

# Exenatide extended-release; clinical trials, patient preference, and economic considerations

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**Abstract:** Type 2 diabetes remains an escalating problem worldwide, despite a range of treatments being available. The revelation that insulin secretion is under the control of a gut hormone, glucagon-like peptide 1, has led to a new paradigm in the management of type 2 diabetes, ie, use of medicines that directly stimulate or prolong the actions of endogenous glucagon-like peptide 1 at its receptors. Exenatide is an agonist at the glucagon-like peptide 1 receptor, and was initially developed as a subcutaneous medication twice daily (ExBID). Clinical trials with ExBID established a role for exenatide in the treatment of type 2 diabetes. Subsequently, exenatide once weekly (ExQW) was shown to have advantages over ExBID, and there is now more emphasis on the development of ExQW. ExQW alone reduces glycosylated hemoglobin (HbA<sub>1c</sub>) and body weight, and is well tolerated. ExQW has been compared with sitagliptin, pioglitazone, and metformin, and been shown to have a greater ability to reduce HbA<sub>1c</sub> than these other medicines. The only preparation of insulin with which ExQW has been compared is insulin glargine, and ExQW had some favorable properties in this comparison, notably causing weight loss compared with the weight gain on insulin glargine. ExQW has been compared with another glucagon-like peptide 1 receptor agonist, liraglutide, and was noninferior to liraglutide in reducing HbA<sub>1c</sub>. The small amount of evidence available shows that subjects with type 2 diabetes prefer ExQW to ExBID, and that adherence is high in the clinical trial setting. Health care and economic modeling suggests that ExQW will reduce diabetic complications and be cost-effective, compared with other medications, in long-term use. Little is known about whether subjects with type 2 diabetes prefer ExQW to other medicines, and whether adherence is good with ExQW in practice. These important topics require further study.

**Keywords:** exenatide, twice daily, once weekly, insulin, metformin, sitagliptin, type 2 diabetes

## Introduction

The prevalence of diabetes in the US is about 8% (24 million people), and 90% is type 2 diabetes, which has both lifestyle and genetic components.<sup>1</sup> Despite the treatments available for type 2 diabetes, about two thirds of subjects die from heart disease or stroke. Diabetes is also a leading cause of blindness, end-stage kidney failure, and lower limb amputations.<sup>1</sup> Clearly, there is a need for good treatments for type 2 diabetes.

Medications are used in subjects with type 2 diabetes, when lifestyle changes have failed to manage their condition. Metformin is the medication of first choice in subjects with the disease. When lifestyle changes and the highest tolerated dose of metformin fail to provide control, a sulfonylurea is often added. The glitazones are an option as dual or additional therapy with metformin and/or a sulfonylurea. Finally, when oral

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medications do not control the disease, injectable insulin is added. Despite these medicines, type 2 diabetes is often progressive, with subjects unable to maintain long-term glycemic control.<sup>2</sup> Also, some of these diabetic medicines (notably insulin and the sulfonylureas) increase body weight, which contributes further to diabetes.

Some recent physiological discoveries have opened up a new paradigm in the treatment of diabetes. In type 2 diabetes, hyperglycemia is due to a relative lack of insulin production and reduction in insulin sensitivity.<sup>1</sup> Classically, glucose levels in the pancreatic cells, which relate to blood glucose levels, were considered to be the main controller of insulin levels. Recently, it has been discovered that gut peptides influence insulin secretion, and these peptides and their receptors are the target for a range of new drugs being introduced into the treatment of type 2 diabetes.

Glucagon-like peptide 1 (GLP-1) and gastric inhibitory peptide are released in response to a meal, and have already been reviewed in detail.<sup>3</sup> Both of these gut hormones augment glucose-mediated insulin secretion, but only GLP-1 suppresses glucagon secretion, inhibits gastric emptying, and reduces appetite.<sup>3</sup> Both GLP-1 and gastric inhibitory peptide are rapidly broken down by dipeptidyl peptidase-4, and thus have only short half-lives and biological effects.<sup>3</sup> Production of both GLP-1 and gastric inhibitory peptide are severely reduced in subjects with type 2 diabetes.<sup>3</sup> Levels of GLP-1 and gastric inhibitory peptide can be increased by inhibiting dipeptidyl peptidase-4, and this in turn will increase glucose-mediated insulin secretion.<sup>3</sup> The major difference between the sulfonylureas and drugs that increase the stimulation of the GLP-1 receptors is that the sulfonylureas increase insulin release independently of glucose, whereas stimulation of the GLP-1 receptor only augments glucose-mediated insulin secretion.

Exendin-4 is a 39-amino acid peptide, which acts as an agonist at GLP-1 receptors and is resistant to breakdown, as described previously.<sup>4</sup> Synthetic exendin-4 (exenatide) is used to stimulate the GLP-1 receptor in type 2 diabetes.<sup>4</sup> Exenatide augments glucose-mediated insulin secretion and inhibits glucagon secretion, and this decreases glycosylated hemoglobin (HbA<sub>1c</sub>) and fasting plasma glucose levels.<sup>4</sup> Exenatide also inhibits gastric emptying, and reduces appetite and food intake.<sup>4</sup> Exenatide was initially used twice a day subcutaneously (ExBID) immediately before breakfast and dinner, but has recently been developed for once a week use (ExQW), and the subcutaneous injection does not need to be before a meal. Recently, several clinical trials and health care and economic modeling studies involving ExQW have

been published, but there have been no reviews as yet that specifically relate to ExQW.

