Value For Money In The Treatment Of Patients With Type 2 Diabetes Mellitus: Assessing The Long-Term Cost-Effectiveness Of IDegLira Versus iGlarLixi In Italy

Objective: Italian treatment guidelines for type 2 diabetes mellitus (T2DM) target good glycemic control but acknowledge the associated risk of hypoglycemia. Unlike traditional antidiabetic therapies, modern treatment options such as fixed-ratio combinations of basal insulin and glucagon-like peptide 1 receptor agonists are associated with improved glycemic control, reduced body weight and low risk of hypoglycemia. The cost-effectiveness of the fixed-ratio combinations of basal insulin and glucagon-like peptide 1 receptor agonists IDeg.Lira and iGlar.Lixi was assessed for Italy in patients with T2DM uncontrolled on basal insulin, to evaluate how short-term clinical benefits translate into long-term health economic outcomes.

Methods: The IQVIA CORE Diabetes Model was used to project clinical and economic outcomes over patient lifetimes. Treatment effects were sourced from an indirect treatment comparison. The analysis captured direct medical costs (expressed in 2017 Euros) from the perspective of the Italian National Health Service (NHS) and patient-related quality of life. Sensitivity analyses were performed.

Results: IDegLira was associated with gains of 0.09 life years and 0.13 quality-adjusted life years (QALYs) relative to iGlarLixi, due to a lower cumulative incidence and delayed onset of diabetes-related complications. IDegLira was associated with an incremental cost of EUR 930 over patient lifetimes, leading to an incremental cost-effectiveness ratio of EUR 7,386 per QALY gained.

Conclusion: Over the lifetime of patients with T2DM uncontrolled on basal insulin, IDegLira was associated with improved clinical outcomes at higher costs relative to iGlarLixi. At a willingness-to-pay threshold of EUR 30,000 per QALY gained, IDegLira was considered to be cost-effective versus iGlarLixi from the perspective of the Italian NHS.

Keywords: cost-effectiveness, fixed-ratio combination, IDegLira, iGlarLixi, Italy, type 2 diabetes

Plain Language Summary
- Treating patients with type 2 diabetes mellitus to glycemic control targets while minimizing hypoglycemic events and avoiding weight gain is key to reducing the risk of diabetes-related complications, which have a significant humanistic and cost burden. Up titration of insulin therapy can be associated with increased hypoglycemic events and weight gain, but use of fixed-ratio combinations of a glucagon-like peptide 1 receptor agonist and a basal insulin can mitigate the adverse effects of therapy.
The aim of the analysis was to assess the cost-effectiveness of IDegLira versus iGlarLixi (two fixed-ratio combinations of a glucagon-like peptide 1 receptor agonist and a basal insulin) for treatment of patients with type 2 diabetes mellitus uncontrolled on basal insulin, to evaluate how short-term clinical benefits translate into long-term health economic outcomes from the perspective of the Italian NHS.

In patients with type 2 diabetes mellitus uncontrolled on basal insulin therapy, IDegLira was associated with increased life expectancy and quality-adjusted life expectancy relative to iGlarLixi over patient lifetimes. IDegLira was associated with an ICER of EUR 7,386 per QALY gained versus iGlarLixi so, at a willingness to pay threshold of EUR 30,000 per QALY gained, was considered cost-effective.

Introduction

More than 3.4 million adults lived with diabetes in Italy in 2017, with mean diabetes-related expenditure of approximately EUR 3,416 per capita.\(^1\) The costs associated with hypoglycemia in particular represent a substantial burden for the Italian National Health Service (NHS). Recent estimates suggested that insulin-related hypoglycemia was associated with annual costs of EUR 145 million, of which EUR 91.7 million were incurred by patients with type 2 diabetes mellitus (T2DM). An estimated EUR 65 million were attributable to severe hypoglycemic episodes (SHEs).\(^2\)

Hypoglycemia is widely considered to be the main barrier to good glycemic control, which is crucial to reducing the incidence of diabetes-related macro- and microvascular complications.\(^3\) Italian guidelines for the treatment of diabetes mellitus specify a glycated hemoglobin (HbA1c) target of 6.5% [48 mmol/mol].\(^4\) If the patient is treated with medications associated with a high risk of hypoglycemia, a higher target (6.5–7.5% [48–58 mmol/mol]) may be chosen, illustrating the trade-off between achieving glycemic control and avoiding hypoglycemia. Pharmacologic treatment in Italy is recommended to start with metformin and add further oral and/or injectable antidiabetic medications if required. If glycemic control is still not achieved, patients should switch to insulin regimens, which, however, are associated with an increased risk of hypoglycemia and weight gain.\(^4,5\)

