



# Cost-Effectiveness Analysis of Exenatide versus GLP-1 Receptor Agonists in Patients with Type 2 Diabetes Mellitus

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## Abstract

**Objective** The aim of this study was to assess the efficiency of exenatide 2 mg/week compared with other glucagon-like peptide-1 (GLP-1) receptor agonists (dulaglutide 1.5 mg/week, liraglutide 1.2 mg/day, liraglutide 1.8 mg/day and lixisenatide 20 µg/day) in adult patients with type 2 diabetes mellitus (T2DM) not adequately controlled on metformin alone from the perspective of the Spanish National Health System (NHS).

**Methods** Quality-adjusted life-years (QALYs) gained and total costs of each assessed drug combined with metformin (2 g/day) were estimated over a 40-year time horizon using the Cardiff Diabetes Model (based on UK Prospective Diabetes Study [UKPDS] 68 equations), which simulates disease progression considering the T2DM-related micro- and macrovascular complications, hypoglycaemia, nausea, body mass index (BMI) changes and treatment discontinuation due to adverse effects (AEs). Drug efficacy derived from an indirect comparison performed in a network meta-analysis. Patient characteristics were obtained from the literature. The baseline utility value (0.80) was derived from the PANORAMA study, applying utility decrements to micro- and macrovascular complications, hypoglycaemia episodes and changes in BMI. Treatment discontinuation due to AEs or poorly controlled diabetes (HbA1c > 7.5%) involved switching to second-line (basal insulin) or third-line (basal-bolus insulin) treatment. Total cost (€, 2018) included the costs of drug acquisition, hypoglycaemia, weight gain, micro- and macrovascular complications, nausea and treatment discontinuation due to AEs. An annual discount rate of 3% was applied to costs and outcomes. Deterministic and probabilistic sensitivity analyses (SA) were performed.

**Results** In base-case, exenatide 2 mg/week resulted in more QALYs (8.26) than dulaglutide 1.5 mg/week (8.19 QALYs), liraglutide 1.2 mg/day (8.10 QALYs), liraglutide 1.8 mg/day (8.20 QALYs) and lixisenatide 20 µg/day (8.13 QALYs). Total cost/patient was €20,423.27 (exenatide 2 mg/week), €22,611.94 (dulaglutide 1.5 mg/week), €21,065.97 (liraglutide 1.2 mg/day), €24,865.69 (liraglutide 1.8 mg/day) and €21,334.58 (lixisenatide 20 µg/day). Deterministic SA confirmed the robustness of the model. In the probabilistic SA, 95–99% of the 1000 Monte Carlo iterations performed were under a hypothetical willingness-to-pay threshold of €20,000/QALY gained.

**Conclusions** Exenatide 2 mg/week would be a dominant strategy (more effective and less costly) versus the other GLP-1 receptor agonists assessed for the treatment of T2DM patients who are not adequately controlled on metformin alone.

## 1 Introduction

Diabetes mellitus (DM) is a chronic disease caused by metabolic abnormalities of multiple aetiologies, and is characterised by chronic hyperglycaemia and abnormalities in carbohydrate, fat, and protein metabolism; it results from defects in insulin secretion, insulin action, or both [1]. The most common type of DM, accounting for up to 90% of diagnosed cases of the disease, is type 2 DM (T2DM) which is characterised by a relative deficit of insulin secretion and/or resistance to its action [2].

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### Key Points for Decision Makers

The results of this cost-effectiveness analysis suggest that exenatide 2 mg/week is a dominant option compared with other glucagon-like peptide-1 (GLP-1) receptor agonists in patients with type 2 diabetes mellitus inadequately controlled on metformin monotherapy in Spain.

Exenatide 2 mg/week provided more quality-adjusted life-years (QALYs) gained compared with dulaglutide 1.5 mg/week, liraglutide 1.2 mg/day, liraglutide 1.8 mg/day and lixisenatide 20 µg/day.

Exenatide 2 mg/week combined with metformin has a lower cost associated with the treatment and management of patients with T2DM versus other GLP-1 receptor agonists.

In Spain, the prevalence of T2DM ranges from 10 to 15% [3–5], increasing progressively as age increases, and reaching 23.1% in the 70–74 years age group [6].

