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# Evaluating the cost-effectiveness of insulin detemir versus neutral protamine Hagedorn insulin in patients with type 1 or type 2 diabetes in the UK using a short-term modeling approach

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**Background:** To estimate the short-term cost-effectiveness of insulin detemir (IDet) versus neutral protamine Hagedorn (NPH) insulin based on the incidence of non-severe hypoglycemia and changes in body weight in subjects with type 1 diabetes (T1D) or type 2 diabetes (T2D) in the UK.

**Methods:** A model was developed to evaluate cost-effectiveness based on non-severe hypoglycemia, body mass index, and pharmacy costs over 1 year. Published rates of non-severe hypoglycemia were employed in the T1D and T2D analyses, while reduced weight gain with IDet was modeled in the T2D analysis only. Effectiveness was calculated in terms of quality-adjusted life expectancy using published utility scores. Pharmacy costs were captured using published prices and defined daily doses. Costs were expressed in 2016 pounds sterling (GBP). Sensitivity analyses were performed (including probabilistic sensitivity analysis).

**Results:** In T1D, IDet was associated with fewer non-severe hypoglycemic events than NPH insulin (126.7 versus 150.8 events per person-year), leading to an improvement of 0.099 quality-adjusted life years (QALYs). Costs with IDet were GBP 60 higher, yielding an incremental cost-effectiveness ratio (ICER) of GBP 610 per QALY gained. In T2D, mean non-severe hypoglycemic event rates and body weight were lower with IDet than NPH insulin, leading to a total incremental utility of 0.120, accompanied by an annual cost increase of GBP 171, yielding an ICER of GBP 1,422 per QALY gained for IDet versus NPH insulin.

**Conclusion:** Short-term health economic evaluation showed IDet to be a cost-effective alternative to NPH insulin in the UK due to lower rates of non-severe hypoglycemia (T1D and T2D) and reduced weight gain (T2D only).

**Keywords:** cost-benefit analysis, insulin, diabetes mellitus type 1, diabetes mellitus type 2, hypoglycemia

## Plain language summary

The present study evaluated the cost-effectiveness of neutral protamine Hagedorn (NPH) insulin relative to insulin detemir ([IDet] Levemir<sup>®</sup>; Novo Nordisk A/S, Bagsværd, Denmark) from the perspective of the UK National Health Service (NHS). Although the two insulins have slightly different durations of action, both are widely used as the “basal” component of a patient’s insulin regimen, providing glycemic control over the course of the day (as opposed to “bolus” insulin, which is administered at mealtimes in patients with type 1 diabetes or more advanced type 2 diabetes). Numerous clinical studies have demonstrated that IDet results in less day-to-day variation in blood glucose levels, fewer episodes of hypoglycemia (very low blood glucose), and less weight gain relative to NPH insulin. In the UK, however, NPH insulin is currently 46%

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cheaper than IDet on a per-unit basis (£0.015 versus £0.028 when each insulin dose is purchased in a pen cartridge for injection). As NHS England faces increasing budget constraints, balancing the additional cost of IDet with the clinical benefits it provides is an important aspect of ensuring good value for money for the NHS. Here, we used a short-term (1 year) computer model to establish if differences between IDet and NPH insulin in terms of insulin dosing, hypoglycemia, and, in type 2 diabetes, body mass index, were worth the additional cost to the NHS.

## Introduction

Long-term studies such as the Diabetes Control and Complications Trial (DCCT) in type 1 diabetes have shown that improved glycemic control leads to improved long-term outcomes.<sup>1</sup> Long-term studies in type 2 diabetes, such as the United Kingdom Prospective Diabetes Study (UKPDS), have similarly shown unequivocal benefits of improved glycemic control in terms of microvascular and macrovascular benefits.<sup>2</sup> Epidemiological studies have also demonstrated reduced incidence of macrovascular complications with improved glycemic control.<sup>3</sup> Lower blood glucose levels are, however, accompanied by an increased risk of hypoglycemia. In the DCCT, patients in the intensive treatment group were exposed to a threefold higher rate of severe hypoglycemia (61.2 events per 100 patient years versus 18.7 events per 100 patient years in the conventional treatment group).<sup>4</sup> The severity of hypoglycemic episodes ranges from relatively mild, which can be remedied by eating fast-acting carbohydrates, through to severe events that can result in seizure, coma, and occasionally death. Real-world data from the UK collected from 466 patients with type 1 diabetes over a period of 4 weeks (7-day recall period) indicated an average non-severe hypoglycemic event rate in individuals with type 1 diabetes of 126.7 events per patient per year, equivalent to experiencing an event every 3 days.<sup>5</sup> While hypoglycemia is less frequent in patients with type 2 diabetes than patients with type 1 diabetes, hypoglycemia becomes progressively more frequent as the disease progresses, with the same study reporting a rate of 41.5 events per patient per year in insulin-using patients with type 2 diabetes.<sup>5,6</sup> Evidence from a variety of sources has also shown that hypoglycemic events reduce quality of life and workplace productivity,<sup>7-14</sup> and increase health care resource utilization.<sup>11</sup>

