Significant reduction of hypoglycaemia in patients with type 1 diabetes with insulin degludec compared with insulin glargine U100: a randomised, double-blind, crossover trial (SWITCH 1)

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Introduction

- Insulin degludec (IDeg) is a basal insulin with a unique mode of protraction and a duration of action greater than 42 hours.[1–3]
- The phase 3a development program included two trials in patients with type 1 diabetes (T1D), which demonstrated HbA_{1c} non-inferiority of IDeg to insulin glargine U100 (IGlar) with lower rates of nocturnal confirmed hypoglycaemia.[4–6]
- Potential limitations of the phase 3a data included: the lack of blinding, inclusion of non-symptomatic hypoglycaemia, exclusion of patients with at least one risk factor for hypoglycaemia, and no recording of the timing of IGlar administration.
- SWITCH 1 was designed to confirm the hypoglycaemia benefit previously seen, address these limitations, and assess the safe switch to IDeg from other insulins.

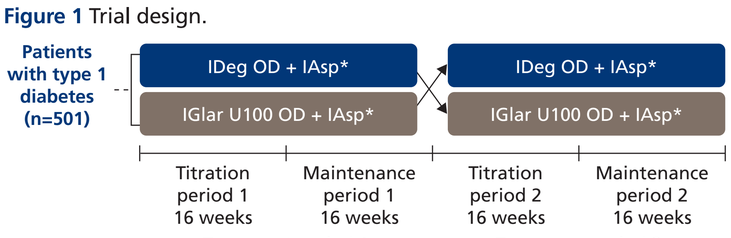
Aims

- Primary: To demonstrate non-inferiority in the rates of severe or blood glucose (BG)-confirmed symptomatic hypoglycaemia episodes for IDeg + insulin aspart (IAsp) versus IGlar+IAsp during the maintenance period (after 16 weeks of treatment). If non-inferiority was confirmed then superiority was assessed based on the upper limit of the 95% confidence interval (CI).
- Secondary: To demonstrate non-inferiority in terms of severe or BG-confirmed symptomatic nocturnal hypoglycaemia in the maintenance period, and to confirm superiority with respect to the proportion of patients with severe hypoglycaemic episodes in the maintenance period. If non-inferiority was confirmed then superiority was assessed based on the upper limit of the 95% CI.

Methods

- This was a 2× 32-week randomised, double-blind, two-period, crossover, multicentre, treat-to-target phase 3b clinical trial conducted in patients with T1D (Figure 1).

Figure 1 Trial design.



*IAsp was administered 2- to 4-times a day as part of a full basal–bolus regimen.
IAsp, insulin aspart; IDeg, insulin degludec; IGlar U100, insulin glargine; OD, once daily

- Patients were randomised 1:1 to morning or evening administration throughout the trial of IDeg or IGlar once daily, both with IAsp 2- to 4-times daily at mealtimes, for 32 weeks, followed by crossover to IGlar or IDeg.
- Eligible patients had at least one of the following hypoglycaemia risk factors:
  - ≥1 severe hypoglycaemic episodes within the last year
  - Moderate chronic renal failure (glomerular filtration rate 30–59 mL/min/1.73 m^2)
  - Hypoglycaemic symptom unawareness
  - Diabetes duration >15 years
  - Episode of hypoglycaemia within the last 12 weeks (according to ADA definition: (≤70 mg/dL [≤3.9 mmol/L]).
- Blinding was ensured by using a vial and syringe for the basal insulin; the starting dose of basal insulin and bolus insulin (algorithm users) was reduced by 20% at randomisation and crossover.
- Titration of basal insulin was according to the trial algorithm (target: 71–90 mg/dL: lowest of three consecutive measurements). Titration of bolus insulin (target: 71–108 mg/dL) was either according to the algorithm or based on the meal carbohydrate content, depending on experience.
- Confirmation of non-inferiority in HbA_{1c} reduction was a prerequisite for conducting the hypoglycaemia analyses.
- Confirmed symptomatic hypoglycaemia was defined by a BG <56 mg/dL (<3.1 mmol/L) with symptoms and nocturnal hypoglycaemia was any episode occurring between 00:01 and 05:59, both inclusive. Severe hypoglycaemia was defined in accordance with ADA guidelines (ADA 2013) and all reported episodes of severe hypoglycaemia were adjudicated by an independent external committee.
- *P*-values were derived using a Poisson model with a logarithm of the exposure time (100 years) as offset; estimates were adjusted for treatment, period, sequence, and dosing time as fixed effects, and patient as a random effect. McNemar's test was used to analyse the secondary confirmatory endpoint of proportion of patients experiencing severe hypoglycaemia.

Results

- Baseline characteristics are shown in Table 1.
- In total, 501 patients were randomised and 500 were exposed to trial product, with 395 (78.8%) completing both treatment periods.

