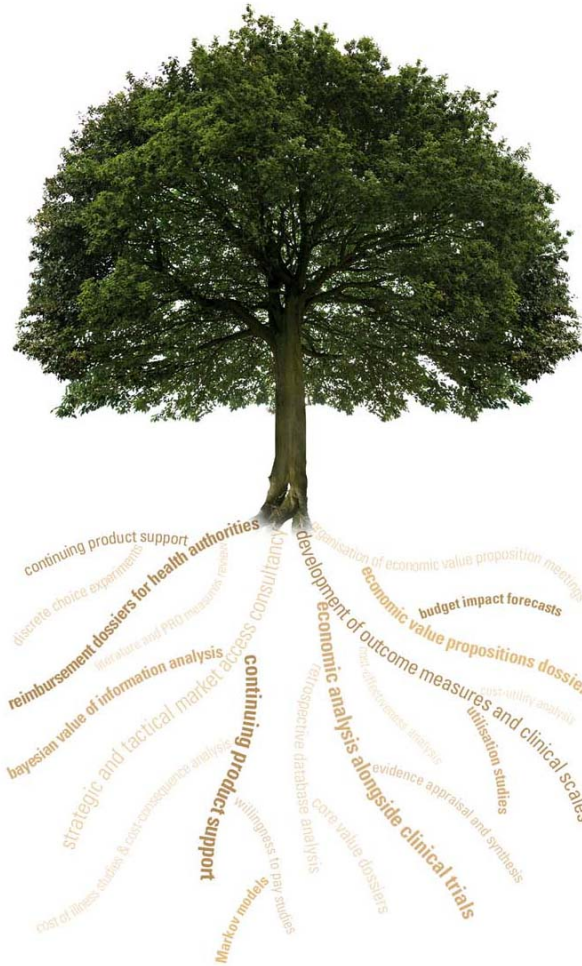


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COST-EFFECTIVENESS ANALYSIS OF INSULIN DEGLUDEC COMPARED WITH INSULIN GLARGINE U100 IN PATIENTS WITH TYPE 1 AND TYPE 2 DIABETES FROM THE PERSPECTIVE OF THE SPANISH NATIONAL HEALTHCARE SYSTEM: EVIDENCE FROM THE SWITCH 1&2 TRIALS



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1. Introduction
2. Objectives
3. Methods
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5. Conclusions

Burden of Diabetes

- Diabetes is a serious chronic disease that occurs when the pancreas does not produce enough insulin (type 1 diabetes) or when the insulin produced is not effectively used by the body (type 2 diabetes)¹.
- In Spain, the number of diabetes cases has increased by 33.41% over the period from 2011 to 2013².
- It is estimated that by 2030 the prevalence of diabetes in Spain will increase further with 32%, with approximately 3.9 million people having a diagnosis of diabetes².
- The prevalence of type 1 diabetes mellitus (T1DM) in Spain ranges from 0.3 to 1.53 cases per 1,000 children younger than 15 years old³.
- Type 2 diabetes mellitus (T2DM) accounts for the 90% of all cases, with approximately 60%-90% of all T2DM cases being related to obesity⁴.
- The progression of the disease depends on blood glucose (BG) levels and to maintain these levels in the target range of the patient.
- In the end, all patients with T1DM will need insulin to control their diabetes, as well as most patients with T2DM as the disease progresses⁵.

Diabetes treatment: insulin degludec and insulin glargine

- The objective of diabetes treatment is to control glucose levels and, at the same time, to avoid or lower the risk of hypoglycemic events. Furthermore, hypoglycemic events have shown to have a significant impact on healthcare costs¹.
- There are several insulin treatments available on the market, being the insulin glargine (IGlar) one of the most used basal insulins to treat T1DM and T2DM in Spain².
- IGlar pharmacological action starts 1-3 hours after its administration and lasts for 24 hours approximately³.
- IGlar should be administered with a short-lasting insulin in case of T1DM patients or with oral medication in case of T2DM patients.
- Insulin degludec (IDeg) is a new basal insulin with ultra-long duration of action (more than 42 hours) and a flat and stable action profile⁴.
- In SWITCH 1&2 trials IDeg was non-inferior in terms of a reduction in HbA_{1c}, and achieved superiority for both the primary and confirmatory secondary hypoglycemia endpoints when compared with IGlar.

2. OBJECTIVES

MAIN OBJECTIVE

The main objective of this study was to evaluate the cost-effectiveness of IDeg versus IGlax in type 1 and type 2 diabetic patients from a Spanish National Healthcare System perspective using evidence data from SWITCH 1&2 trials.

