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SHORT COMMUNICATION

The Distinct Prandial and Basal Pharmacodynamics of IDegAsp Observed in Younger Adults Are Preserved in Elderly Subjects with Type 1 Diabetes

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Abstract

Background Management of diabetes in elderly patients is complicated by the elevated risk of insulin-induced hypoglycaemia. This is the first study to report the pharmacodynamic and pharmacokinetic characteristics of IDegAsp (insulin degludec [IDeg]/insulin aspart [IAsp]), a soluble co-formulation of a long-acting basal insulin analogue (IDeg) and a rapid-acting insulin analogue (IAsp) in a single injection, in elderly and younger adult subjects with type 1 diabetes using a glucose clamp.

Methods In this randomised, single-centre, double-blind, single-dose (SD), two-period, crossover trial, 15 elderly subjects (aged ≥65 years) and 13 younger adults (aged 18–35 years) with type 1 diabetes were randomly assigned to two SD administrations of 0.5 U/kg IDegAsp or biphasic insulin aspart 30 (control) followed by a 26-h euglycaemic glucose clamp and 120-h pharmacokinetic blood sampling. The glucose infusion rate (GIR) profiles were extrapolated to simulated steady-state (SS) conditions using pharmacodynamic models.

Results IDegAsp GIR profiles showed a distinct peak and rapid onset of action from IAsp followed by a separate and flat basal action from IDeg. Mean 24-h area under the GIR curve was similar in elderly subjects vs. younger adults (mean ratio 1.01 [95 % confidence interval 0.69–1.47]). Simulated SS pharmacodynamic profiles with once-daily IDegAsp showed a parallel upshift in GIR profiles vs. SD profiles. The shape of the IDegAsp pharmacodynamic profile was retained with twice-daily dosing under simulated SS conditions. IDegAsp was well tolerated.

Conclusions The distinct prandial and basal pharmacodynamics of IDegAsp observed in younger adults were preserved in elderly subjects with type 1 diabetes. The glucose-lowering effect of IDegAsp was similar in elderly subjects and younger adults with type 1 diabetes.

Key points

This is the first study to demonstrate the pharmacodynamic and pharmacokinetic characteristics of insulin degludec/insulin aspart in elderly subjects vs. younger adult subjects with type 1 diabetes using a glucose clamp.

In this study, the distinct prandial and basal pharmacodynamic properties of insulin degludec/insulin aspart reported in younger adults were preserved in elderly subjects with type 1 diabetes.

The glucose infusion rate profiles in both elderly subjects younger adult subjects with type 1 diabetes demonstrate a distinct peak action owing to the prandial insulin aspart component, followed by a sustained basal action owing to the long-acting insulin degludec component.

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1 Introduction

Management of diabetes in the elderly can be multifaceted owing to the increased frequency of co-morbidities and chronic disorders and the heterogeneous nature of this population compared with younger adults with diabetes [1]. This added complexity also heightens the risk of insulin-induced hypoglycaemia associated with higher morbidity and mortality, especially in elderly subjects at advanced stages of the disease and those receiving multiple medications [2, 3].

Insulin degludec (IDeg) is a new-generation, long-acting basal insulin analogue [4, 5]. The long-acting pharmacokinetic and pharmacodynamic properties of IDeg observed in younger adults with type 1 diabetes (T1DM) also have been shown in elderly subjects [6]. Because of a unique mechanism of protraction, IDeg can be combined with the rapid-acting prandial insulin analogue, insulin aspart (IAsp) [7], in insulin degludec/insulin aspart (IDegAsp), resulting in a soluble co-formulation with 70 % IDeg and 30 % IAsp [8]. IDegAsp is the first combination product to include a long-acting basal insulin analogue, providing both basal insulin coverage and a prandial insulin bolus in a single injection [7].

IDegAsp is recommended for the treatment of diabetes in adults and can be administered once or twice daily (BID) with the main meal(s) [8]. When taken once daily (OD), the patient can change the time of IDegAsp administration as needed, provided it is dosed with the largest meal of the day [8].

