DRUG EVALUATION

Diabetes Management

Soluble co-formulation of insulin degludec and insulin aspart: a new approach to insulin treatment

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Practice points

- Insulin degludec/insulin aspart (IDegAsp), a soluble insulin combination, consists of the basal IDeg and the rapid-acting prandial insulin aspart.
- IDegAsp can be administered once or twice daily with the main meal(s).
- In patients with Type 2 DM combination with oral antidiabetic medicinal products is possible.
- Short acting insulin may be combined at the remaining mealtimes with IDegAsp for patients with Type 1 diabetes mellitus.
- Lower risk of hypoglycemia, noninferiority to different comparators and convenient dosing regimens as combining of two insulins in the same pen with pharmacodynamics preserved suggest that IDegAsp is a safe and efficacious treatment of diabetes mellitus.

SUMMARY Recently introduced, insulin degludec (IDeg) is characterized by a stable glucose-lowering effect, achieved via flat and stable PD profile and an ultralong duration of action. Because of its unique properties, it is possible to co-formulate IDeg with insulin aspart (IAsp). When combined, the pharmacokinetic and pharmacodynamic profiles of IDeg and IAsp are retained. IDegAsp, as a fully soluble, ready-to-use insulin for subcutaneous injection, consists of 70% long-acting IDeg and of 30% rapid-acting IAsp. The safety and efficacy of IDegAsp were investigated in several Phase 2 and Phase 3 clinical trials on patients with Type 1 and Type 2 diabetes mellitus. Lower risk of hypoglycemia, noninferiority to different comparators and convenient dosing regimens as combining of two insulins in the same pen with pharmacodynamics preserved suggest that IDegAsp is a safe and efficacious treatment of diabetes mellitus.

Prolongation of insulin action was possible by increasing its molecular mass, since larger molecules pass slower into circulation from the injection site. For example, human insulin in higher concentrations naturally self-assembles and forms hexamers, which, after injection, dissociate slowly into monomers that are absorbed into the circulation. The molecular mass of insulin has been further increased either by preformulation with protamine (NPH) or by hexamer-dihexamer equilibrium with retaining in the injection depot via albumin binding (insulin detemir) [1]. In the case of insulin glargine, protraction is mainly achieved by a formation of precipitates in the subcutaneous depot with a higher pH than in the pharmaceutical formulation, where glargine is soluble [2]. The aim of this narrative review is to present the clinical data regarding a coformulation of the new long-acting insulin analogue degludec and fast acting insulin aspart. As degludec is present on the market only a

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short time, some general information with pharmacokinetic (PK) and pharmacodynamic (PD) are also provided. We do, however, not discuss the cardiovascular safety of this new insulin and some data questioning it. The reason for that is that the cardiovascular safety of degludec will be assessed in a large ongoing study comparing it with glargine (the results of it will be known probably not earlier than in the year 2019).

• Insulin degludec

Recently a new, long-acting insulin analogue, insulin degludec (IDeg) was introduced. It retains the human insulin sequence except for the deletion of threonine in position B30 (ThrB30) and an addition of a 16-carbon fatty di-acid side chain attached to the lysine in position B29 (LysB29) via a glutamic acid spacer [3].

A novel mechanism of insulin degludec protraction takes advantage of the fact that phenol is commonly used as stabilizing factor in insulin formulations **(Figure 1)**. In its presence, insulin degludec forms stable dihexamers. After injection, phenol disperses from the depot and degludec forms multihexamers linked via contact between fatty-acid moieties and the zinc-containing core of the next hexamer. The average molar mass of such huge, supramolecular structure is >5000 kDa, as compared with 22 kDa for human insulin hexamers [4]. The multihexamers disassemble very slowly, which ensures continuous and uniform absorption of active monomers [3], resulting in a stable glucose-lowering effect achieved with a flat profile (without significant peaks in insulin concentration) and with an ultralong duration of action [5]. Completely new feature of insulin degludec is a possibility of combination with others substances, like rapid-acting insulin aspart or liraglutide, unlike Insulin glargine and insulin detemir. The main reason for that in the case of insuline glargine is different acidic pH required for solution (other insulins are soluble in neutral pH). Insulin detemir, similarly to the insulin degludec, also creates self-associated structures, however, it is less stable and when it is mixed with rapid acting insulin (i.e., insulin aspart) the hybrid hexamers form (inuslin detemir and insulin aspart) with unpredictable profile of action.

