ABSTRACT

Introduction: To evaluate the efficacy and safety as well as the long-term cost-effectiveness of insulin glargine 100 U/mL (IGlar) versus insulin degludec (IDeg) for the treatment of type 2 diabetes mellitus (T2DM) from the Chinese healthcare system perspective.

Methods: A systematic search of English and Chinese electronic databases for randomized controlled trials (RCTs) comparing IGlar with IDeg for the treatment of T2DM was performed, followed by a meta-analysis to compare the efficacy and safety of IGlar versus IDeg. The CORE Diabetes Model was used to estimate lifetime costs, quality-adjusted life years (QALYs) gained, and cost-effectiveness of IGlar versus IDeg. One-way and probabilistic sensitivity analyses were conducted to assess the underlying parameter uncertainty.

Results: Six RCTs were included in the meta-analysis. The IGlar group showed a statistically significant decrease in glycated hemoglobin (HbA1c) from baseline compared to the IDeg group (mean difference [MD] 0.08%, 95% confidence interval [CI] 0.01–0.14%, \( P = 0.02 \)). Body mass index (BMI) control was numerically better in the IGlar group than in the IDeg group (MD 0.07 kg/m\(^2\), 95% CI \(-0.01\) to \(0.14\) kg/m\(^2\), \( P = 0.08 \)). In terms of hypoglycemia, the incidence of non-severe overall hypoglycemia was comparable between the IDeg and IGlar patient groups (\( P \geq 0.05 \)), while the incidence of non-severe nocturnal hypoglycemia (relative risk [RR] 0.79, 95% CI 0.70–0.90, \( P < 0.01 \)) and the event rates of non-severe overall (RR 0.91, 95% CI 0.85–0.97, \( P < 0.01 \)) and non-severe nocturnal hypoglycemia (RR 0.91, 95% CI 0.85–0.97, \( P < 0.01 \)) were lower in the IDeg group. The incidences and event rates of both severe overall and nocturnal hypoglycemia were similar for the two groups (\( P > 0.05 \)). The cost-effectiveness analysis showed that IGlar is the dominant treatment option compared with IDeg, with a lifetime savings of 1004 Chinese yuan in direct medical costs and a net gain of 0.015 QALYs per patient. Both one-way and probabilistic sensitivity analyses confirmed the robustness of the results.
Conclusions: IGlar is a cost-saving option with incremental effectiveness compared with IDeg for the treatment of T2DM in China.

Funding: Sanofi China.

Keywords: Cost-effectiveness; Insulin degludec; Insulin glargine; Meta-analysis; Type 2 diabetes

INTRODUCTION

Type 2 diabetes mellitus (T2DM) is a progressive disease characterized by insulin resistance and the progressive loss of β-cell function, resulting in insulin deficiency. This disease accounts for 95% of all diabetes cases [1], and if uncontrolled, it can result in significant long-term morbidities and early mortality [2].

Globally, an estimated 422 million adults were living with diabetes in 2014, compared to 108 million in 1980. The age-standardized prevalence of diabetes has nearly doubled since 1980, increasing from 4.7 to 8.5% [2]. In China, the estimated overall prevalence of total diabetes was 10.9% among adults (114 million in total) in 2013 [3, 4]. Due to an aging population, it is expected that the absolute number of patients in China will continue to rise in future years.

In 2014, the total healthcare expenditure on diabetes was estimated to be $825 billion worldwide, the largest single share ($170 billion) of which was spent by China [5]. In 2014, the estimated direct cost per diabetic patient per year in China was around $446 [4]. The heavy economic burden of diabetes is mainly due to its complications, including heart attack, stroke, kidney failure, leg amputation, vision loss, and nerve damage. A 2009 Chinese study showed that 60.9% of patients with DM had at least one diabetic complication or related disease, with this percentage increasing to 71.2% in 2011 [6].

A study by Chen et al. revealed that the annual direct medical cost of DM patients with complications was 3.71-fold higher than that of those without a complication [7]. Therefore, both policy-makers and healthcare providers have an invested interest in preventing or slowing the progression of diabetes complications by achieving tight glycemic control.

Owing to the progressive nature of T2DM, a large number of patients require insulins to achieve glycemic control. Recent treatment guidelines have highlighted the importance of basal insulin therapy in people with T2DM [8–11]. Insulin glargine 100 U/mL (IGlar) was the first once-daily, long-acting insulin analog to be marketed, and it has been in clinical use for more than 15 years [12]. Compared with older human insulin formulations, such as Neutral Protamine Hagedorn (NPH), IGlar achieves a similar reduction of glycated hemoglobin (HbA1c) from baseline but with a significantly lower rate of hypoglycemic events [13]. Insulin degludec (IDeg) is described as a second-generation basal insulin with an ultra-long and stable action profile and lower pharmacodynamic variability [14, 15]. Two meta-analyses investigating the efficacy and safety of IGlar versus IDeg have been recently published [16, 17]. Trials included in the meta-analysis conducted by Liu et al. [16] were a mix of different study designs (randomized controlled trials [RCTs] and cross-over trials) and different dosing regimens of IDeg (once daily or three times a week), which may have confounded the findings. The other meta-analysis was conducted by Roussel et al. [17] who only incorporated clinical trials from the BEGIN series programs and ignored other studies. Therefore, an updated meta-analysis is needed to comprehensively illustrate the comparative efficacy and safety between these two basal insulins.

