Cost-effectiveness of exenatide twice daily vs insulin glargine as add-on therapy to oral antidiabetic agents in patients with type 2 diabetes in China

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Aims: To estimate the long-term cost-effectiveness of exenatide twice daily vs insulin glargine once daily as add-on therapy to oral antidiabetic agents (OADs) for Chinese patients with type 2 diabetes (T2DM). Methods: The Cardiff Diabetes Model was used to simulate disease progression and estimate the long-term effects of exenatide twice daily vs insulin glargine once daily. Patient profiles and treatment effects required for the model were obtained from literature reviews (English and Chinese databases) and from a meta-analysis of 8 randomized controlled trials comparing exenatide twice daily with insulin glargine once daily add-on to OADs for T2DM in China. Medical expenditure data were collected from 639 patients with T2DM (aged ≥18 years) with and without complications incurred between January 1, 2014 and December 31, 2015 from claims databases in Shandong, China. Costs (2014 Chinese Yuan [¥]) and benefits were estimated, from the payers' perspective, over 40 years at a discount rate of 3%. A series of sensitivity analyses were performed.

Results: Patients on exenatide twice daily + OAD had a lower predicted incidence of most cardiovascular and hypoglycaemic events and lower total costs compared with those on insulin glargine once daily + OAD. A greater number of quality-adjusted life years (QALYs; 1.94) at a cost saving of ¥117 706 gained was associated with exenatide twice daily vs insulin glargine once daily. (i.e. cost saving of ¥60 764/QALY) per patient. Conclusions: In Chinese patients with T2DM inadequately controlled by OADs, exenatide twice daily is a cost-effective add-on therapy alternative to insulin glargine once daily, and may address the problem of an excess of medical needs resulting from weight gain and hypoglycaemia in T2DM treatment.

KEYWORDS: antidiabetic drug, cost-effectiveness, exenatide, insulin therapy, type 2 diabetes, pharmacoeconomics

1 | INTRODUCTION

Type 2 diabetes mellitus (T2DM) is characterized by chronic hyperglycaemia attributable to insulin resistance and/or insulin deficiency. There were 102.9 million adults with diabetes in China in 2014, accounting for 24.4% of global diabetes.1 Poor management of diabetes over time is associated with the development of myocardial infarction, stroke, blindness and other long-term diabetic complications, which may lead to disability and premature death.2 Blood glucose control is important in preventing and slowing the progression of these complications2-4; however, only 25.8% of Chinese patients receive diabetes treatment and only 39.7% of those treated have adequate glucose control.5 Health expenditure related to diabetes and its complications in China reached US$51 bn in 2015, which ranks second to the USA in worldwide health expenditure.6 Management of diabetes includes lifestyle interventions, patient education to facilitate self-care, and medication to control hyperglycaemia and cardiovascular disease risk.2,7 Glucose-lowering therapy for T2DM includes an oral antidiabetic drug (OAD)-based regimen or OADs plus an injectable drug when OADs fail to control glucose effectively. Exenatide twice daily and insulin glargine once daily, combined with OADs, are recommended as third-line therapy for patients with T2DM in Chinese guidelines for diabetes care.7 Previous studies show that exenatide twice daily and insulin glargine once daily are equally effective in lowering glycated haemoglobin (HbA1c) in patients inadequately controlled by OADs. In addition, exenatide twice daily is able to reduce body weight and has potential benefit with regard to cardiovascular outcomes.8-12 Exenatide twice daily decreases body weight through inhibiting food intake and appetite, promoting fullness and satiety, and reducing total body fat, particularly trunk or visceral fat.13 The major adverse events associated with it are mild gastrointestinal (GI) adverse events, which are usually well tolerated.8,9 Compared with exenatide twice daily, insulin glargine once daily is associated with significant weight gain and more frequent hypoglycaemic events,8-10 which may impede treatment effect, reduce quality of life and increase healthcare costs.14-17 Possible reasons for this weight effect include a proactive increase in caloric intake as a result of fear of hypoglycaemia, less energy loss owing to glycosuria reduction, fat- and muscle-building (anabolic) effects, and effects on the central nervous system influencing food intake18. Therefore, exenatide twice daily may be associated with better treatment adherence,19,20 and may be a cost-effective treatment option as add-on therapy to OADs compared with insulin glargine once daily. The long-term treatment benefit and cost-effectiveness of exenatide twice daily vs insulin glargine once daily has not

yet been determined, however, in real-world clinical practice in China. This would be useful information, in addition to clinical profile, in order to help health insurance providers, for example, to make a decision on reimbursement. The aim of the present study was to estimate the long-term cost-effectiveness of exenatide twice daily vs insulin glargine once daily as add-on therapy to OADs in Chinese patients with T2DM who failed to achieve glycaemic control on an OAD-based therapy regimen, using costs obtained in a real-world setting. Our analysis was performed from the perspective of healthcare payers.