The distinct basal and prandial characteristics of the IDeg and IAsp components of IDegAsp, which are preserved at steady state (SS) in subjects with T1DM [9], help to reduce the risk of hypoglycaemia compared with standard premix insulins such as biphasic insulin apart 30 (BIAsp 30) [10]. However, the need remains to determine the pharmacodynamic profile of IDegAsp in patients of different ages, and, similar to the study with IDeg [6], such data are valuable for clinical practice, as well as required by the regulatory bodies. Thus, the primary objective of this study was to investigate the pharmacodynamic profiles of IDegAsp and BIAsp 30 in elderly subjects (aged ≥65 years) and younger adult subjects (aged 18–35 years) with T1DM.

2 Materials and Methods

2.1 Study Design

This was a randomised, single-centre (Department of Internal Medicine, Division of Endocrinology and Nuclear Medicine, University of Graz, Auenbruggerplatz 15, Graz, Austria), double-blind, single-dose, two-period, crossover trial in subjects with T1DM (Clinical trials.gov number: NCT01174303). Before initiation of the trial, the protocol, consent form and subject information sheet were reviewed and approved by appropriate authorities and the Independent Ethics Committee of the Medical University of Graz (Ethikkommission der Medizinischen Universität Graz) according to local regulations. The trial was performed according to the Declaration of Helsinki [11] and its amendments and Good Clinical Practice as defined by the International Conference on Harmonisation [12]. Subjects were informed of the risks and benefits of the trial and 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.

2.2 Study Population

Subjects were men and women aged ≥65 years (elderly group) or aged 18–35 years (younger adult group) with T1DM for ≥12 months and a fasting C-peptide level <0.3 nmol/L. Other key inclusion criteria included subjects who had been treated with insulin (<1.2 IU/kg/day) for ≥12 months, body mass index (BMI) of 18.0–28.0 kg/m^2 (inclusive) and glycosylated haemoglobin of ≤10.0 %. Key exclusion criteria were the same as in a previous study [6] and included smoking, recurrent severe hypoglycaemia (more than one severe hypoglycaemic event during the last 12 months), hypoglycaemic unawareness and hospitalisation for diabetic ketoacidosis during the previous 6 months.

2.3 Study Procedures

Subjects were randomly assigned to two single-dose administrations of 0.5 U/kg IDegAsp or BIAsp 30 at two separate visits (BIAsp 30 was included primarily as a control for differentiation between drug- and population-related differences in pharmacokinetic and pharmacodynamic properties, in case differences between age groups were observed for IDegAsp). The trial consisted of 10 visits: a screening visit (Visit 1), two treatment periods (Visits 2–5 and Visits 6–9) and a follow-up visit (Visit 10). At each of the two dosing visits, subjects remained hospitalised for 48 h following product administration.

2.4 Euglycaemic Glucose Clamp Procedure

The pharmacodynamic effects of IDegAsp were evaluated using a 26-h euglycaemic clamp procedure (target blood glucose 5.5 mmol/L, [100 mg/dL]), beginning after dosing

during Visit 2 (treatment period 1) and Visit 6 (treatment period 2), similar to the approach described previously [6] (see Supporting information for details). The clamp procedure was terminated early if plasma glucose levels consistently exceeded 11.1 mmol/L (200 mg/dL) without any glucose infusion in the previous 30 min.

2.5 Pharmacokinetic Sampling

Following IDegAsp administration, serum concentrations of IAsp and IDeg were analysed separately. Blood samples were collected at the times specified in Table S1. Serum IAsp concentrations after IDegAsp and BIAsp 30 administration were analysed at the same time points until 12 h and 24 h after dosing, respectively. IDeg concentrations were analysed until 120 h post-dosing. Serum IDeg and serum IAsp concentrations were measured using a validated, specific, sandwich enzyme-linked immunosorbent assay.

2.6 Safety Assessments

Safety endpoints comprised adverse events, including local injection-site reactions, laboratory safety variables, physical examination, vital signs, electrocardiogram and hypoglycaemic episodes (defined as 'confirmed' when they were either 'severe' as defined by the American Diabetes Association [13] or verified by a plasma glucose level of <3.1 mmol/L [56 mg/dL]).