T2DM is one of the main causes of premature morbidity and mortality in the adult population. The disease, alone or combined with risk factors such as high blood pressure and/or overweight/obesity, is a significant risk factor for micro- and macrovascular complications (cardiovascular disease, eye diseases, neuropathies, kidney disease, and amputations) as diabetes progresses [7, 8]. These are some of the main causes of the increased mortality associated with T2DM [9]. Hence, T2DM is one of the most important chronic diseases, with great socioeconomic impact in Spain, not only because of its high prevalence but also because of the acute and chronic complications that occur, which constitute the first cause of years lived with disability (YLD), and because of its high mortality rate [10]. Furthermore, T2DM poses a high economic burden for the National Health System (NHS), with an estimated average cost per patient of €4458 after 2 years [5].

The main treatment aim in patients with T2DM is to reach and maintain glycaemic control goals, both early on and in the long term, without causing hypoglycaemia, in order to prevent or delay the onset of micro- and macrovascular complications and thus improve the patient's quality of life. Notably, adequate treatment of T2DM requires the simultaneous consideration of overweight/obesity and other cardiovascular risk factors such as hypertension, dyslipidaemia or smoking [11, 12].

Personalised treatment is currently the standard therapeutic approach for T2DM. In making decisions, clinicians must consider the particular characteristics of the disease, comorbidity, patient preferences, and available resources [11, 12].

The decision for treatment selection among all available therapies depends on the potency to reduce HbA1c, risk of inducing hypoglycaemia, degree of prior control, influence on body weight and dyslipidaemia, preferential impact on basal or postprandial glycaemia, complications or associated diseases of the patient, risk of drug-related adverse effects (AEs), tolerance, and cost. Initial drug treatment varies depending on the degree of prior control, age, presence of associated diseases, and concomitant use of other drugs [11, 12].

In recent years, incorporating glucagon-like peptide-1 (GLP-1) receptor agonists in the initial treatment with metformin has become increasingly important for the treatment of patients with T2DM due to the combined efficacy of the agonists in significantly reducing HbA1c levels [13, 14] without the adverse effects of hypoglycaemia and weight gain that are associated with other oral antidiabetics [15].

The aim of the present study was to evaluate the cost-effectiveness of exenatide 2 mg/week compared with other GLP-1 receptor agonists available in Spain (dulaglutide 1.5 mg/week, liraglutide 1.2 mg/day, liraglutide 1.8 mg/day, and lixisenatide 20 µg/day) for treating patients with T2DM that is not adequately controlled with metformin alone, providing information related to outcomes and costs which could help decision makers for reallocating available resources.

## 2 Materials and methods

Cost-effectiveness analysis was used to evaluate the efficacy of exenatide combined with metformin versus other GLP-1 receptor agonists available for the management of patients with T2DM in Spain. To perform the analysis in the Spanish environment, a discrete-event stochastic simulation model (Cardiff Diabetes Model) that had been previously validated [16] was used to simulate the progression of patients with T2DM.

The model simulated the natural history of T2DM in a cohort of 1000 patients, while considering treatment efficacy, T2DM-related micro- and macrovascular complications, drug AEs, and associated costs, and was adapted to usual clinical practice in Spain. The risk of microvascular (amputation, blindness, and end-stage renal disease) and macrovascular (ischaemic heart disease, myocardial infarction, stroke, and congestive heart failure) complications was estimated based on UK Prospective Diabetes Study (UKPDS) 68 risk equations [17].

The simulation was performed individually for each patient in the cohort in 6-month cycles until the end of the time horizon considered or the patient's death. The analysis was performed for each treatment option and was subsequently compared to estimate the incremental cost-effectiveness ratio (ICER).

Anthropometric, demographic, and baseline clinical characteristics defining the cohort of patients evaluated were obtained from the literature and represented the profile of patients with T2DM in Spain (Table 1). Demographic characteristics included mean age, proportion of women, mean height, mean duration of T2DM, proportion of smokers and mean patient weight. In the model, the variables that were considered modifiable risk factors to reflect any treatment effect included HbA1c, total cholesterol and HDL cholesterol levels, and systolic blood pressure (SBP).

In this analysis, a long-term time horizon that contemplated the whole life of the patient was considered. It established the maximum simulation duration of 40 years per patient since entering the model. In this way, quality-adjusted life-years (QALYs) gained were estimated, along with the total cost attributable to each treatment alternative from the perspective of the NHS in Spain. An annual discount rate of 3% was applied to both costs and health effects, according to the available recommendations for the development of a cost-effectiveness analysis in Spain [18].

Development of the model required the advice of a panel of experts composed of an endocrinologist and a hospital pharmacist specialising in the treatment of T2DM, to validate and reach a consensus on the values identified in the literature for the parameters included in the model, through a structured questionnaire. All values used in the base-case were agreed upon during a meeting with the experts.