2 | MATERIALS AND METHODS

2.1 | Cost-effectiveness model description

We used a previously validated patient-level fixed-time increment simulation model, the Cardiff Diabetes Model, to conduct the evaluation.21,22 It can run in two modes: deterministic analysis and probabilistic sensitivity analysis, with an additional ability to run univariate sensitivity analysis using its internal Tornado model. The model uses the 68 or 82 risk equations from the UK Prospective Diabetes Study (UKPDS) to estimate the risk of clinical endpoints and predict the occurrence of diabetes-related complications and mortality.23,24 The present study used the UKPDS 68-equation model as these equations are widely implemented in diabetes modelling and are extensively tested and validated compared with the UKPDS 82 equations.25-27 A sensitivity analysis was performed using the latter model. At the beginning of this modelling process, the simulated cohort is initialized with a set of baseline patient profiles (ie, patient characteristics and modifiable risk factors). Then patient characteristics (eg, age, diabetes duration) are updated as time elapses, and risk factors (eg, HbA1c, weight) are updated based on natural progression and treatment effects. The natural progressions of HbA1c, cholesterol and systolic blood pressure are modelled via the implementation of UKPDS 68 equations, and that of weight is modelled linearly based on a weight gain of 0.1 kg per year by default. The model simulates multiple disease courses through treatment-induced changes in HbA1c, cholesterol, systolic blood pressure and weight. It has two therapy arms (treatment and control). Treatment effects vary by therapy arm, resulting in differences in risk factors and clinical events. Each arm comprises 3 therapy lines which reflect the progressive nature of T2DM and the stepwise approach taken to its treatment. A patient receives a particular therapy until his/her HbA1c level crosses the escalation threshold, at which point he/she moves onto the next therapy line. The patient ends the simulation when death occurs or time horizon is reached. Cost-effectiveness is assessed in terms of cost per quality-adjusted life-year (QALY) gained. In the present study, we simulated a cohort of 1000 patients over 40 years, and the simulation was repeated 1000 times. We used an annual discount rate of 3% for costs and benefits based on the World Health Organization guidelines.28 Patient profiles, treatment effects and pharmacy costs for antidiabetic therapies, costs and disutility associated with diabetesrelated events are required to run the model. These data were obtained from literature review and claims database study.

2.2 | Literature review of patient profile and treatment effect

We systematically searched for eligible studies in both English (PubMed, Web of Knowledge, ScienceDirect and OVID) and Chinese (China National Knowledge Infrastructure, Wanfang Data and Chongqing VIP) databases. The keywords used were: exenatide; Byetta; glargine; Lantus; type 2 diabetes; and non-insulindependent diabetes mellitus. The terms were combined and adapted to search relevant publications dating from January 2009 to June 2016, based on time at which approval for the drug was received from the Chinese Food and Drug Administration (exenatide 2009; Table S1). Only head-to-head randomized controlled trials (RCTs) or observational studies comparing treatment effect of exenatide twice daily vs insulin glargine once daily as add-on therapy in Chinese patients (aged ≥18 years), inadequately controlled by OADs alone, were included. Patients were injectable-drug-naive at baseline. The included studies had to have HbA1c as the primary outcome indicator and a study duration of up to 12 weeks. The exenatide treatment regime was administered twice daily (Table S2). Two reviewers independently evaluated the search results and extracted data, and any disagreements between the reviewers were resolved through consultation with a third reviewer. After removal of duplicates, we obtained 383 studies from database searches. Title and abstract screening resulted in 30 papers for detailed review. After examination of the full-text articles, 8 head-to-head RCTs were identified (Figure S1 and Table S3).29-36

2.3 | Meta-analysis of patient profile and treatment effect

A series of independent meta-analyses were performed to synthesize data (ie, patient profiles and treatment effects) for exenatide twice daily + OAD and insulin glargine once daily + OAD from the 8 head-to-head RCTs.29-36 As the data were continuous variables, we used weighted mean difference and 95% confidence intervals to describe them. Meta-analyses were carried out using STATA version 11.0. Heterogeneity was quantified using the I-squared statistic. A fixed-effect model was used when no significant heterogeneity was detected among studies (P > .10, I2 ≤ 50%), otherwise a random-effect model was used (Figures S2-S16 and Tables S4 and S5).

