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ORIGINAL RESEARCH

Cost-effectiveness of Insulin Degludec Versus Insulin Glargine in Adults with Type 1 and Type 2 Diabetes Mellitus

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ABSTRACT

Introduction: To estimate the cost-effectiveness of insulin degludec (IDeg) versus insulin glargine U100 (IGlar U100) and new-to-market basal insulin analogues in patients with diabetes in order to aid decision-making in a complex basal insulin market.

Methods: A simple, short-term model was used to evaluate the costs and effects of treatment with IDeg versus IGlar U100 over a 12-month period in patients with type 1 (T1DM) and type 2 diabetes (T2DM) from the perspective of the UK National Health Service. New-to-market basal insulin analogues were evaluated in scenario analyses.

Results: IDeg is dominant (more effective and less costly) versus IGlar U100 in patients with T1DM and patients with T2DM on a basal-only therapy regimen ($T2DM_{BOT}$), and is cost-effective versus IGlar U100 in patients with T2DM on a basal-bolus regimen ($T2DM_{B/B}$). In T1DM, lower costs are primarily driven by lower insulin costs, as a result of a lower daily dose of IDeg. In $T2DM_{BOT}$, lower overall costs with IDeg are driven by lower costs of severe hypoglycaemic events due to the significant reduction in number of events with IDeg versus IGlar U100. Improvements in clinical outcomes in all three patient groups are a result of the reduced incidence of hypoglycaemic events. Sensitivity analyses demonstrate that the results are robust. Scenario analyses versus two new-to-market basal insulin analogues indicate that in patients with T1DM and $T2DM_{BOT}$, IDeg is likely to be highly cost-effective versus IGlar biosimilar Abasaglar® and dominant versus IGlar U300 (Toujeo®). In $T2DM_{B/B}$, IDeg is likely to be cost-effective versus both comparators, with incremental cost-effectiveness ratios (ICERs) below the accepted threshold.

Conclusion: IDeg is a cost-effective alternative to IGlar U100 for patients with diabetes in the UK, and it also likely to be cost-effective versus two new-to-market basal insulin analogues.

Keywords: Cost-effective; Diabetes; Hypoglycaemia; ICER; Insulin analogue; Insulin degludec; QALY

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INTRODUCTION

The cost of treating diabetes and its related complications represents a major economic burden for healthcare systems. The prevalence of diabetes is increasing and the global expenditure on diabetes is projected to reach $490 billion USD by 2030 [1]. In the UK, diabetes cost approximately £23.7 billion in 2010/2011, and it is projected to cost an estimated £39.8 billion by 2035/2036 [2]. The greatest proportion of diabetes expenditure is for treatment of micro- and macrovascular complications, which are consequences of prolonged hyperglycaemia [2]. A key treatment goal of diabetes therapy is to keep blood glucose levels within recommended targets and ultimately limit the development of diabetes-related complications [3, 4].

Insulin is essential for the treatment of type 1 diabetes (T1DM) [5]. Type 2 diabetes (T2DM) is a progressive disease and although glycaemic control can often be achieved with other classes of glucose-lowering therapies following diagnosis, a significant proportion of patients will eventually need insulin therapy to achieve optimal blood glucose targets [6]. Insulin is the most effective method of reducing blood glucose concentrations; however, despite evidence-based consensus guidance and documented benefits of good glycaemic control, many patients fail to achieve glycaemic targets [7]. Key barriers to insulin therapy include fear and risk of hypoglycaemia, weight gain, restricted lifestyle, reluctance to inject and difficulties with complex treatment regimens [8, 9].

New basal insulin analogues with improved pharmacodynamic and pharmacokinetic profiles, which confer a lower risk of hypoglycaemia and more flexible dosing schedules, have been developed with the aim of improving long-term glycaemic control and the patient's experience with basal insulin therapy.

Insulin degludec (IDeg) is a basal insulin with an ultra-long duration of action (more than 42 h) and a flat and stable action profile [10, 11]. It has four times less day-to-day variability in glucose-lowering effect than insulin glargine U100 (IGlar U100) [12]. In meta-analyses of phase 3a clinical trials, IDeg showed equivalent reductions in HbA_{1c} with a lower risk of hypoglycaemia versus IGlar U100, and at a significantly lower daily dose when compared with IGlar U100 in T1DM (12% lower) and T2DM basal oral therapy (10% lower) [13, 14]. The benefits of IDeg have also been reported in real world clinical practice. A study of 51 patients in routine practice in the UK, who were suffering from recurrent hypoglycaemia on IGlar U100 or insulin detemir, found that switching to IDeg resulted in significant reductions in hypoglycaemia (>90%) and improved glycaemic control [15].

With increasing constraints on healthcare budgets, it is important that new therapies represent good value for money. Cost-effectiveness models estimate the costs of interventions or services in relation to their expected health benefits. Cost-effectiveness modelling helps decision makers determine whether the health benefits associated with adopting the novel treatment are worth the cost compared with existing therapies.

Cost-effectiveness models are developed to compare the overall costs and health outcomes of two or more treatments. Results of an economic model are typically presented as an incremental cost-effectiveness ratio (ICER), which is the difference in cost between one healthcare intervention and an alternative, divided by the difference in health effects. A generally accepted effectiveness measure used in cost-effectiveness analyses is the quality-adjusted life year (QALY). The QALY is an overall measure of health as a combination of the duration of life and the health-related quality of life [16]. The incremental cost-effectiveness per additional QALY gained (cost/QALY) allows decision makers to broadly compare across different disease areas to determine where the provision of healthcare resources will lead to maximal economic and clinical benefits. A financial threshold is often set at which cost-effectiveness is accepted. For the National Institute for Health and Care Excellence, this is £20,000–£30,000/QALY [17].

