Diabetes Ther (2023) 14:93–107
https://doi.org/10.1007/s13300-022-01336-7

ORIGINAL RESEARCH

Long-Term Cost-Effectiveness of Subcutaneous Once-Weekly Semaglutide Versus Polyethylene Glycol Loxenatide for Treatment of Type 2 Diabetes Mellitus in China

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Received: September 28, 2022 / Accepted: October 31, 2022 / Published online: November 22, 2022

ABSTRACT

Objective: This study aimed to evaluate the long-term cost-effectiveness of once-weekly subcutaneous semaglutide versus polyethylene glycol loxenatide (PEG-loxenatide) in patients with type 2 diabetes uncontrolled on metformin, from a Chinese healthcare systems perspective.

Methods: The study applied the Swedish Institute of Health Economics Diabetes Cohort Model to evaluate the long-term clinical and economic outcomes of once-weekly treatment of semaglutide at 0.5 mg and 1.0 mg, respectively, versus PEG-loxenatide 0.2 mg, over a 40-year time horizon. Baseline cohort characteristics were collected from the SUSTAIN China trial. A network meta-analysis was conducted to obtain comparative treatment effects of once-weekly semaglutide and PEG-loxenatide based on two phase 3a clinical trials. Drug costs were sourced from the national bidding price of China. Outcomes were discounted at 5.0% per

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Supplementary Information The online version contains supplementary material available at https://doi.org/10.1007/s13300-022-01336-7.

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annum. One-way sensitivity analysis and probabilistic sensitivity analysis were conducted to assess the uncertainty of the base-case results.
Results: When compared with PEG-loxenatide 0.2 mg, the projections of outcomes over the 40-year time horizon in patients with type 2 diabetes uncontrolled on metformin showed that treatment with once-weekly semaglutide 0.5 mg and 1.0 mg were associated with improved discounted life expectancy by 0.08 and 0.12 years, and improved discounted quality-adjusted life expectancy by 0.16 and 0.22 quality-adjusted life-years, respectively. Once-weekly semaglutide 0.5 mg and 1.0 mg were achieved at lifetime cost savings of 19,309 China Yuan (CNY) and 10,179 CNY, respectively. Sensitivity analyses verified the robustness of the results.
Conclusion: From the perspective of Chinese healthcare systems, treatment with once-weekly subcutaneous semaglutide represents a dominant option versus PEG-loxenatide for patients with type 2 diabetes uncontrolled on metformin.

Keywords: Cost-effectiveness analysis; Type 2 diabetes; Glucagon-like peptide-1 analogue; Semaglutide; PEG-loxenatide; China

Key Summary Points

Why carry out this study?

Type 2 diabetes causes heavy economic and clinical burdens in China.

Once-weekly semaglutide is a novel glucagon-like peptide-1 receptor agonist (GLP-1 RA), and its clinical benefit have been confirmed in the Semaglutide Unabated Sustainability in Treatment of Type 2 Diabetes (SUSTAIN) trials.

Once-weekly semaglutide has been shown to be more cost-effective than dulaglutide in the Chinese setting, but a direct cost-effectiveness comparison between once-weekly semaglutide and the locally preferred once-weekly GLP-1 RA polyethylene glycol loxenatide (PEG-loxenatide) is missing.

What was learned from the study?

Once-weekly semaglutide 0.5 mg and 1.0 mg are cost-saving treatments compared with PEG-loxenatide 0.2 mg in China.

This study highlights the long-term clinical and economic value of once-weekly semaglutide for the treatment of type 2 diabetes patients in China.

INTRODUCTION

Diabetes is one of the most severe threats to global health. In China, diabetes currently affects about 129 million people [1], of whom about 90% have type 2 diabetes (T2D) [2]. However, that of all the patients in China with diabetes, only 36.7% were diagnosed, 32.9% received treatment, and 16.5% achieved the glycemic control target [3]. The International Diabetes Federation estimated that China's total diabetes-related health expenditure was USD 109.0 billion in 2019 [4], which represents

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11.4% of all medical costs in 2019 [5]. Chronic diabetic complications, in particular cardiovascular complications, have been shown to cause most of diabetes-related expenditures [6]. Shen et al. [7] used electronic health records to analyze the components of diabetes-related costs (including costs of antidiabetics and of treating complications) in China, and found that of the total expenditure related to diabetes, 54% was spent on treating the cardiovascular complications of individuals with diabetes. Therefore, it is important that a greater proportion of patients with diabetes achieve glycemic control and multifactorial treatment targets, thereby improving long-term health outcomes and reducing the costs of treating diabetes-related complications both for patients and Chinese society as a whole.