In addition to clinical evidence, economic evidence is of great importance to decision-makers with the aim to optimize resource use and service delivery. Several cost-effectiveness studies [18–23] comparing IGlar with IDeg for treating T2DM have been conducted in Western countries, such as the UK and Spain. All of these studies were conducted with a short time horizon (12 months) based on the rationale that the efficacy data were from treat-to-target trials with insulin doses adjusted to achieve similar glycemic control between treatments and, therefore, long-term modeling would not be informative. However, given that T2DM is a chronic progressive disease that could have
severe and long-term complications, a long-term simulation model is needed to capture the full economic values of the medications. 

The objective of our study was to investigate the efficacy, safety, and long-term cost-effectiveness of IGlar (100 U/ml) versus IDeg in patients with T2DM from the perspective of the Chinese healthcare system.

METHODS

Systematic Review and Meta-Analysis

We searched ten English and Chinese electronic databases (PubMed, Embase, Cochrane Central Register of Controlled Trials [CENTRAL], Web of Science, Cochrane library, ClinicalTrials.gov, CNKI, Wanfang, VIP, Chinese Clinical Trial Registry [ChiCTR; chictr.org.cn]) using the search items ‘glargine’ OR ‘Lantus’ AND ‘degludec’ OR ‘Tresiba.’ The time horizon of the literature search was up to March 2018. Only RCTs comparing IGlar with IDeg among T2DM patients were considered. The exclusion criteria included: not a RCT (i.e. crossover or self-controlled trials were excluded); subgroup analysis if original article was already included; repeat publications; publications not in Chinese or English; or no full text available. A total of six clinical trials were ultimately identified [24–29], among which two trials had extension phases. As several outcomes were not evaluated in the extension phase and their treatment durations were much longer than those of the other studies, we included only the original reports of the trials in our meta-analysis in order to reduce potential heterogeneity. The PRISMA flow chart and characteristics of the included trials are given in the Electronic Supplementary Material (ESM Fig. S1; ESM Table S1).

A total of 4219 T2DM patients who participated in the six clinical trials that compared IGlar (n = 1391) with IDeg (n = 2828) were included in the meta-analysis. The following outcomes were extracted for the meta-analysis: HbA1C reduction from baseline; changes in body mass index (BMI) and weight from baseline; and incidence and episode rates of hypoglycemia. The Cochrane Collaboration’s tool [30] was used to assess the risks of bias for the included studies. The meta-analysis was conducted using Cochrane’s Review Manager (RevMan 5.3). The continuous outcomes were measured by the mean difference (MD), dichotomous outcomes were measured by risk ratio (RR), and the hypoglycemia event rate (per patient year) was measured by log rate ratio.

Cost-Effectiveness Analysis

Model Overview

We employed a validated computer simulation model of diabetes (IQVIA CORE Diabetes model [CDM]) [31, 32] to estimate long-term health outcomes and the economic consequences of implementing interventions during the treatment of diabetes. The CDM allows results to be extrapolated from short-term trials to long-term outcomes. The model comprises 17 interdependent submodels that simulate the complications of diabetes, including angina, myocardial infarction, congestive heart failure, stroke, peripheral vascular disease, diabetic retinopathy, macular edema, cataract, hypoglycemia, ketoacidosis, lactic acidosis, nephropathy and end-stage renal disease, neuropathy, foot ulcer and amputation, pulmonary edema, and depression, in addition to nonspecific mortality. Each submodel is a Markov model using time, state, time-in-state, and diabetes type-dependent probabilities (where appropriate and available) to simulate the progress of patients through different states. For each cycle, the order in which the submodels run changes randomly. Monte-Carlo simulations are performed at the individual patient level using tracker variables to accommodate complex interactions between individual complication submodels. The CDM uses separate transition probabilities and management strategies for type 1 diabetes mellitus and T2DM, and source data for model parameters are obtained from a broad range of published clinical and epidemiological studies. The main sources of the long-term transition data are the Diabetes Control and Complications Trial (DCCT), United Kingdom Prospective Diabetes Studies (UKPDS), and Framingham studies, the
former two of which informed the relationship between glycemic control and diabetes prognosis, while the Framingham studies are a series of long-term, ongoing cardiovascular cohort studies. The CDM allows direct and indirect costs to be estimated, adjusts for quality of life, and allows users to perform cost-effectiveness and cost-utility analyses. Access to the model’s technical documentation that lists all data sources is available from the authors on request. A more detailed description of the structure of the IQVIA CORE model is given in a previous publication [31].

In order to reflect the chronic nature of T2DM and capture both mortality and T2DM-related complications over patients’ lifetime, a lifetime (50 years) horizon was used.

Gain of quality-adjusted life-years (QALYs) and direct costs expressed in 2017 Chinese yuan (CNY) from the perspective of the Chinese healthcare system were calculated. Both costs and clinical benefits were discounted at an annual rate of 3.0%. One-way sensitivity analyses and probabilistic sensitivity analyses were conducted on the key parameters to assess the robustness of the results.