Initially, in this review, there is a brief outline of the clinical trials with ExBID, which established a role for exenatide in the treatment of type 2 diabetes. Subsequently, ExQW was shown to have advantages over ExBID, and there is now more emphasis on the development of ExQW. The comparison of ExQW with other antidiabetic drugs is discussed further on, and ExQW is shown to have some favorable properties compared with the other antidiabetic drugs. In describing clinical trials, only statistically significant differences are considered important, and when there is no significant difference, values are considered to be similar. ExQW is delivered subcutaneously, which contributes to patient preference, and this important issue is also discussed. To date, there are no clinical trials reporting clinical outcomes for ExQW, but the health care and economic considerations have been modeled, and this modeling is discussed. Finally, there is a commentary on the present findings, and the need for future research with ExQW.

## Exenatide twice daily

ExBID has been shown to reduce HbA<sub>1c</sub> and cause weight loss when used alone versus placebo, including in subjects with type 2 diabetes being treated with metformin, a sulfonylurea, or the combination of metformin and a sulfonylurea.<sup>4</sup> ExBID has also been shown to decrease HbA<sub>1c</sub> and body weight in subjects with type 2 diabetes being treated with a thiazolidinedione (pioglitazone or rosiglitazone) in the presence or absence of metformin.<sup>5</sup> Recently, this has been extended to include in the presence of insulin. Thus, ExBID has been shown to reduce HbA<sub>1c</sub> and body weight in subjects with poorly controlled type 2 diabetes, despite taking insulin glargine alone or in combination with metformin or pioglitazone (or both agents).<sup>6</sup>

Importantly, ExBID has been compared with the standard treatments for type 2 diabetes and shown to have some favorable effects. Two studies of subjects with inadequately controlled type 2 diabetes, despite using metformin and/or sulfonylurea therapy, randomized their subjects to either ExBID or insulin glargine, and showed that the reduction in HbA<sub>1c</sub> was the same in both groups, but ExBID caused a reduction in body weight, whereas subjects taking insulin had an increase in body weight. However, ExBID caused more adverse gastrointestinal effects than insulin glargine in both studies.<sup>7,8</sup> In another study, ExBID was compared with premixed insulin aspart in subjects with type 2 diabetes being treated with metformin, and shown to be noninferior

to insulin in reducing HbA<sub>1c</sub>. Again, ExBID was shown to reduce body weight, whereas there was an increase with insulin aspart.<sup>9</sup>

When ExBID was compared with a sulfonylurea, glibenclamide, in subjects with uncontrolled type 2 diabetes despite receiving treatment with metformin, ExBID and glibenclamide decreased HbA<sub>1c</sub> to a similar extent. With ExBID the subjects lost weight, whereas with glibenclamide they gained weight. Fasting insulin levels and insulin resistance were reduced by ExBID, but not by glibenclamide.<sup>10</sup> A comparison of ExBID and another sulfonylurea (glimepiride) also showed that both agents caused a similar decrease in HbA<sub>1c</sub>, but ExBID was associated with body weight loss and reduced insulin resistance, whereas glimepiride did not have these effects.<sup>11</sup>

An important finding regarding ExBID has come from a retrospective database analysis showing that it reduces the risk of cardiovascular events and hospitalizations. The data used were from the LifeLink database of medical and insurance claims. Subjects with type 2 diabetes but no history of cardiovascular events were assigned to an ExBID or non-exenatide cohort on their first new prescription filled. The cohorts were not matched at the start, because the 39,275 patients treated with ExBID were more likely to have ischemic heart disease, obesity, hyperlipidemia, hypertension, and/or other comorbidities at baseline than the 381,218 patients in the non-exenatide cohort. Nevertheless, going forward, the ExBID cohort had a smaller risk of cardiovascular disease events or hospitalizations than the non-exenatide group.<sup>12</sup>

ExBID has been associated with an increased incidence of acute pancreatitis during post-marketing surveillance. However, a retrospective cohort study of 786,656 subjects has shown an increased incidence of pancreatitis in diabetic versus nondiabetic subjects. The same study showed no association between ExBID and acute pancreatitis.<sup>13</sup> Two other recent studies have confirmed that there is no relationship between ExBID and acute pancreatitis.<sup>14,15</sup>

## Efficacy, safety, and tolerability of ExQW versus ExBID ExQW alone

The long-acting formulation of exenatide contains ExBID encapsulated in 0.06 mm diameter microspheres of medical grade poly-(D,L-lactide-co-glycolide). After mechanical suspension and subcutaneous injection, the microspheres hydrate in situ and adhere to one another to form an amalgam. Only the loosely bound surface exenatide (1%) releases in

the first few hours, whereas exenatide lodged in the deeper interstices diffuses out slowly, with a time to maximum concentration of about 2 weeks. Finally, fully encapsulated exenatide, which is inaccessible to diffusion, releases over a longer period, with a time to maximum of about 7 weeks, as already reviewed.<sup>16</sup>

