PDB26

Projected long-term clinical and economic outcomes of exenatide once weekly versus sitagliptin for the treatment of type 2 diabetes in the UK

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BACKGROUND

- Type 2 diabetes mellitus imposes a considerable and increasing burden on healthcare largely as a result of long-term complications associated with hyperglycaemia.[1,2]
- The risk of type 2 diabetes is increased in those with a sedentary lifestyle and overnutrition, which lead to overweight and obesity.[3]
- Therapy for type 2 diabetes mellitus therefore aims to achieve and maintain recommended targets for glycaemic control, while being either weight neutral or associated with weight loss.[3,4]
- Long-term, add-on treatment with the glucagon-like peptide-1 (GLP-1) receptor agonist exenatide twice daily (BID) was associated with sustained improvements in glycaemic control and cardiovascular risk factors, and progressive weight loss during at least 3 years of follow-up.[5] Results of comparative studies have demonstrated that exenatide once weekly (EQW) produced greater improvements in glycaemic control compared with exenatide BID, with both groups achieving similar weight loss.[6,7]
- Sitagliptin is a dipeptidyl peptidase-4 (DPP-4) inhibitor that is well-tolerated, weight-neutral and provides glycaemic control with a low incidence of hypoglycaemia when used as monotherapy or add-on therapy.[8]
- The aim of this analysis was to estimate the long-term incremental clinical and cost outcomes associated with EQW versus sitagliptin therapy in type 2 diabetes patients in the UK.

METHODS

- The published and validated IMS CORE Diabetes Model (CDM)[9,10] was used to make 50-year projections of clinical and cost outcomes based on baseline patient characteristics and results of the DURATION-2 study.
- The model simulates disease progression by combining 15 inter-dependent Markov-based sub-models to determine the occurrence and time to onset of diabetes-related complications, life years gained and quality-adjusted life years (QALYs); and also projects costs.

Base case assumptions

Simulation cohort:

- A subgroup of 326 patients with type 2 diabetes mellitus previously managed with metformin who received either EQW or sitagliptin in the 26-week DURATION-2 phase 3, multinational, randomised, double-blind clinical trial.[11,12]
- Baseline diabetes-related medical histories were based on data from the NICE CG87 cohort.[13,14]
  - For diabetes complications not reported in the CG87 cohort, a baseline prevalence rate of zero was assumed.

Perspective of the analysis:

- The analysis has been conducted from the UK national health service payer perspective.

Time horizon:

- A 50-year time horizon was used.

Primary outcome:

- The cost-effectiveness of EQW compared with sitagliptin as measured by the incremental cost per QALY gained.

Patient characteristics at baseline:

- Table 1 shows baseline characteristics of patients enrolled in DURATION-2.

Treatment pathway:

- Patients received either subcutaneous EQW 2 mg twice daily or oral sitagliptin 100 mg/day for 5 years. After 5 years, patients were switched to insulin glargine for the remainder of the 50-year period or until death, whichever came first.

Costs:

- Complication costs were derived when possible from the UKPDS study. Remaining complication and drug costs were derived from published sources and expressed in 2010 UK Pounds.
  - An annual discount rate of 3.5% was applied to both costs and outcomes, in line with NICE recommendations.

Table 1. Patient characteristics

	EQW	Sitagliptin
	N=160	N=166
Gender, n (%) male	89 (55.6)	86 (51.8)
Age, mean (SD), years	52.4 (10.4)	52.2 (10.5)
Ethnicity, n (%)		
Caucasian	53 (33.1)	50 (30.1)
Black	19 (11.9)	20 (12.0)
Hispanic	50 (31.3)	49 (29.5)
Asian	37 (23.1)	42 (25.3)
Other	1 (0.6)	5 (3.0)
Weight, mean (SD), kg	89.2 (19.6)	87.0 (20.2)
BMI, mean (SD), kg/m^2	32.1 (5.0)	31.8 (5.2)
<30kg/m^2, n (%)	62 (38.8)	75 (45.2)
≥30kg/m^2, n (%)	98 (61.3)	91 (54.8)
HbA_{1c}, mean (SD), %	8.6 (1.2)	8.5 (1.2)
Duration of diabetes, mean (SD), years	6.1 (5.2)	5.4 (4.5)

EQW, exenatide once weekly; SD, standard deviation; BMI, body mass index; HbA_{1c}, glycated haemoglobin.