**Clinical Inputs**

A simulated cohort of patients was defined mainly based on the baseline characteristics of patients in a RCT comparing IGlar with IDeg in Chinese T2DM patients [33]. Other baseline characteristics were sourced from the literature [3, 33–39]. Baseline cohort characteristics are presented in Table 1.

| Cohort                   | Mean | SD  | Source          |
|-------------------------|------|-----|-----------------|
| Start age (years)       | 56.0 | 8.6 | [33], Table 1   |
| Duration of diabetes (years) | 7.9  | 5.4 | [33], Table 1   |
| Proportion male (%)     | 50.8 | –   | [33], Table 1   |
| HbA1c (%)               | 8.2  | 0.9 | [33], Table 1   |
| SBP (mmHg)              | 131.89 | 15.14 | Table 1 |
| DBP (mmHg)              | 81.02 | 11.06 | Table 1 |
| Total cholesterol (mg/dL) | 181.60 | 39.10 | Table 1 |
| HDL-cholesterol (mg/dL) | 52.30 | 14.90 | Table 1 |
| LDL-cholesterol (mg/dL) | 112.92 | 44.86 | Table 1 |
| Triglyceride (mg/dL)    | 191.32 | 138.17 | Table 1 |
| BMI (kg/m²)             | 25.0 | 2.9 | [33], Table 1   |
| eGFR (mL/min/1.73 m²)   | 104.9 | 0   | [35], Table 1   |
| HAEM (g/dL)             | 1.38 | 0   | [35], Table 1   |
| White blood cells (10⁶/ml) | 7.0  | 0   | [35], Table 1   |
| Heart rate (bpm)        | 72   | 12  | [36], Fig 3     |
| Waist–hip rate          | 0.93 | 0   | [37], Table A    |
| UAER (mg/mmol)          | 2.0  | 0   | [35], Table 1    |
| Serum creatinine (mg/dL) | 1.1  | 0   | [37], Table A    |
| Serum albumin (g/dL)    | 3.9  | 0   | [37], Table A    |
| Proportion smokers (%)  | 28   | –   | [3], Table 1     |
| Cigarettes (n/days)     | 15.2 | –   | [38], Table 9.1  |

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This assumption recognizes that intensification to basal-bolus therapy will be required for patients to maintain glycemic control over the long term. Following application of the treatment effects based on the trial data, all treatment variables were assumed to follow the natural progression algorithms built into the CDM (as described by Palmer et al. [31]). For BMI, the treatment effect upon reaching the HbA1c 7.5% threshold was assumed to remain constant during treatment; this was a conservative approach as in reality weight may be regained gradually over time. Upon reaching the 7.5% HbA1c threshold, the treatment effects of basal-bolus therapy were applied to all patients based on data from the published paper [40].

**Costs**

Direct medical costs included acquisition costs for IGlar and IDeg, costs of treatment associated with diabetes-related complications, and costs of routine patient management. All costs were expressed in 2017 CNY. Costs associated with self-monitoring of blood glucose, self-injection, and oral anti-hyperglycemic medications were not included in the analyses as these costs were assumed to be the same across treatment arms. The costs of diabetes-related complications in the year of the event and the annual follow-up costs (each year of the simulation subsequent to the event) were mainly calculated from a study on the direct medical costs of diabetes-related complications using the sampling claims data collected by China Health Insurance Research Association (CHIRA) [41]. The detailed calculation equations are presented in ESM Tables S2 and S3. The costs inputs are shown in Table 3.
Utilities and Disutilities

Utilities and disutilities (measures of the impact on quality of life) associated with complications of diabetes were obtained from published sources as shown in ESM Table S4 \[42–46\].

Sensitivity Analyses

One-way sensitivity analysis and probabilistic sensitivity analysis were performed on selected key variables to explore the robustness of base-case results in relation to parameter uncertainties and modeling assumptions.

| Parameter | Value | Source |
|-----------|-------|--------|
| IGlar unit cost (CNY per IU) | 0.617 | Average bidding prices [51] |
| IDeg unit cost (CNY per IU) | 0.621 | Average bidding prices [51] |
| Insulin lispro unit cost (CNY per IU) | 0.254 | Average bidding prices [51] |

CVD complications

- MI 1st year cost: 73,414 \[41\]
- MI 2nd+ years cost: 23,207 \[41\]
- Angina 1st year cost: 35,486 \[41\]
- Angina 2nd+ years cost: 10,039 \[41\]
- CHF 1st year cost: 35,171 \[41\]
- CHF 2nd+ years cost: 18,658 \[41\]
- Stroke 1st year cost: 29,070 \[41\]
- Stroke 2nd+ years cost: 14,381 \[41\]
- Stroke death within 30 days cost: 15,887 \[41\]
- PVD 1st year cost: 21,375 \[41\]
- PVD 2nd+ years cost: 3358 \[41\]

Renal complications

- HD costs 1st year: 144,238 \[41\]
- Annual costs HD 2+ years: 116,005 \[41\]
- PD costs 1st year: 59,882 \[52\]
- Annual costs PD 2+ years: 48,842 \[52\]
- RT costs 1st year: 259,208 \[52\]
- Annual costs RT 2+ years: 68,572 \[52\]

Acute events

- Non-severe hypoglycemia cost: 801 \[41\]
- Severe hypoglycemia cost: 12,557 \[41\]
- Keto event cost: 12,128 \[41\]
- Lactic acid event cost: 8300 \[41\]
- Edema onset cost: 561 \[41\]

CHF Congestive heart failure, CVD cardiovascular disease, CYN Chinese yuan, HD hemodialysis, MI myocardial infarction, PVD peripheral vascular disease, PD peritoneal dialysis, RT renal transplant

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One-way sensitivity analysis and probabilistic sensitivity analysis were performed on selected key variables to explore the robustness of base-case results in relation to parameter uncertainties and modeling assumptions.
The following one-way sensitivity analyses were conducted: discounting rate (0, 5, or 8%), time horizon (10 or 20 years), the HbA1c threshold for changing treatment line (7 or 8%), hypoglycemic event rate (the same between two groups), BMI (the same between two groups), drug acquisition costs (±30%), and disease management costs (±20%).