Pharmacokinetic & pharmacodynamic properties of IDeg

The PK properties of insulin degludec were described for the first time in a study including 12 subjects with Type 1 diabetes [6]. The steady-state PK profile of patients receiving 5.0 nmol/kg of insulin degludec once daily for 6 days demonstrated a smooth and stable exposure over 24 h. Moreover, following the final dose, IDeg was still detected after 96 h. Similar results were observed in another study, where IDeg showed a stable PK profile, increasing proportionally with the applied dose. Type 1 diabetes patients received one of three doses (0.4, 0.6, 0.8 U/kg) of IDeg once daily for 8 days. IDeg remained detectable in serum at 120 h following the final dose and the mean terminal t1/2 (the time for the plasma level to decline by 50% after the final dose) was 25.4 h. On the other hand, another insulin formulation, insulin glargine, was undetectable after 36–48 h postdosing with a t1/2 around 12.5 h. The ratio of $AUC_{0-12\ h}$ to AUC_{total} was 0.5, indicating that between the first and second 12-h postdosing periods, IDeg was equally distributed in the serum [7]. Similar results for IDeg were obtained in patients with Type 2 diabetes, with t1/2 = 25.1 h, a mean steady state AUC_{total} of 89.64, 130.16 and 177.41 pmol·h/l for a 0.4, 0.6, or 0.8 U/kg dose, respectively [5].

The ultralong PK properties of IDeg are preserved in subjects with renal [8], as well as with hepatic, impairment [9]. Renal impairment did not result in differences on total exposure ($AUC_{0-120\ h,SD}$), maximum concentration ($C_{max,SD}$) or apparent clearance (CL/F_{SD}) of IDeg. Interestingly, hemodialysis did not influence the clearance of IDeg. Similarly, there were no differences in the PK properties of IDeg between subjects with normal function and those with different grades of hepatic impairment. Once-daily dosing of IDeg was sufficient to reach steady-state plasma levels after 2–3 days [10].

In conclusion, the euglycemic clamp studies proved that a stable PK profile reflects the glucose-lowering effect of IDeg.

The PD profile reported in patients with Type 1 diabetes receiving once-daily IDeg was flat, and for the 0.6 and 0.8 U/kg dose, the end of action did not occur within 42 h. For the lowest dose (0.4 U/kg), in only 3 out of 21 patients did the end of action occur before 42 h postinjection [11].

The PD effect after once-daily subcutaneous IDeg (0.4, 0.6, 0.8 U/kg) was also examined in similar study in patients with Type 2 diabetes. Results show that the steady-state 24-h glucose infusion rate (GIR) profile was stable and flat and the glucose-lowering effect was evenly distributed

