

# The Cost-effectiveness of Dulaglutide 1.5mg versus Exenatide QW for the Treatment of Patients with Type 2 Diabetes Mellitus in France

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## ABSTRACT

**Introduction:** Dulaglutide is a novel once-weekly administered glucagon-like peptide 1 receptor agonist (GLP-1 RA) for the management of type 2 diabetes mellitus (T2DM). The objective of this analysis was to estimate the cost-effectiveness of dulaglutide 1.5 mg versus exenatide QW for the management of T2DM in France.

**Methods:** The QuintilesIMS CORE Diabetes Model was used to estimate the expected lifetime direct medical costs and outcomes of T2DM from the perspective of the French National Health Service. In the absence of head-to-head data,

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relative efficacy was derived from a network meta-analysis. Patient cohort characteristics were derived from the AWARD-2 trial. All patients were assumed to remain on treatment for 2 years before escalating to insulin therapy. Costs included treatment costs and costs associated with long-term complications of T2DM. Utilities were estimated based on a recent systematic review. One-way sensitivity analyses (OWSA) and probabilistic sensitivity analysis (PSA) were conducted. Cost-effectiveness acceptability curves (CEACs) were generated.

**Results:** Dulaglutide 1.5 mg was associated with lower costs (lifetime costs €41,562 vs €43,021) and increased health benefits (lifetime quality-adjusted life years: QALYs 9.804 vs 9.757) versus exenatide QW for the treatment of T2DM in France. OWSA and PSA indicated that results were robust across a range of plausible input parameters. The CEAC indicated a 99.5% probability that dulaglutide would be considered cost-effective at a willingness to pay of €30,000.

**Conclusion:** Dulaglutide 1.5 mg reduced expected costs and increased expected QALYs when compared against exenatide QW for the treatment of T2DM in France. Compared with exenatide QW, dulaglutide 1.5 mg can provide additional health benefits for patients with T2DM and may result in cost savings for payers.  
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**Keywords:** Cost–utility; Dulaglutide; Exenatide QW; France; Type 2 diabetes

## INTRODUCTION

Diabetes is an increasingly prevalent metabolic disease associated with a wide range of serious complications. The current prevalence of diabetes in the European region has been estimated at approximately 60 million (10.3% of men and 9.6% of women aged 25 years and over) [1, 2], with estimates for France in the region of 7.4% (range: 6.1–9.1%, age-adjusted prevalence: 5.3%), equating to approximately 3.3 million diagnosed diabetes cases in 2015 [2]. A substantial proportion of these patients remain at suboptimal levels of glucose control, increasing the risk of diabetes-related complications [3, 4]. The life expectancy of patients with diabetes is reduced by up to 10 years compared to the general population, mainly due to the increased risk of cardiovascular death and stroke [5, 6]; in 2015, diabetes accounted for more than 26,000 deaths in France [2]. The majority of diabetes patients (approximately 90%) suffer from type 2 diabetes mellitus (T2DM) [2].

The high prevalence and socioeconomic consequences of T2DM make this disease a prominent public health issue. A 2010 study estimated the total statutory health insurance (SHI) expenditure on diabetes care in France at €17.7 billion. Of this, an annual spend of €2.5 billion was attributed to diabetes treatment and prevention of complications, €4.2 billion was attributed to the treatment of diabetes-related complications (with cardiovascular complications accounting for approximately 20% of this total), and a further €3.6 billion was attributed to the treatment of diabetes-related comorbidities [7]. According to the International Diabetes Federation (IDF) 7th Diabetes Atlas Report, in 2015, France had the sixth highest diabetes-related expenditure worldwide, which is expected to rise to approximately \$19 billion (reported in 2015 international dollars) by 2040 [2]. Dulaglutide is a novel GLP-1 RA administered once weekly via a disposable auto-injection pen with a fixed dosage (1.5 mg). The efficacy and safety of dulaglutide 1.5 mg were established in the AWARD clinical trial program [8–13]. Dulaglutide is an alternative treatment option available for T2DM management. Available

GLP-1 RAs in France currently include exenatide twice daily, liraglutide once daily, and exenatide once weekly (QW). Of the available formulations, the uptake of exenatide twice daily is low (based on MIDAS GLP-1 market share data) [14]. Dulaglutide has been shown to be superior to exenatide twice daily (BID) and has demonstrated noninferiority to liraglutide in terms of glycemic control [8, 9]. In France, the cost of dulaglutide is lower than the cost of exenatide BID or liraglutide [15]. The relative cost-effectiveness of dulaglutide compared with exenatide QW in France has not been previously established. The aim of this study was to compare the cost-effectiveness of dulaglutide 1.5 mg once weekly with that of the once-weekly GLP-1 receptor agonist exenatide QW for the treatment of T2DM patients in France.

## METHODS

### The Model

The QuintilesIMS Core Diabetes Model (CDM) was used to conduct a cost–utility analysis (CUA) in order to compare the cost-effectiveness of dulaglutide 1.5 mg with that of exenatide QW in a simulated cohort of French T2DM patients. The main outcome of a cost–utility analysis is the incremental cost-effectiveness ratio (ICER) or cost per quality-adjusted life year (QALY), which is the ratio of the difference in estimated lifetime costs between the intervention and comparator and the estimated difference in QALYs between the two treatments. No willingness to pay (WTP) threshold has been defined in France, but the figure used by NICE, €30,000, is usually employed as a reference. ICERs below this level are deemed cost-effective. For this CUA treatment, efficacy and adverse event rates were based on data derived from a network meta-analysis (NMA) [16] and the AWARD-2 study [10].