Glucagon-like peptide-1 receptor agonists (GLP-1 RAs) are a class of interventions for T2D associated with improved glycemic control, weight loss benefits and reduced hypoglycemia risk. In addition, some recent cardiovascular outcomes trials (CVOTs) have indicated that several long-acting human GLP-1 RAs are associated with improved cardiovascular outcomes in patients with T2D [8–11]. In China, the latest guideline for type 2 diabetes in China, published by the Chinese Diabetes Society in 2020, recommends that patients with T2D with inadequate glycemic control on metformin treatment and lifestyle intervention are to be treated with GLP-1RAs to improve their glycemic control [2]. In particular, the guideline recommends that GLP-1-RAs in combination with metformin should used for patients with atherosclerotic cardiovascular disease (ASCVD) and/or with high risk of cardiovascular and cerebrovascular disease (CVD), regardless of whether glycated hemoglobin A_{1c} (HbA_{1c}) has reached the target, to improve the CVD outcomes for patients if there is no contraindication [2].

Semaglutide is a novel long-acting, human-based GLP-1RA that has been developed for the treatment of T2D. Semaglutide has 94% structural homology to native human GLP-1. Three minor but important modifications significantly extend the half-life of semaglutide to 165 h and make it suitable to be administered on a once-weekly schedule: amino acid substitutions at position 8 (alanine to alpha-aminoisobutyric acid a synthetic amino acid) and at position 34 (lysine to arginine), and acylation of the peptide backbone with a spacer and C-18 fatty di-acid chain to lysine at position 26 [12, 13]. Throughout the global Semaglutide Unabated Sustainability in Treatment of Type 2 Diabetes (SUSTAIN) trials, compared to all the other comparators once-weekly semaglutide displayed greater short-term efficacy, with more significant reductions in HbA_{1c} and multiple cardiometabolic benefits (including improving the control of blood pressure, blood lipids and body weight, among others) [14–22]. Also, the SUSTAIN China trial showed that the proportion of patients achieving the HbA_{1c} target ($HbA_{1c} < 7\%$) with once-weekly semaglutide was as high as 86.1% in the Chinese diabetes population [23].

In addition to clinical considerations, economic value assessment of a novel intervention is also important for healthcare decisions given the enormous disease burden of diabetes. In China, three once-weekly GLP-1 RAs have been included in the National Reimbursement Drug List, including once-weekly semaglutide (Ozempic®; Novo Nordisk, Bagsværd, Denmark), dulaglutide (Trulicity®; Eli Lilly, Indianapolis, IN, USA), and polyethylene glycol loxenatide (PEG-loxenatide; Fu Laimei®; Hansoh Pharma, Lianyungang, China). The long-term cost-effectiveness of once-weekly semaglutide compared with dulaglutide in the Chinese setting was evaluated in our previous study [24]. However, to date there has been no cost-effectiveness comparison between once-weekly semaglutide and PEG-loxenatide. Semaglutide is available in two treatment doses of 0.5 mg and 1.0 mg, administered once-weekly; PEG-loxenatide is also available in two treatment doses of 0.1 mg and 0.2 mg, administered once-weekly [25]. Because PEG-loxenatide 0.1 mg is rarely used in clinical practice in China, we did not include this dose in our study.

Thus, this study aimed to evaluate the long-term cost-effectiveness of once-weekly semaglutide 0.5 mg and 1.0 mg versus PEG-loxenatide 0.2 mg for the treatment of people

with T2D who were not controlled with metformin from the perspective of Chinese healthcare systems.

METHODS

Model Approach

For the purpose of this cost-effectiveness analysis, we have attempted to use a diabetes model that is easy to use, transparent, and able to conduct uncertainty analysis since these qualities were considered appropriate and expected by Chinese stakeholders. The Swedish Institute of Health Economics Diabetes Cohort Model (IHE-DCM) (version 4.4.2) was used for this study, as it meets these criteria. In recent years, the IHE-DCM has been increasingly applied to health technology assessments of hypoglycemic drugs. The model was designed in Microsoft® Excel (Microsoft Corp., Redmond, WA, USA) using Visual Basic for Applications (VBA). It can be run with one intervention and up to 12 comparator arms, allowing for simultaneous comparison of multiple treatment strategies. The cycle length is 1 year, and the maximum time horizon is 40 years. The IHE-DCM can simulate the occurrence of diabetes-related complications by constructing macrovascular and microvascular Markov sub-models, respectively. The macrovascular Markov chain consists of combinations of stages of ischemic heart disease, myocardial infarction, stroke, and heart failure. The microvascular Markov chain consists of combinations of stages of eye disease, kidney disease, and lower extremity disease. The authors accessed and used the IHE-DCM through a user agreement with the Swedish Institute for Health Economics (Lund, Sweden).