Previous cost-effectiveness analyses, using a short-term model and data from the phase 3a

clinical trials, have demonstrated that IDeg is cost-effective versus IGlar U100 in patients with T1DM and T2DM on basal oral therapy [18–20]. However, since the publication of those evaluations, new basal insulin analogues have come to market: IGlar U300 (Toujeo®) and IGlar biosimilar (Abasaglar®), thus adding more therapeutic options for patients and crowding the basal insulin analogue market. Furthermore, the list price for IDeg was lowered by 35% in July 2016.

The objective of this study was to re-evaluate the cost-effectiveness of IDeg versus IGlar U100 from the perspective of the UK National Health Service, in light of the recent reduction in price of IDeg and the addition of new basal insulin analogues to the market place. The revised model evaluates a more generalisable patient population, including patients with T2DM on a basal-bolus regimen.

METHODS

Model Overview

This cost-utility analysis compared IDeg with IGlar U100 in three separate patient groups; type 1 diabetes mellitus using a basal-bolus regimen (T1DM); type 2 diabetes mellitus using a basal oral therapy regimen ($T2DM_{BOT}$); and T2DM using a basal-bolus regimen ($T2DM_{B/B}$). IGlar U100 is currently the most widely prescribed basal insulin in the UK and was therefore selected as the comparator for the base case analysis, but sensitivity analyses explored the cost-effectiveness of IDeg versus the most recent additions to the basal insulin market.

This short-term model (one-year time horizon) has been previously published [18–20]. Here we used the same modelling framework, with updated data inputs where appropriate. The analysis was conducted from the perspective of the UK National Health Service. This simple and transparent model in Microsoft Excel 2010 (Microsoft Corporation, Redmond, WA, USA) calculated the costs associated with treatment and hypoglycaemic events and calculated QALYs by applying a disutility per hypoglycaemic event (Fig. 1).

DATA USED IN THE MODEL

Clinical Data

Clinical data used in the analysis were derived from the IDeg clinical trial programme. This article does not contain any new studies with human or animal subjects performed by any of the authors.

Insulin Dose

Units of insulin used per day for the IDeg and IGlar U100 treatment groups were the end of trial doses captured from the clinical trial data. The IGlar U100 dose and IDeg/IGlar U100 dose ratio were derived from a meta-analysis of insulin dose [14]. The IDeg dose was calculated using the dose ratio to allow for adjustment of covariate factors such as trial, treatment, antidiabetic therapy at screening, age, sex, region, and baseline dose (Table 1). The doses used may be higher than would be expected in usual clinical practice, but using these documented doses seen in the treat-to-target trials allows for a fair comparison.

Needle Use

One needle per day for the $T2DM_{BOT}$ regimen and four needles per day for both the T1DM and $T2DM_{B/B}$ regimens were assumed. This was based on the Forum for Injection Technique (FIT) recommendations for needle use in the UK and guidance from needle manufacturers, which recommends that pen needles should be used only once [21]. Sensitivity analysis explored the results for when IGlar U100 was used twice daily, which is reported to be common in both T1DM [22, 23] and T2DM [24], due to the intermediate half-life of current basal insulin preparations.

Hypoglycaemia Event Rates

Real-world hypoglycaemic event rates from the UK Hypoglycaemia Study Group (UKHSG) observational study [25] were used as the baseline values for severe and non-severe

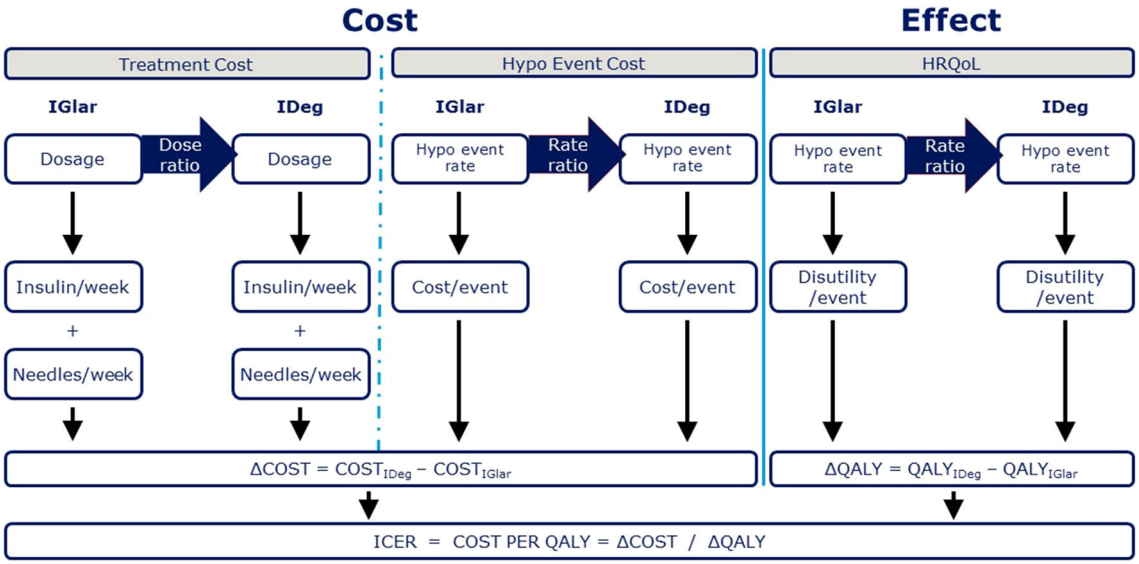

Fig. 1 Overview of the cost-effectiveness model

Table 1 Basal and bolus insulin use

Treatment group	IGlar U100 (units/day)	Dose ratio (IDeg/IGlar U100)	IDeg (units/day)
$T1DM_{B/B}$, total dose		0.88*	
Basal insulin	33.10	0.87*	28.80
Bolus insulin	35.00	0.88*	30.80
$T2DM_{BOT}$, total dose		0.90*	
Basal insulin	51.70	0.90*	46.53
Bolus insulin	Not relevant	Not relevant	Not relevant
$T2DM_{B/B}$, total dose		NS	
Basal insulin	66.60	1.08*	71.93
Bolus insulin	72.70	NS	72.70