The CDM is a fixed-time increment (annual) stochastic simulation model with disease progression based on a series of interdependent Markov submodels which simulate the complications of diabetes (i.e., cardiovascular disease, eye disease, hypoglycemia, nephropathy,

neuropathy, foot ulcer, amputation, stroke, ketoacidosis, lactic acidosis) and mortality. Each submodel incorporates time, state, and diabetes type-dependent probabilities from public sources [17]. Treatment effect is applied in the first year of treatment. The model then uses the UKPDS regression equations to predict the progression of model parameters over the course of the simulation.

Clinical and economic outcomes are calculated within the model using a nonparametric bootstrapping approach. This process simulates the lifetime progression of diabetes in a cohort of hypothetical patients, repeating the process over numerous simulations with outputs used to derive the incremental cost-effectiveness ratio (ICER). In base case analyses, second-order uncertainty is not applied and stability of outcomes is reached through run of 1000 patients through 1000 iterations; in probabilistic sensitivity analyses (PSA), the gold standard approach requires analysis runs of 50,000 patients over 500 iterations [18, 19]. The CDM has been extensively validated against results from both clinical and epidemiological studies [17, 19–22].

### Perspective

The analyses were conducted from a statutory health insurance (SHI) perspective, capturing all relevant direct medical costs (pharmacy costs plus complications and management costs).

### Time Horizon and Discounting

T2DM is a chronic disease that has long-term implications due to diabetes-related complications and mortality. Therefore, a lifetime horizon (40 years) was applied to capture the long-term costs and health benefits associated with diabetes treatment in France. Costs and health benefits were both discounted at 4% annually [18].

### Baseline Characteristics of Patients

The model population comprised patients with T2DM treated with sulphonylurea (SU) and

metformin (MET). The patient cohort was defined using the baseline demographics, complications, and physiological parameters (age, duration of diabetes, baseline metabolic risk factors, and CV complication rates) of patients enrolled in the AWARD-2 trial [10], an international phase III randomized controlled trial (RCT) with a follow-up of 78 weeks which included French patients. The AWARD-2 cohort (the only MET + SU cohort in the AWARD clinical program) was used to inform these parameters within the model, as data were not available from the NMA, and background medications were consistent with those available in France. Country-specific cohort characteristics such as the proportion of smokers, the number of cigarettes per day, and alcohol consumption were derived from official statistics [23, 24]. Table 1 reports the cohort characteristics of the modeled population.

Table S1 in the Electronic supplementary material (ESM) reports the modeled rates of baseline diabetes complications as reported in AWARD-2 and background risk factors as estimated from French-population-specific data [25]. Data on noncardiovascular comorbidities were not collected in the AWARD studies. The prevalence of these comorbidities (renal, retinopathy, ophthalmological, and limb) were estimated based on the T2DM cohort defined in NICE (National Institute for Health and Care Excellence) clinical guideline 87 [26], and have been reported elsewhere. Rates were assumed applicable to a French population due to the similar profiles of the cohorts, including baseline hemoglobin A1c (HbA1c), age, and duration of diabetes.

### Treatment Effects

Dulaglutide and exenatide QW have not been compared in head-to-head trials; key model inputs were therefore derived from a network meta-analysis (NMA) [16]. The analysis presented in this report only includes studies where treatments were administered as an add-on to metformin in combination with sulphonylurea (MET + SU), in line with French clinical guidelines for the management of

**Table 1** Population cohort characteristics

Characteristic	Mean	SD	Sources
HbA1c (%)	8.14	0.99	AWARD-2 trial [10]
Age (years)	56.66	9.47	AWARD-2 trial [10]
Duration of diabetes (years)	9.10	6.04	AWARD-2 trial [10]
Male (proportion)	0.51		AWARD-2 trial [10]
Ethnicity (proportion) (%)			AWARD-2 trial [10]
Caucasian	46.40		
African descent	0.50		
Hispanic	36.10		
Native American	0.00		
Asian/Pacific Islander and other	17.00		
Systolic blood pressure (mmHg)	131.07	15.10	AWARD-2 trial [10]
Baseline total cholesterol (mg/dL)	176.27	40.75	AWARD-2 trial [10]
Baseline HDL-C (mg/dL)	46.34	11.60	AWARD-2 trial [10]
Baseline LDL-C (mg/dL)	95.90	34.42	AWARD-2 trial [10]
Baseline triglycerides (mg/dL)	176.54	116.29	AWARD-2 trial [10]
Body mass index (kg/m <sup>2</sup> )	31.55	5.46	AWARD-2 trial [10]
Proportion of smokers	34.1%		WHO [23]
Cigarettes per day	14		WHO [23]
Alcohol consumption	8.9		WHO [23]

glycemic control in type 2 diabetes [27]. A systematic literature review (SLR) was conducted on a number of comparators, including GLP-1 RAs, sulphonylureas (SU), thiazolidinediones (TZDs), dipeptidyl peptidase-4 (DPP-4) inhibitors, sodium-glucose cotransporter-2 (SGLT-2) inhibitors, and insulins. Studies meeting the inclusion criteria for the systematic review were then assessed for inclusion in the NMA based on treatment regimen, duration, and background therapy. Analyses were stratified by background therapy (add-on to MET; add-on to MET ± SU ± TZD) and time of evaluation [(16, 36) weeks; (37, 56) weeks] to account for some of the heterogeneity between studies. Trials including the background use of TZDs were excluded from the NMA specific for France, as TZDs do not have marketing authorization in