In 62 subjects with type 2 diabetes, a single subcutaneous dose of ExQW at 2.5, 5, 7 or 10 mg gave three peak plasma concentrations after about 3.5 hours, and 2 and 6 weeks, which represents the three phases of drug release from the microspheres. In 45 subjects with type 2 diabetes on weekly injections of ExQW at 0.8 and 2 mg, it was 2 weeks before ExQW 2 mg reached the minimum effective concentration, which remained in the target therapeutic range until the injections were stopped. At the lower dose of ExQW, it took longer to reach the minimum effective concentration. Both doses of ExQW decreased HbA<sub>1c</sub> and fasting plasma glucose, but only the higher dose of the ExQW (2 mg) reduced body weight. Nausea, which was mild, was observed in about one quarter of the subjects taking ExQW compared with 12% in those on placebo. Although hypoglycemia was observed in 25% of subjects with type 2 diabetes on ExQW, none of it was severe.<sup>17</sup>

ExQW 2 mg was tested in 43 subjects with type 2 diabetes and shown to be beneficial in comparison with placebo. The enrolled subjects had a mean HbA<sub>1c</sub> of 8.5% and a fasting blood glucose of 9.9 mmol/L, and most (n = 27) were receiving metformin. The subjects were randomized to placebo or ExQW at 0.8 or 2 mg weekly, and those on the 2 mg dose reached a therapeutic concentration (50 pg/mL) within 2 weeks and retained it for 15 weeks, whereas those on the 0.8 mg only reached a borderline therapeutic concentration. When the ExQW was stopped after week 15, it was 3 weeks before the plasma concentrations became too low to be therapeutic. After 15 weeks, HbA<sub>1c</sub> was reduced by 1.8% and 2.1% on ExQW 0.8 and 2 mg, respectively, and fasting plasma glucose was reduced by about 2.4 mmol/L on each dose strength. The lower dose of exenatide had no effect on body weight whereas exenatide 2 mg caused a weight loss of 3.8 kg. The most common adverse effect was nausea, followed by gastroenteritis and bruising at the injection site. There was no major hypoglycemia with ExQW over 15 weeks.<sup>18</sup>

In 29 Japanese subjects with type 2 diabetes suboptimally controlled on metformin, a sulfonylurea, a thiazolidinedione, or a combination of these, exenatide 0.8 mg and 2 mg once weekly gave steady-state concentrations by week 8. At 10 weeks, exenatide 0.8 and 2 mg once weekly had reduced

HbA<sub>1c</sub> by 0.6% and 1.1%, respectively. Only 2 mg of exenatide had a definite ability to reduce fasting and postprandial glucose. The most common side effect was mild to moderate hardening/thickening of the skin at the injection site followed by mild nausea, and no serious hypoglycemia was observed. Treatment-emergent antibodies to exenatide were present in about two thirds of treated subjects, but did not affect changes in HbA<sub>1c</sub>.<sup>19</sup>

### ExQW compared with ExBID

ExBID and ExQW have been compared in the DURATION-1 (Diabetes Therapy Utilization: Changes in A<sub>1c</sub>, Weight, and Other Factors Through Intervention with Exenatide Once Weekly) study, and the once-weekly formulation was shown to be at least as good as the twice-daily formulation. DURATION-1 was an open-label, noninferiority comparison between ExBID and ExQW. The DURATION-1 study enrolled 295 subjects with type 2 diabetes, a mean age of 55 years, a baseline HbA<sub>1c</sub> of 8.3%, and fasting plasma glucose of about 8.4 mmol/L, who were being managed by diet and exercise (approximately 15%), metformin alone (about 36%), or in combination with other drugs (about 38%), or other antidiabetic drugs. Subjects were randomized, and then underwent a 3-day lead-in period of exenatide 5 µg twice daily, before receiving exenatide 2 mg once a week or exenatide 5 µg twice daily for 28 days followed by 10 µg twice daily for 30 weeks. It only took 2 weeks to obtain the therapeutic range of exenatide with the once-weekly preparation. The two preparations had similar effects on HbA<sub>1c</sub> over 9 weeks, beyond which ExQW caused a greater reduction in HbA<sub>1c</sub> (1.9% at 30 weeks versus 1.5% with ExBID). ExQW also caused a greater reduction in fasting plasma glucose (2.3 mmol/L) than ExBID (1.4 mmol/L), whereas ExBID caused a greater reduction in postprandial glucose (6.9 mmol/L) than ExQW (5.3 mol/L). Both preparations of exenatide caused a similar decrease in low-density lipoprotein cholesterol, triglycerides, systolic and diastolic blood pressure, and body weight (about 3.65 kg). Nausea was more common with ExBID than with ExQW (35% versus 26%), as was vomiting (19% versus 11%), upper respiratory tract infection (17% versus 8%), and bruising at the injection site (10% versus 5%). The incidence of diarrhea, constipation, and urinary tract infection was similar with both preparations, but pruritus at the injection site was more common with ExQW (18%) than with ExBID (1%).<sup>20</sup>