### 2.1 Treatment Alternatives Evaluated

The initial cohort included patients with T2DM who had not achieved adequate glycaemic control with the maximum tolerated dose of oral metformin alone and had started treatment with a GLP-1 receptor agonist combined with metformin. The GLP-1 receptor agonists considered in the model were exenatide 2 mg/week, dulaglutide 1.5 mg/week, liraglutide 1.2 mg/day, liraglutide 1.8 mg/day, and lixisenatide 20 µg/day; all treatments were combined with metformin (2000 mg/day). Each patient received a first-line treatment of GLP-1 receptor agonists combined with metformin as long as HbA1c levels remained below 7.5%

**Table 1** Parameters used in the model

	Parameter	Value	Distribution for PSA			
Demographic characteristics	Mean age (years) [22]	67.7	Normal			
	Proportion female (%) [22]	47.10				
	Mean duration of T2DM (years) [38]	10.07				
	Mean height (m) [51] /weight (kg) [52]	1.67/73.50				
	Proportion smokers (%) [38]	12.10				
Clinical features	Baseline HbA1c level (%) [38]	7.28	Normal			
	Total cholesterol [53] /HDL (mg/dl) [5]	200.60/42.30				
	SBP (mmHg) [54]	125.4				
Utility and utility decrements	Baseline utility (SE) [22]	0.8 (0.20)	Beta			
	Ischaemic heart disease (SE) [23]	- 0.09 (0.02)				
	Myocardial infarction (SE) [23]	- 0.055 (0.01)				
	Congestive heart failure (SE) [23]	- 0.108 (0.03)				
	Stroke(SE) [23]	- 0.164 (0.03)				
	Amputation (SE) [23]	- 0.28 (0.06)				
	Blindness (SE)[23]	- 0.074 (0.03)				
	End-stage renal disease (SE) [24]	- 0.175 (0.03)				
	Severe hypoglycaemic episode (SE) [25]	- 0.047 (0.01)				
	Symptomatic hypoglycaemic episode (SE) [25]	- 0.0142 (0.003)				
	BMI—increase of one unit (SE) [26]	- 0.0472 (0.005)				
BMI—decrease of one unit (SE) [26]	+0.0171 (0.003)					
Efficacy [20]		EQW 2	DULA 1.5	LIRA 1.2	LIRA 1.8	LIXI 20
	ΔHbA1c (%) [SE]	- 1.34 [0.31]	- 1.34 [0.27]	- 0.96 [0.20]	- 1.28 [0.66]	- 0.75 [0.15]
	ΔWeight (kg) [SE]	- 2.04 [1.22]	- 2.38 [0.49]	- 2.72 [0.56]	- 3.09 [0.63]	- 1.84 [0.38]
	Discontinuation due to AEs [SE]	0.063 [0.01]	0.14 [0.03]	0.12 [0.02]	0.13 [0.03]	0.03 [0.01]
	Nausea as AEs [SE]	0.24 [0.05]	0.52 [0.11]	0.44 [0.09]	0.49 [0.10]	0.31 [0.06]
	Symptomatic hypoglycaemia	NA	NA	NA	NA	NA
	Severe hypoglycaemia	NA	NA	NA	NA	NA

T2DM type 2 diabetes mellitus, AEs adverse effects, BMI body mass index, DULA 1.5 dulaglutide 1.5 mg/week, EQW2 exenatide 2 mg/week, HbA1c glycosylated haemoglobin, HDL high-density lipoprotein cholesterol, LIRA 1.2 liraglutide 1.2 mg/day, LIRA 1.8 liraglutide 1.8 mg/day, LIXI 20 lixisenatide 20 µg/day, NA not available, PSA probabilistic sensitivity analyses, SBP systolic blood pressure, SE standard error

[12, 19]; when HbA1c levels exceeded 7.5% or treatment was discontinued, patients switched to a second-line treatment with basal insulin (40 IU/day). Patients receiving basal insulin who had exceeded the established HbA1c threshold switched to a third-line treatment with an intensive insulin regimen (basal insulin [40 IU/day] + bolus insulin [20 IU/day]) and remained on this treatment until the end of the established time horizon or their death. HbA1c levels were checked annually and the treatment was administered to patients with HbA1c levels exceeding the threshold.

