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CLINICAL TRIAL

Efficacy and safety of once-daily insulin degludec dosed flexibly at convenient times vs fixed dosing at the same time each day in a Japanese cohort with type 2 diabetes: A randomized, 26-week, treat-to-target trial

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ABSTRACT

Aims/Introduction: This trial assessed the efficacy and safety of the possibility of varying the daily injection time of once-daily, long-acting basal insulin degludec (IDeg) in Japanese patients with type 2 diabetes inadequately controlled with insulin glargine.

Materials and Methods: This was a 26-week, multicenter, open-label, randomized, treat-to-target trial, with a 2 × 2 factorial design comparing IDeg flexible (allowing dosing ±8 h from an agreed dosing time) with IDeg fixed dosing (at the same time each day). It was carried out in 458 adult patients who were inadequately controlled on insulin glargine with or without oral antidiabetic drugs.

Results: The majority of doses were taken within 2 h of the agreed dosing time, showing a high level of adherence among Japanese patients. After 26 weeks, IDeg flexible was non-inferior to IDeg fixed with respect to change in glycated hemoglobin from baseline, estimated treatment difference 0.08% points (95% confidence interval –0.05; 0.22). Fasting plasma glucose decreased to a similar level with IDeg flexible and IDeg fixed, estimated treatment difference –0.18 mmol/L (95% confidence interval –0.48; 0.12). The rates of confirmed and nocturnal confirmed hypoglycemia were numerically, but not significantly, higher with IDeg flexible vs IDeg fixed dosing. The rates of adverse events with IDeg flexible and IDeg fixed dosing were similar.

Conclusions: These results showed the efficacy and safety of allowing patients to vary the time they dosed IDeg, when necessary, in Japanese patients with type 2 diabetes. Dosing of IDeg at a time convenient to the patient was non-inferior, with respect to glycated hemoglobin, to dosing at the same time each day.

INTRODUCTION

Insulin is the most efficacious glucose-lowering therapy for the treatment of type 2 diabetes, and is typically initiated when patients are unable to achieve glycemic control with lifestyle changes and oral antidiabetic drugs (OADs)[1,2]. Because of the pharmacokinetic profiles of neutral protamine Hagedorn insulin and previously available basal insulin analogs, patients are required to take their basal insulin at the same time each day[3]. These strict dosing schedules might be difficult for patients to adhere to[4], and can make patients reluctant to initiate and continue taking insulin[5]. Several studies have shown that patients frequently miss or mistime their insulin doses when injecting insulin would interfere with daily activities[4,6,7]. Furthermore, a lack of adherence to insulin has been shown to affect glycemic control[8,9].

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Therefore, a basal insulin that affords flexibility in the time of dosing, when necessary, without compromising efficacy or safety, might make it easier for patients to adhere to their treatment regimen. Insulin degludec (IDeg) is a new basal insulin with a long duration of action, a half-life of more than 24 h and a flat, stable profile, as assessed in Japanese[10] and Caucasian populations[11,12]. A large-scale IDeg phase 3a program (BEGIN) showed that IDeg is non-inferior to insulin glargine (IGlar) in treat-to-target trials, with respect to lowering of glycated hemoglobin (HbA_{1c}), and is associated with a lower rate of nocturnal hypoglycemia[13]. One of the phase 3a trials was carried out exclusively in Asian patients with type 2 diabetes, showing that IDeg is efficacious and tolerable in this population, providing similar improvements in long-term glycemic control to IGlar, at a significantly lower rate of overall confirmed hypoglycemia once stable glycemic control and insulin dosing were achieved[14].

Two international, 26-week, phase 3a studies carried out as part of the large-scale IDeg phase 3a program (BEGIN; one in type 1 and one in type 2 diabetes) explored the use of a forced-flexible dosing regimen of IDeg (with alternating dosing intervals of 8 and 40 h) over 26 weeks[15,16]. The use of these extreme dosing intervals resulted in non-inferior HbA_{1c} reductions and similar safety when compared with IGlar given at the same time each day[15,16]. Furthermore, a 26-week extension of the study in type 1 diabetes allowed patients to take their insulin at any time of day, as long as there was a minimum of 8 h and a maximum of 40 h between doses. Change in HbA_{1c} with this flexible dosing regimen was not statistically significantly different to that with IGlar dosed at the same time each day[15]. Furthermore, the mean fasting plasma glucose (FPG) at the end of the extension was significantly lower with IDeg dosed flexibly, and the rate of nocturnal confirmed hypoglycemia was 25% lower vs IGlar.

