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Efficacy and tolerability of exenatide once weekly over 7 years in patients with type 2 diabetes: An open-label extension of the DURATION-1 study

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ABSTRACT

Aims: To investigate the glycemic efficacy, effects on cardiovascular risk factors, and safety of exenatide once weekly (QW) in patients with type 2 diabetes over 7 years in the DURATION-1 study.
Methods: Patients were initially randomized to exenatide QW 2 mg or exenatide twice daily for 30 weeks, after which they received open-label, open-ended treatment with exenatide QW 2 mg for up to 7 years. Efficacy analyses included changes from baseline in glycated hemoglobin (HbA_{1C}) and cardiovascular risk factors.
Results: Of 295 patients in the intention-to-treat population, 122 (41%) completed 7 years of treatment. Patients in the 7-year completer population showed sustained glycemic improvements from baseline (7-year least-squares mean [LSM] change in HbA_{1C}, −1.53%) and significant improvements in several cardiovascular risk factors, including body weight, diastolic blood pressure, total cholesterol, low-density lipoprotein cholesterol, and high-density lipoprotein cholesterol. Seven-year completers who received no additional glucose-lowering therapies ($n = 65$ [53%]) had similar improvements in HbA_{1C} and numerically greater reductions in body weight (7-year LSM change, −6.46 kg vs −3.87 kg), compared with the overall cohort. There were no unexpected safety findings.
Conclusions: Treatment with exenatide QW for 7 years was associated with sustained improvements in glycemic control and several cardiovascular risk factors.

1. Introduction

Type 2 diabetes is a progressive chronic disease that is associated with high morbidity and mortality.[1] Ten-year data from the UK Prospective Diabetes Study (UKPDS) showed that glycemic control was lost during long-term treatment with metformin, sulfonylureas, and insulin, with an initial drop in glycated hemoglobin (HbA_{1C}) and fasting plasma glucose (FPG) being negated by a steady increase in both variables over time, frequently to levels above baseline.[2,3] Thus, once glucose-lowering therapy is initiated in a patient with type 2 diabetes, pharmacologic treatment will most likely be long-term or lifelong. Since the UKPDS, new glucose-lowering therapies have been developed, including glucagon-like peptide-1 receptor agonists (GLP-1RAs) and sodium–glucose cotransporter-2 (SGLT-2) inhibitors, with improved therapeutic properties and a lower intrinsic risk of hypoglycemia.

In patients with type 2 diabetes, GLP-1RAs have been shown to improve glycemic control, body weight, and systolic and diastolic blood pressure and may reduce blood lipids.[4–7] Although cardiovascular outcome studies have shown that HbA_{1C} reductions can be maintained with GLP-1RAs over a median follow-up of 2.1–3.8 years,[8–10] the likelihood of disease progression with GLP-1RAs over 10 years has not been established in long-term randomized controlled trials. Some GLP-1RAs have been shown to improve cardiovascular outcomes, including 3-point major adverse cardiovascular events, cardiovascular mortality, and all-cause mortality risk, without causing significant safety issues.[11] Similarly, SGLT-2 inhibitors, such as empagliflozin[12] and canagliflozin,[13] have also demonstrated reductions in the risk of cardiovascular events with long-term treatment in patients with type 2 diabetes and high cardiovascular disease risk. The underlying mechanism for the reduction in cardiovascular risk with GLP-1RAs is unclear; however, one hypothesis is that intensive therapy that targets multiple cardiovascular risk factors, such as HbA_{1C}, body weight, blood pressure, and lipids, over time may be important.[14]

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Exenatide is a GLP-1RA that is available in short-acting twice daily (BID) and long-acting once weekly (QW) formulations. In the Exenatide Study of Cardiovascular Event Lowering (EXSCEL), among 14,752 patients with type 2 diabetes with or without previous cardiovascular disease, exenatide QW was not associated with an increase in overall cardiovascular risk and was associated with a reduced risk of all-cause mortality (hazard ratio [HR], 0.86 [95% confidence interval (CI), 0.77 to 0.97]), with a nonsignificant trend toward improvement in major adverse cardiovascular events (HR, 0.91 [95% CI, 0.83 to 1.00]).[9] The Diabetes Therapy Utilization: Researching Changes in A1C, Weight, and Other Factors Through Intervention With Exenatide Once Weekly (DURATION-1) study was unique in that patients with type 2 diabetes continued treatment with exenatide QW for a total treatment duration of up to 7 years in an open-ended period after completing a 30-week controlled treatment period that compared exenatide QW with exenatide BID.[15–17] Although adherence to treatment among patients who completed the study was generally higher than that observed in clinical practice,[17] data from these patients may provide insights into the potential durability of improvements in key cardiovascular risk factors over 7 years.

