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ORIGINAL ARTICLE

Insulin degludec in a simple or stepwise titration algorithm in a Japanese population of patients with type 2 diabetes: a randomized, 26-week, treat-to-target trial

Takashi Kadowaki[1] · Hideaki Jinnouchi[2] · Kohei Kaku[3] · Malene L. Hersløv[4] · Jacob Hyllested-Winge[5] · Shuji Nakamura[6]

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Abstract

Aims Managing insulin therapy is a challenge for both patients and healthcare providers.

The primary aim of this trial was to compare the efficacy and safety of insulin degludec (IDeg) in a fixed versus flexible dosing schedule. The secondary aim and subject of this manuscript was to compare a simple versus a stepwise titration algorithm.

Materials and methods This was a 26-week, controlled, multicenter, open-label, randomized, treat-to-target phase 3b trial of Japanese patients with type 2 diabetes inadequately treated with insulin glargine and with/without antidiabetic drugs orally. The trial had a 2 × 2 factorial design whereby 458 patients were randomized 1:1:1:1 to one of two titration algorithms and one of two dosing schedules. IDeg dose was adjusted weekly using a clinician-led, treat-to-target approach in order to ensure optimal insulin titration and glycemic control following self-measured blood glucose (SMBG) readings.

Results Mean insulin dose at the end of the trial was similar in both simple and stepwise titration algorithms. Glycemic control improved in both titration algorithms, with noninferiority in glycated hemoglobin (HbA_{1c}) reduction confirmed when comparing simple and stepwise titration algorithms and no significant differences in fasting plasma glucose or SMBG at 26 weeks. No safety concerns were observed in terms of adverse events, and rates of hypoglycemia were not significantly different between the two algorithms.

Conclusions This trial demonstrated comparable efficacy with noninferior HbA_{1c} and comparable safety of once-daily IDeg using either a simple or stepwise titration algorithm in Japanese patients with type 2 diabetes inadequately controlled with insulin glargine.

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✉ Takashi Kadowaki
kadowaki-3im@h.u-tokyo.ac.jp

[1] Department of Metabolic Diseases, Graduate School of Medicine and Faculty of Medicine, The University of Tokyo, Tokyo, Japan

[2] Iryo Houjin Shadan Jinnouchikai, Jinnouchi Hospital, Kumamoto, Japan

[3] Department of Internal Medicine, Kawasaki Medical School, Okayama, Japan

[4] Medical and Science, Novo Nordisk A/S, Søborg, Denmark

[5] Medical and Scientific Affairs, Novo Nordisk Pharma Ltd, Tokyo, Japan

[6] Iryo Houjin Shadan Kowakai, Heiwadai Hospital, Miyazaki, Japan

Keywords Basal insulin · Titration algorithm · Type 2 diabetes · Insulin degludec

Introduction

Type 2 diabetes (T2D) is characterized by a relative deficiency in insulin secretion accompanied by progressive insulin resistance at the peripheral tissues, resulting in poor glycemic control [1]. The Japan Diabetes Society (JDS) currently recommends initiating insulin therapy after patients with T2D have implemented recommended changes to their diet, exercise, and lifestyle or if their glycemic targets are not met with orally administered antidiabetic

drugs (OADs) alone [2]. Clinical practice guidelines from JDS set a glycemic target of glycated hemoglobin (HbA_{1c}) <7 % with the aim of maintaining tight glycemic control over the long term and preventing the development of complications [2]. Whilst tight glycemic control is the most desirable outcome of any pharmacological intervention in diabetes, the benefits gained from intensifying therapeutic drug regimens also need to be balanced against an individual's life expectancy, risk of hypoglycemia, and the presence of cardiovascular disease. Additionally, patients and healthcare providers can perceive insulin therapy to be burdensome and too complex to manage [3, 4], which may hinder the achievement of glycemic targets. Therefore, where simplified regimens can be proven effective [5–10], global recommendations promote the use of insulins using a less burdensome self-titration regimen [11]. Consequently, self-titration and use of simpler insulin titration regimens have become more commonplace.

