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CLINICAL TRIAL

Insulin degludec/insulin aspart in Japanese patients with type 1 diabetes mellitus: Distinct prandial and basal glucose-lowering effects

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ABSTRACT

Aims/Introduction: Insulin degludec/insulin aspart (IDegAsp) is a soluble co-formulation of long-acting insulin degludec (IDeg) and rapid-acting insulin aspart (IAsp). The present study investigated the pharmacodynamic properties of IDegAsp in Japanese patients with type 1 diabetes mellitus.

Materials and Methods: In this randomized, double-blind, two-period, cross-over trial, 21 Japanese patients with type 1 diabetes mellitus received single doses of 0.5 U/kg IDegAsp and biphasic insulin aspart 30 in a randomized sequence (13–21 days washout between treatments). The pharmacodynamic response was evaluated in a 26-h euglycemic glucose clamp (target 5.5 mmol/L). Single-dose IDegAsp glucose infusion rate (GIR) profiles were extrapolated to steady state using modeling.

Results: The IDegAsp single-dose GIR profile showed a clear distinction between the effects of the bolus (IAsp) and basal (IDeg) components in IDegAsp. When simulated to steady state, the GIR profile of IDegAsp was shifted upwards compared with the single-dose profile, and showed a rapid onset of action and a distinct peak from the IAsp component followed by a separate and sustained basal action from the long-acting IDeg component. For biphasic insulin aspart 30, the initial shape of the GIR profile was similar to IDegAsp, but GIR continuously decreased from maximum and reached zero 18–20 h post-dosing. The characteristics of the GIR profile for IDegAsp were retained when simulated to steady state in a twice-daily dosing regimen.

Discussion: In Japanese patients with type 1 diabetes mellitus, the pharmacodynamic profile of IDegAsp is characterized by distinct prandial and basal effects from the IAsp and IDeg components, consistent with what has been reported previously in Caucasian patients with type 1 diabetes mellitus.

INTRODUCTION

Diabetes is a debilitating disease characterized by deficiencies in insulin secretion, insulin action or both, leading to chronic hyperglycemia. Patients with type 1 diabetes mellitus require insulin treatment from disease onset, whereas in patients with type 2 diabetes mellitus, insulin treatment is a very common consequence as the disease progresses[1]. Because of the high carbohydrate content in the Asian diet, one of the most widely-used therapies for insulin initiation and intensification in type 2 diabetes mellitus in Asia is treatment with biphasic insulin to cover both postprandial plasma glucose excursions and basal insulin needs[2].

Although biphasic insulin represents a step forward in mimicking the physiological insulin secretion pattern by having both bolus and basal components, the pharmacokinetic and pharmacodynamic properties are still suboptimal[3,4]. Interference between the bolus and basal components leads to alterations in the action profiles of the individual components, resulting in an undesired, prolonged effect of the bolus component. In addition, the basal component of biphasic insulin has greater variability and a shorter duration of action compared with long-acting insulin analogs[5].

Insulin degludec/insulin aspart (IDegAsp) is a fixed and soluble combination of the long-acting basal insulin, insulin degludec (IDeg; 70%), and rapid-acting insulin aspart (IAsp; 30%)[6]. The IDegAsp formulation has been designed so that the individual components maintain their independent pharmacokinetic and pharmacodynamic properties. In solution, in the pen device, the IDeg component forms soluble dihexamers at neutral pH, whereas IAsp remains as distinct hexamers. On subcutaneous injection, the IDeg dihexamers immediately self-associate into soluble multihexamers in the subcutaneous tissue from which IDeg monomers dissociate slowly and continuously, and are absorbed into the circulation at a stable rate. In contrast, IAsp hexamers promptly dissociate to monomers that are rapidly absorbed into the circulation[7,8]. Accordingly, in Caucasians, IDegAsp has been shown to provide distinct prandial and basal glucose-lowering effects at steady state[8], and with a sharper separation of the prandial and basal components compared with biphasic insulin aspart 30 (BIAsp 30)[9]. IDegAsp is a fully soluble ready-to-use insulin product; that is, unlike other available biphasic formulations, IDegAsp does not require resuspension before injection, thereby easing the administration.

So far, no studies have investigated the pharmacological properties of IDegAsp in Japanese individuals. Differences in drug responses; that is, in insulin pharmacodynamics, might occur between patient populations of different racial and ethnic background[10,11]. It is therefore important to investigate the pharmacological properties of specific insulins in patient groups of various races and/or ethnicity. The purpose of the present study was to investigate the pharmacodynamic properties of IDegAsp in Japanese individuals and to relate the current trial results to those previously obtained in Caucasians[8,9]. Patients with type 1 diabetes mellitus were included as this enabled assessment of the pharmacodynamic response of IDegAsp in a euglycemic glucose clamp without interference from the effect of endogenous insulin.

