DURATION-1 Extension in Patients With Type 2 Diabetes: Efficacy and Tolerability of Exenatide Once Weekly Over 7 Years

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Introduction

- DURATION-1[1] was a 30-week, randomized, controlled, open-label study comparing the glucagon-like peptide-1 receptor agonists (GLP-1RAs) exenatide once weekly (QW) and exenatide twice daily (BID), followed by an open-label extension phase during which all patients received exenatide QW for 7 years
- This analysis of the open-label extension study assessed the efficacy and safety of exenatide QW after 7 years of treatment

Methods

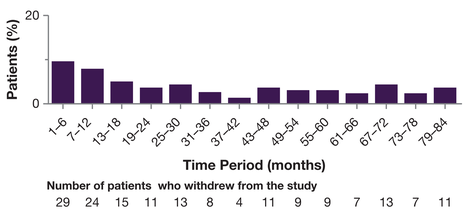
- Patients visited at least once in 4 weeks during the 30-week controlled period and at least once in 8 weeks during the extension period
- Glycemic and weight data were analyzed for the 7-year completer population (n=122), which included all patients exposed to exenatide for 364 weeks
  - Concomitant glucose-lowering medication use was recorded
- Missing data were managed by the last observation carried forward method
- Significance was assessed as follows:
  - ANOVA: adjusted for screening A1C stratum (<9% or ≥9%) and sulfonylurea use
  - ANCOVA: adjusted for baseline value of the variable examined, screening A1C stratum and sulfonylurea use
- Select efficacy measures were reported for a subgroup of the 7-year completers who did not add new glucose-lowering medications (n=65), but no comparisons were made to the 7-year completers

Results

Demographics and Disposition

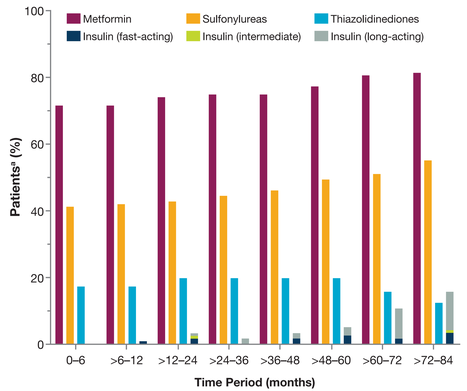
- Of the initial 295 patients in the intent-to-treat (ITT) population, 258 entered the open-ended assessment period and 122 completed 7 years
- The most common reasons for withdrawal during the open-ended assessment period were:
  - Withdrawal of consent: 72 patients (24.4%)
  - Adverse event: 17 patients (5.8%)
  - Investigator decision: 17 patients (5.8%)
  - Loss of glucose control: 12 patients (4.1%)
  - Lost to follow-up: 11 patients (3.7%)

Figure 1. Withdrawals Over Time



- Of the 122 7-year completers, 57 patients added and 65 patients did not add new concomitant glucose-lowering medications

Figure 2. Concomitant Glucose Lowering Medication Use Over Time Among 7-year Completers



[a]Patients were counted if they used a concomitant medication at any point in the time interval. Patients receiving multiple medications were included in all applicable concomitant medication groups.

- There were slight differences in the proportion of males and females and background glucose-lowering medication between 7-year completers overall and 7-year completers with no new concomitant glucose-lowering medications

Table 1. Baseline Characteristics

Parameter	Intent-to-Treat (n=295)	All 7-Year Completers (n=122)	7-Year Completers With no New Concomitant Glucose-Lowering Medications (n=65)
Males, n (%)	157 (53.2)	64 (52.5)	28 (43.1)
Age at consent, years	55.0 ± 9.7	56.3 ± 8.5	57.6 ± 7.9
Race, n (%)			
White	230 (78.0)	101 (82.8)	53 (81.5)
Black	28 (9.5)	15 (12.3)	8 (12.3)
Asian	1 (0.3)	1 (0.8)	1 (1.5)
Hispanic	36 (12.2)	5 (4.1)	3 (4.6)
Body weight, kg	101.8 ± 19.9	101.2 ± 18.1	99.3 ± 19.3
BMI, kg/m^2	34.9 ± 5.0	34.7 ± 4.7	34.3 ± 4.6
A1C, %	8.30 ± 1.0	8.17 ± 1.0	8.16 ± 1.0
FPG, mg/dL	169.4 ± 42.9	166.0 ± 42.1	165.6 ± 40.7
Duration of diabetes, years	6.7 ± 5.0	7.1 ± 5.6	7.5 ± 4.5

Data are mean ± standard deviation unless otherwise noted. BMI, body mass index; FPG, fasting plasma glucose; SU, sulfonylurea; TZD, thiazolidinedione.

Table 1. Baseline Characteristics (cont.)