The current study reports 7-year data in patients treated with exenatide QW in the open-ended period of DURATION-1, including data on glycemic efficacy, cardiovascular risk factors, and safety and tolerability end points.

2. Materials and methods

2.1. Study design

The design of the DURATION-1 study has been previously published.[15] Briefly, the DURATION-1 study enrolled adults with type 2 diabetes who had received ≥2 months of treatment with diet modification and exercise or pharmacotherapy with metformin, a sulfonylurea, a thiazolidinedione, or a combination of two of these agents. Prior to randomization, patients received exenatide BID 5 μg for 3 days; they were subsequently randomized to receive exenatide QW 2 mg or exenatide BID (5 μg for the first 4 weeks, then 10 μg) for 30 weeks (Fig. 1).

At 30 weeks, patients entered an uncontrolled, open-label, open-ended extension period in which all patients received exenatide QW 2 mg. During the open-ended period, investigators were asked to maintain stable dosages of concomitant glucose-lowering therapies where possible. However, changes in concomitant medication use were at the discretion of the investigator or primary care physician and could be made if deemed necessary.

The study protocol was approved at each study site by the appropriate institutional review board, and the study was conducted in accordance with the principles described in the Declaration of Helsinki and a common clinical protocol. Patients provided written informed consent prior to participation.

2.2. End points

Patient study visits were weekly until week 34; patients then had a visit at week 36, followed by visits every 4 weeks from weeks 40–76 and subsequent visits every 8 weeks until the study end or early termination visit (Fig. 1). Assessments at each visit during the open-ended period included HbA_{1C}, FPG, vital signs, anthropometric measures, estimated glomerular filtration rate (eGFR), lipids, and adverse event (AE) and medication review. Data are shown for the visits at specific weeks that correspond with approximately the beginning of each year over 7 years (weeks 52, 108, 156, 212, 260, 316, and 364).

2.3. Statistical analysis

Efficacy analyses are reported for the 7-year completer population, which included all patients who completed 7 years (364 weeks) of treatment. Baseline demographics and characteristics were assessed in the intention-to-treat (ITT) population, comprising individuals who received ≥1 dose of exenatide QW or exenatide BID. AEs were assessed in the patients in the ITT population who received ≥1 dose of exenatide QW during randomized treatment or the open-ended extension period.

Changes in HbA_{1C} were analyzed primarily using analysis of variance (ANOVA; general linear model including baseline HbA_{1C} stratum and concomitant sulfonylurea use at screening) and secondarily using analysis of covariance (ANCOVA; general linear model including concomitant sulfonylurea use at screening and baseline HbA_{1C} values). Other efficacy parameters were analyzed using ANCOVA (general linear model including baseline HbA_{1C} stratum, concomitant sulfonylurea use at screening, and baseline values for the respective parameters).

Least-squares means (LSMs), standard errors, and 95% CIs were calculated for changes from baseline in efficacy parameters. For AEs, overall incidences within the ITT population were calculated. Exposure-adjusted incidence among ITT population who received exenatide QW during the controlled and open-ended periods was also calculated.

Changes in heart rate and the incidences of major and minor hypoglycemia events and AEs of special interest were summarized for the 7-year completer population. Changes in eGFR were also summarized descriptively for the completer population. Post hoc analyses were conducted to determine the timing of specific events over the study duration in the 7-year completer population. Such analyses assessed subgroups with and without the addition of non-GLP-1RA glucose-lowering therapies and the timing of hypoglycemia with and without concomitant sulfonylurea treatment; comparisons between different time points during the study were not made.

3. Results

Of the 295 patients in the ITT population, 122 patients (41%) completed at least 7 years of treatment and were included in the 7-year completer population (Fig. 2A and B). Compared with patients who did not complete 7 years of treatment, 7-year completers differed slightly by race and ethnicity and had somewhat lower mean HbA_{1C} and FPG at baseline (Table 1).

Over the course of the study, the most commonly used concomitant glucose-lowering therapies were metformin, sulfonylureas, and

Fig. 1. Study design of DURATION-1. BID, twice daily; GLT, glucose-lowering therapy; QW, once weekly; R, randomization.