NS nonsignificant; in the case of nonsignificant results, a relative rate of 1 was used in the calculation
* $p < 0.05$

hypoglycaemic events. These rates represent better estimates of real-life event rates than data from clinical trials. The rates selected from the UKHSG for the base case analysis were: T1DM (UKHSG T1DM >15 years): non-severe 29.0 events/patient/year and severe 3.2 events/patient/year; $T2DM_{BOT}$ (UKHSG T2DM <2 years): non-severe 4.08 events/patient/year and severe 0.1 events/patient/year; $T2DM_{B/B}$ (UKHSG T2DM >5 years): non-severe 10.2 events/patient/year and severe 0.7 events/patient/year. Additional published hypoglycaemia rates and rates from the clinical trials (Table S1 in the Electronic supplementary material, ESM) were investigated in sensitivity analyses.

The rates were taken as the base-case event rates in the IGlar U100 group (as this is the existing treatment on the market). Event rates for the IDeg group were calculated using the relative event rate ratios derived from the

meta-analysis of hypoglycaemia [13, 14] (see Table 2), and were adjusted for trial, type of diabetes, treatment, antidiabetic therapy at screening, sex and region as fixed factors and age as a continuous covariate. Event rates were split into three mutually exclusive groups: severe events, non-severe events occurring during the day (diurnal) and non-severe events occurring during the night (nocturnal). Since the cost associated with a severe event is not dependent on when it occurs and there is no significant difference in disutility associated with a nocturnal versus a daytime severe event, the severe events were not split into daytime and nocturnal. Only rate ratios with a documented statistically significant difference between the treatment arms were used. This minimised the influence of random variation on the results.

UTILITY DATA

QALYs were calculated by applying a disutility [26] per hypoglycaemic event. The disutility per hypoglycaemic event was multiplied by the number of events observed in each treatment group. This was done for severe and non-severe events separately. A large-scale time trade-off (TTO) study [26] was used to obtain the disutility incurred per hypoglycaemic event. The study documented a disutility of 0.0565 for a severe event (with no significant difference between daytime and nocturnal severe events) and disutilities of 0.0041 and 0.0067 for non-severe daytime and non-severe nocturnal events, respectively (a significant difference in utility was demonstrated for nocturnal versus daytime non-severe events) [26].

COST DATA

Cost of Insulin and Needles

The cost of insulin was calculated based on prices published in MIMS October 2016 [27] and daily doses observed in the clinical trials. The pack price of IDeg (in FlexTouch® pen) is £46.60

Table 2 Calculation of hypoglycaemic event rates

	$T1DM_{B/B}$			$T2DM_{BOT}$			$T2DM_{B/B}$		
	Non-severe		Severe	Non-severe		Severe	Non-severe		Severe
Baseline hypoglycaemia rate (IGlar U100)	29†		3.20†	4.08†		0.10†	10.2†		0.70†
Daytime/nocturnal split‡	Daytime	Nocturnal	–	Daytime	Nocturnal	–	Daytime	Nocturnal	–
	86.64%	13.36%		75.34%	24.66%		86.57%	13.43%	
Total events per patient per year for IGlar U100	25.13	3.87	3.20	0.10	1.01	0.10	8.83	1.37	0.70
IDeg/IGlar U100 hypoglycaemic event rate ratio	NS	0.83*	NS	0.14*	0.64*	0.14*	0.83*	0.75*	NS
Calculated IDeg hypoglycaemic event rate	25.13	3.22	3.20	0.01	0.63	0.01	7.33	1.03	0.70

NS non-significant; in the case of non-significant results, a relative rate of 1 was used in the calculation

* $p < 0.05$

† Taken from UKHSG [25]

‡ Proportion of daytime nocturnal events for IGlar, taken from the clinical trials

for 1500 units, giving a price per unit of £0.031; IGlar (Lantus® in Solostar® pen) is £41.50 per pack for 1500 units, giving a price per unit of £0.028. The cost of needles was calculated based on the unit cost and number of daily injections. Needle choice was assumed to be the same for all insulins; BD MicroFine® (£9.69 per pack of 100 units; price per unit £0.097) was selected as it is the most commonly used needle in the UK according to 2015 Prescription Cost Analysis (PCA) data.

Cost of Hypoglycaemic Events

The cost per hypoglycaemic event (non-severe nocturnal, non-severe diurnal and severe) was derived from the published literature.

The cost of a severe hypoglycaemic event, £173.03/event for T1DM and £414.09/event for T2DM, was taken from a study specifically designed to evaluate the cost of severe hypoglycaemia across Germany, Spain and the UK [28]. Costs were inflated using the Health Care Service Corporation (HCSC) pay and prices index (from 2008 to 2015), and indirect costs were excluded.