Insulin degludec (IDeg) is a new basal insulin with a long duration of action, a half-life >24 h, and a flat, stable profile as assessed in Japanese [12] and Caucasian populations [13, 14]. The results of a phase 3a program indicated that compared with insulin glargine (IGlar), IDeg potentially fills an unmet need by offering comparable improvements in HbA_{1c}, with fewer episodes of hypoglycemia across a wide range of doses [15–17]. Furthermore, titration of IDeg has been shown to be safe and effective in a phase 3 study using a stepwise algorithm [18]. This has subsequently opened up the possibility of using a simplified titration algorithm—with fewer self-measured blood glucose (SMBG) measurements and simplified titration steps—as supported by results in a multinational population [18].

Pan-Asian studies have demonstrated that IDeg has a comparable safety and efficacy profile to that observed in non-Asian patients [15] and that Asian patients can effectively titrate their basal insulin dose when guided by clinicians [19].

Currently, in Japanese clinical practice, IDeg is administered once daily, and the demanding stepwise algorithm, as per the insulin degludec phase 3 trials, is not commonly used in clinical practice. The primary aim of this trial was to compare the efficacy and safety of IDeg dosed once daily in a flexible regimen compared with fixed dosing at the same time each day in combination with and without OADs in Japanese patients with T2D. These data are presented in a separate manuscript [20]. The secondary aim of the trial, discussed in this manuscript, was to compare two titration algorithms (simple versus stepwise) of IDeg using a simple titration algorithm adapted from previous trials to reflect the need for, and clinical practice of, T2D treatment in Japan.

Methods

Study design and participants

This was a 26-week, multicenter, open-label, randomized, treat-to-target, phase 3b trial conducted in 39 sites in Japan between June 2013 and April 2014. This trial was registered at ClinicalTrials.gov (NCT01880736) and was conducted in accordance with the Declaration of Helsinki [21] and the International Conference of Harmonisation (ICH) Good Clinical Practice [22].

Patients enrolled in the trial were aged ≥20 years, had a diagnosis of T2D for ≥26 weeks prior to screening, HbA_{1c} 7.0–9.5 % (both inclusive), a body mass index (BMI) ≤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

Randomization was performed 1:1:1:1 using an interactive voice/web-response system (Fig. S1). All patients were treated with once-daily IDeg and randomized to one of two dosing schedules and one of two titration algorithms. The 2 × 2 factorial design was used in order to obtain data on two aspects of IDeg dosing: flexible versus fixed time dosing, and simple versus stepwise titration (Fig. S1).

Procedures

IDeg 100 U/mL was administered subcutaneously using FlexTouch prefilled pen (both Novo Nordisk, Bagsværd, Denmark). Patients were switched from their pretrial IGlar dose to IDeg in a unit-to-unit ratio at randomization. IDeg was dosed on an individual basis using a treat-to-target approach in order to ensure optimal insulin titration and glycemic control following measurement of SMBG. Insulin dose was titrated once weekly to a fasting plasma glucose (FPG) target of 4.0–5.0 mmol/L (71–90 mg/dL). IDeg

Table 1 Comparison of insulin degludec titration algorithms

Prebreakfast SMBG		Dose adjustment
mmol/L	mg/dL	U
Simple titration algorithm[a]		
<4.0	<71	–2
4.0–5.0	71–91	0
>5.0	>90	+2
Stepwise titration algorithm[b]		
<3.1	<56	–4 (or 10 % if the dose >45 U)
3.1–3.9	56–70	–2 (or 5 % if the dose >45 U)
4.0–5.0	71–90	0
5.1–7.0	91–126	+2
7.1–8.0	127–144	+4
8.1–9.0	145–162	+6
>9.0	>162	+8