Before the present study, there were no data investigating the efficacy and safety of IDeg when the time of dosing was adjusted on a day-to-day basis in Japanese patients with type 2 diabetes. Furthermore, although the efficacy and safety of IDeg have been investigated extensively in a large international clinical trial program, the dose timing and methods of dose adjustment used in the clinical trials might not be representative of those used in clinical practice.

The aim of the present trial was to compare the efficacy and safety of once-daily IDeg dosed in a regimen that allowed flexibility in dose timing with dosing at the same time each day, with or without OADs, in Japanese patients with type 2 diabetes who were inadequately controlled with IGlar. This trial was carried out in order to investigate a setting more closely resembling that of clinical practice, and it also enabled investigation of the extent to which patients choose to utilize the flexible dosing option. The second aim of this trial was to compare two titration algorithms (simple vs stepwise); these data are presented in a separate manuscript (Kadowaki T, Jinnouchi H, Kaku K, Hersløv ML, Hyllested-Winge J, Nakamura S, manuscript in preparation).

MATERIALS AND METHODS

Study design and participants

This was a 26-week, multicenter, open-label, randomized, treat-to-target phase 3b trial, carried out at 39 sites in Japan between June 2013 and April 2014. The trial was registered at clinicaltrials.gov (NCT01880736), and was carried out in accordance with the Declaration of Helsinki[17] and ICH Good Clinical Practice[18].

Patients enrolled in the trial were aged ≥20 years, had a diagnosis of type 2 diabetes for ≥26 weeks before screening, HbA_{1c} 7.0–9.5% (both inclusive), a body mass index ≤35 kg/m^2 and were treated with IGlar ± OADs for at least 12 weeks; OAD doses were stable during this period. Patients were allowed to continue with up to three of the following OADs during the study: metformin, sulfonylurea/glinide, dipeptidyl peptidase-4 inhibitor, alpha-glucosidase inhibitor or pioglitazone.

Patients were excluded if they had any disorder or disease that the investigator considered might affect safety or protocol compliance. Patients were also excluded if they met any of the following criteria within 26 weeks of the screening visit: stroke, decompensated heart failure, myocardial infarction, unstable angina pectoris or coronary arterial bypass graft or angioplasty, impaired renal function (serum creatinine ≥124 μmol/L for men, ≥115 μmol/L for women), or had current or past malignant neoplasms (except basal cell and squamous cell skin carcinoma).

Randomization and masking

Randomization was carried out 1:1:1:1 using an interactive voice/web-response system (Figure 1). All patients were treated with once-daily IDeg, and were randomized to one of two dosing schedules and one of two titration algorithms. The 2 × 2 factorial design was utilized to obtain data on two aspects of IDeg dosing: flexible vs fixed time dosing, and simple vs stepwise titration (Figure 1). In patients randomized to the IDeg flexible arm, an 'agreed dosing time' was selected with the investigator, and patients were allowed to dose IDeg ±8 h from this agreed dosing time on occasions where dosing at the agreed time was not possible or convenient. In the IDeg fixed arm, IDeg could be dosed at any time of day, and an 'agreed dosing time' was selected with the investigator at randomization; the injection time was to be at approximately the same time of day throughout the trial, as per the Japanese label[19].

Procedures

IDeg 100 U/mL was taken subcutaneously using a FlexTouch prefilled pen (Novo Nordisk, Bagsværd, Denmark). Patients were switched from their pretrial IGlar dose to IDeg in a unit-to-unit ratio at randomization.

Insulin dose was titrated once weekly to an FPG target of 4.0–5.0 mmol/L (71–90 mg/dL). Patients in the simple titration arm based their titration on a single prebreakfast self-measured blood glucose (SMBG) value, and increased their dose by two units if above target and reduced it by two units if below target.