The cost of a non-severe hypoglycaemic event was derived from a real-world study that investigated the frequency of self-reported non-severe hypoglycaemic events across 11 European countries, including the UK [the Hypoglycaemia in Insulin Treated Patients (HIT) study] [29]. The cost in the UK of a non-severe nocturnal event was £3.36 for T1DM and £6.35 for T2DM, and for a non-severe diurnal event it was £2.71 for T1DM and £3.96 for T2DM (exchange rates used: €/£ = 1.36334, recalculated using 2016 resource use costs). Alternative published costs, as well as costs calculated from the clinical trial data, were investigated in sensitivity analyses.

SENSITIVITY ANALYSES

One-way and probabilistic sensitivity analyses were conducted in order to assess the impact of varying key assumptions and outcomes used in the base case analysis (Table 3).

SCENARIO ANALYSES

Two new basal insulin analogues have recently entered the market, IGlar U300 (Toujeo®) and IGlar biosimilar (Abasaglar®). Given that they are new to the market, there are currently no head-to-head data for them versus IDeg. However, scenario analyses were conducted to evaluate the cost-effectiveness of IDeg versus these comparators using available data and plausible assumptions.

IDeg versus Abasaglar®

This scenario analysis assumed that Abasaglar® has the same efficacy and safety as IGlar U100 (Lantus®). However, Abasaglar® is a biosimilar and is not identical to IGlar U100, and EMA approval does not involve any assessment or recommendation regarding interchangeability [33]. The price of Abasaglar® is 15% lower than that of IGlar U100 (Lantus®), so this scenario reflected a 15% reduction in the price of IGlar U100, with no change in any other parameters.

IDeg versus IGlar U300 (Toujeo®)

IGlar U300 is a concentrated insulin glargine product (300 units/ml) for once-daily use for the treatment of T1DM and T2DM in adults. With the IGlar U300 prefilled pen, the maximum dose per injection is 80U [34]. IGlar U300 has a flatter and more prolonged (up to 36 h) profile of insulin concentration and glucose-lowering activity compared with IGlar U100 at the same dose [34]. IGlar U300 is not bioequivalent to IGlar U100 and they are not directly interchangeable. An approximately 10–18% higher dose is required when patients are switched from IGlar U100 to IGlar U300 [34, 35].

In clinical trials, IGlar U300 was non-inferior to IGlar U100 in terms of HbA_{1c} reduction in T1DM, $T2DM_{BOT}$ and $T2DM_{B/B}$ [36–38]. In T1DM, there was no significant difference in hypoglycaemia (severe, nocturnal or overall) between IGlar U300 and IGlar U100 [36]; in $T2DM_{BOT}$ there was no significant difference in

Table 3 Description of sensitivity analyses conducted

Hypoglycaemia rates/ distribution	The base case rate of hypoglycaemia was taken from the published literature as it is believed that this provides a more realistic event rate. Additional published event rates, and the actual reported rates from the clinical trial programme, were investigated in sensitivity analyses
	In addition, a sensitivity analysis was conducted where no hypoglycaemia benefit was assumed for IDeg. As the modelling of QoL is solely dependent on hypoglycaemia, when there is no hypoglycaemia benefit, there is no difference in QoL between IDeg and IGlar and an ICER cannot be calculated
Hypoglycaemia distribution	The proportion of hypoglycaemic events that occur at night time was also investigated. The base case proportion was taken from the clinical trials, with sensitivity analysis varying ±50%
Hypoglycaemia costs	Sensitivity analyses use alternative published values for costs of both severe and non-severe hypoglycaemia, and the cost of hypoglycaemia based on the clinical trial data
Hypoglycaemia disutility	Base case disutilities were from Evans [26]. Alternative disutilities published by Currie [30] were explored
Injection frequency	For a number of patients, current basal insulins need to be taken twice daily to ensure optimal control. The effect of using twice as many needles for the basal injections in the IGlar group was explored
Price	The price of IGlar was varied ±15%
Dosing	The final dose of both IDeg and IGlar and their relationship to each other were investigated (with either a dose ratio based on the published literature or an assumption of equal doses)
Flexible dosing utility	An estimate of the utility benefit of the option of flexible dosing time with IDeg was applied. Utility values from two published sources were explored [31, 32]
IGlar U300	There are no studies comparing IGlar U300 with IDeg, so sensitivity analyses were conducted where the price of IGlar U300 was substituted for the price of IGlar U100 and the insulin dose adjusted according to doses observed in the IGlar U100 versus IGlar U300 clinical trials
Probabilistic sensitivity analysis (PSA)	PSA used the standard errors and appropriate distributions of the parameters. The distributions were assumed to be either normal or lognormal, and each individual parameter was selected independently. The probabilistic sensitivity analyses were run with 1000 iterations. In the primary analysis for each of the groups, the standard error was only applied to differences that were statistically significant; i.e. if statistical significance was not proven, the rate ratio was set to 1 (assumed equivalent) and the S.E. was set to 0 (so as not to introduce random uncertainty)

severe or nocturnal hypoglycaemia but a significantly lower rate of overall hypoglycaemia with IGlar U300 versus IGlar U100 [37]; and in $T2DM_{B/B}$ there was no significant difference in severe or overall hypoglycaemia but a significantly lower rate of nocturnal hypoglycaemia with IGlar U300 versus IGlar U100 [38]. In all three patient groups, the total daily basal

insulin dose was higher with IGlar U300 versus IGlar U100; by 17.5% in T1DM, 17% in $T2DM_{BOT}$ and 10% in $T2DM_{B/B}$ [36–38].