2.7 Data and Statistical Analysis

No formal sample size calculations for this trial were performed. The pharmacodynamic response of IDegAsp was determined by calculating the area under the curve $(AUC)_{GIR,0–24,SD}$ using the linear trapezoidal technique on interpolated data points. The log-transformed $AUC_{GIR,0–24,SD}$ for the IDegAsp treatment was analysed using a linear model with age group (elderly/young adult) and treatment period (period 1/2) as fixed effects. Glucose infusion rate (GIR) data were smoothed using the Loess smoothing technique using a fixed smoothing parameter of 0.1 for the bolus (the first 6 h) and 0.25 for the basal (from 6 h onwards) part of the curve with combined smoothing. GIR data were smoothed to show the mean GIR profiles, excluding fluctuations caused by the clamp method. Smoothed data may not always start at 0 as each point in the smoothed plot is computed as a weighted average of the values before and after the data point, giving most weight to the closest neighbouring data points. Only data after the injection time point are included (non-zero positive values) and therefore the plot does not start at 0 (see "Results"). All pharmacokinetic and pharmacodynamic endpoints and safety endpoints were analysed based on the full analysis set and the safety analysis set, respectively. Safety endpoints were summarised using descriptive statistics.

2.8 Pharmacodynamic Modelling

To simulate SS pharmacodynamic profiles from this single-dose study, a population pharmacodynamic model was used to describe the GIR response for IDegAsp. The model used here has previously been described [9] and a full description of the pharmacodynamic modelling is provided in the supplementary information.

3 Results

3.1 Baseline Characteristics

A total of 28 (15 elderly; 13 younger) subjects were randomised to receive IDegAsp or BIAsp 30. All subjects completed the trial and no subject withdrew or was withdrawn (full analysis set 28; safety analysis set 28) (Fig. S1).

Apart from age and, therefore, duration of diabetes, baseline characteristics were similar for both age groups. The mean duration of diabetes was approximately 21 years longer for elderly subjects compared with the younger adults (Table 1).

3.2 Pharmacodynamics

In elderly and younger adult subjects, the GIR profiles showed rapid onset of action and a distinct peak from the IAsp component followed by a separate and flat basal action of the long-acting IDeg component, which was sustained for the duration of the clamp (see Fig. 1a). The mean $AUC_{GIR,0–24h,SD}$ for IDegAsp was similar for elderly and younger adult subjects (mean ratio elderly/younger adults 1.01, 95 % confidence interval [CI] 0.69–1.47). There were no marked differences between the age groups across the secondary pharmacodynamic endpoints (Table 2).

This study was performed as a single-dose trial but it is possible to extrapolate the comparison of IDegAsp OD GIR profiles to the SS setting. Simulated SS pharmacodynamic profiles for subjects in both age groups are shown in Fig. 1b, where an upshift in the simulated GIR profile at SS was apparent compared with the single-dose profiles.

The onset of action and shape of the single-dose GIR profiles over the first 4 h were similar for IDegAsp and BIAsp 30 in the elderly subjects, although the maximum GIR ($GIR_{max,SD}$) appeared to be lower for IDegAsp compared with BIAsp 30 (Fig. 2a). Afterwards, BIAsp 30 GIR steadily decreased and reached zero 18–20 h after

Table 1 Baseline characteristics

Baseline characteristics	Elderly subjects Mean (minimum; maximum)	Younger adult subjects Mean (minimum; maximum)
No. of subjects	15	13
Age, years	68.2 (65.1; 79.2)	25.4 (19.3; 33.3)
BMI, kg/m^2	25.2 (19.3; 28.7)	23.2 (20.6; 25.9)
Race		
White, *n*	15	13
Sex		
Female, *n*	6	4
Male, *n*	9	9
Duration of diabetes, years	34.4 (2.8; 65.1)	13.0 (6.6; 26.1)
HbA_{1c}, %	7.5 (6.4; 9.6)	7.4 (5.5; 9.2)
Fasting C-peptide, nmol/L	0.02 (0.00; 0.08)	0.01 (0.00; 0.02)