2.4 | Claims database study on healthcare utilization

Expenses for treatment of diabetes-related complications were calculated based on the Jinan Municipal Claims database, with index dates between January 1, 2014 and December 31, 2015. The database contains 639 adult patients with T2DM (aged ≥18 years) who met one of the diagnostic criteria for diabetes based on fasting plasma glucose of ≥7.0 mmol/L, and/or 2-hour postprandial plasma glucose of ≥11.1 mmol/L or repeat glucose testing in case of uncertainty. These patients had regular follow-ups at the Shandong Provincial Hospital for their diabetes care and/or complications. Two medical doctors reviewed the medical records of all these patients and confirmed their clinical diagnoses of diabetes-related complications, including ischaemic heart disease, myocardial infarction, heart failure, stroke, chronic kidney failure, diabetic retinopathy, ulcer or amputation. The costs of glucose-lowering therapy (ie, exenatide twice daily + OAD, insulin glargine once daily + OAD) were estimated based on the Shandong Provincial Claims database, with index dates between January 1, 2014 and December 31, 2014. A total of 699 patients with T2DM aged ≥18 years were identified and included in the data analysis if they had a diagnosis of T2DM based on either a diagnostic code (disease codes of E11, International Classification of Diseases10), or on ≥3 prescriptions of OADs, or OADs plus injectable glucose-lowering drugs in the preceding 6 months. Glucose-lowering drugs included metformin, sulphonylureas, meglitinides, α-glucosidase inhibitors, thiazolidinediones, dipeptidyl peptidase-4 inhibitors, exenatide twice daily or insulin glargine once daily. The study was reviewed and approved by the Medical Ethics Committee of the Shandong Provincial Hospital affiliated to Shandong University (No. 2015057).

2.5 | Model inputs

2.5.1 | Patient profile, treatment strategy and HbA1c threshold The initial simulated cohort consisted of patients inadequately controlled by OADs, for whom baseline patient profiles were mainly synthesized from meta-analyses of the 8 head-to-head RCTs.29-36 As "height" and "proportion of smokers" were unavailable in the RCTs, data from national observational studies in China were used (Table 1).37,38 Patients initialized the model once they were on treatment with either exenatide twice daily + OAD (treatment arm) or insulin glargine once daily + OAD (control arm), which was regarded as "first therapy line" in the present study. In case of inadequate glucose control, therapy intensification commenced. We used an HbA1c level of 7.5% as the escalation threshold for both arms, to switch from "first therapy line" to "second therapy line" and from "second therapy line" to "third therapy line." Basal insulin and neutral protamine hagedorn insulin, being common rescue therapy in China, were used as both second and third therapy lines for both arms.

2.5.2 | Treatment effect and adverse effect The primary benefit applied to exenatide twice daily + OAD and insulin glargine once daily + OAD was a reduction in HbA1c level, which was synthesized from meta-analysis of the 8 head-to-head RCTs.29-36 Other treatment-induced effects, including changes in cholesterol and weight and incidences of adverse events, were also evaluated using the 8 RCTs.29-36 Hypoglycaemia was differentiated as symptomatic or severe in the model, but was not differentiated in most trials; thus the probability of severe hypoglycaemia was assumed to be 2% of all reported hypoglycaemia, with the remaining 98% being symptomatic, based on a Chinese observational study.17 The treatment effects of both second and third therapy line "insulin rescue therapy" used the inherent insulin therapy profile of the Cardiff Diabetes Model (Table 1).39

2.5.3 | Costs From the perspective of healthcare payers, direct medical costs associated with diabetes-related complications, adverse events, body mass index (BMI) changes and drug acquisitions were included. All costs were converted to 2014 Chinese Yuan (¥) using the Chinese Consumer Price Index.40 One US dollar was equal to 6.143 Yuan in 2014.41 Costs for diabetes-related complications were split into fatal or non-fatal costs, which were applied in the cycle where

the event occurred. For those surviving the event, maintenance costs were used in all subsequent years until patient death or end of the simulation. Non-fatal costs and maintenance costs associated with diabetes-related complications were obtained from the Jinan Municipal Claims database. Because fatal costs of all vascular events were unavailable, they were evaluated from a published study in Chinese patients with T2DM (Table 2).42 Costs of drug treatments and related consumables (eg, needle for injection, sterilized medical supplies) were obtained from the Shandong Provincial Claims database. The average annual cost for patients on exenatide twice based on the inherent insulin therapy profile included in the Cardiff Diabetes Model.

