Cost-Effectiveness of iGlarLixi Versus Premix BIAsp 30 in Patients with Type 2 Diabetes Suboptimally Controlled by Basal Insulin in the UK

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ABSTRACT

Introduction: iGlarLixi is indicated as an adjunct to diet and exercise in addition to metformin (with or without sodium-glucose cotransporter-2 inhibitors) to improve glycemic control in adults with insufficiently controlled type 2 diabetes (T2D). A cost-effectiveness analysis was conducted to compare iGlarLixi with premix biphasic insulin aspart 30 (BIAsp 30) in people with T2D suboptimally controlled with basal insulin (BI).

Methods: The IQVIA CORE Diabetes Model was used to estimate lifetime costs and outcomes for people with T2D from a UK health care perspective at a willingness-to-pay threshold of £20,000. Initial clinical data were based on the phase 3 randomized, open-label, active-controlled SoliMix clinical trial which compared the efficacy and safety of once-daily iGlarLixi with that of twice-daily BIAsp 30. Costs associated with management and complications and utilities values were derived from published sources. Lifetime costs (in £GBP) and quality-adjusted life-years (QALYs) were predicted; extensive scenario and sensitivity analyses were conducted.

Results: Estimated QALYs gained were slightly higher with iGlarLixi (8.9 vs. 8.8) compared with premix BIAsp 30, at a higher cost (£23,204 vs. £21,961). The base case incremental cost-effectiveness ratio (ICER) per QALY was £13,598. Treatment acquisition was the main driver of cost differences (iGlarLixi, £11,750; premix BIAsp 30, £10,395). Costs associated with management and complications were generally similar between comparators.

Conclusion: iGlarLixi provides improved QALY outcomes at an acceptable cost compared with premix BIAsp 30, with an ICER below the threshold generally considered acceptable by UK authorities. In people with T2D, iGlarLixi is a simple, cost-effective option for advancing therapy of BI, with fewer daily injections than premix BIAsp 30.

Keywords: BIAsp 30; Cost-effectiveness; Cost-utility; iGlarLixi; Premix; SoliMix; Type 2 diabetes; United Kingdom

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Key Summary Points

Why carry out this study?

Premix insulins, including biphasic insulin aspart 30 (BIAsp 30), are widely used in people with type 2 diabetes (T2D) who require advancement of therapy but who are associated with increased risks of hypoglycemia and weight gain, compared with basal insulin (BI) plus glucagon-like peptide-1 receptor agonists, including the fixed-ratio combination of insulin glargine plus lixisenatide (iGlarLixi).

The randomized phase 3 SoliMix trial demonstrated the efficacy and safety of once-daily iGlarLixi compared with twice-daily premix BIAsp 30 in people with T2D suboptimally controlled on BI.

No economic comparison of iGlarLixi versus BIAsp 30 in the post-BI setting currently exists; the aim of this analysis was to compare the cost-effectiveness of iGlarLixi versus BIAsp 30 in people suboptimally controlled with BI in the context of the UK National Health System.

What was learned from this study?

Estimated quality-adjusted life-years (QALYs) gained were slightly higher with iGlarLixi versus premix BIAsp 30 (8.9 vs. 8.8), at a higher cost (£23,204 vs. £21,961); the base case incremental cost-effectiveness ratio per QALY was £13,598.

In people living with T2D with suboptimal glycemic control during BI therapy, iGlarLixi confers slightly improved QALY outcomes at an acceptable cost compared with premix BIAsp 30.

INTRODUCTION

It is estimated that approximately 3.6 million people are at increased risk of developing type 2 diabetes (T2D) in the UK, and the prevalence of people living with T2D is expected to increase to 5.5 million by 2030 [1]. A substantial proportion of people living with T2D experience suboptimal glycemic control during treatment with basal insulin (BI) analogs and often require dual or triple therapy [2, 3]. Guidelines from the American Diabetes Association (ADA) and the European Association for the Study of Diabetes (EASD) recommend four approaches for advancement of therapy, including the addition of a rapid-acting insulin, multiple daily premix insulin doses (basal and prandial insulin co-formulation), or addition of daily or weekly glucagon-like peptide-1 receptor agonist (GLP-1 RA) to an existing BI regimen, or switching to a once-daily fixed-ratio combination (FRC) of BI and GLP-1 RA [2, 3].