The fixed-ratio combination IDegLira (Xultophy\(^6\), Novo Nordisk) is an alternative to traditional treatment intensification options. IDegLira (approved in the European Union in September 2014) combines insulin degludec (IDeg) and the glucagon-like peptide-1 (GLP-1) receptor agonist liraglutide in a pre-filled pen for once-daily injection.\(^6\) While IDeg offers a stable, long-acting reduction in HbA1c, liraglutide leads to glucose level-dependent hepatic glucose production, slower gastric emptying and decreased appetite. The complementary effect of IDeg and liraglutide was shown to be associated with consistent reductions in HbA1c and body mass index (BMI), at low risk of hypoglycemia, in patients with T2DM.\(^7–9\) More recently, the fixed-ratio combination iGlarLixi (Suliqua\(^7\), Sanofi) received approval in the European Union (January 2017).\(^6\) Combining insulin glargine (IGlar) and the GLP-1 receptor agonist lixisenatide, iGlarLixi was also shown to be associated with reductions in HbA1c and body weight, without increased risk of hypoglycemia.\(^10\)

While the cost-effectiveness of IDegLira has previously been assessed for a range of country settings versus various insulin intensification regimens, it has not yet been evaluated versus iGlarLixi in the Italian setting. In the present study, a long-term cost-effectiveness analysis was conducted for these two fixed-ratio combinations, in order to inform decision-making and resource allocation in the Italian NHS.

Methods

Modeling Approach

Cost-effectiveness was evaluated by projecting health and cost outcomes for IDegLira and iGlarLixi over patient lifetimes in line with published guidance on diabetes modeling. Patients were subject to risk of developing diabetes-related complications, mortality due to complications and background mortality.

Costs, survival, complication incidence and quality of life were obtained for all patients. Duration and quality of life were summarized as quality-adjusted life expectancy, expressed in quality-adjusted life years (QALYs). Both clinical and economic outcomes were discounted at 3% per year. Dividing the difference in mean estimated discounted costs by the difference in mean estimated discounted quality-adjusted life expectancy yielded the incremental cost-effectiveness ratio (ICER), expressed as Euros per QALY gained. To assess cost-effectiveness, the ICER was compared to a willingness-to-pay (WTP) threshold, which, in the absence of an officially established value, was assumed to be EUR 30,000 per QALY gained.
in line with previous cost-effectiveness analyses of anti-diabetic medications in Italy.11

Projections were performed in the IQVIA CORE Diabetes Model (IQVIA, Basel, Switzerland). The model is a non-product-specific analysis tool for anti-diabetic interventions, capable of projecting the long-term progression of T2DM based on a series of interdependent submodels with a semi-Markov structure.12,13 The model has been successfully validated against clinical and real-world data.13,14 The IQVIA CORE Diabetes model is the most widely used health economic model of diabetes. Cost-effectiveness analyses using the model have been reported in over 120 peer-reviewed manuscripts and the model has been used to inform submissions to numerous health technology assessment agencies worldwide, including the National Institute for Health and Care Excellence (NICE) in the UK, Scottish Medicine Consortium (SMC), Pharmaceuticals Pricing Board (Lääkkeiden hintaluettelo) in Finland, and the Pharmaceutical Benefits Advisory Committee (PBAC) in Australia.

Clinical Data

Treatment effects used in the analysis were calculated based on an indirect treatment comparison as no clinical trial data comparing IDegLira and iGlarLixi directly are currently available.15 Indirect treatment comparisons are part of the broader field of multiple treatment comparison, ie of analyses that compare at least two treatments with regard to efficacy, safety or other outcomes.16,17 Different types of multiple treatment comparisons exist. Perhaps the best known approach is the direct comparison of interventions, eg in a clinical trial. If, as is the case for IDegLira and iGlarLixi, a direct comparison is not available, an indirect comparison may still be feasible. Indirect comparisons exploit the fact that a third treatment (the “anchor treatment”) may be available against which the treatments of interest were compared in previous head-to-head studies. The relative efficacy of treatments of interest versus the anchor treatment can then be used to estimate the relative efficacy of the treatments of interest. If both direct and indirect comparisons are available, they can be combined in mixed treatment comparisons.

