Within-Trial Evaluation of Medical Resources, Costs, and Quality of Life Among Type 2 Diabetes Patients Participating in the EXenatide Study of Cardiovascular Event Lowering (EXSCEL)

Running title: Medical Costs and Quality of Life in EXSCEL

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ABSTRACT

Objectives: To compare medical resource use, costs, and health utilities for 14,752 patients with type 2 diabetes randomized to once-weekly exenatide (EQW) or placebo in addition to usual diabetes care in the Exenatide Study of Cardiovascular Event Lowering (EXSCEL).

Research Design and Methods: Medical resource use and EuroQol 5 Dimension (EQ-5D) data were collected at baseline and throughout the trial. Medical resources and medications were valued using US Medicare payments and wholesale acquisition costs, respectively. Secondary analyses used English costs.

Results: Patients were followed for an average of 3.3 years, during which time those randomized to exenatide experienced 0.41 fewer inpatient days (7.05 vs. 7.46; relative rate ratio: 0.91; P=0.05). Rates of outpatient medical visits were similar, as were total inpatient and outpatient costs. Mean costs for non-study diabetic medications over the study period were approximately $1,600 lower with EQW versus placebo (P=0.01). Total within-study costs, exclusive of study medication, were lower in the EQW versus the placebo arm ($28,907 vs. $30,914, $P\leq$0.01). When including the estimated cost of EQW, total mean costs were significantly higher in the EQW group ($42,697 vs. $30,914, P<0.01). With English costs applied, mean total costs, inclusive of exenatide costs, were £1,670 higher in the EQW group arm (£10,874 vs. £9,204, P<0.01). There were no significant differences in EQ-5D health utilities across time between arms.

Conclusions: Medical costs were lower in the EQW arm, but total costs were significantly higher once the cost of branded EQW was incorporated.

Trial Registration: ClinicalTrials.gov identifier: NCT01144338

Diabetes mellitus imposes substantial clinical, social, and economic burdens globally. In 2017 alone, an estimated 5 million deaths were attributable to diabetes from a pool of approximately 451 million adults with the condition worldwide (1). Global health expenditures for patients with diabetes are roughly $850 billion per year (1).

People with type 2 diabetes are at increased risk of coronary heart disease and ischemic stroke, and have higher risks of death from any cause and from cardiovascular causes (2,3). Suboptimal blood glucose control leads to microvascular and macrovascular complications, representing major sources of direct and indirect medical expenditures and reduced health-related quality of life. Pharmacologic management options for type 2 diabetes have multiplied as the understanding of the underlying pathophysiology has evolved. Large-scale cardiovascular outcome trials, performed to assess safety for new diabetes drugs, offer the opportunity to investigate both the clinical and economic impact of these treatments. Data on resource use and quality of life are essential inputs to comparative effectiveness and cost-effectiveness analyses that may inform reimbursement decisions and health technology assessments. Because these assessments are crucial to governing patients' access to and cost-sharing for new drugs, private and public payers are increasingly demanding high-quality, unbiased, comparative data on drugs used in routine medical practice such as those generated from pragmatic randomized trials. Analyses of these data not only provide objective comparisons over moderately long time periods that are of interest to many private payers, they also provide greater transparency about medical resource and health utility inputs applied in model-based cost-effectiveness analyses that project outcomes over longer time periods.

The Exenatide Study of Cardiovascular Event Lowering (EXSCEL), a randomized, placebo-controlled pragmatic study, was designed to assess the long-term cardiovascular safety

and efficacy of a glucagon-like peptide-1 receptor agonist (GLP-1 RA), once-weekly exenatide (EQW), versus placebo in patients with type 2 diabetes with or without previous cardiovascular disease (4,5). One of the prespecified objectives of the trial was to compare medical resource use, direct medical costs, and health-related quality of life between the treatment arms observed during the follow-up period (4). Although EXSCEL was designed to maintain similar glycemic control in both study arms, we hypothesized that EQW would reduce medical resource use and improve health-related quality of life secondary to EQW's previously documented benefits on lipids, blood pressure, and weight, and fewer drug-related adverse events.

RESEARCH DESIGN AND METHODS

EXSCEL Trial Design and Results

The study design and results of the trial have been reported (4,5). Briefly, patients with type 2 diabetes with a glycated hemoglobin level of 6.5 to 10.0% (48–86 mmol/mol) and any level of cardiovascular risk were eligible for participation. Participants were randomly assigned to receive either 2 mg per week EQW or matching placebo in addition to usual diabetes care. The primary composite outcome was time to the first occurrence of cardiovascular death, nonfatal myocardial infarction, or nonfatal stroke.

A total of 14,752 patients from 35 countries were randomized into EXSCEL and included in the intention-to-treat (ITT) analysis, of whom 73.1% had a history of cardiovascular disease. Participants in both study groups were followed for a median of 3.2 years (mean 3.3 years). By study end, 44% of participants had discontinued study medication (EQW 43.0%, placebo 45.2%), although follow-up continued after treatment discontinuation. Only 0.5% of patients were lost to follow-up.

EXSCEL showed that EQW was noninferior to placebo for the primary composite cardiovascular outcome (hazard ratio [HR] 0.91; 95% CI 0.83-1.00; *P*-value for noninferiority <0.001). The numerical advantage for EQW over placebo, however, did not reach statistical significance (*P*-value for superiority 0.06). All-cause mortality was 6.9% in the EQW group and 7.9% in the placebo group (HR 0.86; 95% CI 0.77-0.97), but this difference was only nominally statistically significant given the prespecified hierarchical testing. The rate of severe hypoglycemia did not differ significantly between treatment groups (risk ratio 0.85, 95% CI 0.67-1.08).

Medical Resource Use and Quality-of-Life Data

A detailed costing and data analysis plan was developed and finalized in August 2016. It served to guide cost assignment and statistical analyses of medical resource use, cost, and health utility data. Detailed data on medical resource use, including hospitalizations, major cardiovascular and non-cardiovascular procedures, study visits, outpatient visits to usual diabetes care providers and other providers, concomitant cardiovascular and diabetic medications, and study medications were collected using the trial's case report form for all randomized patients at 1 week as well as at 2, 6, and 12 months and every 6 months thereafter through to the end of follow-up.

Data on admission and discharge dates and primary discharge diagnoses were collected for each hospitalization. Discharge diagnoses were recorded as one of the 52 prespecified diagnoses or free text. Daily doses and drug names were collected for concomitant diabetic medications, while concomitant cardiovascular medications were collected by drug class. Specific start or stop dates were not collected. For the cost analysis, if drug use was reported differently between two consecutive visits, the change in treatment was assumed to have

occurred halfway between visits. Total study drug doses taken by participants were collected, accounting for intermittent and premature discontinuation.

The EQ-5D (EuroQol 5 Dimension), a preference-based measure of health-related quality of life, was administered to patients at baseline, 1 week, and 2, 6, and 12 months, and then every 6 months thereafter through study end. Over the course of the trial, the 5-level version (EQ-5D-5L) was phased in to replace the 3-level version (EQ-5D-3L) as appropriate translations of the 5-level instrument became available. To manage the two versions, responses to the EQ-5D-5L were converted to EQ-5D-3L responses using a crosswalk developed by the EuroQol group (6). Responses on the 5 items of EQ-5D-3L were then converted to US (7) and UK utility weights (8). After patients died, subsequent EQ-5D utilities were set to 0.

Cost Assignment

For the main US and UK analyses, we applied a 'fully-pooled, one-country costing' approach for cost assignment (9). In the US cost analysis, sources for unit costs included 2017 Medicare payments for inpatient and outpatient care and wholesale acquisition costs (WAC) for concomitant medications, with a 23.1% discount applied to branded EQW to approximate net costs after rebates for a branded medication (10). For the English cost analysis, unit costs were sourced from the National Schedule of Reference Costs and the Prescription Cost Analysis database (11, 12). We adjusted length of stay (LOS) to allow for differences in LOS between countries for the same discharge diagnosis, using an approach previously used in other large multinational trials (13, 14). Details on cost assignment are included in the Supplementary Appendix. All costs incurred after the first year were discounted at 3% per year in the US analysis and 3.5% in the UK analysis.

Statistical Analysis

Statistical analysis was guided using the agreed costing and data analysis plan, with an initial focus on reporting descriptive statistics, including means and standard deviations, and mean cumulative counts of hospitalizations per patient that account for censoring across time (15). Mean health utility weights across time were plotted by treatment group.

Generalized linear models were applied to compare medical resource use and costs between treatment arms using SAS's PROC GLIMMIX (SAS Institute, Version 9.4); and Stata's MEGLM was used when GLIMMIX had convergence issues. All medical resource use and cost models were specified with treatment assignment as a fixed effect and log-transformed follow-up duration as an offset variable to account for varying durations of observation across patients. Countries were modeled as random intercepts to allow for different rates of medical resource use and costs in the placebo group across countries. For comparison of medical resources, models were specified with negative binomial error distributions and log links. For cost comparisons, gamma error distributions and log links were specified. Exponentiating the parameter estimates provides estimates of relative rates for resource use and means ratios for costs with exenatide relative to placebo.