The likelihood of clinical events considered in the model was determined by the efficacy of each treatment, which was represented by the reduction of HbA1c levels, changes in body weight, treatment-related AEs (hypoglycaemia and nausea), and the probability of treatment discontinuation (Table 1). Efficacy values for each treatment considered in the analysis were derived from an indirect comparison performed in a meta-analysis [20] in which the relative clinical efficacy of exenatide, as well as its tolerability, were compared with other GLP-1 receptor agonists in treating adult patients with T2DM who were inadequately controlled with metformin. For neutral protamine hagedorn (NPH) insulin, the values proposed in the guideline of the National Institute of Health and Care Excellence (NICE) on the management of adult patients with T2DM were used [19]. The model considered treatment effects during the first year and assumed patients progressed later according to the equations resulting from the UKPDS 68 study [17].

## 2.2 Mortality

All-cause mortality data were applied to show the annual probability of death by age and sex, derived from the Spanish mortality tables [21]. In addition, T2DM patients present with a higher risk of dying from other causes than the general population, therefore mortality related to T2DM and its associated complications were considered in the analysis. These data were estimated from the UKPDS 68 equations [17].

## 2.3 Utilities

Utilities as a reflection of the quality of life of patients in different health states were used to adjust survival and to estimate QALYs. The study considered a baseline utility of 0.80, which was estimated from the results obtained using the EuroQol 5D questionnaire (EQ-5D) in a sample of Spanish patients with T2DM aged over 40 years [22]. Furthermore, baseline utility decrements associated with micro- and macrovascular complications [23, 24], hypoglycaemic episodes [25], and change in body mass index (BMI) [26] were applied. Table 1 describes the utilities and utility decrements used in the present study.

## 2.4 Costs

According to the perspective used, only direct healthcare costs were considered in the analysis (drug acquisition costs, costs of T2DM-related complications, costs associated with BMI increase due to weight gain, and hypoglycaemia, treatment discontinuation, and AE costs). The costs identified in the literature were updated to 2018 values based on the Spanish general consumer price index [27], and all costs were expressed in 2018 Euros (Table 2).

### 2.4.1 Cost of Drug Acquisition

Drug acquisition costs were calculated from the recommended retail price (RRP) + value added tax (VAT) published in the BOT Plus Catalogue of Medicines of the General Council of Official Associations of Pharmacists in Spain [28], applying the deduction corresponding to Royal Decree-Law 8/2010 [29]. The annual exenatide acquisition cost was estimated from the reference price listed in the reference price order [30]. The study considered the lowest price of available preparations (Bydureon 2 mg powder and solvent for prolonged-release suspension for injection in a pre-filled pen, four single-dose pens) (Table 2).

Annual treatment costs considered in the model were determined, along with the recommended dose for each treatment [31]: metformin 2000 mg/day (€33.35), exenatide 2 mg/week (€1217.59), dulaglutide 1.5 mg/week (€1821.42), liraglutide 1.2 mg/day (€1555.97), liraglutide 1.8 mg/day (€2333.95), lixisenatide 20 µg/day (€1503.13), basal insulin (glargine) 40 IU/day (€168.51), and bolus insulin (aspart) 20 IU/day (€673.99).

### 2.4.2 Cost of Type 2 Diabetes Mellitus-Related Complications

The management costs of T2DM-related micro- and macrovascular complications (in which fatal and non-fatal events were distinguished) were obtained from various sources [32–35], updated to 2018 Euros, and applied only during the year the complication occurred. For surviving patients, the annual maintenance costs associated with each complication were considered until the end of the time horizon of the simulation or the patient's death (Table 2).

### 2.4.3 Costs Associated with the Increase in Weight/Body Mass Index

The annual costs associated with the increase in BMI was estimated by sex, based on a study from the UK [36] reporting a direct relationship between the cost of prescription drugs and the increase in a patient's BMI.