MATERIALS AND METHODS
Trial design and participants
This was a single-center (Sumida Hospital, Tokyo, Japan), randomized, double-blind, two-period, cross-over, single-dose trial carried out in Japanese patients with type 1 diabetes mellitus (clinicaltrials.gov identifier: NCT01051102). The trial was approved by a local institutional review board before trial initiation. It was carried out in accordance with the Declaration of Helsinki and its amendments in force at the initiation of the trial[12], and in accordance with the Ministry of Health and Welfare Ordinance on Good Clinical Practice[13]. All participants gave written informed consent before any trial-related activities took place.

Eligible participants were Japanese men and women aged 20–65 years (inclusive), with type 1 diabetes mellitus treated with insulin for ≥12 months, and a basal insulin requirement >0.2 (I)U/kg/day, a body mass index of 18.0–28.0 kg/m^2 (inclusive) and a glycosylated hemoglobin level ≤10.0% (values reported based on Japanese Diabetes Society value). Patients were excluded if they had any history or presence of cancer or cardiovascular disease, supine blood pressure at screening outside the range of 90–140 mmHg for systolic blood pressure and 50–90 mmHg for diastolic blood pressure, proliferative retinopathy or maculopathy, and/or severe neuropathy, recurrent severe hypoglycemia (more than one severe hypoglycemic episode during the past 12 months) or hypoglycemic unawareness, or hospitalization for diabetic ketoacidosis during the past 6 months. Patients who smoked more than five cigarettes or the equivalent per day, as well as pregnant or breastfeeding women, were also excluded.

Trial procedures
The trial consisted of a screening visit, two dosing visits and a follow-up visit. Participants were randomly assigned to one of two treatment sequences (IDegAsp followed by BIAsp 30, or BIAsp 30 followed by IDegAsp).

At each dosing visit, participants received a single-dose administration of 0.5 U/kg IDegAsp or BIAsp 30. IDegAsp and BIAsp 30 were dosed as subcutaneous injections into a lifted skinfold on the anterior surface of the thigh. Both IDegAsp and BIAsp 30 were provided in 3-mL Penfill® cartridges (100 U/mL; Novo Nordisk, Bagsværd, Denmark), and administered using a syringe and needle. Both the investigator and the participants were blinded to trial treatment. In order to maintain the blinding, the trial product was administered by a doctor who was not involved in any other trial activity or assessment.

Before dosing at each dosing visit, participants underwent a washout period, where their usual insulin was not taken for at least 48 h (for insulin detemir or insulin glargine), at least 24 h (for neutral protamine Hagedorn or other intermediate-acting insulin) or at least 14 h (for short-acting insulin). However, up to 6 (I)U of short-acting insulin other than IAsp was allowed between 14 and 9 h pre-dose. For participants normally using insulin detemir or insulin glargine, neutral protamine Hagedorn insulin was used as replacement insulin between 48 and 24 h pre-dose. Likewise, human soluble insulin was used as replacement insulin between 24 and 9 h pre-dose. Participants fasted (with no oral intake other than water) for 14 h prior to dosing. However, up to 20 g of rapidly absorbable carbohydrates could be ingested to prevent hypoglycemia.

At each dosing visit, a euglycemic glucose clamp was carried out until 26 h post-dosing by means of an STG-22 (glucose-controlled insulin infusion system; Artificial Endocrine Pancreas, NIKKISO Co. Ltd., Japan). Approximately 3 h before dosing of trial product, participants received a variable intravenous (IV) infusion of either human insulin or 10% glucose solution to obtain a blood glucose clamp target of 5.5 mmol/L. Blood glucose level was required to be at the target level for at least 1 h before dosing without any glucose infusion. After dosing, the IV insulin infusion (if any) was decreased gradually and stopped completely when blood glucose had decreased by

0.3 mmol/L. Glucose infusion was then initiated to maintain the blood glucose concentration at the clamp target of 5.5 mmol/L. The clamp was planned to continue for 26 h post-dosing, but was terminated earlier if blood glucose exceeded 13.9 mmol/L without any glucose administered for at least 30 min. During the entire clamp procedure, participants remained fasting (with no oral intake other than water), and stayed in a supine or semi-supine position.