Health utilities were analyzed using multilevel mixed-effects linear regression models (MEGLM or MIXED) in Stata (StataCorp LLC, version 14.2). Both countries and patients were modeled as random intercepts to account for the correlated measurements across time for each participant and potential correlation of health utilities within countries. Normal error distributions were specified. Independent variables included baseline health utilities, treatment

assignment, time since baseline, and a term representing the interaction between treatment and time.

Sensitivity Analysis

Sensitivity analyses included discounting costs of non-study concomitant diabetic and non-diabetic medications, not applying a 23.1% discount to branded EQW, and limiting analyses to US participants.

Subgroup Analysis

Subgroup analyses were limited to prespecified clinical and regional subsets examined for the primary clinical endpoint and were performed to evaluate whether certain groups of patients treated with EQW incurred different hospitalization rates and total costs.

RESULTS

Over a mean follow-up of 3.3 years across the 14,752 participants included in the ITT population, nearly 40% of participants in each treatment group were hospitalized at least once (EQW, 38.5%; placebo, 39.0%; *P*=0.50). A total of 6,127 hospitalizations occurred among the 7,356 participants randomized to EQW compared to 6,202 hospitalizations among 7,396 participants randomized to placebo. The accumulation of hospitalizations was constant across time in both treatment groups (**Figure 1**). The mean number of hospitalizations over the full follow-up period was 0.83 in the EQW arm and 0.84 in the placebo arm (**Table 1**; *P*=0.31). When accounting for the duration of hospitalizations, mean cumulative inpatient days were lower in the EQW group at 7.05 days compared with 7.46 days for the placebo group (*P*=0.05).

Mean cumulative counts of outpatient visits were similar in the two groups, at about 21 visits per participant over the follow-up period (P=0.66).

Medications were the largest contributor to total costs in both study groups in the US analysis. Mean non-study medication costs were significantly lower in the EQW arm at $17,098 compared with $18,698 in the placebo arm — a saving of $1,600 ($P$<0.01), which was driven by lower non-study diabetes medication costs. The mean cost of study medication over the duration of the trial was $13,790 per patient in the EQW arm. Inpatient costs averaged $9,654 for patients randomized to EQW and $10,078 for patients randomized to placebo (P=0.10). Mean costs for outpatient visits were similar in both groups, totaling roughly $2,100, of which approximately $550 represented study-related clinic visits. When summing costs for non-study medications, outpatient visits, and hospitalizations, mean total costs were $2,007 (8%) less in the EQW arm at $28,907 compared with $30,914 in the placebo group (P <0.01). With study medications included in the EQW arm, total costs were $42,697, 39% higher than in the placebo arm (P <0.01).

When medical resources were valued using English costs, inpatient costs were the biggest cost driver in both groups and the difference in inpatient costs remained, with means of £5,021 per patient in the EQW arm and £5,204 in the placebo arm (**Table 1**). Mean non-study medications costs were £251 lower in the EQW group (P<0.01). Mean total costs for medical resources, exclusive of exenatide, were 7% lower in the EQW group (P=0.03). However, when the cost of exenatide (£2,084 per patient) was added, total mean costs for the EQW group were 18% (£1,670 per patient) higher than the placebo group (P<0.01).

At baseline, significant proportions of patients in both study groups reported at least some level of problem across the five domains represented in the EQ-5D: mobility (44.8%), self-care

(14.1%), usual activities (31.7%), pain and discomfort (56.2%), and anxiety and depression (32.0%). Despite the prevalence of reported problems across the domains, mean EQ-5D utilities were 0.90 in both study groups at baseline and were similar in both groups across the follow-up period. Both treatment groups showed similar overall declines in utility over time with US and UK utility weights (**Figure 2A and 2B)**. Findings from the multilevel mixed-effects linear regression model confirmed these findings, revealing that mean utility scores did not significantly differ between treatment groups over time ($P>0.05$), and that there was a significant negative time effect (-0.0004 per month with US utility weights, and -0.0006 with UK utility weights, both $P<0.001$), indicating that health-related quality of life decreased across time in both groups. These findings were robust when adding covariates representing baseline history of cardiovascular events or body mass index to the demographic covariates included in the base models (see Supplementary Appendix).

Sensitivity Analysis

When costs for concomitant medications were reduced by 23.1%, to reflect discounts on list prices, the difference in concomitant medication costs decreased from $1,600 to $1,233. When the discount was not applied to branded EQ5D, study drug costs increased from $13,790 to $17,932 in the EQW group. When limiting the analysis to the 3,164 ITT participants enrolled at US sites, the findings from the EQ-5D regression analysis was similar to the full trial cohort. Approximately 47% of US patients in each treatment group were hospitalized at least once. The mean number of hospitalizations and inpatient days per US patient was not different between the two groups even though fewer patients in the EQW group died (9.4% in EQW; 11.5% in placebo). Over the trial follow-up period among US patients, inpatient care costs averaged

$12,736 for EQW compared with $12,862 for placebo; total costs were $52,441 in the EQW group, representing an $11,361 greater cost than for placebo.

Subgroup Analysis

Effects of EQW on hospitalizations and total within-trial costs by prespecified subgroup are presented in **Table 2**. Hospitalization rates were significantly lower in the EQW group than in the placebo group for patients aged 65 and older (P=0.04) and in individuals with less than 5 years' duration of diabetes at randomization (P=0.01). However, tests of statistical interaction between treatment assignment and either age (P=0.76) or duration of diabetes were not statistically significant (P=0.85). Total US costs exclusive of study medication costs were consistently lower in the EQW group. However, with the study medication costs included, total costs were consistently higher in the EQW group than in the placebo group for all subgroups. Total UK costs, inclusive of study medication costs, also were consistently higher in the EQW group than in the placebo group for all subgroups except for patients aged 75 and older (P=0.46), individuals with less than 5 years' duration of diabetes at randomization (P=0.76), and participants enrolled from Latin America (P=0.15).

CONCLUSIONS

EXSCEL provides insights into the incremental effect on medical resource use, costs, and health utilities when branded EQW is added to usual diabetes care for patients with type 2 diabetes, with or without preexisting cardiovascular disease. Based on EQ-5D health utilities, both study groups experienced similar reductions in health related quality of life across the follow-up period. We observed that participants randomized to EQW experienced approximately a half-day

reduction in inpatient days over the course of the trial. It appeared that the nominally significant reduction in mortality in the EQW group (6.9% vs. 7.9%; $p<0.05$) reported in the EXSCEL trial contributed to the reduction in inpatient days. When excluding hospitalizations in which patients died, there remained a significant difference in the mean number of inpatient days between groups (EQW: 6.77; placebo: 7.02; $p=0.05$). Nevertheless, the statistically significant reduction in inpatient days in the main analysis did not translate into significantly lower inpatient costs due to variability in total inpatient costs. Non-study diabetic medication costs also were significantly lower in the EQW group, but these cost savings were more than offset by the higher cost of branded EQW, leading to significantly higher total costs with EQW compared with placebo across the study period.

Higher total costs when adding branded exenatide to usual care was an expected finding given that clinicians were advised to individualize care using predominantly generic medications to allow participants to achieve clinically appropriate glycated hemoglobin targets (5). EXSCEL also revealed a nominally significant reduction in all-cause mortality with EQW, but this did not translate into discernable economic benefit in this within-trial evaluation. Nevertheless, the trial offers an objective reporting of comparative, directly observed medical resource use and directly reported health status, using the EQ-5D, that is free from the selection bias that can plague nonrandomized comparisons.

Our analysis has some limitations. First, by study end, although only 0.5% of trial participants were lost to follow-up, about 40% of participants in both treatment arms had discontinued study medication. Some of those participants transitioned from the study drug to open-label use of GLP-1 RAs, as well as to the use of non-injectable agents such as dipeptidyl peptidase-4 inhibitors and sodium-glucose co-transporter 2 inhibitors. Although we accounted

for these transitions among costs of non-study concomitant medications, greater transition from active study medication to open-label GLP-1 RA therapies would have narrowed the cost savings estimated for concomitant diabetes medications with EQW and may also have affected hospitalization rates. Nevertheless, the cost of additional concomitant medications in the placebo arm did not offset the cost of EQW.

From a methods perspective, we adhered to good practice recommendations, including prospective collection of resource use and health utilities and the development of a detailed costing and data analysis plan (9, 16, 17). It should be noted that if we had not adjusted for differences in length of stay across countries when assigning inpatient costs, countries with longer stays would have had more influence on cost comparisons; this may account for the lack of a significant difference in inpatient costs despite a half-day reduction in inpatient days (18). We also applied hierarchical generalized linear regression methods to control for between-country factors that affect baseline rates of resource use and costs.