SPECIFIC OBJECTIVES

- 1) To calculate the treatment costs for two different types of diabetic patients when treated with IDeg and IGlax: T1DM patients treated with basal-bolus therapy (T1DM B/B) and T2DM patients treated with basal oral therapy (T2DM BOT).
- 2) To calculate the benefits in terms of quality-adjusted life year (QALY) for each treatment regimen alternative (T1DM B/B and T2DM BOT).
- 3) To calculate incremental costs and incremental QALYs for T1DM B/B and T2DM BOT patients.
- 4) To calculate incremental cost-effectiveness ratio (ICER) of IDeg versus IGlax for both patients groups.
- 5) To assess the robustness of the results by means of different sensitivity analyses.

Cost-effectiveness model

- A short-term cost-effectiveness model was developed to estimate cost and effectiveness data for IDeg versus IGlax in two groups of diabetic patients: T1DM B/B and T2DM BOT.
- The number of hypoglycemic events and insulin dose data were obtained from SWITCH 1&2 trials.
- The costs of insulin, needles, blood glucose tests and disutilities for different types of hypoglycemic events have been used to populate the model.
- From the cost-effectiveness analysis we have calculated benefits measured in terms of QALYs and cost-effectiveness data measured in terms of ICERs.
- An univariate sensitivity analysis has been carried out to analyze the consistency of the model. The univariate sensitivity analysis varied seven different parameters: insulin dose, severe and non-severe daytime and nocturnal hypoglycemia rates, number of self-monitoring blood glucose (SMBG) tests, insulin injections per day and costs of severe hypoglycemia.
- A probabilistic sensitivity analysis (PSA) has been conducted to assess the robustness of the results. This PSA varies simultaneously all model parameters and estimates the certainty that the treatment with IDeg is cost-effective compared to the treatment with IGlax at different thresholds of cost-effectiveness.
- The standard errors around the parameters were used and a lognormal distribution around the hypoglycemic event rates and normal distributions around continuous variables were assumed. 5,000 iterations were used to run the PSA.

3. METHODS

Model specifications

- This cost-effectiveness model compares IDeg treatment with IGlAr treatment for two subgroups of diabetic patients under different treatment regimens:

T1DM B/B
T1DM patients treated with
B/B insulin

T2DM BOT
T2DM patients treated with
BOT and insulin

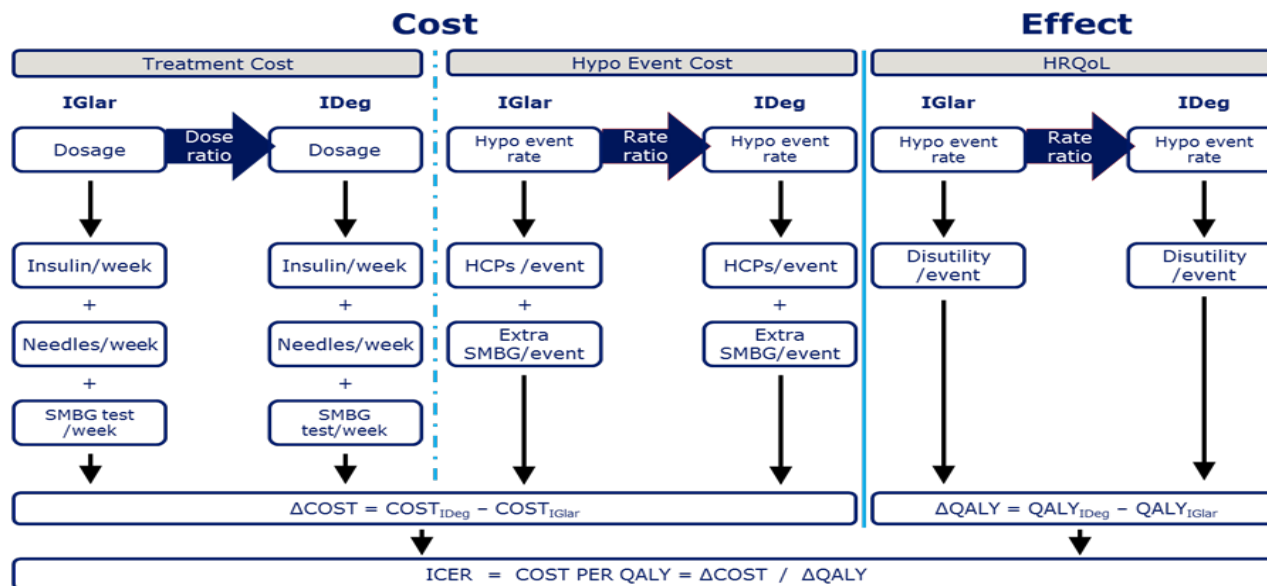
- The cost-effectiveness model was developed in Microsoft Excel 2010 combining the incremental cost of the insulin treatment expressing the benefit it produces in terms of QALYs to allow the comparison of the two types of insulin (IDeg and IGlAr) in both groups of diabetic patients.
- The main outcome measure was the ICER. It reflects the cost per QALY gained, and allows the comparison between the two treatments (IDeg and IGlAr).
- In Spain no official ICER threshold is being available, although an ICER threshold of 30,000 Euros per QALY gained is considered to be an acceptable value for money in Spain¹.
- Costs and benefits were analysed over a five-year time-horizon from the Spanish National Health System perspective.