Premix insulins (basal and prandial insulin co-formulation) are widely used in people who require advancement of therapy, accounting for around 30–36% of people living with T2D taking insulin globally. However, premix insulin is associated with an increased risk of hypoglycemia and weight gain compared with BI plus GLP-1 RAs [3–6]. Additionally, premix insulin requires multiple daily injections and frequent glucose monitoring, which may increase treatment burden and reduce adherence [7–10]. The phase 3 randomized, open-label, active-controlled SoliMix clinical trial compared the efficacy and safety of the once-daily FRC insulin glargine plus lixisenatide (iGlarLixi) with twice-daily premix biphasic insulin aspart 30 (BIAsp 30) in people living with T2D suboptimally controlled on BI combined with one or two oral anti-diabetes drugs (OADs; metformin with or without sodium-glucose cotransporter-2 [SGLT2] inhibitors). Once-daily iGlarLixi provided better glycemic control with weight benefit and less hypoglycemia than premix BIAsp 30 [11].

Insulin glargine 100 units/mL plus lixisenatide (iGlarLixi) is a combination of a long-acting human insulin analog with a GLP-1 RA that

was initially approved in 2016 in the USA and in 2017 in Europe. It is indicated as an adjunct to diet and exercise in addition to metformin (with or without SGLT2 inhibitors) to improve glycemic control in adults with insufficiently controlled T2D [12]. Given the differences in clinical and cost profiles between therapies, cost-effectiveness analyses inform resource allocation within the budget constraints of health care systems. The aim of this analysis was to compare the cost-effectiveness of iGlarLixi versus BIAsp 30 in people with T2D suboptimally controlled with BI in the context of the UK National Health Service (NHS).

METHODS

Study Overview

Cost-effectiveness for iGlarLixi versus premix BIAsp 30 was estimated using version 9.5 of the IQVIA CORE Diabetes Model (CDM). The IQVIA CDM is a non–product-specific computer simulation tool that models the effect of glucose monitoring, diabetes therapies, screening, and treatment strategies on the long-term health and economic outcomes of people living with type 1 and type 2 diabetes. The CDM uses a series of interdependent Markov submodels incorporating time-, state-, and diabetes type-dependent probabilities to simulate progression of disease-related complications using a set of equations for progression of the disease risk factors (United Kingdom Prospective Diabetes Study [UKPDS] Outcomes Model no. 68 [UKPDS 68]) [13] and for predicting the cardiovascular and mortality risk (UKPDS 82) [14]. The IQVIA CDM has been extensively validated and is widely used in diabetes research [15, 16]. The cost-effectiveness analysis reported here was conducted from the perspective of the UK NHS, assuming a willingness-to-pay (WTP) threshold of £20,000 per quality-adjusted life-year (QALY) gained. A hypothetical cohort of 1000 people was used, with a lifetime time horizon, and an annual discount rate of 3.5% for costs and outcomes in line with UK National Institute of Health and Care Excellence Decision Support Unit guidance [17]. This article is based on previously conducted studies and does not contain any new studies with human participants or animals performed by any of the authors.

Model Inputs and Structure

Baseline characteristics were primarily based on those reported in the SoliMix clinical trial (Table 1) [11]. For values not collected in the SoliMix trial (i.e., lipid parameters), data were extracted from the LixiLan-L trial and applied as a proxy for the population of interest [18]. For the other missing values, the CDM default values (population averages based on published literature) were used.

Efficacy data for iGlarLixi and premix BIAsp 30 from the SoliMix trial were used to predict glycated hemoglobin (HbA1c), body mass index (BMI), and hypoglycemia in the first year of the model (Table 2) [11]. After 1 year of treatment, the progression of HbA1c levels and other physiological parameters were predicted by the UKPDS 68 risk equation [13]. Simulated individuals were assumed to receive either iGlarLixi or premix BIAsp 30 until HbA1c returned to SoliMix trial baseline values (8.6%); at this point, individuals were assumed to switch to rescue therapy (consisting of basal plus rapid-acting insulin). HbA1c reductions during rescue therapy were sourced from the GetGoal Duo-2 trial, which reported HbA1c reductions of 0.6% when a prandial insulin bolus was added to BI therapy (with concomitant OADs). The use of iGlarLixi was assumed to result in a BMI decrease, whereas the use of BIAsp 30 was assumed to result in a BMI increase. When individuals switched to rescue therapy, BMI was assumed to increase based on observations from the GetGoal Duo-2 study. In addition, hypoglycemia rates in individuals who switched to rescue therapy were based on observations from the GetGoal Duo-2 study [19].