This within-trial cost analysis revealed that adding EQW to usual care produced significant reductions in inpatient days as well as lower costs for concomitant diabetes medications versus usual care alone. These findings can be useful to planners projecting costs and outcomes who may also be accounting for the drug transitioning to generic status when its cost is expected to decrease precipitously.

The trial also revealed a nominally significant reduction in all-cause mortality with exenatide and non-significant reductions in other cardiovascular events and risk factors. This within-trial costing analysis does not account for these benefits or extrapolate beyond the end of the trial; an economic evaluation estimating the lifetime cost-effectiveness of EQW will be reported separately.

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Author Contributions. SDR, AMG and RRH designed the study during the trial planning period. SDR, YL, HAD, FB, JL, and AMG drafted the costing and data analysis plan. SDR interpreted the findings and wrote the initial draft of the manuscript. YL assigned costs to medical resource use, programmed the statistical analyses of the medical resource use and cost data, generated tables and figures, and edited the manuscript. HAD, FB, JL and AMG provided English cost weights and programmed the statistical analysis of the EQ-5D data, interpreted the findings, and reviewed and edited the manuscript. SMG, BK, and EW provided information about the clinical trial, interpreted the results, and reviewed and edited the manuscript. RJM, NJP, MAB, RRH, and AFH were clinical investigators in the trial; they collected data, reviewed DRG codes assigned to hospitalization, reviewed the analysis plan, assisted with interpreting results, and reviewed and edited the manuscript.

Shelby Reed and Alastair Gray are the guarantors of this work and, as such, had full access to all the data in the study and take responsibility for the integrity of the data and the accuracy of the data analysis.

Previous Presentations. These findings have been presented at the American Diabetes Association and European Association for the Study of Diabetes 2018 annual meetings.

Data sharing: All requests and enquiries concerning access to data should be directed to the study PI (RRH).

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FIGURE LEGENDS

Figure 1. Mean cumulative number of hospitalizations over time by treatment group.

Figure 2. Change from baseline in EQ-5D utility: (A) US weights and (B) UK weights.

Table 1. Total medical resource use and costs throughout trial

	EQW (N=7,356)	Placebo (N=7,396)	Difference (95%CI)*	Relative rate/Means ratio (95%CI)	*P*-value
Medical resource use					
All-cause hospitalizations	0.83 (1.68)	0.84 (1.62)	-0.01 (-0.06 to 0.05)	0.97 (0.91 to 1.03)	0.31
Inpatient days	7.05 (18.24)	7.46 (19.32)	-0.41 (-1.02 to 0.18)	0.91 (0.83 to 1.00)	0.05
Outpatient care visits	21.07 (23.26)	20.92 (23.55)	0.15 (-0.62 to 0.85)	0.99 (0.97 to 1.02)	0.66
Direct medical costs‡ (US$, 2017)					
Inpatient care	9,654 (25,051)	10,078 (26,016)	-424 (-1,290 to 384)	0.92 (0.83 to 1.02)	0.10†
Outpatient care	2,156 (1,872)	2,139 (1,910)	16 (-46 to 75)	1.01 (0.98 to 1.04)	0.68
Medications, excluding EQW	17,098 (15,992)	18,698 (16,899)	-1,600 (-2155 to 1041)	0.91(0.89 to 0.93)	<0.01
Diabetic medications	13,882 (14,592)	15,445 (15,295)	-1,564 (-2068 to -1069)	0.89 (0.87 to 0.92)	<0.01
Other medications	3,216 (3,610)	3,252 (3,876)	-36 (-157 to 82)	0.99 (0.96 to 1.02)	0.39
Total, excluding EQW	28,907 (32,600)	30,914 (34,089)	-2,007 (-3,115 to -939)	0.92 (0.89 to 0.96)	<0.01
EQW	13,790 (8,374)	-	-	-	-
Total Costs	42,697 (34,355)	30,914 (34,089)	11,782 (10,625 to 12,908)	1.39 (1.35 to 1.44)	<0.01
Direct medical costs§ (English £, 2016)					
Inpatient care	5,021 (14,028)	5,204 (13,929)	-183 (-658 to 234)	0.92 (0.83 to1.02)	0.10†
Outpatient care	1,313 (1,231)	1,293 (1,215)	20 (-19 to 56)	1.01 (0.98 to 1.03)	0.74
Medications, excluding EQW	2,457 (2,558)	2,708 (2,913)	-251 (-346 to -162)	0.91 (0.89 to 0.93)	<0.01
Diabetic medications	1,640 (1,618)	1,823 (1,687)	-184 (-240 to -132)	0.89 (0.87 to 0.92)	<0.01
Other medications	817 (1,676)	885 (2,019)	-68 (-132 to -9)	0.96 (0.92 to 0.99)	0.03
Total, excluding EQW	8,790 (15,024)	9,204 (14,970)	-414 (-906 to 95)	0.93 (0.88 to 0.99)	0.02
EQW	2,084 (1,254)	-	-	-	-

Total Costs	10,874 (15,136)	9,204 (14,970)	1,670 (1,182 to 2,184)	1.18 (1.12 to 1.24)	<0.01

Data are mean (SD) unless otherwise indicated.
EQW – once-weekly exenatide.
*95% CIs based on bias-adjusted percentile method with nonparametric bootstrapping.
†*P*-value from Stata MEGLM procedure.
‡Costs discounted at 3% per annum.
§Costs discounted at 3.5% per annum.

Table 2. Impact of EQW on all-cause hospitalizations and total costs inclusive of study medication costs by subgroup

			All-cause hospitalization			Total US costs			Total UK costs		
Subgroups	**Patient population**	**N**	**Relative rate ratio (95%CI)**	***P*-value***	***P*-value†**	**Relative rate ratio (95%CI)**	***P*-value***	***P*-value†**	**Relative rate ratio (95%CI)**	***P*-value***	***P*-value†**
Age	<65 years	8,813	1.02 (0.94 to 1.12)	0.59	0.76	1.44 (1.38 to 1.50)	<0.01	0.01	1.22 (1.14 to 1.31)	<.01	0.27
	≥65 years	5,939	0.92 (0.84 to 0.99)	*0.04*		1.33 (1.27 to 1.40)	<0.01		1.13 (1.05 to 1.22)	<.01	
	<75 years	13,502	0.97 (0.91 to 1.03)	0.32		1.41 (1.36 to 1.45)	<0.01		1.20 (1.13 to 1.26)	<.01	
	≥75 years	1,250	0.99 (0.85 to 1.16)	0.90		1.28 (1.15 to 1.42)	<0.01		1.06 (0.91 to 1.22)	0.46	
Sex	Male	9,149	0.97 (0.90 to 1.05)	0.49	0.89	1.38 (1.33 to 1.43)	<0.01	0.36	1.17 (1.09 to 1.25)	<.01	0.58
	Female	5,603	0.97 (0.87 to 1.07)	0.53		1.42 (1.35 to 1.50)	<0.01		1.21 (1.11 to 1.31)	<.01	
Body mass index	<30 kg/m^2	5,363	0.94 (0.85 to 1.04)	0.27	0.74	1.45 (1.38 to 1.53)	<0.01	0.02	1.18 (1.08 to 1.29)	<.01	0.97
	≥30 kg/m^2	9,239	0.98 (0.91 to 1.05)	0.55		1.36 (1.31 to 1.42)	<0.01		1.18 (1.10 to 1.26)	<.01	
Duration of diabetes	<5 years	2,012	0.78 (0.65 to 0.94)	*0.01*	0.85	1.45 (1.31 to 1.60)	<0.01	<0.01	1.03 (0.87 to 1.21)	0.76	0.59
	5 to <15 years	7,266	1.02 (0.93 to 1.11)	0.67		1.47 (1.41 to 1.53)	<0.01		1.24 (1.15 to 1.33)	<.01	
	≥15 years	5,421	0.97 (.88 to 1.06)	0.50		1.30 (1.24 to 1.37)	<0.01		1.15 (1.07 to 1.25)	<.01	
Congestive heart failure	Yes	2,389	1.05 (0.92 to 1.19)	0.50	0.26	1.40 (1.30 to 1.51)	<0.01	0.67	1.23 (1.09 to 1.38)	<.01	0.64
	No	12,362	0.96 (0.90 to 1.02)	0.19		1.40 (1.36 to 1.45)	<0.01		1.17 (1.11 to 1.24)	<.01	
Baseline insulin use	Yes	6,836	0.96 (0.89 to 1.05)	0.38	0.77	1.28 (1.23 to 1.33)	<0.01	<0.01	1.13 (1.05 to 1.21)	<.01	0.02
	No	7,916	0.98 (0.90 to 1.07)	0.65		1.60 (1.52 to 1.67)	<0.01		1.26 (1.17 to 1.36)	<.01	
Geographic region	Europe	6,788	0.93 (0.86 to 1.01)	0.09	0.12	1.42 (1.35 to 1.48)	<0.01	<0.01	1.20 (1.12 to 1.30)	<.01	0.16
	North America	3,708	0.99 (0.88 to 1.12)	0.86		1.25 (1.18 to 1.33)	<0.01		1.12 (1.01 to 1.23)	0.03	
	Latin America	2,727	0.93 (0.78 to 1.10)	0.39		1.46 (1.34 to 1.59)	<0.01		1.11 (0.96 to 1.28)	0.15	
	Asia Pacific	1,529	1.20 (0.99 to 1.45)	0.06		1.55 (1.43 to 1.69)	<0.01		1.36 (1.19 to 1.55)	<0.01	
History of CV event	Yes	10,782	0.95 (0.89 to 1.02)	0.13	0.15	1.36 (1.31 to 1.41)	<0.01	<0.01	1.15 (1.08 to 1.22)	<0.01	<0.01
	No	3,970	1.07 (0.93 to 1.22)	0.36		1.54 (1.45 to 1.64)	<.01		1.34 (1.21 to 1.50)	<0.01	

EQW – exenatide once-weekly; CV – cardiovascular.

