

COST-EFFECTIVENESS ANALYSIS OF INSULIN DEGLUDEC COMPARED WITH INSULIN GLARGINE U100 FOR THE MANAGEMENT OF TYPE 1 AND TYPE 2 DIABETES MELLITUS – FROM THE SPANISH NATIONAL HEALTH SYSTEM PERSPECTIVE

Mezquita-Raya P¹, Darbà J², Ascanio M³, Ramírez de Arellano A⁴

¹Hospital Torrecardenas, Clínica San Pedro, Almería, Spain; ²Department of Economics. Universitat de Barcelona, Barcelona, Spain; ³BCN Health Economics and Outcomes Research S.L., Barcelona, Spain; ⁴HEOR Europe, Novo Nordisk, Madrid, Spain.

Correspondence to:

Josep Darbà

Department of Economics. Universitat de Barcelona, Diagonal 696, 08034 Barcelona, Spain

Tel. +34 934020110 / + 34 934021937

Fax +34 934039082

E-mail darba@ub.edu

Short title: Cost-effectiveness analysis of insulin degludec in type 1 and 2 diabetes mellitus patients in Spain

Key words: Diabetes type 1, diabetes type 2, Insulin degludec, Insulin glargine, hypoglycaemic episodes, costs, effectiveness, ICER

Abbreviations:

B/B - Basal Bolus

BOT - Basal oral therapy

CEAC - Cost-effectiveness acceptability curves

HRQoL – Health Related Quality of Life

IDeg - Insulin Degludec

IDet - Insulin Detemir

IGlar - Insulin Glargine

T1DM - Type 1 Diabetes Mellitus

T2DM - Type 2 Diabetes Mellitus

NHS - National Health System

PSA - Probabilistic Sensitivity Analysis

QALY - Quality Adjusted Life Year

Abstract

Aims: The objective of this study was to assess the cost-effectiveness of insulin degludec versus insulin glargine, from the Spanish NHS in three groups of patients.

Methods: A short-term cost utility model was developed to estimate effectiveness results in terms of the total number of hypoglycaemic events and their disutility impact throughout the year on the initial level of quality of life for patients in each treatment.

Results: Degludec was the dominant strategy for T2DM BOT and exhibited an incremental cost-effectiveness ratio of 52.70€/QALY and 11,240.88€/QALY for T1DM B/B and T2DM B/B, respectively. Lower costs are primarily driven by lower nocturnal and severe hypoglycaemic events, which were reduced versus IGLar. Improvements in clinical outcomes in all three patient groups are result of the reduced number of hypoglycaemic events showing 0.0211, 0.0328 and 0.0248 QALYs gained when compared to IGLar for T1DM B/B, T2DM BOT and T2DM B/B, respectively. Different scenario analyses showed that the ICERS were stable to plausible variations in the analysed parameters, except when the same number of SMBG for both treatments is used, with T2DM B/B showing an ICER over the accepted threshold.

Conclusion: This analysis demonstrates that degludec is a cost-effective option in the Spanish NHS, when used in patients currently treated with long-acting insulin.

1. INTRODUCTION

Diabetes mellitus accounted for approximately 1.3 million deaths in 2010 worldwide and was ranked at the 4th position in terms of mortality within chronic diseases [1]. In Spain, the number of diabetes cases has increased by 33.41% over the period from 2011 to 2013. 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 diabetes [2].

Diabetes is a chronic metabolic disease characterized by increased blood glucose levels. In people with type 1 diabetes mellitus (T1DM) the body stops making insulin because its immune system destroys the insulin producing beta cells in the pancreas for which they need to take insulin injections each day. Although it can occur at any age, this type of diabetes occurs more often in children and young adults [3]. The prevalence of T1DM in Spain ranges from 0.3 to 1.53 cases per 1,000 children younger than 15 years old [4]. Type 2 diabetes mellitus (T2DM) accounts for the other 90% of all cases, with approximately 60-90% of all T2DM cases being related to obesity. T2DM is a progressive condition, which can be controlled by healthy habits (e.g. diet, exercise, etc.) when being mild [5]. The progression of the disease depends on blood glucose levels and to keep these levels in the target range of the patient [5]. Eventually, patients with higher blood glucose levels will need medication to control them and diminish their resistance to insulin, which leads to a delay of their worsening condition [6]. In the end, all patients with T1DM will need insulin to control their diabetes, as well as most patients of T2DM as the disease progresses [6].

The use of basal insulin analogue of naturally produced insulin is associated with a higher risk of hypoglycaemia compared with new basal insulin analogues with improved pharmacodynamics and pharmacokinetic profiles. Hypoglycaemias have demonstrated to have several effects on the patients' quality of life and management of his/her condition [7]. Hypoglycaemia is a real medical emergency which requires rapid recognition and treatment to prevent organ and brain damage. The diversity of symptoms depends on severity and duration

of hypoglycaemia and varied from behavioural changes to autonomic activation to altered cognitive function to seizures or coma. The long and short term complications include neurologic damage, trauma, cardiovascular events and death [8]. Severe untreated hypoglycaemia can cause a significant economic [9] and personal burden. Therefore, the objective of diabetes treatment is to control glucose levels and at the same time to avoid or lower the risk of hypoglycaemic events.

Several basal insulin treatments are available on the market, with insulin glargine (IGlar) being one of the most commonly used basal since it has been used for 55 years of insulin treatment of patients with T1DM and T2DM in Spain [10]. Its pharmacological action starts 1-3 hours after its administration, and lasts for 24 hours approximately [11]. In case of T1DM, IGlar should be administered with a short-acting insulin, while for T2DM patients, it is also administered with oral medication. A new product is the insulin degludec (IDeg), which mechanism is a basal insulin with an ultra-long duration of action (more than 42 hours) and a flat and stable action profile [12-14]. In phase 3a clinical trials IDeg showed equivalent reductions in HbA_{1c} with a lower risk of hypoglycaemia versus IGlar, and at a significantly lower daily dose when compared with IGlar in T1DM B/B (12% lower) and T2DM BOT (10% lower) [12-14].

The burden of diabetes including the humanistic and economic burden has shown to be high [1,15]. This chronic disease (especially T1DM) that can start at very young ages has a progressive pathology and lead to severe co-morbidities due to its impact at the vascular micro and macro level [16]. Moreover, the treatment of diabetes also has important side-effects that impair the patients' quality of life [9]. As healthcare resources are scarce and budgets restricted, clinical and economic evidence is crucial in order to optimize resource allocation and service delivery for patients.