France. The main assumptions made for the NMA were homogeneity, transitivity, and consistency. All assumptions made were investigated to assess how robust the analysis was to those assumptions, and hence to provide an indication of the reliability of the results. Both fixed and random effects models were assessed for each network where feasible. Placebo was chosen as the reference treatment for the analyses, because it was present in most networks and is a relevant reference treatment for all other comparators. These methods follow standardized and rigorous methodologies required by HTA agencies (for example the UK NICE guidelines for the synthesis of clinical evidence, consistent with the evidence standards of other reimbursement authorities).

**Table 2** Treatment effects and treatment-related events

Characteristic	Mean treatment effect (SE, 95% CI)		Source
	Dulaglutide 1.5 mg	Exenatide QW	
HbA1c (%)	– 1.45 (0.14, – 1.74 to 1.17)	– 0.98 (0.15, – 1.27 to 0.69)	NMA analysis [16]
Systolic blood pressure (mmHg)	0.17 (0.81)	0.17 (0.81)	AWARD-2 trial [10]
Total cholesterol (mg/dL)	0.43 (2.07)	0.43 (2.07)	AWARD-2 trial [10]
LDL-C (mg/dL)	1.12 (1.83)	1.12 (1.83)	AWARD-2 trial [10]
HDL-C (mg/dL)	– 0.35 (0.43)	– 0.35 (0.43)	AWARD-2 trial [10]
Triglycerides (mg/dL)	– 6.47 (6.63)	– 6.47 (6.63)	AWARD-2 trial [10]
Body mass index (kg/m <sup>2</sup> )	– 0.10 (0.18, – 0.47 to 0.24)	– 0.12 (0.19, – 0.50 to 0.24)	NMA analysis [16]
Nausea (event rate per 100 pt years)*	14.3	7.5	NMA analysis [16]
Major hypo (event rate per 100 pt years)	0	0	AWARD-2 trial [10]
Minor hypo (event rate per 100 pt years)**	209	209	AWARD-2 trial [10]
Injection site reaction <sup>‡</sup>	1.9%	16.0%	SmPC [29, 30]

\* Input converted from data provided on the proportion of patients experiencing nausea at 12 months

\*\* Please note that “minor hypo” refers to nonsevere symptomatic hypo events as reported in the AWARD trials, which were based upon documented symptomatic and probable (not documented symptomatic) hypoglycemia

<sup>‡</sup> ISR was judged based on data provided in the SPCs. 95% CI was used in the sensitivity analysis

The NMA estimated two key efficacy outcomes (HbA1c and weight change) and one treatment-related adverse event (nausea). These endpoints were specifically estimated from the NMA, as they are key drivers of clinical and economic outcomes in the model. A study duration of 16–36 weeks provided the most comprehensive data for these endpoints. In networks for all three endpoints, the only study that provided input data for exenatide QW was the DURATION-6 study [28], whereas the AWARD-2 study provided data for dulaglutide. In the absence of data from the NMA, treatment effects associated with other parameters were

assumed to be equivalent to those in the AWARD-2 trial dulaglutide 1.5 mg treatment arm, and were applied to both comparators.

Treatment effects and treatment-related events are reported in Table 2. In the model, after 2 years of initial treatment, both treatment groups escalated to rescue therapy with basal insulin glargine at a daily dose of 40 IU as per World Health Organisation guidelines [31]. This is a conservative assumption of GLP-1 RA treatment duration based on real-world observational studies [32, 33]. The impact of the treatment switch was limited to an effect on BMI within the cohort (no effect on HbA1c or

the hypoglycemic event rate was assumed, as any impact would be equivalent across both treatment arms). Patients switching to insulin glargine experienced a rebound of their BMI to their baseline BMI value at the start of year three (i.e., the initial effect on the BMI was reversed). Other model parameters were assumed to follow natural disease progression as captured within the UK Prospective Diabetes Study (UKPDS) [34].

### Health State Utilities and Disutilities

QALYs, a measure of health outcomes, captures the benefits associated with a treatment in terms of quantity and quality of life. QALYs are valued using utility scores. Each health state in the model was assigned a utility value. Utilities vary from 0 to 1, where 0 represents death and 1 indicates full health. Health-state-related utilities for T2DM and associated complications were derived from a recent systematic literature review [35]. Disutilities associated with treatment-related events (nausea, hypoglycemia, BMI increase) were derived from the best evidence available (Table S2 in the ESM). The impact of BMI on utility was estimated through the assignment of a disutility (of  $-0.0061$ ) per unit gain BMI over a BMI of  $25 \text{ kg/m}^2$ . This value represents a conservative assessment of the potential disutility of weight gain (the highest disutility value reported in the literature) [35]. An annual nausea disutility ( $-0.04$ ) [36] was applied to patients who experienced nausea for the first 3 months in the model ( $-0.01$ ) to account for the transient nature of the event. An injection site reaction (ISR) disutility was applied in the base case analysis by multiplying the percent of patients who experienced ISR by the expected disutility ( $-0.011$ ) [37]. Table S2 in the ESM provides a full list of health state utilities included in the analysis.