In this scenario analysis, the cost of IGlar U300 (£33.13 per pack of 1350 units; £0.025/unit [27]), calculated based on the IGlar U100 dose observed in the clinical trials and the reported dose increase for IGlar U300 [34], was substituted for the IGlar U100 price in the three patient groups. All other parameters remained unchanged. It was assumed, based on the IGlar U300 versus IGlar U100 clinical data and IDeg versus IGlar U100 clinical data that the hypoglycaemia benefit observed with IDeg versus IGlar U100 would be maintained in this comparison versus IGlar U300. However, for transparency, and acknowledging that in a small number of analyses IGlar U300 had a hypoglycaemia benefit over IGlar U100, an additional analysis was conducted where no hypoglycaemia benefit was assumed for IDeg; i.e. that IDeg and IGlar U300 have the same clinical effect. We believe this is conservative, particularly as subjects in the IGlar U300 trials were transferred dose for dose to IGlar U300, which means—based on the higher dose requirement for IGlar U300—that they were underdosed for the titration stages of the trials.

RESULTS

In T1DM, total costs in the IDeg group are estimated at £1330 per patient per year (Table 4). Approximately 52% of this is the cost of insulin and other pharmacy costs, and the remainder is other health care costs associated with hypoglycaemic events, primarily the severe events. The total cost per patient per year in the IDeg group is £41 lower than that in the IGlar U100 group, primarily due to lower insulin costs. The costs of hypoglycaemic events are almost unchanged due to the fact that only the non-severe nocturnal events showed a statistically significant difference between IDeg and IGlar U100, while the severe and daytime events were unchanged. IDeg is associated with significantly fewer non-severe nocturnal hypoglycaemic events, which leads to a QALY gain of 0.0044 versus IGlar U100. Thus, IDeg is the dominant treatment, as it is more effective and less costly than IGlar U100 (Table 4).

In $T2DM_{BOT}$, total costs in the IDeg group are calculated at £585 per patient per year, of which more than 96% is pharmacy costs (insulin and needles) and the remainder is costs of hypoglycaemic episodes (Table 4). Total costs per patient per year are £32 lower than in the IGlar U100 group, driven by lower costs of severe hypoglycaemic events due to the significant reduction in the number of severe hypoglycaemic events with IDeg versus IGlar U100 in this patient group. Due to the significantly fewer nocturnal and severe hypoglycaemic events in this group, IDeg is associated with a QALY gain of 0.0074 versus IGlar U100. Thus, IDeg is again the dominant treatment versus IGlar U100 (Table 4).

In $T2DM_{B/B}$, the total cost in the IDeg group is £1825, which is £135 (8%) higher than in the IGlar U100 group (Table 4). In this setting, 82% of the costs are pharmacy costs. IDeg is associated with significantly fewer non-severe daytime and nocturnal hypoglycaemic events, which leads to a QALY gain of 0.0084 versus IGlar U100. The incremental cost per incremental QALY gained with IDeg versus IGlar U100 is estimated at £15,983 (Table 4). This result falls below commonly accepted thresholds for cost-effectiveness. The higher incremental cost for this group is driven mainly by the slightly higher dose of basal insulin required in the IDeg arm of the clinical trial. In the $T2DM_{B/B}$ clinical trial [14], high insulin doses were observed in both the IDeg and the IGlar U100 treatment arms. The high doses observed in the trial are not expected to be representative of a real-world setting for patients initiating a basal-bolus regimen, as the trial mainly recruited patients who were already uncontrolled on an intensive basal-bolus regimen or uncontrolled on a pre-mixed insulin regimen.

SENSITIVITY ANALYSIS

In T1DM, the favourable cost-effectiveness results are robust and invariant to changes in most of the parameters (Table S2 in the ESM). When equal insulin doses are assumed, the

Table 4 Total costs per patient and incremental cost-effectiveness

	T1DM			$T2DM_{BOT}$			$T2DM_{B/B}$		
	IDeg (£/year)	IGlar U100 (£/year)	Incremental cost (£/year)	IDeg (£/year)	IGlar U100 (£/year)	Incremental cost (£/year)	IDeg (£/year)	IGlar U100 (£/year)	Incremental cost (£/year)
Pharmacy costs									
Insulin	556.26	595.27	−39.02	527.98	522.44	5.54	1357.87	1214.70	143.16
Needles	141.57	141.47	0.00	35.39	35.39	0.00	141.57	141.57	0.00
Hypoglycaemic events									
Non-severe daytime events	68.09	68.09	0.00	12.17	12.17	0.00	29.02	34.97	−5.94
Non-severe nocturnal events	10.80	13.02	−2.21	4.09	6.39	−2.30	6.52	8.70	−2.17
Severe events	553.70	553.70	0.00	5.80	41.41	−35.61	289.86	289.86	0.00
Total costs	1330.42	1371.65	−41.23	585.43	617.80	−32.37	1824.85	1689.80	135.05
Incremental QALYs (IDeg–IGlar U100)	0.0044			0.0073			0.0084		
ICER (cost/QALY)	Dominant			Dominant			15,983.37		

ICER is £8813/QALY gained, or when the price of IGlar U100 is reduced by 15%, the ICER is £2027/QALY gained; both of these are well below commonly accepted thresholds of cost-effectiveness. The ICER remains dominant in all other scenarios tested.

A largely similar pattern is observed for the $T2DM_{BOT}$ treatment regimen. The favourable cost-effectiveness results are invariant to changes in most of the parameters, with the ICER remaining dominant in the majority of analyses (Table S2 in the ESM). As with T1DM, when equal insulin doses are assumed or when the price of IGlar U100 is reduced by 15%, the ICER is no longer dominant, but it still falls well below commonly accepted thresholds of cost-effectiveness (£3609/QALY and £6313/QALY, respectively).

