Cost-effectiveness of insulin degludec versus insulin glargine U300 in the Netherlands: Evidence from a randomised controlled trial (RCT)

Marc Evans;[1] Robert Jan Moes;[2] Katrine Skipper Pedersen;[3] Jens Gundgaard[4]*
[1]University Hospital Llandough, Penarth, UK; [2]Novo Nordisk B.V., Alphen aan den Rijn, Netherlands;
[3]Novo Nordisk Region Europe, Copenhagen, Denmark; [4]Novo Nordisk A/S, Søborg, Denmark
***Presenting author**

Introduction

- Diabetes contributes considerably to healthcare expenditure in the Netherlands, where the total economic burden of type 2 diabetes (T2D) was 5.9 billion euros (EUR) in 2016.[1]
- Hypoglycaemia is a common complication of insulin treatment that causes loss of productivity,[2] contributes substantially to healthcare costs[3] and has a detrimental effect on quality of life for people with diabetes.[4]
- Insulin degludec (degludec) is a long-acting basal insulin with a stable glucose-lowering profile[5] that has been previously shown to significantly reduce rates of hypoglycaemia compared with insulin glargine 300 units/mL (glargine U300) in a real-world setting.[6]
- The CONCLUDE trial (NCT03078478) is a multinational, head-to-head, randomised controlled trial (RCT) comparing the hypoglycaemia risk of degludec U200 with that of glargine U300 in insulin-treated people with T2D.[7]
- In the CONCLUDE trial, the primary endpoint of the rate of overall symptomatic hypoglycaemia was not significantly lower with degludec versus glargine U300 (rate ratio [RR]: 0.88 $[0.73;1.06]_{95\%\ CI}$). However, there were lower rates of severe (RR: 0.20 $[0.07; 0.57]_{95\%\ CI}$) and nocturnal symptomatic hypoglycaemia (RR: 0.63 $[0.48; 0.84]_{95\%\ CI}$) with degludec versus glargine U300.[7]

Aim

- To evaluate the short-term cost effectiveness of degludec versus glargine U300 in insulin-treated people with T2D, from the perspective of a Dutch public healthcare payer.

Methods

Model overview

- A published decision-analytic model was used to estimate costs (2019 EUR) and quality-adjusted life years (QALYs) with degludec versus glargine U300 over a 1-year time horizon.[8]
- The model captured the short-term effects of insulin dosing and hypoglycaemia (non-severe daytime, non-severe nocturnal and severe).
- Clinical model inputs were informed by the CONCLUDE trial, utilising hypoglycaemia data from the 36-week maintenance treatment period and insulin dosing data at end-of-trial.
- Degludec and glargine U300 were administered once daily with or without oral antidiabetic drugs (OADs), excluding sulphonylureas and glinides.[7] Any pre-trial OADs were continued at their pre-trial dose.
- In this analysis, symptomatic hypoglycaemic events in the CONCLUDE trial were categorised into mutually exclusive groups for modelling purposes: non-severe daytime, non-severe nocturnal and severe hypoglycaemia.
- Non-severe hypoglycaemia was defined as symptomatic events with blood glucose <3.1 mmol/L (<56 mg/dL; nocturnal: 00:01–05:59; daytime: 06:00–00:00 or time unknown). Severe hypoglycaemia was defined as symptomatic events requiring third-party assistance.[9]

Model inputs

- Relative treatment effects (rate and insulin dose ratios) for the CONCLUDE trial population were estimated from regression analyses (Table 1).
- The model only captured treatment effects if there was a statistically significant difference between treatment arms, otherwise the glargine U300 event rate or dose was used for both simulation arms.
- For simplicity, the present analysis did not consider the small, but significant, difference in end-of-trial glycaemic control in favour of degludec (estimated treatment difference: –0.10% $[–0.18; –0.02]_{95\%\ CI}$]).[7]
- The following hypoglycaemia RRs for degludec versus glargine U300 were used in the model: severe hypoglycaemia (RR: 0.20 $[0.07; 0.57]_{95\%\ CI}$); non-severe nocturnal hypoglycaemia (RR: 0.63 $[0.48; 0.84]_{95\%\ CI}$) and non-severe daytime hypoglycaemia (RR: 1.09 $[0.88; 1.34]_{95\%\ CI}$).
- There was a significantly lower end-of-trial insulin dose (units/kg) with degludec versus glargine U300 in the CONCLUDE trial (dose ratio: 0.87 $[0.82; 0.92]_{95\%\ CI}$).
- Treatment costs were based on Dutch list prices, while hypoglycaemia costs and utilities were based on published sources (Table 2).[10–13]
- QALYs were calculated by applying a disutility value to each type of hypoglycaemic event.
- Treatment costs relating to the use of OADs were not included in this analysis as assumed to be similar across simulation arms – patients were randomised to insulin treatment arms in the CONCLUDE trial and maintained any pre-trial OADs at their pre-trial dose.
- In the probabilistic sensitivity analysis (PSA), uncertainty was captured based on standard errors around clinical outcomes and used to inform distributions around model parameters.
- PSA outcomes were based on 1000 model iteration sampling from all modelled distributions in each iteration and obtaining an estimate of incremental costs and incremental QALYs for each simulated set of values.

