.8 ± 9.1	60.0 ± 9.6
BMI (kg/m^2)	31.5 ± 5.2	31.0 ± 4.9
Duration of diabetes (years)	13.6 ± 7.6	13.4 ± 7.3
Age at diagnosis of diabetes (years)	46.7 ± 9.7	47.1 ± 10.0
Duration of previous therapy (years)		
Insulin	5.7 ± 5.2	5.1 ± 4.9
OHAs	12.5 ± 7.2	12.3 ± 7.1
HbA_{1c} (%)	7.57 ± 0.91	7.51 ± 0.88
Prior insulin therapy at study entry, *n* (%)[a]		
Short-acting insulin[b]	321 (71.7)	309 (69.9)
Basal insulin[c]	268 (59.8)	277 (62.7)
Mixture insulin	51 (11.4)	59 (13.3)
OHA use at randomization, *n* (%)	151 (33.7)	148 (33.5)
Sulfonylurea[d]	26 (17.2)	28 (18.9)

Values are mean ± standard deviation unless otherwise indicated; RHI, regular human insulin; BMI, body mass index; OHA, oral hypoglycaemic agent.
[a] The numbers in columns are not additive because mixed insulins were counted within short-acting, basal and mixed categories; all randomized and treated patients had been treated with insulin prior to receiving the study medication and the majority had already received short-acting insulin (70.8%).
[b] The majority of patients injected their short-acting insulin three times per day prior to study entry.
[c] The majority of patients injected their basal and mixture insulins one to two times per day prior to study entry.
[d] Treatment groups were balanced for sulfonylurea use.

the patients were receiving OHAs or not (insulin glulisine: −0.3% versus −0.3%; RHI: −0.4% versus −0.3%), as was the incidence of patients reporting any symptomatic hypoglycaemia (insulin glulisine: 49.4% versus 51.0%; RHI: 52.1% versus 55.4%). Thus, the efficacy of insulin glulisine was maintained regardless of OHA use.

3.6. Self-monitored seven-point blood glucose profile

Patients measured their seven-point blood glucose profiles (before and 2 h after breakfast, lunch and dinner, and at bedtime) on 3 different days prior to clinic visits at baseline, and Weeks 12 and 26. At baseline, the self-monitored seven-point blood glucose (SMBG) profiles were similar in the groups, whilst at endpoint, blood glucose values were significantly lower 2 h post-breakfast with insulin glulisine versus RHI (adjusted mean: 8.85 mmol/L versus 9.47 mmol/L [159.3 mg/dL versus 170.5 mg/dL]; $p < 0.001$), and similar at all other time points.

3.7. Blood glucose excursions

Blood glucose excursions at breakfast, lunch and dinner were measured using the SMBG daily profiles of

Table 2
Mean (±standard deviation) HbA_{1c} levels in patients treated with insulin glulisine or regular human insulin (RHI) at baseline, Week 12 and endpoint (intention-to-treat population)

Time	HbA_{1c} levels (%)		*p*-Value for treatment effect
	Insulin glulisine ($n = 429$)	RHI ($n = 431$)	
Baseline	7.58 ± 0.90	7.50 ± 0.89	0.1665
Week 12	7.20 ± 0.84	7.15 ± 0.80	0.3573
Endpoint	7.25 ± 0.95	7.19 ± 0.90	0.5726
Patients with $HbA_{1c} \leq 7\%$ at endpoint	47.1	48.5	0.8962

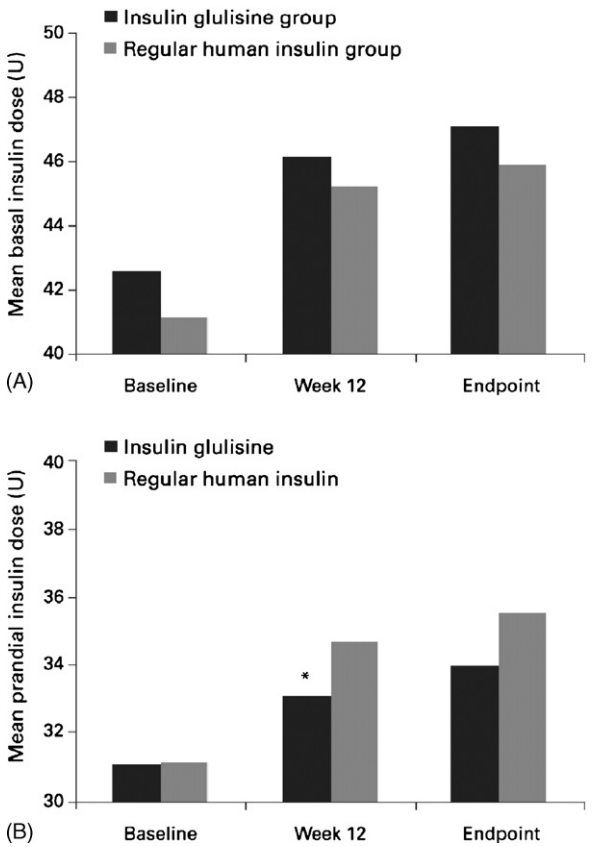

Fig. 3. Mean daily (A) basal and (B) prandial insulin doses of insulin glulisine and regular human insulin throughout the study. $^{*}p = 0.0209$ when comparing values between treatments ($p = 0.0645$ when comparing endpoint values between treatments). Insulin glulisine patient numbers: baseline, 445; Week 12, 415; endpoint, 445; regular human insulin patient numbers: baseline, 438; Week 12, 415; endpoint, 438.