3. METHODS

Model specifications

- A cost-utility model based on the reduction of health-related quality of life (HRQoL) due to hypoglycemic events¹ and SMBG tests² was used to calculate QALYs, as shown in the figure below.
- The analysis was based on SWITCH 1&2 trials data, including patients with T1DM B/B and T2DM BOT, treated with IDeg and with IGlar as comparator of interest.

Schematic model: utilities from hypoglycemic events



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; Δ: change in.

3. METHODS

Clinical data: insulin doses

- Insulin doses and insulin dose ratios for both diabetic patient groups are shown in the table below.
- Units of basal insulin used per day were estimated based on the data from SWITCH 1&2 trials.
- The IDeg/IGlar dose ratios for T1DM B/B and T2DM BOT groups were derived from SWITCH 1&2 trials to estimate IDeg and IGlar doses.

Insulin doses in units per day and dose ratios

		T1DM B/B	T2DM BOT
Basal	Insulin	Insulin units/day	Insulin units/day
	IDeg	40.31	78.65
	IGlar	41.56	81.93
Bolus	IAsp (IDeg)	32.19	-
	IAsp (IGlar)	32.19	-
Basal/Bolus	Insulin	Ratio	Ratio
	IDeg/IGlar	0.97	0.96
	IAsp (IDeg)/IAsp (IGlar)	1	-

IDeg: insulin degludec; IGlar: insulin glargine; IAsp: insulin aspart

3. METHODS

Clinical data: hypoglycemic event rates

- Hypoglycemic event rates per patient/ year for each treatment are shown in the table below.
- Frequency and event rates for both severe hypoglycemic events (SHE) and non-severe hypoglycemic events (NSHE) were derived from the SWITCH 1&2 trials.
- The NSHE was an event with symptoms, with or without blood glucose measurement (BGM), or low BGM without symptoms, which the patient could manage without assistance. SHE was low BGM which required help from a third party to manage the event.
- The event rates for IDeg were determined based on the relative event ratios (IDeg/IGlar) derived from the SWITCH 1&2 trials.
- To estimate the number of non-severe nocturnal hypoglycemic events per patient per year the calculation was as follows: 1) the number non-severe nocturnal hypoglycemic events related to IGlar were equal to 22.56 per patient per year; 2) the relative event ratio (IDeg/IGlar) (only significant differences were used for the modeling) was 0.76; 3) the number of non-severe nocturnal hypoglycemic events related IDeg was $22.56 \times 0.76 = 17.15$ per patient per year.

Relative hypoglycemic event rates per patient/year per treatment regimen

	T1DM B/B			T2DM BOT		
	Frequency	IDeg	IGlar	Frequency	IDeg	IGlar
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

IDeg: insulin degludec; IGlar: insulin glargine; NSHE: non-severe hypoglycemic event; SHE: severe hypoglycemic event

3. METHODS

Clinical data: self-monitoring blood glucose tests and needles

- The number of SMBG tests and needles needed are shown in the table below.
- The number of SMBG tests needed per week associated with IGLar was based on the recommended titration schedule for IGLar in T1DM B/B and T2DM BOT insulin treated patients.
- The patients treated with IDeg are able to monitor their blood glucose more efficiently using fewer SMBG tests per week because IDeg medication has a long half-life and a flat and stable profile in steady state with low variability over the day, so patients use less number of SMBG tests associated with basal injections per week.
- The numbers of needles is the same for both B/B and BOT regimens.