Blood samples for pharmacokinetic assessment were taken regularly until 120 h post-dose both after IDegAsp and BIAsp 30 dosing (in order to maintain the double-blind). After IDegAsp dosing, blood samples were analyzed for serum IDeg concentrations (until 120 h post-dose), and after both IDegAsp and BIAsp 30 dosing, blood samples were analyzed for serum IAsp concentrations (until 12 h post-dose for IDegAsp dosing and until 24 h post-dose for BIAsp 30 dosing) (data not shown).

There was a washout interval of 13–21 days between the two dosing visits. For each dosing visit, participants resumed their own insulin treatment after the last blood sample for pharmacokinetic assessment had been taken at 120 h post-dose. Between clamp termination and 120 h post-dose, insulin treatment was restricted to neutral protamine Hagedorn insulin and human soluble insulin.

Assessments

Pharmacodynamic end-points included the area under the glucose infusion rate (GIR) curve during one 24-h dosing interval ($AUC_{GIR,0-24h,SD}$) and the maximum GIR ($GIR_{max,SD}$) after administration of a single dose of IDegAsp or BIAsp 30.

Safety was monitored for both IDegAsp and BIAsp 30 administration. Safety end-points comprised adverse events, including local injection site reactions, laboratory safety assessments, physical examination, vital signs, electrocardiogram and hypoglycemic episodes (defined as 'confirmed' when they were either 'severe' as according to the American Diabetes Association[14] or verified by a plasma glucose level of <3.1 mmol/L).

Statistical analysis

Pharmacodynamic end-points were based on the full analysis set comprising all randomized participants, whereas safety end-points were based on the safety analysis set comprising all participants who received at least one dose of either IDegAsp or BIAsp 30.

It was important to ensure reliable calculation of all end-points including $GIR_{max,SD}$ without influence from the minor arbitrary fluctuations in GIR introduced by the clamp method. Therefore, GIR data were smoothed using the Loess smoothing technique using a fixed smoothing parameter of 0.1 for the bolus part of the curve (the first 6 h) and 0.25 for the basal part of the curve (from 6 h onwards) using combined smoothing. As an inherent consequence of the smoothing technique, smoothed profiles might not always start at zero. Each point on the smoothed profile is a result of fitting a linear regression,

with most weight assigned to the closest neighboring data. At the very start of the profile, almost all data available for the smoothing are non-zero positive values to the right of the data point, and consequently the smoothed mean profile will not start at zero. Therefore, as a supplement, the raw mean GIR profiles were also plotted.

The pharmacodynamic response of IDegAsp and BIAsp 30 was determined by calculating $AUC_{GIR,0-24h,SD}$ and $GIR_{max,SD}$ from the smoothed GIR profiles. $AUC_{GIR,0-24h,SD}$ was calculated using the linear trapezoidal technique on interpolated data points.

Safety end-points were summarized using descriptive statistics.

Pharmacodynamic modeling

To simulate steady-state IDegAsp pharmacodynamic profiles from this single-dose study, a population pharmacokinetic/pharmacodynamic model was developed based on the IDeg pharmacokinetic, IAsp pharmacokinetic and GIR data from the present study[8]. In addition to separate pharmacokinetic components for IDeg and IAsp (with a total of eight parameters), the model consisted of a compartment describing insulin action for IDeg (with a turnover and an insulin sensitivity parameter), and a compartment describing insulin action for IAsp (with a different turnover and insulin sensitivity parameter) with the assumption that the insulin action contributions from IDeg and IAsp were additive on the GIR scale. The parameters of the model were estimated in a population setting using a non-linear mixed-effects approach, which allowed individual sets of the 12 parameters for each of the participants included in the trial to be obtained. The values of the absorption rate parameter for IDeg were subsequently calibrated based on additional information from the comprehensive clinical pharmacology program with IDeg (the same calibration factor was applied for all participants). Using the individual parameters, simulation of multiple once-daily dosing of IDegAsp was carried out to obtain the mean steady-state GIR profile for IDegAsp. More specifically, multiple once-daily dosing for 6 days at a dose level of 0.5 U/kg/day was simulated by extrapolating the profile for each of the participants and calculating the mean of the profiles on day 6. In a similar manner, simulation of multiple twice-daily dosing of IDegAsp was carried out at a daily dose level of 0.5 U/kg based on the assumption that the once-daily dose of 0.5 U/kg would be divided equally into two for the twice-daily dosing. The modeling was carried out using NONMEM® version 7.1.2 (ICON Development Solutions, Ellicott City, MD, USA).

