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ORIGINAL RESEARCH

Efficacy and Safety of IDegAsp Versus BIAsp 30, Both Twice Daily, in Elderly Patients with Type 2 Diabetes: Post Hoc Analysis of Two Phase 3 Randomized Controlled BOOST Trials

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ABSTRACT

Introduction: The majority of elderly patients (≥ 65 years of age) with type 2 diabetes mellitus (T2DM) will eventually require insulin therapy, but they are particularly vulnerable to hypoglycemia and challenging to treat. Insulin degludec/insulin aspart (IDegAsp) is a novel co-formulation of 70% insulin degludec and 30% insulin aspart administered in a single injection, either once or twice daily with main meals.

Methods: A combined analysis of the phase 3 BOOST INTENSIFY PREMIX I (NCT01009580) and BOOST INTENSIFY ALL (NCT01059812) trials has previously reported lower rates of hypoglycemia during the maintenance period in patients with T2DM treated with IDegAsp twice daily (BID) versus biphasic insulin aspart 30 (BIAsp 30) BID. This post hoc analysis examined the safety and efficacy of IDegAsp versus BIAsp 30 in elderly patients from the global population of these two trials, and also from the Japanese cohort of BOOST INTENSIFY ALL.

Results: Change in HbA_{1c} was similar for IDegAsp versus BIAsp 30 ($p > 0.5$). Compared with BIAsp 30, IDegAsp resulted in significant reductions in fasting plasma glucose ($p < 0.0001$), numerically lower rates of overall and nocturnal hypoglycemia (global estimated rate ratios: 0.92 $[0.67; 1.26]_{95\%\ \text{confidence interval [CI]}}$, $p = 0.5980$ and 0.67 $[0.39; 1.18]_{95\%\ \text{CI}}$, $p = 0.1676$, respectively), and a significantly lower total daily insulin dose at end of trial (global estimated treatment difference 0.79 $[0.73; 0.87]_{95\%\ \text{CI}}$, $p < 0.0001$) in elderly patients.

Conclusion: The results described here are consistent with those of the overall trial populations, demonstrating that IDegAsp BID is efficacious in elderly patients and suggesting that there is no need for special safety precautions.

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PLAIN LANGUAGE SUMMARY

IDegAsp is a new insulin therapy for people with diabetes. It is a combination of two insulins: insulin degludec (IDeg) and insulin aspart (IAsp). Previous studies have compared the IDegAsp combination with biphasic IAsp 30 (a premixed insulin therapy related to IAsp). These studies have shown that IDegAsp improves blood glucose levels with a low risk of harmful side effects. This study examined whether IDegAsp had the same positive effect on people who are aged 65 years or older. This age group is less well represented in clinical trials compared with younger adults, so this study pooled together elderly populations from two trials. Results showed that IDegAsp also improved blood glucose levels with a low risk of harmful side effects in elderly patients, and suggests that IDegAsp can be used in elderly people with diabetes just as it is used in younger adults.

INTRODUCTION

The overall goal of type 2 diabetes mellitus (T2DM) management is to achieve good glycemic control while avoiding the adverse events (AEs) associated with diabetes progression and diabetic therapy. Additional challenges may arise when treating diabetes in elderly patients, particularly at the stage of insulin initiation [1, 2].

Fear of hypoglycemia is a commonly cited barrier to insulin initiation in patients of all ages [3, 4], but hypoglycemia is of particular concern in the elderly population (defined here as $\geq$ 65 years of age). Elderly patients are more susceptible to hypoglycemia because aging is accompanied by an increased risk of impaired counter-regulatory responses to hypoglycemia [5, 6]. Hypoglycemic episodes in elderly patients have also been associated with an increased risk of fall-related events [7] and also of dementia [8, 9] compared with patients who did not experience hypoglycemia. Consequently, achieving tight glycemic control in elderly patients while avoiding hypoglycemia is of critical importance, although frequently challenging [10].

