Cost-effectiveness of Insulin Degludec *versus* Insulin Glargine U100 in Patients with Type 1 and Type 2 Diabetes in Portugal: Evidence from the Switch 1 & 2 Trials

Relação Custo-benefício da Insulina Degludec versus Insulina Glargina 100U em Doentes com Diabetes Tipo 1 e Tipo 2 em Portugal: Evidências dos Estudos Switch 1 e 2

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Abstract

Objectives: To assess the cost-effectiveness of insulin degludec (degludec) *versus* insulin glargine (glargine) U100 from a Portuguese healthcare perspective using data from SWITCH 1 & 2 trials.
Methods: A short-term model estimated cost-effectiveness of degludec *versus* glargine U100 in type 1 diabetes (T1DM) basal bolus (B/B) and type 2 diabetes (T2DM) basal oral therapy (BOT) patients. The model captured hypoglycaemia rates and insulin dosing. Clinical outcomes were obtained from SWITCH 1 & 2. Disutilities related to hypoglycaemic events and insulin, needles and blood glucose tests costs were also included. Benefits were measured in QALYs. One-way and probabilistic sensitivity analyses were conducted.
Results: Degludec was cost-effective compared to glargine U100 in both populations. Cost-effectiveness was driven by significantly lower end-of-trial dose with degludec *versus* glargine U100 in addition to significantly lower non-severe nocturnal and severe hypoglycaemic events with degludec. Non-severe daytime hypoglycaemic events did not show differences in T1DM, while in T2DM there was a significantly lower number of events for degludec. Sensitivity analyses confirmed the robustness of the results.
Conclusions: This cost-effectiveness analysis demonstrated that degludec was dominant *versus* glargine U100 in T1DM B/B and T2DM BOT patients. Results suggest that degludec would represent an efficient use of Portuguese public healthcare resources in both patient populations.

Keywords: cost-effectiveness; insulin degludec; insulin glargine U100; SWITCH 1 & 2 trials

> INTRODUCTION

Diabetes represents a major and growing economic burden for healthcare systems owing to its increased incidence and long-term complications. According to recent data from the 9th edition of the Diabetes Atlas by the International Diabetes Federation (IDF), the total diabetes-related healthcare expenditure in Portugal in 2019 was 1,923.3 million USD for the adult population aged 20-79 years. [(1)] This represented 1.1% of the gross domestic product (GDP) and 13.4% of total healthcare expenditure in Portugal in 2019. [(2)] Total diabetes preva-

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Resumo

Objetivos: Avaliar a relação custo-benefício da insulina degludec (degludec) *versus* insulina glargina (glargina) 100U na perspectiva da saúde em Portugal, usando dados dos estudos SWITCH 1 e 2.
Métodos: Um modelo de curto prazo estimou a relação de custo-efetividade da degludec *versus* glargina 100U em *bolus* basal (B/B) na diabetes tipo 1 (DM1) e na terapêutica oral basal (TOB) da diabetes tipo 2 (DM2). O modelo capturou as taxas de hipoglicemia e a dose de insulina. Os resultados clínicos foram obtidos a partir do SWITCH 1 & 2. Foram também incluídas as desutilidades relacionadas com eventos de hipoglicemia e insulina, agulhas e testes de glicemia. Os benefícios foram medidos em QALYs. Foram realizadas análises de sensibilidade unidirecional e probabilística.
Resultados: Comparativamente à glargina 100U a Degludec foi custo-efetiva em ambas as populações. A relação de custo-eficácia foi determinada pela dose significativamente mais baixa no final do estudo da degludec, *versus* glargina 100U, adicionalmente à redução significativa dos eventos noturnos de hipoglicemia não graves e graves com degludec. Na DM1, não se registaram diferenças entre degludec e glargina a nível da ocorrência de eventos de hipoglicemia diurnos não graves, enquanto que na DM2 ocorreu um número significativamente menor de eventos com a degludec. As análises de sensibilidade confirmaram a robustez dos resultados.
Conclusões: Esta análise de custo-efetividade demonstrou que a degludec foi dominante em comparação com a glargina 100U em doentes DM1 B/B e DM2 TOB. Os resultados sugerem que a degludec representaria um uso eficiente dos recursos públicos de saúde portugueses nas duas populações de doentes.