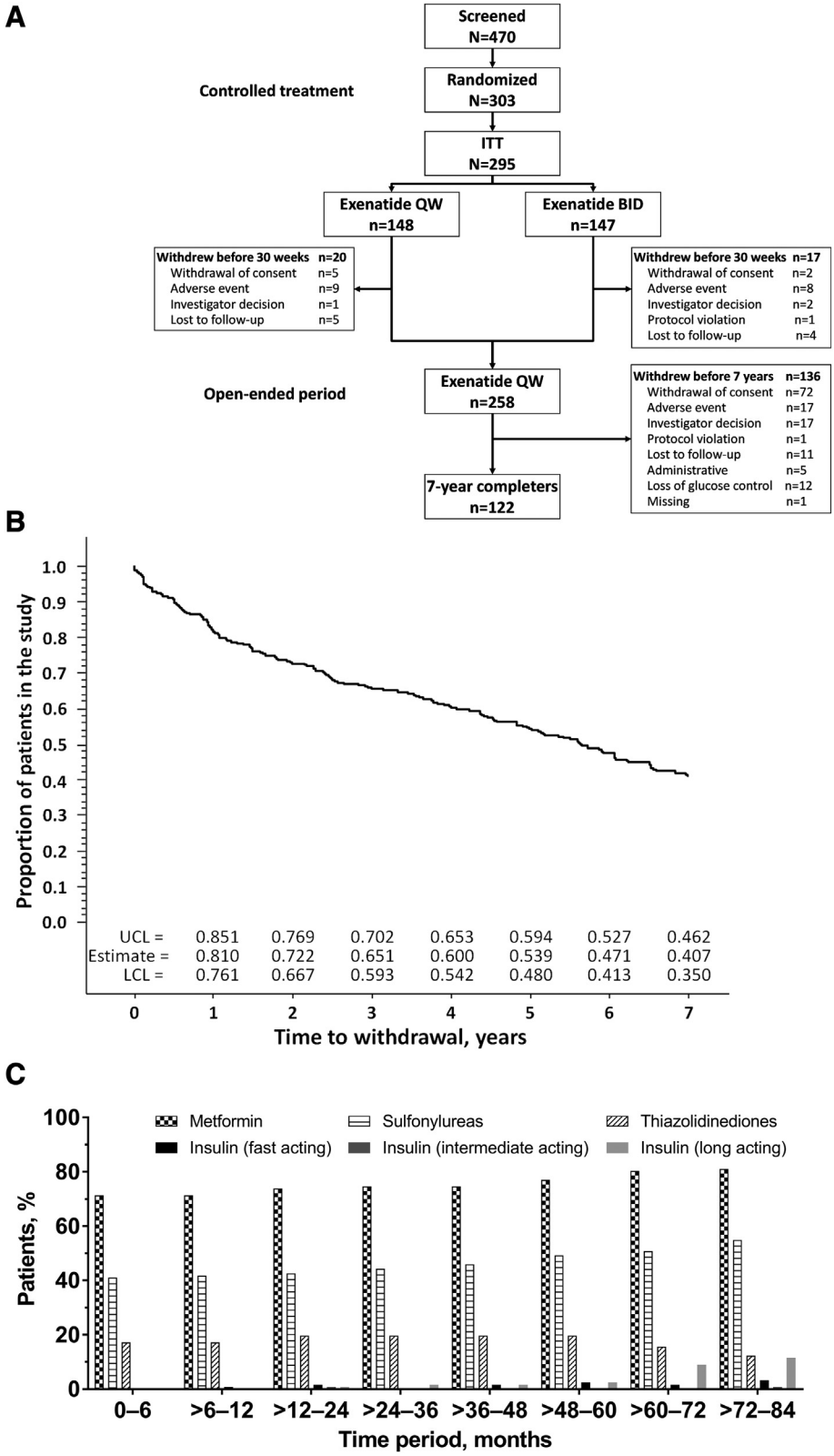

Fig. 2. Flow of patients through study, including timing of withdrawals and use of concomitant glucose-lowering therapies. (A) Patient disposition. (B) Kaplan-Meier plot of time to withdrawal and estimates of proportion of patients remaining in the study. (C) Time course of use of the most common concomitant glucose-lowering therapies in 7-year completers ($n = 122$). BID, twice daily; ITT, intention-to-treat; LCL, lower confidence limit; QW, once weekly; UCL, upper confidence limit.

thiazolidinediones (Fig. 2C). Patients appeared to increase their use of metformin and sulfonylureas and decrease their use of thiazolidinediones over time during the open-ended period. The addition of insulin was less frequent than addition of other glucose-lowering therapies; after 7 years, 3.3%, 0.8%, and 11.5% of patients were using fast-, intermediate-, and long-acting insulins, respectively.

Table 1
Baseline demographics and characteristics.