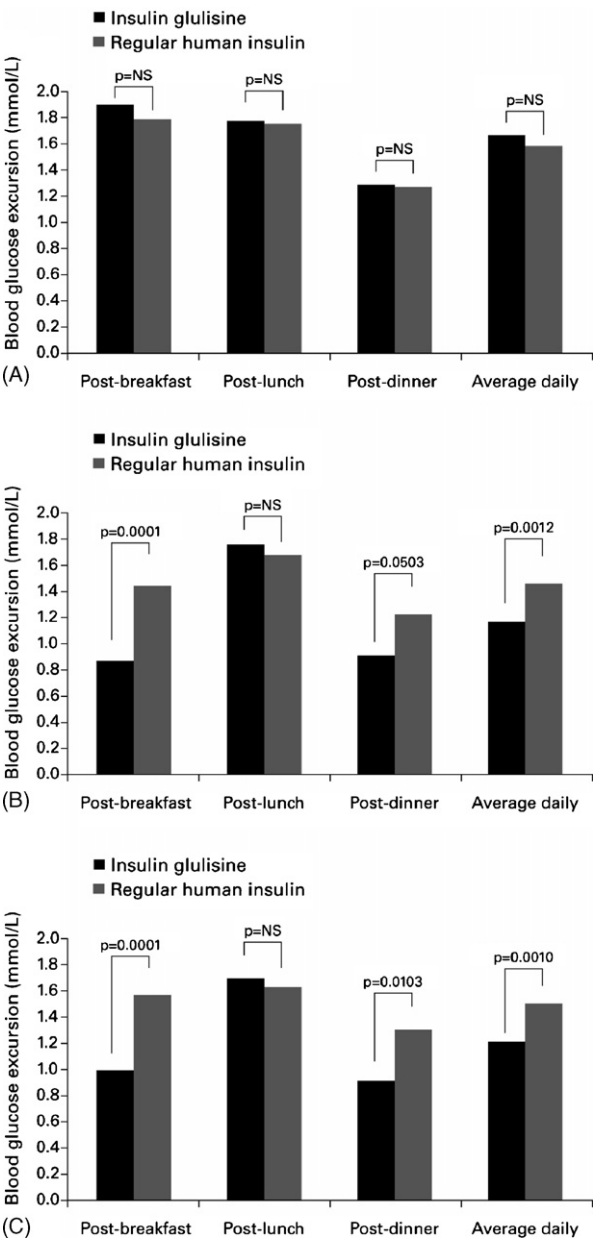

Fig. 4. Blood glucose excursions from self-monitored profiles (mmol/L) at (A) baseline, (B) Week 12 and (C) endpoint (intention-to-treat population). NS, non-significant.

patients; results are shown in Fig. 4. At baseline, no statistical difference was seen in blood glucose excursions in patients in the insulin glulisine group compared with RHI. At Week 12, blood glucose excursions were significantly lower in the insulin glulisine group for breakfast and as a daily average, but were similar in the two groups at lunch. At endpoint, blood glucose excursions were significantly lower with insulin glulisine for breakfast, dinner and as a daily average, but were similar in the two groups at lunch.

3.8. Postprandial and test meal glucose assessments

A standardized in-clinic test meal was performed on Day 1 of study treatment (baseline) and at Week 26, with blood glucose measurements taken before the meal (fasting), and 1 and 2 h after the meal. At baseline, the FPG and 1 and 2 h postprandial measurements were similar for the groups. At endpoint, FPG remained similar for the two groups (Table 3); however, the postprandial measurements were significantly lower with insulin glulisine versus RHI at 1 and 2 h after the meal at Week 26, and at 2 h after the meal at endpoint. Adjusted mean plasma glucose excursions at 1 and 2 h after the test meal were significantly lower with insulin

Table 3
Fasting plasma glucose and plasma glucose excursions during test meals at endpoint (intention-to-treat population)

Time of measurement	Insulin glulisine		RHI		Insulin glulisine–RHI, 95% CI	*p*-Value for treatment effect
	n	Adjusted mean (mmol/L)	*n*	Adjusted mean (mmol/L)		
Prior to test meal (FPG)	238	9.28	250	9.27	(−0.51; 0.54)	0.9559
1 h after test meal	237	13.23	250	13.77	(−1.20; 0.11)	0.1051
2 h after test meal	235	14.14	248	15.28	(−1.87; −0.40)	0.0025
Excursion 1 h after test meal	236	3.99	249	4.59	(−1.10; −0.12)	0.0151
Excursion 2 h after test meal	234	4.87	247	6.03	(−1.77; −0.55)	0.0002

Adjusted means and differences from ANOVA model; RHI, regular human insulin; CI, confidence interval; FPG, fasting plasma glucose.

glulisine versus RHI both at Week 26 and endpoint (Table 3).