*P-values for treatment assignment for each subgroup. †P-values for interactions between treatment arm and continuous measurement for age, body mass index, duration of diabetes, and between treatment arm and categorical subgroup for sex, prior history of heart failure, insulin therapy at baseline, and geographic region.

Within-Trial Evaluation of Medical Resources, Costs, and Quality of Life Among Type 2 Diabetes Patients Participating in the EXenatide Study of Cardiovascular Event Lowering (EXSCEL)

Running title: Medical Costs and Quality of Life in EXSCEL

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ABSTRACT

Objectives: To compare medical resource use, costs, and health utilities for 14,752 patients with type 2 diabetes randomized to once-weekly exenatide (EQW) or placebo in addition to usual diabetes care in the Exenatide Study of Cardiovascular Event Lowering (EXSCEL).

Research Design and Methods: Medical resource use and EuroQol 5 Dimension (EQ-5D) data were collected at baseline and throughout the trial. Medical resources and medications were valued using US Medicare payments and wholesale acquisition costs, respectively. Secondary analyses used English costs.

Results: Patients were followed for an average of 3.3 years, during which time those randomized to exenatide experienced 0.41 fewer inpatient days (7.05 vs. 7.46; relative rate ratio: 0.91; P=0.05). Rates of outpatient medical visits were similar, as were total inpatient and outpatient costs. Mean costs for non-study diabetic medications over the study period were approximately $1,600 lower with EQW versus placebo (P=0.01). Total within-study costs, exclusive of study medication, were lower in the EQW versus the placebo arm ($28,907 vs. $30,914, $P\leq$0.01). When including the estimated cost of EQW, total mean costs were significantly higher in the EQW group ($42,697 vs. $30,914, P<0.01). With English costs applied, mean total costs, inclusive of exenatide costs, were £1,670 higher in the EQW group arm (£10,874 vs. £9,204, P<0.01). There were no significant differences in EQ-5D health utilities across time between arms.

Conclusions: Medical costs were lower in the EQW arm, but total costs were significantly higher once the cost of branded EQW was incorporated.

Trial Registration: ClinicalTrials.gov identifier: NCT01144338

Diabetes mellitus imposes substantial clinical, social, and economic burdens globally. In 2017 alone, an estimated 5 million deaths were attributable to diabetes from a pool of approximately 451 million adults with the condition worldwide (1). Global health expenditures for patients with diabetes are roughly $850 billion per year (1).

People with type 2 diabetes are at increased risk of coronary heart disease and ischemic stroke, and have higher risks of death from any cause and from cardiovascular causes (2,3). Suboptimal blood glucose control leads to microvascular and macrovascular complications, representing major sources of direct and indirect medical expenditures and reduced health-related quality of life. Pharmacologic management options for type 2 diabetes have multiplied as the understanding of the underlying pathophysiology has evolved. Large-scale cardiovascular outcome trials, performed to assess safety for new diabetes drugs, offer the opportunity to investigate both the clinical and economic impact of these treatments. Data on resource use and quality of life are essential inputs to comparative effectiveness and cost-effectiveness analyses that may inform reimbursement decisions and health technology assessments. Because these assessments are crucial to governing patients' access to and cost-sharing for new drugs, private and public payers are increasingly demanding high-quality, unbiased, comparative data on drugs used in routine medical practice such as those generated from pragmatic randomized trials. Analyses of these data not only provide objective comparisons over moderately long time periods that are of interest to many private payers, they also provide greater transparency about medical resource and health utility inputs applied in model-based cost-effectiveness analyses that project outcomes over longer time periods.

The Exenatide Study of Cardiovascular Event Lowering (EXSCEL), a randomized, placebo-controlled pragmatic study, was designed to assess the long-term cardiovascular safety

and efficacy of a glucagon-like peptide-1 receptor agonist (GLP-1 RA), once-weekly exenatide (EQW), versus placebo in patients with type 2 diabetes with or without previous cardiovascular disease (4,5). One of the prespecified objectives of the trial was to compare medical resource use, direct medical costs, and health-related quality of life between the treatment arms observed during the follow-up period (4). Although EXSCEL was designed to maintain similar glycemic control in both study arms, we hypothesized that EQW would reduce medical resource use and improve health-related quality of life secondary to EQW's previously documented benefits on lipids, blood pressure, and weight, and fewer drug-related adverse events.

RESEARCH DESIGN AND METHODS

EXSCEL Trial Design and Results

The study design and results of the trial have been reported (4,5). Briefly, patients with type 2 diabetes with a glycated hemoglobin level of 6.5 to 10.0% (48–86 mmol/mol) and any level of cardiovascular risk were eligible for participation. Participants were randomly assigned to receive either 2 mg per week EQW or matching placebo in addition to usual diabetes care. The primary composite outcome was time to the first occurrence of cardiovascular death, nonfatal myocardial infarction, or nonfatal stroke.

A total of 14,752 patients from 35 countries were randomized into EXSCEL and included in the intention-to-treat (ITT) analysis, of whom 73.1% had a history of cardiovascular disease. Participants in both study groups were followed for a median of 3.2 years (mean 3.3 years). By study end, 44% of participants had discontinued study medication (EQW 43.0%, placebo 45.2%), although follow-up continued after treatment discontinuation. Only 0.5% of patients were lost to follow-up.

EXSCEL showed that EQW was noninferior to placebo for the primary composite cardiovascular outcome (hazard ratio [HR] 0.91; 95% CI 0.83-1.00; *P*-value for noninferiority <0.001). The numerical advantage for EQW over placebo, however, did not reach statistical significance (*P*-value for superiority 0.06). All-cause mortality was 6.9% in the EQW group and 7.9% in the placebo group (HR 0.86; 95% CI 0.77-0.97), but this difference was only nominally statistically significant given the prespecified hierarchical testing. The rate of severe hypoglycemia did not differ significantly between treatment groups (risk ratio 0.85, 95% CI 0.67-1.08).

Medical Resource Use and Quality-of-Life Data

A detailed costing and data analysis plan was developed and finalized in August 2016. It served to guide cost assignment and statistical analyses of medical resource use, cost, and health utility data. Detailed data on medical resource use, including hospitalizations, major cardiovascular and non-cardiovascular procedures, study visits, outpatient visits to usual diabetes care providers and other providers, concomitant cardiovascular and diabetic medications, and study medications were collected using the trial's case report form for all randomized patients at 1 week as well as at 2, 6, and 12 months and every 6 months thereafter through to the end of follow-up.

Data on admission and discharge dates and primary discharge diagnoses were collected for each hospitalization. Discharge diagnoses were recorded as one of the 52 prespecified diagnoses or free text. Daily doses and drug names were collected for concomitant diabetic medications, while concomitant cardiovascular medications were collected by drug class. Specific start or stop dates were not collected. For the cost analysis, if drug use was reported differently between two consecutive visits, the change in treatment was assumed to have

occurred halfway between visits. Total study drug doses taken by participants were collected, accounting for intermittent and premature discontinuation.

The EQ-5D (EuroQol 5 Dimension), a preference-based measure of health-related quality of life, was administered to patients at baseline, 1 week, and 2, 6, and 12 months, and then every 6 months thereafter through study end. Over the course of the trial, the 5-level version (EQ-5D-5L) was phased in to replace the 3-level version (EQ-5D-3L) as appropriate translations of the 5-level instrument became available. To manage the two versions, responses to the EQ-5D-5L were converted to EQ-5D-3L responses using a crosswalk developed by the EuroQol group (6). Responses on the 5 items of EQ-5D-3L were then converted to US (7) and UK utility weights (8). After patients died, subsequent EQ-5D utilities were set to 0.