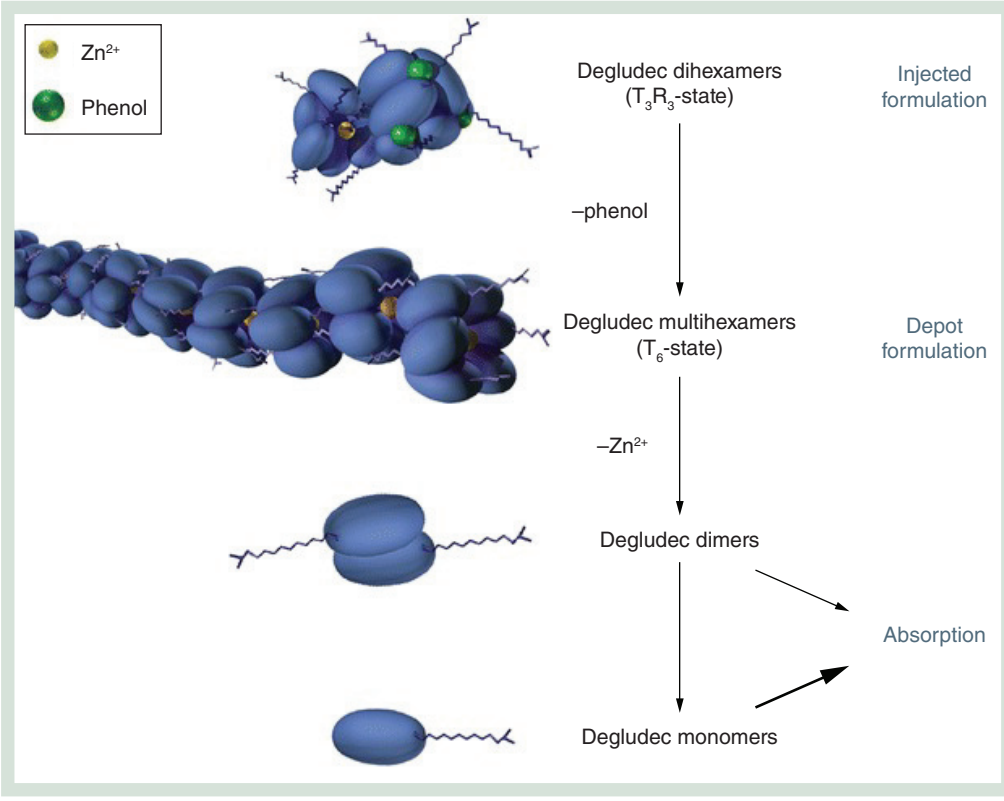

Figure 1. Insulin degludec protraction mechanism. Dihexamers in the pharmaceutical formulation assemble into multihexamer chains immediately after subcutaneous injection. These slowly disassemble with the diffusion of zinc to release a steady supply of degludec monomers into the circulation.
Adapted with permission from [3].

across dosing intervals (first and second 12 h periods) for all tested doses, which reflects the PK data [5].

In terms of variability of the glucose-lowering effect, IDeg is more predictable than insulin glargine, which was shown by Heise *et al.* in a double blind, parallel-group study [12]. In total, 54 patients with Type 1 diabetes received 0.4 U/kg of IDeg or insulin glargine for 12 days. All patients underwent 24-h euglycemic clamps on days 6, 9 and 12. The variability of the GIR was reduced by 75% for IDeg compared with insulin glargine ($AUC_{GIR\,0–24\,h}$ CV values of 20 and 82%, and CV values for maximum effect [GIR_{max}] of 18 vs 60%, for IDeg and insulin glargine, respectively). The lower within-subject variability of IDeg was found when GIR data were divided into values for 2-h intervals. The coefficients of variation for AUC_{GIR} were 33% from 0–2 h, 32% from 10–12 h and 33% from 22–24 h, compared with 60, 155 and 115%, respectively, for insulin glargine [12]. In summary, the presented data show a 4× lower day-to-day variability in the glucose lowering effect of IDeg compared with insulin glargine.

Finally, the injection site of IDeg had little or no effect on its glucose lowering properties when administrated into the thigh, abdomen or deltoid [13].

• IDeg/insulin aspart co-formulation (IDegAsp)

Pharmacokinetic & pharmacodynamic properties of IDeg/insulin aspart formulation

IDeg/insulin aspart (IDegAsp) is the first fully soluble, ready-to-use insulin product for subcutaneous injection. It consists of both basal and bolus insulin components. Once injected into subcutaneous tissue, IDeg forms a depot of multihexamers from which insulin monomers are slowly and continuously absorbed into circulation. On the contrary, insulin aspart hexamers dissociate into monomers immediately after injection and are rapidly absorbed into the circulation.

The pharmacokinetic and pharmacodynamic data of the IDeg component of IDegAsp was

Table 1. Overview of insulin degludec/aspart clinical trial Phase 3 programs.

Type 1 diabetes	Type 2 diabetes	
	Once-daily dosing	*b.i.d dosing*
BOOST® T1	BOOST JAPAN Insulin-naive patients treated with metformin	BOOST INTENSIFY PREMIX I Intensification from premix in patients treated with metformin ± DPP-4 inhibitors ± pioglitazones
vs Insulin detemir (basal–bolus)	vs insulin glargine once daily	vs biphasic insulin aspart 30 twice daily BOOST:INTENSIFY ALL Intensification in insulin users treated with metformin ± vs biphasic insulin aspart 30 twice daily

Adapted with permission from [19].

discussed previously in this review. The second component, insulin aspart, reaches maximum blood concentration within 30 min and acts for 3–5 h when injected subcutaneously [14]. It was demonstrated by *in vitro* size-exclusion chromatography that both two insulins remain separate when co-formulated in IDegAsp [15]. The pharmacodynamic data of IDegAsp shows that its glucose-lowering effect lasts for at least 24 h. The pharmacodynamic profile, described as GIR, shows a peak action due to prandial insulin aspart, and a separate, stable, longer than 24-h basal action of IDeg [16]. This gradual reduction may be translated into a potential reduction in risk of hypoglycemia and an improvement of fasting plasma glucose.