3.9. Symptomatic hypoglycaemia

No noteworthy differences occurred between the groups in the frequencies and monthly rates of all symptomatic hypoglycaemia throughout the study, and in particular during the main period of interest (Month 4 to treatment end, representing the time period when patients were acclimatized to the investigational agent; Table 4). While not significant, the frequencies and monthly rates of severe symptomatic hypoglycaemia were lower with insulin glulisine than with RHI.

Fewer insulin glulisine patients reported at least one episode of nocturnal symptomatic hypoglycaemia from Month 4 to treatment end versus RHI (9.1% versus 14.5%; $p = 0.029$). Likewise, the monthly rate of nocturnal symptomatic hypoglycaemia was lower with insulin glulisine versus RHI in this period. These findings were corroborated by analyses in six-hourly intervals over a 24 h period, which showed that the difference between the two groups in reporting of all symptomatic hypoglycaemia was statistically significant for the time period 00.00 to <06.00 from Month 4 to treatment end ($p = 0.032$). For all other 6 h intervals during the day the frequencies of symptomatic hypoglycaemia were similar in the two groups.

3.10. Safety

3.10.1. Adverse events

No noteworthy between-treatment differences in the frequency and type of TEAEs were observed. A total of 260 patients (58.0%) in the insulin glulisine group and 260 patients in the RHI group (58.8%) reported at least one TEAE. Serious TEAEs were reported in 43 patients (9.6%) receiving insulin glulisine and 52 patients (11.8%) receiving RHI. There were three deaths (two in the insulin glulisine group and one in the RHI group), none which were deemed related to study medication.

4. Discussion

The results from this study showed that insulin glulisine and RHI both reduced HbA_{1c} levels from baseline to endpoint to a similar degree, demonstrating that insulin glulisine shows comparable efficacy with RHI, when examining the change in HbA_{1c} levels from baseline.

In patients with T2DM whose overall hyperglycaemia is mild-to-moderate, it has recently been shown that postprandial glycaemic excursions make a significant contribution to HbA_{1c} levels [4]. Therefore, for patients with HbA_{1c} levels of <8.4%, prandial hyperglycaemia should be addressed. The study population presented here had mean HbA_{1c} levels of approximately 7.5% and so fitted into this category.

Table 4
Patients with at least one hypoglycaemic episode from Month 4 to treatment end (intention-to-treat population)

	Hypoglycaemia, *n* (%)		*p*-Value
	Insulin glulisine (*n* = 448)	RHI (*n* = 442)	
All symptomatic hypoglycaemia	140 (32.8)	144 (33.2)	0.9888
Severe hypoglycaemia	2 (0.5)	7 (1.6)	0.1726
Nocturnal hypoglycaemia	39 (9.1)	63 (14.5)	0.0290
Severe nocturnal hypoglycaemia	–	3 (0.7)	0.1414

A previous study showed that 2 h postprandial plasma glucose is a better predictor of deaths from all causes and cardiovascular disease compared with FPG [15]. In this study, insulin glulisine provided superior control of postprandial glycaemia compared with RHI, which was achieved with less prandial insulin; therefore, insulin glulisine may help patients with T2DM achieve glycaemic control targets of HbA_{1c} levels <7.0%, with the additional advantage of improved control of postprandial hypoglycaemia.

Significantly, lower blood glucose excursions were observed after breakfast and dinner in the insulin glulisine group compared with RHI, but no difference was observed following lunch. This was not surprising as approximately one-third of the patients received their twice-daily injections prior to breakfast and dinner, with no injection before lunch unless the investigator judged that more were required.

In this study, insulin glulisine was also associated with a low rate of nocturnal hypoglycaemia that was lower than with RHI. This may be clinically important, as it has been shown that a fear of hypoglycaemia is associated with poor insulin therapy compliance in T2DM patients and contributes to frequent failure to achieve HbA_{1c} targets [16].

Although insulin glulisine is a new insulin analogue, data are gathering in the literature to support its efficacy in patients with diabetes. A similar study carried out in T2DM patients demonstrated improved efficacy with insulin glulisine versus RHI [17]. In studies in patients with Type 1 diabetes mellitus (T1DM), insulin glulisine has been demonstrated to result in equivalent or improved efficacy in terms of HbA_{1c} decrease compared with RHI [13]. Insulin glulisine has also been shown to exert similar benefits in terms of reduction in HbA_{1c} as insulin lispro in patients with T1DM [18].

Insulin glulisine is a rapid-acting insulin analogue with a faster onset and shorter duration of action compared with RHI [6,19], and therefore more closely resembles the physiological insulin response to a meal than RHI, minimizing a potential mismatch between insulin action and carbohydrate absorption. This study demonstrated that insulin glulisine is as effective as RHI in reducing HbA_{1c} levels, and is well tolerated in patients with T2DM. In addition, patients receiving insulin glulisine demonstrated superior postprandial glucose control and showed a reduction in nocturnal hypoglycaemia, in comparison with those receiving RHI, suggesting a possible clinical benefit for insulin glulisine relative to RHI.

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