The aim of this analysis was to evaluate the cost-effectiveness of IDeg versus IGlár in patients considered appropriate for treatment with a long acting insulin analogue from the perspective of the Spanish National Health System. For the purpose of the current analysis a short-term 1-year approach has been used that focuses on the impact of other important aspects of insulin therapy such as hypoglycaemia and dosing, allowing an economic assessment of new insulin analogues based on data derived from phase 3b trials.

2. METHODS

2.1 Model specifications and participants

The current cost-effectiveness (CE) model compares IDeg once-daily (OD) with IGlár once-daily (OD) in subgroups of patients including different treatment regimens: 1) patients with T1DM who are considered appropriate for basal-bolus (B/B) insulin treatment, 2) patients with T2DM who are considered appropriate for B/B insulin treatment and 3) patients with T2DM who are considered appropriate for basal supported oral therapy (BOT) with insulin treatment.

The CE model was developed in Microsoft Excel 2010 (Microsoft Corporation, Redmond, WA, USA) combining the incremental cost of the intervention expressing the benefit it produces in terms of quality-adjusted life-years (QALYs) in order to allow the comparison of the two types of insulin IDeg and IGlár in the three different groups of diabetic patients. The main outcome measure, in this cost-effectiveness analysis (CEA), was the incremental cost-effectiveness ratio (ICER). The ICER reflects the cost per QALY gained, and allows the comparison between the two treatments (IDeg and IGlár). In Spain, no official ICER threshold is available; although an ICER threshold of €30.000 per QALY gained is considered to be an acceptable value for money in Spain [17].

Costs and benefits in the current CEA were analysed over a one-year time-horizon from the perspective of the Spanish NHS. The data used came from clinical trials that were designed as treat-to-target, with insulin doses adjusted in order to achieve similar HbA_{1c} levels between treatments. Thus, long-term modelling was not meaningful. This short-term approach was

used to match the annualised steady state time period of the IDeg as studied in clinical trials, for which no discounting rates in this model were applied. This short-term model has been previously published [18-21]. Here, we used the same modelling framework, with updated data inputs.

A cost-utility model based on the reduction of health related quality of life (HRQoL) due to hypoglycemic events [22] and self-monitoring blood glucose tests [23] was used to calculate QALYs, as shown in Figure 1.

The analysis was based on clinical trial data including patients with T1DM and T2DM in which IDeg was administered OD and IGl_{ar}, also administered OD, was the comparator of interest [24]. Data was based on six phase 3 clinical trials grouped as follows: T1DM patients treated with B/B, T2DM patients treated with BOT and T2DM patients treated with B/B.

The total number of patients included was 3,889 of which 958 were T1DM patients and 2,931 were T2DM patients. The T1DM patients included were adults (aged ≥ 18 years) with clinically diagnosed T1DM and treated with B/B regimen for at least one year, HbA_{1c} $\leq 10\%$ and BMI ≤ 35 kg/m². Subjects with recurrent severe hypoglycaemia (>1 severe event during the last year), hypoglycaemic unawareness, or significant concomitant illness were excluded. The T2DM patients were divided into two groups, the BOT treated patients and the B/B treated patients. The T2DM patients treated with BOT included in the study were adults with clinically diagnosed T2DM for ≥ 6 months, HbA_{1c} between 7.0 and 10.0% and BMI ≤ 40 kg/m² (two trials) or ≤ 45 kg/m² (one trial). Subjects with significant concomitant illness and subjects with recurrent severe hypoglycaemia or hypoglycaemic unawareness were excluded. Finally, the T2DM patients treated with B/B included in the analysis were adults with clinically diagnosed T2DM for at least 6 months who had been treated with any insulin regimen for at least 3 months with or without oral antidiabetic drug before screening, and had HbA_{1c} concentrations of 7.0-10.0% and a BMI of 40.0kg/m² or less. Patients were excluded if they had taken glucagon-like peptide-1 receptor agonists or rosiglitazone within the previous 3 months.

Patients with significant concomitant illness and subjects with recurrent severe hypoglycaemia or hypoglycaemic unawareness were also excluded.

2.2 Model data

Clinical data

1. Insulin doses. Units of basal insulin used per day for IGl_r for the three subgroups of patients were estimated based on the data from the meta-analysis [24]. Vora et al., 2014 performed a patient-level meta-analysis with the seven phase 3a clinical trials that compared IDeg with IGl_r. The clinical trials were divided in three categories (T1DM B/B, T2DM BOT and T2DM B/B) and the endpoints analysed were the HbA_{1c} levels, fasting plasma glucose, insulin dose and three different hypoglycaemia rates (non-severe nocturnal events non-severe daytime events and severe events).

The IGl_r dose and the IDeg/IGl_r dose ratios for T1DM patients treated with B/B insulin and T2DM patients treated with B/B and BOT were derived from the meta-analysis [24] to estimate corresponding IDeg doses (Table 1). The doses used may be higher than the doses used in clinical practice, but using these doses seen in the treat-to-target trials allows for a fair comparison.

To obtain the corresponding IDeg basal dose for T1DM B/B patients the calculation was as follows: 1) the IGl_r basal dose for T1DM B/B patients was 33.10units/day; 2) the IDeg/IGl_r basal dose ratio was 0.87; 3) the IDeg basal dose for T1DM B/B patients was $33.10 \times 0.87 = 28.80$ units/day. In patients with T2DM treated with B/B and BOT insulin, the estimation of IGl_r OD was based on a randomised, 52-week, treat-to-target trial comparing insulin detemir (IDet) with insulin IGl_r by Rosenstock et al., 2007 [25]. After 52 weeks the once-daily dose of IDet (n=102) was 0.52 U/kg. Therefore, dose IDet (one injection) was 51.70units/day. The mean dosage to achieve glucose goal was the same with both insulins: IDet and IGl_r for which similar calculations applied to IGl_r as for IDet [26]. Based on that, the corresponding doses for

IGlar OD in T2DM patients treated with B/B and BOT insulin were 66.60 units/day and 51.70 units/day, respectively (Table 1).

2. Hypoglycaemia Event Rates. Frequency and event rates for both severe hypoglycaemic event (SHE) and non-severe hypoglycaemic events (NSHE) were derived from a Spanish observational study [27]. Baseline hypoglycaemic event rates associated with IGLar were considered to be similar as those reported in the Spanish observational study (Orozco-Beltrán et al., 2014). This local study informed about patient-reported rates of NSHE, SHE, hypoglycaemia awareness and reporting hypoglycaemia to general practitioners or specialists in Spain [26]. Patients included T1DM B/B and T2DM B/B and BOT treated and other treated patients <15 years old via existing panels to complete four questionnaires at 7-day intervals. NSHE data were reported for a 7-day recall period; SHE was reported as events in the last year. 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. In total 630 patients (47% were T1DM and 53% were T2DM) completed 2238 patient weeks.