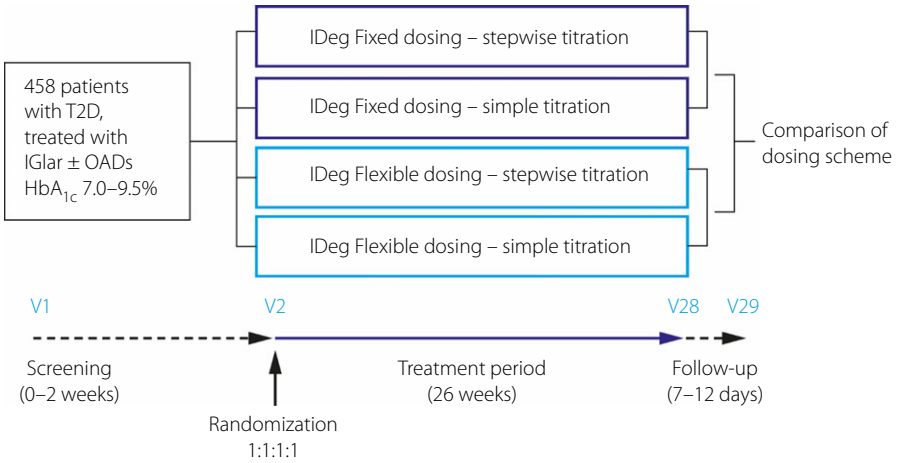

Figure 1 | Study design. HbA_{1c}, glycated hemoglobin; IDeg, insulin degludec; IGlar, insulin glargine; OADs, oral antidiabetic drugs; T2D, type 2 diabetes; V, visit.

Patients in the stepwise arm titrated the dose based on the mean of three consecutive prebreakfast SMBG values; the dose was increased or decreased in multiples of two units to a maximum of eight units depending on the SMBG value (Kadowaki *et al.*, manuscript in preparation).

End-points

The primary end-point of the trial was change from baseline in HbA_{1c} after 26 weeks of treatment. Secondary efficacy end-points were the number of responders for HbA_{1c} based on reaching the target of <7.0% after 26 weeks of treatment, change from baseline in FPG after 26 weeks of treatment, SMBG (8-point profile and mean of 8-point profile) and insulin dose after 26 weeks of treatment.

The incidence of treatment-emergent adverse events (AEs) was documented throughout the trial, and events were treated by established standards of care. The number of treatment-emergent episodes of confirmed hypoglycemia, defined as plasma glucose <3.1 mmol/L (56 mg/dL) or severe hypoglycemia, requiring third-party assistance, were documented. Nocturnal confirmed hypoglycemia was defined as confirmed hypoglycemia occurring between 00.01 and 05.59 h, both inclusive. After 26 weeks of treatment, change from baseline in bodyweight, vital signs, fundoscopy and electrocardiogram, and laboratory safety variables (hematology and biochemistry) were assessed. Laboratory analyses were carried out by Quintiles Central Laboratories (Tokyo, Japan).

Statistical analysis

The sample size was determined to meet the primary objective using a *t*-statistic under the assumption of a one-sided test of size 2.5% and a zero mean treatment difference, as well as a standard deviation of 1.3% for change in HbA_{1c}. The total number of randomized participants was to be at least 452 participants in order to have at least 85% power in the evaluation of the per protocol analysis set.

The interaction between dosing regimen and titration algorithm based on a 2 x 2 factorial design was analyzed statistically for all end-points in order to investigate any possible interactions. As there were no statistically significant interactions for any end-points, it is considered valid to estimate one common treatment difference on dosing regimen (flexible vs fixed) regardless of titration algorithm (simple vs stepwise), and vice versa.