In the $T2DM_{B/B}$ group, the results fluctuate above and below the base case ICER of £15,983/QALY gained, but most results remain below the threshold of £20,000–£30,000/QALY gained (Table S2 in the ESM). Varying the rate of non-severe hypoglycaemia has an impact on the ICER in this group due to the significant reduction of non-severe events with IDeg versus IGlar U100. When the number of non-severe events/year is reduced to 8.3 using data from Dornhorst [39], the ICER increases to £19,862/QALY gained. Conversely, when the annual number of non-severe hypoglycaemic events is increased to 48, using data from the real-world study by Frier [40], the ICER drops to £2640/QALY gained. The price of IGlar U100 also has a noticeable impact on the ICER. When the price of IGlar U100 is reduced by 15%, the ICER is increased to £27,932/QALY gained, and when the price of IGlar U100 is increased by 15%, the ICER is reduced to £4035/QALY gained.

SCENARIO ANALYSIS

IDeg versus Abasaglar®

In both the T1DM and the $T2DM_{BOT}$ groups, IDeg is highly cost-effective versus Abasaglar®, with ICERs of £2027/QALY gained and £6313/QALY gained, respectively. In T1DM, IDeg is associated with a £8.94 higher annual per patient cost and a QALY gain of 0.0044 versus Abasaglar®, and in $T2DM_{BOT}$ it is associated with a £45.99 higher annual per patient cost and a 0.0073 QALY gain. In $T2DM_{B/B}$, the ICER (£27,932/QALY gained) is on the border of the commonly accepted threshold of cost-effectiveness. IDeg is associated with a £236.00 higher annual per patient cost and a QALY gain of 0.0084 in this group versus Abasaglar®. In the $T2DM_{B/B}$ clinical trial [14], high insulin doses were observed in both the IDeg and the IGlar U100 treatment arms, which drive the incremental insulin costs up in this analysis.

IDeg versus IGlar U300 (Toujeo®)

In both the T1DM and $T2DM_{BOT}$ groups, the ICER for IDeg versus IGlar U300 is dominant. Annual per patient costs are £53.36 lower in T1DM and £52.12 lower in $T2DM_{BOT}$ with IDeg versus IGlar U300, primarily due to the increased basal insulin dose with IGlar U300 (17.5% increase in T1DM [36], and 17% increase in $T2DM_{BOT}$ [37]). IDeg is associated with QALY gains of 0.0044 and 0.0073 versus IGlar U300 in T1DM and $T2DM_{BOT}$, respectively.

In $T2DM_{B/B}$, the incremental cost per incremental QALY gained with IDeg versus IGlar U300 is estimated at £17,918 (£154.50 higher annual per patient cost and 0.0084 QALY gain with IDeg versus IGlar U300). This result falls below the commonly accepted threshold for cost-effectiveness. Even when no hypoglycaemia benefit for IDeg is assumed, it is less costly than IGlar U300 in T1DM and $T2DM_{BOT}$, with an annual treatment cost difference of −£53.15 and −£14.21, respectively. In $T2DM_{B/B}$, if no hypoglycaemia benefit is assumed, the annual treatment cost difference for IDeg versus IGlar U300 is £159.51.

PROBABILISTIC SENSITIVITY ANALYSIS

In T1DM, the PSA results indicate that IDeg is dominant over IGlar U100. All the results are cost-saving, with some results showing health gains and some a negative QALY gain (Fig. 2a).