The IHE-DCM projects long-term outcomes based on user inputs and user-defined selection of risk equations. User inputs comprise cohort baseline characteristics, treatment algorithms and clinical effects, cost, and health utility. The mortality risk equations are sourced from the UK Prospective Diabetes Study (UKPDS) 68 [26] or UKPDS 82 [27]. Users can choose four sets of macrovascular risk equations among UKPDS 68 [26], UKPDS 82 [27], the Swedish National Diabetes Register (NDR) [28], or the Australian Fremantle Diabetes Study (FDS) [29]. Users do not need to select the microvascular risk equation because there is only one set of risk equations in the model [30–32]. Outputs of the IHE-DCM include cumulative incidence of macro- and microvascular complications, life expectancy, quality-adjusted life-years (QALYs), costs, and incremental cost-effectiveness ratio (ICER).

For the whole analysis, the Consolidated Health Economic Evaluation Reporting Standards (CHEERS) checklist was followed [33].

Discount and Time Horizon

A 40-year time horizon was applied in this study. The projected clinical and economic outcomes were discounted at a rate of 5.0% annually, which is in line with the guideline of cost-effectiveness analysis in China [34].

Baseline Cohort Characteristics

The target population of this study was assumed to be a cohort of patients with T2D uncontrolled with metformin in China. Baseline demographic characteristics, baseline HbA_{1c}, body mass index (BMI), and estimated glomerular filtration rate were derived from the SUSTAIN China trial [23]. The SUSTAIN China study was a 30-week, randomized, double-blind, multicenter clinical trial with the aim to evaluate the efficacy and safety of once-weekly semaglutide in patients with T2D inadequately controlled on metformin treatment. Participants' mean age at baseline was 52.27 years; the mean duration of diabetes was 6.07 years; and the proportion of women was 39.50%. Other baseline biochemical parameters and baseline risk of diabetes-related microvascular and macrovascular complications were mainly sourced from another study of Chinese patients with T2D [35] (see Electronic Supplementary Material [ESM] Table 1).

Treatment Algorithm and Treatment Effects

In the base-case simulation, patients initiate a 3-year treatment of once-weekly semaglutide (0.5 or 1.0 mg) or PEG-loxenatide (0.2 mg). The treatment period is consistent with previously published cost-effectiveness studies [36–38]. It was assumed that the GLP-1RA treatment effect would last for 3 years, following which treatment with once-weekly semaglutide and PEG-loxenatide would cease and treatment with basal insulin (insulin glargine) would be initiated and used for the remainder of the patient's lifetime.

A network meta-analysis (NMA) was conducted to compare the efficacy and safety of once-weekly semaglutide and PEG-loxenatide by R 4.2.0 software ® Foundation for Statistical Computing, Vienna, Austria) since there is no head-to-head clinical trial. This NMA was performed according to the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) statement [39]. The NMA showed that once-weekly semaglutide 0.5 and 1.0 mg were associated with greater reductions in HbA_{1c}, BMI, and systolic blood pressure (SBP) and greater improvements in blood lipid levels, compared with PEG-loxenatide 0.2 mg. Further details on this NMA are provided in ESM Tables 2, 3; ESM Fig. 1, including the search strategy, study selection, and results of the difference in treatment effect between once-weekly semaglutide and PEG-loxenatide.

In the cost-effectiveness analysis, the treatment effects on HbA_{1c}, BMI, SBP, low-density lipoprotein cholesterol, high-density lipoprotein cholesterol, and triglyceride for patients treated with once-weekly semaglutide and PEG-loxenatide were obtained from the NMA. The cardiovascular protection effect of once-weekly semaglutide was collected from the cardiovascular outcome of SUSTAIN 6 [9]. It was assumed that PEG-loxenatide has no cardiovascular protective effect since there was no evidence to show the cardiovascular benefit of PEG-loxenatide. Rates of hypoglycemia events were taken from their respective clinical trials [14, 25]. All of the treatment effects and adverse event rates are summarized in Table 1.