Palavras-chave: relação de custo-efetividade; insulina degludec; insulina glargina 100U; estudos SWITCH 1 e 2

lence in Portugal in 2019 was estimated at 14.2% for the population aged 20-79 years, [1] or more than one million patients. With a projected growth in diabetes cases (15% by 2045), healthcare costs are expected to increase significantly in the years to come. [1]

T1DM is a chronic disease that can be only controlled by using daily insulin injections to keep glucose levels in the proper range, thus preventing many of the complications associated with diabetes. [1]

T2DM is a progressive disease that can be controlled by diet and exercise in its early stages, [3] but its progression depends on blood glucose levels and eventually many T2DM patients will need insulin therapy. [4] Earlier insulin initiation in T2DM patients, together with a controlled diet and regular exercise may allow better control and prevent development of diabetes related complications. [5]

The main objective of diabetes treatment is to control blood glucose levels and avoid or lower the risk of hypoglycaemic events that may worsen patients' quality of life and the management of their condition. [6] Furthermore, hypoglycaemic events have a substantial impact on healthcare costs. [7]

Several insulin treatments are available in Portugal, where insulin glargine U100 (glargine U100) is one of the most used long-acting basal insulins to treat T1DM and T2DM. Insulin degludec (degludec) is a basal insulin therapy with an ultra-long duration of action [8] and a flat and stable action profile. [9,10] In phase 3a trials degludec has shown equivalent HbA_{1c} reductions with less risk of hypoglycaemic events, at a significantly lower dose compared to glargine U100 in T1DM patients treated with a basal-bolus (B/B) (12% lower) and T2DM patients treated with basal oral therapy (BOT) (10% lower). [11,12,13] Besides, in phase 3b trials degludec has demonstrated non-inferiority in terms of HbA_{1c} reduction and achieved superiority for the primary hypoglycaemia endpoint when compared with glargine U100. [14,15] SWITCH 1 (NCT02034513) and SWITCH 2 (NCT02030600) were two 2-period 32-week randomized, double-blind, crossover, multicentre, treat-to-target phase 3b clinical trials. [14,15]

The main objective of this analysis is to assess the cost-effectiveness of degludec when compared to glargine U100 from the perspective of the Portuguese National Healthcare System. The patients considered in this analysis were T1DM B/B regimen and T2DM BOT patients. A short-term five-year approach that focuses on the impact of hypoglycaemia and insulin dosing has been used.

> METHODS

Model Specifications

This cost-effectiveness analysis compared degludec with glargine U100 in two different groups of patients: T1DM B/B and T2DM BOT.

The cost-utility model used in this analysis was previously published. [16-22] It was developed in Microsoft Excel 2010 (Microsoft Corporation, Redmond, WA, USA) to evaluate clinical and economic outcomes associated with the use of degludec and glargine U100 in T1DM B/B and T2DM BOT over an up to five-year time horizon (as applied in the present analysis). The basal and bolus and total insulin doses, incidence rates of non-severe and severe hypoglycaemic events, frequency of SMBG measurements, and timing of dose administration were specified for each insulin therapy in the different diabetes patient subgroups.

Based on these characteristics, the model estimated the total costs associated with insulin use, SMBG, needles, hypoglycaemia, as well as benefits in terms of quality-adjusted life years (QALYs) for both degludec and glargine U100. A discount of a 5% was applied on both costs and clinical parameters, as suggested by the 'Guidelines for economic drug evaluation studies' of the Portuguese Health Authority (INFARMED). [17] Costs were estimated from a healthcare payer perspective in Portugal. All costs were expressed in 2018 Euros (EUR). INFARMED [18] does not use an official willingness-to-pay (WTP) threshold when assessing ICERs. We have assumed a WTP threshold of 30,000 Euros per QALY gained, the value for money commonly used for health economic studies in Portugal. Clinical outcomes captured all hypoglycaemia related outcomes for the patient. Only statistically significant parameters were used to minimise modelling uncertainty. A scheme of the model structure is shown in Figure 1.

The clinical data for this analysis were derived from the SWITCH 1 trial for T1DM B/B patients and from the SWITCH 2 trial for T2DM BOT patients. The main objective of both trials was to confirm superiority of degludec compared with glargine U100 in the rates of severe or blood glucose-confirmed symptomatic hypoglycaemia during the maintenance period. Both trials also evaluated the number of severe and nocturnal hypoglycaemia and rates of severe hypoglycaemia between the two treatments during maintenance.