TABLE 1 Data inputs: baseline patient profile and treatment effects

Baseline patient profile[a]	Inputs	Source
Patient characteristics		
Age, year	50.59 (1.81)	29,31–36
Female, %	46 (3)	30,31,34,36
Duration of diabetes, year	4.78 (0.46)	29,31,32,34,36
Height, meter	1.64 (0)	37
Current smokers, %	18 (0)	38
Modifiable risk factors		
HbA1c, %	8.77 (0.11)	29–36
Total cholesterol, mmol/L	5.5 (0.22)	31,33,34,36
HDL cholesterol, mmol/L	1.09 (0.04)	33,34,36
Systolic blood pressure, mm Hg	133.23 (1.33)	36
Weight[b], kg	78.75 (2.23)	29–36
Treatment effects of exenatide twice daily + OAD[a]	**Inputs**	**Source**
HbA1c change, %	−1.77 (0.24)	29–36
Total cholesterol change, mmol/L	−0.76 (0.32)	31,33,34,36
HDL cholesterol change, mmol/L	0.12 (0.08)	33,34,36
Weight change[b], kg	−7.33 (1.79)	29–36
Probability of symptomatic hypoglycaemia	0.068 (0.017[c])	17,29,31–36
Probability of severe hypoglycaemia	0.001 (0.003[c])	17,29,31–36
GI adverse events	0.31 (0.03[c])	29,31,33–36
Treatment effects of insulin glargine once daily + OAD[a]	**Inputs**	**Source**
HbA1c change, %	−1.59 (0.26)	29–36
Total cholesterol change, mmol/L	0.02 (0.08)	31,33,34,36
HDL cholesterol change, mmol/L	0.15 (0.1)	33,34,36
Weight change[b], kg	1.80 (0.25)	29–36
Probability of symptomatic hypoglycaemia	0.149 (0.024[c])	17,29,31–36
Probability of severe hypoglycaemia	0.003 (0.004[c])	17,29,31–36
GI adverse events	0.04 (0.01[c])	29,31,33–36
Treatment effects of insulin rescue therapy[d]	**Inputs**	**Source**
HbA1c change, %	−1.11	39
Total cholesterol change, mmol/L	0	39
HDL cholesterol change, mmol/L	0	39
Weight change, kg	1.9	39
Probability of symptomatic hypoglycaemia	0.616	39
Probability of severe hypoglycaemia	0.022	39

Data are mean (standard error).

[a] Most variables were estimated from pooled data from 8 head-to-head RCTs using meta-analysis. Unavailable data were obtained from published observational studies.

[b] For studies only reporting BMI, weight was calculated by: weight = BMI*height 2, with height assumed to be 1.64 m.

[c] Calculated as Square Root Calculations (probability* (1 − probability)/ numbers of subjects).

[d] Variables used the inherent insulin therapy profile of the Cardiff Diabetes Model, in which all standard errors are 0.

TABLE 2 Data inputs: annual direct medical costs for events (2014¥)

Fatal costs of complications[a]	Inputs
Ischaemic heart disease	–
Myocardial infarction	46547.02
Congestive heart failure	15479.64
Stroke	14059.41
Blind	–
End-stage renal disease	–
Amputation	18232.95
Ulcer	0
Non-fatal costs of complications[a]	**Inputs**
Ischaemic heart disease	13158.69 (479.5)
Myocardial infarction	38068.42
Congestive heart failure	14620.27 (1070.25)
Stroke	13331.72 (764.48)
Blind	14602.46 (444.85)
End-stage renal disease	14471.55 (516.84)
Amputation	20182.62
Ulcer	17483.38 (1315.17)
Maintenance costs of complications[a]	**Inputs**
Ischaemic heart disease	2982.78 (394.09)
Myocardial infarction	5926.58
Congestive heart failure	2819.93 (1628.24)
Stroke	3871.55 (665.8)
Blind	4734.56 (439.19)
End-stage renal disease	5068.07 (492.13)
Amputation	3208.62
Ulcer	5309.61 (1397.7)
BMI-related prescription costs[b]	**Inputs**
24	1519.5
25	3742.7
26	5965.9
27	8189
28	10412.2
29	12635.4
30	14858.6
31	17081.7
32	19304.9
33	21528.1
34	23751.2
35	25974.4
36	28197.6
37	30420.8
38	32643.9
39	34867.1
≥40	37090.3

Data are mean (standard error).

[a] Non-fatal and maintenance costs were obtained from claims database, with fatal costs obtained from a published study.[42]

[b] Costs were estimated from an observational study.[43] Assumptions: the starting point BMI = 25 kg/m^2, BMI-related costs per month = ¥246.8; the slope (cost per month/BMI) = ¥146.6 in 2007. For BMI ≤ 23 kg/m^2 the cost was set to 0.

daily + OAD was ¥5238.85, and for those on insulin glargine once daily + OAD it was ¥3797.91. The insulin cost per kg weight per day for rescue therapy was estimated and assumed to be ¥0.137,