Long-term Parameter Progression

According to the study of Kahn et al. [40], it was assumed that HbA_{1c} would drift upwards at a rate of 0.14% per year. Other biomarkers, such as SBP and lipid levels, were assumed to remain at the same level as when GLP-1 RA treatment was discontinued. Risk equations sourced from the NDR were employed to predict the incidence of macrovascular complications because they could provide the best fit for macrovascular outcomes when compared with UKPDS 68 and UKPDS 82 [41]. UKPDS 82 was used to predict the incidence of mortality.

Costs and Utilities

From the perspective of Chinese healthcare systems, this study captured direct medical costs (including medication costs, treatment costs associated with diabetes-related complications and hypoglycemic events) in 2021 Chinese Yuan (CNY).

Medication costs were obtained from the national average bidding price in June 2022. The dosage of insulin glargine U100 was based on a meta-analysis evaluating the daily dosage of basal insulin among Chinese patients with T2D [42]. It was assumed that treatment adherence for each intervention was 100%. Annual costs also captured concomitant medication (i.e., metformin) and needle use. According to the assumption that there was no difference in the frequency of self-monitoring of blood glucose (SMBG) between GLP-1 RA treatments, the cost of SMBG was not included. Annual medication costs are given in ESM Table 4.

The costs of diabetes-related complications were obtained from published literature [35, 43–48]. The costs from the literature were inflated to 2021 CNY through China's healthcare consumer price index (ESM Table 5).

The utility of the patient at baseline and the disutility of complications and demographic factors were taken from published literature [47, 49–52] and are given in ESM Table 6.

Table 1 Treatment effects and adverse event rate included in the analysis

Treatment effects, mean (SD)	OW semaglutide 0.5 mg	OW semaglutide 1.0 mg	PEG-loxenatide 0.2 mg
HbA_{1c} (%)	− 1.60 (0.16)	− 1.70 (0.17)	− 1.34 (0.13)
BMI (kg/m^2)	− 1.30 (0.10)	− 1.59 (0.040)	− 0.23 (0.001)
SBP (mmHg)	− 3.17 (0.32)	− 3.05 (2.68)	− 3.11 (0.10)
TC (mmol/L)	− 0.37 (0.04)	− 0.61 (0.660)	− 0.16 (0.003)
LDL (mmol/L)	− 0.09 (0.009)	− 0.30 (0.450)	− 0.14 (0.010)
HDL (mmol/L)	0.02 (0.002)	− 0.02 (0.110)	0.02 (0.004)
TG (mmol/L)	− 0.09 (0.030)	− 0.11 (0.950)	0.06 (0.038)
Cardioprotective effects (hazard ratio)[a]			
IHD	1	1	1
MI	0.74	0.74	1
Stroke	0.61	0.61	1
HF	1.11	1.11	1
CVD mortality	0.98	0.98	1
Hypoglycemic events rate (per patient-year)			
Non-severe hypoglycemic events	0 (0)	0 (0)	0.04 (0)
Severe hypoglycemic events	0 (0)	0 (0)	0 (0)

OW Once-weekly, *PEG-loxenatide* polyethylene glycol loxenatide, *HbA_{1c}* glycated hemoglobin A_{1c}, *BMI* body mass index, *SBP* systolic blood pressure, *TC* total cholesterol, *LDL* low-density lipoprotein, *HDL* high-density lipoprotein, *TG* triglyceride, *IHD* ischemic heart disease, *MI* myocardial infarction, *HF* heart failure, *CVD* cardiovascular and cerebrovascular disease

[a]The effects of once-weekly semaglutide (0.5 mg and 1.0 mg) were pooled in SUSTAIN 6 and results showed that similar risk reductions were observed with both doses of semaglutide

Sensitivity Analyses

As the extrapolation of outcomes over patients' lifetimes from short-term clinical data is associated with uncertainty, sensitivity analyses were performed on key assumptions and key parameters to test the robustness of the base-case analysis. Variations included in the one-way sensitivity analyses were: (1) shortening the time horizon to 20 and 30 years, respectively; (2) applying discount rates of 0%, 3% and 8% for clinical and cost outcomes; (3) assuming the annual drift in HbA_{1c} was 0.1%, 0.2%, and drift using the UKPDS progression, respectively; (4) assuming treatment switching after 2 years and when HbA_{1c} exceeded 7.0%; (5) costs of complications increasing and decreasing by 10%; (6) applying the UKPDS 68 risk equations to predict the macrovascular complications and mortality; (7)assuming no cardioprotective effect for treatments; and (8) applying BMI disutility value from the Lane et al. [53] study. In addition, probabilistic sensitivity analysis (PSA) was performed.