**Table 2** Unitary cost (€, 2018)

Parameter	Unit cost (€, 2018)			Distribution for PSA
	First-year cost		Maintenance cost (€)	
	Fatal event (€)	Non-fatal event (€)		
<b>T2DM complications</b>				
Ischaemic heart disease (SE) [32]	–	2335 (476.63)	887 (181.06)	Gamma
Myocardial infarction (SE) [32]	4755 (970.61)	5132 (1047.57)	887 (181.06)	Gamma
Stroke (SE) [33]	4755 (970.61)	6532 (1333.34)	2551 (520.72)	Gamma
Congestive heart failure (SE) [32]	4755 (970.61)	3451 (704.43)	3662 (747.50)	Gamma
Amputation (SE) [32]	3782 (772)	11,605 (2368.86)	1702 (347.42)	Gamma
Blindness (SE) [34]	–	1932 (394.37)	829 (169.22)	Gamma
End-stage renal disease (SE) [35]	–	31,451 (6419.91)	31,451 (6419.91)	Gamma
Cost (€)				
<b>Hypoglycaemic episode</b>				
Severe hypoglycaemia (SE) [37]			1154 (235.56)	Gamma
<b>Adverse effects</b>				
Nausea (SE) [35]			59.77 (12.20)	Gamma
Treatment discontinuation (SE) [35]			59.77 (12.20)	Gamma
<b>Drug treatment [28]</b>	<b>Dose</b>	<b>RRP per pack (€)</b>	<b>RRP + VAT (€)</b>	<b>Annual cost (€)</b>
Metformin	2000 mg/day	1.94	1.94	33.35
Exenatide <sup>a</sup>	2 mg/week	89.75	93.34	1217.59
Dulaglutide	1.5 mg/week	145.14	150.95	1821.42
Liraglutide	1.2 mg/day	132.84	138.16	1555.97
	1.8 mg/day	132.84	138.16	2333.95
Lixisenatide	20 µg/day	119.78	124.57	1503.13
Basal insulin (glargine)	40 IU/day	55.49	57.71	168.51
Bolus insulin (aspart)	20 IU/day	45.17	46.97	673.99

T2DM type 2 diabetes mellitus, RRP recommended retail price, PSA probabilistic sensitivity analyses, SE standard error, VAT value added tax

<sup>a</sup>Reference RRP is considered

#### 2.4.4 Cost of Hypoglycaemia and Adverse Effects

In relation to hypoglycaemic episodes, only the cost of severe hypoglycaemia was considered [37], assuming that symptomatic hypoglycaemic episodes do not involve health resource consumption. The cost of AEs included the costs associated with nausea and treatment discontinuation, assuming the cost equivalent for a primary care physician visit for the management of each issue. The cost of the visit was derived from a health costs database at the national level [35] (Table 2).

#### 2.5 Sensitivity Analysis

To evaluate the influence of parameter variation on the model results and to confirm model robustness, univariate and probabilistic sensitivity analyses (SA) were performed.

In univariate SA, different parameters were modified individually, including the time horizon of the study (20 years),

discount rate (0% and 5%), utility value (0.684 derived from the CODE-2 study [38]), utility decrement value associated with the change in BMI ( $\pm 0.0061$ ) [22], HbA1c threshold of 8.5% for switching to the next line of treatment [39], and bolus insulin dose (40 IU/day). Additionally, the impact of a weight increase (2.82 kg) [40] in patients reaching the third line of intensive insulin treatment was explored.

In order to explore the uncertainty of assumptions carried out to the mean baseline HbA1c value, a univariate SA was performed using the mean baseline HbA1c (8.2%) applied in the network meta-analysis in relation to the HbA1c reductions of the treatment effects [20]. Furthermore, to express the lower baseline HbA1c value used in the present model (7.28%), the efficacy estimates for the different drugs observed in the network meta-analysis were down-adjusted by a factor of 7.28%/8.2%.

The probabilistic SA consisted of the simultaneous change of all potentially relevant parameters by a Monte Carlo simulation (1000 iterations) by applying different

probability distributions to the considered parameters. Applied functions had a normal distribution for baseline characteristics, gamma distribution for cost parameters, and beta distribution for utility data (Fig. 1).

### 3 Results

#### 3.1 Base-Case

Exenatide 2 mg/week was associated with 8.26 QALYs and was the most effective option compared with dulaglutide 1.5 mg/week (8.19 QALYs), liraglutide 1.2 mg/day (8.10 QALYs), liraglutide 1.8 mg/day (8.20 QALYs), and lixisenatide 20 µg/day (8.13 QALYs).

The total cost per patient at the end of the simulation was €20,423.27 with exenatide 2 mg/week, €22,611.94 with dulaglutide 1.5 mg/week, €21,065.97 with liraglutide 1.2 mg/day, €24,865.69 with liraglutide 1.8 mg/day, and €21,334.58 with lixisenatide 20 µg/day.

Based on these results, exenatide 2 mg/week combined with metformin for the treatment of patients with T2DM was a dominant alternative, i.e. it is more effective and less costly than dulaglutide 1.5 mg/week, liraglutide 1.2 mg/day, liraglutide 1.8 mg/day, and lixisenatide 20 µg/day (Table 3).

#### 3.2 Sensitivity Analysis

Univariate SA confirmed the robustness of the results in the 10 proposed scenarios. Exenatide 2 mg/week was a dominant strategy over dulaglutide 1.5 mg/week, liraglutide 1.2 mg/day, liraglutide 1.8 mg/day, and lixisenatide 20 µg/day in all deterministic SA performed (Table 4).