A Monte Carlo simulation was used to perform probabilistic sensitivity analysis (PSA) with parameter inputs (utilities, costs, treatment effects, and cohort characteristics) sampled from fixed distributions with the mean and standard deviation values. For costs data, a range of ±10% was applied. The PSA used 1000 simulated patients over 1000 iterations to ensure stability of the results.

Compliance with Ethics Guidelines

This research is entirely based on secondary data sources and does not contain any studies with human participants or animals performed by any of the authors.

RESULTS

Meta-Analysis

The meta-analysis indicated that HbA1c reduction (%) from baseline to study end was significantly greater in patients on IGlar versus those on IDeg (Fig. 1a; MD 0.08%, 95% confidence interval [CI] 0.01–0.14%). In addition, both body weight gain (Fig. 1b; MD 0.17 kg, 95% CI –0.05 to 0.38 kg) and BMI (Fig. 1c; MD 0.07 kg/m², 95% CI –0.01 to 0.14 kg/m²) favored the IGlar group, but the differences between groups were not statistically significant.

In terms of hypoglycemia, the incidences (percentage of patients who experienced hypoglycemia) of non-severe overall hypoglycemia (Fig. 2a; RR 0.96, 95% CI 0.89–1.02), severe overall hypoglycemia (Fig. 2c; RR 0.68, 95% CI 0.40–1.14), and severe nocturnal hypoglycemia (Fig. 2d; RR 0.98, 95% CI 0.35–2.75) were comparable between the IDeg and IGlar groups, while the incidence of non-severe nocturnal hypoglycemia was significantly lower in IDeg group (Fig. 2b; RR 0.79, 95% CI 0.70–0.90).

The events rates (rate per patient-year) of non-severe overall hypoglycemia (Fig. 2e; RR 0.91, 95% CI 0.85–0.97) and non-severe nocturnal hypoglycemia (Fig. 2f, RR 0.70, 95% CI 0.61–0.82) were significantly lower in IDeg group than in IGlar group. The events rate of severe hypoglycemia was comparable between IDeg and IGlar (Fig. 2g; RR 0.92, 95% CI 0.53–1.59). Due to the rareness of the severe nocturnal hypoglycemia event reported in the clinical studies, the meta-analysis of severe nocturnal hypoglycemia event rate could not be performed.

Cost-Effectiveness Analysis

Base-Case Analysis

As illustrated in Table 4, patients treated with IGlar were projected with a net increase of 0.015 (95% CI 0.006–0.025) QALY gains over a patient’s lifetime compared with those treated with IDeg. The clinical benefit was the result of the reduced cumulative incidence of diabetes-related complications in the IGlar group (ESM Tables S5, S6). The mean lifetime discounted direct cost for the IGlar group was CNY 1004 lower (95% CI –1758 to –251) than that for the IDeg group, primarily owing to differences in the costs of drug acquisition and treatment of complications (i.e. cardiovascular disease and renal diseases). Consequently, the use of IGlar was found to predominate relative to the use of IDeg for the treatment of T2DM in China.

One-Way Sensitivity Analysis

One-way sensitivity analyses showed that the results were robust to parameter changes (Table 5). IGlar remained dominant in all scenarios tested, with the exception of the time horizon of 10 years, in which IGlar was the dominant medication. Within the range of all parameter changes, the results were most sensitive to the reduction of the discount rate to 0%.
Probabilistic Sensitivity Analysis

With 1000 Monte Carlo simulations, assuming a willingness-to-pay threshold of CNY 178,980 per QALY gained (threefold the gross domestic product per capita in 2017 in China), the probabilistic sensitivity analyses indicated that IGlar was dominant (more effective and less costly) in 22.4% of the simulations and cost-effective in 55.7% of the simulations. The incremental cost-effectiveness plane is presented in Fig. 3, and the resulting cost-effectiveness acceptability curve is presented in Fig. 4.

**DISCUSSION**

This is the first long-term cost-effectiveness analysis comparing IGlar with IDeg for the
treatment of patients with T2DM. Our study indicated that, compared with IDeg, IGlar was the dominant medication with a greater QALY gain and at a lower medical cost for T2DM patients in China. One-way and probabilistic sensitivity analyses pointed to the robustness of the results.