Table 2: Input parameters – costs and utilities

Parameter	Mean	Unit	Source
Costs			
Degludec†	0.0347	EUR	Z-Index 2019[10]
Glargine U300‡	0.0303	EUR	Z-Index 2019[10]
Needle§	0.1670	EUR	Z-Index 2019[10]
SMBG test¶	0.1916	EUR	Z-Index 2019[10]
Non-severe hypoglycaemia	2	EUR	Adapted from de Groot *et al.* 2018[11]
Severe hypoglycaemia	524	EUR	Adapted from de Groot *et al.* 2018[11]
Utilities			
Base	0.9020	Utility	Adapted from Freemantle *et al.* 2013[12]
Non-severe daytime hypoglycaemia††	–0.0041	Disutility	Evans *et al.* 2013[13]
Non-severe nocturnal hypoglycaemia††	–0.0067	Disutility	Evans *et al.* 2013[13]
Severe hypoglycaemia††	–0.0565	Disutility	Evans *et al.* 2013[13]

Hypoglycaemia costs were inflation-adjusted to 2018 EUR (latest available year) using the Consumer Price Index.[14] †Insulin degludec (in FlexTouch® pen) EUR 62.39 for 1800 units. ‡Insulin glargine U300 (in SoloStar® pen) EUR 40.89 for 1350 units. §BD Micro-Fine™ needles EUR 16.70 for 100 needles. ¶SMBG test costs based on Glukotest test strips (EUR 4.88 for 50 strips) and OneTouch® UltraSoft® lancets (EUR 0.94 for 10 lancets). ††Time trade-off elicited by the general population from five countries. EUR, euros; glargine U300, insulin glargine 300 units/mL; SMBG, self-measured blood glucose.

Results

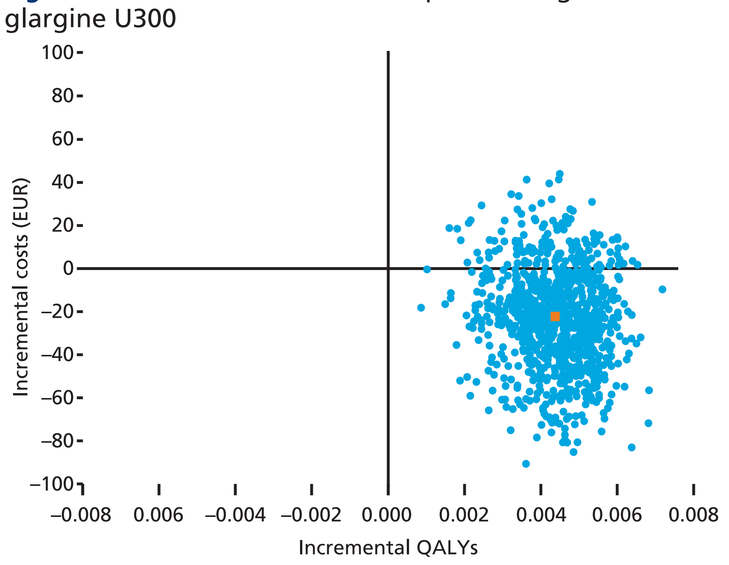
- Treatment with degludec was associated with mean annual cost savings per patient (EUR 24.71) relative to glargine U300 (Table 3).
- Cost savings were predominately driven by a lower basal insulin dose and somewhat by the lower rates of severe hypoglycaemia with degludec, which more than offset the slightly higher basal insulin unit cost.
- Treatment with degludec was also associated with improved effectiveness (+0.0045 QALYs) compared with glargine U300.
- Quality-of-life benefits resulted from reduced rates of non-severe nocturnal (+0.0023 QALYs) and severe hypoglycaemia (+0.0022 QALYs) with degludec relative to glargine U300 (Table 3).
- In the PSA, all data points fell in the eastern quadrants, demonstrating an improvement in quality-adjusted life expectancy with degludec versus glargine U300 (Figure 1). The majority of the data points were in the lower right quadrant, indicating that there were also lower costs with degludec.
- Overall, degludec was dominant relative to glargine U300, resulting in improved effectiveness at lower cost. The overall result was robust in the PSA.