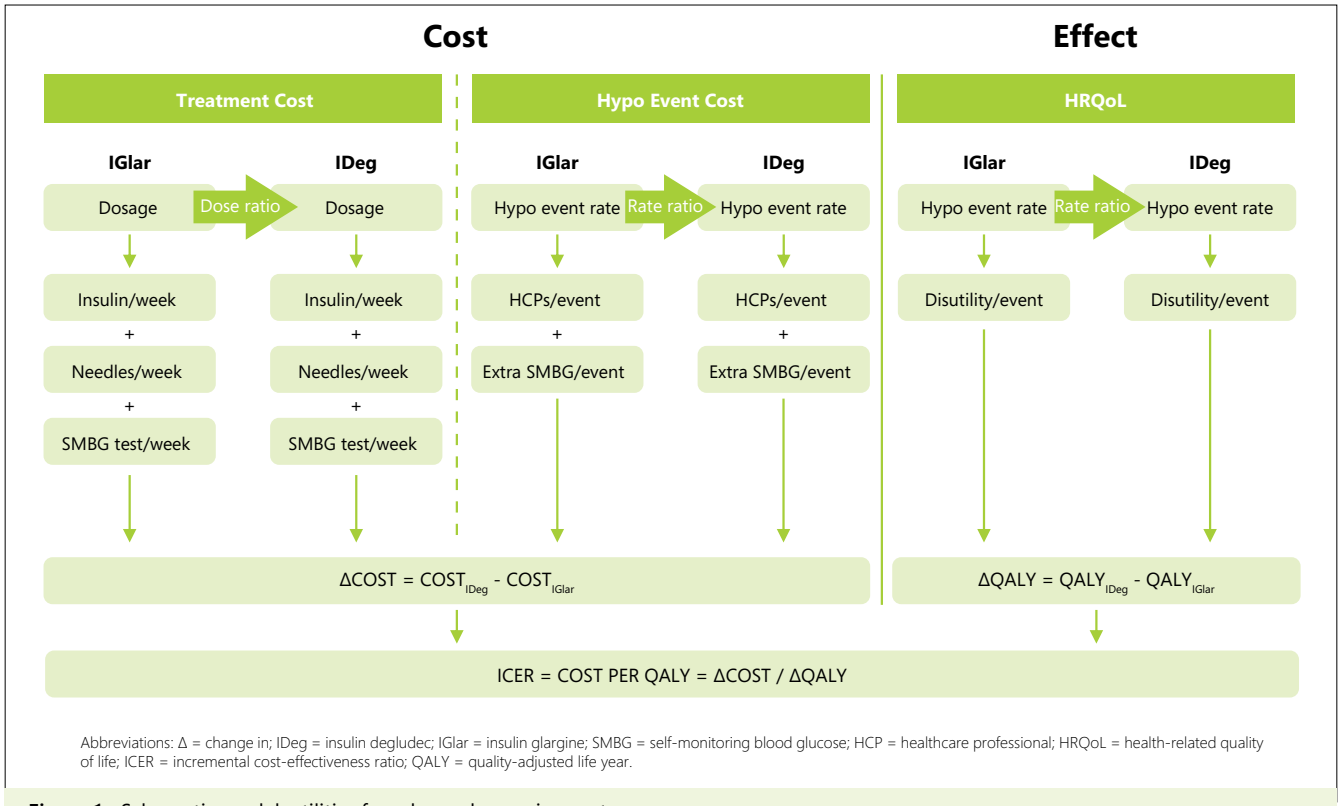
Clinical Data

Clinical data used in this analysis were obtained from the SWITCH 1 and SWITCH 2 trials. These clinical trials were designed as treat-to-target so that insulin doses were adjusted in order to achieve similar HbA_{1c} levels between treatments and therefore no HbA_{1c} level differences were observed.

Insulin Doses

The degludec/glargine U100 dose ratios to estimate degludec doses as well as units of basal glargine U100 insulin used daily for T1DM B/B and T2DM BOT patients were extracted from the SWITCH 1 and SWITCH 2 trials' data, respectively. The end-of-trial glargine U100 doses were 40.58 units/day for T1DM B/B patients and 82.66 units/day for T2DM BOT patients (Table I).

The procedure to estimate the degludec dose for T1DM B/B was the following: 1) the glargine U100 dose for T1DM B/B was 40.58 units/day; 2) the relative dose ratio (degludec/glargine U100) was 0.97; 3) the degludec do-



Abbreviations: Δ = change in; IDeg = insulin degludec; IGlar = insulin glargine; SMBG = self-monitoring blood glucose; HCP = healthcare professional; HRQoL = health-related quality of life; ICER = incremental cost-effectiveness ratio; QALY = quality-adjusted life year.

Figure 1 - Schematic model: utilities from hypoglycaemic events.

se for T1DM B/B patients was 40.58 x 0.97 = 39.36 units/day (Table I). To estimate the degludec dose for T2DM BOT, the calculation was as follows: 1) the glargine U100 dose for T2DM BOT was 82.66 units/day; 2) the relative dose ratio was 0.96; 3) the degludec dose for T2DM BOT patients was 82.66 x 0.96 = 79.35 units/day (Table I).

Hypoglycaemic Event Rates

The frequencies of severe and non-severe symptomatic hypoglycaemic events (SHE and NSHE) were obtained from the SWITCH 1 and SWITCH 2 trials. The SHE was defined in accordance with ADA guidelines [19] as "an event requiring assistance of another person to actively administer carbohydrates, glucagon, or take other corrective actions". The NSHE was an event with symptoms of hypoglycaemia, with or without blood glucose measurement, or asymptomatic with a low blood glucose measurement (<3.1mmol/L), which the patient could manage without assistance.

In both trials, nocturnal NSHE and overall (daytime and nocturnal) SHE were significantly lower for patients treated with degludec. Moreover, daytime NSHE did not show a statistically significant difference in SWITCH 1 while in SWITCH 2 there was a significantly lower number of events in the degludec group. The event rates used to obtain the number of hypoglycaemic events for degludec were derived from a Spanish observational study. [20] The event rates for degludec were determined based on the relative event ratios (degludec/glargine U100) derived from the SWITCH 1 and SWITCH 2 trials multiplied by the events rate for glargine U100 obtained from the observational study (Table II).