SMBG self-measured blood glucose, *U* units of insulin

[a] Dose change based on a single SMBG measurement

[b] Dose change based on the mean of three prebreakfast SMBG values measured on the day of contact and 2 days before; if one of the blood glucose values is below target (<4 mmol/L), insulin degludec dose should be reduced

dose was adjusted weekly in connection with a site visit or telephone contact to ensure the enforced titration toward a tight glycemic target. For patients in the simple titration algorithm, IDeg dose was adjusted weekly in connection with a single prebreakfast SMBG measurement. IDeg dose was increased by 2 U if above target and reduced by 2 U if below target (Table 1). Patients in the stepwise arm titrated their insulin dose based on the mean of three consecutive prebreakfast SMBG values (measured on the day of the contact and the 2 days prior), with dose increased or decreased in multiples of 2 U to a maximum of 8 U (Table 1) but decreased in the presence of symptomatic hypoglycemia or low SMBG values (<4.0 mmol/L) occurring without explanation.

Endpoints

The primary endpoint of the trial was change from baseline in HbA_{1c} after 26 weeks of treatment. Secondary efficacy endpoints were the number of responders for HbA_{1c} based on reaching target <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) after 26 weeks of treatment, and insulin dose at the end of treatment. Incidence of treatment-emergent adverse events (AEs) was documented throughout the trial and 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 and requiring third-party assistance, were documented. Nocturnal confirmed hypoglycemia was defined as occurring between 00:01 and 05:59 a.m., both inclusive.

After 26 weeks of treatment, change from baseline in body weight, vital signs, funduscopy, echocardiography (ECG), and laboratory safety variables (hematology and biochemistry) were assessed. Laboratory analyses were performed by Quintiles Central Laboratories (Shinjuku-ku Tokyo, Japan).

Statistical methods

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

Interaction between dosing regimen and titration algorithm based on a 2×2 factorial design was analyzed statistically for all safety and efficacy endpoints in order to investigate any possible interactions. Since there were no statistically significant interactions for any endpoints, it is considered valid to estimate one common treatment difference on titration algorithm (simple versus stepwise) regardless of dosing regimen (flexible versus fixed), and vice versa.

Change from baseline in HbA_{1c} and FPG and mean of the 8-point SMBG after 26 weeks of treatment were analyzed using an analysis of variance (ANOVA) 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. Noninferiority was confirmed if the upper limit of the two-sided 95 % confidence interval (CI) for treatment difference was $\leq$0.4 % 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 8-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 the 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 covariate.

The full analysis set included all randomized patients and was used to analyze HbA_{1c}, FPG, SMBG, and hypoglycemia. Safety endpoints were summarized using the safety analysis set, which included patients who had received at least one dose of IDeg. Missing values were imputed using last observation carried forward.

Results

Patient disposition and withdrawal criteria

Patient disposition is summarized in Fig. 1.

Demographics and baseline characteristics

Participants were allocated using a 2 × 2 factorial design to the flexible-simple/fixed-simple, flexible-stepwise/fixed-stepwise regimens. Interaction between dosing regimen and titration algorithm was analyzed statistically for all endpoints to investigate any possible interactions; there were no statistically significant interactions for any endpoints. Patients were divided into simple ($n = 229$) and stepwise ($n = 229$) titration algorithms, and their baseline characteristics are shown in Table S1.

Insulin dose

Mean insulin dose at end of treatment was similar in both simple and stepwise IDeg titration groups: 27 U (0.40 U/kg) and 29 U (0.41 U/kg), respectively (Fig. S2). Most patients (98 %) were treated for >25 weeks, with similar patient-years of exposure (PYE) to IDeg in both simple (113.18 PYE) and stepwise (112.31 PYE) titration groups. Mean prescribed doses were similar to, or slightly lower than, doses recommended by the titration guideline in both simple (Fig. 2a) and stepwise (Fig. 2b) titration groups.

Efficacy endpoints

After 26 weeks of treatment, HbA_{1c} decreased from 7.8 % at baseline to 7.2 % in both algorithms (Fig. 3). Noninferiority for IDeg simple was demonstrated, as the upper limit of the 95 % CI for the estimated mean treatment difference (ETD) was ≤0.4 % (IDeg simple/IDeg stepwise 0.03 % points, 95 % CI −0.10; 0.17).