DURATION-1 has been followed up at 52 weeks, with subjects taking ExQW continuing on this therapy, and the subjects with type 2 diabetes taking ExBID being switched

to ExQW 2 mg. In the subjects continuing with ExQW, the reduction in HbA<sub>1c</sub> was maintained at 52 weeks, whereas those who switched to ExQW had an improvement in HbA<sub>1c</sub>. Subjects on ExBID who were switched to ExQW had a transient increase in fasting blood glucose, followed by a decrease after 2 weeks, and this increase was probably due to short-term subtherapeutic levels of exenatide. By 52 weeks, the reduction in diastolic and systolic blood pressure on both exenatide protocols had reached clinical significance, with decreases of 6.2/2.8 mmHg in those continuing on ExQW. The switch to ExQW was associated with an increase in pruritus at the injection site. There were no episodes of major hypoglycemia, and only minor hypoglycemia occurred in subjects taking sulfonylureas.<sup>21</sup>

A further follow-up of DURATION-1 out to 2 years showed that ExQW continued to be well tolerated. Follow-up also demonstrated sustained glucose control, weight loss, and blood pressure reductions. There were also small decreases in cholesterol, low-density lipoprotein cholesterol, and triglycerides.<sup>22</sup>

DURATION-5 was similar in design to DURATION-1, and had similar findings. DURATION-5 enrolled 252 subjects with type 2 diabetes and an HbA<sub>1c</sub> of 8.4%, and the reduction in HbA<sub>1c</sub> after 24 weeks was greater with ExQW (1.6%) than with ExBID (0.9%). Weight loss was similar in both groups. Heart rate increased by 4.1 and 2.1 beats per minute with ExQW and ExBID, respectively. Nausea was less common with ExQW than with ExBID (14% versus 35%), as was vomiting (5% versus 9%), but erythema at the injection site was more common with ExQW than with ExBID (5.4% versus 2.4%).<sup>23</sup>

The results from DURATION-1 and DURATION-5 have been combined for analysis of safety and tolerability. Nausea was less common with ExQW (20.9%) than with ExBID (35.7%), as was vomiting (7.9% versus 14.2%, respectively), and both of these adverse effects decreased in incidence with time. Erythema and pruritus at the injection site were more common with ExQW than ExBID (erythema, 6.5% versus 1.1%; pruritus, 11.9% versus 1.1%), and these adverse effects also decreased over time. No subjects had major hypoglycemia, but subjects in both groups using sulfonylureas did have some minor hypoglycemia.<sup>24</sup>

Subpopulation analysis of the data with ExQW has been undertaken by Amylin Pharmaceuticals (San Diego, CA), the company developing ExQW. This analysis included data from DURATION 1–6, and another trial that has not been published as yet in a peer-reviewed journal. ExQW reduced HbA<sub>1c</sub> levels, fasting glucose, and body weight in

all subpopulations (< or  $\geq$ 65 years, gender, race, duration of diabetes, and body mass index). Low-density lipoprotein, cholesterol, and blood pressure was reduced in all subpopulations except Blacks. Hypoglycemia was uncommon (2.3%) except in subjects who were also taking sulfonylureas.<sup>25</sup>

## Comparative clinical trials of ExQW and other antidiabetic drugs

### Comparison with sitagliptin, pioglitazone, and metformin

ExQW has been compared with sitagliptin, pioglitazone, and metformin and shown to have a favorable profile compared with each of these agents. In DURATION-2, ExQW was compared with sitagliptin or pioglitazone in subjects with type 2 diabetes taking metformin in a double-blind, double-dummy clinical trial. The 491 enrolled subjects had a mean age of 52 years and an HbA<sub>1c</sub> of about 8.5%, and were randomized to ExQW 2 mg, sitagliptin 100 mg, or pioglitazone 45 mg for 26 weeks. The HbA<sub>1c</sub> levels were lowered to 7.2% with ExQW, which was significantly greater than the 7.7% with sitagliptin or 7.4% with pioglitazone. Fasting blood glucose was lowered by 1.8 mmol/L with ExQW, which was similar to that with pioglitazone (1.5 mmol/L) but greater than with sitagliptin (0.9 mmol/L). Subjects taking ExQW lost 2.3 kg, which was greater than the loss with sitagliptin (0.8 kg), whereas subjects taking pioglitazone gained 2.8 kg. ExQW caused a reduction in systolic blood pressure (4 mmHg), whereas sitagliptin and pioglitazone had little effect on blood pressure after 16 weeks.<sup>26</sup>

There was no major hypoglycemia with ExQW, sitagliptin, or pioglitazone in DURATION-2. Minor hypoglycemia occurred in 1% of subjects with type 2 diabetes taking ExQW, 3% of those on sitagliptin, and 1% of those on pioglitazone. The most common adverse effects were nausea and diarrhea with ExQW and sitagliptin. With pioglitazone, the most common adverse effects were upper respiratory tract infection and peripheral oedema.<sup>26</sup>

Subsequently, all subjects with type 2 diabetes in DURATION-2 received ExQW. After 26 weeks, the subjects who changed from sitagliptin to ExQW had reduced HbA<sub>1c</sub>, fasting plasma glucose, and weight, whereas subjects who were changed from pioglitazone to ExQW has no change in HbA<sub>1c</sub> or fasting blood glucose, but did lose weight.<sup>27</sup>