The term network meta-analysis is also used in this context and reflects that treatment comparisons can often be laid out in the form of a network, where nodes represent treatments and edges represent trials.16,17 More specifically, the term “network meta-analysis” has been suggested to apply to any comparison (indirect or mixed) of more than two treatments that combines more than two randomized controlled trials (RCTs).16 In practice, however, many of the terms described above are used somewhat interchangeably. In the present study, “indirect treatment comparison” is used in line with the terminology of the study from which treatment effects were obtained.15

In the network developed by Evans et al to assess the relative efficacy of IDegLira versus iGlarLixi, the anchor treatment was IGLar U100, which was linked to IDegLira via the DUAL V trial and to iGlarLixi via the LixiLan-L trial.8,10,15 In addition, the DUAL II (IDegLira versus IDeg) and SWITCH 2 (Iglar U100 versus IDeg) trials were included in the network.7,15 Outcomes, comparing IDegLira versus iGlarLixi, were mean (95% confidence interval [CI]) treatment differences in HbA1c of −0.4% (95% CI −0.7 to −0.2% [−5 mmol [−8 to −2 mmol/mol]]), in bodyweight of −1.42 kg (95% CI −2.50 to −0.35 kg) and in daily insulin dose of −3.6 international units (−10.3 to 3.3 international units). The difference in weight was converted to a difference in BMI based on the mean height (168 cm) of patients in the IDegLira arm of DUAL II. The indirect treatment comparison also reported a rate ratio of 0.51 (95% CI 0.29 to 0.90) for severe or blood glucose-confirmed hypoglycemia.

These differences were applied to the treatment effects for IDegLira, which were sourced from the IDegLira arm of DUAL II, in order to obtain treatments effects for iGlarLixi (Table 1).7,15 Simulated patients were assumed to receive IDegLira or iGlarLixi for the first 5 years of the analysis before intensifying to basal-bolus therapy in order to maintain glycemic control. In the first year of the analysis, treatment effects for HbA1c, BMI and hypoglycemia (both non-severe hypoglycemic events [NSHEs] and SHEs) were applied and maintained over the first 5 years, ie while treatments differed. During basal-bolus therapy, HbA1c was assumed to be at 7.0% [53 mmol/mol] (reflecting

<table>
<thead>
<tr>
<th>Table 1 Treatment Effects Applied In The Analysis</th>
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<tr>
<td><strong>IDegLira</strong></td>
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<tr>
<td>Change in HbA1c (%) [mmol/mol]</td>
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<tr>
<td>Change in BMI (kg/m²)</td>
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<tr>
<td>Daily dose (units)</td>
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<td>NSHE rate (events per 100 patient-years)</td>
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<td>SHE rate (events per 100 patient-years)</td>
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Abbreviations: BMI, body mass index; HbA1c, glycated hemoglobin; NSHE, non-severe hypoglycemic event; SHE, severe hypoglycemic event.
treatment targets) in both arms, with BMI at the baseline level. Rates of hypoglycemic events were the same in both arms. This approach implied that clinical differences were observable only when there was a cost difference between the treatment arms.

All remaining baseline characteristics (including diabetes-related complications at baseline) of the simulated cohort were obtained from the IDegLira arm of DUAL II and assumed to be the same in both arms of the cost-effectiveness analysis. Baseline age was 56.8 years (standard deviation [SD] 8.9 years), with a mean diabetes duration of 10.3 years (SD 6.0 years). Baseline HbA1c was 8.7% (SD 0.7%) [72 mmol/mol (SD 8 mmol/mol)] and baseline BMI was 33.6 kg/m$^2$ (SD 5.70 kg/m$^2$). Patterns of cigarette and alcohol consumption in the general Italian population were assumed to apply to simulated patients, and background mortality data were sourced from Italian lifetables.18–20