Long-acting insulin analogues such as IDet can reduce the rate of non-severe hypoglycemia in individuals with type 1 or type 2 diabetes relative to NPH insulin. Indeed, several trials have provided evidence that treatment with IDet results in predictable glycemic control with less

day-to-day variation, fewer hypoglycemic episodes, and decreased weight gain in comparison with NPH insulin.<sup>15-21</sup> The clinical benefit of reduced non-severe hypoglycemia comes at an additional cost, however, with drug costs associated with IDet being higher than those of NPH insulin in most countries.

The present modeling analysis is therefore designed to provide an insight into whether the additional cost of IDet is justified in terms of the clinical benefit it provides in patients with type 1 or type 2 diabetes.

## Methods

A cost-effectiveness model was developed in Microsoft Excel 2010 to evaluate the cost-effectiveness of IDet relative to NPH insulin in patients with type 1 or type 2 diabetes. The model adopted the perspective of a UK health care payer (the National Health Service), and the base-case analysis was conducted over a 1-year time horizon, negating the need for discounting of cost or effectiveness outcomes. The 1-year time horizon was selected on the grounds that NPH insulin and IDet both have the same mechanism of action, and any differences in the long-term incidence of diabetes complications could be mitigated by adjusting the respective insulin doses.

The model captured insulin, needle and self-monitoring of blood glucose (SMBG) costs, costs of other antidiabetes therapies, and costs associated with non-severe hypoglycemic events. All costs were expressed in 2016 pounds sterling (GBP). Concomitant medication costs such as antihypertensive and lipid lowering agents were assumed to be equivalent in both arms and excluded from the analysis. Differences in glycemic control and other risk factors such as blood pressure were also excluded on the grounds that glycemic control can be achieved by simply titrating up the dose of insulin and high blood pressure can be controlled using relatively low-cost antihypertensives. However, differences in body mass index (BMI) were captured in the analysis of type 2 diabetes to evaluate the effect on health-related quality of life.

## Hypoglycemia rates

Hypoglycemia rates in patients with type 1 or type 2 diabetes using IDet were taken from a 2013 UK-specific study on self-reported rates of hypoglycemia in 1,038 adult patients with type 1 (n=466) or type 2 (n=572) diabetes.<sup>5</sup> In the type 1 base-case analysis, the non-severe hypoglycemic event rate for patients receiving NPH insulin was calculated by applying a rate ratio of 1.19 (the reciprocal of 0.84) to the

UK base rate of 126.7 events per patient year with IDet, yielding a deterministic rate estimate with NPH insulin of 150.8 events per patient year. The rate ratio was taken from a meta-analysis of six clinical trials of IDet versus NPH insulin comprising over 2,109 subjects with type 1 diabetes as part of a health technology assessment by the Canadian Agency for Drugs and Technology in Health (CADTH) published in 2008.<sup>22</sup> The mean reciprocal rate ratio of 1.19 was used in the base-case analysis and the corresponding 95% CI of 1.03–1.35 was used both for probabilistic sensitivity analysis (PSA) and to calculate the non-severe hypoglycemic event rate on NPH insulin for “pessimistic” and “optimistic” scenarios, respectively.

The type 2 base-case analysis utilized an overall hypoglycemia relative rate from the same CADTH meta-analysis as used in the analysis of type 1 diabetes, with a mean rate ratio of 0.59 for IDet relative to NPH insulin. The reciprocal rate ratio of 1.69 (95% CI 1.39–2.08) was applied to the IDet base rate of 41.5 events per patient year from the UK self-report study, to give a deterministic rate estimate of 70.34 events per patient year with NPH insulin.