### Treatment Costs

Treatment costs comprised drug cost, needle cost (applicable to insulin as rescue therapy), and the costs associated with self-monitoring of blood glucose (SMBG). SMBG frequency

followed the approach recommended by Owens et al. [38]. Three times weekly monitoring is recommended for patients on oral antihyperglycemic drug regimens which include SU (the NMA population); daily monitoring is recommended for regimens including basal insulin. Public drug costs were obtained from Ameli, the French national health insurance website [15]. Needle and SMBG costs were sourced from national tariffs [39]. Annual treatment costs are reported in Table S3 of the ESM [39]. The costs of background therapies were not included in the analyses as these therapies were assumed to be constant across treatment settings. January 2016 drug prices were used for treatment cost calculations [15].

### Management Costs

T2DM-associated complications include CV disease, renal complications, acute events, ophthalmological events, and events related to neuropathy and limb complications. The cost estimates were derived from a combination of a targeted literature search and a review of published tariffs [15, 40–46]. Where possible, diabetes-specific French costs were used. Costs associated with the management of complications are reported in Table S4 of the ESM. Where necessary, costs were inflated to 2014 values, using the consumer price index (CPI) for health products and services published by the French National Statistics Institute [47].

### Exploring Uncertainty

One-way sensitivity analyses (OWSA) were conducted to assess the impact on the base-case results. Dulaglutide treatment effects on HbA1c and BMI were set to upper and lower 95% credible intervals reported from the NMA (while exenatide QW inputs were kept stable) to assess the impact of alternate efficacy assumptions. Patients were assumed to remain on treatment for 1 and 3 years, compared to the base case assumption of 2 years of treatment. Complication costs were varied simultaneously by  $\pm 30\%$  to account for uncertainty around the point estimates used in the model. Shorter and longer

**Table 3** Base-case and sensitivity analyses: cost-effectiveness outputs

Population/analysis	Cost (€)			QALYs			ICER (Euro)
	Dulaglutide 1.5 mg	Exenatide QW	Difference (€)	Dulaglutide 1.5 mg	Exenatide QW	Difference	
Base case	41,562	43,021	– 1459	9.804	9.757	0.047	DOMINANT
PSA	44,669	45,794	– 1125	9.418	9.364	0.054	DOMINANT
Treatment effects*							
HbA1c upper limit	42,539	43,021	– 482	9.766	9.757	0.009	DOMINANT
HbA1c lower limit	41,268	43,021	– 1753	9.834	9.757	0.077	DOMINANT
BMI upper limit	41,683	43,021	– 1338	9.787	9.757	0.030	DOMINANT
BMI lower limit	41,514	43,021	– 1507	9.813	9.757	0.056	DOMINANT
Treatment duration							
1 year	41,220	42,528	– 1308	9.817	9.768	0.049	DOMINANT
3 years	42,039	43,566	– 1527	9.794	9.751	0.043	DOMINANT
Economics*							
Economics +30%	50,444	52,348	– 1904	9.804	9.757	0.047	DOMINANT
Economics –30%	32,679	33,695	– 1016	9.804	9.757	0.047	DOMINANT
Utilities							
ISR disutility excluded	41,562	43,021	– 1459	9.804	9.760	0.044	DOMINANT
BMI disutility excluded	41,562	43,021	– 1459	10.379	10.331	0.048	DOMINANT
Nausea disutility excluded	41,562	43,021	– 1459	9.805	9.758	0.047	DOMINANT
Inclusion of ease of use utility	41,562	43,021	– 1459	9.823	9.757	0.066	DOMINANT
Time horizon							
10 years	12,169	12,418	– 249	5.422	5.402	0.020	DOMINANT
50 years	43,050	44,110	– 1060	9.907	9.848	0.059	DOMINANT
Discounting							
0% costs and benefits	87,722	90,628	– 2906	16.198	16.108	0.090	DOMINANT
6% costs and benefits	30,518	31,592	– 1074	8.009	7.973	0.036	DOMINANT

**Table 3** continued

Population/analysis	Cost (€)			QALYs			ICER (Euro)
	Dulaglutide 1.5 mg	Exenatide QW	Difference (€)	Dulaglutide 1.5 mg	Exenatide QW	Difference	
Alternate price for rescue therapy							
Costs equal to biosimilar insulin glargine	40,466	41,929	– 1463	9.804	9.757	0.047	DOMINANT

\* Where parameter = *upper limit*: upper bound of dulaglutide confidence interval from NMA used as model input (comparator kept constant); where parameter = *lower limit*: lower bound of dulaglutide confidence interval used as model input; *Economics*: T2D management costs and costs of T2D complications

time horizons were used (10 and 50 years). Alternative discount rates applied to both costs and benefits were explored (0 and 6%). Rescue treatment costs were assumed to be equal to a biosimilar insulin glargine (Abasaglar) to assess the impact of a reduction in rescue therapy costs. Finally, disutilities relating to BMI, nausea, and ISR were sequentially excluded from the base case.