The availability of rising numbers of noninsulin antidiabetic agents has fostered a reluctance to use insulin among both physicians and patients. Nevertheless, in terms of achieving good glycemic control, the use of insulin, sooner rather than later, significantly reduces the risk of diabetic complications and may also slow or even halt diabetes progression [47]. Therefore, basal insulin is recommended for the treatment of newly-diagnosed T2DM patients with a HbA1c of ≥ 9.0% or fasting plasma glucose of ≥ 11.1 mmol/L, or patients with a HbA1c of ≥ 7.0% after 3 months of oral antidiabetic drug treatment [8]. When choosing basal insulin, physicians need to balance the efficacy of glycemic control and hypoglycemia risk.

Fig. 2 continued
HbA1c is the gold-standard of treatment efficacy as it measures glycemic control over several months and has a predictive value for diabetes complications [17]. The most recent meta-analysis [16] revealed that IGlar achieved a significantly greater HbA1c reduction from baseline than did IDeg, which is similar to our results. Several other previously published meta-analyses [48–50] reported non-inferior efficacy of HbA1c reduction between IGlar and IDeg. In our meta-analysis, IGlar was associated with significantly greater HbA1c reduction compared with IDeg. Apart from the efficacy, side effects, such as hypoglycemia, which is commonly associated with insulin treatments, also have a major impact on a patient’s life and pose a substantial cost burden through increased treatment costs and reduced productivity [23]. In our study, the incidence of non-severe overall hypoglycemia was comparable between the IDeg and IGlar patient groups, while the incidence of non-severe nocturnal hypoglycemia and the event rates of non-severe overall and non-severe nocturnal hypoglycemia were lower in the IDeg group. The incidence and event rate of several hypoglycemia were comparable between the two groups.

Long-term cost-effectiveness analysis that weighs the benefits of HbA1c reduction and risks of hypoglycemic episodes provides an integrated benefit–risk profile and a unique perspective that is needed for decision-making. In our study, after extrapolating the short-term efficacy data to predict long-term clinical outcomes and corresponding costs, we found that IGlar was associated with more QALY gains and lower costs for T2DM patients in China compared with IDeg over a lifetime horizon. As mentioned above, several other published economic analyses have explored the short-term cost-effectiveness of IGlar versus IDeg and concluded that IDeg is more cost-effective primarily due to the lower risk of hypoglycemic events [18–23]. However, for a chronic progressive disease that is prone to severe and long-term complications, a long-term simulation model is more likely to capture the full clinical and economic values of the medications. Another possible reason why our results differ from those of published papers is that the current study modeled multiple complications rather than only hypoglycemic events. For people with diabetes, complications, such as cardiovascular disease and foot ulcer, tend to consume more medical resources than does the management of hypoglycemic events.

There are several limitations to our study. First, the transition probabilities used in the CORE model were mainly derived from clinical trials and epidemiological studies conducted in Western populations. Potential differences may exist between Western and Chinese patient

### Table 4 Base-case analysis

| Parameter                  | IGlar   | IDeg    | Difference |
|----------------------------|---------|---------|------------|
| Discounted life expectancy (years) | 14.554  | 14.531  | 0.023      |
| Discounted QALYs           | 9.526   | 9.511   | 0.015      |
| Discounted direct costs (CNY) | 468,515 | 469,519 | - 1004     |
| Drug acquisition            | 121,307 | 121,244 | - 63       |
| Management                  | 1065    | 1063    | 2          |
| CVD                        | 135,739 | 136,541 | - 802      |
| Renal                      | 17,824  | 18,301  | - 477      |
| Ulcer/amputation/neuropathy | 100,792 | 100,888 | - 96       |
| Eye                        | 5084    | 5148    | - 64       |
| Hypoglycemia               | 86,704  | 86,334  | 370        |
| ICER (life expectancy)     | IGlar dominant |
| ICER (QALYs)               | IGlar dominant |

ICER Incremental cost-effectiveness ratio, QALY quality-adjusted life year

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There are several limitations to our study. First, the transition probabilities used in the CORE model were mainly derived from clinical trials and epidemiological studies conducted in Western populations. Potential differences may exist between Western and Chinese patient
populations. In the absence of any long-term followup data on Chinese diabetes patients, the transition probabilities from Western populations are still the best data currently available. Secondly, this study only considered direct costs, and indirect costs, such as costs associated with lost productivity, were not included. If a societal perspective is adopted, the overall benefit of IGlar may be underestimated due to the lower incidence of diabetic complications. Lastly, even though our study indicated that IGlar was the dominant treatment option compared with IDeg, the QALYs gained were fairly small, as illustrated through the CE plane that centered the cloud not far from 0 in the PSA. Consequently, caution is advised in interpreting these results.