Change from baseline in HbA_{1c} and FPG, and the mean of eight-point SMBG after 26 weeks of treatment, were analyzed using an analysis of variance with dosing scheme (IDeg flexible or IDeg fixed), titration scheme (IDeg simple or IDeg stepwise), interaction between dosing and titration scheme, antidiabetic therapy at screening and sex as fixed factors, and age and baseline HbA_{1c} as covariates. Non-inferiority was confirmed if the upper limit of the two-sided 95% confidence interval for the treatment difference was 0.4% or less in change from baseline in HbA_{1c} after 26 weeks of treatment. The proportion of treatment responders was analyzed using a logistic regression model. A mixed-effects model was fitted to analyze the eight-point SMBG profile data. The number of treatment-emergent confirmed hypoglycemic and nocturnal confirmed hypoglycemic episodes were analyzed separately using a negative binomial regression model with a log–link function and the logarithm of the time-period considered treatment-emergent as offset. For responders, SMBG and hypoglycemia, the fixed factors used in the analysis model, were the same as per the HbA_{1c} analysis, with age as the covariate.

The full analysis set included all randomized patients, and was used to analyze HbA_{1c}, FPG, SMBG and hypoglycemia. The safety end-points were summarized using the safety analysis set, which included all participants receiving at least one

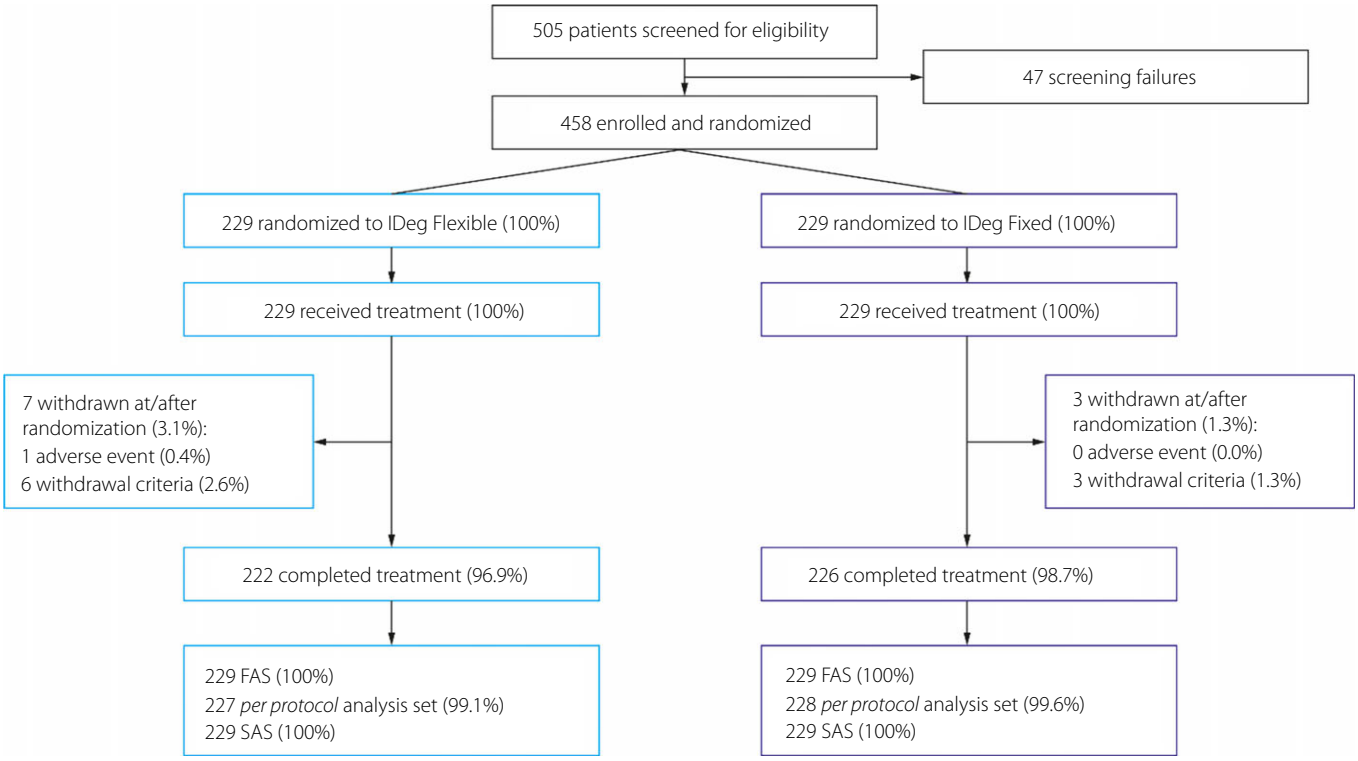

Figure 2 | Patient disposition. FAS, full analysis set; IDeg, insulin degludec; SAS, safety analysis set.

dose of the investigational product. Missing values were imputed using last observation carried forward.