	ITT population ($N = 295$)	7-year completers ($n = 122$)	7-year noncompleters ($n = 173$)
Male, *n* (%)	157 (53.2)	64 (52.5)	93 (53.8)
Age at consent, y	55.0 ± 9.7	56.3 ± 8.5	54.2 ± 10.4
Race/ethnicity, *n* (%)			
White	230 (78.0)	101 (82.8)	129 (74.6)
Black	28 (9.5)	15 (12.3)	13 (7.5)
Hispanic	36 (12.2)	5 (4.1)	31 (17.9)
Asian	1 (0.3)	1 (0.8)	0
Duration of diabetes, y	6.7 ± 5.0	7.1 ± 5.6	6.4 ± 4.6
HbA_{1C}, %	8.30 ± 0.99	8.17 ± 0.96	8.39 ± 1.01
FPG, mmol/L	9.4 ± 2.4	9.2 ± 2.3	9.5 ± 2.4
Body weight, kg	101.8 ± 19.9	101.2 ± 18.1	102.3 ± 21.1
BMI, kg/m^2	34.9 ± 5.0	34.7 ± 4.7	35.1 ± 5.3
Diabetes management method at screening, *n* (%)			
SU based	109 (36.9)	49 (40.2)	60 (34.7)
SU only	16 (5.4)	9 (7.4)	7 (4.0)
SU + metformin	82 (27.8)	34 (27.9)	48 (27.7)
SU + TZD	10 (3.4)	5 (4.1)	5 (2.9)
SU + metformin + TZD	1 (0.3)	1 (0.8)	0
Non-SU based	186 (63.1)	73 (59.8)	113 (65.3)
Diet and exercise	43 (14.6)	15 (12.3)	28 (16.2)
Metformin only	106 (35.9)	43 (35.2)	63 (36.4)
TZD only	9 (3.1)	6 (4.9)	3 (1.7)
Metformin + TZD	28 (9.5)	9 (7.4)	19 (11.0)

Data are mean ± standard deviation unless otherwise noted.
BMI, body mass index; FPG, fasting plasma glucose; HbA_{1C}, glycated hemoglobin; ITT, intention-to-treat; SU, sulfonylurea; TZD, thiazolidinedione.

3.1. Efficacy

3.1.1. Glycemic variables

In patients who completed 7 years of treatment in DURATION-1, exenatide QW significantly improved HbA_{1C} from baseline at each annual time point, as assessed by ANOVA. At 7 years, patients had an LSM change in HbA_{1C} of −1.53% (95% CI, −1.76% to −1.31%) (Fig. 3A).

When changes from baseline were assessed by ANCOVA, significant improvements from baseline in HbA_{1C} were also seen (LSM change at 7 years, −1.09% [95% CI, −1.27% to −0.91%]) (Fig. 3B). Among the 7-year completers over 1, 2, 3, and 4 years, the proportion of patients who achieved an HbA_{1C} target of <7.0% or ≤6.5% decreased; however, after 5 years, the proportion of patients achieving HbA_{1C} goals stabilized (Supplementary Fig. 1). At the end of the 7-year assessment period, 45.9% of patients achieved HbA_{1C} <7.0% and 30.3% achieved HbA_{1C} ≤6.5%.

Consistent with the HbA_{1C} reductions, exenatide QW also significantly reduced FPG from baseline at each time point in patients who completed 7 years of treatment (LSM change at 7 years, −1.31 mmol/L [95% CI, −1.83 to −0.79 mmol/L]) (Fig. 3C).

The use of background sulfonylureas at baseline had no significant effect on the changes observed for HbA_{1C} or FPG (Supplementary Fig. 2).

3.1.2. Cardiovascular risk factors

Body weight was significantly reduced at each annual time point; at 7 years, patients had an LSM change from baseline in body weight of −3.87 kg (95% CI, −5.36 to −2.37 kg) (Fig. 3D). As with changes in HbA_{1C} and FPG, the use of background sulfonylureas had no significant effect on the changes observed in body weight (Supplementary Fig. 2).

Reductions in systolic and diastolic blood pressure from baseline were observed in the 7-year completer population over the first 2 years of treatment. Although reductions in diastolic blood pressure were sustained at 7 years (mean change, −2.7 mm Hg), the reductions in systolic blood pressure were not maintained (Supplementary Fig. 3).

After 7 years of treatment, improvements in levels of total cholesterol (LSM change, −0.25 mmol/L [95% CI, −0.42 to −0.08 mmol/L]), low-density lipoprotein (LDL) cholesterol (LSM change, −0.27 mmol/L [95% CI, −0.42 to −0.12 mmol/L]), and high-density lipoprotein (HDL) cholesterol (LSM change, +0.07 mmol/L [95% CI, +0.03 to +0.12 mmol/L]) were observed (Supplementary Fig. 4). Triglycerides also improved (geometric LSM ratio of 7 years to baseline, 0.93 [95% CI, 0.85 to 1.01]). However, over the 7-year treatment period, rates of lipid-modifying agent use increased from 65.6% to 77.9%.