Three mutually exclusive groups of hypoglycaemia to prevent the possible double counting of events were considered when obtaining event rates: severe events, non-severe events occurring during the day (daytime) and non-severe events occurring during the night (nocturnal).

The following calculations were done to estimate the number of non-severe nocturnal hypoglycaemic events for T1DM B/B patients: 1) the number of non-severe nocturnal hypoglycaemic events related to glargine U100 for T1DM B/B patients was 22.56 per patient per year; 2) the relative event ratio (degludec/glargine U100) was 0.76; 3) the number of non-severe nocturnal hypoglycaemic events related to degludec was 22.56 x 0.76 = 17.15 per patient per year. The calculation to estimate the number of non-severe nocturnal hypoglycaemic events for T2DM BOT was as follows: 1) the number of non-severe nocturnal hypoglycaemic events related to glargine U100 for T2DM BOT patients was 5.53 per patient per year; 2) the relative event ratio was 0.76; 3) the number of non-severe nocturnal hypoglycaemic events related to degludec was 5.53 x 0.76 = 4.20 per patient per year.

The procedure mentioned above was used to estimate the number of non-severe daytime and severe hypoglycaemic events.

Tabel I - Insulin doses in units per day and dose ratios.

		T1DM B/B	T2DM BOT
	Insulin	**Insulin units/day**	**Insulin units/day**
Basal	Degludec	39.36†	79.35
	Glargine	40.58†	82.66
Bolus	IAsp (Degludec)	31.93	–
	IAsp (Glargine)	31.93	–
	Insulin	**Ratio**	**Ratio**
Basal/Bolus	Degludec/Glargine	0.97	0.96
	IAsp (Degludec)/IAsp (Glargine)	1*	–

Abbreviations: Degludec: insulin degludec; Glargine: insulin glargine; IAsp: insulin aspart; B/B: basal bolus; BOT: basal oral therapy; T1DM: type 1 diabetes; T2DM; type 2 diabetes.
†These numbers are calculated.
*This is not significant and therefore set to 1.

Tabel II - Relative hypoglycaemic event rate-ratios (RR) per patient/year per treatment regimen.

	T1DM B/B			T2DM BOT		
	Frequency	**Degludec RR**	**Glargine RR**	**Frequency**	**Degludec RR**	**Glargine RR**
Daytime NSHE	65.40	1*	1	12.74	0.80	1
Nocturnal NSHE	22.56	0.76	1	5.53	0.76	1
SHE	0.90	0.74	1	0.30	0.49	1

Abbreviations: B/B: basal bolus; BOT: basal oral therapy; T1DM: type 1 diabetes; T2DM: type 2 diabetes; Degludec: insulin degludec; Glargine: insulin glargine; NSHE: non-severe hypoglycaemic event; SHE: severe hypoglycaemic event; RR: rate-ratio.
*In case of non-significant results, a relative rate of 1 was used in the calculation.

Self-Monitoring Blood Glucose Tests and Needles

The number of SMBG tests per week associated with glargine U100 was based on the recommended titration schedule for glargine U100 in T1DM B/B and T2DM BOT insulin treated patients. [21] Patients treated with degludec are able to monitor their blood glucose more efficiently and use fewer SMBG tests [22] per week because degludec has a long half-life and a flat, stable profile in steady state with low variability over the day. [9,23] Therefore, degludec has the potential to be monitored and titrated with a lower number of SMBG tests associated with basal injections per week for T1DM B/B and T2DM (Table III). Lastly, the number of needles used with BOT or B/B regimens is equal for degludec and glargine U100 (Table III).

Tabel III - Number of needles and SMBG tests associated with degludec and glargine.

		T1DM B/B		T2DM BOT	
		Degludec	Glargine	Degludec	Glargine
Number of SMBG test/week	Total	25	28	4	7
	Basal injections	4	7	4	7
	Bolus injections	21	21	–	–
Number of needles	Basal injections/day	1	1	1	1
	Bolus injections/day	3	3	–	–
Number of additional SMBG test per hypoglycaemic event	Daytime NSHE	5	5	5.90	5.90
	Nocturnal NSHE	5	5	5.90	5.90
	SHE	–	–	–	–

Abbreviations: B/B: basal bolus; BOT: basal oral therapy; Degludec: insulindegludec; Glargine: insulinglargine; SMBG: self-monitoringbloodglucose; T1DM: type 1 diabetes; T2DM: type 2 diabetes; NSHE: non-severehypoglycaemicevent; SHE: severehypoglycaemicevent.

Tabel IV - Unit costs for insulin, needles and SMBG tests.