Number of needles and SMBG tests associated with IDeg and IGLar

		T1DM B/B		T2DM BOT	
		IDeg	IGlar	IDeg	IGlar
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 hypoglycemia	Daytime NSHE	5	5	5.90	5.90
	Nocturnal NSHE	5	5	5.90	5.90
	SHE	-	-	-	-

3. METHODS

Unit costs: insulin, needles and SMBG tests

- For both patient groups, direct medical costs included: the drug cost (number of insulin units used, needles and SMBG tests) and costs related to severe and non-severe hypoglycemic events.
- All other unit costs were assumed to be equivalent for both treatment groups.
- All costs referred to EUR 2016 and were updated with the Consumer Price Index to the reference year, if applicable.

Unit costs for insulin, needles and SMBG tests

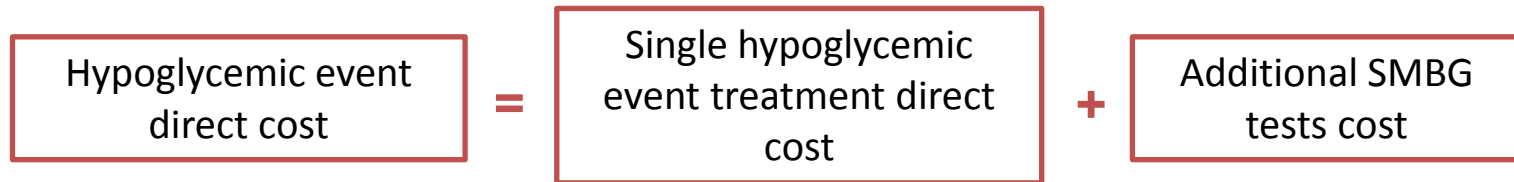
Product	Type		Price per pack size	Units per pack size	Price per unit
Insulin	Basal	IDeg	€52.95	1,500	€0.0353
		IGlar	€36.90	1,500	€0.0246
	Bolus	IAsp	€27.90	1,500	€0.0186
		Resource	Pack cost	Units per pack size	Price per unit
Needles			€6.26	100	€0.06
SMBG tests		Test strip	€20	100	€0.20
		Lancet	€10	200	€0.05
		SMBG test	-	-	€0.25

IDeg: insulin degludec; IGlar: insulin glargine; IAsp: insulin aspart; SMBG: self-monitoring blood glucose

3. METHODS

Unit costs: hypoglycemic events

- The direct cost associated with a hypoglycemic event consisted of the direct cost to treat a single hypoglycemic event plus the cost of additional SMBG tests in the week following the event.



- The cost of managing a SHE in Spain was estimated at **€577** for patients with **T1DM** and **€691** for patients with **T2DM**¹.
- These costs for a severe hypoglycemic event included the use of additional SMBG tests in the week following a severe event. In case of a NSHE, the use of additional SMBG tests were taken from Brod et al., 2011² based on patient reported experiences.
- According to the patients' reports, there were no differences between IDeg and IGLar with respect to the proportion of patients contacting a hospital/healthcare professional or in the number of SMBG test strips used following a hypoglycemic event.
- The behavior after a hypoglycemic event was assumed to be similar, irrespective of therapy. Hence, the difference in treatment related costs originated only from the difference in hypoglycemic events rate and not from the cost per event.

Utility data

- In the base case analysis, a marginal decreasing disutility approach was used in order to calculate QALYs by applying a disutility or a reduction in HRQoL per hypoglycemic event.
- In this approach, the initial quality of life at the beginning of the year was reduced according to the number of hypoglycemic events occurred throughout the year in each treatment group.
- The relation between the number of hypoglycemic events and the reduction of a patient's average HRQoL followed a diminishing marginal impact pattern.
- The corresponding disutility for a hypoglycemic event was derived from a recent Time-Trade-Off (TTO) study¹.
- The TTO study reported the following disutilities:
 - 0.0565 for a severe hypoglycemic event^{*}
 - 0.0041 for non-sever daytime hypoglycemic event[†]
 - 0.0067 for non-severe nocturnal hypoglycemic event[†]

^{*}without significant differences between daytime and nocturnal severe hypoglycemic events.