BMI body mass index, *HbA_{1c}* glycosylated haemoglobin

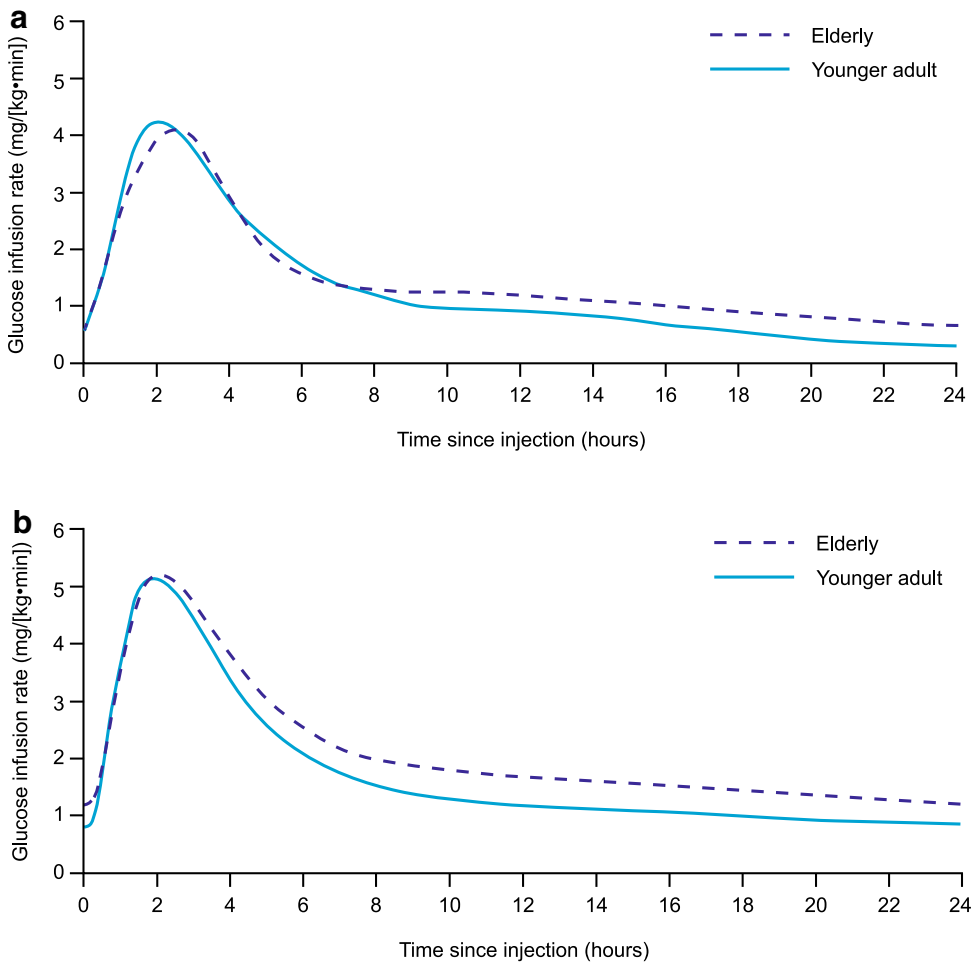

Fig. 1 **a** Mean glucose infusion rate profiles following a single dose (0.5 U/kg) of insulin degludec/insulin aspart in subjects of two different age groups with type 1 diabetes. **b** Simulated mean glucose infusion rate profiles of insulin degludec/insulin aspart (0.5 U/kg) at steady state in elderly and younger adult subjects with type 1 diabetes

injection. In contrast, the mean GIR for IDegAsp rapidly declined from $GIR_{max,SD}$ until approximately 7 h post-dosing, after which GIR continued to decline slowly at a constant and sustained rate for the remainder of the clamp. Graphs are shown for smoothed (Fig. 2a) and raw (Fig. 2b) mean GIR profiles, the shapes of the smoothed and raw profiles are comparable. The GIR profiles for elderly and younger adults for IDegAsp or BIAsp 30 were consistent

Table 2 Pharmacodynamic endpoints in elderly and younger adult subjects with type 1 diabetes treated with single-dose insulin degludec/insulin aspart (IDegAsp)

	IDegAsp	
	Elderly subjects	Younger adult subjects
No. of subjects	15	13
$AUC_{GIR,\ 0–24h,SD}$, mg/kg (CV, %)[a]	1794 (62)	1786 (28)
$AUC_{GIR,\ 0–6h,SD}$, mg/kg, (CV, %)[a]	909 (45)	1001 (25)
$GIR_{max,SD}$, mg/(kg min), (CV, %)[a]	3.9 (53)	4.4 (30)
$tGIR_{max,SD}$, h, (CV, %)[b]	2.7 (31)	2.2 (35)

AUC area under the curve. *CV* coefficient of variation, *GIR* glucose infusion rate, *max* maximum, *SD* single dose, $tGIR_{max}$ time to maximum glucose infusion rate