For the derivation of QALYs, utility values for health-related quality of life were obtained from published literature (Electronic Supplementary Material [ESM] Table S1) [20]. QALYs were assessed using the additive "Core Default Method," in which current utility was based on

Table 1 Baseline characteristics

Variable	Mean (SD)	Source
Patient demographics		
Start age (years)	59.8 (10.20)	SoliMix trial [11]
Duration of diabetes (years)	13.0 (7.20)	
Proportion male (%)	49.8	
Baseline risk factors		
HbA1c (%)	8.6 (0.70)	SoliMix trial [11]
Systolic blood pressure (mmHg)	131.7 (13.70)	
Diastolic blood pressure (mmHg)	77.80 (8.60)	
Total cholesterol (mg/dL)	180.52 (44.76)	LixiLan-L study report[a] [18]
High-density lipoprotein (mg/dL)	50.62 (13.18)	
Low-density lipoprotein (mg/dL)	100.55 (37.79)	
Triglycerides (mg/dL)	149.13 (98.39)	
Body mass index (kg/m^2)	29.90 (4.90)	SoliMix trial [11]
Estimated glomerular filtration rate (mL/min/1.73 m^2)	86.10 (23.56)	
Hemoglobin (g/dL)	13.90 (1.5)	
White blood cells (10^6/mL)	7.55 (1.86)	
Heart rate (bpm)	77.00 (9.00)	
Waist-to-hip ratio	0.93	CDM default
Urinary albumin to creatinine ratio	3.10	
Serum creatinine (mg/dL)	0.85 (0.21)	SoliMix trial [11]
Serum albumin (g/dL)	3.90	CDM default
Waist circumference (cm)	87.84	CDM default
Proportion smoker	0.12	SoliMix trial [11]
Cigarettes/day	13.20	
Alcohol consumption (oz/week)	92.01	
Racial characteristics		
Proportion White	0.630	SoliMix trial [11]
Proportion Black	0.002	
Proportion Hispanic	0.000	
Proportion Native American	0.017	
Proportion Asian/Pacific Islander	0.351	

Table 1 continued

Variable	Mean (SD)	Source
Baseline cardiovascular complications		
Proportion myocardial infarction	0.027	SoliMix trial [11]
Proportion angina	0.041	
Proportion peripheral vascular disease	0.006	
Proportion stroke	0.020	
Proportion heart failure	0.021	
Proportion atrial fibrillation	0.016	
Proportion left ventricular hypertrophy	0.001	
Baseline renal complications		
Proportion microalbuminuria	0.001	SoliMix trial [11]
Proportion macroalbuminuria	0.000	
Proportion end-stage renal disease	0.000	
Baseline retinopathy complications		
Proportion background diabetic retinopathy	0.151	SoliMix trial [11]
Proportion proliferative diabetic retinopathy	0.142	
Proportion severe vision loss	0.006	
Baseline proportion macular edema	0.000	SoliMix trial [11]
Baseline proportion cataract	0.050	SoliMix trial [11]
Baseline foot ulcer complications		
Proportion ulcer	0.001	SoliMix trial [11]
Proportion history of amputation	0.001	
Baseline neuropathy		
Proportion neuropathy	0.277	SoliMix trial [11]
Proportion depression	0.026	

bpm beats per min, *CDM* CORE Diabetes Model, *HbA1c* glycated hemoglobin, *SD* standard deviation

[a]Data on cholesterol, high-density lipoprotein, low-density lipoprotein, and triglycerides were not collected in the SoliMix trial; therefore, baseline values for these variables were taken from the LixiLan-L trial

the lowest-state utility of all concurrent comorbidities, and subsequent disutilities for complication events occurring in that year were applied; this results in an annual utility score for each simulated individual living with T2D.

Cost Data

Direct medical costs, comprising pharmacy costs, management costs (glucose test, needles, concomitant medication), and costs of T2D complications (cardiovascular disease

Table 2 Treatment effects used in the base case analysis

Treatment effects	iGlarLixi	Premix BIAsp 30
LSM (SE) change in HbA1c from baseline (%)	− 1.30 (0.06)	− 1.05 (0.06)
LSM (SE) change in BMI from baseline (kg/m²)	− 0.20 (1.10)	0.50 (1.10)
Insulin daily dose (from end of week 26) (dose steps)	40	58
Non-severe hypoglycemia events (per 100 patient-years)[a]	245	348
Severe hypoglycemia events (per 100 patient-years)	0.5	1