3.1.3. Efficacy in patients who received no additional glucose-lowering therapies

Sixty-five of the 122 patients who completed 7 years of treatment (53%) received no additional glucose-lowering therapies during the study. Improvements from baseline in HbA_{1C} and FPG in this subgroup of patients were similar to those seen in the overall 7-year completer population. At 7 years, patients who received no additional glucose-lowering therapies during the treatment period had an LSM change from baseline in HbA_{1C} of −1.77% (95% CI, −2.07% to −1.47%), as assessed by ANOVA, and of −1.30% (95% CI, −1.53% to −1.06%), as assessed by ANCOVA (Fig. 3A and B). Patients who did not receive any additional glucose-lowering therapies had an LSM change from baseline in FPG of −1.26 mmol/L (95% CI, −1.81 to −0.70 mmol/L) at 7 years (Fig. 3C).

Improvements in body weight observed in patients who received no additional glucose-lowering therapies were numerically greater than those in the overall cohort; at 7 years, LSM reduction from baseline in body weight in this subgroup was −6.46 kg (95% CI, −8.10 to −4.81 kg) (Fig. 3D). Reductions in systolic and diastolic blood pressure were seen after 7 years of treatment in this subgroup (LSM change, −1.5 mm Hg [95% CI, −4.7 to +1.8 mm Hg] and −3.5 mm Hg [95% CI, −5.5 to −1.4 mm Hg], respectively).

The improvements in lipids seen in patients who did not receive any additional glucose-lowering therapies after 7 years of treatment were similar to those observed in the overall 7-year completer population. In this subgroup, total cholesterol and LDL cholesterol levels decreased (LSM change, −0.28 mmol/L [95% CI, −0.48 to −0.09 mmol/L] and −0.27 mmol/L [95% CI, −0.45 to −0.10 mmol/L], respectively), and HDL cholesterol levels increased (LSM change, +0.07 mmol/L [95% CI, +0.01 to +0.13 mmol/L]). Triglyceride levels also improved (geometric LSM ratio of 7 years to baseline, 0.89 [95% CI, 0.80 to 0.98]).

3.2. Safety and tolerability

3.2.1. Adverse events

In the ITT population who received ≥1 dose of exenatide QW ($n = 278$), no unexpected safety findings were observed with long-term exenatide QW treatment. Over 7 years of treatment, 96.8% of patients experienced an AE, 25.5% experienced a serious AE, and 10.1% withdrew from the study because of an AE.

During the controlled treatment period, the most common AEs were gastrointestinal disorders, with nausea having the highest incidence (Table 2).[15] The rate of nausea and other gastrointestinal AEs subsequently decreased over time, with lower exposure-adjusted event rates over the 7-year open-ended period than in the 30-week controlled treatment period (Supplementary Fig. 5).

In the ITT population, the incidence of myocardial infarction, congestive heart failure, and ischemic stroke was 1.1%, 1.1%, and 0.4%, respectively. Over 7 years, there were 5 deaths (1.8% of patients), none of which were considered by the investigator to be related to study medication. Causes of death were reported as arrhythmia, myocardial infarction, pancreatic carcinoma, cardiac arrest, and arteriosclerosis. The incidence of AEs of special interest over 7 years was low. In the ITT and 7-year completer populations, the rates of AEs of special interest were acute renal failure ($n = 4$ [1.4%] and $n = 4$ [3.3%], respectively), renal failure ($n = 2$ [0.7%] and 1 [0.8%], respectively), pancreatitis ($n = 2$ [0.7%] and $n = 1$ [0.8%], respectively), pancreatic carcinoma ($n = 1$ [0.4%] and $n = 0$ [0.0%], respectively), and benign thyroid neoplasm ($n = 1$ [0.4%] and $n = 1$ [0.8%], respectively).

In the 7-year completer population, an initial small increase from baseline in heart rate was observed, with a peak after 2 years (+3.7 beats/