Severe hypoglycemic events were not included in either the type 1 or type 2 analyses as the same CADTH meta-analysis reported a non-significant difference between treatments, with a rate ratio for severe hypoglycemia of 0.95 (95% CI 0.65–1.38) in patients on IDet relative to NPH insulin.<sup>22</sup>

## Insulin dosing and concomitant medications

Insulin doses in the analysis of patients with type 1 diabetes were derived from a population of 437 adults enrolled in the Dose Adjustment For Normal Eating (DAFNE) structured education program.<sup>23</sup> Specifically, mean basal insulin dosing was modeled at 24.35 IU per day, while mean bolus insulin dosing was assumed to be 27.88 IU per day. In the type 1 base-case analysis, dosing of IDet and NPH insulin was assumed to be equivalent. In the type 2 (basal-only) analysis, insulin doses were modeled in line with data from the PREDICTIVE study, assuming doses of 0.47 IU/kg/day for NPH insulin and 0.59 IU/kg/day for IDet and based on a mean body weight of 76 kg in line with the baseline weight of the UKPDS insulin starter group.<sup>2,24</sup> In addition to insulin, patients with type 2 diabetes were assumed to take 2,000 mg of metformin a day and 60 mg of gliclazide in line with the World Health Organization defined daily doses of metformin and sulfonylurea, respectively.

## Self-monitoring of blood glucose

Patients with type 1 diabetes were assumed to perform SMBG tests four times daily in line with 2015 guidance from the National Institute for Health and Care Excellence, which specifically recommends “testing at least 4 times a day, including before each meal and before bed” in patients with type 1 diabetes without any specific need to test more frequently.<sup>25</sup> This is likely to be a conservative estimate as many patients meet the criteria for more frequent testing, such as involvement in sports or high-risk activities, impaired awareness of hypoglycemia, illness, pregnancy, or failure to achieve the desired glycated hemoglobin (HbA1c) target. Patients with type 2 diabetes were assumed to perform SMBG three times a day on 2 days a week (an average of 0.86 tests per day) in line with the DiGEM trial, which investigated the effect of different SMBG strategies on glycemic control in patients with type 2 diabetes.<sup>26,27</sup>

## Quality of life

In the base-case analysis, a quality of life disutility of –0.004 was associated with each non-severe hypoglycemic event, based on a 2013 study by Evans et al.<sup>28</sup> The type 2 diabetes analysis also associated a disutility with increased BMI derived from the CADTH meta-analysis. The difference in body weight reported in the meta-analysis (0.96 kg higher with NPH insulin than with IDet) was converted to a mean difference in BMI using a mean height of 1.72 m, and a disutility of –0.0061 per additional BMI unit was applied based on the time trade-off model coefficient for each BMI unit over 25 kg/m<sup>2</sup> reported by Bagust and Beale.<sup>29,30</sup> Baseline quality of life with no complications in patients with type 1 or type 2 diabetes was taken to be 0.81 based on a 2011 meta-analysis by Lung et al.<sup>31</sup>

## Unit costs

Costs of insulin (NPH, IDet, and bolus insulin in the type 1 analysis), metformin, and sulfonylurea were taken from the British National Formulary (Table 1). Costs of needles, SMBG test strips, and lancets were taken from the NHS Business Services Authority. The cost of hypoglycemic events was taken from a recent analysis of the cost of non-severe hypoglycemia in 10 European countries including the UK.<sup>32</sup> The analysis was based on data from the Hypoglycaemia in Insulin Treated Patients (HIT) study,<sup>5</sup> and captured costs of additional SMBG test strip use and contact with health care professionals (either by telephone consultation, or visit to a nurse or primary care physician) in a country-specific proportion of patients with type 1 or type 2 diabetes.

**Table 1** Unit costs in the base-case analysis

	Cost	Cost basis	Reference
NPH insulin (GBP per IU)	0.015	Insulatard Penfill® cartridge 100 IU/mL, 5×3 mL	BNF, September 2016
Insulin detemir (GBP per IU)	0.028	Levemir® Penfill® cartridge 100 IU/mL, 5×3 mL	BNF, September 2016
Bolus insulin (GBP per IU)	0.019	NovoRapid® Penfill® cartridge 100 IU/mL, 5×3 mL	BNF, September 2016
Metformin (GBP per gram)	0.027	Metformin tablets, 850 mg, 56 tablet pack	BNF, September 2016
Gliclazide (GBP per milligram)	0.003	Gliclazide tablets, 40 mg, 28 tablet pack	BNF, September 2016
Needles (GBP per needle)	0.03	BD Micro-Fine 0.3 mm/30 gauge, 200 needle pack	NHS BSA, September 2016
SMBG test strip (GBP per strip)	0.319	Accu-Chek Aviva, 50 strip pack	NHS BSA, September 2016
Lancet (GBP per lancet)	0.049	FastClix (Roche Diabetes Care Ltd), 204 lancet pack	NHS BSA, September 2016
Hypoglycemic event T1D (GBP)	2.193	Additional strips and HCP contacts	33
Hypoglycemic event T2D (GBP)	3.066	Additional strips and HCP contacts	33

**Abbreviations:** NPH, neutral protamine Hagedorn; BD, Becton Dickinson; GBP, 2016 pounds sterling; HCP, health care professional; IU, international units; NHS BSA, National Health Service Business Services Authority; SMBG, self-monitoring of blood glucose; BNF, British National Formulary; T1D, type 1 diabetes; T2D, type 2 diabetes.