A probabilistic sensitivity analysis (PSA) was performed to assess the uncertainty in model outputs associated with the uncertainty in parameter inputs. A second-order Monte Carlo simulation was used with the parameter inputs (utilities, costs, treatment effects, cohort characteristics, and clinical events) sampled from fixed distributions. The process was repeated using 50,000 simulated patients over 1000 iterations in order to obtain stable analysis outcomes.

### Compliance with Ethics Guidelines

This study is based on previously conducted trials and did not involve any new studies of human or animal subjects by any of the authors.

## RESULTS

### Base-Case Analyses

Under base-case assumptions, dulaglutide 1.5 mg was dominant compared to exenatide QW.

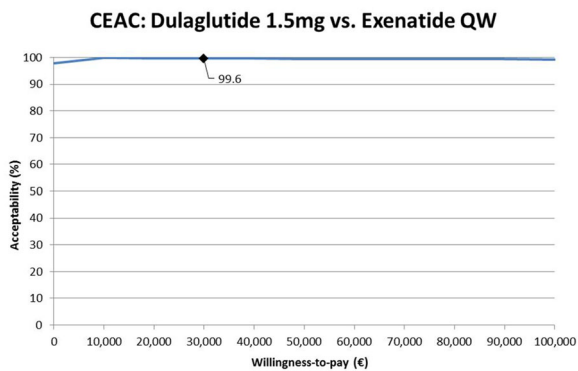
Dulaglutide 1.5 mg was associated with an increase in QALYs of +0.047 (dulaglutide: 9.804 vs exenatide QW: 9.757) and a total cost reduction of €1459 (lifetime costs: dulaglutide: €41,562 vs exenatide QW: €43,021). Dulaglutide reduced the expected cost of complications (– €1489), but was associated with an increase in treatment (+ €21) and management costs (+ €8). The lifetime cumulative incidence of diabetes-related complications was lower for dulaglutide 1.5 mg, with the exception of peripheral vascular disease (PVD) onset and nausea (Fig. S1 in the ESM). Overall, patients remained alive and free of complications for similar lengths of time (dulaglutide patients for approximately 3 months longer than exenatide QW patients).

### Sensitivity Analyses

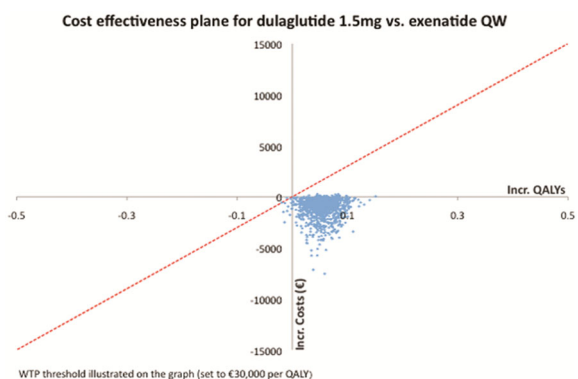
The OWSAs carried out indicated that dulaglutide may remain the dominant treatment across all scenarios. Within this framework, expected outcomes were most sensitive to variation in treatment efficacy (upper 95% limit of BMI and HbA1c) and assumptions relating to time on treatment and model time horizon. Full analysis results are reported in Table 3.

PSA results were in line with the base-case analyses. Dulaglutide 1.5 mg was more effective and less costly in 96.8% of the iterations. The cost-effectiveness acceptability curve (CEAC) (Fig. 1) showed that dulaglutide 1.5 mg had a 99.5% probability of being cost-effective at a WTP threshold of €30,000 per QALY gained.





**Fig. 1** Cost-effectiveness acceptability curve



**Fig. 2** Cost-effectiveness plane for dulaglutide 1.5 mg versus exenatide QW. Note that individual dots on the cost-effectiveness plane represent different ICER estimates produced from the PSA analysis

The incremental cost-effectiveness pairs for costs and QALYs gained are presented in Fig. 2, with a cost per QALY threshold of €30,000 added to the graph to represent an assumed threshold of WTP [48].

## DISCUSSION

Under current assumptions, dulaglutide 1.5 mg was found to be less costly (– €1459) and more effective (+ 0.047 QALYs) than exenatide QW. Findings were driven by the improved initial HbA1c and BMI treatment effect for dulaglutide 1.5 mg, and remained stable to plausible changes in initial treatment effects (OWSAs using 95% confidence intervals). Dulaglutide 1.5 mg remained dominant versus exenatide QW for all of the OWSAs. Absolute costs were lower when

biosimilar insulin glargine was used as rescue therapy. From a French payer perspective and under base-case assumptions, dulaglutide 1.5 mg dominated exenatide QW (it was more effective and less costly), suggesting that it could be a viable treatment option for patients with T2DM, and might result in cost savings to the French payer.