The DURATION-4 trial compared ExQW with metformin 2 g/day, sitagliptin 100 mg/day, or pioglitazone 45 mg/day in 822 subjects with type 2 diabetes who were diabetes drug-naïve. After 26 weeks, HbA<sub>1c</sub> was decreased by

1.5% by ExQW, 1.5% by metformin, 1.6% by pioglitazone, and 1.2% by sitagliptin. Body weight decreased with ExQW, metformin, and sitagliptin, but increased with pioglitazone. Nausea and injection site reactions were only observed with ExQW. There were no incidents of major hypoglycemia.<sup>28</sup>

## Comparison with insulin

The only preparation of insulin which ExQW has been compared with in a peer-reviewed journal is insulin glargine, and ExQW showed some favorable properties in this comparison. In DURATION-3, ExQW was compared with insulin glargine in subjects with type 2 diabetes. In this open-label, randomized, parallel-group Phase III study, 456 subjects with suboptimal glycemic control despite maximum tolerated doses of metformin or a combination of metformin and sulfonylureas were randomized to ExQW or insulin glargine. Subjects started insulin glargine 10 IU/day, measured their fasting blood glucose concentrations every morning, and adjusted insulin doses to achieve a plasma glucose of 4.0–5.5 mmol/L. After 26 weeks, the reduction in HbA<sub>1c</sub> from a baseline of 8.3% was 1.5% with ExQW, which was significantly greater than the 1.3% with insulin glargine. There was a larger reduction in fasting blood glucose with insulin glargine (2.8 mmol/L) than with ExQW (2.1 mmol/L), but a bigger reduction in postprandial glucose with ExQW than insulin glargine. Body weight decreased by 2.6 kg with ExQW, but increased by 1.4 kg with insulin glargine. ExQW reduced blood pressure by 4.2/1.5 mmHg and increased heart rate by 1.97 beats per minute, whereas insulin glargine only reduced systolic blood pressure and had no effect on heart rate.<sup>29</sup>

In DURATION-3, minor hypoglycemia was observed in fewer subjects receiving ExQW (8%) than those on insulin glargine (26%), as was the occurrence of symptoms of hypoglycemia (13% versus 31%). Gastrointestinal side effects were more common with ExQW than insulin glargine, whereas nasopharyngitis and headache were more common with insulin than exenatide. One subject taking ExQW had edematous pancreatitis but made a full recovery.<sup>29</sup>

ExQW has also been compared with insulin glargine in 427 Japanese subjects with type 2 diabetes and already taking oral drugs for treatment of diabetes. After 26 weeks, HbA<sub>1c</sub> was reduced by 1.1% and 0.7% in the ExQW and insulin groups, respectively. Body weight was decreased by ExQW but increased slightly with insulin glargine. ExQW decreased low-density lipoprotein cholesterol, whereas insulin did not. ExQW had a lower risk of hypoglycemia

than insulin glargine, but a higher risk of adverse effects at the injection site.<sup>30</sup>

## Comparison with liraglutide

ExQW was compared with liraglutide in DURATION-6. Liraglutide is also an agonist at the GLP-1 receptor, and is used subcutaneously at 1.8 mg once a day in the treatment of type 2 diabetes. DURATION-6 enrolled 911 subjects with type 2 diabetes, which was poorly controlled despite the use of metformin, a sulfonylurea, or metformin and a sulfonylurea or pioglitazone. In the first four weeks of the trial, 15 subjects in the liraglutide group withdrew because of adverse gastrointestinal effects, whereas none in the ExQW withdrew for this reason. At baseline, HbA<sub>1c</sub> was about 8.4%, and after 26 weeks was reduced by 1.3% on ExQW and 1.5% on liraglutide. Although the effect on HbA<sub>1c</sub> was greater with liraglutide than with ExQW, statistical analysis showed that ExQW was noninferior to liraglutide. Weight loss was greater with liraglutide than with ExQW (about 3.5 kg versus 2.8 kg at 26 weeks). Adverse gastrointestinal effects remained more common with liraglutide than with ExQW (nausea, 21% versus 9%; vomiting, 11% versus 4%; diarrhea, 13% versus 6%), whereas injection site nodules were more common with ExQW than with liraglutide (3% versus <1%). No major hypoglycemia was observed with either drug, but minor hypoglycemia in the absence of a sulfonylurea was observed in 3% of subjects taking liraglutide and 4% taking ExQW. In subjects taking sulfonylureas, the rate of minor hypoglycemia was 12% with liraglutide and 15% with ExQW.<sup>31</sup>

A meta-analysis that combined all the information for ExQW and liraglutide showed that HbA<sub>1c</sub> was lowered by 1.15% on ExQW, 1.01% on liraglutide 1.2 mg, and 1.18% on liraglutide 1.8 mg, and concluded that there were no meaningful differences in HbA<sub>1c</sub>-lowering with ExQW and the two doses of liraglutide.<sup>32</sup>

## Patient preference and adherence

In DURATION-1, treatment adherence (measured as injections received/injections planned) was 98% for both ExBID and ExQW over 30 weeks.<sup>19</sup> During DURATION-1 and its extension to 52 weeks, treatment satisfaction was assessed using the Diabetes Treatment Satisfaction Questionnaire (DTSQ).<sup>33</sup> The DTSQ assesses six items, ie, “current treatment”, “convenience”, “flexibility”, “understanding”, “recommend”, and “continue”, and uses a Likert scale of 0–7 for each item. After 30 weeks of ExQW, there were improvements for all items except for perceived hypoglycemic frequency.