BIAsp 30 biphasic insulin aspart 30, *BMI* body mass index, *iGlarLixi* insulin glargine 100 units/mL plus lixisenatide, *LSM* least squares mean, *SE* standard error

[a]Hypoglycemia ≤ 70 mg/dL (≤ 3.9 mmol/L)

Table 3 Annual treatment costs in first-line and rescue therapy

Annual costs	iGlarLixi	Premix BIAsp 30
First-line therapy		
Acquisition cost (first year) (£)	949.88	408.03
Acquisition cost (≥ second year)[a] (£)	782.04	423.30
Metformin add-on (£)	44.37	44.37
Administration costs (needles) (£)	37.62	75.24
Self-glucose monitoring (£)	90.55	181.09
Annual cost (first year) (£)	1122.42	708.73
Annual cost (≥ second year) (£)	954.58	724.00
Rescue therapy		
Basal insulin (£)	445.14	445.14
Bolus insulin (£)	139.52	139.52
Metformin add-on (£)	44.37	44.37
Administration costs (needles) (£)	37.62	37.62
Self-glucose monitoring	90.55	90.55
Annual cost (£)	757.20	757.20

All drug costs are from the British National Formulary [31]

complications, renal complications, acute events, eye disease, neuropathy, foot ulcer, amputation [ESM Table S2]) were calculated (all sources were converted to £2021). Unit costs were collected from published literature and UK national sources (Table 3). Per the SoliMix study design, self-monitoring blood glucose was assumed to occur once daily for individuals on iGlarLixi and twice daily for those on premix BIAsp 30; all patients were assumed to be also receiving metformin as concurrent oral diabetes therapy [11, 21].

In Europe, iGlarLixi is available as two formulations: 100 units/mL insulin glargine plus 50 µ/mL lixisenatide (Suliqua® SoloStar pen 10–40 units) and 100 units/mL insulin glargine plus 33 µ/mL lixisenatide (Suliqua® SoloStar pen 30–60 units [iGlarLixi 100/33]). A weighted average of the two formulations based on average daily dosing in the SoliMix trial was calculated for the first year. From the second year onward, it was assumed that only the iGlarLixi 100/33 formulation was used for the maintenance phase, considering the end-of-trial dose (40 units).

Analyses

Incremental differences in costs and QALYs were obtained for iGlarLixi versus premix BIAsp 30; incremental cost-effectiveness ratio (ICER) estimates for iGlarLixi relative to premix BIAsp 30 were calculated as the cost differential divided by the difference in QALYs and reported as costs per QALY. Scenario analyses were performed on key parameters to assess the robustness of the base case findings (ESM Table S3). A probabilistic sensitivity analysis (PSA) was also conducted to test uncertainty in the model by random variation of key parameter inputs within plausible distributions. Probabilistic distribution of key transition probabilities (myocardial infarction, stroke, congestive heart failure, angina) were applied by bootstrap sampling around the 95% confidence interval of the regression coefficient. For utilities and treatment effects, mean and standard error values were used to generate random sampling within a beta-distribution function. Direct costs (excluding acquisition costs, which were assumed to be fixed) were randomly sampled based on log-normal distribution within a 20% variance.

RESULTS

Base Case Analysis

In the base case analysis, iGlarLixi was associated with a slightly higher QALY gain over the model time horizon (8.9 vs. 8.8; Table 4). Costs were slightly higher with iGlarLixi (£23,204 vs. £21,961), resulting in an ICER of £13,598 per QALY. Event rates for key diabetes-related complications were comparable for both treatment arms (ESM Fig. S1). Treatment switch to rescue therapy happened after year 6 in the iGlarLixi arm and after year 5 in the BIAsp 30 arm. In addition, treatment with iGlarLixi was associated with an initial decline in BMI, while patients receiving BIAsp 30 had an initial increase in BMI and a further increase when switched to rescue therapy (ESM Fig. S2). Cumulative incidence per 1000 patient-years of any hypoglycemic event was lower for iGlarLixi (40.42) compared with premix BIAsp 30 (43.27) and was similar for severe hypoglycemia incidence (0.12 vs. 0.13, respectively). A breakdown of the costs indicated that treatment acquisition was the main cost driver for both iGlarLixi (£11,750) and premix BIAsp 30 (£10,395; ESM Table S4). Costs associated with management and complications were generally similar between comparators.

Scenario Analyses

The robustness of the base case results was confirmed by extensive scenario analyses. iGlarLixi was shown to be a cost-effective alternative to BIAsp 30 in all scenarios tested, with all ICER estimates less than the WTP threshold of £20,000 per QALY (ESM Table S5).