The probabilistic SA revealed that exenatide 2 mg/week was more cost effective than the other GLP-1 receptor agonists evaluated, with a probability of between 95 and 99%; this analysis assumed the latest willingness-to-pay threshold of €20,000 per QALY gained proposed for Spain (Fig. 1) [41].

### 4 Discussion

The present study shows exenatide 2 mg/week is an economically dominant strategy compared with dulaglutide 1.5 mg/week, liraglutide 1.2 mg/day, liraglutide 1.8 mg/day, and lixisenatide 20 µg/day. The results obtained in the univariate SA did not vary significantly with respect to the base case.

T2DM has a significant impact due to its economic burden [42]. In this sense, the present analysis suggests that treatment with exenatide 2 mg/week combined with

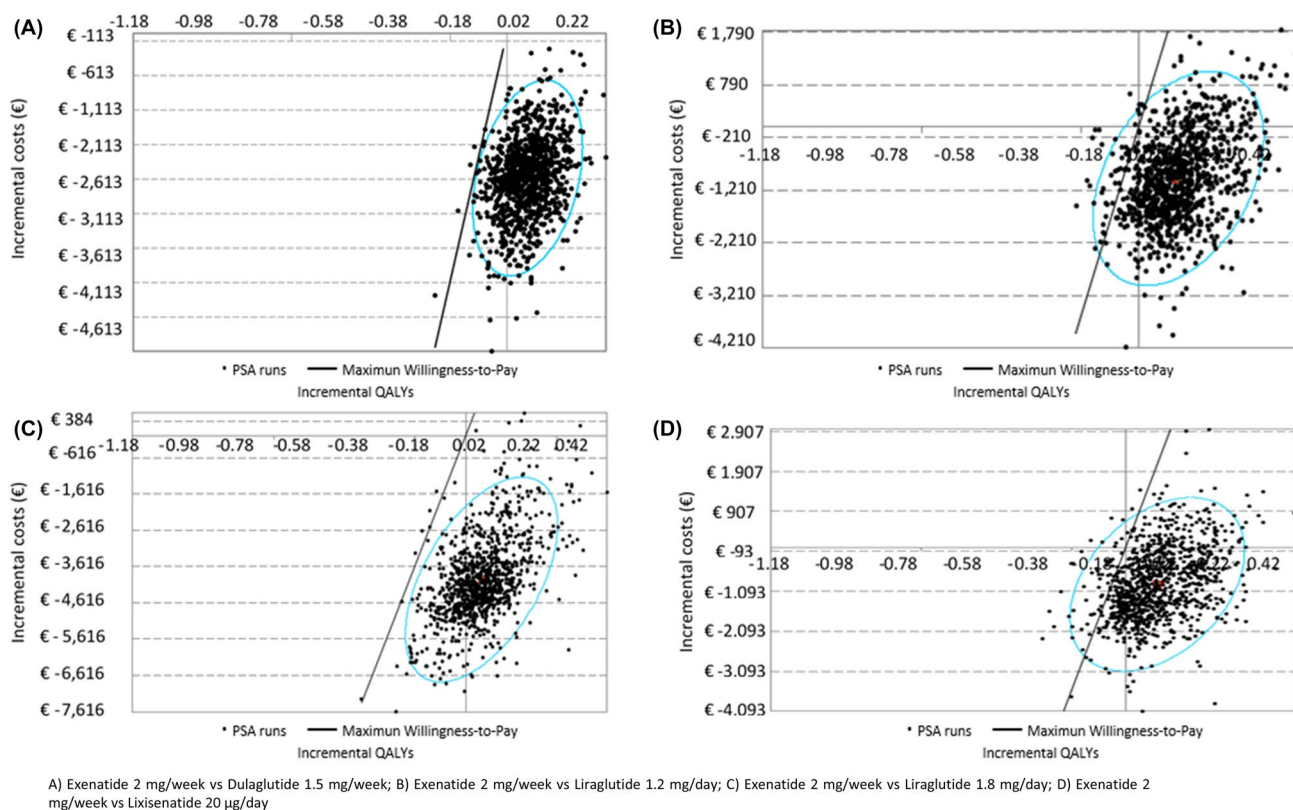


Fig. 1 Probabilistic sensitivity analyses

**Table 3** Base-case results

	Exenatide 2 mg	Dulaglutide 1.5 mg	Liraglutide 1.2 mg	Liraglutide 1.8 mg	Lixisenatide 20 µg
QALY	8.26	8.19	8.10	8.20	8.13
Total costs (€)	20,423.27	22,611.94	21,065.97	24,865.69	21,334.58
Drug acquisition cost (€)	10,840.29	12,988.86	11,406.55	15,228.39	11,691.97
Cost of T2DM complications (€)	8026.08	8057.27	8097.98	8073.31	8089.01
Cost of changes in BMI (€)	1546.39	1544.04	1542.66	1543.43	1542.83
Cost of hypoglycaemia	–	–	–	–	–
Cost of adverse effects (€)	10.51	21.77	18.78	20.56	10.77
	$\Delta$ QALY		$\Delta$ Costs (€)		ICER
Exenatide 2 mg vs.					
Dulaglutide 1.5 mg	0.07		– 2189		Dominant
Liraglutide 1.2 mg	0.15		– 643		Dominant
Liraglutide 1.8 mg	0.06		– 4442		Dominant
Lixisenatide 20 µg	0.12		– 911		Dominant

QALY quality-adjusted life-year, T2DM type 2 diabetes mellitus, BMI body mass index, ICER incremental cost-effectiveness ratio

metformin could be a dominant treatment option versus other GLP-1 receptor agonists by reducing costs associated with the treatment and management of patients with T2DM.

The available evidence shows that the effectiveness and tolerability of exenatide is comparable to those of other GLP-1 receptor agonists. Based on these conclusions, the clinical prescription of a GLP-1 receptor agonist should consider treatment personalisation, cost, and efficiency [43].

To our knowledge, this is the first study of a cost-effectiveness analysis in Spain comparing exenatide with dulaglutide, liraglutide, and lixisenatide in patients with T2DM that is inadequately controlled with metformin alone. Therefore, in the Spanish context, it is not possible to compare the results with other studies. Nevertheless, our results are similar to those published in an economic analysis performed in the UK [44].