Product	Type		Price per pack size (EUR)	Units per pack size	Price per unit (EUR)
Insulin	Basal	Degludec	70.29	1,500	0.0469
		Glargine	55.28	1,500	0.0369
	Bolus	IAsp	27.90	1,500	0.0186
		Resource	Pack cost (EUR)	Units per pack size	Price per unit (EUR)
Needles			7.19	100	0.07
SMBG tests		Test strip	18.29	50	0.37
		Lancet	11.5	200	0.06
		SMBG test	–	–	0.42

Abbreviations: Degludec: insulin degludec; Glargine: insulin glargine; IAsp: insulin aspart; SMBG: self-monitoring blood glucose.

Cost Data

Costs were estimated from the Portuguese National Healthcare System perspective. For all patient groups, direct medical costs included the drug cost and costs related to severe and non-severe hypoglycaemic events. All costs were expressed in 2018 Euros.

Cost of Insulin, Needles and SMBG Tests

All insulin costs (Table IV) were based on the public sales price (PSP) + VAT. The costs of needles, SMBG test strips, and lancets were based on law decree and tender resolution [24] (Table IV).

Cost of Hypoglycaemic Events

The direct cost of managing a single hypoglycaemic event and the cost of extra SMBG tests used in the week after the event were included in the direct cost associated with a hypoglycaemic event.
The cost of managing a SHE in Portugal was estimated at EUR 1,493 [25] for both T1DM and T2DM patients. These costs for SHE included the SMBG tests used the week following the severe event. In case of NSHE the costs for the additional SMBG tests used were derived from the number of additional tests (obtained from Brod *et al.*, 2011, [6] a study based on patient-reported experiences) (Table III).
The number of SMBG strips used the week after a hypoglycaemic event or the proportion of patients contacting a healthcare professional or a hospital reported by Brod *et al.*, 20116 was assumed to be relevant for both degludec and glargine U100 treatment.
Regardless of insulin treatment, the behaviour of patients after a hypoglycaemic event was assumed to be similar. Therefore, the difference in treatment costs was not due to the cost per hypogly-

caemic event but only due to the difference in the number of hypoglycaemic events.

Utility data

A marginal decreasing disutility approach was used in the base case analysis to estimate QALYs by reducing the HRQoL per hypoglycaemic event and applying the disutility per each hypoglycaemic event.
The initial quality of life was reduced according to the number of hypoglycaemic events that occurred during the year in each treatment group. The disutility per hypoglycaemic event was multiplied by the number of events observed in each treatment regimen (Table II). This was carried out for severe and non-severe hypoglycaemic events separately.
The disutilities per hypoglycaemic event were obtained from a large-scale time trade-off (TTO) study. [11] This TTO study reported a disutility of 0.0565 for a severe event (without significant differences between daytime and nocturnal SHE) and disutilities of 0.0041 and 0.0067 for non-severe daytime and non-severe nocturnal hypoglycaemic events, respectively (significant difference in utility was demonstrated for daytime compared to nocturnal non-severe events). [11]

Sensitivity Analysis

To assess the impact of varying key assumptions and outcomes used in the base case analysis, one-way and probabilistic sensitivity analyses were conducted.

One-way Sensitivity Analysis

The parameters assessed in the one-way sensitivity analysis for both treatment groups were:

1. Insulin dose from EU-TREAT [26] (glargine U100 doses: 23.1U and 25.5U as basal and bolus doses for the T1DM group and 33.4U as basal dose for the T2DM BOT group. [27] Degludec doses: 22.1U and 23.8U as basal and bolus doses for the T1DM group and 35.4U as basal dose for the T2DM BOT group); [33]
2. No difference in daytime non-severe hypoglycaemia;
3. No difference in nocturnal non-severe hypoglycaemia;
4. No difference in severe hypoglycaemia;
5. No difference in SMBG tests;
6. Costs of severe hypoglycaemia -50% (EUR 746.5);
7. Price of biosimilar used for glargine U100 (EUR 36.70).

The EU-TREAT study was a European, multicentre, retrospective, non-interventional study that used medical records of patients with T1DM or T2DM who switched from any basal insulin to degludec. The main objective of this study was to assess the clinical effectiveness of degludec, used with any other antidiabetic treatment, by analysing whether treatment was associated with a change in HbA1c after 6 months compared with the last value on the previous basal insulin before switch. [32]

Probabilistic Sensitivity Analysis (PSA)

The PSA varied simultaneously all model parameters within a probable range and evaluated the probability that degludec treatment would be cost-effective compared to glargine U100 treatment under different cost-effectiveness thresholds.
A lognormal distribution around the hypoglycaemic event rates and normal distributions around continuous variables were assumed and the standard errors around the parameters were used. The PSA has been run with 5,000 iterations.

> RESULTS

Degludec confirmed to be a dominant option when compared to glargine U100 for both T1DM B/B and T2DM BOT because of its reduced costs and increased QALY (Table V). For T1DM B/B, treatment with degludec demonstrated cost savings of -1,682.25 EUR and a QALY gain of 0.0737 while T2DM BOT treatment with degludec was associated with cost savings of -387.87 EUR and a QALY gain of 0.0682. In both cases the increase in cost was mainly driven by basal insulin costs, but this was entirely offset by the reduction in severe and non-severe nocturnal hypoglycaemic event costs in the degludec arm. The difference in number of SMBG tests used also contributed to the cost difference.