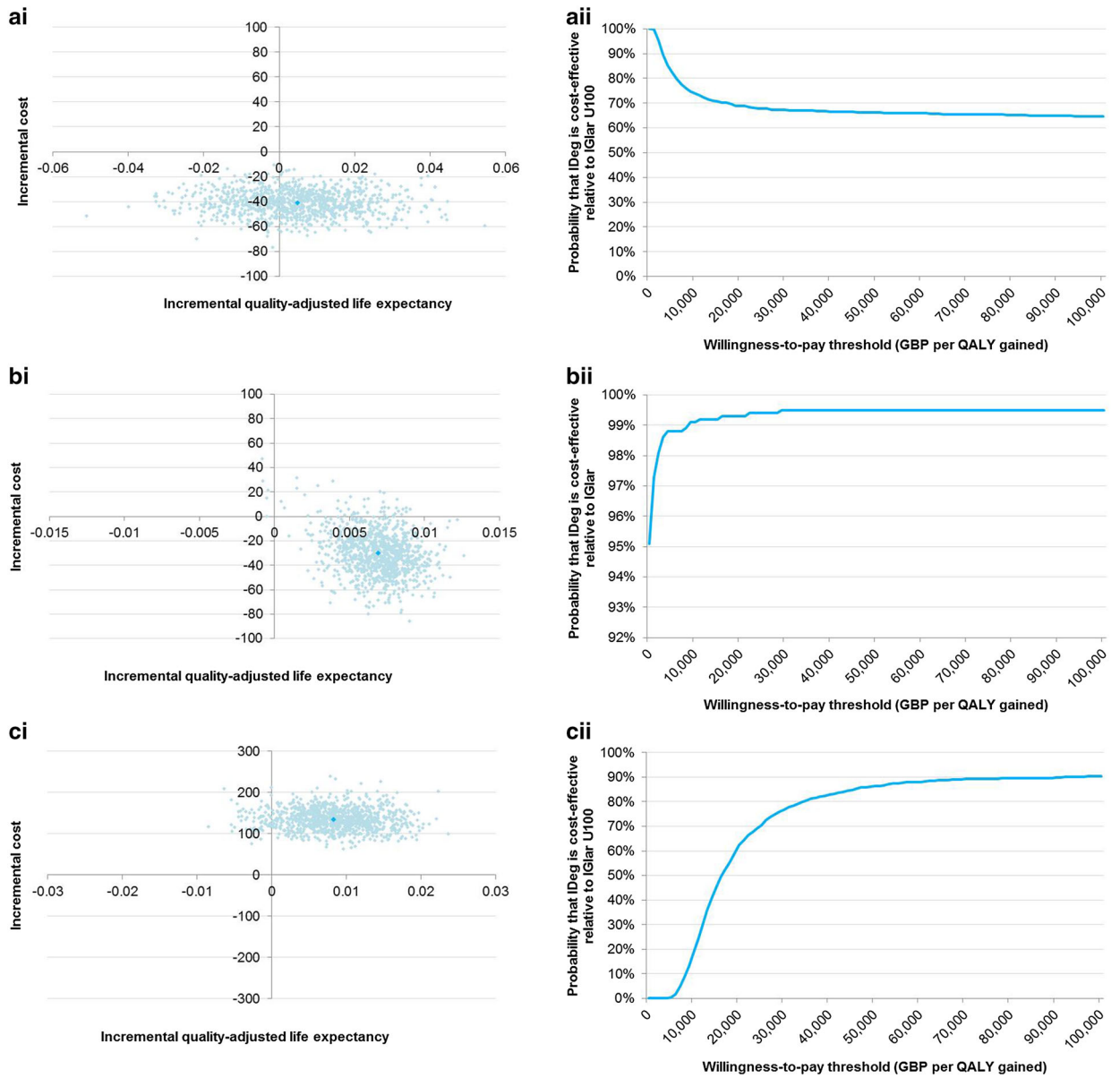

Fig. 2 PSA results: cost-effectiveness scatterplots and acceptability curves

The cost-effectiveness acceptability curve (CEAC) shows that the chances of IDeg being cost-effective are approximately 65–70% at any willingness to pay threshold in excess of £10,000.

In $T2DM_{BOT}$, the results indicate that IDeg is dominant over IGlar U100, with the vast majority of simulations resulting in a positive QALY gain and a decrease in costs (Fig. 2b). The CEAC shows that in excess of 99% of the results are cost-effective at a willingness to pay threshold of just £10,000.

In $T2DM_{B/B}$, the results indicate that IDeg increases the annual per-patient cost in this group of patients whilst also providing a benefit in QALYs in the majority of simulations

(Fig. 2c). The CEAC shows that IDeg is cost-effective, with a probability of 62.5% and 76.8% at a willingness to pay threshold of £20,000 and £30,000, respectively.

DISCUSSION

This simple, short-term cost-utility analysis suggests that the use of IDeg is highly likely to be cost-effective compared with IGlar U100 in the UK. IDeg is dominant (i.e. both more effective and less costly) versus IGlar U100 in patients with T1DM and patients with $T2DM_{BOT}$, and is cost-effective versus IGlar U100 in patients with $T2DM_{B/B}$ (ICER £15,983/QALY). In T1DM, lower costs are primarily driven by lower insulin costs, as a result of a lower daily dose of IDeg. In $T2DM_{BOT}$, lower overall costs with IDeg are driven by lower costs of severe hypoglycaemic events, due to the significant reduction in the number of severe hypoglycaemic events with IDeg versus IGlar U100 in this patient group. Improvements in clinical outcomes in all three patient groups are a result of the reduced incidence of hypoglycaemic events.

Sensitivity analyses demonstrate that the results are robust and invariant to changes in most of the input parameters. In patients with T1DM and $T2DM_{BOT}$, the ICER remains dominant in the majority of analyses conducted. In patients with $T2DM_{B/B}$, the ICER remains below the threshold of £20,000–£30,000/QALY gained in almost all analyses. PSA shows that there is a high probability that IDeg will be cost-effective versus IGlar U100 in all three patient groups.

With a number of new insulin formulations on the market, decision-making based on clinical and economic evidence is essential, as healthcare providers aim to maximise health outcomes with restricted budgets. Scenario analyses were conducted to estimate cost-effectiveness versus two new-to-market basal insulin analogues. In the absence of a direct comparison between IDeg and these new comparators, the analyses were based on available data and plausible assumptions, and the results should be interpreted accordingly. In patients with T1DM and $T2DM_{BOT}$, IDeg is likely to be highly cost-effective versus IGlar biosimilar (Abasaglar®) and dominant to IGlar U300 (Toujeo®), and in $T2DM_{B/B}$, IDeg is cost-effective versus both comparators with ICERs below the £20,000/QALY gained threshold. IDeg has recently been approved by the Scottish Medicines Consortium and All Wales Medicines Strategy Group for the treatment of diabetes mellitus in adults in Scotland [41] and Wales [42], respectively.

Cost-effectiveness analyses of diabetes interventions are traditionally performed by estimating the long-term clinical consequences as a function of differences in glycaemic control. However, the treat-to-target clinical trial design enforces a similar level of glycaemic control across interventions, resulting in non-inferior and non-significant differences, and thus rendering long-term modelling based on HbA_{1c} differences inappropriate. This short-term approach focuses on the impact of other important aspects of insulin therapy such as hypoglycaemia and dosing, and enables economic evaluation of new insulin analogues based on data derived from treat-to-target studies. Although a short-term (1 year) time horizon is used, results are not only applicable for the cost-effectiveness of IDeg within the first year of treatment. As the model can be replicated for subsequent years, the outcomes represent the average annual cost-effectiveness.