The event rates for IDeg were determined based on the relative event ratios (IDeg/IGlar) derived from the pre-specified meta-analysis based on the phase 3a program of hypoglycaemia [13] (Table 2). For the purpose of this CEA, the rates of hypoglycaemia were divided in three mutually exclusive groups of hypoglycaemia in order to avoid potential double counting of events including severe events, daytime non-severe events and nocturnal non-severe events.

To estimate the number of non-severe nocturnal hypoglycaemic events the calculation was as follows: 1) the number non-severe nocturnal hypoglycaemic events related to IGLar were equal to 22.6 per patient per year; 2) the relative event ratio (IDeg/IGlar) (only significant differences were used for the modelling) was 0.83 [27]; 3) the number of non-severe nocturnal hypoglycaemic events related IDeg was $22.6 \times 0.83 = 18.76$ per patient per year.

3. Self-Monitored Blood Glucose Testing and needles. The number of self-monitored blood glucose tests (SMBG) per week associated with IGlAr was based on the recommended titration schedule for IGlAr in T1DM B/B and T2DM BOT and B/B insulin treated patients (Table 3) [18].

The patients treated with IDeg are able to monitor their blood glucose more efficiently and use fewer SMBG tests per week because the IDeg medication has a long half-life and a flat, stable profile in steady state with low variability over the day [18]. Consequently, IDeg has the potential to be monitored and titrated with less number of SMBG tests associated with basal injections per week for T1DM B/B and T2DM [28]. Lastly, the number of needles is equal for each BOT or B/B regimens (Table 3).

2.3 Cost data

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

1. Cost of Insulin, Needles and SMBG tests. Costs of insulin were based on the corresponding public sale prices (PSP) plus VAT for each type of insulin and were taken from the Spanish Medication Database [29]. In order to adjust the analysis to the current situation in the Spanish market, the price of the biosimilar of glargine (Abasaglar) was used as the price of the comparator. Costs of needles and SMBG test strips and lancets were based on prices from a tender resolution of by the Spanish Ministry of Health, Social Services and Equality [30] (Table 4).

2. Cost of Hypoglycaemic Events. The direct cost associated with a hypoglycaemic event consisted of the direct cost to treat a single hypoglycaemic 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 €726.93 in Euros of 2016 for both patients with T1DM and T2DM. The cost is based on the average weight obtained from an observational study by Hammer et al., 2009 [31]. These costs for a severe hypoglycaemic 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., 2011 based on patient reported experiences [7] (Table 3).

According to the patients' reports, there were no differences between IDeg and IGlir with respect to the proportion of patients contacting a hospital/HCP or in the number of SMBG test strips used following a hypoglycaemic event. The behaviour after a hypoglycaemic event was assumed to be similar, irrespective of therapy. Hence, the difference in treatment related costs originated only from the difference in hypoglycaemia events rate and not from the cost per event. Related resource use for an average severe or non-severe hypoglycaemic event for the three groups of patients is displayed in Table 3.

2.4 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 hypoglycaemic event. In this approach, the initial quality of life at the beginning of the year was reduced according to the number of hypoglycaemic events occurred throughout the year in each treatment group. The relation between the number of hypoglycaemic events and the reduction of a patient's average HRQoL followed a diminishing marginal impact pattern.

The corresponding disutility for a hypoglycaemic event was derived from a recent Time-Trade-Off (TTO) study [22]. A disutility of 0.0565 was reported for a severe event and disutilities of 0.0041 and 0.0067 for non-severe daytime and non-severe nocturnal events, respectively [22].

2.5 Sensitivity Analysis

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

One-Way Sensitivity Analysis

The parameters varied in the one-way sensitivity analysis for all three groups of patients were:

1. No difference in insulin dose;
2. No difference in non-severe day-time hypoglycaemia;
3. No difference in non-severe nocturnal hypoglycaemia;
4. No difference in severe hypoglycaemia;
5. Hypoglycaemic events disutilities -50%;
6. Hypoglycaemic events disutilities +50%;
7. Two glargine injections per day;
8. No difference in SMBG tests;
9. Cost of severe hypoglycaemia -50%;

Probabilistic Sensitivity Analysis (PSA)

The PSA varies simultaneously, within a plausible range, all model parameters and estimates the certainty that the intervention in question is cost-effective at different thresholds of cost-effectiveness. The standard errors around the parameters were used and a lognormal distribution around the rate-ratios and normal distributions around continuous variables were assumed 1000 iterations were used to run the PSA.

3. RESULTS

In T1DM B/B, total costs for IDeg treatment are calculated at €1,764.24 per patient per year, which is €1.11 (0.06%) higher than for the IGLar treatment (Table 5). The costs of hypoglycaemic events are almost unvaried since only the nocturnal NSHE showed statistically significant changes, while daytime NSHE and SHE remained unchanged. IDeg is associated with a QALY gain of 0.0211 compared with IGLar because of the less number of nocturnal NSHE related to IDeg. The ICER obtained for IDeg compared to IGLar was 52.70€/QALY gained, a value below the cost-effectiveness threshold considered in Spain (Table 5).

In T2DM BOT, the total cost per patient per year related to IDeg was €727.15, of which more than 85% is insulin and needles costs (Table 5). Total costs were €93.95 lower than in the IGLar treatment due to the lower number of SHE with IDeg versus IGLar that led to less costs of SHE. Because of the significantly lower number of nocturnal NSHE and SHE, IDeg is associated with a QALY gain of 0.0382 versus IGLar. Thus, IDeg is the dominant treatment, as it is more effective and less costly than IGLar (Table 5).

In T2DM B/B, total cost in the IDeg treatment is €2,102.01, which is €278.93 (13.3%) higher than for the IGLar treatment. In this setting, 72% of the costs are due to insulin and needles costs. IDeg is associated with fewer nocturnal and daytime NSHE, which led to QALY gain of 0.0248 versus IGLar. The ICER obtained for IDeg versus IGLar was 11,240.88€/QALY gained, a value below the cost-effectiveness threshold considered in Spain.