[a] Geometric mean

[b] Median

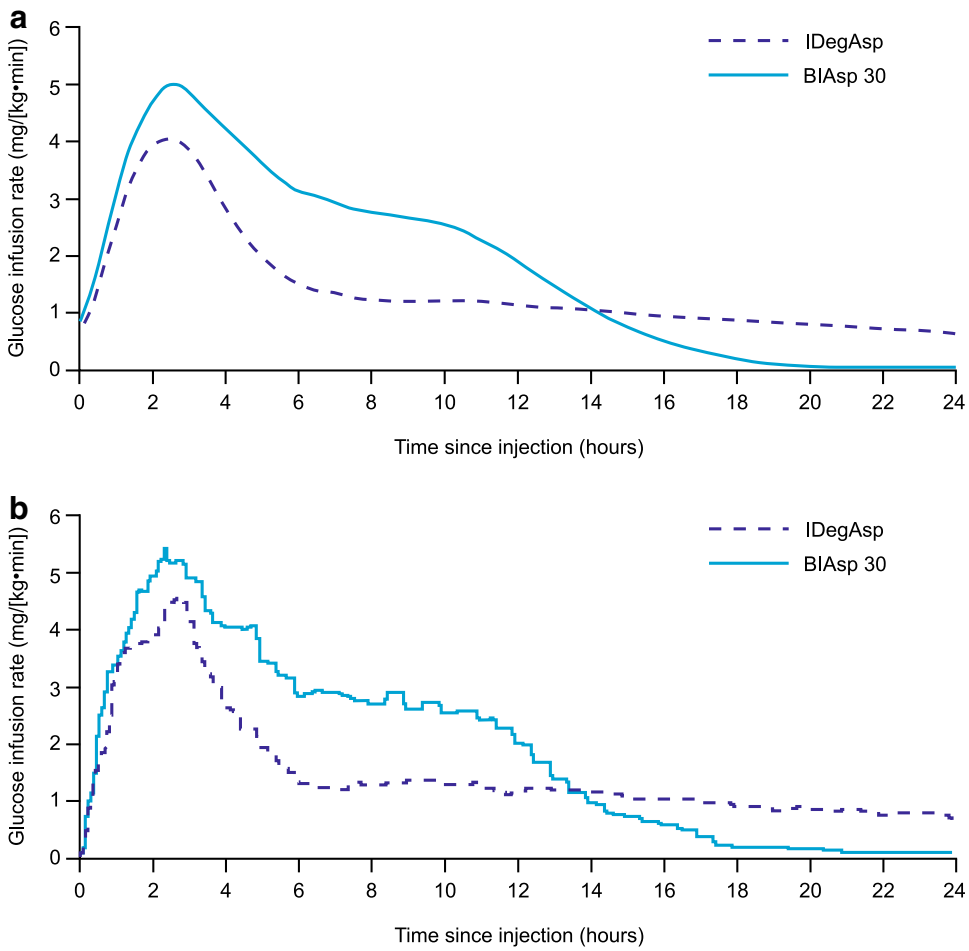

Fig. 2 **a** Mean glucose infusion rate profile following a single dose (0.5 U/kg) of insulin degludec/insulin aspart (IDegAsp) or biphasic insulin apart 30 (BIAsp 30) in elderly subjects with type 1 diabetes. **b** Raw mean glucose infusion rate profile

with the profiles previously reported for adults with T1DM [14]. However, caution should be taken when comparing the effect of single doses of IDegAsp and BIAsp 30 directly. This is because of the long-acting nature of IDeg, the basal component in IDegAsp, further discussed in Sect. 4 and pharmacodynamic variables at SS or after a single dose for IDegAsp or BIAsp 30 for elderly and younger adult subjects are shown in Table 3.

A simulated model of pharmacodynamic response to IDegAsp BID at SS in both age groups indicated that distinct IAsp and IDeg peaks in IDegAsp are retained following each dose (Fig. 3). The profile shapes over each

Table 3 Pharmacodynamic parameters in elderly and younger adult subjects with type 1 diabetes at steady state (SS) or following a single-dose (SD) of insulin degludec/insulin aspart (IDegAsp) or biphasic insulin aspart 30 (BIAsp 30)

	IDegAsp (SD)		IDegAsp (SS)		BIAsp 30 (SD)	
	Elderly subjects	Younger adult subjects	Elderly subjects	Younger adult subjects	Elderly subjects	Younger adult subjects
$AUC_{GIR,\ 0-24h,SD}$, mg/kg (CV, %)	1794 (62)	1786 (28)	2550 (70)	2427 (30)	2349 (57)	2375 (42)
$GIR_{max,SD}$, mg/(kg min) (CV, %)	3.9 (53)	4.4 (30)	4.7 (57)	5.1 (30)	4.9 (46)	6.1 (47)