Resource Use And Economic Data

Daily IDegLira dose data were obtained from the IDegLira arm of DUAL II, to which the treatment effect reported by the indirect treatment comparison was applied to obtain the daily dose for iGlarLixi.7,15 Daily doses of IGlar U100 (Lantus®) and insulin aspart during basal-bolus therapy were taken from the DUAL VII RCT.9 Throughout the analysis, patients were assumed to receive concomitant metformin (no other concomitant anti-diabetes medications were included in the analysis). During fixed-ratio combination treatment, patients were assumed to require one needle and to perform one self-monitoring of blood glucose (SMBG) test per day. During basal-bolus therapy, four needles and four SMBG tests per day were assumed. Patient management-related resource use, including concomitant medications, were assumed to be the same as in the general Italian population with T2DM. Costs of anti-diabetic and concomitant medications, SMBG equipment and patient management were obtained from the published literature and the Italian Medicines Agency.21–24

The analysis accounted for the costs of treating diabetes-related complications, including myocardial infarction, stroke, severe vision loss, amputation and adverse events (NSHE and SHE), with costs also obtained from official fee schedules and the literature.24–32 The analysis was conducted from the perspective of the Italian NHS. Costs were expressed in 2017 Euros.

Quality Of Life Data

As diabetes-related complications are associated with reduced quality of life, health-state and event utilities were included in the analysis. Published utility values for patients with T2DM were sourced from a systematic literature review and a time trade-off survey for disutilities associated with hypoglycemia.33,34

Sensitivity Analyses

Sensitivity analyses are recommended to investigate the uncertainty associated with long-term projections, and to explore the impact of data inputs and assumptions on cost-effectiveness outcomes.35 For this analysis, a series of deterministic sensitivity analyses were performed, including use of shorter time horizons (5, 10, 20 and 35 years) and alternative discount rates (0% and 8%). Key clinical drivers were evaluated by abolishing differences in HbA1c, BMI and hypoglycemia rates in turn (keeping all other treatment effects as in the base case). In another analysis, differences in HbA1c and BMI were maintained over patient lifetimes, applying other treatment effects as in the base case. An additional analysis was conducted in which only statistically significant treatment effects were used, with other treatment effects set to zero. For HbA1c, the impact of using the United Kingdom Prospective Diabetes Study (UKPDS) progression equation from the start of the simulation was explored. Additionally, lower and upper bounds of 95% CIs for treatment differences in HbA1c, BMI and daily dose changes were used. With regard to treatment intensification, both earlier (after 1 and 3 years) and later (after 7 years) intensification to basal-bolus therapy was explored.

Costs were varied by increasing and decreasing the cost of complications by 10%, and by reducing the costs of SMBG testing by 50% relative to the base case. Using the cost of Abasaglar® instead of Lantus® as the basal insulin component during basal-bolus therapy was also investigated. The impact of utilities was explored by applying different utilities for BMI and hypoglycemic events, in addition to assuming a diminishing impact of hypoglycemic events on disutilities.36–38

Results

Base Case Analysis

Over patient lifetimes, IDegLira was associated with incremental gains in life expectancy (+0.09 years) and quality-adjusted life expectancy (+0.13 QALYs). Clinical benefits
were due to reduced incidence and delayed onset of diabetes-related complications (Figure 1).

With the exception of stroke, the cumulative incidence was lower for all complications in the IDegLira arm. The marginally higher incidence of stroke was a consequence of the survival paradox: Patients treated with IDegLira benefited from increased survival and reached higher ages, which was associated with an increased risk of stroke.39

IDegLira was associated with incremental lifetime costs of EUR 930 versus iGlarLixi. Pharmacy acquisition costs for IDegLira were higher by EUR 1,778 over patient lifetimes but were partially offset by reduced costs of treatment of diabetes-related complications, particularly ulcer/neuropathic complications (EUR 485 per patient) and cardiovascular complications (EUR 175 per patient).

Increased quality-adjusted life expectancy at increased costs for IDegLira versus iGlarLixi yielded an ICER of EUR 7,368 per QALY gained (Table 2). As the ICER fell below the WTP threshold of EUR 30,000 per QALY gained, IDegLira was considered to be cost-effective versus iGlarLixi.