The majority of elderly patients with a longer duration of T2DM require, or will require at some point, insulin therapy to achieve glycemic control; however, insulin therapy is often underutilized in this population for the reasons described above [11]. Reducing the risk of hypoglycemia is an important focus of T2DM management and, thus, therapy design.

Long-acting (basal) and rapid-acting (bolus) insulin analogs were developed to provide a more physiological insulin action profile compared with human insulins [12]. Basal–bolus regimens can effectively control postprandial and fasting hyperglycemia; however, this involves multiple daily injections, which are another patient-perceived barrier to insulin initiation/intensification [3, 13, 14]. Although the benefit of convenience with premixed insulin compared with a basal–bolus regimen is attractive to elderly patients, traditional premixed insulin can result in an increased risk of hypoglycemia versus basal–bolus therapy [15], and—as mentioned above—this is particularly deleterious in the elderly population [5, 13, 16].

Insulin degludec/insulin aspart (IDegAsp; Ryzodeg®, Novo Nordisk A/S, Søborg, Denmark) is the first co-formulation of these two insulins, 70% insulin degludec (IDeg) and 30% insulin aspart (IAsp), in a single injection, and is administered once or twice daily with main meals [17]. Importantly, the molecular properties of IDegAsp are such that the mechanism of action of each monocomponent remains unchanged and their distinct pharmacokinetic (PK)/pharmacodynamic (PD) properties are preserved in co-formulation, as well as following injection.

The basal component, IDeg, has a flat PK profile over 24 h and, at steady state, provides a stable, long-lasting, glucose-lowering effect, whereas the bolus component, IAsp, has a rapid onset of action and reduces glucose excursions at mealtimes [17]. Studies have shown that these PK/PD properties are preserved across special patient populations [18]. A glucose

clamp study demonstrated that PD properties of IDegAsp, following once- or twice-daily dosing, were consistent across younger and elderly adults [19]. While previous findings have suggested that variables such as race and ethnicity may influence the pharmacological properties of rapid- and long-acting insulin analogs [20], a single-dose, euglycemic glucose clamp study demonstrated that the distinct basal and prandial components of IDegAsp that have been described in Caucasian populations are also observed in Japanese patients with type 1 diabetes mellitus (T1DM) [21]. Therefore, from a pharmacological perspective, these studies suggest that the action of IDegAsp is similar in populations of different ages and races [18].

The IDegAsp clinical trial program (BOOST) builds on that of IDeg [22–29] and demonstrates the efficacy and safety profiles of IDegAsp in the treatment of patients with T1DM and T2DM [30–32]. Global findings from the overall population of the BOOST clinical trial program suggest that IDegAsp would benefit elderly patients. For example, a combined analysis of two pivotal phase 3a trials (BOOST INTENSIFY PREMIX I [NCT01009580] and BOOST INTENSIFY ALL [NCT01059812]) has previously reported lower rates of hypoglycemia during the maintenance period in patients with T2DM treated with IDegAsp twice daily versus biphasic insulin aspart 30 (BIAsp 30) twice daily [33].

The clinical outcomes of treatment with IDegAsp compared with that of BIAsp 30 can be partly explained by their pharmacokinetic/pharmacodynamic properties. In contrast with the glucose-lowering profile of IDegAsp, which consists of two distinct phases of action, the glucose-lowering effects of the soluble and protaminated fractions of BIAsp 30 overlap at approximately 6 h after dosing. This "shoulder effect" is partly responsible for the day-to-day variability in glycemic control observed with the intermediate-acting BIAsp 30 [18]. A rapid increase in serum concentration is observed after BIAsp 30 administration (maximum concentration reached in 2.1–2.6 h), followed by a gradual decline [34]. Appropriate timing of the second administration to ensure adequate insulin concentrations throughout the day and night and avoid episodes of hypo- or hyperglycemia is important.

This manuscript presents a post hoc pooled subanalysis of the elderly population from these two trials. In addition, a subanalysis was performed on the Japanese population of BOOST INTENSIFY ALL, because elderly Japanese patients of BOOST INTENSIFY ALL comprised the largest elderly subpopulation in these two trials [31, 32]. In addition, the Japanese population is of special interest for investigation, as Japan has a large and growing elderly population [35], and IDegAsp use is greater in Japan than in any other country.