In this analysis, the model inputs were based on a combination of data derived from the head-to-head AWARD-2 clinical trial and on outputs derived from a NMA. While the lack of direct evidence is a limitation, NMA is an increasingly established method that is widely accepted by health technology assessment agencies and subject to a number of clear international guidelines [49–51]. There is limited published evidence on economic evaluations conducted in the French setting with which to compare the outcome of these analyses. However, a recent analysis, although focused on different comparators, found similar values for reported annual cost and expected accumulated quality-adjusted life years [48].

This analysis was subject to limitations common to most diabetes-modeling analyses. Firstly, as with any cost-effectiveness model, in the absence of lifetime data, a number of core assumptions were applied within the CDM in order to extrapolate short-term clinical trial data to long-term outcomes, but these assumptions were consistent with disease progression and based on established risk equations. Evidence relating to expected time on treatment remains limited. The model is sensitive to this parameter, and while the base-case estimate of 2 years reflects current understanding, emerging real-world evidence on the duration of treatment and long-term treatment effects will allow for better future estimates of core model inputs.

Identifying precise, coherent, up-to-date, and relevant data for the many inputs required to model T2DM represents a challenge. Nevertheless, the best available data were used and tested thoroughly by means of sensitivity analyses, with a clear focus on the use of local data where possible. The primary limitations of this analysis are common to other T2DM analyses, and computer simulation modeling remains the best option currently available to estimate the

clinical and economic consequences of therapeutic interventions in the medium-to-long term.

## CONCLUSION

This analysis indicated that, in a French health-care setting, and under the model assumptions applied, dulaglutide 1.5 mg can be considered a dominant treatment alternative to exenatide QW in patients with T2DM. Compared with exenatide QW, dulaglutide 1.5 mg provides an additional health benefit for T2DM patients, and may result in cost savings for payers.

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**Compliance with Ethics Guidelines.** This study is based on previously conducted trials and did not involve any new studies of human or animal subjects by any of the authors.

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## REFERENCES

1. World Health Organization Regional Office for Europe. Facts and figures: the challenge of diabetes. Copenhagen: WHO Europe; 2015.
2. International Diabetes Federation. IDF diabetes atlas, 7th Edition. Brussels: International Diabetes Federation; 2015. <http://www.diabetesatlas.org/component/attachments/?task=download&id=116>. Accessed 5 Feb 2016.
3. UK Prospective Diabetes Study (UKPDS) Group. Intensive blood-glucose control with sulphonylureas or insulin compared with conventional treatment and risk of complications in patients with type 2 diabetes (UKPDS 33). *Lancet*. 1998;352(9131):837–53.
4. Gaede P, Vedel P, Larsen N, Jensen GV, Parving HH, Pedersen O. Multifactorial intervention and cardiovascular disease in patients with type 2 diabetes. *N Engl J Med*. 2003;348(5):383–93.
5. Almdal T, Scharling H, Jensen JS, Vestergaard H. The independent effect of type 2 diabetes mellitus on ischemic heart disease, stroke, and death: a population-based study of 13,000 men and women with 20 years of follow-up. *Arch Intern Med*. 2004;164(13):1422–6.
6. Roper NA, Bilous RW, Kelly WF, Unwin NC, Conolly VM. Excess mortality in a population with diabetes and the impact of material deprivation: longitudinal, population based study. *BMJ*. 2001;322(7299):1389–93.