Table 5 One-way sensitivity analyses

| Parameters                                      | QALY | IDeg | Difference | Cost (CNY) | IDeg | Difference | ICER                |
|------------------------------------------------|------|------|------------|------------|------|------------|---------------------|
| Discount rate 0%                                | 13.611 | 13.581 | 0.03       | 729,228     | 730,440 | −1212 | Dominant          |
| Discount rate 5%                                 | 7.81  | 7.799 | 0.01       | 365,673     | 366,540 | −867  | Dominant          |
| Discount rate 8%                                 | 6.064 | 6.058 | 0.005      | 266,543     | 267,239 | −696  | Dominant          |
| Time horizon 10 years                            | 5.377 | 5.381 | −0.001     | 205,164     | 205,506 | −343  | 77,843 (IDeg is cost-effective) |
| Time horizon 20 years                            | 8.196 | 8.195 | 0.001      | 366,787     | 367,446 | −659  | Dominant          |
| Change in line when HbA1c reaches at 7%         | 9.506 | 9.479 | 0.027      | 474,562     | 481,634 | −7072 | Dominant          |
| Change line when HbA1c reaches at 8%            | 9.541 | 9.526 | 0.015      | 458,073     | 464,290 | −6217 | Dominant          |
| Same hypoglycemia event rate                     | 9.526 | 9.509 | 0.017      | 468,515     | 469,734 | −1219 | Dominant          |
| No difference in BMI                             | 9.526 | 9.513 | 0.013      | 468,515     | 469,573 | −1058 | Dominant          |
| Drug costs increase 30%                          | 9.526 | 9.511 | 0.015      | 504,907     | 505,892 | −985  | Dominant          |
| Drug costs decrease 30%                          | 9.526 | 9.511 | 0.015      | 432,123     | 433,146 | −1023 | Dominant          |
| Management costs increase 20%                   | 9.526 | 9.511 | 0.015      | 537,956     | 539,174 | −1218 | Dominant          |
| Management costs decrease 20%                   | 9.526 | 9.511 | 0.015      | 399,073     | 399,863 | −790  | Dominant          |
| The treatment effects in IDeg group from Pan’s study [33] | 9.526 | 9.525 | 0.001      | 468,515     | 470,420 | −1905 | Dominant          |

Fig. 3 Incremental cost-effectiveness plane in probabilistic sensitivity analysis. CYN Chinese yuan
CONCLUSION

Compared with IDeg, IGlar appears to be an agent of choice for the treatment of T2DM patients in China. Over the lifetime treatment horizon, treatment with IGlar is projected to result in a small but significant (95% CI 0.006–0.025) QALY gain at a lower treatment cost.

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**Data Availability.** Qualified researchers may request access to patient level data and related study documents, including the clinical study report, study protocol with any amendments, blank case report form, statistical analysis plan, and dataset specifications. Patient-level data will be anonymized, and study
documents will be redacted to protect the privacy of trial participants. Further details on Sanofi’s data sharing criteria, eligible studies, and process for requesting access can be found at “https://doi.org/10.1007/s13300-015-0096-0”.

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REFERENCES

1. Hu H, Sawhney M, Shi L, Duan S. A systematic review of the direct economic burden of type 2 diabetes in China. Diabetes Ther. 2015;6(1):7–16. https://doi.org/10.1007/s13300-015-0096-0.

2. World Health Organization. Global report on diabetes. Geneva: World Health Organization. https://www.who.int/substance_abuse/publications/global_alcohol_report/en/. Accessed 8 Aug 2018.

3. Wang L, Gao PZM. Prevalence and ethnic pattern of diabetes and prediabetes in China in 2013. JAMA. 2017;317(24):2515–23. https://doi.org/10.1001/jama.2017.7596.

4. International Diabetes Federation. IDF diabetes atlas 8th edition. Brussels: International Diabetes Federation. https://diabetesatlas.org/resources/2017-atlas.html. Accessed 8 Aug 2018.

5. NCD Risk Factor Collaboration (NCD-RisC). Worldwide trends in diabetes since 1980: a pooled analysis of 751 population-based studies with 4.4 million participants. Lancet. 2008;371(9607):1513–30. https://doi.org/10.1016/s0140-6736(16)00618-8.

6. Huang Y, Vemer P, Zhu J, Postma MJ, Chen W. Economic burden in Chinese patients with diabetes mellitus using electronic insurance claims data. PLoS One. 2016;11(8):e0159297. https://doi.org/10.1371/journal.pone.0159297.

7. Chen XB, Tang L, Chen HY, Zhao LYHS. Assessing the impact of complications on the costs of type 2 diabetes in urban China. Chin J Diabetes. 2003;11(4):238–41.

8. Chinese Diabetes Society. Treatment guidelines for type 2 diabetes in China. Chin J Diabetes Mellit. 2018;10(1):4–67.

9. Ganda OP, Segal A, Blair E, Beaser R, Gagliardi J, Halprin E. GRM of the JCOC. CHAPTER 5. Clinical guideline for pharmacological management of adults with type 2 diabetes. Am J Manag Care. 2018;24(7):SP253–62. https://doi.org/10.1111/jmca.12102.

10. Internal Clinical Guidelines Team. Type 2 diabetes in adults: management. NICE guideline, no 28. London: National Institute for Health and Care Excellence (NICE);2015.

11. Inzucchi SE, Bergenstal RM, Buse JB, et al. Management of hyperglycemia in type 2 diabetes: a patient-centered approach: position statement of the American Diabetes Association (ADA) and the European Association for the Study of Diabetes (EASD). Diabetes Care. 2012;35(6):1364–79.

12. Owens DR, Biol FJ. Insulin preparations with prolonged effect. Diabetes Technol Ther. 2011;13:55–14. https://doi.org/10.2337/dc12-0413.

13. Horvath K, Jeitler K, Berghold A, et al. Long-acting insulin analogues versus NPH insulin (human isophane insulin) for type 2 diabetes mellitus (review). Cochrane Database Syst Rev. 2007;18(2):CD005613.