AUC area under the curve, *CV* coefficient of variation, *GIR* glucose infusion rate

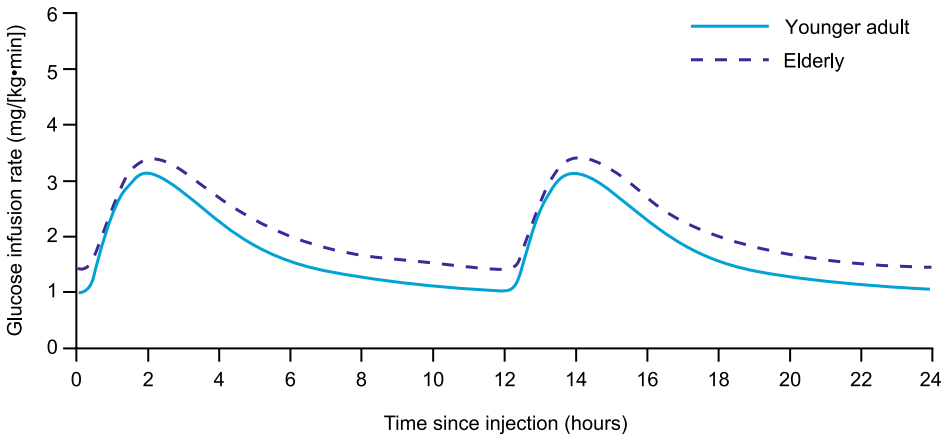

Fig. 3 Simulated mean glucose infusion rate profiles of insulin degludec/insulin aspart administered twice daily (0.25 U/kg per dose) at steady state in elderly and younger adult subjects with type 1 diabetes

dosing interval are similar to those observed with IDegAsp OD simulations at SS (Fig. 1b).

3.3 Pharmacokinetics

The total exposure of IAsp in IDegAsp ($AUC_{IAsp,0-12h,SD}$) was statistically significantly higher in elderly compared with younger adult subjects; the estimated mean age group ratio (elderly subjects/younger adults) was 1.37 (95 % CI 1.01–1.87). In a sensitivity analysis that excluded one subject (subject 20) with physiologically implausible high IAsp concentrations, the difference between elderly subjects and younger adults was not statistically significant (estimated mean age group ratio [elderly subjects/younger adults]) for IAsp (1.27; 95 % CI 0.97–1.65). The total exposure of IDeg in IDegAsp ($AUC_{IDeg,0-120h,SD}$) was not significantly different between the two age groups, with an estimated mean age group ratio (elderly subjects/younger adults) of 1.24 (95 % CI 0.90–1.70). Without the outlier, the ratio for IDeg was 1.12 (95 % CI 0.89–1.40).

The mean concentration–time profiles for IAsp in IDegAsp (subject 20 excluded) were similar for elderly and younger adult subjects (data not shown). In the sensitivity analysis (subject 20 excluded), maximum serum concentration for IAsp in IDegAsp was 305 pmol/L in the elderly subjects and 221 pmol/L in the younger adults.

3.4 Safety

IDegAsp was well tolerated in both elderly and younger adult subjects and no safety issues were identified during the trial. There were no episodes of severe hypoglycaemia.

4 Discussion

This study was the first to evaluate pharmacodynamic and pharmacokinetic properties of IDegAsp using a euglycaemic clamp procedure in elderly and younger adult subjects with T1DM. The pharmacodynamic profiles of IDegAsp as assessed by $AUC_{GIR,0-24h,SD}$ were similar for elderly and younger adult subjects and IDegAsp was well tolerated in the study population. The mean GIR profiles of IDegAsp reflected the different and distinct actions of its bolus and basal insulin components, as shown by a rapid increase after dosing until $GIR_{max,SD}$ followed by a rapid decline, after which the GIR stabilised for the remainder of the clamp period. This was also previously demonstrated during a euglycaemic clamp procedure with increasing IDegAsp doses [15]. It is noteworthy that in the present study the variability in the $AUC_{GIR,0-24,SD}$ between subjects seemed greater in the elderly subjects than in the younger adults based on the standard deviation (Table 3). This may be because of the heterogeneity of insulin

resistance among the elderly, as insulin resistance can increase with age [16].