This post hoc analysis aimed to evaluate the safety and efficacy of IDegAsp in elderly patients with T2DM.

METHODS

Trial Design

The trial designs for BOOST INTENSIFY PREMIX I (global population) and BOOST INTENSIFY ALL (pan-Asian population) have been described previously [31, 32] and are similar (Fig. 1). Both trials were phase 3a, randomized, parallel, open-label, multicenter trials with an intent-to-treat design and a duration of 26 weeks.

Participants

In BOOST INTENSIFY PREMIX I, eligible patients had been treated previously with either premixed or self-mixed insulin (once or twice daily) ± oral antidiabetic drugs (metformin, sulfonylureas, glinides, alpha-glucosidase inhibitors, dipeptidyl peptidase-4 inhibitors, and pioglitazone) for ≥ 3 months. In BOOST INTENSIFY ALL, patients who had been receiving once- or twice-daily basal insulin, a premixed insulin, or a self-mixed insulin ± metformin were eligible. Inclusion criteria for the two trials were otherwise similar; patients were eligible for inclusion if they were ≥ 18 years of age (≥ 20 for BOOST INTENSIFY ALL participants in Japan and Taiwan), with glycated hemoglobin (HbA_{1c}) 7.0–10.0% (53–86 mmol/mol) and body mass index (BMI) < 40 kg/m^2 (BOOST INTENSIFY