## Sensitivity analysis

A series of sensitivity analyses were conducted to establish the magnitude by which model outcomes changed in response to changes in individual input parameters. In the type 2 diabetes analyses, insulin doses were changed to match those reported by Eliasson et al (29.9 IU/day with NPH insulin and 42.1 IU/day with IDet).<sup>33</sup> In both type 1 and type 2 diabetes analyses, the hypoglycemia rate ratio was set at 0.78 (from Bartley et al) in the type 1 diabetes analysis and 0.7 (from Tajima et al) in the type 2 diabetes analysis, compared to 0.84 and 0.59 in the respective base-case analyses.<sup>21,34</sup> The base rates of hypoglycemia in the IDet arm were also modified to match those reported by the UK Hypoglycemia Study Group (UKHSG; 35.5 events per patient per year for type 1 diabetes and 4.08 events per patient per year for type 2 diabetes).<sup>35</sup> Further analyses were conducted in which the quality of life disutility associated with each hypoglycemic event was changed to values from Currie et al<sup>10</sup> (−0.0035), Levy et al (−0.0033, SD=0.0004),<sup>7</sup> and using a diminishing marginal hypoglycemia utility model published by Lauridsen et al.<sup>36</sup> Finally, the disutility associated with increased BMI was abolished in an analysis around the type 2 diabetes base case.

## Results

Using non-severe hypoglycemia rate ratios and body weight differences from a recent CADTH meta-analysis, the present analysis showed IDet to be cost-effective relative to NPH insulin in patients with either type 1 or type 2 diabetes in the UK setting over a 1-year time horizon.

In patients with type 1 diabetes, the deterministic analysis showed an increase in costs of GBP 60 with IDet relative to NPH insulin over a 1-year time horizon (GBP 1,301 relative to GBP 1,241). The reduced rate of hypoglycemia resulted in a quality-adjusted life expectancy gain of 0.099 quality-adjusted life years (QALYs), resulting in an incremental

cost-effectiveness ratio (ICER) of GBP 610 per QALY gained (Table 2). The equivalent analysis in patients with type 2 diabetes showed a cost increase of GBP 171 with IDet relative to NPH insulin over a 1-year time horizon (GBP 798 relative to GBP 627). The reduced rate of hypoglycemia with IDet combined with the smaller increase in BMI resulted in a gain of 0.120 QALYs, resulting in an ICER of GBP 1,422 per QALY gained.

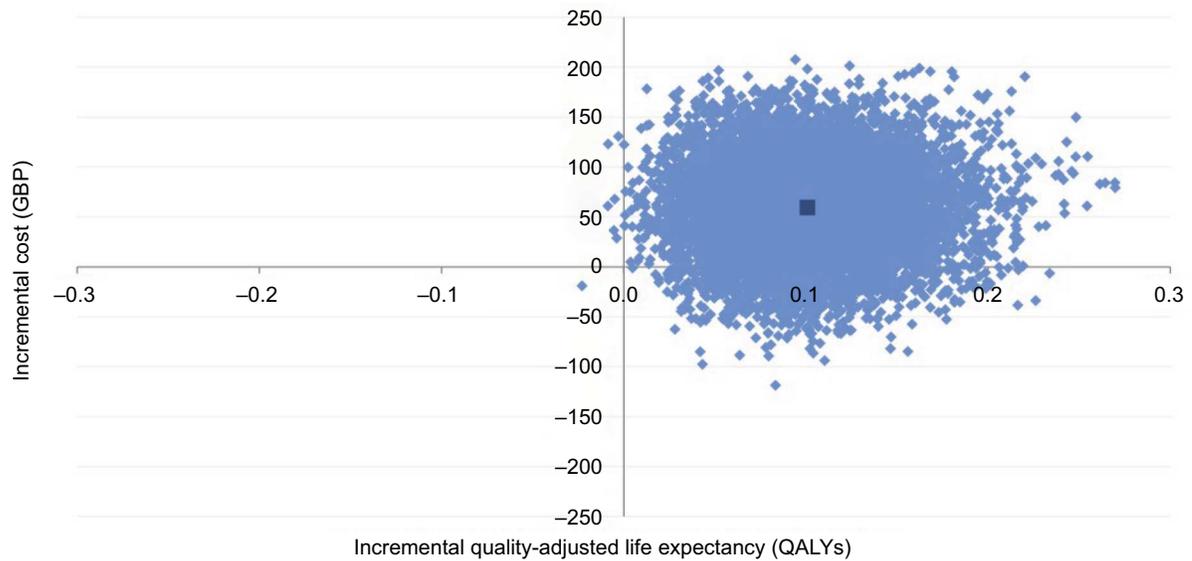
PSA yielded similar outcomes to the deterministic base-case analyses with incremental quality-adjusted life expectancy of 0.101 QALYs (standard deviation [SD] 0.038 QALYs) and incremental costs of GBP 59 (SD GBP 45) in the type 1 analysis, resulting in an ICER of GBP 587 per QALY gained. In the type 2 diabetes PSA, incremental costs were GBP 173 (SD GBP 202) and incremental quality-adjusted life expectancy was 0.123 QALYs (SD 0.028 QALYs), resulting in an ICER of GBP 1,408 per QALY gained. Results of the 10,000 model iterations were plotted on a scatterplot, and cost-effectiveness acceptability curves were generated over a range of willingness-to-pay (WTP) thresholds (Figures 1–4). At a WTP threshold of GBP 10,000 per QALY gained, there was a 99.9% likelihood that detemir would be cost-effective relative to NPH insulin in patients with type 1 diabetes. In patients with type 2 diabetes, there was a 100% likelihood of cost-effectiveness at the same WTP threshold.

