Original Research

Pharmacokinetic and Pharmacodynamic Responses of Insulin Degludec in African American, White, and Hispanic/Latino Patients With Type 2 Diabetes Mellitus

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ABSTRACT

Background: Pharmacokinetic and pharmacodynamic profiles of exogenous insulin may be affected by intrinsic factors, such as age, ethnicity/race, and hepatic and renal function. Insulin degludec (IDeg) is a basal insulin with an ultralong duration of action and a flat and stable glucose-lowering effect profile.

Objective: The purpose of this study was to investigate whether the pharmacokinetic and pharmacodynamic responses to IDeg at steady state vary according to patient race/ethnicity.

Methods: This randomized, single-center, double-blind, 2-period crossover trial investigated responses to IDeg in 59 patients with type 2 diabetes mellitus from 3 groups: African American, Hispanic/Latino, and white. Patients were allocated randomly to a sequence of 2 treatment periods, separated by a 7- to 21-day washout period, with once-daily IDeg or insulin detemir dosing for 6 days at a predefined fixed dose level (0.6 U/kg). Differences in pharmacokinetic and pharmacodynamic variables among groups were analyzed using an ANOVA with treatment period, an interaction between race/ethnicity, and treatment as fixed factors, subject as a random effect, and residual variance, depending on treatment.

Results: Total exposure to IDeg during one dosing interval at steady state ($AUC_{IDeg,\tau,SS}$) was similar among the racial/ethnic groups (ratio [95% CI]: African American vs white, 1.10 [0.91–1.31]; African American vs Hispanic/Latino, 1.13 [0.95–1.34]; and Hispanic/Latino vs white, 0.97 [0.82–1.16]). The total glucose-lowering effect of IDeg ($AUC_{GIR,\tau,SS}$) was also similar among the groups, with no statistically significant difference in pairwise comparisons (1940, 1735, and 2286 mg/kg in African American, white, and Hispanic/Latino patients, respectively). Steady state was reached in all groups after 2 to 3 days of dosing. In all groups, both exposure and glucose-lowering effect for IDeg were evenly distributed between the first and second 12 hours of the 24-hour dosing interval at steady state (mean $AUC_{IDeg,0–12h,SS}/AUC_{IDeg,\tau,SS}$ = 53%–54%; $AUC_{GIR,0–12h,SS}/AUC_{GIR,\tau,SS}$ = 47%–52%).

Conclusion: The similar pharmacokinetic and pharmacodynamic responses to IDeg in 3 racial/ethnic groups of patients with type 2 diabetes mellitus suggest that the flat, stable, and ultralong pharmacokinetic and pharmacodynamic profiles of IDeg are preserved irrespective of race/ethnicity. Although insulin doses must be adjusted on an individual basis, similar pharmacokinetic and pharmacodynamic responses to IDeg are observed in patients with differing race/ethnicity. (*Clin Ther*. 2014;36:507–515) © 2014 The Authors. Published by Elsevier HS Journals, Inc.

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Key words: Insluin degludec, ethnicity, race, pharmacokinetics, pharmacodynamics, type 2 diabetes.

INTRODUCTION

The goal of insulin therapy in patients with type 1 diabetes mellitus (T1DM) and type 2 diabetes mellitus (T2DM) is to mimic normal endogenous insulin secretion to maintain control of plasma glucose levels.[1,2] In patients with T1DM or T2DM, intermediate- or long-acting insulins are now widely used to cover basal insulin needs.[3–5]

Insulin degludec (IDeg) is a new-generation basal insulin with an ultralong duration of action. On subcutaneous injection, IDeg forms long chains of multihexamers that result in a soluble depot in the subcutaneous tissue from which IDeg monomers gradually separate.[6,7] IDeg has a distinct, slow, and continuous absorption into the circulation, leading to a flat and stable glucose-lowering effect at steady state.[8] This glucose-lowering effect is characterized by low hour-to-hour and day-to-day variability within patients.[8,9] IDeg has a duration of action that exceeds 42 hours[6–8] and a half-life of approximately 25 hours,[8] which is approximately twice as long as that for insulin glargine.[8,10]

Clinical studies have found that the ultralong and stable glucose-lowering effect of IDeg can achieve glycosylated hemoglobin (HbA_{1c}) levels similar to insulin glargine in patients with T1DM and T2DM.[11–13] However, pooled data confirm that the improvement in HbA_{1c} levels with IDeg occurs with fewer hypoglycemic episodes, particularly nocturnal episodes, than with insulin glargine.[11–14] Furthermore, the pharmacokinetic and pharmacodynamic profiles allow patients to adjust their injection time when this is more convenient because of changes in their daily schedules, without compromising efficacy or tolerability.[15]