Sensitivity Analysis

The one-way sensitivity analysis confirmed that degludec remains dominant over glargine U100, and the ICERs were stable to variations in non-severe daytime and nocturnal hypoglycaemic event rates and number of SMBG tests, but also when the insulin dose from the EU-TREAT study was applied (Table VI). The parameter most sensitive to changes was the severe hypoglycaemic event rate. When assuming no difference in severe hypoglycaemic event rates, an ICER of 2,286.68 EUR/QALY for T1DM B/B and 28,725.21 EUR/QALY for T2DM BOT was reached. The use of the price of biosimilar glargine U100 resulted in an ICER of 19,027.65 EUR/QALY for T2DM BOT and remained dominant for the T1DM B/B

group. Finally, the reduction in cost of severe hypoglycaemia resulted in an ICER of 2,734.56 EUR/QALY for the T2DM BOT group, and remained stable for the T1DM B/B group.

The cost-effectiveness acceptability curves display the increasing probability of degludec being a more cost-effective treatment than glargine U100 given a threshold that reflects the increasing willingness-to-pay (WTP) for this treatment. For T1DM B/B, there is a 91.58% probability of degludec being more cost-effective than glargine U100 while for T2DM BOT there is an 82.14% probability with the WTP threshold of 30,000 Euros per QALY (see Figure 2 and Figure 3).

Tabel V - Base case cost-effectiveness analysis results.

	T1DM B/B			T2DM BOT		
Cost (EUR)	**Degludec**	**Glargine**	**Degludec-Glargine**	**Degludec**	**Glargine**	**Degludec-Glargine**
Basal injections	3,136.64	2,543.12	593.52	6,119.72	5,013.43	1,106.29
Bolus injections	994.14	994.14	0.00	0.00	0.00	0.00
Needles	477.53	661.84	-184.31	119.38	119.38	0.00
SMBG test	2,510.18	2,811.40	-301.22	401.63	702.85	-301.22
NSHE daytime	629.23	629.23	0.00	115.48	144.64	-29.16
NSHE nocturnal	164.54	217.09	-52.55	47.57	62.77	-15.20
SHE	5,025.32	6,763.01	-1,737.69	1,105.75	2,254.34	-1,148.59
Total	12,937.59	14,619.84		7,909.53	8,297.40	
Δ Cost	-1,682.25			-387.87		
Δ QALY	0.0737			0.0682		
Incremental Cost-Effectiveness						
ICER	**Dominant**			**Dominant**		

Abbreviations: T1DM: type 1 diabetes; T2DM: type 2 diabetes; B/B: basal bolus; BOT: basal oral therapy; Degludec: insulin degludec; Glargine: insulin glargine; SMBG: self-monitoring blood glucose; NSHE: non-severe hypoglycaemic event; SHE: severe hypoglycaemic event; QALY: quality-adjusted life years; ICER: incremental cost-effectiveness ratio.

Tabel VI - One-way sensitivity analyses of CEA of degludec vs. glargine.

Degludec vs. Glargine	T1DM B/B	T2DM BOT
Base case	Dominant	Dominant
Insulin dose from EU-TREAT	Dominant	Dominant
No difference in daytime non-severe hypoglycaemia	Dominant	Dominant
No difference in nocturnal non-severe hypoglycaemia	Dominant	Dominant
No difference in severe hypoglycaemia	2,286.68 EUR/QALY	28,725.21 EUR/QALY
No difference in SMBG tests	Dominant	Dominant
Costs of severe hypoglycaemia -50% (EUR 746.5)	Dominant	2,734.56EUR/QALY
Price of biosimilar used for glargine U100 (EUR 36.70)	Dominant	19,027.65 EUR/QALY

Abbreviations: CEA: cost-effectiveness analysis; Degludec: insulin degludec; Glargine: insulin glargine; T1DM: type 1 diabetes; T2DM: type 2 diabetes; B/B: basal bolus; BOT: basal oral therapy; SMBG: self-monitoring blood glucose; QALY: quality-adjusted life years.

> DISCUSSION

Economic evaluations are formally requested in drug reimbursement process in most European countries nowadays and are also increasingly used to assess the economic value of other healthcare interventions. Economic evaluation provides a framework to identify and compare health interventions in terms of costs and outcomes. By informing decision-makers about the cost-effectiveness of healthcare interventions, economic evaluations aim to help make rational decisions and efficiently allocate healthcare resources. The current study assessed the cost-effectiveness of degludec compared with glargine U100 in patients with T1DM and T2DM. The analysis was conducted from the perspective of the Portuguese National Healthcare System for two groups of patients: patients with T1DM treated with B/B therapy and patients with T2DM treated with BOT.