### Sensitivity Analyses

Base case findings were confirmed by deterministic sensitivity analyses, which all yielded ICERs falling below the WTP threshold of EUR 30,000 per QALY gained (Figure 2). Clinical data were identified as key drivers of cost-effectiveness results, in particular the HbA1c benefit of IDegLira relative to iGlarLixi. When the HbA1c difference was

### Table 2 Long-Term Cost-Effectiveness Outcomes

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<tr>
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<th>IDegLira</th>
<th>iGlarLixi</th>
<th>Difference</th>
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<tbody>
<tr>
<td>Discounted life expectancy (years)</td>
<td>14.58</td>
<td>14.49</td>
<td>+0.09</td>
</tr>
<tr>
<td>Discounted quality-adjusted life expectancy (QALYs)</td>
<td>9.35</td>
<td>9.23</td>
<td>+0.13</td>
</tr>
<tr>
<td>Discounted direct costs (EUR)</td>
<td>62,886</td>
<td>61,956</td>
<td>+930</td>
</tr>
<tr>
<td>ICER (based on quality-adjusted life expectancy)</td>
<td>EUR 7,368 per QALY gained</td>
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Note: Rounding may lead to variation in the values shown in the Difference column.

Abbreviations: EUR, 2017 Euros; ICER, incremental cost-effectiveness ratio; QALYs, quality-adjusted life years.
abolished, the ICER increased, while maintaining the HbA1c difference over patient lifetimes yielded a reduced ICER of EUR 796 per QALY gained.

As expected, use of the lower/upper 95% CI bounds for the HbA1c treatment effect difference decreased/increased ICERs relative to the base case while use of the UKPDS progression equation for HbA1c yielded an ICER of EUR 9,006 per QALY gained. Similarly, reducing or abolishing other clinical between-treatment differences such as limiting the analyses to statistically significantly differences only, using upper 95% CI bounds for BMI and dose differences, and abolishing differences in BMI and hypoglycemia increased ICERs relative to the base case as the benefits associated with IDegLira were reduced. Conversely, using lower 95% CI bounds and maintaining clinical differences over patient lifetimes were associated with lower ICERs.

Shorter time horizons were associated with higher ICERs as not all long-term complications and benefits of IDegLira were captured. Indeed, after 5, 10, 20 and 35 years, about 91%, 80%, 55% and 16% of simulated patients, respectively, were still alive. Higher/lower discount rates increased/decreased ICERs relative to the base case, while the use of alternative disutilities for hypoglycemia (including a diminishing approach to hypoglycemia disutilities) and for BMI had little impact on cost-effectiveness outcomes. Similarly, using alternative costs for treatment of diabetes-related complications, SMBG testing and basal insulin during intensification was associated with only small changes in ICERs. Earlier intensification was associated with reduced ICERs while delayed intensification had the opposite effect.

At a WTP threshold of EUR 30,000 per QALY gained, PSA indicated a 79% probability that IDegLira was cost-effective relative to iGlarLixi (Figure 3).
Different WTP thresholds
The lower hypoglycemia rates associated to date, one other
In the absence of Pöhlmann et al. IDegLira was associated with improved clinical
The analysis This may be considered a limitation as obtain-
EUR, 2017 Euros; QALY, quality-adjusted life year; WTP, willingness to pay.

Discussion
The cost-effectiveness of the fixed-ratio combination treatments IDegLira and iGlarLixi was assessed from the perspective of the Italian NHS. Long-term projections of clinical and cost outcomes suggested that IDegLira was associated with clinical benefits and higher costs (due to higher acquisition costs although these were partially offset by reduced complication-related treatment costs) relative to iGlarLixi. The base case ICER for IDegLira versus iGlarLixi was EUR 7,386 per QALY gained.

At a WTP threshold of EUR 30,000 per QALY gained, IDegLira was considered cost-effective versus iGlarLixi for treatment of patients with T2DM uncontrolled on basal insulin. Cost-effectiveness was driven by reductions in HbA1c, hypoglycemia rates and daily doses with IDegLira, which translated into long-term benefits, including lower cumulative incidence and delayed onset of diabetes-related complications. Of note, an official WTP threshold does not exist in Italy so a threshold of EUR 30,000 per QALY gained was chosen, in line with previous cost-effectiveness analyses for treatments of T2DM in Italy. Different WTP thresholds have also been used previously but the current analysis suggested that IDegLira would be cost-effective even if the WTP threshold was reduced by two-thirds.