The IDegAsp clinical trial program – Phase 2

The efficacy of IDegAsp in patients with Type 2 diabetes in this phase was examined in two multicenter, open-label, randomized trials. One of them compared IDegAsp with insulin glargine, both administered once daily [17], and the other study compared twice-daily IDegAsp with twice-daily biphasic insulin aspart [18]. Since both studies used a treat-to-target design, insulin doses were titrated to achieve a prebreakfast and/or predinner self-measured plasma glucose (SMPG) targeted to the FPG level of 4–6 mmol/l. Both are described in detail below.

In the study comparing the efficacy and safety of the once-daily IDegAsp (n = 59) with insulin glargine (IGlar) (n = 60) in insulin-naive Type 2 diabetes patients, the mean HbA_{1c} decreased in both groups to similar levels (IDegAsp: 7%, IGlar: 7.1%). This was expected because of the treat-to-target design of the study, although this effect was achieved at the cost of a lower insulin dose (0.38 U/kg) for IDegAsp than for insulin glargine (0.45 U/kg) treated patients. During the last four weeks of the study, 51% of patients treated with IDegAsp and 50% treated with IGlar achieved HbA1c lower than 7.0% without confirmed hypoglycemia. The rates of confirmed hypoglycemia were similar in the two groups throughout the study. Fasting plasma glucose (FPG) was similar, but the mean postdinner increase of glycemia was lower for IDegAsp (2.34 mg/dl) than for IGlar (29.34 mg/dl). In summary, the presented data suggest that once-daily IDegAsp provides better postprandial glucose control in comparison with IGlar with similar rates of hypoglycemia and overall glucose control [17].

The second Phase 2 study was performed in insulin-naive patients with Type 2 diabetes and compared the safety and efficacy of IDegAsp with BIAsp 30 in a twice daily regimen [18]. Both IDegAsp and BIAsp 30 contain the same proportion of rapid-acting insulin aspart, but are different in the type of long-acting insulin formulation, with protamine-crystalized insulin aspart in BIAsp 30 and IDeg in IDegAsp.

During the study, a similar mean HbA1c reduction was observed (again, this result was expected because of the treat-to-target design), but at the end of the study, the proportion of subjects achieving HbA1c below 7% without confirmed hypoglycemia was significantly higher in the IDegAsp group than in the BIAsp 30 group (67 vs 40%, p-value not stated). Additionally, in the IDegAsp group, the mean FPG at week 16 was lower than in the BIAsp 30 group (115.2 mg/ml and 135 mg/dl, respectively). The mean daily insulin dose was 0.57 U/kg in the IDegAsp group and 0.66 U/kg in the BIAsp 30 group, and the small increase in body weight was similar in both groups (1.1 vs 1.4 kg, respectively). No severe hypoglycemia was reported, confirmed nocturnal hypoglycemia was less frequent for the IDegAsp group than for BIAsp 30 group (7 and 20 episodes, respectively), and

the rate of confirmed hypoglycemia was 58% lower for the IDegAsp group compared with the BIAsp 30 group. In summary, the overall glycemic control of twice-daily IDegAsp was similar to BIAsp 30, with a significantly lower rate of confirmed hypoglycemia and lower FPG [18].

In Phase 2 of clinical trials IDegAsp was compared with insulin glargine and biphasic insulin aspart. Direct comparison of IDegAsp and insulin glargine used once daily revealed better glucose control by IDegAsp at 90 min after dinner SMPG timepoint in comparison with IGlar with similar rates of hypoglycemia and overall glucose control [17]. Furthermore, comparison of IDegAsp and biphasic insulin aspart showed that treatment by IDegAsp is connected with lower rates of confirmed hypoglycemia and lower level of FPG after 16 weeks of treatment [18].

The IDeg/insulin aspart clinical trial program – Phase 3

Clinical trials included in the clinical development program were designed to test the potential use of IDegAsp in both Type 1 and Type 2 diabetes patients. IDegAsp treatment initiation in newly diagnosed subjects was investigated as well as insulin treatment intensification with IDegAsp with advanced diabetes **(Table 1)**.