14. Heise T, Hermanski L, Nosek L, Feldman A, Rasmussen S, Haahr H. Insulin degludec: four times lower pharmacodynamic variability than insulin glargine under steady-state conditions in type 1 diabetes. Diabetes Obes Metab. 2012;14(9):859–64. https://doi.org/10.1111/j.1463-1326.2012.01627.x.

15. Heise T, Nosek L, Bettcher SG, Hastrup HHH. Ultra-long-acting insulin degludec has a flat and stable glucose-lowering effect in type 2 diabetes. Diabetes Obes Metab. 2012;14(10):944–50.

16. Liu W, Yang X, Huang J. Efficacy and safety of insulin degludec versus insulin glargine: a systematic review and meta-analysis of fifteen clinical trials. Int J Endocrinol. 2018;2018:8726046. https://doi.org/10.1155/2018/8726046.

17. Roussel R, Ritzel R, Boëlle-Le Corfec E, Balkau B, Rosenstock J. Clinical perspectives from the BEGIN and EDITION programmes: trial-level meta-analyses outcomes with either degludec or glargine 300 U/mL vs glargine 100 U/mL in T2DM. Diabetes Metab. 2018;44(5):402–9. https://doi.org/10.1016/j.diabet.2018.02.002.
18. Evans M, Mehta R, Gundgaard J, Chubb B. Cost-effectiveness of insulin degludec vs. insulin glargine U100 in type 1 and type 2 diabetes mellitus in a UK setting. Diabetes Ther. 2018;9(5):1919–30. https://doi.org/10.1016/j.diabet.2018.02.002.

19. Lalic N, Russel-Szymczyk M, Culic M, Tikkanen CKCB. Cost-effectiveness of insulin degludec versus insulin glargine U100 in patients with type 1 and type 2 diabetes mellitus in Serbia. Diabetes Ther. 2018;9(3):1201–16. https://doi.org/10.1007/s13300-018-0426-0.

20. Mezquita-Raya P, Darba J, Ascanio M, Ramírez de Arellano A. 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. Expert Rev Pharmacoecon Outcomes Res. 2017;17(6):587–95. https://doi.org/10.1080/14737167.2017.1345628.

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):275–91. https://doi.org/10.1007/s13300-017-0236-9.

22. Pollock RFTC. A short-term cost-utility analysis of insulin degludec versus insulin glargine U100 in patients with type 1 or type 2 diabetes in Denmark. J Med Econ. 2017;20(3):213–20. https://doi.org/10.1080/13696998.2016.1245663.

23. Evans M, Wolden M, Gundgaard J, Chubb B, Christensen T. 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):366–75. https://doi.org/10.1111/dom.12250.

24. Gough SC, Bhargava A, Jain R, Mersebach H, Rasmussen SBR. Low-volume insulin degludec 200 units/ml once daily improves glycemic control similarly to insulin glargine with a low risk of hypoglycemia in insulin-naive patients with type 2 diabetes: a 26-week, randomized, controlled, multinational, treat-to-target trial. Diabetes Care. 2013;36(9):2536–42. https://doi.org/10.2337/dc12-2329.

25. Meneghini L, Atkin SL, Gough SC, et al. BKN-3668 (BEGIN FTI)The efficacy and safety of insulin glargine and insulin degludec dosed at the same time daily. Diabetes Care. 2013;36(4):858–64. https://doi.org/10.2337/dc12-1668.

26. Onishi Y, Iwamoto Y, Yoo SJ, Clauson P, Tamer SCPS. Insulin degludec compared with insulin glargine in insulin-naive patients with type 2 diabetes: a 26-week, randomized, controlled, Pan-Asian, treat-to-target trial. J Diabetes Investig. 2013;4(6):605–12. https://doi.org/10.1111/jdi.12102.

27. Pan C, Gross JL, Yang W, Lv X. A multinational, randomized, open-label, treat-to-target trial comparing insulin degludec and insulin glargine in insulin-naive patients with type 2 diabetes mellitus naïve. Drugs R&D. 2016;16(2):239–49. https://doi.org/10.1007/s40268-016-0134-z.

28. Garber AJ, King AB, Del Prato S, et al. Insulin degludec, an ultra-long-acting basal insulin, versus insulin glargine in basal-bolus treatment with metatile insulin aspart in type 2 diabetes (BEGIN basal-bolus type 2): a phase 3, randomised, open-label, treat-to-target non-inferiority trial. Lancet. 2012;379(9825):1498–507. https://doi.org/10.1016/S0140-6736(12)60205-0.

29. Zinman B, Philis-Tsimikas A, Cariou B, et al. MCN-3579 (BEGIN OLTI)Insulin degludec versus insulin glargine in insulin-naive patients with type 2 diabetes: a 1-year, randomized, treat-to-target trial (BEGIN Once Long). Diabetes Care. 2012;35(12):2464–71. https://doi.org/10.2337/dc12-1205.

30. Higgins JPT, Green S (editors). Cochrane handbook for systematic reviews of interventions. Chichester: John Wiley & Sons, 2011.

31. Palmer AJ, Roze S, Valentine WJ, et al. The CORE diabetes model: projecting long-term clinical outcomes, costs and cost-effectiveness of interventions in diabetes mellitus (types 1 and 2) to support clinical and reimbursement decision-making. Curr Med Res Opin. 2004;20 Suppl 1:S5–26. https://doi.org/10.1185/030079904X1980.