RESULTS

Participants

A total of 32 patients were screened, 21 patients were randomized and exposed to at least one trial drug administration, and 20 patients completed the trial. One participant was withdrawn after the second treatment period, as the participant had been

diagnosed with Basedow's disease (but was included in all analyses). The 21 participants in the full analysis set and the safety analysis set were equally distributed with respect to sex (11 men and 10 women), and mean (standard deviation) age at baseline was 40.6 years (11.1 years). Mean (standard deviation) body mass index at baseline was 21.9 kg/m^2 (2.2 kg/m^2) and mean (standard deviation) duration of diabetes was 18.1 years (11.1 years). Mean (standard deviation) glycosylated hemoglobin and fasting C-peptide concentrations were 7.5% (1.3%) and 0.06 nmol/L (0.05 nmol/L), respectively.

Pharmacodynamics

The single-dose GIR profile of IDegAsp (Figure 1, dotted line; and Figure 2a) shows a clear distinction between the pharmacodynamic effects of the bolus (IAsp) and basal (IDeg) components in IDegAsp. As this trial was carried out as a single-dose trial, the IDegAsp single-dose GIR profile was extrapolated to the more clinically relevant steady-state setting. The simulated steady-state GIR profile for once-daily IDegAsp is shown in Figure 1 (solid line). An upshift in the simulated GIR profile at steady state was apparent compared with the single-dose profile, as a result of the long duration of action of IDeg, the basal component in IDegAsp. At steady state, the GIR profile for IDegAsp showed a rapid onset of action and a distinct peak from the IAsp component followed by a separate and sustained basal action from the long-acting IDeg component. In contrast, as can be seen in Figure 2b, the GIR profile for BIAsp 30 continuously decreased from its maximum level and reached zero at 18–20 h after dosing. Hence, because of the glucose-lowering effect of BIAsp 30 lasting less than 24 h, the single-dose GIR profile for BIAsp 30 also reflects what would be expected in a steady-state setting after once-daily dosing of BIAsp 30.

Smoothed and raw single-dose GIR profiles are shown in Figure 2 for IDegAsp and BIAsp 30. The shapes of the smoothed and raw GIR profiles were comparable; however, as expected, only the raw GIR profiles started at zero (see Statistical Analysis). Also, the onset of action and the shape of the single-dose GIR profiles over the first 4 h were similar for IDegAsp and BIAsp 30, although GIR$_{max,SD}$ was lower for IDegAsp compared with BIAsp 30 (Table 1). It is, however, important to note that caution should be taken when directly comparing the GIR profiles of IDegAsp and BIAsp 30 after single-dose administration. For IDegAsp, the single-dose GIR profile is not representative of the clinical setting, as the steady state for the IDeg component is not achieved until 2–3 days of once-daily dosing (as further addressed in the Discussion).

The geometric mean and coefficient of variation for AUC$_{GIR,0-24h,SD}$ and GIR$_{max,SD}$ are shown in Table 1 both for IDegAsp and BIAsp 30 after single-dose administration, as well as for IDegAsp simulated to once-daily steady state. A sensitivity analysis, excluding the participant with Basedow's disease from the statistical analysis, suggested that this participant did not impact the results (data not shown).

The simulated steady-state GIR profile for twice-daily IDegAsp (Figure 3) showed that the distinct IAsp and IDeg components of the GIR profile of IDegAsp are retained after each dose in a twice-daily regimen. The GIR profile characteristics over each dosing interval were similar to that observed with IDegAsp once-daily simulation to steady state (Figure 1).

Safety

Both IDegAsp and BIAsp30 were well tolerated. Just three adverse events were reported in a single participant during the trial (all mild and unrelated to trial product; all after BIAsp 30 treatment). No serious adverse events were reported, and there were no clinically significant findings among clinical laboratory tests, physical examination, vital signs or electrocardiogram. There were no local injection site reactions reported during the trial. No episodes of severe hypoglycemia were reported, and
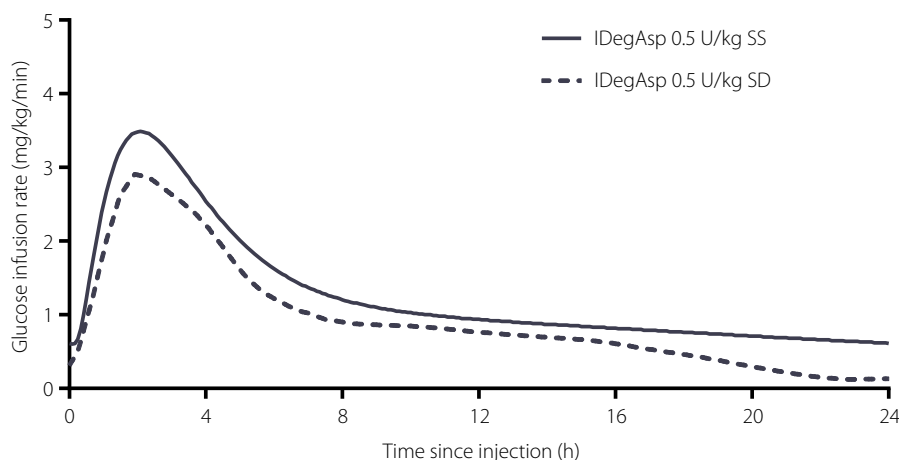