Cost Assignment

For the main US and UK analyses, we applied a 'fully-pooled, one-country costing' approach for cost assignment (9). In the US cost analysis, sources for unit costs included 2017 Medicare payments for inpatient and outpatient care and wholesale acquisition costs (WAC) for concomitant medications, with a 23.1% discount applied to branded EQW to approximate net costs after rebates for a branded medication (~~9~~10). For the English cost analysis, unit costs were sourced from the National Schedule of Reference Costs and the Prescription Cost Analysis database (11~~0~~, 12~~1~~). We adjusted length of stay (LOS) to allow for differences in LOS between countries for the same discharge diagnosis, using an approach previously used in other large multinational trials (13~~2~~, 14~~3~~). Details on cost assignment are included in the Supplementary Appendix. All costs incurred after the first year were discounted at 3% per year in the US analysis and 3.5% in the UK analysis.

Statistical Analysis

Statistical analysis was guided using the agreed costing and data analysis plan, with an initial focus on reporting descriptive statistics, including means and standard deviations, and mean cumulative counts of hospitalizations per patient that account for censoring across time (154). Mean health utility weights across time were plotted by treatment group.

Generalized linear models were applied to compare medical resource use and costs between treatment arms using SAS's PROC GLIMMIX (SAS Institute, Version 9.4); and Stata's MEGLM was used when GLIMMIX had convergence issues. All medical resource use and cost models were specified with treatment assignment as a fixed effect and log-transformed follow-up duration as an offset variable to account for varying durations of observation across patients. Countries were modeled as random intercepts to allow for different rates of medical resource use and costs in the placebo group across countries. For comparison of medical resources, models were specified with negative binomial error distributions and log links. For cost comparisons, gamma error distributions and log links were specified. Exponentiating the parameter estimates provides estimates of relative rates for resource use and means ratios for costs with exenatide relative to placebo.

Health utilities were analyzed using multilevel mixed-effects linear regression models (MEGLM or MIXED) in Stata (StataCorp LLC, version 14.2). Both countries and patients were modeled as random intercepts to account for the correlated measurements across time for each participant and potential correlation of health utilities within countries. Normal error distributions were specified. Independent variables included baseline health utilities, treatment

assignment, time since baseline, and a term representing the interaction between treatment and time.

Sensitivity Analysis

Sensitivity analyses included discounting costs of non-study concomitant diabetic and non-diabetic medications, not applying a 23.1% discount to branded EQW, and limiting analyses to US participants.

Subgroup Analysis

Subgroup analyses were limited to prespecified clinical and regional subsets examined for the primary clinical endpoint and were performed to evaluate whether certain groups of patients treated with EQW incurred different hospitalization rates and total costs.

RESULTS

Over a mean follow-up of 3.3 years across the 14,752 participants included in the ITT population, nearly 40% of participants in each treatment group were hospitalized at least once (EQW, 38.5%; placebo, 39.0%; *P*=0.50). A total of 6,127 hospitalizations occurred among the 7,356 participants randomized to EQW compared to 6,202 hospitalizations among 7,396 participants randomized to placebo. The accumulation of hospitalizations was constant across time in both treatment groups (**Figure 1**). ~~Heart failure, myocardial infarction, and 'cancer' were the most frequently reported hospital discharge diagnoses, representing about 11% of all hospitalizations.~~ The mean number of hospitalizations over the full follow-up period was 0.83 in the EQW arm and 0.84 in the placebo arm (**Table 1**; *P*=0.31). When accounting for the duration

of hospitalizations, mean cumulative inpatient days were lower in the EQW group at 7.05 days compared with 7.46 days for the placebo group (*P*=0.05). Mean cumulative counts of outpatient visits were similar in the two groups, at about 21 visits per participant over the follow-up period (*P*=0.66).

Medications were the largest contributor to total costs in both study groups in the US analysis. Mean non-study medication costs were significantly lower in the EQW arm at $17,098 compared with $18,698 in the placebo arm — a saving of $1,600 (*P*<0.01), which was driven by lower non-study diabetes medication costs. The mean cost of study medication over the duration of the trial was $13,790 per patient in the EQW arm. Inpatient costs averaged $9,654 for patients randomized to EQW and $10,078 for patients randomized to placebo (*P*=0.10). Mean costs for outpatient visits were similar in both groups, totaling roughly $2,100, of which approximately $550 represented study-related clinic visits. When summing costs for non-study medications, outpatient visits, and hospitalizations, mean total costs were $2,007 (8%) less in the EQW arm at $28,907 compared with $30,914 in the placebo group (*P* <0.01). With study medications included in the EQW arm, total costs were $42,697, 39% higher than in the placebo arm (*P* <0.01).

When medical resources were valued using English costs, inpatient costs were the biggest cost driver in both groups and the difference in inpatient costs remained, with means of £5,021 per patient in the EQW arm and £5,204 in the placebo arm (**Table 1**). Mean non-study medications costs were £251 lower in the EQW group (*P*<0.01). Mean total costs for medical resources, exclusive of exenatide, were 7% lower in the EQW group (*P*=0.03). However, when the cost of exenatide (£2,084 per patient) was added, total mean costs for the EQW group were ~~£10,874, which~~ 18% ~~was (~~£1,670 per patient) higher than the placebo group (*P*<0.01).

At baseline, significant proportions of patients in both study groups reported at least some level of problem across the five domains represented in the EQ-5D: mobility (44.8%), self-care (14.1%), usual activities (31.7%), pain and discomfort (56.2%), and anxiety and depression (32.0%). Despite the prevalence of reported problems across the domains, mean EQ-5D utilities were 0.90 in both study groups at baseline and were similar in both groups across the follow-up period. Both treatment groups showed similar overall declines in utility over time with US and UK utility weights (**Figure 2A and 2B)**. Findings from the multilevel mixed-effects linear regression model confirmed these findings, revealing that mean utility scores did not significantly differ between treatment groups over time ($P>0.05$), and that there was a significant negative time effect (-0.0004 per month with US utility weights, and -0.0006 with UK utility weights, both $P<0.001$), indicating that health-related quality of life decreased across time in both groups. These findings were robust when adding covariates representing baseline history of cardiovascular events or body mass index to the demographic covariates included in the base models (see Supplementary Appendix).

Sensitivity Analysis

When costs for concomitant medications were reduced by 23.1%, to reflect discounts on list prices, the difference in concomitant medication costs decreased from $1,600 to $1,233. When the discount was not applied to branded EQ5D, study drug costs increased from $13,790 to $17,932 in the EQW group. When limiting the analysis to the 3,164 ITT participants enrolled at US sites, the findings from the EQ-5D regression analysis was similar to the full trial cohort. Approximately 47% of US patients in each treatment group were hospitalized at least once. The mean number of hospitalizations and inpatient days per US patient was not different between the

two groups even though fewer patients in the EQW group died (9.4% in EQW; 11.5% in placebo). Over the trial follow-up period among US patients, inpatient care costs averaged $12,736 for EQW compared with $12,862 for placebo; total costs were $52,441 in the EQW group, representing an $11,361 greater cost than for placebo.

Subgroup Analysis

Effects of EQW on hospitalizations and total within-trial costs by prespecified subgroup are presented in **Table 2**. Hospitalization rates were significantly lower in the EQW group than in the placebo group for patients aged 65 and older (P=0.04) and in individuals with less than 5 years' duration of diabetes at randomization (P=0.01). However, tests of statistical interaction between treatment assignment and either age (P=0.76) or duration of diabetes were not statistically significant (P=0.85). Total US costs exclusive of study medication costs were consistently lower in the EQW group. However, with the study medication costs included, total costs were consistently higher in the EQW group than in the placebo group for all subgroups. Total UK costs, inclusive of study medication costs, also were consistently higher in the EQW group than in the placebo group for all subgroups except for patients aged 75 and older (P=0.46), individuals with less than 5 years' duration of diabetes at randomization (P=0.76), and participants enrolled from Latin America (P=0.15).

CONCLUSIONS

EXSCEL provides insights into the incremental effect on medical resource use, costs, and health utilities when branded EQW is added to usual diabetes care for patients with type 2 diabetes, with or without preexisting cardiovascular disease. Based on EQ-5D health utilities, both study

groups experienced similar reductions in health related quality of life across the follow-up period. We observed that participants randomized to EQW experienced approximately a half-day reduction in inpatient days over the course of the trial. It appeared that the nominally significant reduction in mortality in the EQW group (6.9% vs. 7.9%; $p<0.05$) reported in the EXSCEL trial contributed to the reduction in inpatient days. When excluding hospitalizations in which patients died, there remained a significant difference in the mean number of inpatient days between groups (EQW: 6.77; placebo: 7.02; $p=0.05$). Nevertheless, the statistically significant reduction in inpatient days in the main analysis did not translate into significantly lower inpatient costs due to variability in total inpatient costs. Non-study diabetic medication costs also were significantly lower in the EQW group, but these cost savings were more than offset by the higher cost of branded EQW, leading to significantly higher total costs with EQW compared with placebo across the study period.