Pharmacokinetic and pharmacodynamic profiles of insulin may be affected by intrinsic factors, such as age, race/ethnicity, and hepatic or renal function.[16] Thus, it is important to determine whether there is a difference in effect among different patient populations to provide evidence of consistency of insulin absorption across different biological factors. The aim of this study was to investigate whether the pharmacokinetic and pharmacodynamic responses to IDeg at steady state differ in patients of varying race/ethnicity with T2DM.

MATERIALS AND METHODS

Study Design

This randomized, single-center, double-blind, 2-period, crossover trial of patients with T2DM investigated the pharmacokinetic and pharmacodynamic properties of IDeg in 3 groups of patients based on their race/ethnicity. These groups were African American, white, or Hispanic/Latino (ClinicalTrials.gov identifier: NCT01043510).

Each patient was randomly allocated to a sequence of 2 treatment periods, each with once-daily IDeg or insulin detemir (IDet) dosing for 6 days at a predefined fixed-dose level (0.6 U/kg). IDet was included primarily as a control in case differences among the groups were observed for IDeg. Racial/ethnic differences in pharmacokinetic and pharmacodynamic parameters were not seen with IDet, as previously reported[17]; IDet data are not included in this report.

Before trial initiation, the protocol was reviewed and approved by the RCRC Independent Review Board. The trial was performed in accordance with the Declaration of Helsinki and its amendments in force at the initiation of the trial. Patients were informed verbally and in writing that they could withdraw from the trial at any time for any reason. Consent was obtained in writing before any trial-related activities, and the investigator retained the consent forms.

Study Participants

Eligible male and female participants were aged 18 through 70 years with clinically diagnosed T2DM for $\geq$12 months. Patients were African American but not of Hispanic or Latino origin (African American), white of Hispanic or Latino origin (Hispanic/Latino), and white not of Hispanic or Latino origin (white). All patients had a current daily basal insulin requirement of $\geq$0.2 U/kg and had received this treatment for $\geq$3 months, alone or in combination with $\leq$2 oral antidiabetic agents. All patients had a body mass index of $\leq$40.0 kg/m^2, an HbA_{1c} level of $\leq$10.0%, and a fasting C-peptide level of $<$1.0 nmol/L.

Patients were excluded if they had a history or presence of cancer, cardiac diseases, proliferative retinopathy or maculopathy and/or severe neuropathy, or a supine blood pressure at screening of $\geq$180 mm Hg (systolic) and/or $\geq$100 mm Hg (diastolic). Patients were also excluded if they were receiving current treatment with systemic corticosteroids, monoamine oxidase inhibitors, nonselective β-blockers, growth hormone, herbal

products, or nonroutine vitamins. Patients with recurrent severe hypoglycemia (>1 severe hypoglycemic event in the preceding 12 months) or hypoglycemic unawareness were excluded, as were women who were pregnant, intending to become pregnant, or breastfeeding.

Interventions and Pharmacokinetic Sampling

Before entering the IDeg and IDet treatment periods, patients treated with oral antidiabetic agents underwent a washout period of at least 7 days for those receiving sulfonylurea and/or acarbose therapy and at least 21 days for those receiving metformin therapy. During this washout period, the patient's current insulin regimen was intensified and/or additional insulin products were added (NPH insulin and/or insulin aspart), if judged necessary by the investigator, with the aim of ensuring adequate glycemic control.

IDeg and IDet were provided in 3-mL Penfill cartridges (100 U/mL; Novo Nordisk A/S, Bagsværd, Denmark). Trial product was administered via subcutaneous injection at a dose level of 0.6 U/kg into a lifted skinfold on the anterior surface of the thigh. Dosing occurred at approximately 20.00 hours each day.

Both investigator and patients were masked to the trial treatment. To maintain masking, a person not otherwise involved in the conduct of the trial prepared the doses. During treatment periods, blood glucose levels were controlled by bolus injections of insulin aspart, which were injected subcutaneously into a lifted skinfold of the lower abdominal wall. Adjustments of the bolus doses were supervised by the investigator on a daily basis and based on daily blood glucose readings. The 2 treatment periods were separated by a washout period of 7 to 21 days, and patients resumed their normal insulin treatment during this time.