A similar proportion of patients in both the IDeg simple [39.7 % (91/229)] and IDeg stepwise [41.0 % (94/229)] treatment arms achieved the HbA_{1c} target of <7.0 % at the end of the trial: estimated odds ratio (OR) (IDeg simple/IDeg stepwise 0.94, 95 % CI 0.63; 1.40). FPG decreased from 7.3 and 7.5 mmol/L at baseline to 5.8 and 6.0 mmol/L at week 26 in the IDeg simple and IDeg stepwise treatment arms, respectively (Fig. S3). No significant difference was observed between algorithms in change from baseline to week 26 of treatment: ETD (IDeg simple/IDeg stepwise −0.15 mmol/L, 95 % CI –0.46; 0.15). There was no significant difference in the mean 8-point SMBG profiles or SMBG at any of the eight measured time points after 26 weeks (Fig. S4)—except for 90 min after the start of breakfast (where SMBG for IDeg stepwise was lower than for IDeg simple).

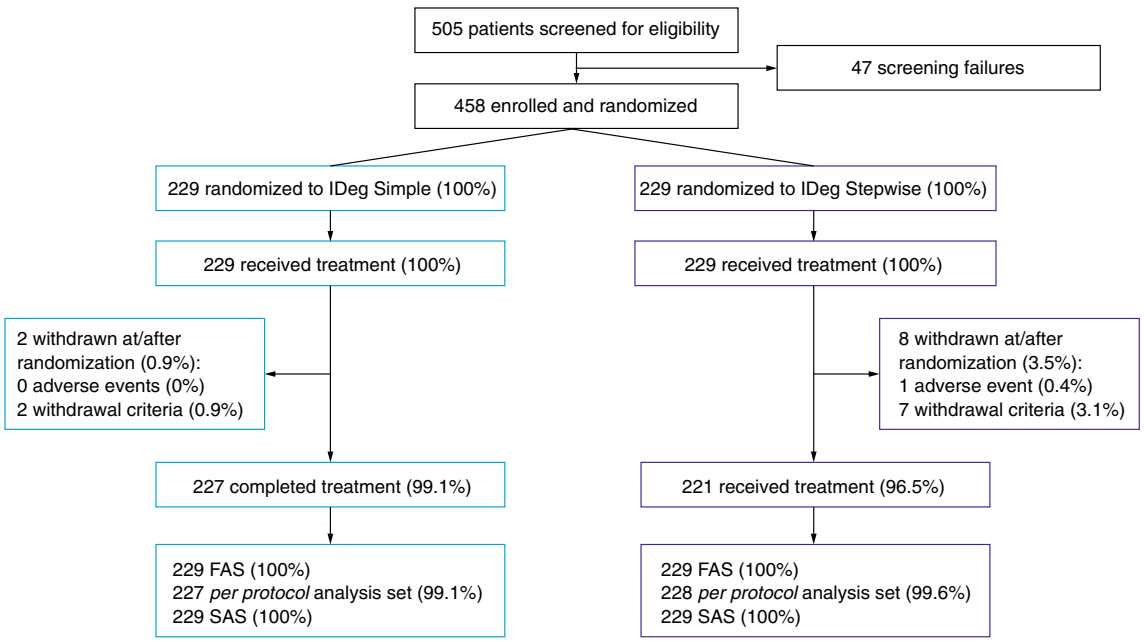

Fig. 1 Patient disposition. *FAS* full analysis set, *IDeg* insulin degludec, *SAS* safety analysis set