No prior economic evaluations of IDegLira versus iGlarLixi have been conducted for Italy but IDegLira was recently compared with basal-bolus insulin in a cost-minimization analysis, based on the DUAL VII trial. The analysis showed that IDegLira was associated with higher acquisition costs which were partially offset by reduced needle, SMBG testing and hypoglycemia costs. Importantly, these findings were based on dosing regimens used in the DUAL VII trial, which were considered to be higher than doses typically used to achieve glycemic control in Italian clinical practice. When lower IDegLira doses were used, IDegLira was cost saving relative to basal-bolus therapy. From the perspective of the Italian NHS, IDegLira was considered to offer an important alternative to basal-bolus insulin therapy. To date, one other cost-effectiveness analysis comparing IDegLira with iGlarLixi has been published. This analysis in the Czech Republic produced similar outcomes to the present analysis in Italy. IDegLira was associated with improved clinical outcomes and increased costs compared with iGlarLixi, but was likely to be considered cost-effective in the Czech Republic. Combined with the results of the present analysis, it seems plausible that IDegLira offers patients good glycemic control with reductions in BMI at a low risk of hypoglycemia (as recommended in national treatment guidelines) and thereby reduces healthcare costs associated with diabetes.

The simplicity of IDegLira treatment, with one daily injection and titration of a single product, and its good safety profile may also contribute to reducing clinical inertia and non-adherence, which are linked to low health literacy and fear of adverse events. The lower hypoglycemia rates associated with IDegLira relative to iGlarLixi and basal-bolus therapy are particularly relevant for the Italian setting, where uptake of SMBG testing among patients with T2DM was found to be insufficient so patients are at relatively high risk of hypoglycemia.

At the time of writing, no direct comparison of IDegLira and iGlarLixi was available. The assessment of cost-effectiveness therefore relied on a recent indirect treatment comparison. This may be considered a limitation as obtaining treatment effects from an indirect treatment comparison requires more assumptions, eg regarding the construction and evaluation of the evidence network, than an RCT. This challenge is common in epidemiology, health technology assessment and health economics. In the absence of RCTs, indirect treatment comparisons are often considered the best, or indeed only, source for relative treatment efficacy.

Another limitation common to health economic analyses, which also affected the presented study, was the use of short-term data in long-term projections. Estimates were therefore associated with uncertainty. This issue was addressed by using a validated diabetes model and by exploring a series of alternative data inputs and assumptions in sensitivity analyses. Using short-term data as the base for long-term projections is often unavoidable as
long-term evidence may not be available within the decision time frame of a healthcare payer. Despite their uncertainty, lifetime analyses are generally recommended for the health economic analysis of anti-diabetic treatments to capture fully the clinical, quality of life and economic impact of long-term complications.\textsuperscript{35}

The benefits of IDegLira observed in RCTs and the present long-term projections were matched by real-world evidence. Weight loss and reductions in HbA1c, at low risk of hypoglycemia, were demonstrated in observational studies of patients with T2DM.\textsuperscript{45,46} Primary and secondary care physicians reported high levels of satisfaction with and confidence in the clinical benefits as well as the simplicity of therapy and good adherence to IDegLira relative to basal-bolus insulin.\textsuperscript{47} With its potential to improve clinical outcomes and medication adherence, in addition to its treatment simplicity, IDegLira may contribute to reducing widespread clinical inertia in Italy.\textsuperscript{42,44,48} Better conformance with clinical guidelines, in turn, may improve anti-diabetic care and reduce its costs.\textsuperscript{42,43,49}

Conclusions

In patients with T2DM uncontrolled on basal insulin therapy, IDegLira was associated with increased life expectancy and quality-adjusted life expectancy relative to iGlarLixi over patient lifetimes, due to a reduced incidence and delayed onset of diabetes-related complications. While acquisition costs were higher for IDegLira than for iGlarLixi, they were partially offset by reduced costs due to diabetes-related complications avoided. Overall, IDegLira was associated with an ICER of EUR 7,386 per QALY gained versus iGlarLixi so, at a WTP threshold of EUR 30,000 per QALY gained, was considered cost-effective. From the perspective of the Italian NHS, IDegLira offers good value for money for the treatment of patients with uncontrolled T2DM on basal insulin.

Ethics Approval

This article is based on previously conducted studies and does not contain any studies with human participants or animals performed by any of the authors.

Data Statement

Data reported in this manuscript are available from the corresponding author on reasonable request.

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Author Contributions

All authors contributed to study conception and design, data acquisition, analysis and interpretation. All authors contributed to drafting and/or revising the article for intellectual content. All authors approved the final version of the manuscript and agree to be accountable for all aspects of the work.

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Disclosure

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References