Blood samples for assessment of serum IDeg concentration were taken before each dose (at −15 minutes and 0 hours), at 1- or 2-hour intervals until 24 hours, and then at 30, 36, 48, 72, 96, and 120 hours after the last dose to estimate IDeg concentration in the terminal phase. Serum IDeg concentrations were measured using a specific ELISA that is highly specific for IDeg.

Pharmacodynamic Measurements (Clamp Procedure)

Immediately after the last dose, a 24-hour euglycemic glucose clamp was performed using a Biostator controlled glucose infusion system (Life Science Instruments, Elkhart, Indiana).[8] In brief, approximately 5 to 6 hours before trial product administration, patients received a variable intravenous infusion of human regular insulin (Novolin® R; Novo Nordisk A/S) or glucose to obtain a blood glucose target level of 5.0 mmol/L (90 mg/dL). Blood glucose had to be at the target level no later than 2 hours before trial product administration. From 1 hour before trial product administration, the insulin infusion rate (if any) was reduced as much as possible while still keeping the blood glucose concentration at the clamp target level. During the last 10 minutes, the infusion of insulin was gradually reduced and terminated immediately before trial product administration. Blood glucose concentration was maintained at the clamp blood glucose target level of 5.0 mmol/L (90 mg/dL) until 24 hours after trial product administration.

The clamp was to be terminated early if the blood glucose level exceeded 11.1 mmol/L (200 mg/dL) without any glucose infusion for at least 30 minutes; however, this did not occur for any participant in this trial. Patients remained fasting during the entire clamp procedure, with no oral intake other than water, and remained in a supine or semisupine position.

Assessments

The aim of the study was to investigate whether the pharmacokinetic and pharmacodynamic responses of IDeg at steady state vary among the 3 different groups of patients based on race/ethnicity. Responses were based on serum IDeg concentration–time profiles and glucose infusion rate (GIR) profiles obtained during a 24-hour dosing interval at steady state. Tolerability assessments included adverse events (AEs), confirmed hypoglycemic episodes (either severe as defined by the American Diabetes Association[18] or verified by a plasma glucose concentration <3.1 mmol/L [56 mg/dL]), injection site reactions, ECG, vital signs, physical examination, and laboratory tolerability parameters.

Data and Statistical Analyses

Total exposure of IDeg at steady state ($AUC_{IDeg,\tau,SS}$) was calculated as the area under the serum IDeg concentration–time curve during a 24-hour dosing interval. Distribution of IDeg exposure was assessed by comparing the ratios of the AUC_{IDeg} for the first 12-hour interval versus the entire 24-hour interval ($AUC_{IDeg,0–12h,SS}/AUC_{IDeg,\tau,SS}$). To calculate the time to reach pharmacokinetic steady state, serum IDeg trough concentrations were measured at the end of

each 24-hour dosing interval. Terminal half-life for IDeg was estimated from the individual log-concentration-time profiles after the last dose of IDeg and calculated as $\log(2)/\lambda_{z,IDeg,SS}$.

Total glucose-lowering effect of IDeg at steady state ($AUC_{GIR,\tau,SS}$; primary end point) was calculated as the area under the smoothed GIR curve using the linear trapezoidal technique on interpolated points. The GIR profiles were smoothed by the Loess smoothing technique using a fixed smoothing parameter of 0.25 and sampling with 5-minute intervals. The distribution of glucose-lowering effect during a 24-hour dosing interval at steady state was quantified by estimating the ratio of AUC_{GIR} for the first 12-hour interval versus the entire 24-hour interval ($AUC_{GIR,0–12h,SS}$/$AUC_{GIR,\tau,SS}$).

The $AUC_{IDeg,\tau,SS}$ and $AUC_{GIR,\tau,SS}$ were both compared among the racial/ethnic groups using an ANOVA method with treatment period, and an interaction between race/ethnicity and treatment, as fixed factors, subject as a random effect, and residual variance depending on treatment. $AUC_{IDeg,\tau,SS}$ was log-transformed before analysis, whereas $AUC_{GIR,\tau,SS}$ was analyzed on the original scale because the prespecified model on a log scale was not feasible because of an outlier; sensitivity analyses with this patient excluded confirmed the results.