One-way sensitivity analysis results showed the model to be sensitive to assumptions around the hypoglycemia base rate and rate ratios, and the use of a per-event utility model versus a diminishing marginal utility (DMU) model (Table 3). Notably, setting the hypoglycemia rate ratio to 0.78 resulted in an analysis in which IDet was relatively more effective than NPH insulin in type 1 diabetes, with an incremental quality-adjusted life expectancy of 0.147 QALYs and additional costs of GBP 35 with IDet, resulting in an ICER of GBP 238 per QALY gained. In the type 2

**Table 2** Cost-effectiveness of insulin detemir versus NPH insulin in the UK

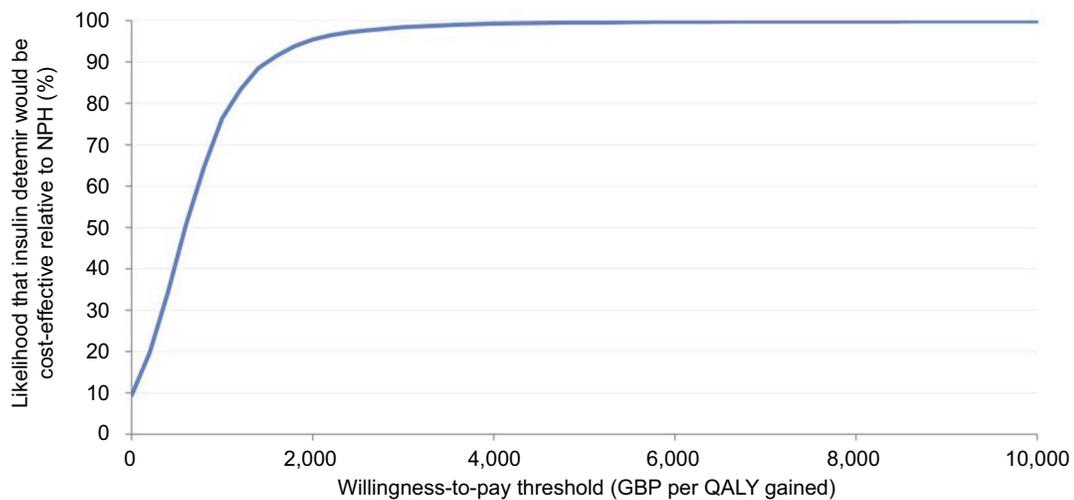
	NPH insulin cost (GBP)	Insulin detemir cost (GBP)	Incremental cost (GBP)	NPH effectiveness (QALYs)	Insulin detemir effectiveness (QALYs)	Incremental effectiveness (QALYs)	ICER (GBP per QALY gained)
Type 1 diabetes	1,241	1,301	+60	0.192	0.291	0.099	610
Type 2 diabetes	627	798	+171	0.520	0.640	0.120	1,422

**Abbreviations:** GBP, 2016 pounds sterling; NPH, neutral protamine Hagedorn; QALY, quality-adjusted life year; ICER, incremental cost-effectiveness ratio.



**Figure 1** Cost-effectiveness scatter plot for insulin detemir relative to NPH insulin in patients with type 1 diabetes.