RESULTS

Of the 505 patients screened, 458 were randomized to receive trial product, 229 to the IDeg flexible and 229 to the IDeg fixed arm (Figure 2). In total, 96.9% of patients in the IDeg flexible arm and 98.7% in the IDeg fixed arm completed the trial. There were no major differences between the treatment groups in baseline and demographic characteristics or treatment at screening (Table 1, Table S1). Most (43.9%) patients were treated with two OADs, whereas 31.4% were treated with one OAD and 20.3% were treated with more than two OADs. Overall, the most common OAD used was metformin, followed by dipeptidyl peptidase-4 inhibitor and sulfonylurea. No statistically significant interactions for any end-points were found between dosing regimen and titration algorithm.

Table 1 | Baseline characteristics

Characteristic	IDeg flexible *n* = 229	IDeg fixed *n* = 229
Female, *n* (%)	84 (36.7)	82 (35.8)
Race, Asian non-Indian (%)	100	100
Age (years)	60.1 ± 10.8	60.5 ± 10.5
Bodyweight (kg)	67.0 ± 13.1	66.9 ± 12.3
BMI (kg/m^2)	25.3 ± 3.7	25.2 ± 3.4
Duration of diabetes (years)	13.0 ± 7.5	13.7 ± 7.6
HbA_{1c} (%)	7.8 ± 0.6	7.8 ± 0.6
FPG, mmol/L (mg/dL)	7.4 ± 2.0 (133.1 ± 36.6)	7.4 ± 2.0 (132.9 ± 34.4)
Prestudy treatment, *n* (%)		
Basal only	11 (4.8)	9 (3.9)
Basal + 1 OAD	78 (34.1)	66 (28.8)
Basal + 2 OADs	95 (41.5)	106 (46.3)
Basal + >2 OADs	45 (19.7)	48 (21.0)

Data are mean ± standard deviation unless otherwise stated. BMI, body mass index; FPG, fasting plasma glucose; IDeg, insulin degludec; *n*, number of patients; OAD, oral antidiabetic drug.

Insulin dose and dose timing

Patients in the IDeg flexible arm were allowed to dose ±8 h from their agreed dosing time on occasions where dosing at the same time was not possible or convenient. In total, 87.3% of IDeg flexible doses were taken within a time interval of 2 h or less from the agreed dosing time, compared with 97.0% of IDeg fixed doses (Table 2, Figure S1). In the IDeg flexible arm, 6.8% of doses were taken 2–4 h, and 5.4% of doses were administered 4–8 h from the agreed dosing time. This corresponded to 73 and 48% of patients in the IDeg flexible arm taking doses 2–4 and 4–8 h, respectively, from the agreed

Table 2 | Insulin dose and dose timing

	IDeg flexible *n* = 229		IDeg fixed *n* = 229	
Time difference between actual and agreed dosing time				
Time (min)				
Mean	24 ± 112		12 ± 55	
Absolute mean	58		23	
Median (min; max)	2 (–1000; 1385)		0 (–720; 850)	
	Patients, *n* (%)	Doses, *n* (%)	Patients, *n* (%)	Doses, *n* (%)
Total number of doses (*n*†)	–	40,543	–	41,060
≤2 h	227 (99.1)	35,395 (87.3)	229 (100)	39,823 (97.0)
>2 and ≤4 h	167 (72.9)	2749 (6.8)	109 (47.6)	794 (1.9)
>4 and ≤8 h	109 (47.6)	2176 (5.4)	72 (31.4)	391 (1.0)
>8 h	32 (14.0)	221 (0.5)	20 (8.7)	49 (0.1)
Time not recorded	2 (0.9)	2 (<0.1)	1 (0.4)	3 (<0.1)
Dose (U/kg)				
Baseline	0.24 ± 0.14		0.23 ± 0.14	
End-of-trial (week 25)	0.40 ± 0.22		0.41 ± 0.21	

Data are mean ± standard deviation. †Total number of doses excluding the first dose. IDeg, insulin degludec.