RESULTS

Study Participants

Of 233 patients screened, 63 (18 African American, 22 Hispanic/Latino, and 23 white) were included in the trial, randomized, and exposed to the trial product. Fifty-seven patients completed the trial (17 African American, 22 Hispanic/Latino, and 18 white). Fifty-nine patients (18 African American, 22 Hispanic/Latino, and 19 white) completed the IDeg treatment period and were thus included in the IDeg analyses at steady state. Baseline characteristics of each race/ethnicity group are summarized in Table I.

Steady-State Pharmacokinetic Profiles

The mean steady-state IDeg pharmacokinetic profiles were similar for the 3 race/ethnicity groups (Figure 1). The $AUC_{IDeg,\tau,SS}$ was similar for the 3 groups, with mean pairwise ratios between the groups close to 1 (Table II). The exposure to IDeg was similar during the first and second 12 hours for all 3 groups because the ratio of $AUC_{IDeg,0–12h,SS}/AUC_{IDeg,\tau,SS}$ was close to 50% in all race/ethnicity groups (African American, 53%; Hispanic/Latino, 54%; and white, 54%). The terminal half-life for IDeg was within the same range for the African American (harmonic mean, 28.5 hours), Hispanic/Latino (22.8 hours), and white (27.1 hours) patients. Pharmacokinetic steady state for IDeg was reached after 2 to 3 days of dosing in all 3 race/ethnicity groups.

Steady-State Pharmacodynamic Profiles

The GIR profiles for IDeg were flat and stable in all 3 race/ethnicity groups (Figure 2). The $AUC_{GIR,\tau,SS}$ was similar among the race/ethnicity groups, with no statistically significant differences in pairwise comparisons (ie, zero was within the 95% CI of the

Table I. Baseline characteristics.*

Characteristic	African American	White	Hispanic/Latino
Patients, No.	18	23	22
Sex (male/female), No.	11/7	13/10	13/9
Age, y	48.9 (8.4)	55.1 (8.9)	51.5 (8.3)
BMI, kg/m^2	35.3 (3.7)	32.3 (5.6)	30.2 (4.4)
Duration of diabetes, y	9.3 (3.0)	12.1 (6.7)	13.4 (7.5)
HbA_{1c}, %	8.3 (1.4)	8.1 (1.2)	8.4 (1.1)
C-peptide, nmol/L	0.44 (0.24)	0.54 (0.27)	0.49 (0.26)

BMI = body mass index; HbA_{1c} = glycosylated hemoglobin.
*Data are mean (SD) unless otherwise specified.

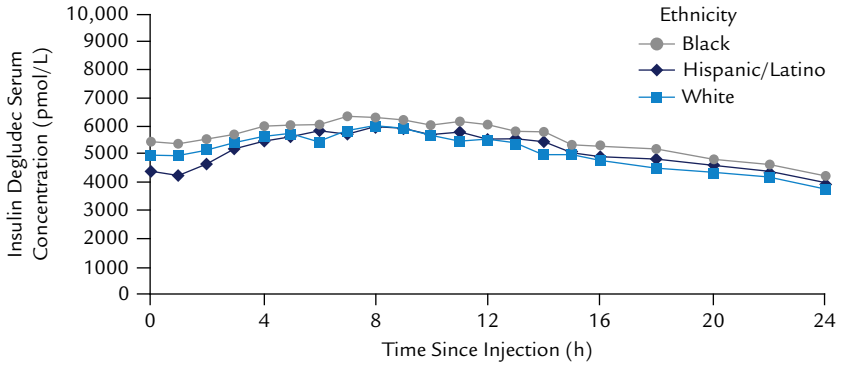

Figure 1. Mean insulin degludec pharmacokinetic profiles at steady state in African American, white, and Hispanic/Latino patients with type 2 diabetes mellitus (dose, 0.6 U/kg).

estimated mean differences among the groups; Table III). The ratio between the glucose-lowering effect in the first 12 hours and in the whole dosing interval ($AUC_{GIR,0–12h,SS}/AUC_{GIR,\tau,SS}$) was close to 50% for all 3 race/ethnicity groups (African American, 52%; Hispanic/Latino, 50%; and white, 47%). This result indicates that the glucose-lowering effect of IDeg was evenly distributed between the first and second 12 hours of the dosing interval at steady state in all groups. For all 3 race/ethnicity groups, blood glucose concentrations were maintained at 5.0 mmol/L (90 mg/dL) throughout the euglycemic clamp. End of action (defined as the time point when blood glucose concentration was consistently >150 mg/dL [8.3 mmol/L] during the glucose clamp[19]) did not occur in any patients; thus, the glucose-lowering effect of IDeg extended beyond the clamp duration of 24 hours in all patients in all 3 race/ethnicity groups.