Higher total costs when adding branded exenatide to usual care was an expected finding given that clinicians were advised to individualize care using predominantly generic medications to allow participants to achieve clinically appropriate glycated hemoglobin targets (5). EXSCEL also revealed a nominally significant reduction in all-cause mortality with EQW, but this did not translate into discernable economic benefit in this within-trial evaluation. Nevertheless, the trial offers an objective reporting of comparative, directly observed medical resource use and directly reported health status, using the EQ-5D, that is free from the selection bias that can plague nonrandomized comparisons.

Our analysis has some limitations. First, by study end, although only 0.5% of trial participants were lost to follow-up, about 40% of participants in both treatment arms had discontinued study medication. Some of those participants transitioned from the study drug to

open-label use of GLP-1 RAs, as well as to the use of non-injectable agents such as dipeptidyl peptidase-4 inhibitors and sodium-glucose co-transporter 2 inhibitors. Although we accounted for these transitions among costs of non-study concomitant medications, greater transition from active study medication to open-label GLP-1 RA therapies would have narrowed the cost savings estimated for concomitant diabetes medications with EQW and may also have affected hospitalization rates. Nevertheless, the cost of additional concomitant medications in the placebo arm did not offset the cost of EQW.

From a methods perspective, we adhered to good practice recommendations, including prospective collection of resource use and health utilities and the development of a detailed costing and data analysis plan (9~~15~~, 16, 17). It should be noted that if we had not adjusted for differences in length of stay across countries when assigning inpatient costs, countries with longer stays would have had more influence on cost comparisons; this may account for the lack of a significant difference in inpatient costs despite a half-day reduction in inpatient days (18). We also applied hierarchical generalized linear regression methods to control for between-country factors that affect baseline rates of resource use and costs.

This within-trial cost analysis revealed that adding EQW to usual care produced significant reductions in inpatient days as well as lower costs for concomitant diabetes medications versus usual care alone. These findings can be useful to planners projecting costs and outcomes who may also be accounting for the drug transitioning to generic status when its cost is expected to decrease precipitously.

The trial also revealed a nominally significant reduction in all-cause mortality with exenatide and non-significant reductions in other cardiovascular events and risk factors. This within-trial costing analysis does not account for these benefits or extrapolate beyond the end of

the trial; an economic evaluation estimating the lifetime cost-effectiveness of EQW will be reported separately.

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Author Contributions. SDR, AMG and RRH designed the study during the trial planning period. SDR, YL, HAD, FB, JL, and AMG drafted the costing and data analysis plan. SDR interpreted the findings and wrote the initial draft of the manuscript. YL assigned costs to medical resource use, programmed the statistical analyses of the medical resource use and cost data, generated tables and figures, and edited the manuscript. HAD, FB, JL and AMG provided English cost weights and programmed the statistical analysis of the EQ-5D data, interpreted the findings, and reviewed and edited the manuscript. SMG, BK, and EW provided information about the clinical trial, interpreted the results, and reviewed and edited the manuscript. RJM, NJP, MAB, RRH, and AFH were clinical investigators in the trial; they collected data, reviewed DRG codes assigned to hospitalization, reviewed the analysis plan, assisted with interpreting results, and reviewed and edited the manuscript.

Shelby Reed and Alastair Gray are the guarantors of this work and, as such, had full access to all the data in the study and take responsibility for the integrity of the data and the accuracy of the data analysis.

Previous Presentations. These findings have been presented at the American Diabetes Association and European Association for the Study of Diabetes 2018 annual meetings.

Data sharing: All requests and enquiries concerning access to data should be directed to the study PI (RRH).

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FIGURE LEGENDS

Figure 1. Mean cumulative number of hospitalizations over time by treatment group.

Figure 2. Change from baseline in EQ-5D utility: (A) US weights and (B) UK weights.

Table 1. Total medical resource use and costs throughout trial

	EQW (N=7,356)	Placebo (N=7,396)	Difference (95%CI)*	Relative rate/Means ratio (95%CI)	*P*-value
Medical resource use					
All-cause hospitalizations	0.83 (1.68)	0.84 (1.62)	-0.01 (-0.06 to 0.05)	0.97 (0.91 to 1.03)	0.31
Inpatient days	7.05 (18.24)	7.46 (19.32)	-0.41 (-1.02 to 0.18)	0.91 (0.83 to 1.00)	0.05
Outpatient care visits	21.07 (23.26)	20.92 (23.55)	0.15 (-0.62 to 0.85)	0.99 (0.97 to 1.02)	0.66
Direct medical costs‡ (US$, 2017)					
Inpatient care	9,654 (25,051)	10,078 (26,016)	-424 (-1,290 to 384)	0.92 (0.83 to 1.02)	0.10†
Outpatient care	2,156 (1,872)	2,139 (1,910)	16 (-46 to 75)	1.01 (0.98 to 1.04)	0.68
Medications, excluding EQW	17,098 (15,992)	18,698 (16,899)	-1,600 (-2155 to 1041)	0.91(0.89 to 0.93)	<0.01
Diabetic medications	13,882 (14,592)	15,445 (15,295)	-1,564 (-2068 to -1069)	0.89 (0.87 to 0.92)	<0.01
Other medications	3,216 (3,610)	3,252 (3,876)	-36 (-157 to 82)	0.99 (0.96 to 1.02)	0.39
Total, excluding EQW	28,907 (32,600)	30,914 (34,089)	-2,007 (-3,115 to -939)	0.92 (0.89 to 0.96)	<0.01
EQW	13,790 (8,374)	-	-	-	-
Total Costs	42,697 (34,355)	30,914 (34,089)	11,782 (10,625 to 12,908)	1.39 (1.35 to 1.44)	<0.01
Direct medical costs§ (English £, 2016)					
Inpatient care	5,021 (14,028)	5,204 (13,929)	-183 (-658 to 234)	0.92 (0.83 to1.02)	0.10†
Outpatient care	1,313 (1,231)	1,293 (1,215)	20 (-19 to 56)	1.01 (0.98 to 1.03)	0.74
Medications, excluding EQW	2,457 (2,558)	2,708 (2,913)	-251 (-346 to -162)	0.91 (0.89 to 0.93)	<0.01
Diabetic medications	1,640 (1,618)	1,823 (1,687)	-184 (-240 to -132)	0.89 (0.87 to 0.92)	<0.01
Other medications	817 (1,676)	885 (2,019)	-68 (-132 to -9)	0.96 (0.92 to 0.99)	0.03
Total, excluding EQW	8,790 (15,024)	9,204 (14,970)	-414 (-906 to 95)	0.93 (0.88 to 0.99)	0.02
EQW	2,084 (1,254)	-	-	-	-

Total Costs	10,874 (15,136)	9,204 (14,970)	1,670 (1,182 to 2,184)	1.18 (1.12 to 1.24)	<0.01

Data are mean (SD) unless otherwise indicated.
EQW – once-weekly exenatide.
*95% CIs based on bias-adjusted percentile method with nonparametric bootstrapping.
†*P*-value from Stata MEGLM procedure.
‡Costs discounted at 3% per annum.
§Costs discounted at 3.5% per annum.

Table 2. Impact of EQW on all-cause hospitalizations and total costs inclusive of study medication costs by subgroup