Probabilistic Sensitivity Analysis

In the PSA analysis, 67% of iterations fell in the northeast quadrant of the cost-effectiveness plane, indicating that iGlarLixi was associated with an increase in QALY gained versus BIAsp 30, at a higher cost (Fig. 1a). At a WTP threshold of £20,000–30,000 per QALY gained, iGlarLixi was cost-effective in ~ 55–61% of cases (Fig. 1b).

DISCUSSION

In this study, iGlarLixi was associated with slightly more QALYs gained versus premix

Table 4 Cost-effectiveness results (base case analysis)

Cost-effectiveness parameters	iGlarLixi	Premix BIAsp 30
QALY (years)	8.9	8.8
Total cost (£)	23,204	21,961
Incremental QALY (years)	–	0.1
Incremental costs (£)	–	1243
ICER (£ per QALY gained)	–	13,598

ICER incremental cost-effectiveness ratio, *QALY* quality-adjusted life-year

BIAsp 30 in people with T2D suboptimally controlled with BI. The ICER for iGlarLixi was below the accepted WTP threshold of £20,000 per QALY gained, demonstrating that iGlarLixi is a cost-effective alternative to BIAsp 30 in this population; extensive scenario and sensitivity analyses confirmed the robustness of the base case findings. Although the unit cost of iGlarLixi is higher than BIAsp 30, this is partially offset by the reduced dosing frequency with iGlarLixi.

These findings support recent cost-effectiveness assessments comparing iGlarLixi with other BI plus GLP-1 RA combinations for the treatment of T2D in post–BI and post–GLP-1 RA settings [22, 23]. However, these studies used estimated relative treatment effects from indirect treatment comparisons to inform the model; the present study uses direct observations from SoliMix, the first randomized trial comparing BI and the GLP-1 RA fixed-ratio combination with premix insulin in adults living with T2D advancing from BI plus one or two OADs (metformin with or without SGLT2 inhibitors). Because results from a clinical trial were used to inform the model, the impact of treatment burden (i.e., the number of daily injections people living with T2D must endure) on medication adherence was not considered. Adherence to anti-diabetic medication is associated with glycemic control [24], and increased regimen complexity has been associated with poorer adherence in people living with diabetes receiving anti-diabetic medications [9, 25]. Therefore, it seems plausible that the simpler once-daily iGlarLixi regimen would be

associated with reduced treatment burden and better adherence than the twice-daily premix BIAsp 30 regimen, resulting in higher utility values and subsequent QALY estimates, but this remains to be confirmed. Additionally, the reduced nocturnal hypoglycemia and consequent improvement in quality of life observed with iGlarLixi versus BIAsp 30 observed in the SoliMix trial was not adequately captured by the present analysis and therefore not reflected in the QALYs gained.