The results of this short-term cost-effectiveness analysis indicate that the use of degludec would be cost-effective compared with glargine U100 in Portugal. Degludec is a dominant therapy *versus* glargine U100 in both T1DM B/B and T2DM BOT patients, with savings primarily driven by lower costs of severe hypoglycaemic

events (SHE) due to the significant reduction in the number of SHE in both patient groups.

One-way and probabilistic sensitivity analyses demonstrated the consistency of the model results showing stable ICERs when applying changes to the parameters analysed. In patients with T1DM B/B and T2DM BOT, the ICER remains dominant in most of the analyses conducted. The PSA shows that it is highly likely that degludec will be cost-effective when compared to glargine U100 for both T1DM B/B and T2DM BOT patients.

In phase 3a trials [12] degludec proved equivalent reductions in HbA1c levels with significantly lower rates of confirmed overall and nocturnal hypoglycaemic episodes reported with degludec vs. glargine U100 in the overall T2DM population and a significantly lower rate of nocturnal confirmed episodes with degludec vs. glargine U100 during the maintenance period in the T1DM population. These hypoglycaemia benefits of degludec have been observed also in the EU-TREAT study, with reductions of up to 90% in patients switching to degludec due to hypoglycaemia experienced on glargine treatment. [32] The phase 3b trial SWITCH 2 [15] confirmed the hypoglycaemia benefit observed with degludec compared with glargine U100 in the phase 3a clinical trials in patients with T2DM.

Regarding the use of SMBG tests, in 2017 the use of FreeStyle Libre® was approved in Portugal for patients with T1DM. [28] The use of this device reduces the number of SMBG tests. Taking into account that the device is a new monitoring system that automatically measures glucose levels for up to 14 days by using sensors, the cost for both degludec and glargine U100 treatments are assumed to be the same in patients using FreeStyle Libre®.

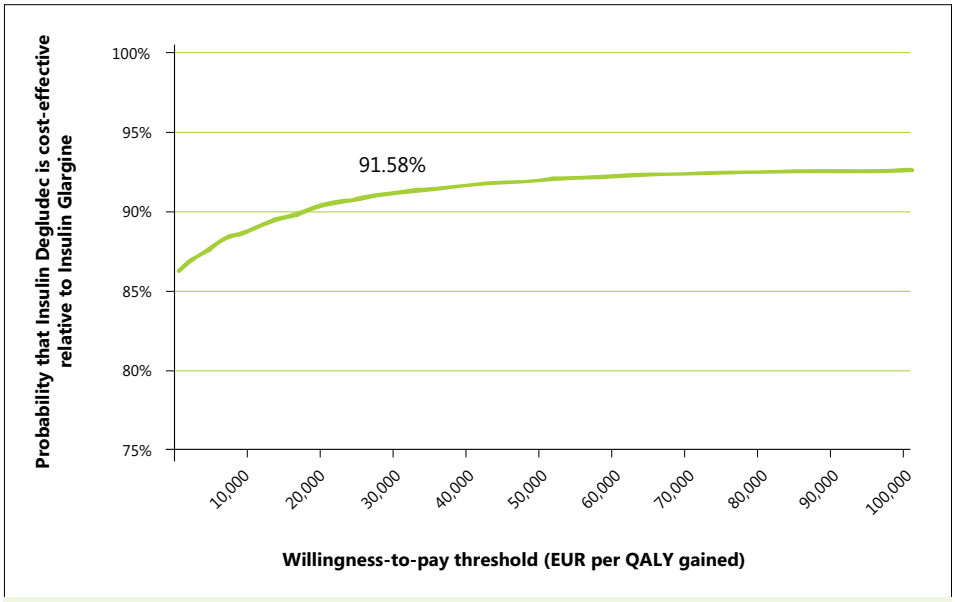


Figure 2 - Cost-effectiveness acceptability curve for T1DM B/B.