METHODS CONT.

Key treatment-associated changes:

- Key projected effects of 26 weeks of EQW or sitagliptin were determined using data from DURATION-2 (Table 2) applied for the first year, then progressed according to data from the UKPDS or Framingham study.

Statistical analyses:

- Data were analysed both deterministically (base case results), for which simulated cohorts of 1,000 patients were repeated through 1,000 iterations to generate results, and using probabilistic sensitivity analyses (PSA), which were performed for a cohort of 25,000 patients and 500 iterations.
  - All results are presented as mean values with standard deviation (SD), standard error (SE) and/or 95% confidence intervals (CIs).
  - Treatment-group differences are expressed as EQW minus sitagliptin.

Sensitivity analyses

- Various deterministic sensitivity analyses were performed:
  - The projected effect of EQW on glycated haemoglobin (HbA_{1c}), body mass index (BMI), systolic blood pressure and lipids was adjusted to the upper and lower 95% confidence interval (projected effects of sitagliptin were fixed).
  - Complication costs were varied up and down by 20%.
  - Selected utility values were included or excluded.
  - The time horizon was varied to 10 and 20 years.
  - The duration of therapy was varied to 3 and 8 years.

Table 2. Key projected treatment-associated changes at 26 weeks

	EQW	Sitagliptin
	N=160	N=166
HbA_{1c}, mean (SE), %	-1.55 (0.01)	-0.92 (0.00)
Systolic blood pressure, mean (SE), mmHg	-3.60 (0.08)	0.20 (0.07)
Total cholesterol, mean (SE), mg/dl	-0.60 (0.20)	3.10 (0.19)
Low-density cholesterol, mean (SE), mg/dl	-1.00 (0.16)	1.80 (0.16)
High-density cholesterol, mean (SE), mg/dl	2.00 (0.05)	2.00 (0.05)
Triglycerides, mean (SE), mg/dl	-11.40 (6.93)	-7.70 (8.12)
BMI, mean (SE), kg/m^2	-0.84 (0.01)	-0.28 (0.01)
Major hypoglycaemia, events/100 patient years	0	0
Minor hypoglycaemia, events/100 patient years	3	12

EQW, exenatide once weekly; HbA_{1c}, glycated haemoglobin; SE, standard error; BMI, body mass index.

RESULTS

- Compared with sitagliptin, EQW treatment was projected to improve QALYs (Tables 3 and 4).
- Total direct medical costs were projected to be higher over patient lifetimes with EQW than with sitagliptin (Tables 3 and 4).
  - This was due to higher drug acquisition costs, which were partially offset by the projected lower incidence of most diabetes-related complications during treatment with EQW (Table 5, Figure 1).
- The projected incremental cost-effectiveness ratio (ICER) of EQW compared with sitagliptin was £6,418 (95% CI: 1,893 to 14,672) per QALY gained (PSA analysis).

Sensitivity analyses

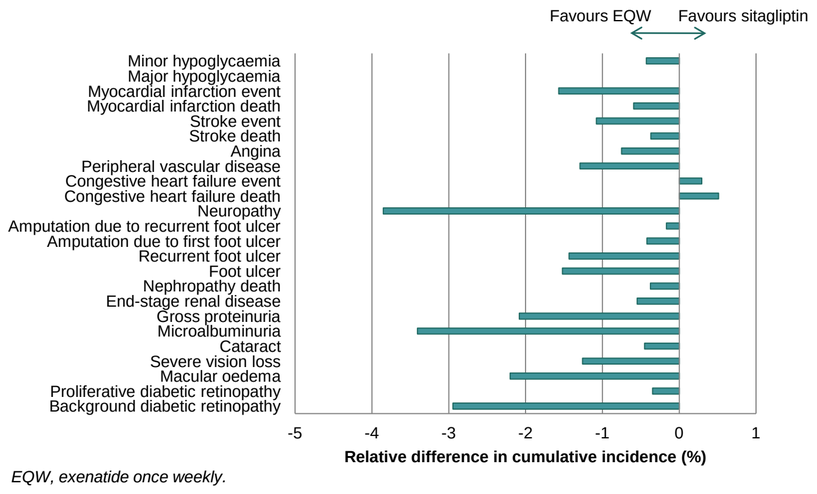
- Results of deterministic sensitivity analyses are shown in Table 4.
  - The ICER was influenced by a reduction in time horizon, decrease in EQW benefits on HbA_{1c} and increased time on EQW.