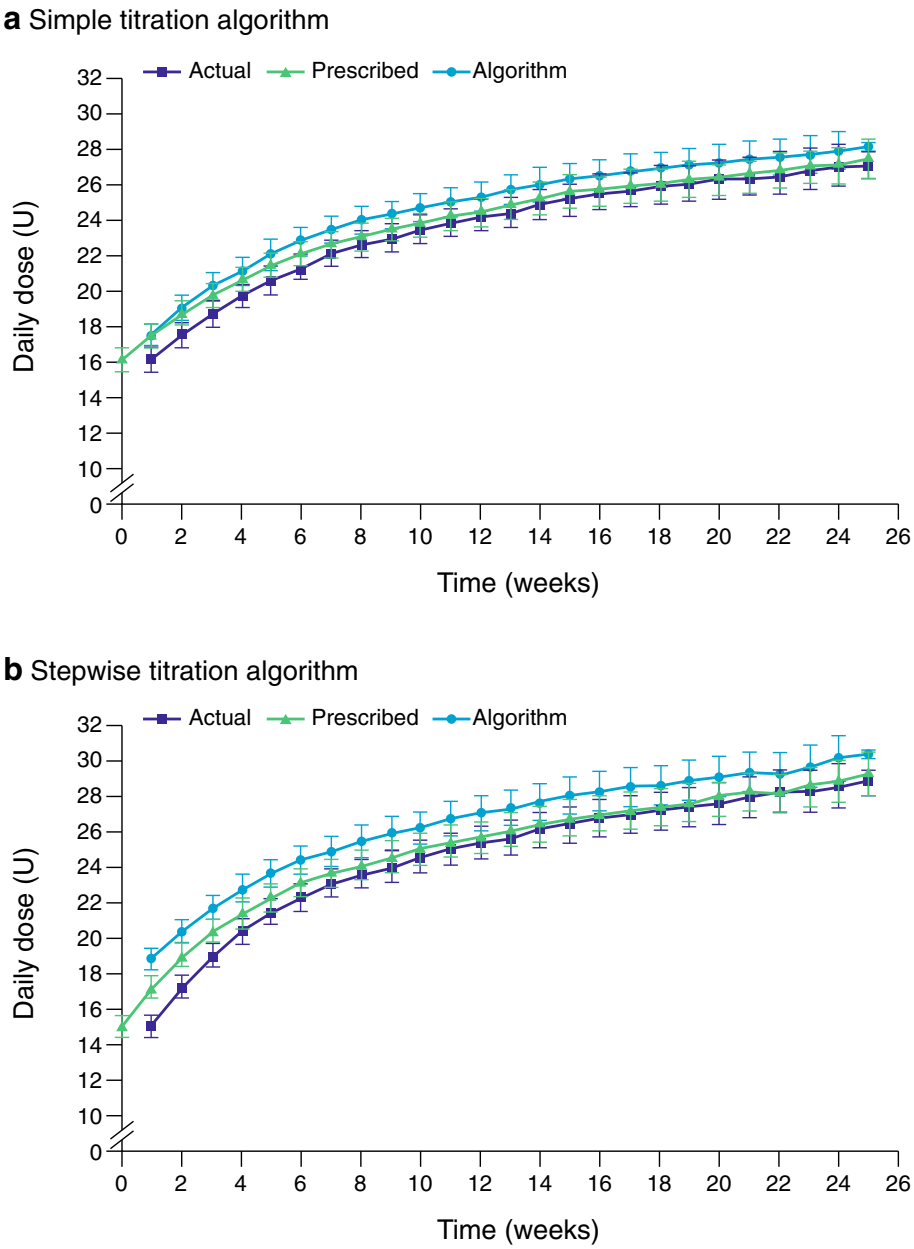

Fig. 2 Daily dose of insulin degludec according to simple (**a**) and stepwise (**b**) titration algorithm: prescribed and actual dose taken. Data are SAS, LOCF. *LOCF* last observation carried forward, *SAS* safety analysis set, *U* units of insulin

Safety endpoints

There was no significant difference in hypoglycemia between groups. The observed rate of confirmed hypoglycemia (Table S2) was numerically higher with IDeg simple versus IDeg stepwise (414 versus 337 events per 100 PYE, respectively, but was not statistically significant: estimated rate ratio (IDeg simple/IDeg stepwise 1.28, 95 % CI 0.92; 1.80). One severe hypoglycemic episode occurred in the IDeg simple arm (fixed dosing). Observed rates of nocturnal confirmed hypoglycemia (Table S2) were also numerically higher, with IDeg simple versus IDeg stepwise (71 versus 49 events per 100 PYE, respectively), but not statistically significant: estimated treatment ratio (IDeg simple/IDeg stepwise 1.29, 95 % CI 0.74; 2.25).