			All-cause hospitalization			Total US costs			Total UK costs		
Subgroups	**Patient population**	**N**	**Relative rate ratio (95%CI)**	***P*-value***	***P*-value†**	**Relative rate ratio (95%CI)**	***P*-value***	***P*-value†**	**Relative rate ratio (95%CI)**	***P*-value***	***P*-value†**
Age	<65 years	8,813	1.02 (0.94 to 1.12)	0.59	0.76	1.44 (1.38 to 1.50)	<0.01	0.01	1.22 (1.14 to 1.31)	<.01	0.27
	≥65 years	5,939	0.92 (0.84 to 0.99)	*0.04*		1.33 (1.27 to 1.40)	<0.01		1.13 (1.05 to 1.22)	<.01	
	<75 years	13,502	0.97 (0.91 to 1.03)	0.32		1.41 (1.36 to 1.45)	<0.01		1.20 (1.13 to 1.26)	<.01	
	≥75 years	1,250	0.99 (0.85 to 1.16)	0.90		1.28 (1.15 to 1.42)	<0.01		1.06 (0.91 to 1.22)	0.46	
Sex	Male	9,149	0.97 (0.90 to 1.05)	0.49	0.89	1.38 (1.33 to 1.43)	<0.01	0.36	1.17 (1.09 to 1.25)	<.01	0.58
	Female	5,603	0.97 (0.87 to 1.07)	0.53		1.42 (1.35 to 1.50)	<0.01		1.21 (1.11 to 1.31)	<.01	
Body mass index	<30 kg/m^2	5,363	0.94 (0.85 to 1.04)	0.27	0.74	1.45 (1.38 to 1.53)	<0.01	0.02	1.18 (1.08 to 1.29)	<.01	0.97
	≥30 kg/m^2	9,239	0.98 (0.91 to 1.05)	0.55		1.36 (1.31 to 1.42)	<0.01		1.18 (1.10 to 1.26)	<.01	
Duration of diabetes	<5 years	2,012	0.78 (0.65 to 0.94)	*0.01*	0.85	1.45 (1.31 to 1.60)	<0.01	<0.01	1.03 (0.87 to 1.21)	0.76	0.59
	5 to <15 years	7,266	1.02 (0.93 to 1.11)	0.67		1.47 (1.41 to 1.53)	<0.01		1.24 (1.15 to 1.33)	<.01	
	≥15 years	5,421	0.97 (.88 to 1.06)	0.50		1.30 (1.24 to 1.37)	<0.01		1.15 (1.07 to 1.25)	<.01	
Congestive heart failure	Yes	2,389	1.05 (0.92 to 1.19)	0.50	0.26	1.40 (1.30 to 1.51)	<0.01	0.67	1.23 (1.09 to 1.38)	<.01	0.64
	No	12,362	0.96 (0.90 to 1.02)	0.19		1.40 (1.36 to 1.45)	<0.01		1.17 (1.11 to 1.24)	<.01	
Baseline insulin use	Yes	6,836	0.96 (0.89 to 1.05)	0.38	0.77	1.28 (1.23 to 1.33)	<0.01	<0.01	1.13 (1.05 to 1.21)	<.01	0.02
	No	7,916	0.98 (0.90 to 1.07)	0.65		1.60 (1.52 to 1.67)	<0.01		1.26 (1.17 to 1.36)	<.01	
Geographic region	Europe	6,788	0.93 (0.86 to 1.01)	0.09	0.12	1.42 (1.35 to 1.48)	<0.01	<0.01	1.20 (1.12 to 1.30)	<.01	0.16
	North America	3,708	0.99 (0.88 to 1.12)	0.86		1.25 (1.18 to 1.33)	<0.01		1.12 (1.01 to 1.23)	0.03	
	Latin America	2,727	0.93 (0.78 to 1.10)	0.39		1.46 (1.34 to 1.59)	<0.01		1.11 (0.96 to 1.28)	0.15	
	Asia Pacific	1,529	1.20 (0.99 to 1.45)	0.06		1.55 (1.43 to 1.69)	<0.01		1.36 (1.19 to 1.55)	<0.01	
History of CV event	Yes	10,782	0.95 (0.89 to 1.02)	0.13	0.15	1.36 (1.31 to 1.41)	<0.01	<0.01	1.15 (1.08 to 1.22)	<0.01	<0.01
	No	3,970	1.07 (0.93 to 1.22)	0.36		1.54 (1.45 to 1.64)	<.01		1.34 (1.21 to 1.50)	<0.01	

EQW – exenatide once-weekly; CV – cardiovascular.

*P-values for treatment assignment for each subgroup. †P-values for interactions between treatment arm and continuous measurement for age, body mass index, duration of diabetes, and between treatment arm and categorical subgroup for sex, prior history of heart failure, insulin therapy at baseline, and geographic region.

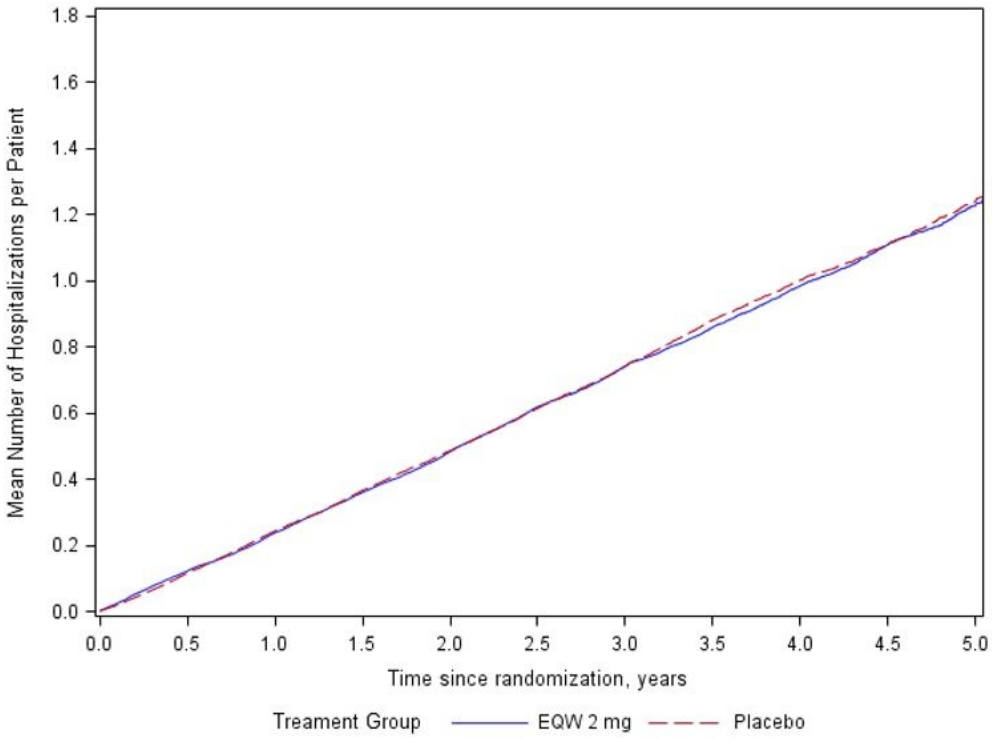
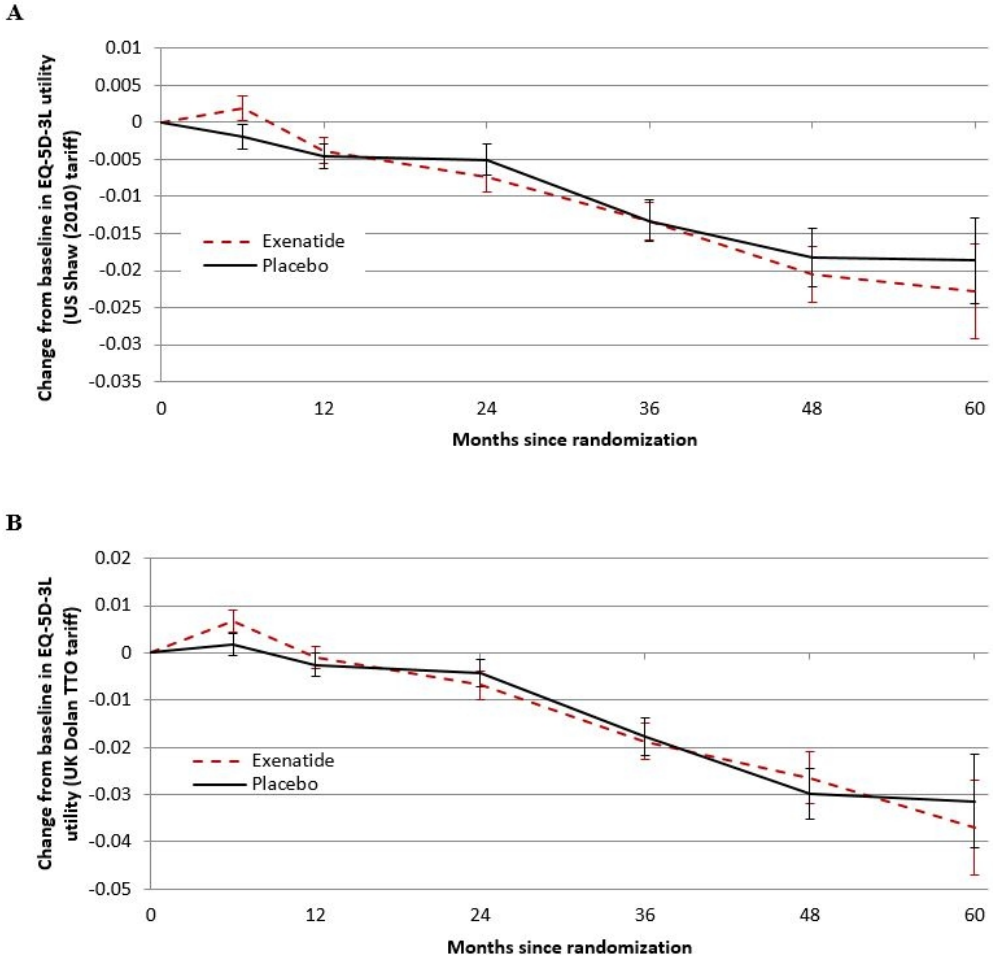


Figure 1

198x149mm (96 x 96 DPI)

Figure 2.