Sensitivity Analysis

The univariate sensitivity analysis showed that the ICERs were stable to plausible variations in non-severe day-time and nocturnal hypoglycaemia event rates, severe hypoglycaemia costs, but also were stable when the insulin dose is considered to be the same for both treatments (IDeg and IGLar). Further, when two IGLar injections per day were assumed, the analysis presented dominant results for IDeg versus IGLar for the three treatment regimens subgroups: T1DM B/B, T2DM BOT and T2DM B/B (Table 6). Likewise, IDeg showed to be the dominant strategy compared to IGLar for patients with T2DM BOT under alternative scenarios, except when there is no difference in severe hypoglycaemia event rates. Besides, it is noteworthy that the most sensitive parameter was the number of SMBG, which affected all the treatment subgroups. The most influenced subgroup was the T2DM B/B which showed an ICER higher than the cost-effectiveness threshold.

The cost-effectiveness acceptability curves display the increasing probability that IDeg is more cost-effective than IGLar given a threshold that reflects the willingness to pay for this treatment, in this case 30,000 Euros per QALY gained (See Figures 2-4).

4. DISCUSSION

All in all, the economic evaluation is a usual practice in addition to the clinical analysis. Given that diabetes is one of the most expensive chronic diseases [32], economic modelling should be a tool in order to allocate resources in a more consistent and transparent way. Specifically, this study investigated the cost-effectiveness of IDeg compared with IGLar in patients with diabetes treated with once-daily basal insulin injections. The analysis was conducted from the perspective of the Spanish National Healthcare System for three specific subgroups of patients. The results for the IDeg therapy are strongly dominant relative to the IGLar in T2DM BOT treatment regimen.

The present study follows a similar methodology applied by Evans et al., 2013 [22] and sources for the patient population were also meta-analysis; hence, selection bias may be present and it can limit the transferability of the analysis for the whole Spanish population.

The univariate sensitivity analysis confirmed the consistency of the model. Given that hypoglycaemic events are associated with the use of SMGB tests, most of the univariate analyses include a reasonable variation in these variables. Interestingly, despite the variation of values could favour IGLar, the IDeg treatment showed to be the dominant strategy compared to IGLar for the T2DM BOT treatment regimen subgroup.

It is also noteworthy to mention the assumption that only hypoglycaemia confirmed by SMGB utilization have been taken as a hypoglycaemic event. However, it is reasonable to think patients in real-life may need healthcare attention and use additional SMBG tests when suffering neuroglycopenic symptoms, whose number could be underestimate.

Despite the utilization of the IGLar therapy was applied according to the prescription that optimizes the efficacy of this treatment, higher percentage of hypoglycaemic events was reported associated with its utilization. Given these very positive results, an analysis with real-world data potentially would lead to similar conclusions.

A clear advantage of the current analysis is the transparency and simplicity of the model used to assess cost-effectiveness. Most of the published cost-effectiveness analyses of type 1 and 2 diabetes treatments have used a long-term perspective to evaluate clinical and cost outcomes over patient lifetime [33-36]. A long-term approach is consistent with the diabetes progression, with diabetes-related complications having a significant impact on QoL and medical costs. To achieve glycaemic control is the main objective to minimize the complications risk over patient lifetime. There is growing evidence that, with the appropriate titration, alternative insulin treatments can be used to achieve a good glycaemic control [37-39]. For that reason, the current study has assessed the cost-effectiveness with a short-term approach that focuses on the impact of hypoglycaemia and dosing, and enables economic evaluation of new insulin analogues based on data derived from treat-to-target studies. Although a one-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 following years, the outcomes represent the average annual cost-effectiveness.

Commonly, the CE analysis has some limitation and it is not easy to include societal cost [40], such as future cost [41] associated with the diabetes' progression. This lack of information might distort the results, underestimating the benefits of an efficient treatment. For example, the inclusion of reduction of absenteeism caused by hypoglycaemic events or the higher likelihood that patients adhere to the treatment are values that may increase the cost-effectiveness ratio favouring of IDeg [5,9,17].

As with all modelling studies, the limitations of this study should be considered when putting findings into context. Meta-analyses of different clinical trials data are used in this model to increase the sample size and the power of the parameters estimated from the different individual studies. However, it is assumed that data from clinical trials is replicated in daily clinical practice. The clinical trials used a treat-to-target approach, where insulin doses were titrated until the targeted HbA_{1c} level was achieved. In clinical practice, optimal glycaemic

control may not be achieved for a variety of reasons, such as missed clinical appointments or non-adherence. Moreover, in the observational study [27] used to obtain data for the frequencies of hypoglycaemic events, has been observed that the frequency of NSHE in T1DM is twice the frequency of NSHE in T2DM. It has been suggested that the risk of hypoglycaemia in T2DM patients treated with insulin increases with longer diabetes duration [42] and Henderson et al [43] reported that NSHE frequency in T2DM patients reached the same level as in T1DM patients after 10 years of insulin treatment. In the observational study only the 32% of T2DM patients has received insulin for over 10 years which may partly explain the lower frequency of NSHE.

Our approach to investigating the true ICER of IDeg versus IGlax is quite static and do not reflect the plausible reduction of the risk of hypoglycaemia [44,45] that may influence a more efficient dosage, thus influence the number of glucose control could diminish the burden of the disease and cost-effectiveness ratio could be even more positive.

5. CONCLUSIONS

The potential improvements in quality of life associated to Degludec have been confirmed. IDeg represents a highly cost-effective option compared to IGlax in patients under three alternative regimens T1DM B/B, T2DM BOT and T2DM B/B, even when the price of the biosimilar is used. Further, the IDeg showed to be the dominant strategy (less costs and higher effectiveness) compared to IGlax in patients with once-daily basal insulin injections in T2DM BOT treatment regimen.

6. KEY ISSUES

- Diabetes is a chronic disease that can start at very young ages and has a progressive pathology. Diabetic patients lead to severe co-morbidities due to diabetes impact at the vascular micro and macro level. Moreover, the treatment of diabetes also has important side-effects that impair the patients' quality of life.

- Several basal insulin treatments are available on the market, being insulin glargine one of the most commonly used basal. Insulin degludec is a new product, which mechanism is a basal insulin with an ultra-long duration of action and a flat and stable action profile.
- Insulin degludec showed equivalent reductions in HbA_{1c} with a lower risk of hypoglycaemia versus insulin glargine, and at a significantly lower daily dose when compared with insulin glargine.
- This paper demonstrates that insulin degludec is a cost-effective therapy compared to insulin glargine in type 1 and type 2 diabetic patients from the Spanish NHS perspective. Besides, potential improvements in quality of life associated to insulin degludec have been confirmed.
- This study provides information related to the cost-effectiveness of insulin degludec compared to insulin glargine in type 1 and type 2 diabetic patients.