Table 3: Short-term cost-effectiveness of degludec versus glargine U300 in insulin-treated people with T2D (base case analysis) **Key result**

	Degludec	Glargine U300	Difference
Costs (EUR)			
Total costs	944.22	968.93	**–24.71**
Pharmacy costs	935.01	938.58	**–3.57**
Insulin†	804.03	807.60	–3.57
Needles	61.00	61.00	0.00
SMBG tests (routine tests)	69.98	69.98	0.00
Hypoglycaemic events	9.21	30.35	**–21.15**
Non-severe daytime events	2.92	2.92	0.00
Non-severe nocturnal events	1.17	1.86	–0.69
Severe events	5.11	25.57	–20.46
QALYs			
Total QALYs	0.8915	0.8870	**0.0045**
Baseline utility	0.9020	0.9020	0.0000
Non-severe daytime hypoglycaemia	–0.0060	–0.0060	0.0000
Non-severe nocturnal hypoglycaemia	–0.0039	–0.0062	0.0023
Severe hypoglycaemia	–0.0006	–0.0028	0.0022
ICER			Dominant

Difference presented for degludec minus glargine U300. Dominant refers to improved clinical outcomes at a lower cost and is not reported as per convention. The disutility associated with hypoglycaemia was captured by multiplying an annualised disutility by the annual event rate. †The insulin dose ratio (in favour of degludec) was factored into the insulin cost calculations. EUR, euros; glargine U300, insulin glargine 300 units/mL; ICER, incremental cost-effectiveness ratio; SMBG, self-measured blood glucose; QALY, quality-adjusted life year; T2D, type 2 diabetes.

Figure 1: Cost-effectiveness scatterplot for degludec versus glargine U300



The orange square represents the average value for incremental cost and incremental quality-adjusted life expectancy. EUR, euros; glargine U300; insulin glargine 300 units/mL; QALY, quality-adjusted life year.

Discussion

- Cost savings with degludec were driven by a lower basal insulin dose and a lower rate of severe hypoglycaemia compared with glargine U300, while QALY gains resulted from reduced rates of non-severe nocturnal and severe hypoglycaemia.
- A potential limitation of this analysis is the short-term perspective. However, a 1-year time horizon may be more representative of steady-state maintenance treatment than longer time horizons, and can be justified in analyses where there is no evidence of differential mortality between comparators.[15]
- Our short-term modelling analysis suggests that degludec represents a cost-effective use of Dutch public healthcare resources in insulin-treated people with T2D.

Conclusion

- This short-term cost-effectiveness analysis, informed by the latest head-to-head RCT evidence, demonstrated that degludec was a dominant treatment option versus glargine U300 in insulin-treated people with T2D, from the perspective of a Dutch public healthcare payer.

Table 1: Input parameters – clinical outcomes from the CONCLUDE trial

	Degludec/glargine U300 ratio	SE	95% CI	*p*-value	Glargine U300	Degludec (predicted)†
Hypoglycaemia					Event rate (events/PYO)	
Non-severe daytime	1.09‡	0.1069	0.88; 1.34	0.4293	1.46	1.46
Non-severe nocturnal	0.63‡	0.1430	0.48; 0.84	0.0015	0.93	0.59
Severe	0.20‡	0.5354	0.07; 0.57	0.0027	0.05	0.01
Insulin dose					Mean dose (U)	
	0.87§	0.0273	0.82; 0.92	<0.0001	73.0	63.5

†Model inputs for the degludec arm were estimated by applying the degludec/glargine U300 ratio to the corresponding glargine U300 arm value, if there was a significant difference between treatments ($p \leq 0.05$). ‡Rate ratio of hypoglycaemia recorded in the 36-week maintenance period. §End-of-trial (Week 88) insulin dose ratio (units/kg). CI, confidence interval; glargine U300, insulin glargine 300 units/mL; PYO, patient-year of observation; SE, standard error; U, units.

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Presenter Jens Gundgaard is an employee of Novo Nordisk and also owns stocks in the company.
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