Efficacy

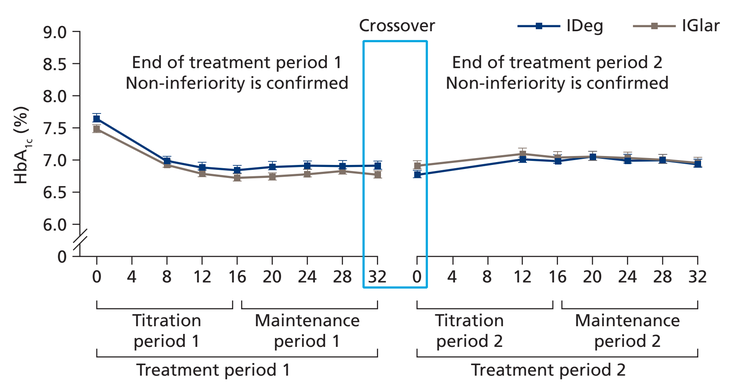
- The pre-requisite of achieving HbA_{1c} non-inferiority in both treatment periods was met (Figure 2); estimated treatment difference (ETD) in treatment period 1: 0.03 %-points $[-0.10; 0.15]_{95\%\ CI}$ (0.29 mmol/mol $[-1.09; 1.67]_{95\%\ CI}$). In treatment period 2, the ETD was 0.11%-points $[-0.00; 0.23]_{95\%\ CI}$ (1.23 mmol/mol $[-0.01; 2.47]_{95\%\ CI}$).
- Mean HbA_{1c} at the end of treatment period 1 was 6.92% (52.2 mmol/mol) for IDeg versus 6.78% (50.6 mmol/mol) for IGlar, and at the end of treatment period 2 was 6.95% (52.4 mmol/mol) for IDeg versus 6.97% (52.7 mmol/mol) for IGlar (Figure 2).

Table 1 Baseline characteristics.

Characteristic	Total
Full analysis set (FAS), n (%)	501
Male, %	53.7
Race, White/Black/Asian/Other, n (%)	92.2/6.4/0.4/1.0
Ethnicity, Hispanic or Latino, n (%)	51 (10.2)
Age, years	45.9 (14.2)
Weight, kg [lb]	80.5 (17.4) [177.5 (38.3)]
BMI, kg/m^2	27.5 (4.8)
Duration of diabetes, years	23.4 (13.4)
HbA_{1c}, % [mmol/mol]	7.6 (1.0) [59.6 (10.9)]
FPG, mg/dL [mmol/L]	169.8 (79.6) [9.4 (4.4)]
eGFR (mL/min/1.73 m^2)	90.0 (21.1)
Insulin treatment at screening	
Continuous subcutaneous insulin infusion (CSII)	97 (19.4)
Basal OD + 2–4 bolus injections	224 (44.7)
Basal BID + 2–4 bolus injections	179 (35.7)

BID, twice daily; BMI, body mass index; eGFR, estimated glomerular filtration rate; FPG, fasting plasma glucose; OD, once daily.

Figure 2 Mean HbA_{1c} over time in treatment periods 1 and 2.



IDeg, insulin degludec; IGlar, insulin glargine.

- Mean FPG for both groups also decreased during treatment period 1. In treatment period 2, the mean FPG for those switching to IDeg continued to decrease; however, the mean FPG for those switching to IGlar increased slightly.

Hypoglycaemia (Figure 3, Table 2)

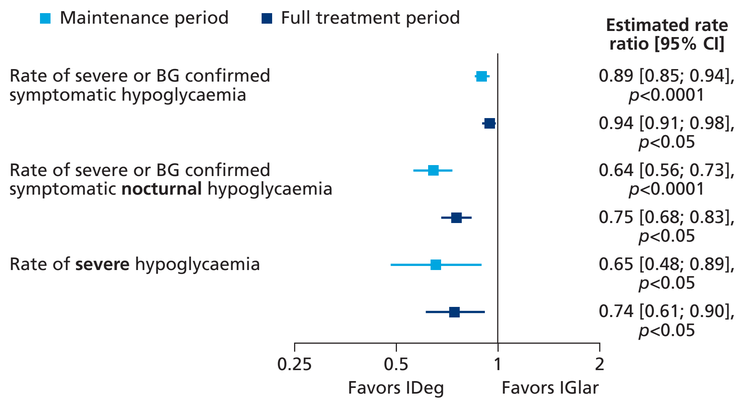
- Non-inferiority and superiority for the primary endpoint was achieved (significant 11% lower rate of severe or BG-confirmed symptomatic hypoglycaemia with IDeg versus IGlar) in the maintenance periods. To avoid one episode of severe or BG-confirmed symptomatic hypoglycaemia, one patient would need to be treated for 4 months with IDeg instead of IGlar.

Table 2 Hypoglycaemia summary.