**Abbreviations:** NPH, neutral protamine Hagedorn; QALY, quality-adjusted life year; GBP, 2016 pounds sterling.

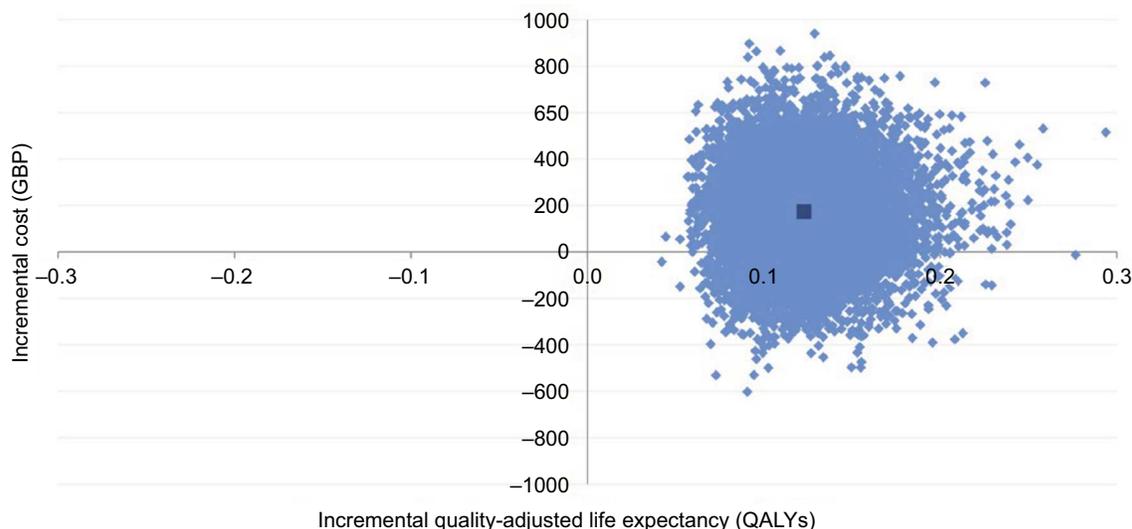


**Figure 2** Cost-effectiveness acceptability curve for insulin detemir relative to NPH insulin in patients with type 1 diabetes.

**Abbreviations:** NPH, neutral protamine Hagedorn; QALY, quality-adjusted life year; GBP, 2016 pounds sterling.

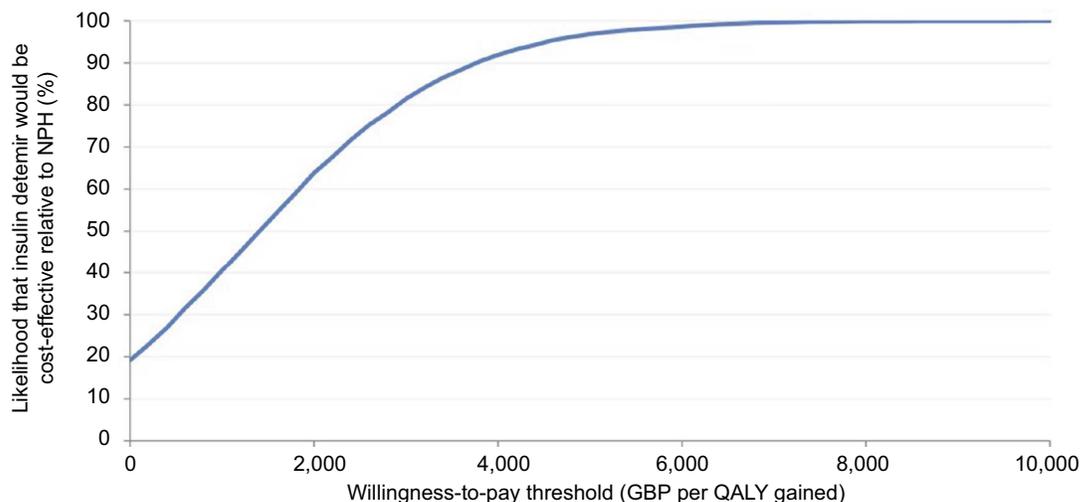
diabetes analysis, reducing the hypoglycemia rate difference to that reported by Tajima et al increased the ICER to GBP 2,735 per QALY gained.<sup>34</sup> Changing the hypoglycemia disutilities to values from studies other than Evans et al on

a per-event basis resulted in relatively small changes in the ICER, while switching to use the Lauridsen et al’s diminishing hypoglycemia utility model increased the ICER to GBP 13,578 per QALY gained and GBP 14,533 per QALY



**Figure 3** Cost-effectiveness scatter plot for insulin detemir relative to NPH insulin in patients with type 2 diabetes.