Adverse events

Overall safety profiles were similar in both titration regimens, with the majority of AEs being mild or moderate in severity. A higher percentage of patients reported treatment-emergent AEs in the IDeg stepwise (72.5 %) than the simple (60.3 %) treatment arm, but the majority of events were considered unrelated to IDeg. This was mirrored by a higher event rate for IDeg stepwise (377 per 100 PYE) versus IDeg simple (322 per 100 PYE) (Table S3). The rate

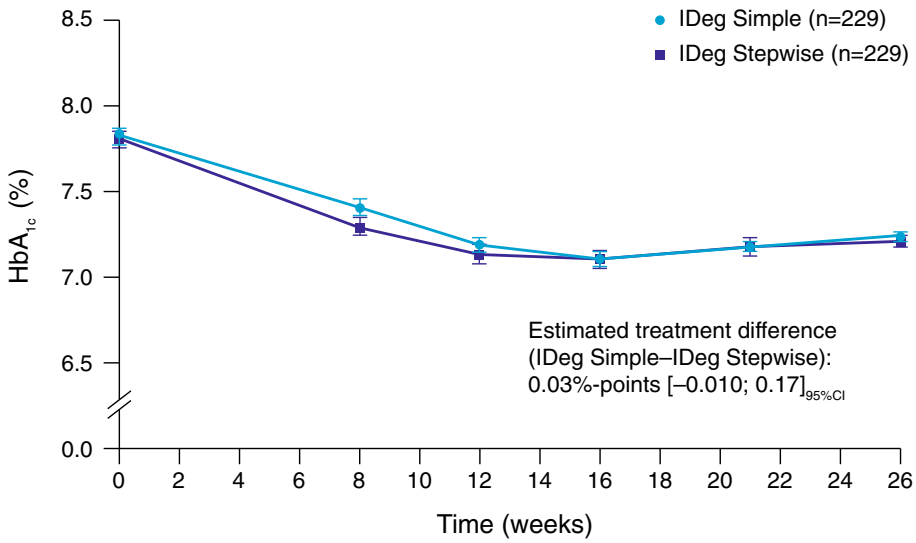

Fig. 3 Glycated hemoglobin (HbA_{1c}) over time. Data are FAS; LOCF. *CI* confidence interval, *IDeg* insulin degludec, *LOCF* last observation carried forward, *SAS* safety analysis set

of AEs possibly or probably related to IDeg was higher in the stepwise regimen (22 per 100 PYE for IDeg simple; 30 per 100 PYE for IDeg stepwise). Serious AEs were reported by 3.1 % of patients in both the simple and stepwise arms (Table S3). One death (suicide) occurred in the stepwise arm (flexible dosing). This death was not considered related to the investigational product and was the only AE leading to withdrawal during the trial.

Discussion

Study results demonstrated the efficacy and safety of simple titration compared with stepwise titration in Japanese patients with T2D inadequately controlled with IGlar, with or without OADs.

The prescribed dose was similar to or slightly lower than the dose recommended by the titration guideline in both the simple and stepwise titration groups, indicating generally good compliance with the respective titration algorithms throughout the trial. Similar results have previously been shown in a multinational phase 3b trial [18] examining simple and stepwise titration algorithms in US and European patients.

However, in the Philis-Tsimikas et al. study, dose adjustments were larger in the simple (±4 U) titration algorithm compared with the stepwise (±2 U) titration algorithm [18]. This point of differentiation resulted in faster dose adjustment and higher end-of-trial IDeg doses in patients using the simple algorithm. Despite this difference, the greater decrease in FPG and higher rates of confirmed and nocturnal confirmed hypoglycemia in the simple algorithm did not reach statistical significance. In addition, whilst similar reductions in HbA_{1c} were observed in both algorithms, a higher proportion of patients on the simple algorithm reached HbA_{1c} target of <7 %, but there were no differences in the proportion of patients meeting target without confirmed hypoglycemia.