Error bars represent standard errors.

Figure 2

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Appendix: Cost Assignment to Medical Resources Collected in EXSCEL

US cost assignment

Hospitalization costs were assigned using Diagnosis-Related Group (DRG)-based 2017 US Medicare reimbursement rates.[1] DRG codes were assigned to both prespecified and free-text discharge diagnoses. To address variations in length of stay (LOS) between countries for the same discharge diagnosis, we applied an approach to inpatient cost assignment previously used in other large multinational trials.[2,3] Specifically, Medicare payments for each DRG code were divided by the median LOS published by the Centers for Medicare and Medicaid Services to estimate daily hospital costs.[1] To account for varying LOS between countries, daily hospital costs for hospitalizations outside the United States were first adjusted using conversion factors computed by dividing the mean LOS across all trial hospitalizations in the United States by the mean LOS across hospitalizations in each non-US country participating in EXSCEL. Then, these country-specific conversion factors were multiplied by the LOS for each hospitalization and DRG-specific daily hospital costs. Physician fees for inpatient services as well as inpatient and outpatient procedures were assigned using the 2017 Medicare Physician Fee Schedule based on Current Procedural Terminology codes.[4]

For concomitant diabetes and cardiovascular medications, daily costs were based on the 2017 wholesale acquisition costs (WAC) available via RED BOOK Online.[5] WACs represent each manufacturer's published list price to wholesalers or direct purchasers and may not represent pharmacy retail prices. Generic drugs, when available in the United States, were used as the basis for daily cost estimates. We multiplied the daily drug costs by the number of days each drug was taken. Patients receiving insulin were assumed to use Lantus insulin pens. We assumed patients taking insulin would perform one glucose test daily, a cost of $0.14 for one glucose test strip (current price on Amazon.com for Genultimate Blood Glucose Test Strips for Use with One Touch Ultra Meter). We also accounted for the cost of one glucometer at $22.75 every two years (Amazon price for One Touch Ultra2 System Kit 1), resulting in a daily cost of $0.03.

To better approximate net costs for a branded medication, a discount of 23.1%,[6] the mean rebate on the average manufacturer's price of brand name medications for Medicaid, was applied to the

2017 WAC for weekly exenatide 2 mg ($155.7), which reduced the price to $119.7 per dose. All costs incurred after the first year were discounted at 3% per year for the US analysis.

English cost assignment

To assign UK cost to hospitalizations, US medical DRGs were cross-matched into English Healthcare Resource Groups (HRGs) using the English Reference Cost HRG4+ Grouper software or the UK OPCS Classification of Interventions and Procedures version 4 (OPCS-4) or directly into HRGs, where appropriate. The cost of hospital admissions was based on the Department of Health English National Schedule of Reference Costs for 2015/2016.[7] For each HRG code, the cost per inpatient day was computed by dividing the Reference Costs at the spell level by the respective mean length of stay published by the Department of Health. In the UK setting, there were different unit costs conditional on length of stay (short stays of < 2 days or stays of ≥2 days) and on whether the admission was elective or an emergency. We averaged elective and emergency admission costs together into a single unit cost separately for short and long stays using the number of spells for both types of admission at HRG level as reported by the Department of Health. When several HRGs mapped to a single DRG, we calculated the weighted average cost per hospitalization day using the activity levels per HRG reported by the Department of Health. This resulted in a set of English unit costs for short stays and long stays that were matched to each US DRG. Then, these daily cost estimates were merged with hospitalizations in EXSCEL that had the corresponding DRG code assigned.

The same approach described above for the US costs was used to adjust length of stay for hospitalizations outside the UK to approximate the length of stay as if the patient had been treated at a UK facility. UK-specific conversion factors were computed by dividing the mean LOS across all trial hospitalizations in the UK by the mean LOS across hospitalizations in each non-UK country. Then, the DRG-specific cost per inpatient day was multiplied by the UK-adjusted LOS estimates to calculate inpatient costs for each admission. For hospitalizations not assigned a DRG, we applied the daily inpatient cost averaged across all DRG-coded hospitalizations in EXSCEL.

Outpatient visits to diabetes care providers and other care providers were costed using 2015/2016 Department of Health Reference Costs.[7] Since there was a difference in the cost of general practitioner visits versus a hospital outpatient consultation, we calculated a weighted average cost for diabetes-related consultations and non-diabetes consultations that represented the proportion of visits that were likely to be with a general practitioner and the proportion that were likely to be at the hospital. Counts for each type of consultation were based on national data reported by the Department of Health.[8] We estimated that around 28% of all consultations were outpatient visits, based on an average 3.8 general practitioner visits per year (adults, England), an English population of 54 million,[9] and around 82 million outpatient visits.[10]

Drug costs were based on the list prices available in the Prescription Cost Analysis database.[11] Exenatide and non-insulin diabetes medications were costed based on the specific doses and drugs used. For insulin, the case report form recorded the number of units used per day, but not the specific formulation. We therefore used prescribing data from the Prescription Cost Analysis database to calculate a weighted average cost per unit of insulin (weighted by the total quantity prescribed) and applied this to each unit of insulin used by EXSCEL participants. Patients receiving insulin were assumed to be prescribed typical quantities of pens, syringes, needles, and glucose test strips based on a National Institute for Health and Care Excellence (NICE) guideline.[12] Consumables were costed based on the information included in the NICE guideline and unit costs inflated to 2015/2016 prices using the hospital and community health services (HCHS) index provided by the Personal Social Services Research Unit.[13]

For cardiovascular medications, the case report form recorded only the class of medication. These were costed using the totals for British National Formulary subparagraphs within the Prescription Cost Analysis, which provides the weighted average cost per prescription. We calculated a daily cost assuming that each prescription lasts 28 days, in line with UK practice. The weekly cost of exenatide was £18.3 with no discount applied.

All costs were discounted at 3.5% per year beyond the first year of follow-up according to NICE recommended guidelines.[14]

Appendix Table S1. Comparisons of Health Utilities

	Model 1 (base-case)		Model 2		Model 3		Model 4	
	US	*UK*	*US*	*UK*	*US*	*UK*	*US*	*UK*
N (observations)	52,845		52,835		52,835		51,789	
Fixed effects, mean (robust standard error)								
Baseline EQ-5D	0.5978 (0.0354)*	0.6133 (0.0288)*	0.5884 (0.0370)*	0.6008 (0.0310)*	0.5836 (0.0369)*	0.5955 (0.0307)*	0.5679 (0.0391)*	0.5798 (0.0309)*
Treatment group (0=placebo, 1=Exenatide)	0.0023 (0.0028)	0.0039 (0.0046)	0.0023 (0.0029)	0.0038 (0.0046)	0.0024 (0.0029)	0.0040 (0.0047)	0.0022 (0.0026)	0.0034 (0.0042)
Time since baseline, months	-0.0004 (0.0001)*	-0.0006 (0.0001)*	-0.0004 (0.0001)*	-0.0006 (0.0001)*	-0.0004 (0.0001)*	-0.0006 (0.0001)*	-0.0004 (0.0001)*	-0.0006 (0.0001)*
Treatment group × time since baseline	0.0000 (0.0001)	-0.0001 (0.0002)	0.0000 (0.0001)	-0.0001 (0.0002)	0.0000 (0.0001)	-0.0001 (0.0002)	0.0000 (0.0001)	-0.0001 (0.0001)
Random effects, mean (95% CI)								
Country	0.0003 (0.0002; 0.0005)	0.0008 (0.0005; 0.0012)	0.0002 (0.0001; 0.0005)	0.0006 (0.0003; 0.0011)	0.0002 (0.0001; 0.0005)	0.0006 (0.0004; 0.0012)	0.0002 (0.0001; 0.0004)	0.0006 (0.0003; 0.0011)
Patient	0.0072 (0.0062; 0.0083)	0.0145 (0.0134; 0.0158)	0.0070 (0.0061; 0.0081)	0.0142 (0.0131; 0.0154)	0.0070 (0.0060; 0.0081)	0.0141 (0.0130; 0.0153)	0.0067 (0.0058; 0.0077)	0.0136 (0.0126; 0.0147)

Results from multilevel mixed-effects linear regression with robust standard errors and random effects on country and patient level. Model 1 includes covariates in table: baseline EQ-5D, treatment group, time since baseline, interaction between time and treatment group; Model 2 includes Model 1 covariates plus age at baseline, sex, ethnicity; Model 3 includes Model 2 covariates in table plus baseline history of CV event; Model 4 includes Model 3 covariates in table plus body mass index; US = EQ-5D value set for the US; UK = EQ-5D value set for the UK. Results reported as coefficients (robust standard errors); *P ≤0.01.

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