Compliance with Ethics Guidelines

This article is based on previously conducted clinical trials and does not contain any studies

Table 2 Base case results

Health outcomes	OW semaglutide 0.5 mg	PEG-loxenatide 0.2 mg	Difference
Discounted life expectancy (years)	13.16	13.08	0.08
Discounted quality-adjusted life expectancy (QALYs)	7.85	7.69	0.16
Discounted total direct medical cost (CNY)	322,489	341,798	− 19,309
ICER (CNY/QALY gained)	–	–	Dominant
Health outcomes	**OW semaglutide 1.0 mg**	**PEG-loxenatide 0.2 mg**	**Difference**
Discounted life expectancy (years)	13.19	13.08	0.12
Discounted quality-adjusted life expectancy (QALYs)	7.91	7.69	0.22
Total direct medical cost (CNY)	331,619	341,798	− 10,179
ICER (CNY/QALY gained)	–	–	Dominant

QALY(s) Quality-adjusted life-year(s), *CNY* Chinese Yuan, *ICER* incremental cost-effectiveness ratio

with human participants or animals performed by any of the authors.

RESULTS

Base-Case Analysis

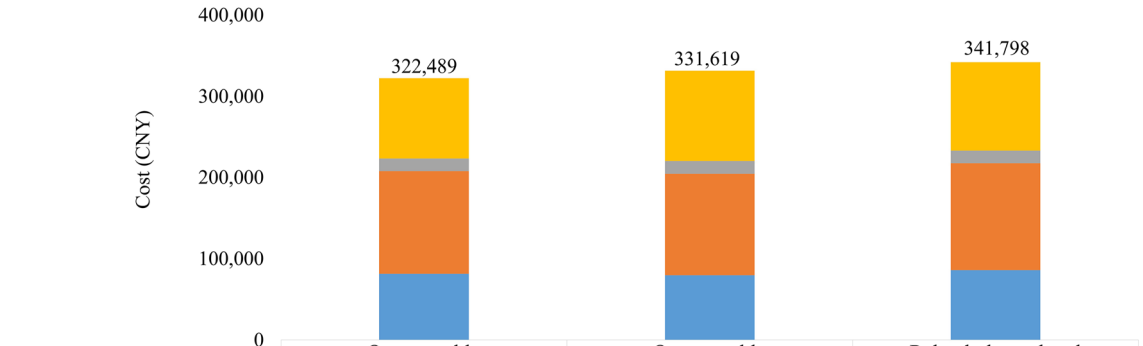
Long-term projection over the 40-year time horizon in patients with T2D uncontrolled on metformin in China revealed that once-weekly semaglutide 0.5 mg and 1.0 mg were associated with an improved discounted life expectancy of 0.08 and 0.12 years, respectively, and improved discounted quality-adjusted life expectancy of 0.16 and 0.22 QALYs, respectively, versus PEG-loxenatide 0.2 mg (Table 2). The clinical benefits were due to the multifactorial risk-reduction effects of semaglutide, resulting in delaying time to onset and reduced cumulative incidence of diabetes-related complications (ESM Table 7).

Semaglutide 0.5 mg and 1.0 mg were associated with a cost saving of CNY 19,309 and CNY 10,179 per pa0tient compared with PEG-loxenatide 0.2 mg (see Table 2). The treatment cost, microvascular complications cost, and macrovascular complications cost were all lower for once-weekly semaglutide 0.5 mg than for PEG-loxenatide 0.2 mg. For once-weekly semaglutide 1.0 mg, the treatment cost was slightly higher than that for PEG-loxenatide 0.2 mg, but the increased treatment cost was fully offset by the reduced costs of micro- and macrovascular complications (see Fig. 1).

Sensitivity Analyses

The base-case result was shown to be robust across all one-way sensitivity analyses (Table 3). Once-weekly semaglutide 0.5 mg was dominant in all sensitivity analyses, compared with PEG-loxenatide 0.2 mg. Once-weekly semaglutide 1.0 mg was also dominant compared with PEG-loxenatide 0.2 mg in all but one analysis. When treatment switching occurred at the HbA_{1c} threshold of 7.0%, once-weekly semaglutide 1.0 mg was associated with an ICER value of CNY 7400/QALY gained. In this analysis, patients received once-weekly semaglutide 1.0 mg for 5 years and PEG-loxenatide 0.2 mg for 3 years, resulting in a higher treatment cost for once-weekly semaglutide 1.0 mg.