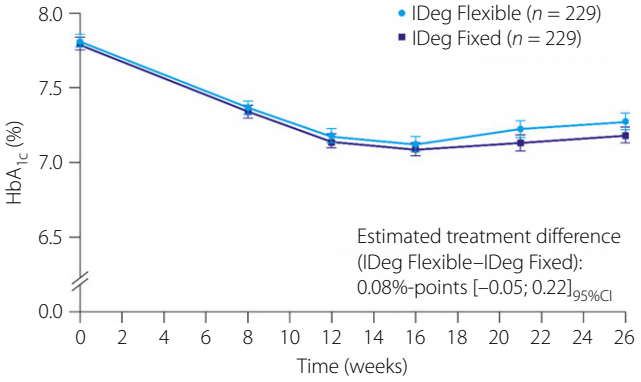

Figure 3 | Glycated hemoglobin (HbA_{1c}) over time. Data are full analysis set; last observation carried forward. CI, confidence interval; IDeg, insulin degludec.

dosing time on one or more occasions. In comparison, 1.9 and 1.0% of doses in the IDeg fixed arm were taken 2–4 h and 4–8 h from the agreed dosing time, respectively (Table 2). The absolute mean time difference between actual and agreed dosing time appeared to be slightly higher with IDeg flexible compared with IDeg fixed dosing: 58 min vs 23 min (Table 2).

Basal insulin dose increased in both arms during the trial (Table 2). The mean daily insulin dose at the end of treatment was similar with IDeg flexible (0.40 U/kg, 28 U) and IDeg fixed dosing (0.41 U/kg, 28 U): the ratio of mean doses IDeg flexible/IDeg fixed (U/kg) was 1.00.

Glycemic control

During the 26 weeks of treatment, similar HbA_{1c} reductions were observed in both arms. In the IDeg flexible arm, mean observed HbA_{1c} decreased from 7.8 to 7.3%, with an observed mean (standard deviation) change from baseline of –0.54% points (0.76); and in the IDeg fixed arm, HbA_{1c} decreased from 7.8 to 7.2%, with an observed mean (standard deviation) change from baseline of –0.62% points (0.75). Accordingly, the primary end-point of non-inferiority was met, with an estimated treatment difference of 0.08% points (95% confidence interval –0.05; 0.22; Figure 3). The proportion of patients in each arm who reached the target HbA_{1c} <7.0% was 39.3% with IDeg flexible and 41.5% with IDeg fixed (not significant).

With IDeg flexible, the mean observed FPG decreased from 7.4 to 5.8 mmol/L, and with the IDeg fixed arm, it decreased from 7.4 to 6.0 mmol/L (Figure S2), resulting in a non-significant estimated treatment difference of –0.18 mmol/L (95% confidence interval –0.48; 0.12) after 26 weeks of treatment.

The mean eight-point SMBG profiles decreased in both treatment arms from baseline to end-of-trial (Figure S3), with no significant differences between treatments at any of the measured time-points or for the mean of the eight-point SMBG profile.

Hypoglycemia and adverse events

In total, the numbers, proportions and rates of AEs reported with IDeg flexible and IDeg fixed dosing were similar, with event rates of 355 (IDeg flexible) and 344 (IDeg fixed) per 100 patient-years of exposure (Table S2). Most AEs were mild in severity, and the most frequently reported AEs in both treatment arms were nasopharyngitis and diabetic retinopathy. None of the serious AEs in the IDeg flexible arm were considered possibly or probably related to investigational product. Two serious AEs with a possible or probable relationship to the investigational product occurred in the IDeg fixed arm; these were non-cardiac chest pain and hypoglycemia. One death (suicide) occurred in the IDeg flexible arm (with stepwise titration). This death was not considered related to the investigational product, and was the only AE leading to withdrawal during the trial. Five acute coronary syndrome events occurred during the trial in four patients; one of these events was adjudicated as a major adverse coronary event, an acute myocardial infarction in a patient in the IDeg fixed arm (with stepwise titration), which was judged as unlikely to be as a result of the investigational product. At end-of-trial, there were no clinically relevant differences in vital signs, physical findings or fundoscopy between the two dosing regimens.