The maximum GIR was lower after single doses of IDegAsp compared with BIAsp 30 in elderly or younger adult subjects. However, for BIAsp 30, GIR returned to baseline values 18–22 h after injection, namely before the next dose in a OD regimen. By comparison, a greater glucose-lowering effect has been demonstrated with IDegAsp at SS compared with a single dose [9] owing to the long-acting nature of IDeg, which persists beyond a 24-h dosing interval. At SS, the total and maximum glucose-lowering effects for IDegAsp were comparable to BIAsp 30 in both populations (Table 3). As a basal insulin analogue with a half-life extending beyond 24 h, IDeg achieves SS in 2–3 days (defined as a serum concentration reaching 90 % of the final plateau concentration and an intake of a drug in dynamic equilibrium with its elimination) [17]. The longer duration of action provided by the IDeg component in IDegAsp, compared with the protaminated form of IAsp in BIAsp 30, shows that the long-acting, flat and sustained basal insulin properties of IDeg observed at SS [17] are preserved in IDegAsp. SS therefore represents a more clinically relevant context in which to investigate the pharmacodynamic profile of IDegAsp when comparing this formulation with other insulins.

Modelling of simulated SS pharmacodynamic profiles in this study showed a parallel upshift in GIR profiles under simulated SS conditions compared with single-dose GIR profiles. The GIR (including GIR_{max}) and the duration of action of IDegAsp are higher and longer, respectively, under simulated SS conditions compared with single-dose profiles. The findings at simulated SS conditions are in alignment with the results recently published for IDeg at SS in patients with T1DM [6]. In the study by Korsatko et al. [6] the long-acting properties of IDeg were comparable in elderly subjects and in younger adults.

Because IDegAsp can be administered OD or BID, pharmacodynamic profiles for both age groups were also simulated at SS using an IDegAsp BID model, by dividing the IDegAsp dose by two (0.25 U/kg BID). The basal glucose-lowering effect (owing to the IDeg component) was the same with OD or BID dosing because this is dependent on total dose rather than on the dosing frequency of IDegAsp. In contrast, as expected, the IAsp (bolus component) peak was approximately half the size with IDegAsp BID compared with IDegAsp OD. Similar results were also observed in a previous study with IDegAsp in adult subjects with T1DM [9].

In this study, the total exposure of both insulin components of IDegAsp was found to be similar between elderly subjects and younger adults (one subject with implausibly high exposure concentrations was removed). The mean concentration–time profiles were also similar between both age groups, indicating that the absorption properties of IDeg and IAsp observed in younger adults are preserved in the elderly. Similar findings have also been reported by Korsatko et al. [6] regarding the properties of IDeg in elderly subjects vs. younger adults at SS.

This study is the first of its type to report the properties of IDegAsp in the elderly population where the management of diabetes is further complicated by existing co-morbidities. A strength of this study is the use of a euglycaemic glucose clamp, which is considered as the 'gold standard' in determining pharmacodynamic properties of insulin [18]. The investigation of these properties in only patients with T1DM enabled the assessment of pharmacodynamic response under clamp conditions without interference from endogenous insulin, a potential complication and challenge when studying subjects with type 2 diabetes. The main limitation of this study is that the results are based on single-dose administrations rather than performed at SS conditions. While the simulated SS models are a valuable indicator of IDegAsp in this setting, it is important to verify these properties under clinical SS settings. In addition, the study included a relatively small number of subjects and larger-scale clinical trials with more patients and a narrower range of age groups with IDegAsp are therefore warranted.

5 Conclusions

This study showed the distinct prandial and basal pharmacodynamic properties of IDegAsp previously reported in adults [9] and for treatment with IDeg [6] are preserved in elderly subjects. The glucose-lowering profile of IDegAsp over 24 h is preserved in elderly subjects with T1DM, consisting of a distinct peak action owing to the prandial IAsp component, in addition to the sustained long-acting effect of IDeg. The single-dose GIR profile observed for younger adults in this study was similar to those observed previously and modelling of OD IDegAsp effects at SS showed a slight upshift to a flatter profile owing to the IDeg component. The basal glucose-lowering effect of IDegAsp was retained under simulated SS conditions with BID dosing of IDegAsp.

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