7. Chevreur K, Brigham KB, Bouche C. The burden and treatment of diabetes in France. *Global Health*. 2014;10(1):1.
8. Wysham C, Blevins T, Arakaki R, Colon G, Garcia P, Atisso C, et al. Efficacy and safety of dulaglutide added onto pioglitazone and metformin versus exenatide in type 2 diabetes in a randomized controlled trial. *Diabetes Care*. 2014;37(8):1259–2167.
9. Dungan KM, Povedano ST, Forst T, Gonzalez JGG, Atisso C, Sealls W, et al. Once-weekly dulaglutide versus once-daily liraglutide in metformin-treated patients with type 2 diabetes (AWARD-6): a randomised, open-label, phase 3, non-inferiority trial. *Lancet*. 2014;384(9951):1349–57.
10. Giorgino F, Benroubi M, Sun JH, Zimmermann AG, Pechtner V. Efficacy and safety of once-weekly dulaglutide versus insulin glargine in patients with type 2 diabetes on metformin and glimepiride (AWARD-2). *Diabetes Care*. 2015;38(12):2241–9.
11. Umpierrez G, Tofe PS, Perez MF, Shurzinske L, Pechtner V. Efficacy and safety of dulaglutide monotherapy versus metformin in type 2 diabetes in a randomized controlled trial (AWARD-3). *Diabetes Care*. 2014;37(8):2168–76.
12. Blonde L, Jendle J, Gross J, Woo V, Jiang H, Fahrbach JL, et al. Once-weekly dulaglutide versus bedtime insulin glargine, both in combination with prandial insulin lispro, in patients with type 2 diabetes (AWARD-4): a randomised, open-label, phase 3, non-inferiority study. *Lancet*. 2015;385(9982):2057–66.
13. Nauck M, Weinstock RS, Umpierrez GE, Guerci B, Skrivaneck Z, Milicevic Z. Efficacy and safety of dulaglutide versus sitagliptin after 52 weeks in type 2 diabetes in a randomized controlled trial (AWARD-5). *Diabetes Care*. 2014;37(8):2149–58.
14. IMS Health Ltd. SMART—Global MIDAS edition: market share data for GLP-1 molecules in France. Milton Keynes: IMS Health Ltd.; 2016.
15. l'Assurance Maladie. Base des médicaments et Informations Tarifaires. 2015. [http://www.codage.ext.cnamts.fr/codif/bdm\\_it/index.php?p\\_site=AMEL](http://www.codage.ext.cnamts.fr/codif/bdm_it/index.php?p_site=AMEL). Accessed 15 Jan 2016.
16. Eli Lilly and Company. Network meta analysis based on publicly available information on type 2 diabetes medications (data analysis on file). Indianapolis: Eli Lilly and Company; 2014.
17. Grant D, Foos V, Palmer J, Lloyd A, Evans M, McEwan P. Long-term validation of the IMS CORE Diabetes Model in type 1 and type 2 diabetes. Presented at 72nd Scientific Sessions of the American Diabetes Association (ADA), Philadelphia, PA, USA, 2012 June 8–12.
18. Haute Autorite de Sante. A methodological guide: choices in methods for economic evaluation. 2012. [https://www.has-sante.fr/portail/upload/docs/application/pdf/2012-10/choices\\_in\\_methods\\_for\\_economic\\_evaluation.pdf](https://www.has-sante.fr/portail/upload/docs/application/pdf/2012-10/choices_in_methods_for_economic_evaluation.pdf). Accessed 31 Jan 2017.
19. McEwan P, Foos V, Palmer JL, Lamotte M, Lloyd A, Grant D. Validation of the IMS CORE diabetes model. *Value Health*. 2014;17(6):714–24.
20. Palmer AJ, Roze S, Valentine WJ, Minshall ME, Foos V, Lurati FM, et al. The CORE diabetes model: projecting long-term clinical outcomes, costs and cost-effectiveness of interventions in diabetes mellitus (types 1 and 2) to support clinical and reimbursement decision-making. *Curr Med Res Opin*. 2004;20(Suppl 1):S5–26.
21. Palmer AJ, Roze S, Valentine WJ, Minshall ME, Foos V, Lurati FM, et al. Validation of the CORE Diabetes Model against epidemiological and clinical studies. *Curr Med Res Opin*. 2004;20(Suppl 1):S27–40.
22. Hornberger J. Computer modeling of diabetes and its complications: a report on the Fifth Mount Hood Challenge Meeting. *Value Health*. 2013;16(4):453–4.
23. World Health Organization. WHO Report on the Global Tobacco Epidemic, 2014. [http://who.int/tobacco/surveillance/policy/country\\_profile/frapdf?ua=1](http://who.int/tobacco/surveillance/policy/country_profile/frapdf?ua=1).
24. World Health Organization. Global Health Observatory Data Repository. France statistics summary (2002–present). 2014. <http://apps.who.int/gho/data/node.country.country-FRA>. Accessed 31 Jan 2017.
25. Bouee S, Cochinaire A, Godard C (2013) Real world incidence and cost of T2D complications leading to hospitalization in France. doi:10.1016/j.jval.2013.08.637.
26. NICE. Type 2 diabetes: newer agents for blood glucose control in type 2 diabetes. London: NICE; 2009.
27. Haute Autorite de Sante. Chronic disease guide to care management of type 2 diabetes. 2013. [https://www.has-sante.fr/portail/jcms/c\\_419389/fr/ald-n8-diabete-de-type-2](https://www.has-sante.fr/portail/jcms/c_419389/fr/ald-n8-diabete-de-type-2). Accessed 31 Jan 2017.
28. Buse JB, Nauck M, Forst T, Sheu WH, Shenouda SK, Heilmann CR, et al. Exenatide once weekly versus liraglutide once daily in patients with type 2 diabetes (DURATION-6): a randomised, open-label study. *Lancet*. 2013;381(9861):117–24.