After 30 weeks, subjects taking ExBID were switched to ExQW, and this improved the DTSQ score. The Impact of Weight on Quality of Life Questionnaire-Lite (IWQOL),<sup>34</sup> which has domains on “physical function”, “self-esteem”, “sex life”, “public distress”, and “work” was improved by both ExQW and ExBID. Furthermore, when subjects switched from ExBID to ExQW, there was a further improvement in quality of life. Nausea with exenatide did not alter the improvements in DTSQ score or IWQOL.<sup>35</sup>

In DURATION-2, ExQW was more effective than sitagliptin or pioglitazone in reducing HbA<sub>1c</sub>, and also reduced body weight.<sup>26</sup> After 26 weeks, the DTSQ score was improved by ExQW, sitagliptin, and pioglitazone in DURATION-2. However, the improvement was greater with ExQW than with sitagliptin. IWQOL was improved by ExQW and sitagliptin, but not by pioglitazone, which increased body weight. The Psychological General Well-Being (PGWB) index has six dimensions, ie, anxiety, depressed mood, positive well-being, self-control, general health, and vitality.<sup>36</sup> ExQW, sitagliptin, and pioglitazone all improved the PGWB.<sup>26,37</sup>

There is very little information about adherence with exenatide. In DURATION-1, adherence with ExQW and ExBID was very high at 98% for both formulations over 30 weeks.<sup>20</sup> A retrospective cohort analysis of adherence with ExBID or insulin glargine used the HealthCore Integrated Research Database™, and calculated adherence as the 12-month medication ratio, ie, the aggregate days of supply of all fills for therapy observed over 12 months after initiation divided by 365 days. Adherence was 68% with ExBID, which was significantly higher than the 58% for insulin glargine.<sup>38</sup>

## Health care and economic considerations

### Center for Outcomes Research model

The Center for Outcomes Research (CORE) has developed a diabetes model which determines the long-term health outcomes and economic consequences of implementing different treatment strategies. The model takes account of baseline cohort characteristics, any past history of complications, current and future diabetes management, and concomitant medications. From this model, development of complications, life expectancy, quality-adjusted life expectancy, and total costs within populations can be calculated.<sup>39</sup>

In subjects with poorly controlled diabetes, despite use of metformin and/or sulfonylureas, Phase III clinical trials have shown that ExBID reduced HbA<sub>1c</sub>,<sup>40–42</sup> and these data have been used in the CORE diabetes model to determine

the effect of adding ExBID versus not adding ExBID. This modeling showed that the increased cost over 30 years with ExBID was associated with increased life expectancy and increased quality-adjusted life expectancy.<sup>43</sup>

CORE has also been applied to DURATION-2, in which ExQW was compared with sitagliptin or pioglitazone in subjects with poorly controlled diabetes, despite taking metformin, and it was shown that subjects on ExQW achieved a bigger reduction in HbA<sub>1c</sub> than those on sitagliptin or pioglitazone.<sup>26</sup> In this model, use of ExQW was extended beyond the 6 months of DURATION-2, with a deterioration of glycemic control until the subjects were switched to basal insulin after 3 years. After 35 years, in the CORE modeling of DURATION-2, ExQW increased life expectancy by 0.28 and 0.17 years, and quality-adjusted life years by 0.28 and 0.24 years, compared with sitagliptin and pioglitazone, respectively. The risk of 14 of 16 diabetic complications (eg, myocardial infarction, renal disease, eye disease, ulcer, neuropathy) was lower with ExQW than with sitagliptin, but for two other complications, ie, first stroke and heart failure, the risk was slightly higher with ExQW than with sitagliptin. The relative risk of 13 of 16 complications was also lower with ExQW than with pioglitazone, but the risk of acute myocardial infarction, stroke, and angina was slightly higher with ExQW than with pioglitazone. ExQW had lower complication costs of US\$2215 and US\$933 versus sitagliptin and pioglitazone, respectively. The biggest limitation in this study is that a relative short clinical trial of 6 months with surrogate endpoints only had been used in the modeling over 35 years.<sup>44</sup>

The CORE model has also been applied to DURATION-3, the trial showing that subjects with suboptimally managed diabetes despite taking metformin alone or with sulfonylureas had a bigger reduction in HbA<sub>1c</sub> with ExQW than with insulin glargine 10 IU/day, and weight loss was observed with ExQW, whereas insulin glargine increased body weight.<sup>29</sup> From the CORE diabetes model, life expectancy and quality-adjusted life expectancy were higher with ExQW than with insulin glargine, and there was also an increased time to diabetic complications with ExQW compared with insulin glargine. At the time of the analysis, the cost of ExQW was unknown, but if it was the same as liraglutide 1.8 mg, the ExQW would be more costly than insulin glargine. However, it should be noted that this was partly due to the increased life expectancy with ExQW, and thus may be acceptable.<sup>45</sup>