Using one time gross domestic progduct per capita as the willingness-to-pay threshold, the PSA showed 100% probability that once-weekly semaglutide 0.5 mg and 1.0 mg were both cost-effective compared with PEG-loxenatide 0.2 mg in patients whose diabetes was uncontrolled on metformin (Fig. 2).



	Once-weekly semaglutide 0.5mg	Once-weekly semaglutide 1.0mg	Polyethylene glycol loxenatidee 0.2mg
Treatment cost	99,146	111,420	108,753
Hypoglycemia	15,629	15,685	15,600
Microvascular complications	126,394	124,845	131,536
Macrovascular complications	81,320	79,670	85,909

Fig. 1 Mean direct cost over a patient's lifetime (in 2021 Chinese Yuan [CNY])

DISCUSSION

This study is the first to compare the cost-effectiveness of once-weekly semaglutide with PEG-loxenatide in the Chinese setting. the results showed that, in China, once-weekly semaglutide 0.5 mg and 1.0 mg were both cost-saving treatments compared with PEG-loxenatide in patients with T2D uncontrolled on metformin. Once-weekly semaglutide 0.5 mg and 1.0 mg were associated with improvements of 0.16 and 0.22 QALYs, and with lifetime cost savings of CNY 19,309 and CNY 10,179, respectively, meaning that it dominated PEG-loxenatide.

In this cost-effectiveness analysis, a NMA was performed to obtain the comparative treatment effects of once-weekly semaglutide and PEG-loxenatide in patients with T2D, since there has been no head-to-head clinical trial comparing the efficacy of these treatments. This methodology is aligned with the *Chinese Guidelines for Pharmacoeconomic Evaluations*, which indicate that clinical data from NMA is preferred in health economic evaluations when there is no clinical data available from the head-to-head trial [34]. Trials included in the NMA were derived from a systematic literature review, and only trials with similar study designs were included to ensure the compatibility of the studies. The NMA showed greater reductions in HbA_{1c}, BMI and SBP and greater improvements in blood lipid levels with once-weekly semaglutide than with PEG-loxenatide. However, further studies based on direct comparison are necessary to reassess the cost-effectiveness of once-weekly semaglutide compared with PEG-loxenatide.

The patients included in this study were assumed to receive once-weekly semaglutide or PEG-loxenatide for 3 years in the base-case analysis before switching to the basal insulin treatment, which is consistent with treatments reported in previous studies [36, 38]. However, in real-world practice, patients may maintain their current treatment if their glucose level is well controlled, which means that treatment with a greater reduction in HbA_{1c} would be associated with a delayed time to insulin intensification. In the sensitivity analysis, when an HbA_{1c} threshold of 7.0% was used as the treatment switching criterion, the groups with once-weekly semaglutide 0.5 mg and 1.0 mg, respectively, were switched to intensification treatment at the fifth year, with a 2-year delay compared to PEG-loxenatide (intensification at the third year). The results showed that once-weekly semaglutide would achieve more quality-adjusted life expectancy compared with the base-case result. Once-weekly semaglutide 0.5 mg was still a cost-saving treatment, while once-weekly semaglutide 1.0 mg was associated with a slight increase in total cost (+

Table 3 One-way sensitivity analyses results

Analysis	OW Semaglutide 0.5 mg vs. PEG-loxenatide 0.2 mg			OW Semaglutide 1.0 mg vs. PEG-loxenatide 0.2 mg		
	△QALYs	△ Total cost (CNY)	ICER	△ QALYs	△ Total cost (CNY)	ICER
Base case	0.16	− 19,309	Dominant	0.22	− 10,179	Dominant
30-year time horizon	0.15	− 19,253	Dominant	0.20	− 10,157	Dominant
20-year time horizon	0.11	− 16,035	Dominant	0.15	− 5885	Dominant
0% discount rates	0.38	− 32,442	Dominant	0.51	− 26,632	Dominant
3% discount rates	0.22	− 23,173	Dominant	0.30	− 14,964	Dominant
8% discount rates	0.11	− 15,576	Dominant	0.14	− 5,693	Dominant
Annual drift in HbA_{1c} of 0.1%	0.15	− 17,460	Dominant	0.20	− 7,674	Dominant
Annual drift in HbA_{1c} of 0.2%	0.17	− 21,125	Dominant	0.23	− 12,633	Dominant
HbA_{1c} drift using UKPDS progression	0.13	− 14,514	Dominant	0.18	− 3,703	Dominant
Treatment switching after 2 years	0.17	− 21,238	Dominant	0.21	− 10,316	Dominant
HbA_{1c} threshold of 7.0%	0.20	− 13,519	Dominant	0.27	1964	7400
Cost of complications + 10%	0.16	− 20,282	Dominant	0.22	− 11,472	Dominant
Cost of complications − 10%	0.14	− 18,630	Dominant	0.22	− 8882	Dominant
UKPDS 68 risk equations applied	0.14	− 17,401	Dominant	0.19	− 7368	Dominant
No cardioprotective effect	0.15	− 18,490	Dominant	0.20	− 9380	Dominant
Lane et al. [53] BMI disutility applied	0.74	− 19,309	Dominant	0.95	− 10,179	Dominant