7. ACKNOWLEDGEMENT

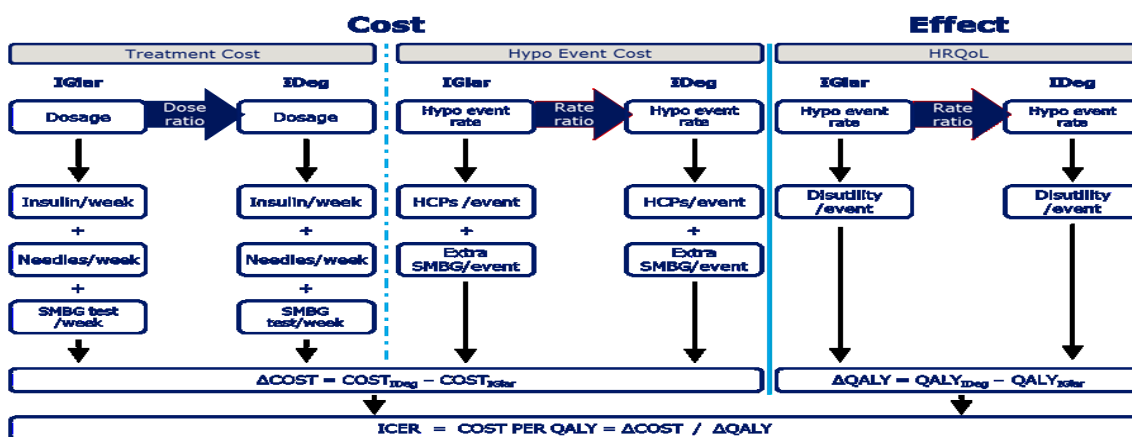
BCN Health Economics and Outcomes Research S.L. provided statistical analysis and editorial support.

8. DECLARATION OF INTEREST

This study was sponsored by Novo Nordisk Pharma SA. PMR is employed by Hospital Torrecardenas. JD is employed by the University of Barcelona. MA is an employee of BCN Health Economics & Outcomes Research S.L., Barcelona, Spain, an independent contract health economic organization. ARA is employed by Novo Nordisk Pharma SA. The authors have no other relevant affiliations or financial involvement with any organization or entity with a financial interest in or financial conflict with the subject matter or materials discussed in the manuscript apart from those disclosed.

Figure 1. Schematic model: utilities from hypoglycaemic events

Utilities from hypoglycaemic events



Note: This model calculated treatment costs including insulin, needles and costs associated with self-monitored blood glucose (SMBG) testing and the costs associated with for both insulin degludec (IDeg) and insulin glargine (IGlar). Abbreviations: Δ = Change in; HCP = Healthcare professional; HRQoL = Health-related quality of life; ICER = Incremental cost-effectiveness ratio; IDeg = Insulin degludec; IGlar = Insulin glargine; QALY = Quality-adjusted life year; SMBG = Self-Monitored Blood Glucose.

Table 1. Insulin doses in units per day and dose ratios

		T1DM B/B	T2DM BOT	T2DM B/B
		Insulin units/day	Insulin units/day	Insulin units/day
Basal	Insulin			
	IDeg OD	28.80	46.53	71.93
	IGlar OD	33.10	51.70	66.60
Bolus	IAsp (IDeg OD)	30.80	-	72.70
	IAsp (IGlar OD)	35.00	-	72.70
		Ratio (SE)	Ratio (SE)	Ratio (SE)
Basal	IDeg OD/IGlar OD	0.87 (0.02)	0.90 (0.03)	1.08 (0.03)
Bolus	IAsp (IDeg OD)/IAsp (IGlar OD)	0.88 (0.03)	-	1.00*(0.05)

Abbreviations: B/B = Basal bolus; BOT = Basal oral therapy; IDeg = Insulin degludec; IDet = Insulin detemir; IGlar = Insulin glargine; OD = Once-daily; T1DM = Type 1 diabetes; T2DM = Type 2 diabetes; SE: standard error.

*This is not significant and therefore set to 1.

Table 2. IDeg versus IGlar: Relative hypoglycaemic event rates per patient/year (standard error) per treatment regimen

		T1DM B/B	T2DM BOT	T2DM B/B
Daytime NSHE	Frequency	65.40	12.74	28.79
	IDeg	1 (0.071)	1 (0.093)	0.83* (0.095)
	IGlar	1	1	1
Nocturnal NSHE	Frequency	22.60	5.53	13.31
	IDeg	0.83* (0.096)	0.64* (0.152)	0.75* (0.137)
	IGlar	1	1	1
SHE	Frequency	0.90	0.30	0.30
	IDeg	1 (0.258)	0.14* (0.819)	1 (0.329)
	IGlar	1	1	1

Abbreviations: B/B = Basal bolus; BOT = Basal oral therapy; IDeg = Insulin degludec; IGlar = Insulin glargine; NSHE = Non-Severe Hypoglycaemic event; SHE = Severe Hypoglycaemic event; T1DM = Type 1 diabetes; T2DM = Type 2 diabetes.

Note: in case of non-significant results, a relative rate of 1 was used in the calculation.

*Statistically significant differences ($p < 0.05$).

Table 3. Number of SMBG tests and needles associated with IDeg once-daily and IGlar once-daily

		T1DM B/B		T2DM BOT		T2DM B/B	
		IDeg OD	IGlar OD	IDeg OD	IGlar OD	IDeg OD	IGlar OD
Number of SMBG tests/week	Total	25	28	4	7	25	28
	Basal injections	4	7	4	7	4	7
	Bolus injections	21	21	-	-	21	21
Number needles	Bolus injections/day	1	1	1	1	1	1
Number of additional SMBG tests per hypoglycaemia	NSHE daytime	3	3	-	-	3	3
	NSHE nocturnal	5.32	5.32	5.32	5.32	5.32	5.32
	SHE	5.32	5.32	5.32	5.32	5.32	5.32

Abbreviations: B/B = Basal bolus; BOT = Basal oral therapy; IDeg = Insulin degludec; IGlar = Insulin glargine; OD = Once-daily; SMBG = Self-Monitored Blood Glucose; T1DM = Type 1 diabetes; T2DM = Type 2 diabetes.