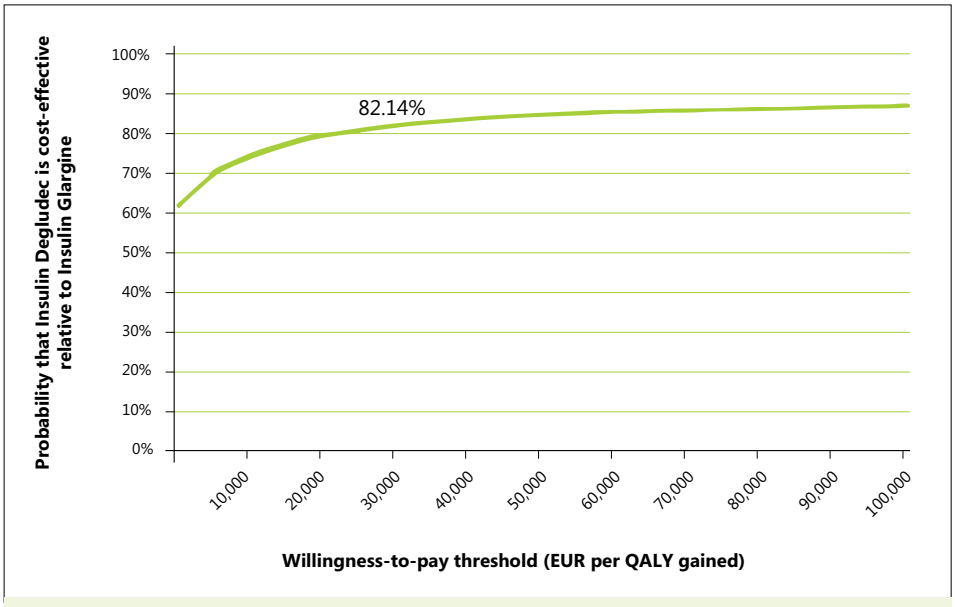


Figure 3 - Cost-effectiveness acceptability curve for T2DM BOT.

The current cost-effectiveness analysis may have limitations due to inherent challenges with including the social costs [29] and future costs [30] associated with the progression of diabetes in time. This information gap might impact the results by minimising the benefits of degludec treatment. For example, the higher likelihood that patients adhere to therapy or the inclusion of reduction of absenteeism caused by hypoglycaemic events are values that may improve the cost-effectiveness ratio in favour of degludec. [3,7,14] Health economic guidance in Portugal [31] stated that a societal perspective should be used for health

economic analyses. This approach was investigated, but the required Portugal-specific days off work estimates for each diabetes-related complication were no available. Therefore indirect costs were not included in the present base case analysis. This is likely to be a conservative approach, as degludec was associated with a reduced incidence of complications, and therefore less lost productivity.

> CONCLUSIONS

Based on the current analysis, degludec is a cost-effective alternative to glargine U100 for patients with T1DM B/B and T2DM BOT from the perspective of the Portuguese National Healthcare System. Furthermore, degludec was the dominant treatment strategy for both groups of patients due to its lower costs and higher effectiveness.

In addition, potential improvements in quality of life related to degludec have been confirmed for both T1DM B/B and T2DM BOT patients. These improvements in quality of life have been reflected in the incremental QALYs.

Finally, sensitivity analyses confirmed that the conclusions were robust with ICER values not impacted by changes in the input parameters and modelling assumptions. <

Conflicts of interest/Conflitos de interesse:

J. Darbà is employed by the University of Barcelona. M. Ascanio is an employee of BCN Health Economics & Outcomes Research S.L., an independent contract health economic organisation. D. Carvalho is employed by the Centro Hospitalar Universitário São João & Faculty of Medicine, Instituto de Investigação e Inovação em Saúde (i3S), Universidade do Porto. V. Conde is an employee of Novo Nordisk Portugal. K.S. Pedersen is an employee of Novo Nordisk Region Europe and owns stocks/shares in the company. The authors have no other relevant affiliations or financial involvement with any organisation or entity with a financial interest in or financial conflict with the subject matter or materials discussed in the manuscript apart from those disclosed. BCN Health Economics and Outcomes Research S.L. provided statistical analysis and editorial support. BCN Health Economics & Outcomes Research services have been funded by Novo Nordisk/*J Darbà trabalha na Universidade de Barcelona. M. Ascanio é funcionário da BCN Health Economics & Outcomes Research S.L., uma organização independente de economia da saúde. D. Carvalho trabalha no Centro Hospitalar Universitário de São João e no Instituto de Investigação e Inovação em Saúde (i3S) da Faculdade de Medicina da Universidade do Porto. V. Conde é funcionário da Novo Nordisk Portugal. K.S. Pedersen é funcionário da Novo Nordisk Region Europe e possui ações da empresa. Os autores não têm outras afiliações ou envolvimento financeiro relevante com nenhuma organização ou entidade com interesse financeiro ou conflito financeiro com o assunto ou os materiais discutidos no manuscrito, além dos já referidos. A BCN Health Economics & Outcomes Research S.L. propvidenciou análise estatística e apoio editorial. Os serviços da BCN Health Economics & Outcomes Research S.L. foram financiados pela Novo Nordisk.*

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J Darbà, M Ascanio, D Carvalho, V Conde and KS Pedersen meet the International Committee of Medical Journal Editors (ICMJE) criteria for authorship for this manuscript, take responsibility for the integrity of the work as a whole, and have given final approval for the version to be published. All authors had full access to all of the data in this study and take responsibility for the integrity of the data and accuracy of the data analysis./*J. Darbà, M. Ascanio, D. Carvalho, V. Conde e K.S. Pedersen cumpriram os critérios de autoria para este manuscrito do "International Committee of Medical Journal Editors (ICMJE)", assumem a responsabilidade pela integridade do trabalho como um todo e deram a aprovação final para a versão a ser publicada. Todos os autores tiveram acesso total a todos os dados deste estudo e assumem a responsabilidade pela integridade dos dados e precisão da análise dos dados.*

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