△ Change, *UKPDS* United Kingdom Prospective Diabetes Study

CNY 1964), leading to an ICER value of CNY 7400/QALY gained. Although there is no officially acknowledged willingness-to-pay threshold in China, semaglutide 1.0 mg could still be considered a cost-effective treatment in this scenario.

The treatment of T2D often focuses on lowing HbA_{1c} [54–57]. However, recent studies have demonstrated further benefits from reductions in other risk factors, including body weight and BMI [58, 59]. The NMA showed that once-weekly semaglutide was associated with greater body weight and BMI reductions versus PEG-loxenatide. In the base-case analysis, the disutility value per unit increase in BMI was set as − 0.006, which is consistent with values reported in other cost-effectiveness studies [60, 61]. However, in a recent study evaluating the relationship between body weight and quality of life in Canadian patients with T2D, researchers observed that for each unit increase in BMI, the utility of the patient would decrease by 0.0472 [53]. In the sensitivity analysis of this study, once-weekly semaglutide showed a greater increase in quality-adjusted life expectancy (+ 0.74 QALYs for semaglutide 0.5 mg, + 0.95

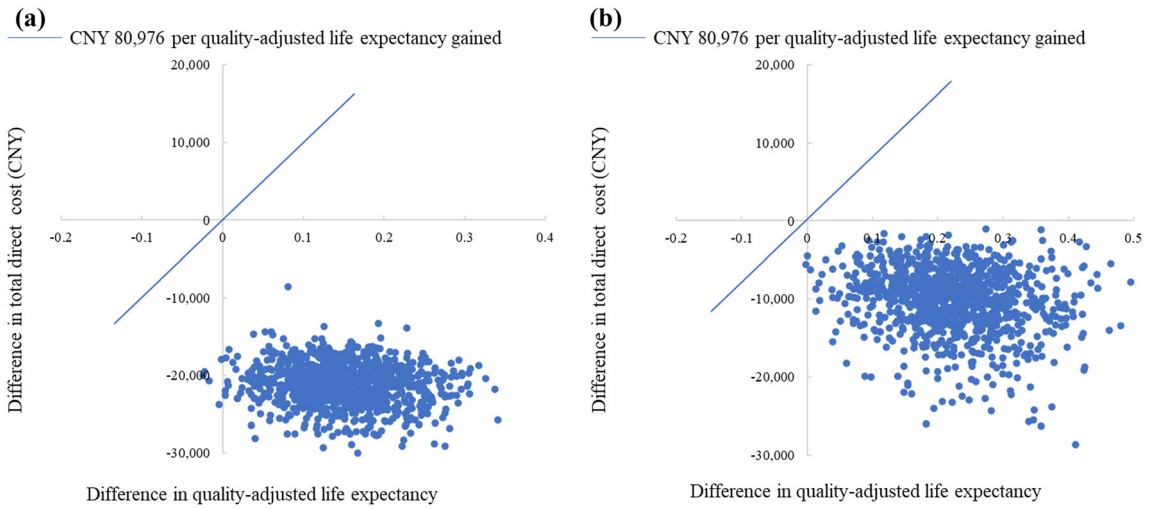


Fig. 2 Probabilistic sensitivity analyses scatter plot of once-weekly semaglutide 0.5 mg vs. polyethylene glycol loxenatide 0.2 mg (**a**) and once-weekly semaglutide 1.0 mg vs. polyethylene glycol loxenatide 0.2 mg (**b**)

QALYs for semaglutide 1.0 mg) compared with PEG-loxenatide 0.2 mg when the larger disutility value in BMI was applied.