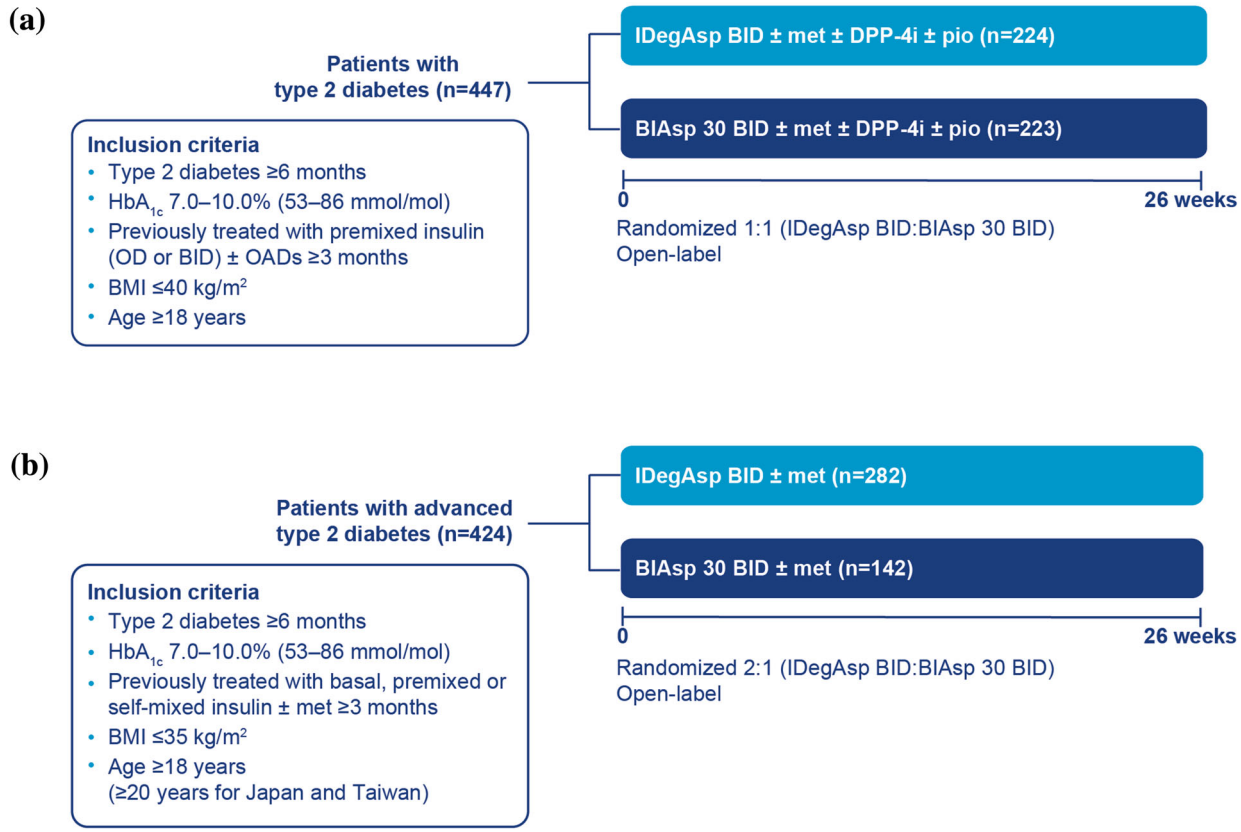

Fig. 1a–b Trial designs for **a** BOOST INTENSIFY PREMIX I (global patient population) [31] and **b** BOOST INTENSIFY ALL (pan-Asian patient population) [32]. *BIAsp 30* biphasic insulin aspart 30, *BID* twice daily, *BMI* body mass index, *DPP-4i* dipeptidyl peptidase-4 inhibitor, *HbA_{1c}* glycated hemoglobin, *IDegAsp* insulin degludec/insulin aspart, *met* metformin, *n* number randomized, *OAD* oral antidiabetic drug, *OD* once daily, *pio* pioglitazone

PREMIX I) or < 35 kg/m^2 (BOOST INTENSIFY ALL). In both trials, patients were excluded if they had a history of recurrent severe hypoglycemia or hypoglycemic unawareness. The Japanese subgroup was drawn from the overall population. For this post hoc analysis, all patients who were aged 65 years or over were included.

Compliance with Ethics Guidelines

The protocols, protocol amendments, consent forms, and subject information sheets of the original BOOST INTENSIFY PREMIX I and BOOST INTENSIFY ALL trials were reviewed and approved by health authorities according to local regulations and by the local independent ethics committees prior to trial initiation [31, 32]. The trials were performed in accordance with the Declaration of Helsinki and good clinical practice [36, 37]. In summary, all procedures performed in studies involving human participants were in accordance with the ethical standards of the institutional and/or national research committee and with the 1964 Declaration of Helsinki and its later amendments or comparable ethical standards. Informed consent was obtained from all individual participants included in the study.

Assessments and Statistical Analyses

The current analyses present pooled data from both trials for the elderly subpopulation. The

primary endpoint in both trials was change from baseline in HbA_{1c} after 26 weeks of treatment. A linear regression model (analysis of covariance) was used to analyze the change in HbA_{1c} from baseline to end of treatment with trial, treatment, sex, geographic region, and antidiabetic treatment at screening as grouping factors and age and baseline response as covariates. For individual trial groups, trial is not included as a fixed effect. Missing data were accounted for using the last observation carried forward method. Fasting plasma glucose (FPG) and insulin dose (log transformed) were analyzed using the same model.

The number of treatment-emergent confirmed hypoglycemic events was analyzed with a negative binomial regression model, using a log-link function adjusted for trial, treatment, sex, geographic region, and antidiabetic treatment at screening as fixed effects, age as covariate, and the logarithm of the exposure time as offset.

Hypoglycemia Classification

Confirmed hypoglycemia included severe episodes (episodes requiring the assistance of another person to actively administer carbohydrate, glucagon, or other resuscitative actions) and episodes confirmed by plasma glucose (PG; < 56 mg/dL [3.1 mmol/L]) or full blood glucose (< 50 mg/dL [2.8 mmol/L]) measurements that were handled by the patient himself/herself, and could be with or without symptoms consistent with hypoglycemia. Nocturnal hypoglycemia was defined as episodes of confirmed hypoglycemia that occurred between 00:01 and 05:59 h (inclusive).