Severe hypoglycaemia is an event requiring medical assistance because of severe impairment in consciousness,7 and is associated with healthcare costs (annual costs: ¥3829.96) which were abstracted from a Chinese observational study.17 Because the GI effects of exenatide twice daily

usually do not need to be treated with medication, their related costs were unavailable in the claims database and published studies. We assumed there was no cost for them. Based on interview of physicians, annual costs of ¥200 to ¥1000 per patient for treating severe GI adverse events were set in the sensitivity analyses. BMI-related prescription costs which relate to increased prescribing costs per BMI unit increase, were calculated and estimated from an observational study in China (Table 2).43

2.5.4 | Utilities Because there is a lack of country-specific utility decrements for diabetes-related events in China, the data were primarily adopted from the UKPDS 62 study.44 For those data unavailable in the UKPDS study, such as disutility for end-stage renal disease and blindness,45 hypoglycaemic events,16 changes in BMI46 and GI adverse events,47 we used utility obtained from other studies (Table 3).

2.5.5 | Sensitivity analyses A series of sensitivity analyses were conducted to assess the impact of uncertainty and variability with regard to the model inputs, such as patient characteristics, adverse events, time horizon, discount rate, costs and disutility associated with weight change and diabetesrelated events, and maintenance of weight effect with exenatide twice daily + OAD. We also tested assumptions that therapy discontinuation rates of exenatide twice daily would be 34.7% and of insulin glargine once daily would be 38.3% (by day 365 of follow-up), based on published real-world data20 and on alternative patient profiles and treatment effects synthesized from meta-analysis of the head-tohead RCTs with study duration of up to 24 weeks.29,31,32,35,36 Firstly, an initial tornado model was conducted to investigate key model variables, then, detailed univariate and multi-way sensitivity analyses were successively conducted to further assess the effects of certain variables. In the probabilistic sensitivity analysis, treatment-induced HbA1c effects and weight changes were sampled from a normal distribution, costs were modelled using a gamma distribution and utility decrements followed a beta distribution. A scatter plot of the incremental cost-effectiveness ratios (ICERs) and a cost-effectiveness acceptability curve were generated.

TABLE 3 Data inputs: health utility changes for events

Health utility changes	Inputs	Source
Ischaemic heart disease	−0.09	44
Myocardial infarction	−0.055	44
Congestive heart failure	−0.108	44
Stroke	−0.164	44
Blindness	−0.074	45
End stage renal disease	−0.263	45
Amputation	−0.28	44
Ulcer	−0.059	44
Severe hypoglycaemia	−0.047	16
Symptomatic hypoglycaemia	−0.0142	16
BMI (per unit increase)	−0.0472	46
BMI (per unit decrease)	+0.0171	46
GI adverse reaction	−0.04	47

3 | RESULTS

3.1 | Predicted health events and costs

In the base case analysis, both arms showed positive effects in lowering HbA1c levels for patients. Exenatide twice daily + OAD was associated with a decrease in weight, while insulin glargine once daily + OAD was associated with an increase in weight (Figures S17 and S18). Overall, the model predicted lower incidence of most vascular events, mortality and hypoglycaemic events in patients receiving exenatide twice daily + OAD compared with those on insulin glargine once daily + OAD. Correspondingly, the costs for treating most events were lower for exenatide twice daily + OAD, except for congestive heart failure, blindness and nephropathy, which were a little higher for exenatide twice daily + OAD. In addition, exenatide twice daily + OAD was associated with lower pharmacy costs and BMI-related prescription costs than insulin glargine once daily + OAD. In general, exenatide twice daily + OAD was associated with lower total costs of long-term medical care than insulin glargine once daily + OAD (Table S6).

3.2 | Incremental cost-effectiveness ratio

For an individual patient, the total discounted costs accumulated over 40 years on exenatide twice daily + OAD were ¥117 706 lower than insulin glargine once daily + OAD, whilst 1.94 more QALYs were gained with exenatide twice daily + OAD than insulin glargine once daily + OAD. This resulted in a mean cost saving of ¥60 764 per QALY gained with exenatide twice daily + OAD (ie, the ICER was −¥60 764/ QALY gained for exenatide twice daily + OAD vs insulin glargine once daily

+ OAD), indicating that exenatide twice daily + OAD would lead to more QALYs and lower costs for patients (Table 4).