Figure 1 | Mean glucose infusion rate profiles of 0.5 U/kg insulin degludec/insulin aspart (IDegAsp) after single dose (SD) and simulated to once-daily steady state (SS) in Japanese patients with type 1 diabetes mellitus.
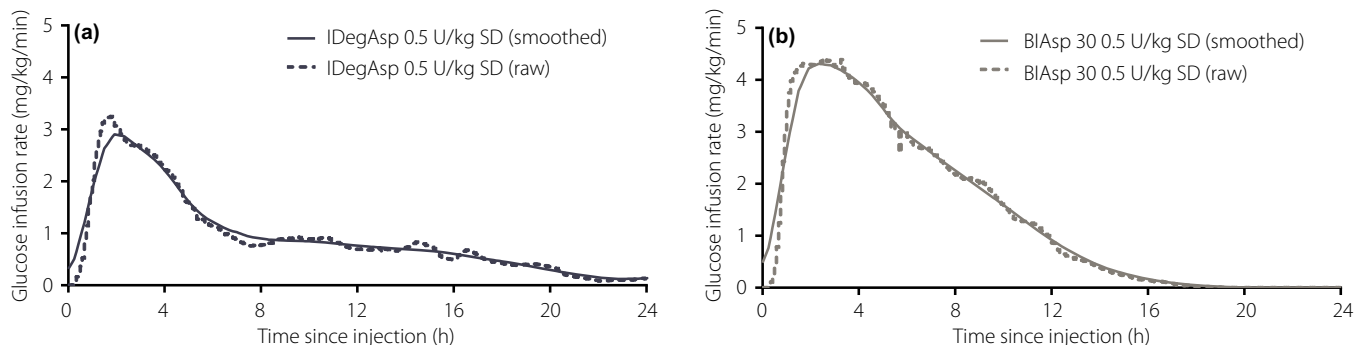
Figure 2 | Smoothed and raw mean glucose infusion rate profiles after single dose (SD) of (a) 0.5 U/kg of insulin degludec/insulin aspart (IDegAsp) and (b) biphasic insulin aspart 30 (BIAsp 30) in Japanese patients with type 1 diabetes mellitus.

there were no apparent differences in the number of hypoglycemic episodes between IDegAsp and BIAsp 30.

DISCUSSION

The present single-dose study, which is the first to investigate the pharmacodynamic properties of IDegAsp in Japanese

Table 1 | Pharmacodynamic parameters after a single dose of 0.5 U/kg insulin degludec/insulin aspart or biphasic insulin aspart 30 and simulated to once-daily steady state for insulin degludec/insulin aspart 0.5 U/kg in Japanese patients with type 1 diabetes mellitus

	IDegAsp SD	IDegAsp SS	BIAsp 30 SD
$AUC_{GIR,0-24h}$ (mg/kg)	1,170 (52)	1,610 (62)	1,856 (47)
GIR_{max} (mg/[kg × min])	3.0 (32)	3.3 (52)	4.5 (38)

Data are geometric mean (coefficient of variation %). AUC, area under the curve; BIAsp 30, biphasic insulin aspart 30; GIR, glucose infusion rate; GIR_{max}, maximum glucose infusion rate; IDegAsp, insulin degludec/insulin aspart; SD, single dose; SS, steady state.

individuals, showed a clear separation of the effects of the bolus (IAsp) and basal (IDeg) components in IDegAsp. IDegAsp showed a rapid onset of action and distinct peak attributable to the IAsp component, followed by a flat and stable glucose-lowering effect attributable to the IDeg component. The latter was particularly obvious when the single-dose GIR profile was extrapolated to the more clinically relevant steady-state setting. In contrast, with BIAsp 30, the bolus part of the glucose-lowering effect was prolonged leading to a 'shoulder' effect seen from approximately 6–10 h followed by a continued decline in effect towards zero at approximately 18–20 h post-dose. Single doses of IDegAsp and BIAsp 30 were well tolerated in Japanese patients with type 1 diabetes mellitus.