Safety

IDeg was well tolerated, and no unexpected tolerability concerns were identified. There were no observed differences among the 3 race/ethnicity groups in reported AEs. Sixty-five treatment-emergent AEs were reported in 34 patients (55%). All AEs were mild or moderate. Six of the AEs in 5 patients were judged

Table II. Total exposure to insulin degludec (IDeg; 0.6 U/kg) at steady state ($AUC_{IDeg,\tau,ss}$) in African American Black, White and Hispanic/Latino patients with type 2 diabetes mellitus.

Race/ethnic group	Black	White	Hispanic/Latino
$AUC_{IDeg,\tau,ss}$ (pmol·h/L)			
Geometric mean (CV)	131,578 (22)	120,380 (36)	116,940 (25)
Group ratio estimates*			
Pairwise comparisons (pmol·h/L) [95% CI]			
Black vs White	1.10 [0.91, 1.31]		
Black vs Hispanic/Latino	1.13 [0.95, 1.34]		
Hispanic/Latino vs White		0.97 [0.82, 1.16]	

*Group ratio estimates are based on least square means.
CV, Coefficient of variation in %

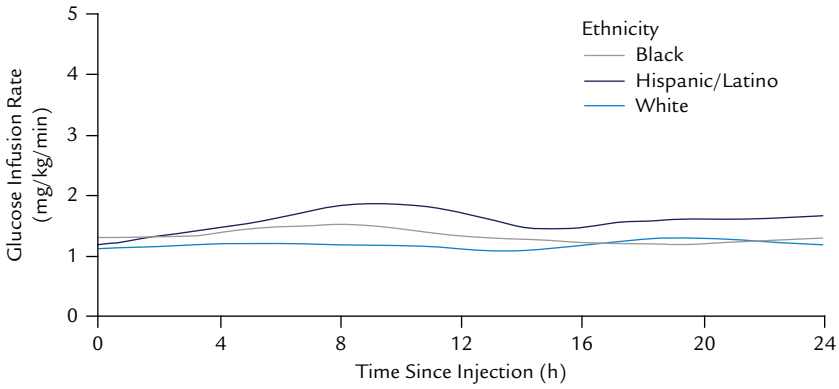

Figure 2. Mean glucose infusion rate profiles at steady state in African American, white, and Hispanic/Latino patients with type 2 diabetes treated with insulin degludec (dose, 0.6 U/kg).

to be probably or possibly related to IDeg or insulin aspart. No severe or serious AEs were reported in this trial. The most common AEs were headache (16 events in 13 patients) and back pain (5 events in 4 patients). Mild injection-site reactions were reported in 2 of >300 injections with IDeg. One reaction in one patient was classified as an administration-site condition, and the other in another patient was classified as erythema under skin and subcutaneous tissue disorders. A total of 44 confirmed treatment-emergent hypoglycemic episodes were reported in 23 patients treated with IDeg (7 African Americans, 8 Hispanics/Latinos, and 8 whites). No clinically significant changes in vital signs, ECG, or laboratory tolerability parameters were observed during the study.

DISCUSSION

This clinical trial evaluated the pharmacokinetic and pharmacodynamic properties of IDeg at steady state to determine whether specific dosing recommendations should be provided to certain

Table III. Total glucose-lowering effect of insulin degludec (IDeg; 0.6 U/kg) at steady state ($AUC_{GIR,\tau,ss}$) in Black, White and Hispanic/Latino patients with type 2 diabetes mellitus.

Race/ethnic group	Black	White	Hispanic/Latino
$AUC_{GIR,\tau,SS}$ (mg/kg)			
Mean (SD)	1940 (1373)	1735 (1057)	2286 (1061)
Group difference estimates*			
Pairwise comparisons (mg/kg) [95% CI]			
Black vs White	218 [-551, 986]		
Black vs Hispanic/Latino	-346 [-1088, 396]		
Hispanic/Latino vs White		564 [-168, 1295]	

*Group difference estimates are based on least square means.
SD, standard deviation

racial/ethnic groups. In African American, Hispanic/Latino, and white patients with T2DM, the pharmacokinetic profiles of IDeg at steady state were comparable, with total exposure being similar across all 3 race/ethnicity groups. The glucose-lowering effect of IDeg was flat and stable during a 24-hour dosing interval, irrespective of race/ethnicity, with total glucose-lowering effect also similar across all groups. Furthermore, the glucose-lowering effect extended beyond 24 hours in all African American, Hispanic/Latino, and white patients. These results suggest that the pharmacokinetic and pharmacodynamic properties of IDeg are preserved among different race/ethnicity groups.