TABLE 4 Data outputs: costs, QALYs and cost-effectiveness results for exenatide twice daily + OAD vs insulin glargine once daily + OAD in the base case analysis (per patient)

Cost-effectiveness	Insulin glargine once daily + OAD	Exenatide twice daily + OAD	Difference
Discounted cost	357268.39	239562.34	−117 706
Discounted QALYs	12.33	14.26	1.94
Discounted life-years	16.17	16.2	0.03
Cost per QALY		Dominates	−60 764
Cost per life-year		Dominates	−4 081 711

3.3 | Variables influencing the ICER

The results of the sensitivity analyses verified the base case results, which calculated that exenatide twice daily + OAD was cost-saving and generated more QALY benefit compared with insulin glargine once daily + OAD. The tornado model showed that BMI, utility and HbA1c were influential variables in the ICER result. Exenatide twice daily + OAD remained superior to insulin glargine once daily + OAD, when age changed from 40 to 70 years, proportion of women (or smoking) changed from 0 to 1, and when HbA1c level (or utility, cholesterol level, adverse events, costs) changed to the upper (+25%) and lower (−25%) percentage of their distributions (Figure S19). In the univariate sensitivity analysis, when an HbA1c threshold value of 8.0% for therapy switch was used, both the cost saving and incremental QALY benefits gained by exenatide twice daily + OAD were slightly reduced, but exenatide twice daily + OAD remained superior with an ICER of −¥63 363/QALY. BMI-associated disutility was varied. In the scenario where utility change per unit BMI change was 0, although the incremental QALYs gained by exenatide twice daily + OAD decreased to 0.01, the result still favoured exenatide twice daily + OAD. In the scenarios where disutility per unit of BMI gain halved or an alternative disutility profile was used, the resulting cost savings gained by exenatide twice daily + OAD remained high at −¥101 754/QALY

TABLE 5 Data outputs: costs, QALYs and cost-effectiveness results for exenatide twice daily + OAD vs insulin glargine once daily + OAD in the sensitivity analysis (per patient)

Sensitivity analysis	Difference in Cost, ¥	Difference in QALY	ICER, ¥
Univariate sensitivity analysis			
HbA1c threshold value for therapy switch 8.0%	−116 653	1.84	−63 363
Utility decrement per unit BMI gain halved	−117 706	1.16	−101 754
Utility weight +0.014 per unit BMI decrease and −0.014 per unit BMI increase	−117 706	0.77	−152 413
Utility change per unit BMI change = 0	−117 706	0.01	−17 993 707
BMI-related prescription costs halved	−60 093	1.94	−31 022
BMI-related prescription costs = 0	−2480	1.94	−1280
Weight loss with exenatide twice daily + OAD was regained after 2 years	−21 333	0.58	−36 614
All hypoglycaemias of both drugs are severe events	−118 073	1.94	−60 856
Hypoglycaemia of insulin glargine once daily + OAD = exenatide twice daily + OAD	−117 691	1.93	−60 832
Cost of severe hypoglycaemia halved	−117 662	1.94	−60 741
Utility decrement of hypoglycaemia doubled	−117 706	1.95	−60 446
GI adverse events in insulin glargine once daily + OAD = exenatide twice daily + OAD	−117 706	1.96	−60 116
Cost of GI adverse events ¥200	−117 542	1.94	−60 679
Cost of GI adverse events ¥1000	−116 887	1.94	−60 341
Utility decrement of GI adverse events doubled	−117 706	1.9	−61 792
Discount rate (costs and benefits) 5%	−96 222	1.56	−61 639
Alternative costs of diabetes-related complications from published article[42]	−117 735	1.94	−60 779
Model time horizon set to be 10 years	−58 638	0.86	−67 877
Model time horizon set to be 20 years	−96 428	1.59	−60 833
Model time horizon set to be 30 years	−116 261	1.9	−61 248
Therapy discontinuation rates of exenatide twice daily are 34.7% and insulin glargine once daily are 38.3% based on published real-world data[20]	−119 039	1.97	−60 541
Use UKPDS 82 risk equations to run model	−138 408	2.29	−60 338
Annual additional disutility due to one more daily injection with exenatide twice daily set at 0.01	−117 706	1.91	−61 687
Multi-way sensitivity analysis			
Use alternative patient profile and treatment effect from head-to-head RCTs ≥24 weeks	−117 059	1.91	−61 319
BMI-related costs = 0 and utility change per unit BMI change = 0	−2480	0.01	−379 043
BMI-related costs = 0 and model time horizon = 20 years	−1483	1.59	−936
BMI-related costs = 0 and use of UKPDS 82 risk equations	−4290	2.29	−1870
Weight loss with exenatide twice daily + OAD was regained after 2 years and model time horizon = 20 years	−16 231	0.50	−32 568
Probabilistic sensitivity analysis	**−123 945**	**1.90**	**−65 228**