The characteristics of the GIR profile of IDegAsp, as shown here in Japanese patients with type 1 diabetes mellitus, are in line with those observed in Caucasians. Thus, the clearly separate effects of the bolus and basal components in IDegAsp have been shown in single-dose glucose clamp studies in younger adult Caucasian patients with type 1 diabetes mellitus[9], as well as in elderly Caucasian patients with type 1 diabetes mellitus.[15]
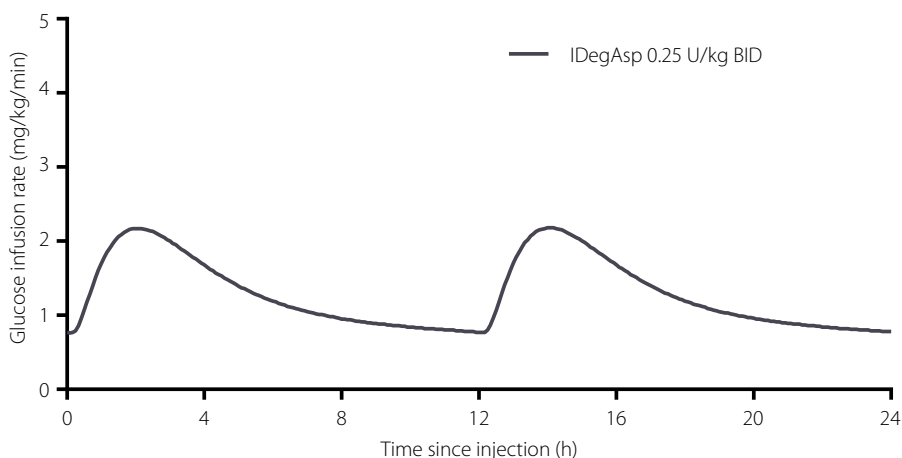

Figure 3 | Mean glucose infusion rate profile of insulin degludec/insulin aspart (IDegAsp; 0.25 U/kg per dose) simulated to twice-daily (BID) steady state in Japanese patients with type 1 diabetes mellitus.

Furthermore, in a multiple-dose study in Caucasian patients with type 1 diabetes mellitus, the glucose-lowering effect profile of IDegAsp at steady state showed rapid onset of action, a distinct peak, and a stable and sustained basal effect lasting beyond 30 h in all participants[8]. These characteristics reflect the unique mechanism of action of IDegAsp, where the two insulin components act independently after subcutaneous injection[7]. This is in contrast to previous attempts to combine short-acting and long-acting insulin analogs, where interference between the insulin components led to prolonged action of the bolus component and shorter duration of action of the basal component.[16] It is also in contrast to other biphasic insulin formulations, where the overlapping effects of the bolus and basal components give rise to a 'shoulder' effect beyond the time required for prandial control, in addition to suboptimal duration of action being considerably less than 24 h in many patients[3,4,17].

In accordance with findings in Caucasians[9], the total and maximum glucose-lowering effect after a single dose ($AUC_{GIR,0-24h,SD}$ and $GIR_{max,SD}$) were lower for IDegAsp than for BIAsp 30 in the present study in Japanese patients with type 1 diabetes mellitus. However, the glucose-lowering effect of BIAsp 30 returned to zero within 18–20 h after dosing; that is, before next dose administration during once-daily dosing. Hence, the single-dose pharmacodynamic profile of BIAsp 30 is representative of clinical practice in a once-daily regimen. In contrast, the glucose-lowering effect of IDegAsp is greater at steady state than after single-dose, which is shown in the present study by a simulation of GIR profiles at steady state. The greater glucose-lowering effect at steady state than after a single dose of IDegAsp is due to the long duration of action of the IDeg component as seen in multiple-dose studies with IDeg alone both in Japanese and Caucasian patients[18,19]. In Japanese patients with type 1 diabetes mellitus, pharmacokinetic steady state with IDeg was reached after 2–3 days of treatment in all participants, and at steady-state duration of action was beyond the clamp duration of 26 h in all participants[18]. Also, in Caucasian patients with type 1 diabetes mellitus, duration of action was shown to extend beyond the maximum clamp duration of 42 h in all participants, with the exception of three participants where the duration of action ranged from 33 to 39 h.[19] Furthermore, IDeg administered alone provides a flat and stable glucose-lowering effect at steady state both in Japanese and Caucasian patients with type 1 diabetes mellitus.[18,20] Importantly, this characteristic is preserved in IDegAsp, as can be seen in the present study and in previous studies in Caucasians[8,9,15].