This model has been previously used to evaluate the cost-effectiveness of IDeg versus IGlar U100 in patients with T1DM and T2DM. In this re-evaluation, a number of revisions were made to the modelling framework. As a consequence of the ultra-long duration of action, flat and stable action profile [10, 11], and lower variability over the day than IGlar U100 [12], there is evidence to suggest that titration and maintenance with IDeg is possible with fewer weekly SMBG tests [43]. Cost savings may therefore be made through the use of fewer SMBG tests with IDeg; however, a change in testing behaviour may take time to translate into clinical practice, so it was excluded from this re-evaluation. Similarly, if administration at the same time of day is not possible, the ultra-long and stable action profile of IDeg allows for flexibility of dosing time without

compromising efficacy or risk of hypoglycaemia. In the previous evaluation, an estimate of the utility benefit associated with the option of flexible dosing with IDeg was applied for the calculation of QALYs. This was excluded from the current re-evaluation in recognition that not all patients will benefit from this attribute, but it was included as a sensitivity analysis. The potential for flexible dosing may translate into additional economic value in patients who find it difficult to adhere to a strict dosing regimen (e.g. shift workers or frequent travellers), or those who rely on a carer to administer their insulin.

As with all modelling studies, the limitations of this study should be considered when putting the findings into context. Meta-analyses of clinical trial data are used in our model to increase the sample size and power of the parameter estimates derived from individual studies. However, it is assumed that the data collected in the clinical trials is replicated in routine clinical practice. The clinical trials used a treat-to-target approach, where insulin doses were titrated until the glycaemic target was achieved. In clinical practice, optimal glycaemic control may not be achieved for a variety of reasons, such as non-adherence or missed clinic appointments. However, the extensive sensitivity analyses suggest that the conclusions are robust and invariant to changes in a variety of alternative modelling assumptions.

Real-world studies are a valuable source of evidence and are increasingly being used to complement clinical trial data in the decision-making process. A study has evaluated the real-world cost-effectiveness of switching patients with T1DM ($n = 35$) to IDeg in clinical practice in the UK [15]. The long-term cost-effectiveness of IDeg versus IGlar U100 or insulin detemir in people with T1DM experiencing hypoglycaemia was evaluated using the IMS CORE Diabetes Model [44]. The model was run over a patient lifetime and the benefits and costs were discounted at 3.5%. Over a lifetime, treatment with IDeg is less costly and more effective than treatment with IGlar/insulin detemir (dominant). This is driven by a reduction in HbA_{1c} and the lower rate of hypoglycaemia [15]. This evaluation of real-world data supports that from the clinical trial programme, and indicates that IDeg is a cost-effective alternative to IGlar in patients experiencing problems with hypoglycaemia in clinical practice. The analysis was conducted using the old pack price of IDeg (£72.00/pack); thus, with the recent price reduction to £46.60/pack, IDeg represents even better value. Another study evaluated the cost-effectiveness of switching to IDeg from other basal insulins in people with T1DM ($n = 476$) using real-world evidence from Sweden [45]. The Core Diabetes Model was used to predict long-term outcomes, and the costs associated with treatment and long-term complications of diabetes were included. Again, the results of the analysis showed that IDeg was less costly than the patients' previous insulin treatment and was associated with improvements in health-related quality of life (dominant). Thus, for patients with T1DM in Sweden, switching to IDeg was cost-effective when compared with treatment with their prior insulin.

Another economic assessment which may be informative for decision makers is a budget impact analysis. A budget impact analysis estimates the financial consequences of adopting a new intervention for local, regional and national budgets. It identifies the size of the population affected by the intervention and the effect of implementation on costs over the short term. This study calculated the total cost per patient per year, comprisiing the annual pharmacy cost and the annual cost of hypoglycaemic events, for a patient with T1DM, $T2DM_{BOT}$ or $T2DM_{B/B}$ treated with IDeg or IGlar U100 (Table 4). These costs can be utilised to calculate the annual budget impact of treatment with IDeg or IGlar U100 for a defined local patient population, whereby the annual per patient cost is simply multiplied by the number of patients treated. The breakdown of costs in Table 4 allows the impact on different budgets to be calculated.

In phase 3a clinical trials, IDeg showed equivalent reductions in HbA_{1c} with a lower risk of hypoglycaemia versus IGlar U100 [13, 14]. The hypoglycaemia benefits of IDeg have also been reported in real-world clinical practice, with reductions of up to 90% observed in

patients switching to IDeg because of problems with hypoglycaemia on IGlar or insulin detemir [15]. Two phase 3b studies, SWITCH 1 and SWITCH 2, in patients with T1DM and T2DM, respectively, were designed to confirm the hypoglycaemia benefit observed with IDeg versus IGlar U100 in the phase 3a studies [46, 47]. These studies sought to investigate the efficacy and safety of IDeg in diabetes populations with an increased risk of hypoglycaemia and to assess the safety of IDeg in transfers from other basal insulins. IDeg demonstrated non-inferiority to IGlar U100 in glycaemic control (HbA_{1c}) in patients with T1DM and T2DM in these treat-to-target trials. Equivalent reductions in HbA_{1c} were achieved with a lower total daily insulin dose at end-of-trial, and with a lower risk of hypoglycaemic episodes versus IGlar U100 [46, 47]. An economic evaluation of the data from these clinical trials would be beneficial to demonstrate the cost-effectiveness of IDeg in these high hypoglycaemia risk populations.

CONCLUSIONS

Based on this short-term economic model, IDeg is a cost-effective alternative to IGlar U100 for patients with T1DM and T2DM in the UK. Results also suggest that IDeg is likely to be cost-effective versus two new-to-market basal insulin analogues. IDeg may particularly benefit those suffering with hypoglycaemia while on other basal insulin analogues, or may prove useful to patients who would benefit from the additional flexibility.

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Data Availability. All data generated or analysed during this study are included in this published article/as supplementary information files.

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