Table 4. 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	1500	€ 0.0353
		IGlar	€ 36.90	1500	€ 0.0246
	Bolus	IAsp	€ 27.90	1500	€ 0.0186
	Resource	Pack cost	Units per pack size	Price per unit	
Needles †			€ 6.26	100	€ 0.06
SMBG tests ‡		Test strip	€ 20.00	100	€ 0.20
		Lancet	€ 10.00	200	€ 0.05
		SMBG test	-	-	€ 0.25

Abbreviations: IAsp = Insulin aspart; IDeg = Insulin degludec; IGlar = Insulin glargine; SMBG = Self-Monitored Blood Glucose Testing.

*Based on Spanish Medication Database BOT plus web 2013

†It is assumed that the needles for IDeg and IGlar are similar. It is assumed that all patients use a new needle for every injection as recommended.

‡The unit cost of one SMBG test is calculated as the price of one test strip plus one lancet.

Table 5. Incremental cost-effectiveness results for patients treated once-daily with basal IGlar

	T1DM B/B		T2DM BOT		T2DM B/B	
	IDeg	IGlar	IDeg	IGlar	IDeg	IGlar
Cost (€)						
Basal injections	371.29	297.41	599.93	464.53	927.39	598.41
Bolus injections	209.24	237.78	0.00	0.00	493.90	493.90
Needles	91.46	91.46	22.86	22.86	91.46	91.46
SMBG test	362.12	365.25	52.18	91.31	326.12	365.25
NSHE daytime	86.98	86.98	16.94	16.94	31.78	38.28
NSHE nocturnal	24.91	30.01	4.71	7.35	13.28	17.70
SHE	654.24	654.24	30.53	218.08	218.08	218.08
Total	1,764.24	1,763.13	727.15	821.10	2,102.01	1,823.08
Δ Cost		1.11		-93.95		278.93
Δ QALY		0.0211		0.0382		0.0248
Incremental Cost-Effectiveness						
ICER		52.70		Dominant		11,240.88

All incremental cost-effectiveness ratio (ICER). IDeg = Insulin degludec, IGlar = Insulin glargine, QALY = Quality adjusted life years, SMBG = Self-Monitored Blood Glucose, NSHE = Non-Severe Hypoglycaemic event, SHE = Severe Hypoglycaemic event

Table 6. Univariate sensitivity analyses of CEA of IDeg vs. IGlar

IDeg vs. IGlar	T1DM B/B	T2DM BOT	T2DM B/B
Base case: "IGlar Once-Daily-Injection"	52.70€/QALY	Dominant	11,240.88€/QALY
No difference in insulin dose	4,034.68€/QALY	Dominant	8,472.27€/QALY
No difference in non-severe day-time hypoglycaemia	52.70€/QALY	Dominant	12,910.07€/QALY
No difference in non-severe nocturnal hypoglycaemia	355.87€/QALY	Dominant	14,051.88€/QALY
No difference in severe hypoglycaemia	52.70€/QALY	4,118.25€/QALY	11,240.88€/QALY
Hypoglycaemic events disutilities -50%	44.63€/QALY	Dominant	8,093.10€/QALY
Hypoglycaemic events disutilities +50%	59.16€/QALY	Dominant	14,052.78€/QALY
Two glargine injections per day	Dominant	Dominant	Dominant
No difference in SMBG tests	11,060.70€/QALY	Dominant	43,256.45€/QALY
Cost of severe hypoglycaemia -50%	52.70€/QALY	Dominant	11,240.88€/QALY

Abbreviations: IDeg = Insulin degludec, IGlar = Insulin glargine, QALY = Quality adjusted life years, SMBG = Self-Monitored Blood Glucose

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

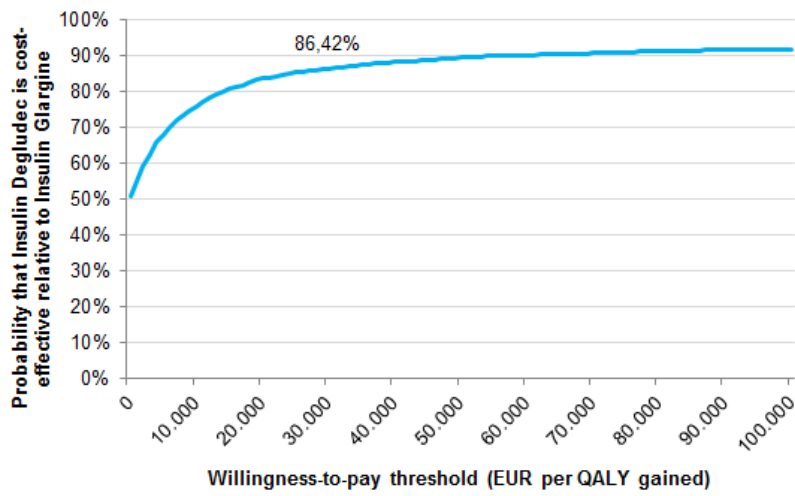


Figure 3. Cost-effectiveness acceptability curve for T2DM BOT

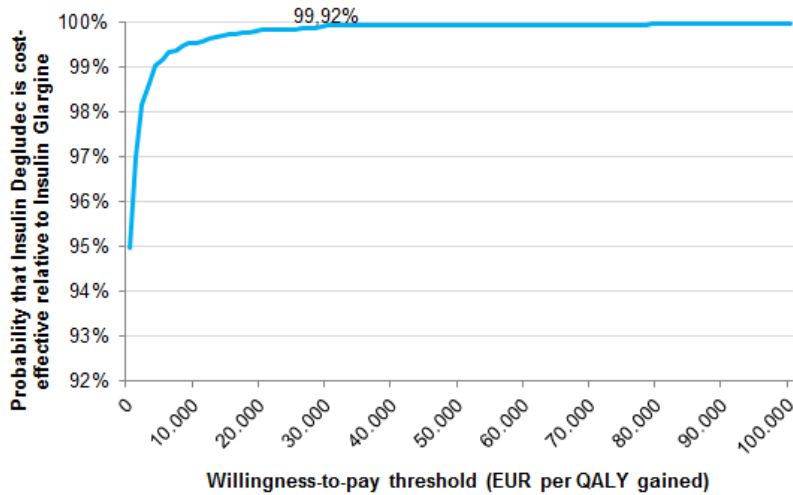
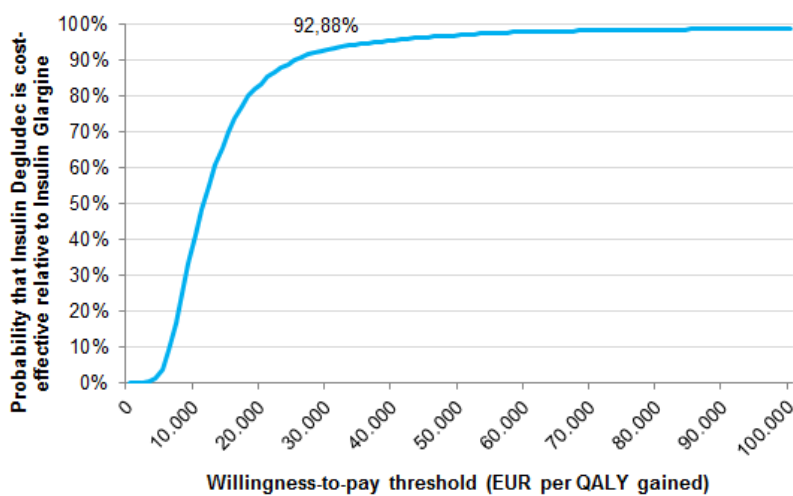