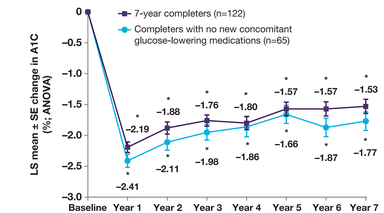
Parameter	Intent-to-Treat (n=295)	All 7-Year Completers (n=122)	7-Year Completers With no New Concomitant Glucose-Lowering Medications (n=65)
Diabetes management method at screening, n (%)			
SU-based therapy	109 (36.9)	49 (40.2)	24 (36.9)
SU only	16 (5.4)	9 (7.4)	3 (4.6)
SU + metformin	82 (27.8)	34 (27.9)	19 (29.2)
SU + TZD	10 (3.4)	5 (4.1)	2 (3.1)
SU + metformin + TZD	1 (0.3)	1 (0.8)	0 (0.0)
Non–SU-based therapy	186 (63.1)	73 (59.8)	41 (63.1)
Diet and exercise only	43 (14.6)	15 (12.3)	7 (10.8)
Metformin only	106 (35.9)	43 (35.2)	27 (41.5)
TZD only	9 (3.1)	6 (4.9)	1 (1.5)
Metformin + TZD	28 (9.5)	9 (7.4)	6 (9.2)

Data are mean ± standard deviation unless otherwise noted. BMI, body mass index; FPG, fasting plasma glucose; SU, sulfonylurea; TZD, thiazolidinedione.

Efficacy

- Significant reductions from baseline in A1C were seen over 7 years for all 7-year completers and 7-year completers with no new concomitant glucose-lowering medications

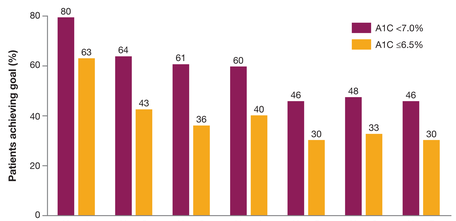
Figure 3. Change in A1C Over Time



*P<0.05. ANOVA, analysis of variance; LS, least squares; SE, standard error.

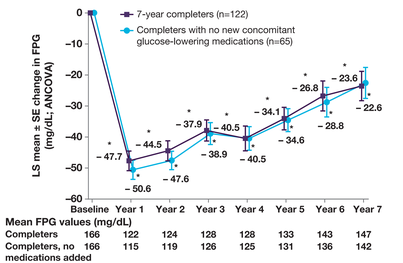
- Percentages of patients at goal decreased initially but was stable after Year 5

Figure 4. Percentages of Patients at Goal Over Time



- FPG remained significantly below baseline after 7 years

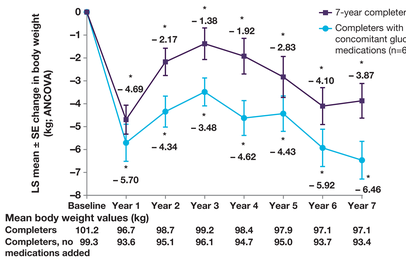
Figure 5. FPG Over Time



*P<0.05. ANCOVA, analysis of covariance; FPG, fasting plasma glucose; LS, least squares; SE, standard error.

- Reduction from baseline in body weight over 7 years was greater among 7-year completers with no new concomitant glucose lowering medications than all 7-year completers

Figure 6. Change in Body Weight Over Time

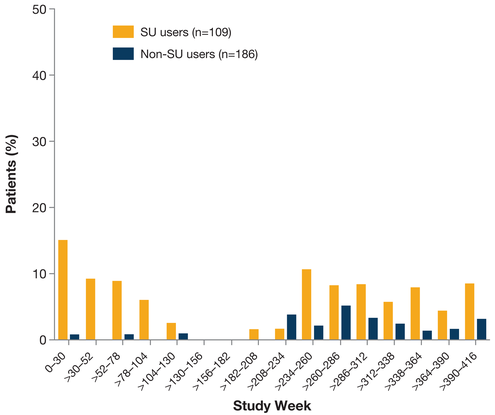


*P<0.05. ANCOVA, analysis of covariance; LS, least squares; SE, standard error.

Safety

- The incidence of AEs was similar for both the 7-year completer and ITT populations, with upper respiratory tract infection (53.3% and 45.7%, respectively), nasopharyngitis (41.0% and 29.1%, respectively), and diarrhea (36.1% and 26.7%, respectively) as the most frequent AEs
- Serious AEs occurred in 71 patients (25.5%) within the ITT population
  - Each type of serious AE occurred in ≤2% patients, with the exception of osteoarthritis, which occurred in 6 patients (2.2%)
- Nausea occurred in 105 (35.8%) patients during the first 30 weeks and in 74 (28.7%) patients thereafter
- No patients in the ITT population experienced major hypoglycemia
- Among the ITT population, minor hypoglycemia occurred more frequently with concomitant sulfonylurea use

Figure 7. Minor Hypoglycemia Over Time for the ITT Population



SU, sulfonylurea.

Conclusions

- These 7-year data represent the longest follow-up of patients with T2D treated with a GLP-1RA
  - Among patients completing 7 years of treatment, improvements in A1C, FPG, and weight from baseline were maintained throughout the observation period
- A gradual increase in A1C, FPG, and weight occurred over the 7-year extension period, which may represent disease progression
- More patients maintained glycemic control without than with additional glucose-lowering medication
- No new or unexpected safety findings were observed

References

1. Drucker DJ, et al. *Lancet*. 2008;372(9645):1240–1250.

Acknowledgments

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