Another group applied the CORE diabetes model to DURATION-3, with the known price of ExQW in the US,

and came up with similar results. Compared with insulin glargine, ExQW over 35 years would reduce the risk of cardiovascular disease (except stroke), renal disease, eye disease, and ulcer/neuropathy. ExQW would increase life expectancy and quality-adjusted life expectancy, and this would lead to increased costs with ExQW compared with insulin glargine of US\$15,936 per quality-adjusted life year, which is under the acceptable rate for a quality-adjusted life year of US\$50,000.<sup>46</sup>

The LEAD-6 (Liraglutide Once Daily Compared With Exenatide Twice Daily) trial comparing liraglutide with ExBID was also subjected to the CORE diabetes model, which showed that liraglutide improved quality of life and reduced the incidence of diabetes-related complications compared with ExBID. Liraglutide was cost-effective from a health care perspective in Switzerland, Denmark, Norway, The Netherlands, and Austria.<sup>47</sup> As noted in the previous section, ExQW is more effective than ExBID at lowering HbA<sub>1c</sub> and fasting glucose, and is more convenient to use than ExBID. Thus, a more appropriate comparison would be liraglutide and ExQW.

## The Archimedes model

Another model/simulation has been used to predict cardiovascular outcomes with a once-weekly GLP-1 receptor agonist such as ExQW in subjects with type 2 diabetes. The Archimedes model is a clinically detailed simulation model of human physiology, disease progression, and health care delivery which was initially developed as a diabetes model.<sup>48</sup> The Archimedes diabetes model was then validated against more than 50 major clinical trials, including some in subjects with diabetes.<sup>49</sup>

For the Archimedes diabetes modeling of the effect of GLP-1 agonists, the population used in the simulation study were derived from the National Health and Nutrition Examination Survey (NHANES). In the NHANES virtual population with type 2 diabetes, the HbA<sub>1c</sub> level is 8.1% despite use of metformin with or without a sulfonylurea.<sup>50</sup> Four populations were simulated, ie, standard care, intensive glycemic control, glycemic control and weight reduction, and one with additional improvements in systolic blood pressure and lipids, with these last two simulations representing the effects of GLP-1 receptor agonist. In this model, the GLP-1 receptor agonist achieved a decrease in HbA<sub>1c</sub> over the first year, with some upward drift over time. By year 20, intensive glycemic control led to a 6.1% reduction in macrovascular events relative to standard care, and this represented a reduction in fatal and nonfatal myocardial infarction, stroke, and

death from coronary artery disease of 9.2%, 2.2%, and 10.2%, respectively. With glycemic control and weight reduction, the rates of myocardial infarction, stroke, and coronary death were increased to 19.5%, 6.2%, and 17.6%, respectively. With the addition of reduced blood pressure and lipid controls, the reductions in myocardial infarction, stroke, and coronary death were 26.7%, 10.7%, and 24.8%, respectively. Only the GLP-1 receptor agonist simulations led to a reduction in the early signs of renal disease (macroalbuminuria).<sup>51</sup>

The Archimedes model and the NHANES population have also been used to compare ExQW with insulin and pioglitazone in subjects with type 2 diabetes taking metformin. The model included both moderate and high adherence with insulin. Data from four of the DURATION trials (1, 2, 3, and 5) were used to quantify the effects of ExQW. With this model, after one year, HbA<sub>1c</sub> decreased by about 1.5% with ExQW, which was more than the 1% with pioglitazone and high adherence with insulin and the 0.5% with moderate adherence with insulin. Body weight decreased with ExQW, but increased with insulin and pioglitazone. After 20 years, major adverse cardiovascular events were lower in this simulation with ExQW than with high or moderate adherence to insulin or pioglitazone. At 5 years, there were increased life years and quality-adjusted life years with ExQW, compared with insulin and pioglitazone, and this continued up to the 20-year mark. A limitation of this study was that subjects with type 2 diabetes were assumed to be 100% adherent with ExQW, with high adherence to insulin and pioglitazone, which is not realistic.<sup>52</sup>

## Commentary

### Long-term studies of clinical endpoints and safety with ExQW

The trials of ExQW discussed in this review have described the effects on surrogate endpoints (eg, HbA<sub>1c</sub>) for type 2 diabetes. The much more important endpoints are clinical ones, such as myocardial infarction and hospitalization. Recently, a retrospective cohort trial has suggested that ExBID is associated with a lower risk of cardiovascular disease events and hospitalizations than treatment with other glucose-lowering therapies,<sup>12</sup> but such information is not available from a prospective trial or for ExQW. The modeling studies suggest that ExQW will reduce cardiovascular endpoints, but it is important that clinical trials or evaluations are undertaken to determine whether ExQW does lower the incidence of cardiovascular disease and hospitalizations.

Based on postmarketing data, ExBID was associated with acute pancreatitis, including fatal and nonfatal hemorrhagic

or necrotizing pancreatitis.<sup>53</sup> Although recent evidence suggests that ExBID is not linked with pancreatitis, as discussed earlier, it does raise the issue of long-term safety with ExQW, which is yet to be evaluated in large numbers of subjects with type 2 diabetes.