Limitations

Because the analysis was conducted from a UK perspective, the results may not be applicable to other countries and currencies. Additionally, the data used in the analysis to predict long-term outcomes were relatively short term (26 weeks in the SoliMix trial); however, the robustness of the results were confirmed with sensitivity and scenario analyses. Owing to more rigorous monitoring and follow-up in the context of a randomized controlled trial, the incidence of severe hypoglycemia is generally lower than seen in routine clinical practice. As severe hypoglycemia rates were relatively low in the SoliMix trial, the impact on severe hypoglycemia in this analysis may be underestimated in those from an older—and therefore more frail—population and in those requiring third-party administration. In addition, this analysis did not consider the societal cost-effectiveness impact, including differences in administration burden with once-daily iGlarLixi versus twice-daily BIAsp 30 incurred by
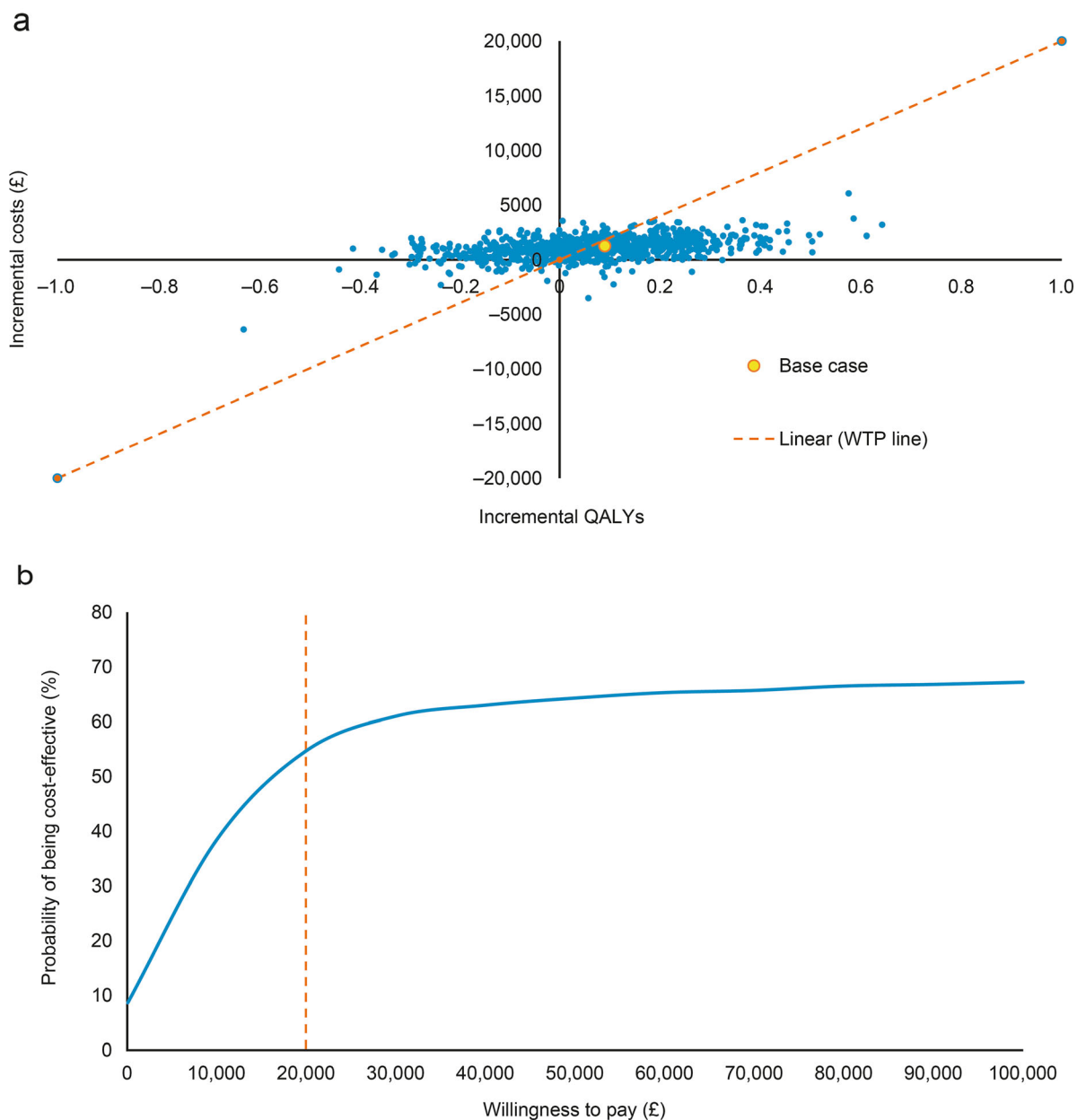
Fig. 1 Base case cost-effectiveness plane (**a**) and cost-effectiveness acceptability curve (**b**). *QALY* quality-adjusted life-year, *WTP* willingness-to-pay

health care practitioners in community settings. Furthermore, the risk equations for progression of disease risk factors were based on the UKPDS 68 [13] and UKPDS 82 models [14]. The UKPDS risk equations are widely used in diabetes simulation models [26–30]. It should be noted that the UKPDS trial ended in 2007 and UKPDS equations may not fully reflect current clinical practice. Finally, these findings use clinical trial data of people receiving iGlarLixi and BIAsp 30 and do not evaluate how differences in adherence, timing of initiation and health care

professional interaction may differ in routine clinical practice and any potential impact on outcomes observed. However, this limitation applies to all cost-effectiveness analyses applying trial data. Due consideration should also be given to other outcome measures, such as adverse events and patient-related outcome measures, when advancing diabetes therapy.

CONCLUSION

Over the lifetime of individuals living with T2D suboptimally controlled on BI therapy, iGlarLixi was associated with improved clinical outcomes at higher costs relative to premix BIAsp 30. At a WTP threshold of £20,000 per QALY gained, iGlarLixi was considered to be cost-effective versus premix BIAsp 30 from the perspective of the UK NHS.

ACKNOWLEDGEMENTS

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