A previous systematic literature review on the cost-effectiveness analysis of once-weekly semaglutide versus other GLP-1RAs in T2D found that the cardiovascular benefit of once-weekly semaglutide may have been under-estimated in previous studies [62]. The importance of HbA_{1c} in long-term cardiovascular risk has been confirmed by a UKPDS study, which showed that well-controlled HbA_{1c} could reduce macrovascular complications after many years [63]. However, increasingly more CVOTs are finding that some novel hypoglycemic agents can obtain cardiovascular benefits in a relatively short follow-up duration. For example, after a median observation time of 2.1 years in the SUSTAIN 6 clinical trial, once-weekly semaglutide was shown to significantly reduce the rate of nonfatal myocardial infarction, nonfatal stroke and cardiovascular death in patients with T2D who were at high cardiovascular risk [9]. Data derived from SUSTAIN 6 were applied in our study to inform the cardiovascular protective effect of once-weekly semaglutide. Since there was no evidence for PEG-loxenatide, it was assumed in this study that PEG-loxenatide has no cardioprotective effects. In addition, Naveed et al. [64] reported that the exendin-4 based GLP-1 RAs may have no significant effect in reducing the incidence of major adverse cardiovascular events. It should be noted that the patient population in the SUSTAIN 6 study consisted of patients with T2D and cardiovascular risk, which was different from the target population in the present study. However, the study by Naveed et al. [64] found that the cardiovascular protective effect of GLP-1 RAs in patients with established cardiovascular disease was not statistically significantly different from that of patients without the established cardiovascular disease. In order to test the impact of the uncertainty of cardioprotective effects on the results, a sensitivity analysis which applied no cardiovascular protective effect to GLP-1 RA treatments was conducted. The results showed that once-weekly semaglutide was still a dominant option compared with PEG-loxenatide.

There are several limitations to the research reported here. First, the treatment effects were derived from treatment-naïve patients; this patient population is slightly different from the patients in the target population who were being adequately controlled on metformin monotherapy. The target population was consistent with the approved indications of once-weekly semaglutide in China. Nevertheless, the clinical trials of PEG-loxenatide were conducted only in treatment-naïve patients with T2D. To

ensure the comparability of studies, the study of Sorli et al. [14] and the study of Shuai et al. [25] were included in the NMA to obtain the treatment effects of once-weekly semaglutide and PEG-loxenatide, both of which were performed in treatment-naïve patients. Further analysis based on clinical outcomes of patients with T2D uncontrolled on metformin would be necessary to reassess the cost-effectiveness of once-weekly compared with PEG-loxenatide.

Second, this study was aimed to predict long-term outcomes from relatively short-term clinical trial data, which ware inherent to all long-term health economic analyses. Third, the assumption that the treatment compliance was 100% may not reflect real-world practice. Fourth, some health utility data were from studies in other countries due to the lack of local data, which may not fully reflect the situation of the Chinese population. Future studies addressing these shortcomings with domestic and real-world data are suggested.

CONCLUSION

The results of this study suggest that compared with PEG-loxenatide 0.2 mg, subcutaneous once-weekly semaglutide 0.5 mg and 1.0 mg are both cost-saving treatments for patients with T2D inadequately controlled on metformin, from a perspective of Chinese healthcare systems.

ACKNOWLEDGEMENTS

The authors would like to thank for the comments on early visions from their colleagues at the University of Macau.

Funding. Funding for this study and the journal's Rapid Service Fees charges was provided by Novo Nordisk (China) Pharmaceuticals Co., Ltd. This supplement has been sponsored by Novo Nordisk (China) Pharmaceuticals Co., Ltd..

Author Contributions. All named authors meet the International Committee of Medical Journal Editors (ICMJE) for authorship for this manuscript, take responsibility for the integrity of the work as a whole, and have given their approval for this version to be published. The study was conceived and designed by Hao Hu and Lixin Guo. Zhen Ruan and Yang Shen conducted the modeling analysis. Lei Liu and Yawen Zhang drafted the manuscript. The final vision was reviewed, revised, and approved by all authors.

Disclosures. Yawen Zhang is an employee of Novo Nordisk. Other authors declare no conflict of interest.

Prior Presentation. The preliminary result of manuscript is based on work that is presented at ISPOR Europe 2022, 6-9 November, Vienna, Austria and virtually.

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

Data Availability. All data generated or analyzed during this study are included in this published article and supplementary material. Access to the IHE-DCM is at the discretion of the Swedish IHE, Lund, Sweden, which holds the proprietary right.

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