or -¥152 413/QALY. Decreases in BMI-related prescription costs would have negative effects on the results, but when the costs were halved or excluded from the model, exenatide twice daily + OAD remained superior to insulin glargine once daily + OAD, with ICERs of -¥31 022/QALY or -¥1280/QALY. In the scenario where initial weight loss with exenatide twice daily + OAD was regained after 2 years, the cost saving per QALY gained by exenatide twice daily + OAD decreased by 39.7%, but it remained superior. Adverse events, including hypoglycaemia and GI reactions, were also investigated. Changes in the incidence, costs and disutility of the adverse events resulted in corresponding changes in cost savings and/or incremental QALY benefits, but they were small and did not change the result. In addition, alternative discount rate, costs of diabetes-related complications and time horizon, as well as the assumption on therapy discontinuation and the use of UKPDS 82 risk equations did not change the conclusion (Table 5). In the multi-way sensitivity analysis, alternative profiles from RCTs of up to 24 weeks resulted in similar cost savings and incremental QALYs gained by exenatide twice daily + OAD compared with that of the base case; however, when no BMI-related costs and no quality-oflife impacts were considered, both the cost savings and QALYs reduced greatly, but the results still favoured exenatide twice daily + OAD. Other scenario analyses also showed that exenatide twice daily + OAD was superior to insulin glargine once daily + OAD (Table 5). In the probabilistic sensitivity analysis, exenatide twice daily + OAD generated an incremental QALY benefit of 1.90 at a cost saving of ¥123 945 vs insulin glargine once daily + OAD. This resulted in an ICER of -¥65 228/QALY, higher than that of the base case. Almost all of the simulations were located in the southeast quadrant of the ICER scatter plot figure, which means exenatide twice daily + OAD gained more QALY benefits at a lower cost than insulin glargine once daily + OAD. Exenatide twice daily + OAD was cost-effective in 100% of the simulations, using a cost-effective threshold value of ¥46 629 (GDP per capita in China in 2014; Figures S20 and S21).

4 | DISCUSSION

From the perspective of healthcare payers, the present study provides the first comparison of long-term cost-effectiveness of exenatide twice daily vs insulin glargine once daily as add-on therapy in patients with T2DM who are inadequately controlled on OADs, by using the real-world costs from a claims database in China. The results indicated that exenatide twice daily + OAD was a superior therapy (with higher total QALY benefits gained but lower total costs) to insulin glargine once daily + OAD, offering an effective third-line therapy for the management of T2DM. The cost-effectiveness results remained stable in the sensitivity analyses. Treatment of T2DM should not only provide optimum efficacy, tolerability and safety for patients, but also needs to minimize adverse events and support comprehensive cardiovascular risk reduction.49,50 Obesity or being overweight is common in patients with diabetes, which is usually complicated with hypertension, dyslipidaemia and risk of cardiovascular disease,2,7,38 and is associated with a reduction in quality of life and treatment adherence, and healthcare costs increment.7,15,46 Unfortunately, weight gain is a common adverse effect related to many antidiabetes agents, including insulin.7 Even modest weight losses of 5% to <10% are associated with significant improvements in cardiovascular disease risk factors (eg, HbA1c, triglycerides and blood pressure),14 and avoidance of weight gain in T2DM treatments may reduce costs in the long term.15 The results of the present study further confirm the importance of treatment-induced weight effect on the long-term cost-effectiveness results. Either when disutility and costs associated with weight changes were varied, or when weight regain with exenatide twice daily + OAD was considered, the cost savings and/or incremental QALYs changed to a great extent, although the result still favoured exenatide twice daily + OAD. Thus, agents such as exenatide twice daily that not only improve glucose

control, but also have a beneficial weight control effect and cardioprotective efficacy, may bring extra benefit to patients.11,12 Hypoglycaemia is also a common adverse event associated with many antidiabetes drugs. It may impede treatment effect by suboptimal adherence, and affect quality of life and increase healthcare costs.7,16,17 In the present study, exenatide twice daily + OAD was associated with lower incidence of hypoglycaemia than insulin glargine once daily + OAD, but the incidence rates in both arms were low and did not differ significantly; thus, hypoglycaemia had little influence on the results. Although exenatide twice daily + OAD was associated with a higher incidence of GI adverse events, it did not significantly affect the results, even in the scenarios where annual costs of ¥200 to ¥1000 per patient for treating the events were assumed. An international study found that, despite an additional daily injection