Figure 4. Cost-effectiveness acceptability curve for T2DM B/B



REFERENCES

Papers of special note have been highlighted as:

* of interest

** of considerable interest

1. WHO: Noncommunicable diseases country profiles 2014 [Internet]. Geneva (Switzerland): World Health Organization; 2014 [cited 2014 Sept 15]. Available from: <http://www.who.int/nmh/publications/ncd-profiles-2014/en/>.
2. Whiting DR, Guariguata L, Weil C, et al. IDF diabetes atlas: global estimates of the prevalence of diabetes for 2011 and 2030. *Diabetes Res Clin Pract*. 2011; 94(3):311-321.
3. Health at a Glance 2011: OECD Indicators [Internet]. OECD iLibrary; 2011 [cited 2014 Sept 15]. Available from: http://www.oecd-ilibrary.org/sites/health_glance-2011-en/01/10/index.html;jsessionid=1agb3d4ehfyfy.x-oecd-live-01?itemId=/content/chapter/health_glance-2011-13-en&_csp_=e25d9e9cf4373302c9fcef4e6b64239f.
4. Giralt Muiña P, Ballester Herrera MJ, Palomo Atance E, et al. Estudio epidemiológico de la diabetes tipo 1, en menos de 15 años en Castilla-La Mancha [Epidemiological study of type 1 diabetes in less than 15 years in Castilla-La Mancha]. *An Pediatr (Barc)*. 2012; 76(2):83-91.
5. IMAGE project: Development and Implementation of a European Guideline and Training Standards for Diabetes prevention [Internet]. IMAGE project; 2010 [cited 2014 Sept 15]. Available from: <http://www.image-project.eu/>.
6. Guías Clínicas-Diabetes Mellitus [Clinical Guidelines-Diabetes Mellitus][Internet].Fisterra; 2014 [cited 2014 Sept 15]. Available from: <http://www.fisterra.com/guias-clinicas/diabetes-mellitus-tipo-2/#21311>.
7. Brod M, Christensen T, Thomsen TL, et al. The impact of non-severe hypoglycemic events on work productivity and diabetes management. *Value Health*. 2011; 14(5):665–671.
8. Control D, group CTR: Adverse events and their association with treatment regimens in the Diabetes Control and Complications Trial. *Diabetes Care* 1995, 18: 1415–1427.
9. Orozco-Beltrán D, Mezquita-Raya P, Ramírez de Arellano A, et al. Incidence and frequency of Patient-Reported Hypoglycaemic Events in Spain. Poster submitted to ADA Congress; 2013 June 21; Chicago (USA).
10. La sociedad Española de Diabetes analiza el uso de la insulina glargina [The Spanish society of Diabetes analyses the use of insulin glargine][Internet]. Fundación Diabetes;

- 2004 [cited 2014 Sept 15] Available at: www.fundaciondiabetes.org/upload/noticias/3427/71.pdf.
11. Principios activos: InsulinaGlargina [Active ingredients: Insulin Glargine] [Internet]. Vademecum; 2014 [cited 2014 Sept 15]. Available from: <http://www.vademecum.es/principios-activos-insulina+glargina-a10ae04>.
 12. Rodbard HW, Gough S, Lane W, et al. Reduced risk of hypoglycemia with insulin degludec versus insulin glargine in patients with type 2 diabetes requiring high doses of Basal insulin: a meta-analysis of 5 randomized begin trials. *Endocr Pract.* 2013; 20(4):285-292.
* A meta-analysis of phase 3a trials where IDeg showed equivalent reductions in HbA1c levels with lower risk of hypoglycaemia versus IGlar.
 13. Ratner R, Gough S, Mathieu C, et al. Hypoglycaemia risk with insulin degludec compared to insulin glargine in type 2 and type 1 diabetes: a pre-planned meta-analysis of phase 3 trials. *Diabetes Obes Metab.* 2013; 15(2): 175-184.
* A meta-analysis of phase 3a trials where IDeg showed equivalent reductions in HbA1c levels with lower risk of hypoglycaemia versus IGlar.
 14. Onishi Y, Iwamoto Y, Jib Yoo S, et al. Insulin degludec compared with insulin glargine in insuline-naïve patients with type 2 diabetes: A 26-week, randomized, controlled, Pan-Asian, treat-to-target trial. *J Diabetes Investig.* 2013; 4(6):605-612.
 15. Los costes de la diabetes, directamente relacionados con la existencia de complicaciones [The costs of diabetes, directly related to the existence of complications] [Internet]. *Economía de la Salud*; 2014 [cited 2014 Sept 15]. Available from: www.economiadelasalud.com/ediciones/.../analisiscostesdeladiabetes.pdf.
 16. Chaturvedi N. The burden of diabetes and its complications: trends and implications for intervention. *Diabetes Res Clin Pract.* 2007; 76(3): S3-S12.
 17. Sacristán JA, Oliva J, del Llano J, et al. What is an efficient health technology in Spain? *Gac Sanit.* 2002;16(4):334–343.
 18. Evans M, Wolden M, Gundgaard J, et al. Cost-effectiveness of insulin degludec compared with insulin glargine in a basal –bolus regimen in patients with type 1 diabetes mellitus in the UK. *J Med Econ.* 2015;18(1):56-68.
 19. Ericsson A, Pollock RF, Hunt B, et al. Evaluation of the cost-utility of insulin degludec vs insulin glargine in Sweden. *J Med Econ.* 2013;16(12):1442-1452.
 20. Evans M, Wolden M, Gundgaard J, et al. Cost-effectiveness of insulin degludec compared with insulin glargine for patients with type 2 diabetes treated with basal insulin- from the UK health care cost perspective. *Diabetes Obes Metab.* 2014;16(4):366-375.