Table 3. Summary of IMS CORE model results - deterministic base case analyses

Parameter	EQW	Sitagliptin	Ratio or between-treatment-group difference
	N=160	N=166	
Direct costs, £	22,188	20,711	1,477
Life expectancy, years	13.061	12.846	0.215
QALYs, years	8.932	8.707	0.225
ICER: Cost/life-year gained, £			6,880
ICER: Cost/QALY, £			6,554

EQW, exenatide once weekly; QALY, quality-adjusted life years; ICER, incremental cost-effectiveness ratio.

Figure 1. Projected cumulative incidence of complications



EQW, exenatide once weekly.

RESULTS CONT.

Table 4. Sensitivity analyses (treatment differences)

Parameter	QALYs	Cost (£)	ICER (£/QALY)
Base case – deterministic analyses	**0.225**	**1,477**	**6,554**
Deterministic sensitivity analyses			
HbA_{1c} upper CI for EQW	0.252	1,318	5,238
HbA_{1c} lower CI for EQW	0.168	1,694	10,074
SBP upper CI for EQW	0.251	1,470	5,865
SBP lower CI for EQW	0.193	1,562	8,094
Lipids upper CI for EQW	0.255	1,388	5,440
Lipids lower CI for EQW	0.181	1,569	8,669
BMI upper CI for EQW	0.230	1,481	6,431
BMI lower CI for EQW	0.218	1,473	6,758
Complication costs increased by 20%	0.225	1,287	5,712
Complication costs decreased by 20%	0.225	1,666	7,396
No hypoglycaemia disutility	0.224	1,477	6,600
No BMI disutility	0.222	1,477	6,644
No nausea disutility	0.228	1,477	6,475
Injection site reaction disutility included	0.220	1,477	6,698
Treatment frequency and flexibility utility benefits included	0.326	1,477	4,523
Time horizon – 10 years	0.066	1,964	29,685
Time horizon – 20 years	0.161	1,471	9,138
First treatment for 3 years	0.216	615	2,841
First treatment for 8 years	0.237	2,558	10,781
PSA results (95% CI)	**0.219 (0.122 – 0.321)**	**1,405 (444 – 1,982)**	**6,418 (1,893 – 14,672)**

QALY, quality-adjusted life years; ICER, incremental cost-effectiveness ratio; HbA_{1c}, glycated haemoglobin; CI, confidence interval; EQW, exenatide once weekly; SBP, systolic blood pressure; BMI, body mass index; PSA, probabilistic sensitivity analysis.

Table 5. Projected time alive and free of complications (years)

	EQW	Sitagliptin	Difference
	N=160	N=166	
Any complications	**4.74**	**4.12**	**0.62**
Background diabetic retinopathy	13.15	12.51	0.64
Proliferative diabetic retinopathy	18.57	18.11	0.46
Microalbuminuria	13.52	12.57	0.95
Gross proteinuria	18.50	17.90	0.60
End-stage renal disease	19.20	18.75	0.45
Foot ulcer	17.69	17.15	0.54
Amputation	18.89	18.43	0.46
Neuropathy	12.33	11.37	0.96
Peripheral vascular disease	18.17	17.61	0.56
Congestive heart failure	17.37	16.94	0.43
Angina	17.73	17.23	0.50
Myocardial infarction	16.66	16.12	0.54
Stroke	16.47	15.99	0.48
Cataract	17.92	17.45	0.47
Macular oedema	17.33	16.63	0.70
Severe vision loss	18.23	17.68	0.55

EQW, exenatide once weekly.

CONCLUSIONS

- In the UK setting, EQW was associated with greater projected improvements in long-term clinical outcomes than sitagliptin.
- Based on projections from the DURATION-2 trial, EQW can be considered cost-effective versus sitagliptin in the UK setting from the NHS perspective, mainly because of the lower projected incidence of most diabetes-related complications during treatment with EQW.
- Limitations: Patients were switched to insulin glargine after five years; intermediate end points (e.g. HbA_{1c}, systolic blood pressure, lipids, BMI) were used to project long term outcomes; intervention effects were applied in the first year only.

Acknowledgements:

This work was supported by an unrestricted grant from Eli Lilly. The authors acknowledge Caroline Spencer (Rx Communications, UK) for medical writing assistance with the preparation of this poster, funded by Eli Lilly.

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