**Abbreviations:** NPH, neutral protamine Hagedorn; QALY, quality-adjusted life year; GBP, 2016 pounds sterling.



**Figure 4** Cost-effectiveness acceptability curve for insulin detemir relative to NPH insulin in patients with type 2 diabetes.

**Abbreviations:** NPH, neutral protamine Hagedorn; QALY, quality-adjusted life year; GBP, 2016 pounds sterling.

gained in the analyses of type 1 and type 2 diabetes, respectively.<sup>28,36</sup> Changing the insulin dose assumptions in the type 2 diabetes analysis based on Eliasson et al resulted in an ICER of GBP 1,459 per QALY gained, a slight increase over the base-case analysis.<sup>33</sup> Finally, by using rates of hypoglycemia from the UKHSG substantially increased the ICERs from GBP 610 per QALY gained to GBP 3,550 per QALY gained in the type 1 analysis, and from GBP 1,422 per QALY gained to GBP 18,429 per QALY gained in the type 2 analysis.

## Discussion

The modeling approach used in the present analyses demonstrated that IDet would be considered cost-effective relative to NPH insulin in patients with type 1 or type 2 diabetes in the

UK. The analysis only captured differences in costs associated with antidiabetic medications and non-severe hypoglycemic events, and did not take into consideration other differences such as severe hypoglycemia and glycemic control. Needles and SMBG were also captured in the analysis, but were not a driver of differences between IDet and NPH insulin. The modeling approach is likely to be conservative with regard to the incremental cost-effectiveness of IDet relative to NPH insulin. For instance, randomized controlled trials and meta-analyses have demonstrated improved glycemic control with IDet relative to NPH, including a 2011 systematic review and meta-analysis of 10 randomized controlled trials including 3,825 patients, which showed a weighted mean HbA1c difference of  $-0.073\%$  ( $p=0.021$ ) with IDet relative to NPH and

**Table 3** One-way sensitivity analysis results

	<b>NPH insulin cost (GBP)</b>	<b>Insulin detemir cost (GBP)</b>	<b>Incremental cost (GBP)</b>	<b>NPH effectiveness (QALYs)</b>	<b>Insulin detemir effectiveness (QALYs)</b>	<b>Incremental effectiveness (QALYs)</b>	<b>ICER (GBP per QALY gained)</b>
<b>Type 1 diabetes</b>							
Base case	1,241	1,301	+60	0.192	0.291	+0.099	610
Hypoglycemia rate ratio of 0.78 <sup>21</sup>	1,266	1,301	+35	0.144	0.291	+0.147	238
Levy et al hypoglycemia disutility <sup>7</sup>	1,241	1,301	+60	0.312	0.392	+0.080	757
Currie et al hypoglycemia disutility <sup>10</sup>	1,241	1,301	+60	0.282	0.367	+0.084	714
Diminishing hypoglycemia utility	1,241	1,301	+60	0.733	0.737	+0.004	13,578
UKHSG base hypoglycemia rate	1,003	1,101	+98	0.637	0.664	+0.028	3,550
<b>Type 2 diabetes</b>							
Base case	627	798	+171	0.520	0.640	+0.120	1,422
No BMI disutility	627	798	+171	0.522	0.640	+0.118	1,446
Hypoglycemia rate ratio of 0.7 <sup>39</sup>	593	798	+205	0.565	0.640	+0.075	2,735
Levy et al hypoglycemia disutility <sup>7</sup>	627	798	+171	0.576	0.673	+0.097	1,760
Currie et al hypoglycemia disutility <sup>10</sup>	627	798	+171	0.562	0.665	+0.103	1,661
Diminishing hypoglycemia utility	627	798	+171	0.748	0.760	+0.012	14,533
Eliasson et al insulin doses <sup>33</sup>	594	770	+175	0.520	0.640	+0.120	1,459
UKHSG base hypoglycemia rate	432	683	+251	0.780	0.793	+0.014	18,429

**Abbreviations:** GBP, 2016 pounds sterling; ICER, incremental cost-effectiveness ratio; QALY, quality-adjusted life year; UKHSG, UK Hypoglycemia Study Group; NPH, neutral protamine Hagedorn; BMI, body mass index.

a relative risk of severe hypoglycemia of 0.665 ( $p < 0.001$ ) in patients with type 1 diabetes.<sup>37</sup> While this is a limitation of the analyses presented here, the decision to exclude severe hypoglycemia and improved glycemic control resulted in a highly conservative analysis over a longer time horizon.