Safety

All patients receiving at least one dose of trial product were included in the safety analysis set. Safety was assessed using overall confirmed hypoglycemia and nocturnal hypoglycemia, based on the Novo Nordisk classification for hypoglycemia (plasma glucose 56 mg/dL [< 3.1 mmol/L]). Adverse events were coded using the most recent version of Medical Dictionary for Regulatory Activities (MedDRA) coding (version 13.0 for BOOST INTENSIFY PREMIX I and version 13.1 for BOOST INTENSIFY ALL).

RESULTS

Baseline Characteristics

The combined analysis comprised 271 patients (representing 31.2% of the total population from the two trials), of whom 146 were treated with IDegAsp twice daily and 125 were treated with BIAsp 30 twice daily. Japanese patients comprised the largest subgroup ($N = 72$, 26.6% of the analyzed cohort). Baseline characteristics for the subpopulation of patients aged ≥ 65 years from each trial and from the pooled data are shown in Table 1. The mean age at baseline, BMI, duration of diabetes, HbA_{1c} (%; mmol/mol), and FPG were similar for both treatment arms in the pooled data. BMI at baseline was lower in the pan-Asian population compared with the global population. Duration of diabetes was longer in the pan-Asian population compared with the global population.

Glycemic Control

There were no statistically significant differences in HbA_{1c} in the combined analysis between treatment with IDegAsp or BIAsp 30 (estimated treatment different [ETD, IDegAsp–BIAsp 30]: −0.02% [− 0.19; 0.15]$_{95\%\ CI}$, $p = 0.8455$). A significant reduction in FPG was observed with IDegAsp versus BIAsp 30 (ETD [IDegAsp–BIAsp 30]: − 1.41 mmol/L [− 1.85; − 0.96]$_{95\%\ CI}$, $p < 0.0001$). Similar results were observed in Japanese patients, with an ETD (IDegAsp–BIAsp 30) of − 0.01% [− 0.31; 0.29]$_{95\%\ CI}$, $p = 0.9521$ for HbA_{1c} and − 1.86 mmol/L [− 2.75; − 0.97]$_{95\%\ CI}$, $p < 0.0001$ for FPG (Table 2).

Hypoglycemia

Overall confirmed and nocturnal hypoglycemic events by classification are shown, by trial population and for the combined analysis, in

Table 1 Demographics and baseline characteristics of elderly patients (≥ 65 years of age) with type 2 diabetes mellitus included in the analysis

Characteristic	BOOST INTENSIFY PREMIX I (global patient population)		BOOST INTENSIFY ALL (pan-Asian patient population)		Total included in combined analysis	
	IDegAsp BID	BIAsp 30 BID	IDegAsp BID	BIAsp 30 BID	IDegAsp BID	BIAsp 30 BID
Full analysis set, *n*	66	70	80	55	146	125
Males, %	62.1	47.1	50.0	52.7	55.5	49.6
Age, years	70.0 (4.4)	69.5 (3.5)	70.9 (4.3)	70.2 (4.5)	70.5 (4.3)	69.8 (4.0)
BMI, kg/m^2	30.0 (4.5)	29.9 (4.8)	24.6 (2.8)	24.6 (3.5)	27.1 (4.5)	27.6 (5.0)
Duration of diabetes, years	15.8 (7.5)	17.0 (8.3)	20.7 (8.1)	19.2 (8.8)	18.5 (8.2)	18.0 (8.6)
HbA_{1c}, %	8.0 (0.7)	8.1 (0.8)	8.4 (0.8)	8.3 (0.9)	8.2 (0.8)	8.2 (0.8)
HbA_{1c}, mmol/mol	64.1 (7.9)	65.2 (8.7)	68.1 (8.3)	67.7 (9.4)	66.3 (8.3)	66.3 (9.1)
FPG, mg/dL	156.3 (42.0)	151.1 (36.2)	142.6 (44.9)	146.4 (51.7)	148.8 (44.0)	149.0 (43.6)
FPG, mmol/L	8.7 (2.3)	8.4 (2.0)	7.9 (2.5)	8.1 (2.9)	8.3 (2.4)	8.3 (2.4)