29. EMA. Bydureon: summary of product characteristics. 2011. [http://www.ema.europa.eu/docs/en\\_GB/document\\_library/EPAR\\_-\\_Product\\_Information/human/002020/WC500108241.pdf](http://www.ema.europa.eu/docs/en_GB/document_library/EPAR_-_Product_Information/human/002020/WC500108241.pdf). Accessed 31 Jan 2017.
30. EMA. Trulicity: summary of product characteristics. 2014. [http://www.ema.europa.eu/docs/en\\_GB/document\\_library/EPAR\\_-\\_Product\\_Information/human/002825/WC500179470.pdf](http://www.ema.europa.eu/docs/en_GB/document_library/EPAR_-_Product_Information/human/002825/WC500179470.pdf). Accessed 31 Jan 2017.
31. World Health Organisation. WHO ATC/DDD index. Geneva: WHO; 2016. Accessed 27 Nov 2015.
32. Divino V, DeKoven M, Hallinan S, Varol N, Wirta SB, Lee WC, et al. Glucagon-like peptide-1 receptor agonist treatment patterns among type 2 diabetes patients in six European countries. *Diabetes Ther*. 2014;5(2):499–520.
33. Levin PA, Wei W, Zhou S, Xie L, Baser O. Outcomes and treatment patterns of adding a third agent to 2 OADs in patients with type 2 diabetes. *J Manag Care Spec Pharm*. 2014;20(5):501–12.
34. Holman R. UK Prospective Diabetes Study. 2016. <https://www.dtu.ox.ac.uk/UKPDS/>.
35. Beaudet A, Clegg J, Thuresson PO, Lloyd A, McEwan P. Review of utility values for economic modeling in type 2 diabetes. *Value Health*. 2014;17(4):462–70.
36. Matza LS, Boye KS, Yurgin N, Brewster-Jordan J, Mannix S, Shorr JM, et al. Utilities and disutilities for type 2 diabetes treatment-related attributes. *Qual Life Res*. 2007;16(7):1251–65.
37. Boye KS, Matza LS, Walter KN, Van BK, Palsgrove AC, Tynan A. Utilities and disutilities for attributes of injectable treatments for type 2 diabetes. *Eur J Health Econ*. 2011;12(3):219–30.
38. Owens D, Barnett A, Pickup J. Blood glucose self-monitoring in type 1 and type 2 diabetes: reaching a multidisciplinary consensus. *Diabetes Prim Care*. 2004;6(1):8–19.
39. Comité économique des produits de santé (CEPS) (2015) Prix des médicaments. Paris: Ministère des Affaires et de la Santé; 2015. (1-2-2016).
40. Agence Technique de l'Information sur l'Hospitalisation. Hospital data on ATIH website. 2014. <http://www.atih.sante.fr/>. Accessed 31 Jan 2017.
41. Ghatnekar O, Willis M, Persson U. Cost-effectiveness of treating deep diabetic foot ulcers with promogran in four European countries. *J Wound Care*. 2002;11(2):70–4.
42. Girod I, Valensi P, Laforet C, Moreau-Defarges T, Guillon P, Baron F. An economic evaluation of the cost of diabetic foot ulcers: results of a retrospective study on 239 patients. *Diabetes Metab*. 2003;29(3):269–77.
43. l'Assurance Maladie. Tarifs conventionnels des médecins généralistes en France métropolitaine. 2013. <http://www.ameli.fr/professionnels-de-sante/medecins/votre-convention/tarifs/tarifs-conventionnels-des-medecins-generalistes/tarifs-des-medecins-generalistes-en-metropole.php>. Accessed 1 June 2013.
44. l'Assurance Maladie. Table Nationale de codage de Biologie. 2013. [http://www.codage.ext.cnamts.fr/codif/nabm/index.php?p\\_site=AMELI](http://www.codage.ext.cnamts.fr/codif/nabm/index.php?p_site=AMELI). Accessed 1 June 2013.
45. l'Assurance Maladie. Liste des produits et prestations (LPP). Protheses list. 2013. <http://www.ameli.fr/professionnels-de-sante/medecins/exercer-au-quotidien/nomenclatures-et-codage/liste-des-produits-et-prestations-lpp/liste-des-produits-et-prestations-lpp/consultation-et-telechargement-de-la-lpp.php>. Accessed 1 June 2013.
46. l'Assurance Maladie. L'Echantillon généraliste de bénéficiaires. 2013. [http://www.ameli.fr/fileadmin/user\\_upload/documents/point\\_de\\_repere\\_n\\_25.pdf](http://www.ameli.fr/fileadmin/user_upload/documents/point_de_repere_n_25.pdf). Accessed 1 May 2013.
47. INSEE (Institut National de la Statistique et des Etudes Economiques). Indice des prix à la consommation (mensuel, ensemble des ménages, métropole + DOM, base 1998) (Index of consumer prices (Health products and services) (base 100 = 1998)). 2015. <https://www.insee.fr/fr/statistiques/serie/000637733>. Accessed 31 Jan 2017.
48. Roussel R, Martinez L, Vandebrouck T, Douik H, Emiel P, Guery M et al. Evaluation of the long-term cost-effectiveness of liraglutide therapy for patients with type 2 diabetes in France. *J Med Econ* 2016;19:121–34.
49. Hoaglin DC, Hawkins N, Jansen JP, Scott DA, Itzler R, Cappelleri JC, et al. Conducting indirect-treatment-comparison and network-meta-analysis studies: report of the ISPOR Task Force on Indirect Treatment Comparisons Good Research Practices: part 2. *Value Health*. 2011;14(4):429–37.
50. Jansen JP, Fleurence R, Devine B, Itzler R, Barrett A, Hawkins N, et al. Interpreting indirect treatment comparisons and network meta-analysis for health-care decision making: report of the ISPOR Task Force on Indirect Treatment Comparisons Good Research Practices: part 1. *Value Health*. 2011;14(4):417–28.

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51. Ades AE, Caldwell DM, Reken S, Welton NJ, Sutton AJ, Dias S. NICE DSU Technical Support Document 7: Evidence synthesis of treatment efficacy in decision making: a reviewers checklist. 2012. [\[scharr.dept.shef.ac.uk/nicedsu/wp-content/uploads/sites/7/2016/03/TSD7-reviewer-checklist.final\\\_.08.05.12.pdf\]\(http://scharr.dept.shef.ac.uk/nicedsu/wp-content/uploads/sites/7/2016/03/TSD7-reviewer-checklist.final\_.08.05.12.pdf\). Accessed 31 Jan 2017.](http://</a></p></div><div data-bbox=)