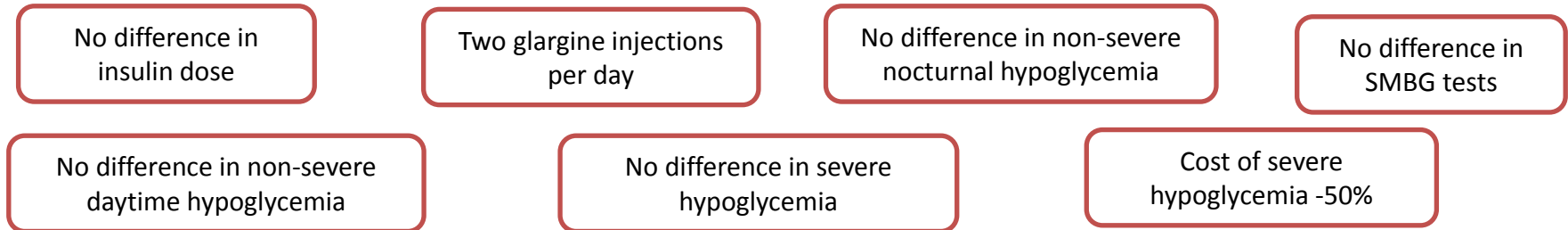
[†]with significant differences in utility for nocturnal compared to daytime non-severe hypoglycemic events.

Sensitivity analysis

- Univariate and probabilistic sensitivity analysis were conducted in order to determine the impact of varying key assumptions and outcomes used in the base case analysis.

Univariate sensitivity analysis

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



Probabilistic sensitivity analysis (PSA)

- The PSA varies simultaneously all model parameters within a plausible range and estimates the probability that the IDeg treatment is cost-effective compared to the IGlAr treatment at different thresholds of cost-effectiveness.
- The standard errors around the parameters were used to run the PSA.
- A lognormal distribution around the hypoglycemic event rates and normal distributions around continuous variables were assumed.
- 5.000 iterations were used to run the PSA.

4. RESULTS

Cost-effectiveness analysis

- The base case cost-effectiveness analysis results for IDeg compared to IGlAr for T1DM B/B and T2DM BOT patients are shown in the table below.
- IDeg displayed less costs and more benefits than IGlAr in terms of QALYs for T1DM B/B patients, meaning that IDeg was the dominant treatment option over IGlAr for this group of patients.
- T2DM BOT patients showed more costs and more clinical benefits in terms of QALYS for IDeg compared with IGlAr.
- The ICERs for both alternative regimens were below the willingness-to-pay (WTP) threshold of €30,000 per QALY gained, which means that IDeg is a cost-effective option relative to the IGlAr treatment in patients under both alternative regimens.

Base case cost-effectiveness analysis results

IDeg vs. IGlAr	Incremental cost (EUR)	Incremental effectiveness (QALYs)	ICER (EUR per QALY gained)
T1DM B/B	-154.41	0.0757	Dominant
T2DM BOT	595.48	0.0701	8,497.12

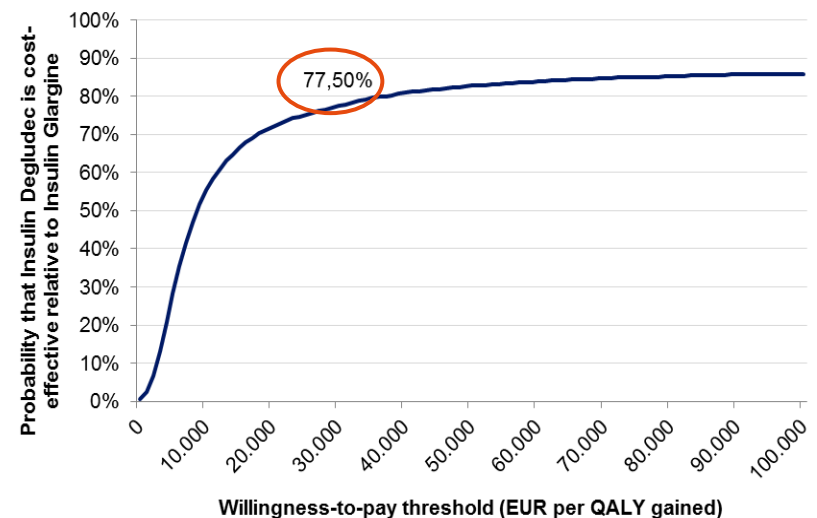
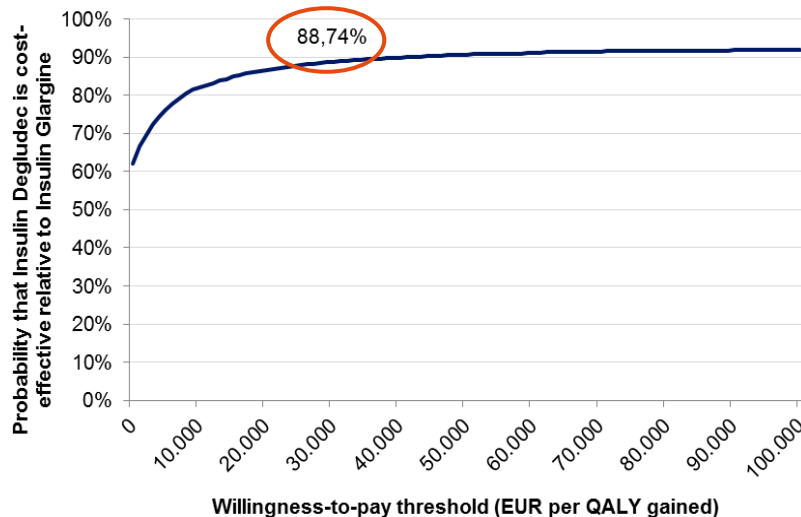
IDeg: insulin degludec; IGlAr: insulin glargine; B/B: basal bolus; BOT: basal oral therapy; QALY: quality-adjusted life years; ICER: incremental cost-effectiveness ratio