Data are mean (SD) unless otherwise stated

BIAsp 30 biphasic insulin aspart 30, *BID* twice daily, *BMI* body mass index, *FPG* fasting plasma glucose, *HbA_{1c}* glycated hemoglobin, *IDegAsp* insulin degludec/insulin aspart, *n* number of patients, *SD* standard deviation

Table 3. The estimated rate ratios for overall confirmed and nocturnal confirmed hypoglycemia for the combined analysis are shown in Fig. 2. In the combined analysis, there were fewer overall confirmed hypoglycemic events with IDegAsp (1041.18 events/100 patient-years of exposure [PYE]) compared with BIAsp 30 (1134.40 events/100 PYE), estimated rate ratio (ERR): 0.92 $[0.67; 1.26]_{95\%\ CI}$, $p = 0.5980$. There were fewer nocturnal hypoglycemic events in patients treated with IDegAsp compared with patients treated with BIAsp 30, ERR (IDegAsp/BIAsp 30): 0.67 $[0.39; 1.18]_{95\%\ CI}$, $p = 0.1676$. In the Japanese patient population, there was a 12% lower rate of overall confirmed hypoglycemia with IDegAsp compared with BIAsp 30, ERR: 0.88 $[0.47; 1.66]_{95\%\ CI}$; $p = 0.7026$. There was also a 42% lower rate of nocturnal hypoglycemia with IDegAsp compared with BIAsp 30, which was not significant, ERR: 0.58 $[0.22; 1.51]_{95\%\ CI}$, $p = 0.2643$, in the Japanese subpopulation.

Insulin Dose

Mean insulin dose at the end of the trial was significantly lower for patients treated with IDegAsp than for patients treated with BIAsp 30, with an estimated treatment ratio (ETR) of 0.79 $[0.73; 0.87]_{95\%\ CI}$, $p < 0.0001$. Results were similar and also significant in Japanese patients, with an ETR of 0.78 $[0.65; 0.95]_{95\%\ CI}$, $p = 0.0121$ (Table 2).

Safety

Overall, 271 patients were included in the safety analysis set, 146 of whom were in the IDegAsp treatment arm and 125 were in the BIAsp 30 treatment arm. A slightly higher percentage of patients reported one or more AE with IDegAsp versus BIAsp 30 (70.5% vs. 60.8%, respectively). There were more withdrawals among patients treated with BIAsp 30 (19.0%) than with IDegAsp (14.4%), but the majority of the

Table 2 Overview of results for the elderly Japanese subpopulation of BOOST INTENSIFY ALL

Characteristic	*n*	IDegAsp BID	*n*	BIAsp 30 BID	IDegAsp–BIAsp 30
HbA_{1c}, (mmol/mol)					
Baseline	44	67.0 (6.5)	28	67.8 (8.6)	ETD: −0.10 $[-3.38; 3.18]_{95\%\ CI}$, $p = 0.9521$
End of trial	44	53.2 (7.2)	28	53.5 (7.9)	
HbA_{1c}, (%)					
Baseline	44	8.3 (0.6)	28	8.4 (0.8)	ETD: −0.01 $[-0.31; 0.29]_{95\%\ CI}$, $p = 0.9521$
End of trial	44	7.0 (0.7)	28	7.0 (0.7)	
FPG, (mg/dL)					
Baseline	44	147.2 (40.6)	28	151.7 (46.0)	ETD: −33.58 $[-49.63; -17.53]_{95\%\ CI}$, $p < 0.0001$
End of trial	44	92.5 (26.8)	28	125.9 (40.3)	
FPG, (mmol/L)					
Baseline	44	8.2 (2.3)	28	8.4 (2.6)	ETD: −1.86 $[-2.75; -0.97]_{95\%\ CI}$, $p < 0.0001$
End of trial	44	5.1 (1.5)	28	7.0 (2.2)	
Insulin dose (U)					
Baseline	43	27.0 (13.8)	28	22.8 (11.8)	ETR: 0.78 $[0.65; 0.95]_{95\%\ CI}$, $p = 0.0121$
End of trial	43	34.9 (20.3)	28	39.3 (21.7)	