32. McEwan P, Foos V, Palmer JL, Lamotte M, Lloyd A, Grant D. Validation of the IMS CORE diabetes model. Value Health. 2014;17(6):714–24. https://doi.org/10.1016/j.jval.2014.07.007.

33. Mu Y, Guo L, Li L, et al. The efficacy and safety of insulin degludec versus insulin glargine in insulin-naive subjects with type 2 diabetes: results of a Chinese cohort from a multinational randomized controlled trial. Chin J Intern Med. 2017;56(9):660–6.

34. Ji L-N, Lu J-M, Guo X-H, et al. Glycemic control among patients in China with type 2 diabetes mellitus receiving oral drugs or injectables. BMC Public Health. 2013;13(1):602. https://doi.org/10.1186/1471-2458-13-602.

35. Yang X, Ma RC, So W-Y, et al. Development and validation of a risk score for hospitalization for heart failure in patients with type 2 diabetes mellitus. Cardiovasc Diabetol. 2008;7(1):9. https://doi.org/10.1186/1475-2840-7-9.
36. Hayes AJ, Leal J, Gray AM, Holman RR, Clarke PM. UKPDS outcomes model 2: a new version of a model to simulate lifetime health outcomes of patients with type 2 diabetes mellitus using data from the 30 year United Kingdom Prospective Diabetes Study: UKPDS 82. Diabetologia. 2013;56(9):1925–33.

37. Folsom AR, Chambless LE, Duncan BB, Gilbert AC, Pankow JS. Prediction of coronary heart disease in middle-aged adults with diabetes. Diabetes Care. 2003;26(10):2777–84. https://doi.org/10.2337/diacare.26.10.2777.

38. Yang Yan, Nan Yi, Mengwu Tu, Wang Jijiang, Lili Wang YJ. Major finding of 2015 China adults tobacco survey. Chin J Health Manag. 2015;2016(2):85–7.

39. World Health Organization. Country profiles. Global status report on alcohol and health 2014. Geneva: World Health Organization.

40. Freemantle N, Mamdani M, Vilsbøll T, Kongsø JH, Kvist K, Bain SC. IDegLira versus alternative intensification strategies in patients with type 2 diabetes inadequately controlled on basal insulin therapy. Diabetes Ther. 2015;6(4):573–91. https://doi.org/10.1007/s13300-015-0142-y.

41. Duan X, Li C, Li YLQ. Epidemiological characteristics, medical cost and healthcare resource utilization of diabetes-related complications among Chinese patients with type 2 diabetes mellitus. Value Health 2018;21:540.

42. Beaudet A, Clegg J, Thuresson P-O, Lloyd A, McEwan P. Review of utility values for economic modeling in type 2 diabetes. Value Health. 2014;17(4):462–70. https://doi.org/10.1016/j.jval.2014.03.003.

43. Goldney RD, Phillips PJ, Fisher LJWD. Diabetes, depression, and quality of life: a population study. Diabetes Care. 2004;27(5):1066–70.

44. Marc E, Kamlesh K, Muhammad M, et al. Health-related quality of life associated with daytime and nocturnal hypoglycaemic events: a time trade-off survey in five countries. Health Qual Life Outcomes. 2013;11(90):1–9. https://doi.org/10.1186/1477-7525-11-90.

45. Marret E, Radican L, Davies MJ, Zhang Q. Assessment of severity and frequency of self-reported hypoglycaemia on quality of life in patients with type 2 diabetes treated with oral antihyperglycemic agents: a survey study. BMC Res Notes. 2011;4:251–8. https://doi.org/10.1186/1756-0500-4-251.

46. Matza LS, Boye KS, Yurgin N, Brewster-Jordan J, Mannix S, Shorr JMBB. Utilities and disutilities for type 2 diabetes treatment-related attributes. Qual Life Res. 2007;16(7):1251–65. https://doi.org/10.1007/s11136-007-9226-0.

47. Lovre D, Fonseca V. Benefits of timely basal insulin control in patients with type 2 diabetes. J Diabetes Complications. 2015;29(2):295–301. https://doi.org/10.1016/j.jdiacomp.2014.11.018.

48. Rodbard HW, Gough S, Lane W. 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. 2014;20(4):285–92. https://doi.org/10.4158/ep13287.or.

49. Vora J, Christensen T, Rana A, Bain SC. Insulin degludec versus insulin glargine in type 1 and type 2 diabetes mellitus: a meta-analysis of endpoints in phase 3a trials. Diabetes Ther. 2014;5(2):435–46. https://doi.org/10.1007/s13300-014-0076-9.

50. Einhorn D, Handelsman Y, Bode BW, Endahl LA, Mersebach H, King AB. Patients achieving good glycemic control (HBA1c <7%) experience a lower rate of hypoglycemia with insulin degludec than with insulin glargine: a meta-analysis of phase 3A trials. Endocr Pract. 2015;21(8):917–26. https://doi.org/10.4158/EP14523.OR.

51. Yaozhi database. China’s provincial drug bidding price [DB/OL]. https://db.yaozh.com/yaopinzhongbiao.

52. Wu J, Xiaoning HYL. Cost-effectiveness analysis of insulin aspart 30 versus insulin glargine in patients with type 2 diabetes in China. Chin Pharm J. 2016;51(5):242–7.