and a higher rate of GI adverse events for exenatide twice daily, patient-reported outcomes with exenatide twice daily were similar to those with insulin glargine once daily.51 Our sensitivity analysis on disutility associated with injection confirmed this finding. Intensive blood glucose control has been shown to lower risks of microvascular complications, myocardial infarction, stroke and deaths for patients with T2DM.2-4 Treatment persistence is inferred to be the most important ingredient in achieving intensive glucose control and therapeutic success2; however, the real-world management of T2DM is often suboptimal, characterized by high rates of discontinuation, lack of treatment modification and poor adherence.52 Intolerable adverse events, poor treatment outcomes, inconvenient administration, and high healthcare costs are reported to affect treatment adherence negatively.50,53 Exenatide twice daily can reduce weight without increasing hypoglycaemia risks, while insulin glargine once daily was associated with weight gain and higher hypoglycaemia risks. Moreover, although exenatide twice daily is used twice daily, it is a fixed-dose therapy, while insulin glargine once daily requires dose adjustment according to blood glucose level; therefore, patients with exenatide twice daily may have better adherence than those on insulin glargine once daily.19,20,29 Considering the poor management and heavy disease burden of T2DM, the use of exenatide twice daily may provide a treatment option for patients who have conditions that pose treatment challenges, such as obesity, hypoglycaemia, increased risk of cardiovascular disease and poor adherence. Despite a lack of long-term observational studies in China to verify the present findings, observational studies from other countries have reported that exenatide twice daily as add-on therapy was associated with greater treatment persistence, significant or similar HbA1c reduction, weight loss and reduced macrovascular risks, without a higher rate of hypoglycaemia compared with insulin glargine once daily in real-world settings.11,54,55 The Liraglutide Effect and Action in Diabetes: Evaluation of Cardiovascular Outcome Results (LEADER) study has recently shown the effect of liraglutide, a product of the glucagon-like peptide-1 receptor agonist class, on reducing the occurrence of cardiovascular events and death.4 Furthermore, studies on healthcare utilization showed that patients treated with exenatide had a lower likelihood of hospitalization related to macroand microvascular complications and hypoglycaemic events, and this was associated with significantly lower annual direct medical costs as a result of significantly fewer inpatient, outpatient and emergency room visits, despite the higher pharmacy costs compared with insulin glargine.56,57 There is a series of long-term cost-effectiveness studies on exenatide twice daily vs insulin glargine once daily as add-on therapy to OADs worldwide, including studies from Germany, Switzerland, the UK, Portugal, Turkey and Spain. Overall, exenatide twice daily was projected to generate more clinical benefits and increased direct medical costs for patients compared with insulin glargine once daily. It was considered to be a cost-effective treatment alternative (good value for money) to insulin glargine once daily in different healthcare settings.58-63 The present findings partially support these results. In addition to a beneficial QALY profile, exenatide twice daily also reduced total medical costs compared with insulin glargine once daily in the present study. The discrepancies may be related to the differences in BMI-related prescription costs and the economic evaluation model used, as previous studies were based on an IMS CORE diabetes model which does not include a variable for BMI-related prescription costs, unlike the Cardiff Diabetes Model. A previous study using the Cardiff Diabetes Model in China also confirmed that exenatide twice daily was superior to insulin glargine once daily25; however, one study has also shown that exenatide twice daily does not represent a cost-effective treatment option for patients with T2DM compared with insulin glargine once daily.64 This result could potentially be attributed to the exclusion of cost and utility changes associated with BMI changes in that study. Cost and utility changes associated with weight changes have become increasingly important45,46; the estimation of the cost-effectiveness of the study drugs without considering these changes can lead to selection bias, particularly in situations where the two drugs under investigation have opposite effects on weight changes. The present study is limited by the lack of long-term observational studies on exenatide twice daily vs insulin glargine once daily in Chinese patients inadequately controlled on OADs. The treatment effects and most patient profiles were obtained from 8 head-to-head RCTs, but treatment adherence in real-world settings may be poorer than that observed in RCTs, which may negatively influence treatment effect, healthcare costs and patients′ utilities. This may result in uncertainty regarding the input variables. In addition, we only included head-to-head studies, which may preclude studies that could be connected via a network. As with other Cardiff modelling studies, although the present study used well-established UKPDS 68 risk equations to project long-term outcomes of targeted drugs based on clinical inputs from short-term

trials, the results might not accurately reflect outcomes in real-world settings in China, as the risk equations were for a UK population. There are currently no available risk equations for Chinese people with diabetes and future studies may address this; however, as the present study was a comparison study, our principal aim was to obtain relative outcomes of exenatide twice daily + OAD vs insulin glargine once daily + OAD, therefore, using the same UKPDS equations for both arms may be acceptable. Lastly, utility decrements of diabetes-related events were adopted from studies in other countries because of a lack of country-specific utility in China, which may have led to a potential bias. In conclusion, in Chinese patients with T2DM inadequately controlled by OADs alone, exenatide twice daily is a cost-effective add

on therapy alternative compared with insulin glargine once daily, with higher QALY gains and lower costs. This may address an excess of medical needs attributed to weight gain and hypoglycaemia in T2DM treatment as well as reduce the disease burden of T2DM.