Type 1 diabetes

The efficacy and safety of IDegAsp in Type 1 diabetes patients was compared with insulin detemir (IDet) in a Phase 3, 26-week, open-label, treat-to-target study **(Table 2)** [20]. A total of 548 subjects with Type 1 diabetes were randomized in a ratio of 2:1 to the IDegAsp or the IDet group. IDegAsp was administrated once daily with any meal of the day, and could be moved to another meal at any time during the trial with insulin aspart administered with the two remaining meals. Insulin detemir was administered at the same time each day, with the evening meal or at bedtime, with the possibility to change the regimen for twice-daily (b.i.d.) injections after 8 weeks in cases of inadequate glycemic control. The treat-to-target principle of the study required adjustment of the insulin dose for each individual subject with the aim of achieving pre-breakfast SMPG targets of 4.0–4.9 mmol/l for both IDegAsp and IDet.

Overall glycemic control defined by the HbA1c level improved in both the IDegAsp and IDet groups to 7.6%, and no significant difference in the percentage of patients with HbA1c below 7% was observed (IDegAsp: 24.6%, IDet: 20.3%). At the end of study, the mean FPG decreased to similar levels, reaching 8.7 mmol/l in the IDegAsp group and

Table 2. Summary of Phase 3 clinical trials for insulin degludec/aspart in Type 1 diabetes.

Parameter	IDegAsp (b.i.d.)† insulin users [21]	BIAsp 30 (b.i.d.)† insulin users [21]	IDegAsp (b.i.d.)‡ insulin users [19]	BIAsp 30 (b.i.d.)‡ insulin users [19]
n	224	222	280	142
Mean HbA1c (%):				
– End of trial	7.1	7.1	7.1	7.0
– Mean change			-1.38	-1.42
	Difference: -0.03 [-0.18;0.13]		*Difference: 0.05* [-0.10;0.20]	
FPG (mmol/l):				
– End of trial	5.8	6.8	5.4	6.5
– Mean change			-2.55	-1.47
	Difference: -1.14 [-1.53;-0.76]		*Difference: -1.06* [-1.43;-0.70]	
Hypoglycemia rate (per patient year of exposure):				
– Severe	0.09	0.25	0.05	0.03
– Confirmed§	9.72	13.96	9.56	9.52
	Ratio: 0.68 [0.52;0.89]		*Ratio: 1.00* [0.76;1.32]	
Nocturnal confirmed§	0.74	2.53	1.11	1.55
	Ratio: 0.27 [0.18;0.41]		*Ratio: 0.67* [0.43;1.06]	

†Twice-daily regimen ± metformin ± pioglitazone ± DPP-4 inhibitor.

‡Twice-daily regimen ± metformin.

§Confirmed hypoglycemia was defined as episodes confirmed by plasma glucose <3.1 mmol/l or by the patient needing third party assistance – nocturnal confirmed hypoglycemia was defined as episodes between midnight and 6 am.

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Table 3. Summary of Phase 3 clinical trials for insulin degludec/aspart in Type 2 diabetes.

Parameter	IDegAsp (o.d.)[†] [20]	IDet (o.d./b.i.d.)[‡] [20]
n	366	182
Mean HbA1c (%):		
– End of trial	7.6	7.6
– Mean change	-0.73	-0.68
	Difference: -0.05 [-0.18;0.08]	
FPG (mmol/l):		
– End of trial	8.7	8.6
	Difference: 0.23 [-0.46;0.91]	
Hypoglycemia rate (per patient year of exposure):		
– Severe	0.33	0.42
– Confirmed[§]	39.17	44.3
	Ratio: 0.91 [0.76;1.09]	
Nocturnal confirmed[§]	3.71	5.72
	Ratio: 0.63 [0.49;0.81]	

Results of a 26-week trial in Type 1 diabetes mellitus.
[†]Once-daily regimen + insulin aspart to cover mealtime insulin requirements.
[‡]Once- or twice-daily regimen + insulin aspart to cover mealtime insulin requirements.
[§]Confirmed hypoglycemia was defined as episodes confirmed by plasma glucose <3.1 mmol/l or by the patient needing third party assistance – nocturnal confirmed hypoglycemia was defined as episodes between midnight and 6 am.
Adapted with permission from [19].