One severe hypoglycemic episode occurred during the trial, in the IDeg fixed arm (simple titration scheme). There was no significant difference in the rate of confirmed hypoglycemia between arms, although the rate was numerically higher in the

IDeg flexible arm, with an estimated rate ratio IDeg flexible/IDeg fixed of 1.33 (95% confidence interval 0.95; 1.86; Figure S4a, Table S3). The rate of nocturnal confirmed hypoglycemia was also numerically, but not significantly, higher in the IDeg flexible vs IDeg fixed arm, estimated rate ratio 1.25 (95% confidence interval 0.71; 2.20; Figure S4b, Table S3).

DISCUSSION

The present trial showed that a flexible dosing regimen of IDeg (allowing dosing ±8 h from their agreed dosing time on occasions where dosing at the same time was not possible or convenient) in Japanese patients with type 2 diabetes was non-inferior, with respect to change in HbA_{1c}, to IDeg dosed at the same time each day, with glycemic control improving in both arms vs prior treatment with IGlar. However, it should be noted that the majority of doses were taken within a 2-h window of the agreed dosing time (87% with IDeg flexible vs 97% with IDeg fixed). Although the data from the present trial show a high level of adherence to the agreed dosing time in Japanese patients with type 2 diabetes, it is important to recognize that they also show a need for some patients to be able to adjust dose timing in situations where dosing at the same time is not possible or convenient. Overall, 73 and 48% of patients in the IDeg flexible arm utilized the option of flexibility, and took their dose 2–4 and 4–8 h, respectively, from the agreed dosing time on one or more occasions. In general, the recommendation to dose IDeg at the same time every day remains; however, the present results show that there is a need for some flexibility in the dosing regimen by patients, and this can be accommodated with IDeg, without loss of efficacy or any other adverse clinical effects. The rates of confirmed and nocturnal confirmed hypoglycemic episodes were numerically higher with IDeg flexible compared with IDeg fixed dosing, although they were not statistically significantly different. Furthermore, a *post-hoc* analysis was carried out to investigate whether shorter or longer intervals between doses had an impact on the frequency of hypoglycemia. No specific patterns in the occurrence of hypoglycemic episodes by dosing interval were observed (data not shown).

Two international phase 3a trials have previously shown how IDeg dosed in a forced-flexible regimen (with intervals of 8–40 h) did not compromise efficacy or safety compared with IDeg dosed at the same time each day[15,16]. Although the trial designs are different to the design reported here, these results all suggest that in clinical practice, some flexibility can be afforded by IDeg, which could help patients to better adhere to their treatment by reducing the treatment burden.

The results of the present randomized, controlled, 26-week, 2 x 2 factorial design trial show the efficacy and safety of allowing patients to vary the time they dosed the basal insulin degludec (±8 h from their agreed dosing time on occasions where dosing at the same time was not possible or convenient) in Japanese patients with type 2 diabetes inadequately controlled with IGlar with or without oral therapies. These data show a high level of adherence to the agreed dosing time in Japanese patients, with the majority of doses taken within a 2-h window of the agreed dosing time. IDeg used in a flexible dosing regimen effectively improved long-term glycemic control, as measured by HbA_{1c}, and was non-inferior to a fixed-time dosing regimen. The rates of confirmed and nocturnal confirmed hypoglycemia were numerically, but not significantly, higher with flexible compared with fixed dosing.

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DISCLOSURE

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SUPPORTING INFORMATION

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

Figure S1 | Agreed dosing time schedule.
Figure S2 | Fasting plasma glucose over time.
Figure S3 | Mean eight-point self-measured blood glucose profiles at baseline and end-of-trial.
Figure S4 | Cumulative confirmed (a) hypoglycemia and (b) nocturnal hypoglycemia.
Table S1 | Oral antidiabetic drugs at screening.
Table S2 | Adverse events.
Table S3 | Summary of hypoglycemic episodes.