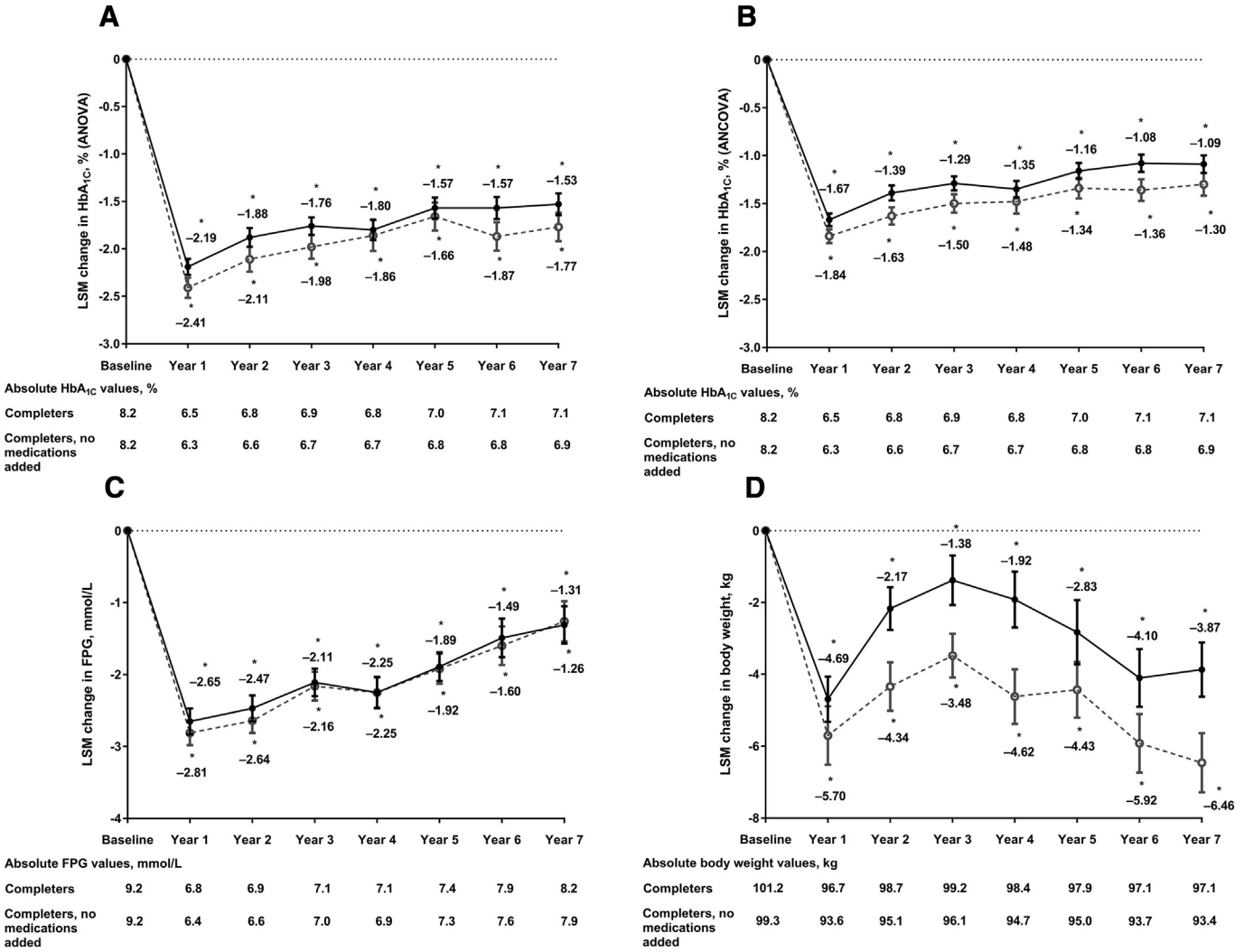

Fig. 3. Key efficacy parameters in all 7-year completers ($n = 122$) and those not on additional glucose-lowering therapies ($n = 65$). LSM ± SE changes from baseline in (A) HbA_{1C} by ANOVA; (B) HbA_{1C} by ANCOVA; (C) FPG, (D) body weight. Error bars show the SE. ANCOVA, analysis of covariance; ANOVA, analysis of variance; FPG, fasting plasma glucose; LSM, least-squares mean; SE, standard error. $^{*}P < 0.05$ for change from baseline.

min); however, the difference from baseline decreased and stabilized over the 7-year treatment period (change at 7 years: +1.2 beats/min; Supplementary Fig. 6).

3.2.2. Hypoglycemia

No major hypoglycemia events were reported in patients who completed 7 years of treatment. In these patients, most minor hypoglycemia events that occurred over 7 years were reported in patients who were receiving a concomitant sulfonylurea at baseline (Supplementary Fig. 7). Of the patients who were receiving a concomitant sulfonylurea or insulin at baseline ($n = 37$), 17 had discontinued these medications prior to hypoglycemia occurrence. Eleven patients who had minor hypoglycemia events were not receiving a concomitant sulfonylurea or insulin at baseline; six of these patients added a sulfonylurea or insulin prior to the minor hypoglycemia event.

3.2.3. Renal function

In the completer population, mean eGFR decreased from baseline over 7 years of treatment, but remained within the normal range (Supplementary Fig. 8). Mean eGFR values decreased from 87.2 mL/min/1.73 m^2 (median, 86.6 mL/min/1.73 m^2) at baseline to 74.9 mL/min/1.73 m^2 (median, 77.0 mL/min/1.73 m^2) at year 7 (mean change from baseline, −12.5 mL/min/1.73 m^2 [median, −9.5 mL/min/1.73 m^2]).