4. RESULTS

Probabilistic sensitivity analysis

- The cost-effectiveness acceptability curve for both groups of patients is shown in the figures below.
- This cost-effectiveness acceptability curve displays the increasing probability that IDeg is a more cost-effective treatment than IGlar for each group of patients given a threshold that reflects the WTP for this treatment, in this case 30,000 Euros per QALY gained.
- For **T1DM B/B** patients, there is a **88.74%** probability of IDeg being more cost-effective than IGlar taking into account a WTP threshold of 30,000 Euros per QALY gained.
- For **T2DM BOT** patients, there is a **77.50%** probability of IDeg being more cost-effective than IGlar taking into account a WTP threshold of 30,000 Euros per QALY gained.

Cost-effectiveness acceptability curves for T1DM B/B patients and T2DM BOT patients



4. RESULTS

Univariate sensitivity analysis

- The results for the univariate sensitivity analysis are shown in the table below.
- The univariate sensitivity analysis showed that the ICERs were stable under plausible variations in non-severe daytime and nocturnal hypoglycemia rates, severe hypoglycemia costs, but also when the insulin dose is considered to be the same for both insulin treatments (IDeg and IGlAr).
- The analysis displayed dominant results for IDeg over IGlAr for both alternative therapeutic regimen groups (T1DM B/B and T2DM BOT) when two IGlAr injections per day were assumed.
- The most sensitive parameter was the severe hypoglycemia events rate. It is noteworthy that the variation of this parameter for T2DM BOT group showed an ICER higher than the cost-effectiveness threshold of €30,000 per QALY gained.

Univariate sensitivity analyses of CEA of IDeg vs. IGlAr

IDeg vs. IGlAr	T1DM B/B	T2DM BOT
Base case	Dominant	8,497.12€/QALY
No difference in insulin dose	Dominant	11,314.71€/QALY
No difference in non-severe daytime hypoglycemia	Dominant	10,468.06€/QALY
No difference in non-severe nocturnal hypoglycemia	Dominant	11,123.95€/QALY
No difference in severe hypoglycemia	18,822.97€/QALY	40,004.40€/QALY
Two glargine injections per day	Dominant	Dominant
No difference in SMBG tests	376.03€/QALY	11,106.66€/QALY
Costs of severe hypoglycemia -50%	2,078.34€/QALY	12,018.58€/QALY

5. CONCLUSIONS

- IDeg treatment represents a cost-effective option compared to IGlax in patients under both alternative treatment regimens: T1DM B/B and T2DM BOT.
- IDeg has shown to be a least costly therapy when compared to IGlax for T1DM B/B patients, but not for T2DM BOT patients.
- Potential improvements in quality of life associated to IDeg have been confirmed for both alternative treatment regimens. These improvements in quality of life have been reflected in the incremental QALYs.
- IDeg therapy has shown to be the dominant strategy (less cost and higher effectiveness) over IGlax therapy in patients under T1DM B/B treatment regimen.
- IDeg has confirmed to be a dominant therapy compared to IGlax with a 89.30% probability of being cost-effective for T1DM B/B patients and a 76.76% probability for T2DM BOT patients when a WTP threshold of 30,000€ per QALY gained is being considered.
- The univariate and probabilistic sensitivity analyses have demonstrated the robustness of the results.