## Gliptins

The gliptins inhibit dipeptidyl peptidase-4 and increase levels of endogenous glucagon-like peptide-1 to augment glucose-mediated insulin secretion. To date, ExQW has only been compared with one dipeptidyl peptidase-4 inhibitor, which was sitagliptin, and ExQW was shown to lower HbA<sub>1c</sub> to a greater extent than sitagliptin. It has been suggested that vildagliptin is more potent than sitagliptin at reducing HbA<sub>1c</sub> in Japanese subjects with type 2 diabetes.<sup>54</sup> Thus, it is possible that ExQW may not be more potent than gliptins other than sitagliptin. Thus, a direct comparison of ExQW and vildagliptin should be undertaken in subjects with type 2 diabetes. Further, it is possible that the effects of ExQW and the gliptins are additive, with ExQW directly stimulating the receptor for glucagon-like peptide-1, and the gliptins causing a buildup of endogenous glucagon-like peptide-1, which also stimulates the receptor. This should be tested in subjects with poorly managed type 2 diabetes despite using either ExQW or a gliptin.

## Comparison with sulfonylureas

When metformin is ineffective at controlling type 2 diabetes alone, the standard group of drugs added are the sulfonylureas. Although effective at reducing HbA<sub>1c</sub> in the presence of metformin, the sulfonylureas increase the incidence of hypoglycemia. Thus, when type 2 diabetes is not controlled by metformin alone, ExQW should be trialed as an alternative to a sulfonylurea. Such a trial should compare not only the incidence of hypoglycemia between ExQW and a sulfonylurea, but also efficacy and other aspects of safety in subjects with type 2 diabetes being poorly managed with metformin.

## Add-on to insulin

Adding ExBID to insulin glargine has been shown to be effective in the treatment of subjects with type 2 diabetes. Thus, addition of ExBID is associated with a lowering of HbA<sub>1c</sub>, lower basal insulin requirements, and with weight loss or less weight gain, as extensively reviewed elsewhere.<sup>55</sup> However, the effects of adding ExQW to insulin glargine have not been assessed in a clinical trial, and should be.



## Preference and adherence

There is limited information available for preference and adherence with ExQW. ExQW was preferred to ExBID in DURATION-1, as discussed earlier. However, it is not known whether ExQW is preferred to other diabetic medicines, and this needs to be investigated.

Because it takes 3 weeks to drop from steady state to below therapeutic levels with ExQW,<sup>18</sup> subjects with type 2 diabetes who miss the occasional dose of ExQW may maintain reasonable glycemic control, and this needs to be investigated. Other antidiabetic medicines, including ExBID, have shorter durations of action than ExQW, and nonadherence with these other diabetic medicines may be associated with poorer glycemic control than with ExQW. This comparison also needs to be undertaken. Very high adherence to ExQW has been reported in the clinical trial setting,<sup>20</sup> but this needs to be assessed in practice. Higher adherence with ExBID than with insulin glargine has been reported,<sup>35</sup> but comparison of adherence rates between ExQW and insulin glargine needs investigating.

## Archimedes diabetes simulation and AHEAD trial

In the modeling of a GLP-1 agonist in diabetes, Peskin et al considered the agonist to be equivalent to glycemic control and weight reduction or these plus additional improvements in systolic blood pressure and lipids.<sup>51</sup> This modeling suggested that there would be improvements in cardiovascular outcomes associated with these changes.<sup>51</sup> The Action for Health in Diabetes (Look AHEAD) trial was designed to determine whether intensive lifestyle changes compared with diabetes support and education would improve cardiovascular outcomes.<sup>56</sup> In this trial, after 4 years, physical activity was greater, weight loss was about 5 kg, and HbA<sub>1c</sub> was lowered by 0.5% in the lifestyle group.<sup>57</sup> However, there was no evidence of improved cardiovascular outcomes in the intensive lifestyle change group, compared with the diabetes support and education group, and the trial has been abandoned for futility.<sup>58</sup>

Given that Archimedes modeling of the GLP-1 agonist was based on it being equivalent to lifestyle changes,<sup>51</sup> similar results from the simulation and real trial might be expected, but this did not occur. One possible explanation for this is that the modeling produced much larger decreases in body weight and HbA<sub>1c</sub> than were observed in the Look AHEAD trial, and these larger decreases are needed to achieve an improvement in cardiovascular outcomes.

## Conclusion

The clinical trials with ExBID established a role for exenatide in the treatment of type 2 diabetes. Subsequently, ExQW was shown to have advantages over ExBID, and there is now more emphasis on the development of ExQW. ExQW alone reduces HbA<sub>1c</sub> and body weight, and is well tolerated. ExQW has been compared with sitagliptin, pioglitazone, and metformin, and shown to have a greater ability to reduce HbA<sub>1c</sub> than these other medicines. ExQW has been compared with insulin glargine, and ExQW causes weight loss compared with a weight gain with insulin glargine. ExQW has been compared with another GLP-1 receptor agonist, liraglutide, and the results suggest that ExQW is noninferior to liraglutide. The small amount of evidence available shows that subjects with type 2 diabetes prefer ExQW to ExBID, and that adherence was high in the clinical trial setting. Health care and economic modeling suggests that ExQW will reduce diabetic complications and be cost-effective compared with other medications in long-term use. Little is known about whether subjects with type 2 diabetes prefer ExQW to other medicines and whether adherence with ExQW is good in practice, and these important topics require further study.

## Disclosure

The author reports no conflicts of interest in this work.

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