An important strength of the current study was the inclusion of patients with type 1 diabetes mellitus, which is the preferred population in which to investigate pharmacodynamic properties of insulin products in glucose clamp studies. Patients with type 1 diabetes mellitus are characterized by absolute endogenous insulin deficiency, and combined with pre-dose washout of current insulin treatment, this enables the study of the pharmacological properties of the investigational insulin without interference from endogenous or irrelevant exogenous insulin.

The main limitation of the present study was that it was carried out as a single-dose study. Hence, direct measurement of the pharmacodynamic effect of IDegAsp in the present study is only representative of the first day of treatment. However, simulation of GIR profiles in the steady-state setting showed that both in a once-daily as well as in a twice-daily dosing regimen, the distinct prandial and basal components in IDegAsp are retained in Japanese patients with type 1 diabetes mellitus.

Another limitation of the present study was the experimental set-up pertaining to all glucose clamp studies, which might make it difficult to relate study findings to clinical use. Therefore, it is important that the clinical benefits of IDegAsp expected from the rapid onset of action and distinct peak followed by the sustained basal action have been confirmed in large phase 3 trials in Japanese patients with type 2 diabetes mellitus. In insulin-experienced Asian patients with type 2 diabetes mellitus, including Japanese patients, IDegAsp administered twice daily improved glycemic control and provided significantly greater reduction in fasting plasma glucose (FPG) levels, a similar rate of overall hypoglycemia and a numerically lower rate of nocturnal hypoglycemia compared with BIAsp 30[21]. In a subgroup analysis of Japanese patients in the same trial[21], FPG reduction was significantly greater, the rate of overall confirmed hypoglycemia was similar and the rate of nocturnal confirmed hypoglycemia was significantly lower with IDegAsp vs BIAsp 30[22]. A pooled analysis including the trial in Asian patients[21] and a corresponding global phase 3 trial[23] further supported the benefits of IDegAsp vs BIAsp 30 with respect to FPG reduction and lower risk of hypoglycemia[24]. Furthermore, in insulin-naïve Japanese patients with type 2 diabetes mellitus, IDegAsp administered once daily with the main meal has been shown to provide superior glycosylated hemoglobin reduction, similar FPG reduction, and a numerically lower rate of overall and nocturnal hypoglycemia (compared with insulin glargine)[25].

In conclusion, the present study shows that the pharmacodynamic profile of IDegAsp is characterized by distinct prandial and basal glucose-lowering effects from the IAsp and IDeg components in Japanese patients with type 1 diabetes mellitus, consistent with what has been reported previously in Caucasian patients with type 1 diabetes mellitus[8,9,15]. Although insulin doses must always be adjusted individually, the results from the current study suggest no requirement for specific dosing recommendations for IDegAsp based on race in Japanese patients with diabetes. Based on the improved pharmacodynamic properties of IDegAsp vs BIAsp 30 observed in Japanese patients, IDegAsp appears to represent a clinical advantage compared with other available biphasic insulin products in treatment of Japanese patients with type 2 diabetes mellitus.

DISCLOSURE

Hanne Haahr, Tomio Sasaki, and Lars Bardtrum are employees and shareholders of Novo Nordisk. Ippei Ikushima declares no conflict of interest.