Definition	IDeg		IGlar	
	Incidence n (%)	Rate/100 PYE	Incidence n (%)	Rate/100 PYE
Maintenance period				
Severe or BG-confirmed symptomatic hypoglycaemia	323 (77.3)	2200.9	337 (79.9)	2462.7
Severe or BG-confirmed nocturnal symtomatic hypoglycaemia	137 (32.8)	277.1	182 (43.1)	428.6
Severe hypoglycaemia	43 (10.3)	69.1	72 (17.1)	92.2
Full trial period				
Severe or BG-confirmed symptomatic hypoglycaemia	377 (83.0)	2044.2	398 (86.5)	2168.0
Severe or BG-confirmed symptomatic nocturnal hypoglycaemia	210 (46.3)	281.2	248 (53.9)	371.9
Severe hypoglycaemia	90 (19.8)	86.4	119 (25.9)	104.8

BG, blood glucose; IDeg, insulin degludec; IGlar, insulin glargine; PYE, patient-year of exposure.

Figure 3 Forest plot showing the rates of the respective hypoglycaemia endpoints in both the maintenance and overall treatment periods.



P-values derived using a Poisson model with logarithm of the exposure time (100 years) as offset; estimates adjusted for treatment, period, sequence and dosing time as fixed effects, and patient as a random effect.
BG, blood glucose (<56 mg/dL); CI, confidence interval; IDeg, insulin degludec; IGlar, insulin glargine U100.

- Non-inferiority and superiority were also achieved for the secondary endpoint of the number of severe or BG-confirmed symptomatic nocturnal hypoglycaemic episodes in the maintenance periods (significant 36% reduction) for IDeg versus IGlar. To avoid one episode of severe or BG-confirmed symptomatic nocturnal hypoglycaemia, one patient would need to be treated for 1 year with IDeg instead of IGlar.
- Severe hypoglycaemia was significantly reduced by 35% in the maintenance period. To avoid one episode of severe hypoglycaemia, three patients would need to be treated for 1 year with IDeg instead of IGlar.
- Similar results were seen for the full treatment period.
- IDeg was superior to IGlar regarding a lower proportion of patients experiencing severe hypoglycaemia during the maintenance (p=0.0016) and total (p=0.0090) treatment periods.

Safety

- At the end of treatment period 1, mean IDeg dose increased from 29 U to 39 U and mean IGlar dose from 24 U to 36 U. At the end of treatment period 2, mean IDeg dose increased from 36 U to 37 U and mean IGlar dose from 39 U to 41 U. A *post hoc* analysis confirmed a 3% significantly lower basal insulin dose with IDeg versus IGlar.
- Mean total daily insulin dose (basal plus bolus) increased from 53 U to 69 U for IDeg and from 46 U to 63 U for IGlar in treatment period 1, and from 63 U to 64 U for IDeg and from 69 U to 69 U for IGlar at the end of treatment period 2. A *post hoc* analysis confirmed a 3% significantly lower total insulin dose with the IDeg versus IGlar arm.
- Weight changes were comparable between IDeg and IGlar in treatment period 1 and treatment period 2 (2.6 vs. 2.7 kg and 0.7 vs. 0.0 kg, respectively).
- Adverse event rates and serious adverse event rates were similar between treatment groups (356.8 events/100 patient-years vs. 358.5 events/100 patient-years and 39.0 events/100 patient-years vs. 45.1 events/100 patient-years for IDeg and IGlar, respectively).
- The most common adverse events were nasopharyngitis, upper respiratory tract infections, and hypoglycaemia.
- One fatality occurred in the IDeg group (respiratory fume inhalation disorder) and three in the IGlar group (one acute coronary syndrome, one cardiac death, one pneumonia).

References

1. Jonassen *et al. Pharm Res* 2012;29:2104–14. 2. Heise *et al. Diabetes Obes Metab* 2012;14:859–64. 3. Heise *et al. Diabetes Obes Metab* 2012;14:944–50. 4. Heller *et al. Lancet* 2012;379:1489–97. 5. Bode *et al. Diabet Med* 2013;30:1293–97. 6. Mathieu *et al. J Clin Endocrinol Metab* 2013;98:1154–62.

Conclusions

- In this double-blind crossover trial in patients with T1D, IDeg was non-inferior in terms of a reduction in HbA_{1c}, and achieved superiority for both the primary and confirmatory secondary hypoglycaemia endpoints compared with IGlar.
- For the maintenance period, results show:
  - 11% lower rate of severe or BG-confirmed symptomatic hypoglycaemia
  - 36% lower rate of severe or BG-confirmed symptomatic nocturnal hypoglycaemia
  - 35% lower rate of severe hypoglycaemia.
- Similar significant benefits were also seen in the full treatment period.
- The proportion of patients with severe hypoglycaemic episodes was significantly lower for IDeg versus IGlar in both the maintenance and full treatment periods.
- There was no apparent difference between IDeg and IGlar for the standard efficacy parameters or in terms of adverse events.
- SWITCH 1 demonstrates a significant hypoglycaemia benefit with IDeg versus IGlar and provides reassurance that in a T1D population, there were no safety concerns in switching to IDeg from any other basal insulin regimen, or from continuous subcutaneous insulin infusion.

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