BIAsp 30 biphasic insulin aspart 30, *BID* twice daily, *CI* confidence interval, *ETD* estimated treatment difference, *ETR* estimated treatment ratio, *FPG* fasting plasma glucose, HbA_{1c} glycated hemoglobin, *IDegAsp* insulin degludec/insulin aspart, *n* number of patients

withdrawals were not a result of AEs (Table 4). The majority of the AEs were considered unlikely to be related to trial production in BOOST INTENSIFY PREMIX I (71% with IDegAsp and 57% with BIAsp 30) and BOOST INTENSIFY ALL (69% with IDegAsp and 58% with BIAsp 30).

DISCUSSION

This post hoc analysis of a pooled population of elderly patients demonstrates that treatment with IDegAsp provides effective glycemic control consistent with the effects of BIAsp 30. No statistically significant differences were seen between the two therapies in HbA_{1c} and in overall confirmed or nocturnal hypoglycemic events. Similar findings were observed in the subanalysis of Japanese patients. Our results are largely in agreement with those reported for the overall trial population [33], although the lower rates of hypoglycemia reported for IDegAsp vs. BIAsp 30 in the elderly population did not reach statistical significance. However, mean insulin dose at the end of the trial was significantly lower for elderly patients treated with IDegAsp compared with BIAsp 30. The safety profile was similar for each treatment.

Hypoglycemia is a major barrier to achieving glycemic control for anyone with diabetes, but definitions of hypoglycemia vary between studies, and this can have a major effect on the reported incidence [38]. Furthermore, the outcomes and experience associated with biochemically similar hypoglycemic events can vary for different patients. Therefore, this analysis assessed the incidence of hypoglycemia with IDegAsp when applying the PG threshold of < 56 mg/dL (3.1 mmol/L), which is similar to the threshold that the 2017 Joint Position Statement of the American Diabetes Association and the European Association for the Study of

Table 3 Overall confirmed and nocturnal confirmed hypoglycemic episodes for elderly patients (≥ 65 years of age) with type 2 diabetes mellitus

	BOOST INTENSIFY PREMIX I (global patient population)					
	IDegAsp BID			BIAsp 30 BID		
	n (%)	*E*	*R*	*n* (%)	*E*	*R*
Confirmed	50 (75.8)	332	1093.64	52 (74.3)	407	1367.34
Nocturnal confirmed	16 (24.2)	20	65.88	25 (35.7)	53	178.06
	BOOST INTENSIFY ALL (pan-Asian patient population)					
	IDegAsp BID			**BIAsp 30 BID**		
	***n* (%)**	***E***	***R***	***n* (%)**	***E***	***R***
Confirmed	62 (77.5)	418	1156.10	40 (72.7)	253	1031.69
Nocturnal confirmed	19 (23.8)	58	160.42	19 (34.5)	37	150.88
	BOOST INTENSIFY ALL (Japanese subpopulation)					
	IDegAsp BID			**BIAsp 30 BID**		
	***n* (%)**	***E***	***R***	***n* (%)**	***E***	***R***
Confirmed	31 (70.5)	249	1246.54	22 (78.6)	187	1441.57
Nocturnal confirmed	11 (25.0)	30	150.19	12 (42.9)	29	223.56
	POOLED ANALYSIS (global patient population)					
	IDegAsp BID			**BIAsp 30 BID**		
	***n* (%)**	***E***	***R***	***n* (%)**	***E***	***R***
Confirmed	112 (76.7)	750	1127.59	92 (73.6)	660	1215.72
Nocturnal confirmed	35 (24.0)	78	117.27	44 (35.2)	90	165.78

Confirmed hypoglycemia: patient unable to treat himself/herself and/or has a recorded plasma glucose < 56 mg/dL (3.1 mmol/L)

BIAsp 30 biphasic insulin aspart 30, *BID* twice daily, *E* number of events, *IDegAsp* insulin degludec/insulin aspart, *n* number of patients, *R* event rate per 100 patient-years of exposure

Diabetes recommends that all studies should report, as it is considered to be clinically significant and associated with an unequivocal hypoglycemic episode [39]. The findings presented here show that IDegAsp results in a lower rate of hypoglycemia compared with BIAsp 30 when using this threshold in the elderly subpopulation. As hypoglycemia is of particular concern in the elderly, the results of this post hoc analysis are reassuring.