REFERENCES

1. Home P, Riddle M, Cefalu WT, *et al*. Insulin therapy in people with type 2 diabetes: opportunities and challenges? *Diabetes Care* 2014; 37: 1499–1508.
2. Chan JC, Malik V, Jia W, *et al*. Diabetes in Asia: epidemiology, risk factors, and pathophysiology. *JAMA* 2009; 301: 2129–2140.
3. Hirao K, Maeda H, Urata S, *et al*. Comparison of the pharmacokinetic and pharmacodynamic profiles of biphasic insulin aspart 50 and 30 in patients with type 2 diabetes mellitus: a single-center, randomized, double-blind, two-period, crossover trial in Japan. *Clin Ther* 2007; 29: 927–934.
4. Rave K, Heinemann L, Puhl L, *et al*. Premixed formulations of insulin lispro. Activity profiles in type 1 diabetic patients. *Diabetes Care* 1999; 22: 865–866.
5. Evans M, Schumm-Draeger PM, Vora J, *et al*. A review of modern insulin analogue pharmacokinetic and pharmacodynamic profiles in type 2 diabetes: improvements and limitations. *Diabetes Obes Metab* 2011; 13: 677–684.
6. Ma Z, Parkner T, Christiansen JS, *et al*. IDegAsp: a novel soluble insulin analogs combination. *Expert Opin Biol Ther* 2012; 12: 1533–1540.
7. Havelund S, Ribel U, Hubálek F, *et al*. Investigation of the physico-chemical properties that enable co-formulation of basal insulin degludec with fast-acting insulin aspart. *Pharm Res* 2015; 32: 2250–2258.
8. Heise T, Nosek L, Roepstorff C, *et al*. Distinct prandial and basal glucose-lowering effects of insulin degludec/insulin aspart (IDegAsp) at steady state in subjects with type 1 diabetes mellitus. *Diabetes Ther* 2014; 5: 255–265.
9. Heise T, Nosek L, Klein O, *et al*. Insulin degludec/insulin aspart produces a dose-proportional glucose-lowering effect in subjects with type 1 diabetes mellitus. *Diabetes Obes Metab* 2015; 17: 659–664.
10. Morello CM. Pharmacokinetics and pharmacodynamics of insulin analogs in special populations with type 2 diabetes mellitus. *Int J Gen Med* 2011; 4: 827–835.
11. Chen ML. Ethnic or racial differences revisited: impact of dosage regimen and dosage form on pharmacokinetics and pharmacodynamics. *Clin Pharmacokinet* 2006; 45: 957–964.
12. World Medical Association, Declaration of Helsinki. Ethical Principles for Medical Research Involving Human Subjects. 59th WMA General Assembly, Seoul, October 2008.
13. Ministry of Health and Welfare Ordinance on Good Clinical Practice (MHW Ordinance No. 28). March 27, 1997. Available from: http://www.pmda.go.jp/files/000152996.pdf. Accessed September 10, 2015.
14. American Diabetes Association. Defining and reporting hypoglycaemia in diabetes: a report from the American Diabetes Association Workgroup on Hypoglycaemia. *Diabetes Care* 2005; 28: 1245–1249.
15. Brunner M, Pieber T, Korsatko S, *et al*. The distinct prandial and basal pharmacodynamics of IDegAsp observed in younger adults are preserved in elderly subjects with type 1 diabetes. *Drugs Aging* 2015; 32: 583–590.
16. Cengiz E, Swan KL, Tamborlane WV, *et al*. The alteration of aspart insulin pharmacodynamics when mixed with detemir insulin. *Diabetes Care* 2012; 35: 690–692.
17. Heise T, Eckers U, Kanc K, *et al*. The pharmacokinetic and pharmacodynamic properties of different formulations of biphasic insulin aspart: a randomized, glucose clamp, crossover study. *Diabetes Technol Ther* 2008; 10: 479–485.
18. Ikushima I, Kaku K, Hirao K, *et al*. Pharmacokinetic and pharmacodynamic properties of insulin degludec in Japanese patients with type 1 diabetes mellitus reflect similarities with Caucasian patients. *J Diabetes Investig* 2016; 7: 270–275.
19. Haahr H, Heise T. A review of the pharmacological properties of insulin degludec and their clinical relevance. *Clin Pharmacokinet* 2014; 53: 787–800.
20. Heise T, Hövelmann U, Nosek L, *et al*. Comparison of the pharmacokinetic and pharmacodynamic profiles of insulin degludec and insulin glargine. *Expert Opin Drug Metab Toxicol* 2015; 11: 1193–1201.
21. Kaneko S, Chow F, Choi DS, *et al*. Insulin degludec/insulin aspart versus biphasic insulin aspart 30 in Asian patients with type 2 diabetes inadequately controlled on basal or pre-/self-mixed insulin: a 26-week, randomised, treat-to-target trial. *Diabetes Res Clin Pract* 2015; 107: 139–147.
22. Kaneko S, Nishida T, Clauson P. Insulin degludec with insulin aspart improves long-term glycemic control with less nocturnal hypoglycemia compared with biphasic insulin aspart 30 in a Japanese subpopulation from a global study. Japan Diabetes Society - 55th Annual Meeting, 2012.
23. Fulcher GR, Christiansen JS, Bantwal G, *et al*. Comparison of insulin degludec/insulin aspart and biphasic insulin aspart 30 in uncontrolled, insulin-treated type 2 diabetes: a phase 3a, randomized, treat-to-target trial. *Diabetes Care* 2014; 37: 2084–2090.
24. Vaag A, Christiansen J, Niskanen L, *et al*. Lower rates of overall, nocturnal and severe hypoglycaemia during maintenance treatment with IDegAsp vs biphasic insulin aspart 30 in patients with type 2 diabetes mellitus: a meta-analysis. *Diabetologia* 2013; 56: S83.
25. Onishi Y, Ono Y, Rabøl R, *et al*. Superior glycaemic control with once-daily insulin degludec/insulin aspart versus insulin glargine in Japanese adults with type 2 diabetes inadequately controlled with oral drugs: a randomized, controlled phase 3 trial. *Diabetes Obes Metab* 2013; 15: 826–832.