4. Discussion

In patients with type 2 diabetes, sustained poor glycemic control is associated with an increase in microvascular and macrovascular events,[18] emphasizing the importance of long-term glycemic control. Long-term studies have previously shown that glycemic control in patients with type 2 diabetes decreases over time.[2,3,19] In these studies, patients were treated with oral glucose-lowering therapies, such as metformin and sulfonylureas, and/or insulin; however, the GLP-1RA class of glucose-lowering therapy was not used.

To date, published data for DURATION-1 includes up to 6 years of treatment with the GLP-1RA exenatide QW in patients with type 2 diabetes.[16,17,20–22] In the current analysis, 7-year data from DURATION-1 show that exenatide QW was associated with clinically significant and sustained improvements in glycemic and metabolic control, with no new safety findings, in patients who completed 7 years of

Table 2
Treatment-emergent adverse events with an incidence of ≥10% reported in patients receiving exenatide once weekly during the 30-week randomized treatment period or the open-ended extension period (intention-to-treat population).

Adverse event	30-week assessment ($n = 148$)		7-year assessment[a] ($n = 278$)	
	Incidence, %	Annual event rate, events/y	Incidence, %	Annual event rate, events/y
Upper respiratory tract infection	8.1	0.162	44.6	0.177
Nausea	27.0	0.846	29.5	0.122
Diarrhea	16.2	0.373	28.4	0.112
Nasopharyngitis	6.8	0.187	28.1	0.156
Sinusitis	4.7	0.087	23.7	0.096
Urinary tract infection	10.1	0.224	22.7	0.091
Arthralgia	4.7	0.124	20.9	0.068
Back pain	4.7	0.087	19.8	0.056
Vomiting	10.8	0.361	19.4	0.082
Hypertension	3.4	0.062	17.6	0.046
Bronchitis	2.7	0.050	16.5	0.049
Pain in extremity	0.7	0.025	15.8	0.046
Musculoskeletal pain	1.4	0.025	14.4	0.038
Constipation	10.1	0.199	14.4	0.039
Injection site pruritus	18.2	0.510	14.4	0.044
Gastroesophageal reflux disease	7.4	0.149	14.0	0.036
Headache	6.1	0.261	13.7	0.046
Gastroenteritis, viral	8.1	0.149	13.3	0.038
Cough	3.4	0.062	11.9	0.033
Influenza	1.4	0.025	10.8	0.026

[a] 30-week assessment and open-ended assessment.

treatment. Exenatide QW provided sustained reductions in HbA_{1C} over 7 years, with a low rate of insulin initiation. Although slight decreases in glycemic control over time were observed after initial HbA_{1C} reductions at year 1, many patients (45.9%) achieved the HbA_{1C} goal of <7.0%, and 30.3% of patients achieved HbA_{1C} ≤6.5%.

Approximately half (53%) of patients who completed 7 years of treatment did not require additional glucose-lowering therapies. Possible explanations for this observation may be that these patients were somewhat younger and had shorter duration of type 2 diabetes or possibly had less severe disease at baseline, enabling them to maintain glycemic control with fewer medications, as well as interpatient variability of response to treatment.

Exenatide QW was also associated with body weight reductions ranging from −1.38 kg to −4.69 kg over 7 years, with a reduction of −3.87 kg at year 7; however, the extent of weight loss was less during years 2–5 compared with earlier and later annual assessments. Changes in concomitant glucose-lowering therapies may have contributed in part to variable weight reductions. Weight loss was greater and more stable in patients with no additional glucose-lowering therapies during the 7-year follow-up.

Multiple cardiovascular risk factors remained stable or improved over 7 years of treatment, including changes in diastolic blood pressure, total cholesterol, and LDL cholesterol. However, the use of lipid-modifying agents increased over the course of the study, which may have confounded assessment of the long-term effects of exenatide on lipid profiles. Reductions in systolic blood pressure observed at year 1 and year 2 were not maintained in the following years. However, this finding is not surprising, as adequate control of blood pressure is difficult to maintain in clinical practice. Furthermore, changes in background blood pressure medications occurred throughout the study and would be expected to impact the findings. Mean heart rates showed initial slight increases from baseline (+3.2 to +3.7 beats/min) at year 1 and year 2, but then stabilized to +1.2 beats/min at year 7 (Supplementary Fig. 6).