An important limitation of this analysis was the relatively low number of elderly patients, and the low number of hypoglycemic episodes,

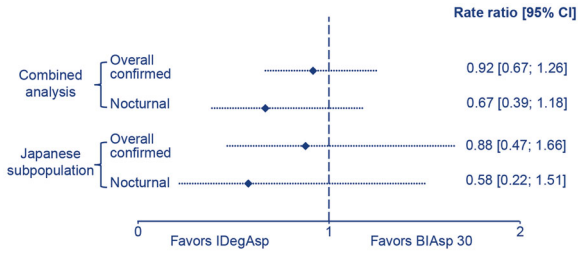

Fig. 2 Estimated rate ratios for overall confirmed and nocturnal confirmed hypoglycemia. *BIAsp 30* biphasic insulin aspart 30, *CI* confidence interval, *IDegAsp* insulin degludec/insulin aspart

Table 4 Withdrawals of elderly patients (≥ 65 years of age) with type 2 diabetes mellitus participating in BOOST INTENSIFY PREMIX I and BOOST INTENSIFY ALL

	IDegAsp BID		BIAsp 30 BID		Total	
	Number of withdrawals *n* (%)	Withdrawn due to AE *n* (%)	Number of withdrawals *n* (%)	Withdrawn due to AE *n* (%)	Number of withdrawals *n* (%)	Withdrawn due to AE *n* (%)
BOOST INTENSIFY PREMIX I	8 (12.1)	2 (25.0)	16 (22.5)	2 (12.5)	24 (17.5)	4 (16.7)
BOOST INTENSIFY ALL	13 (16.3)	6 (46.2)	8 (14.5)	3 (37.5)	21 (15.6)	9 (42.9)
Overall	21 (14.4)	8 (38.1)	24 (19.0)	5 (20.8)	45 (16.5)	13 (28.9)

AE adverse event, *BIAsp 30* biphasic insulin aspart 30, *BID* twice daily, *IDegAsp* insulin degludec/insulin aspart, *n* number of patients withdrawn at or after randomization

which prohibited statistical analysis of the incidence of severe hypoglycemia. Nonetheless, our findings show that IDegAsp results in a numerically lower rate of hypoglycemia compared with BIAsp 30, and that there were no additional safety signals in this population that might require further investigation.

CONCLUSION

In conclusion, the analytical results for elderly patients with T2D included in the phase 3 BOOST INTENSIFY PREMIX I and BOOST INTENSIFY ALL studies are consistent with those for the overall trial populations, and the low rates of hypoglycemia are reassuring, suggesting that there is no need for special precautions when using IDegAsp twice daily in elderly patients—it should be administered in a similar manner to how it is administered in younger adults.

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Edmond G. Fita and Magnus Ekelund contributed to the design, conduct/data collection, analysis, and manuscript writing for this study.

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Compliance with Ethics Guidelines. The protocol, protocol amendments, consent form, and subject information sheet of the original BOOST INTENSIFY PREMIX I and BOOST INTENSIFY ALL trials were reviewed and approved by health authorities according to local regulations, and by the local independent ethics committees prior to trial initiation [31, 32]. The trials were performed in accordance with the Declaration of Helsinki and good clinical practice [36, 37]. In summary, all procedures performed in studies involving human participants were in accordance with the ethical standards of the institutional and/or national research committee and with the 1964 Helsinki Declaration and its later amendments or comparable ethical standards. Informed consent was obtained from all individual participants included in the study.

Data Availability. The datasets generated during and/or analyzed during the current study are available from the corresponding author on reasonable request.

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