Reports of differences in the pharmacokinetic and pharmacodynamic profiles of insulins among patients of differing race/ethnicity are limited.[16] There was no anecdotal evidence of differences among patients of varying race/ethnicity in the large therapeutic confirmatory studies of IDeg in patients with T1DM and T2DM,[11,12] although most patients in those trials were white.[11,12] In the present study, the similar results across racial/ethnic groups are consistent with previous results for other available insulins. In a study evaluating the pharmacokinetic and pharmacodynamic properties of IDet in African American, Hispanic/Latino, and white patients with T2DM, similar results were observed among the groups.[17] These results are supported by the findings in the present study where no statistically significant differences in the pharmacokinetic and pharmacodynamic profiles were observed between race/ethnicity groups for IDeg and IDet. Furthermore, no difference in absorption for insulin aspart was found in patients of differing race/ethnicity.[20] Therefore, it is proposed that for these insulins, no adjustment of dose is necessary based on the race/ethnicity of the patient.[16] On the basis of the results in the present study, dosing recommendations for IDeg should not require specific adjustments for race/ethnicity in African American, Hispanic/Latino, or white patients. The similar time to reach steady-state IDeg levels with once-daily dosing across differing patient groups supports these dosing recommendations.[21] However, it is recognized that all insulins must be adjusted to the clinical response in each individual given the range of insulin resistance and clinical responses among individuals.[22]

One of the strengths of the study design used here is the acquisition of data at steady state. Because IDeg reaches clinical steady state within 2 to 3 days in a once-daily dosing regimen, steady state represents the longest treatment time for patients in clinical practice and in this study. Therefore, it is the most clinically relevant context in which to examine pharmacokinetic and pharmacodynamic properties of IDeg. Furthermore, this study used a euglycemic glucose clamp, considered to be the gold standard for assessing the glucose-lowering effects of insulin products.[2]

One of the limitations of this study is that the euglycemic glucose clamp procedure is, by nature, innately distinct from the clinical environment, making it difficult to relate study findings to clinical reality. This study was conducted in patients with T2DM, implying the possibility that the glucose clamp results might be affected by endogenous insulin secretion. However, the glucose clamp target was set relatively low (5.0 mmol/L [90 mg/dL]) to suppress endogenous insulin secretion, and, as assessed from the individual C-peptide profiles during the glucose clamp, endogenous insulin secretion was suppressed in all patients throughout the clamp. Another aspect of T2DM that could potentially affect the trial results was the use in some cases of oral antidiabetic agents. However, patients being treated with oral antidiabetic agents underwent a washout period before starting on the trial product. This was to allow estimation of the pharmacodynamic response of IDeg without interference from the effect of concomitant antidiabetic drugs.

In the present study, no obvious differences were found in the pattern of hypoglycemic episodes among the 3 groups of varying race/ethnicity. It is possible in this small group of patients that the rate of hypoglycemic events may be artificially high because of the study design because patients received a fixed dose (0.6 U/kg) of insulin that was independent of the patients' individual insulin requirement. IDeg should be titrated in line with individual requirements to optimize insulin therapy and reduce the risk of hypoglycemic events.

CONCLUSION

IDeg resulted in similar pharmacokinetic and pharmacodynamic responses in patients with T2DM irrespective of race/ethnicity. These results confirm that the ultralong pharmacologic properties of IDeg are preserved in the 3 racial/ethnic groups tested. Although insulin doses must be adjusted on an individual basis,

the results from this trial imply that no specific dose adjustments are required in these populations.

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CONFLICTS OF INTEREST STATEMENT

Dr Hompesch is a consultant via the Profil Institute for Clinical Research and is a Profil employee and stockholder. Dr Morrow is an employee and stockholder of Profil. Dr Watkins is a board member of the San Diego County Medical Society and is an employee of Profil. Dr Roepstorff is an employee and stockholder of Novo Nordisk A/S. Dr Thomsen is an employee of Novo Nordisk A/S. Dr Haahr is an employee and stockholder of Novo Nordisk A/S.

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