In the analyses of both type 1 and type 2 diabetes, reductions in the rate of non-severe hypoglycemia with IDet relative to NPH insulin were derived from a meta-analysis performed by CADTH.<sup>22</sup> While the meta-analysis reported an overall hypoglycemia rate ratio for IDet relative to NPH insulin of 0.84 (95% CI 0.74–0.97) in patients with type 1 diabetes, non-severe hypoglycemia was not reported separately and the overall rate was therefore used as a proxy. This was a conservative approach compared with using the rate ratio from the Bartley et al clinical trial (mean rate ratio 0.78, 95% CI 0.52–1.16), which was investigated in sensitivity analysis and reduced the ICER to GBP 238 per QALY gained in patients with type 1 diabetes.<sup>21</sup>

In type 2 diabetes, the selected rate ratio of 0.59 (95% CI 0.48–0.72) for non-severe hypoglycemia was based on the CADTH meta-analysis of overall hypoglycemia rates in patients with type 2 diabetes using oral antidiabetic agents in combination with IDet or NPH insulin.<sup>22</sup> While the meta-analysis finding was significant, the outcome was based on just three randomized controlled trials, which exhibited a high degree of heterogeneity in the reported outcomes ( $I^2 = 86.9%$  based on a chi-squared test outcome of 15.28 over 2 degrees

of freedom).<sup>22,34,38,39</sup> The CADTH analysis authors noted that the heterogeneity may have been driven by the dosing frequency of IDet and NPH, which was not consistent across the three studies. Despite the high degree of heterogeneity, the studies were all directionally in agreement, with mean rate ratios of 0.52, 0.54, and 0.70 for IDet relative to NPH insulin in the Philis-Tsimikas et al, Hermansen et al, and Tajima et al studies, respectively.<sup>22,34,38,39</sup> CADTH also noted that the difference was driven by a significant reduction in the frequency but not the risk of overall hypoglycemia, implying that the reductions were a result of reduced rates of hypoglycemia in patients prone to experiencing hypoglycemia rather than a reduction in the proportion of patients having hypoglycemic events.<sup>22</sup> Such a finding would be congruous with the findings of trials such as HypoAna, which demonstrated significant reductions in hypoglycemia rates in patients prone to recurrent severe hypoglycemia.<sup>40</sup> Even these reductions may be conservative relative to the differences observed in routine clinical practice, as Phase III regulatory studies of insulin (which need to demonstrate safety) tend to exclude patients who are prone to hypoglycemia.

Sensitivity analyses showed that the results were most sensitive to the use of DMU model to evaluate the effect of hypoglycemia on the quality of life. Such models reduce the incremental disutility associated with each additional hypoglycemic event as overall frequency increases, in this case using a weighted power function to determine the exact

relationship.<sup>36</sup> The authors of the DMU model noted that the reduced utility for additional events may be reflective of a range of phenomena, including patients learning to cope with hypoglycemia, an unwillingness to trade-off remaining lifetime after a certain point, or simply respondents paying more attention to the health-state descriptions than the event frequencies. The question of minimally important differences (MIDs) in quality of life should also be considered with regard to the DMU model, as the incremental disutility of additional hypoglycemic events in the model falls below the MIDs for generic instruments such as the Health Utilities Index, EuroQoL-5D (EQ-5D), and 36-Item Short Form Health Survey (SF-36).<sup>41,42</sup> The DMU model did not capture any reduction in quality of life associated with the fear of hypoglycemia, which has been shown to be greater in patients with experience of hypoglycemia relative to those without, and greater in patients with more severe symptoms of hypoglycemia.<sup>43</sup> The effects of fear may mitigate some of the effects of the DMU model, making the sensitivity analysis highly conservative. Regardless of its conservatism, the analyses in both type 1 and type 2 diabetes still yielded ICERs lower than GBP 20,000 per QALY gained.

Considerable evidence has been published supporting the long-term cost-effectiveness of IDet versus NPH insulin.<sup>44–46</sup> Whilst these more complex modeling studies are valuable in the absence of long-term clinical trial data, they do not address the requirements of health care payers for whom short-term cost-effectiveness is more relevant to immediate budget considerations. The present study addresses this need by presenting a transparent, short-term analysis of the cost-effectiveness of IDet versus NPH insulin based on up-to-date cost data in the UK setting.

## Conclusion

This short-term health economic evaluation showed IDet to be a cost-effective alternative to NPH insulin in both type 1 and type 2 diabetes in the UK. This evaluation reflects the clinically relevant reported reductions in non-severe hypoglycemic episodes, particularly at night, in people with diabetes. In light of the challenging new National Institute for Health and Care Excellence HbA1c targets it may be worth starting longer acting insulin analogues as first line, not only in people with type 1 diabetes but also when initiating insulin therapy in type 2 diabetes patients.

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