21. Evans M, Chubb B, Gundgaard J. Cost-effectiveness of Insulin Degludec Versus Insulin Glargine in Adults with Type 1 and Type 2 Diabetes Mellitus. *Diabetes Ther.* 2017;8(2):275-291.
22. Evans M, Khunti K, Mamdani M, et al. Health-related quality of life associated with daytime and nocturnal hypoglycaemic events: a time trade-off survey of five countries. *Health Qual Life Outcomes.* 2013; 11(9):90.
* A Time-Trade-Off study that reported disutilities for hypoglycaemic events.
23. Simon J, Gray A, Clarke P, et al. Cost effectiveness of self monitoring of blood glucose in patients with non-insulin treated type 2 diabetes: economic evaluation of data from the DiGEM trial. *BMJ.* 2008; 336(7654): 1177-1180.
24. Vora J, Christensen T, Rana A, et al. Insulin degludec versus insulin glargine in type 1 and type 2 diabetes mellitus: a meta-analysis of endpoints in phase 3a trials. *Diabetes Therapy.* 2014; 5(2):435-446.
** A meta-analysis of seven phase 3a clinical trials from which insulin doses were estimated for this study.
25. Rosenstock J, Davies M, Home PD, et al. A randomised, 52-week, treat-to-target trial comparing insulin Detemir with insulin glargine when administered as add-on to glucose-lowering drugs in insulin-naive people with type 2 diabetes. *Diabetologia.* 2008; 51(3):408-416.
26. King AB. No Higher Dose Requirements with Insulin Detemir than Glargine in Type 2 Diabetes: A Crossover, Double-Blind, and Randomized Study Using Continuous Glucose Monitoring. *J Diabetes Sci Technol,* 2010; 4,(1):151-154.
27. Orozco-Beltrán D, Mezquita-Raya P, Ramírez de Arellano A, et al. Self-Reported Frequency and Impact of Hypoglycemic Events in Spain. *Diabetes Therapy.* 2014; 5(1):155–168.
**Spanish observational study from which frequency and event rates were derived for this study.
28. Philis-Tsimikas A, Brod M, Niemeyer M, et al. Insulin degludec once-daily in type 2 diabetes: simple or step-wise titration (BEGIN: once simple use). *Adv Ther.* 2013;30(6):607-622.
29. *BOT Plus web.* Base de Datos de Medicamentos del Consejo General de Colegios Farmacéuticos [Drug Database of the General Council of Pharmaceutical Colleges]. *BOT Plus*; [cited 2014 Jul 20]. Available from: <https://botplusweb.portalfarma.com/>
30. Data not published. Novo Nordisk Tender HUC-CA-022/10 Resolution Date 06/20/2011.

31. Hammer M, Lammert M, Mejias SM, et al. Costs of managing severe hypoglycaemia in three European countries. *J Med Econ.* 2009; 12:(4):281-290.
32. The role of B.I.R.O in implementing the diabetes EU Policy Recommendations. A policy document by the B.I.R.O EU Project Consortium [Internet]. BIRO; 2006 [cited 2014 Jul 20]. Accessible from: <http://www.biro-project.eu>
33. Yang L, Christensen T, Sun F, et al. Cost-effectiveness of switching patients with type 2 diabetes from insulin glargine to insulin detemir in Chinese setting: a health economic model based on the PREDICTIVE study. *Value Health.* 2012;15(1):S56-59.
34. Pfohl M, Schädlich PK, Dippel FW, et al. Health evaluation of insulin glargine vs NPH insulin in intensified conventional therapy for type 1 diabetes in Germany. *J Med Econ.* 2012;15(2):14-27.
35. Pollock RF, Curtis BH, Valentine WJ. A long-term analysis evaluating the cost-effectiveness of biphasic insulin lispro mix 75/25 and mix 50/50 versus long-acting basal insulin analogs in the United States. *J Med Econ.* 2012;15(4):766-775.
36. Kamble S, Schluman KA, Reed SD. Cost-effectiveness of sensor-augmented pump therapy in adults with type 1 diabetes in the United States. *Value Health.* 2012;15(5):632-638.
37. Holman RR, Thorne KI, Farmer AJ, et al. Addition of biphasic, prandial, or basal insulin to oral therapy in type 2 diabetes. *N Eng J Med.* 2007;257(17):1716-1730.
38. Horvath K, Jeitler K, Berghold A, et al. Long-acting insulin analogues versus NPH insulin (human isophane insulin) for type 2 diabetes mellitus.
39. Farcasiu E, Ivanyi T, Mozejko-Pastewka B, et al. Efficacy and safety of prandial premixed therapy using insulin lispro mix 50/50 3 times daily compared with progressive titration of insulin lispro mix 75/25 or biphasic insulin aspart 70/30 twice daily in patients with type 2 diabetes mellitus: a randomized, 16-week, open-label study. *Clin Ther.* 2011;33(11):1682-1693.
40. Poley MJ, Stolk EA, Tibboel D, et al. The Cost-Effectiveness of Treatment for congenital diaphragmatic Hernia. *J Pediatr Surg.* 2002; 37(9):1245-1252.
41. Gaber AM, Phelps CE. Future cost and the future of cost-effectiveness analysis. *J Health Econ.* 2008; 27(4): 819-821.
42. Donnelly LA, Morris AD, Frier BM, et al. Frequency and predictors of hypoglycaemia in Type 1 and insulin-treated Type2 diabetes: a population based study. *Diabet Med.* 2005;22(6):749-755.
43. Henderson JN, Allen KV, Deary IJ, et al. Hypoglycaemia in insulin-treated Type 2 diabetes: frequency, symptoms and impaired awareness. *Diabet Med.* 2003;20(12):1016-1021.

44. Ahrén B. Avoiding hypoglycemia: a key to success for glucose-lowering therapy in type 2 diabetes. *Vasc Health Risk Manag.* 2013; 9:155-163.
45. Henderson JN, Allen KV, Deary IJ, et al. Hypoglycemia in insulin-treated Type 2 diabetes: Frequency, symptoms and impaired awareness. *Diabet Med.* 2003; 20(12):1016-1021.