In a review of the literature, four economic analyses were identified comparing one GLP-1 receptor agonist with another. These studies were conducted in France [45], Italy [46], the UK [47], and Spain [48]. The diversity of methods and treatment alternatives used in these analyses prevented comparing the conclusions with those of the present study.

As a limitation and possible analysis bias, one could comment on the methodology used to consider efficacy variables. Due to the absence of direct-comparison clinical trials among the alternatives evaluated, efficacy data from an indirect comparison performed in a meta-analysis were used [20]. Although indirect comparisons are a standard method that can provide useful and complementary data about the relative efficacy of compared interventions [49], they are subject to greater bias than direct comparisons and may overestimate the effectiveness of interventions. One

underlying assumption is the application of HbA1c reduction estimates from the meta-analysis, which were derived from studies with mean baseline HbA1c levels of 8.2%, to the Spanish hypothetical cohort with a baseline HbA1c set at 7.28% in the case base. However, the efficacy estimates for the different drugs are all derived in the same way, therefore incremental differences in outcomes are not expected to affect the estimated pairwise ICERs. The influence of this parameter was tested in a SA, where it was found that there were no differences in the results obtained in the base case.

Another possible limitation is related to the use of data extracted from the literature of studies conducted in other countries, as no studies have been conducted specifically in Spain. Utility decrements associated with micro- and macrovascular complications [17], and those related to hypoglycaemia [25], used in the model were derived from two studies in the UK, while utility decrements associated with weight gain were derived from a Canadian study [26]. In the same way, data obtained from a study in the UK [36] were used to estimate costs associated with weight gain in patients with T2DM. All these data were validated by the panel of experts who considered the data representative of the Spanish population with T2DM.

In this sense, there is published evidence suggesting that utility decrement values for different health states in six European countries (Finland, Germany, The Netherlands, Spain, Sweden and the UK) could be described by a common model; therefore, no relevant influence is expected to be associated with the use of disutility values from the UK population, instead of specific values for Spanish patients [50].