Exenatide QW was well tolerated, with no unexpected safety findings reported over the 7-year treatment period. Rates of gastrointestinal AEs, including nausea, decreased during the open-ended treatment period, and most patients who experienced a minor hypoglycemia event were receiving a concomitant sulfonylurea at baseline. The frequency of hypoglycemic events seemed to inversely reflect weight reductions over time (Fig. 3D; Supplementary Fig. 7).

It is unclear whether the long-term benefits of exenatide QW observed in this study can translate into the cardiovascular effects seen in the EXSCEL study (i.e., numerically fewer major cardiovascular events and a reduction in all-cause mortality).[9] Possible evidence includes a study by Gæde et al. demonstrating the benefit of management of multiple cardiovascular risk factors,[14] as well as a reduction in vascular inflammation, with exenatide.[23] It should be noted that 73% of patients in the EXSCEL study had previous cardiovascular disease at baseline,[9] while patients with clinically significant medical conditions (including cardiovascular disease) were excluded from the DURATION-1 study, making the extrapolation more difficult.[15] However, GLP-1RAs have been shown to reduce the risk of adverse cardiovascular outcomes. Over a median of 3.8 years, treatment with liraglutide in the LEADER study resulted in significantly fewer adverse cardiovascular events versus placebo (HR, 0.87 [95% CI, 0.78 to 0.97]).[8] In a subsequent meta-analysis of cardiovascular outcomes with GLP-1RAs that included the EXSCEL, LEADER, SUSTAIN-6 (semaglutide), and ELIXA (lixisenatide) studies, GLP-1RAs demonstrated a 10% reduction in the relative risk of major adverse cardiovascular events versus that with placebo ($P = 0.033$) and a 13% reduction in the risk of cardiovascular mortality ($P = 0.007$) over a median follow-up of 2.1–3.8 years,[11] suggesting a class effect of GLP-RAs.

This report marks the longest clinical study of a GLP-1RA to date. The results of this analysis extend those reported for the 6-year follow-up of the DURATION-1 study,[17] and confirm the 2.5- to 3-year extension data for exenatide QW and 3-year data for exenatide BID showing sustained glycemic control and weight loss.[24–26] In an analysis of 3-year data from DURATION-3, a randomized, open-label trial of exenatide QW versus insulin glargine, lower HbA_{1C} and FPG values at 26 weeks were associated with a greater likelihood of sustaining an HbA_{1C} goal of <7.0% over 3 years.[27] Data from studies of 2- to 3-year duration have been reported for several other GLP-1RAs, including liraglutide, albiglutide, and dulaglutide, supporting sustained glucose control with GLP-RAs. Patients completing 2 years of treatment with 1.2- and 1.8-mg liraglutide in the LEAD-3 study had reductions in HbA_{1C} of −0.9% and −1.1%, respectively,[28] while 2 years of treatment with albiglutide in the HARMONY-3 study was associated with an HbA_{1C} reduction of −0.6%.[29] In the AWARD-5 study, 2 years of treatment with dulaglutide 1.5 and 0.75 mg was associated with changes from baseline in HbA_{1C} of −1.0% and −0.7%, respectively.[30]

This analysis was limited by the lack of a comparator arm. In addition, there is a lack of information regarding the reasons why more than half of the ITT population (58.6% [$n = 173$]) prematurely withdrew from study treatment. Long-term data on 7-year noncompleter patients may help to better understand the course of type 2 diabetes disease. Although the demographics of the 7-year noncompleter population were similar to those of the 7-year completer population, premature discontinuation may be an indicator of lack of efficacy, which could lead to a bias in efficacy results. Furthermore, completers may have been more adherent than patients in routine clinical practice. In addition, the addition of concomitant glucose-lowering therapies and lipid-lowering therapies during treatment may have influenced the observed efficacy and safety findings.

Despite the limitations, these findings for the 7-year completer population demonstrate that exenatide QW is effective and safe over long periods of time, and patients with initial good response to treatment are likely to benefit from continuing long-term treatment.

5. Conclusions

Overall, the 7-year results of DURATION-1 show that long-term treatment with exenatide QW allowed a significant proportion of

patients to achieve sustained HbA_{1C} reductions and improvements in several cardiovascular risk factors, including body weight, diastolic blood pressure, total cholesterol, and LDL cholesterol, over this time period. No new safety signals emerged during long-term use of exenatide QW.

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Author contributions

AP-T provided study supervision, reviewed the data, and participated in preparation of the manuscript. CHW provided study supervision, reviewed the data, and participated in preparation of the manuscript. EH participated in data interpretation and preparation of the manuscript. JH participated in the study design, writing the statistical analysis plan, data analysis, and preparation of the manuscript. NI participated in data interpretation and preparation of the manuscript.

Appendix A. Supplementary data

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