8.6 mmol/l in the IDet group. Both, daily total (DTID) and daily basal (DBID) insulin doses at the end of study were lower than with IDet (DTID: 69 U and 79U, DBID: 29U and 36U, respectively; $p < 0.0001$). No significant difference in the mean daily bolus insulin dose was observed. Weight increase was slightly higher in the IDegAsp group (2.3 kg) than in the IDet group (1.3 kg; $p < 0.05$).

There was no statistically significant difference between IDegAsp and IDet in the rates of severe hypoglycemia (0.33 and 0.42 episodes/patient-year, respectively) or overall confirmed (plasma glucose, 3.1 mmol/l) hypoglycemia (39.17 and 44.34 episodes/patient-year, respectively). The nocturnal confirmed hypoglycemia rate was 37% lower with IDegAsp than with IDet (3.71 vs 5.72 episodes/patient-year; $p < 0.05$). No treatment differences were detected in health-related quality of life, laboratory measurements, physical examination, vital signs, electrocardiograms, fundoscopy or adverse events. In summary, in patients with Type 1 diabetes with similar glycemic control but a lower prevalence of nocturnal hypoglycemia, IDegAsp has added the convenience of fewer daily injections than conventional basal-bolus IDet therapy [20] Of course, in spite of the fact that such regimen has proved to be safe and effective in an average patient, IDegAsp may not be suitable for those patients in whom evening meal content and insulin requirement is changing and the constant proportion of short and long acting insulin does not allow to adjust the dose appropriately.

Type 2 diabetes

Phase 3 clinical trial programs for patients with Type 2 diabetes compared IDegAsp with other active comparators. An overview of the IDegAsp clinical trial Phase 3 programs is presented in **Table 3.** The authors concentrate only on published results.

In all trials, the primary end point was defined as a change in glycosylated hemoglobin A1c (HbA1c) from baseline to the end of the study (26 weeks of treatment).

In the 26-week, randomized, open-label, multinational, treat-to-target trial, participants (mean age 58.7 years, duration of diabetes 13 years, BMI 29.3 kg/m2 and HbA1c 8.4% [68 mmol/mol]) were exposed to twice daily injections of IDegAsp (n = 224) or BIAsp 30 (n = 222), administered with breakfast and the main evening meal and dose titrated to a self-measured pre-meal plasma glucose (PG) target of 4.0–5.0 mmol/l. Twice-daily treatment with IDegAsp and BIAsp 30 showed similar reduction of HbA1c. According to the treat-to-target design of all described studies, in previously treated subjects, IDegAsp was noninferior to BIAsp 30 [21].

In terms of lowering fasting plasma glucose, IDegAsp administrated b.i.d. was even superior

to BIAsp 30 b.i.d., in Fulcher GR *et al.* reported mean FPG decreased from 8.9 ± 2.9 mmol/l at baseline to 5.8 ± 1.9 mmol/l for IDegAsp and from 8.6 ± 2.6 mmol/l to 6.8 ± 2.4 mmol/l for BIAsp 30. IDegAsp was superior to BIAsp 30 in lowering FPG (estimated treatment difference [ETD] -1.14 mmol/l [95% CI: -1.53 to -0.76]; $p < 0.001$) [21].

In almost all Phase 3 studies in Type 2 diabetes, the incidence of confirmed and nocturnal hypoglycemia was lower with IDegAsp in comparison with the comparator **(Table 3)**. In summary, a co-formulation of IDeg and insulin aspart is a unique, soluble combination of fast-acting and ultralong-acting insulin analogues. In all presented trials, IDegAsp was noninferior to comparators in terms of reducing HbA1c (primary end point). Even more important is that IDegAsp treatment in different trials was rather uniformly associated with a lower rate of hypoglycemia (confirmed, nocturnal confirmed). In conclusion, noninferiority to three different comparators and dosing regimens associated with a lower risk of hypoglycemia suggest that IDegAsp can be used as a safer treatment of diabetes mellitus in adults.

Financial & competing interests disclosure

E Franek has served on the advisory board for Boehringer Ingelheim/Lilly, Novartis, Novo-Nordisk and received consultancy or speaker fees from Bioton, BMS/Astra Zeneca, Boehringer Ingelheim/Lilly, Merck, Novartis, Novo-Nordisk, Polpharma, Sanofi, Servier, TEVA. Ł Hak is an employee of Medical Department Novo Nordisk. The authors have no other relevant affiliations or financial involvement with any organization or entity with a financial interest in or financial conflict with the subject matter or materials discussed in the manuscript apart from those disclosed.

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