The ability to effectively titrate IDeg may be based on its lower rates of hypoglycemia compared with IGlar [15–17]. In the current study, the rates of confirmed and nocturnal confirmed hypoglycemia, in both the simple and stepwise algorithms, were comparable with rates observed in a Pan-Asian study of IDeg patients with T2D [15]. In line with the results from the multinational population study [18], the rates of hypoglycemic episodes (confirmed and nocturnal confirmed) in the current study were numerically higher (although not statistically significant) with IDeg simple and resulted in one severe hypoglycemic episode. The lower incidence of hypoglycemic episodes with the stepwise algorithm may be explained by the increased frequency of SMBG measurements leading up to the dose adjustment, resulting in a lower incidence of hypoglycemic episodes. Additionally, there were no safety issues identified with IDeg, with no apparent differences between the simple or stepwise titration algorithms with respect to AE profiles and standard safety parameters.

This study demonstrated for the first time that a simple algorithm with ±2 U adjustments might be an alternative option to the stepwise algorithm when care is taken to adjust IDeg doses on an individual basis—depending on hypoglycemic symptoms (where more frequent SMBG measurements aid dose adjustments) and the glycemic response.

Results of this randomized, controlled, 26-week, 2 × 2, factorial design trial demonstrate the efficacy and safety of simple titration compared with stepwise titration for once-daily IDeg with or without OADs in Japanese patients with T2D inadequately treated with IGlar ± OADs.

Based on the data, IDeg titrated using a simple titration algorithm effectively improved long-term glycemic control (as measured by HbA_{1c}) since the noninferiority in change from baseline HbA_{1c} versus the stepwise titration algorithm was confirmed. FPG decreased to a similar level with both titration algorithms. Rates of confirmed and nocturnal confirmed hypoglycemic episodes were numerically higher with the simple titration algorithm compared with the stepwise titration algorithm, although this was not statistically significant.

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Compliance with ethical standards

Conflict of interest TK is a member of the National Advisory Board for Novo Nordisk Japan; reports funded research courses from MSD, Nippon Boehringer Ingelheim, Novartis, Takeda and Novo Nordisk; lecture fees from Astellas, AstraZeneca, Eli Lilly, Kissei, Kowa, Mitsubishi Tanabe, MSD, Nippon Boehringer Ingelheim, Novo Nordisk, Ono, Sumitomo Dainippon, and Takeda; manuscript fees from Eli Lilly; scholarship grants and endowments from Daiichi Sankyo, Mitsubishi Tanabe, Sumitomo Dainippon, and Takeda; and funds for clinical research from Daiichi Sankyo, Sanwa Kagaku, and Takeda. HJ has received lecture fees and clinical research grants from AstraZeneca, Astellas Pharma, Boehringer Ingelheim, Daiichi Sankyo, Eli Lilly, Takeda, Novartis Pharmaceuticals, Novo Nordisk and Sanofi. KK has received lecture fees from Astellas, Kissei, Sumitomo Dainippon Pharma, Sanwa Kagaku Kenkyusho Co., Sanofi, Novo Nordisk Pharma, Takeda, Ono Pharmaceutical Co., MSD, Novartis, Boehringer Ingelheim, Mitsubishi Tanabe Pharma, Taisho Toyama Pharmaceutical Co. and Kowa Pharmaceuticals. MLH and JH-W are employees of Novo Nordisk. SN has received honoraria for lectures from Novo Nordisk Pharma Ltd. All authors meet the International Committee of Medical Journal Editors (ICMJE) criteria for authorship for this manuscript and were involved in data interpretation, drafting/critically revising the article, and shared in the final responsibility for the content of the manuscript and the decision to submit it for publication, and take full responsibility for the contents.

Human rights statement All procedures followed were in accordance with the ethical standards of the responsible committee on human experimentation (institutional and national) and with the Declaration of Helsinki 1964 and later versions.

Informed consent Informed consent or substitute for it was obtained from all patients for being included in the study.

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