**Table 4** Deterministic sensitivity analysis results

Sensitivity analysis			$\Delta$ QALY	$\Delta$ Costs (€)	ICER
20-year time horizon	Exenatide 2 mg vs.	Dulaglutide 1.5 mg	0.07	- 2224	Dominant
		Liraglutide 1.2 mg	0.16	- 654	Dominant
		Liraglutide 1.8 mg	0.06	- 4433	Dominant
		Lixisenatide 20 $\mu$ g	0.12	- 923	Dominant
Discount rate 0%	Exenatide 2 mg vs.	Dulaglutide 1.5 mg	0.08	- 2314	Dominant
		Liraglutide 1.2 mg	0.18	- 637	Dominant
		Liraglutide 1.8 mg	0.07	- 4701	Dominant
		Lixisenatide 20 $\mu$ g	0.15	- 936	Dominant
Discount rate 5%	Exenatide 2 mg vs.	Dulaglutide 1.5 mg	0.06	- 2111	Dominant
		Liraglutide 1.2 mg	0.14	- 645	Dominant
		Liraglutide 1.8 mg	0.05	- 4284	Dominant
		Lixisenatide 20 $\mu$ g	0.11	- 897	Dominant
Utility value 0.684	Exenatide 2 mg vs.	Dulaglutide 1.5 mg	0.06	- 2189	Dominant
		Liraglutide 1.2 mg	0.15	- 643	Dominant
		Liraglutide 1.8 mg	0.05	- 4442	Dominant
		Lixisenatide 20 $\mu$ g	0.12	- 911	Dominant
Weight gain utility decrement Increase in BMI: -0.0061 Decrease in BMI: +0.0061	Exenatide 2 mg vs.	Dulaglutide 1.5 mg	0.05	- 2189	Dominant
		Liraglutide 1.2 mg	0.12	- 643	Dominant
		Liraglutide 1.8 mg	0.05	- 4442	Dominant
		Lixisenatide 20 $\mu$ g	0.09	- 911	Dominant
HbA1c threshold 8.5%	Exenatide 2 mg vs.	Dulaglutide 1.5 mg	0.11	- 3802	Dominant
		Liraglutide 1.2 mg	0.11	- 2504	Dominant
		Liraglutide 1.8 mg	0.09	- 7700	Dominant
		Lixisenatide 20 $\mu$ g	0.01	- 2701	Dominant
Weight change (third-line treatment) 2.82 kg	Exenatide 2 mg vs.	Dulaglutide 1.5 mg	0.07	- 2180	Dominant
		Liraglutide 1.2 mg	0.15	- 640	Dominant
		Liraglutide 1.8 mg	0.06	- 4435	Dominant
		Lixisenatide 20 $\mu$ g	0.12	- 896	Dominant
Bolus insulin dose 40 IU/day	Exenatide 2 mg vs.	Dulaglutide 1.5 mg	0.07	- 2254	Dominant
		Liraglutide 1.2 mg	0.15	- 665	Dominant
		Liraglutide 1.8 mg	0.06	- 4498	Dominant
		Lixisenatide 20 $\mu$ g	0.12	- 1031	Dominant
Mean baseline HbA1c value 8.2%	Exenatide 2 mg vs.	Dulaglutide 1.5 mg	0.05	- 1381	Dominant
		Liraglutide 1.2 mg	0.17	- 193	Dominant
		Liraglutide 1.8 mg	0.03	- 2834	Dominant
		Lixisenatide 20 $\mu$ g	0.16	- 2086	Dominant
Treatment effects of HbA1c were down-adjusted by a factor of 7.28%/8.2%	Exenatide 2 mg vs.	Dulaglutide 1.5 mg	0.05	- 1819	Dominant
		Liraglutide 1.2 mg	0.09	- 1364	Dominant
		Liraglutide 1.8 mg	0.04	- 3668	Dominant
		Lixisenatide 20 $\mu$ g	0.04	- 1459	Dominant

The different profile of each drug could drive differences in outcomes for some specific subgroups, but the absence of robust evidence prevented performing this approach.

Despite the limitations described and the assumptions adopted, the results of univariate and probabilistic SAs confirmed the robustness of the base-case results.

## 5 Conclusions

This analysis suggests that exenatide 2 mg/week is a dominant alternative (i.e. it is more effective and less costly) to dulaglutide 1.5 mg/week, liraglutide 1.2 mg/day, liraglutide 1.8 mg/day, and lixisenatide 20  $\mu$ g/day to treat patients with T2DM that is inadequately controlled by metformin alone.



**Author Contributions** IO and MM performed the economics analysis with the support of MC. AC and RMR provided clinical expert opinion on the disease area. The manuscript was drafted by IO and MM. All authors contributed to the interpretation and presentation of the findings, revised the article critically for important intellectual content, and approved the final version of the manuscript for submission.

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**Data Availability Statement** All data used in the analyses are available in this published article. The Microsoft Excel model described in this study is the proprietary of AstraZeneca, and access to the model is at the discretion of AstraZeneca.

## Compliance with ethical standards

**Conflicts of Interest** María Mareque and Itziar Oyagüez are currently employed by PORIB, a consultant company specialising in economic evaluations of health interventions that received financial support from AstraZeneca for the development of this study. Andreea Ciudin and Raquel María Rodríguez-Rincón have received honoraria from PORIB for advocacy tasks related to this project. Margarita Capel and Susana Simón are employees of AstraZeneca Spain.

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