Switching to once-daily liraglutide from twice-daily exenatide further improves glycemic control in patients with type 2 diabetes using oral agents

Short Running Title: Switching from exenatide to liraglutide

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**Objective:** To evaluate efficacy and safety of switching from twice-daily exenatide to once-daily liraglutide or of 40 weeks of continuous liraglutide therapy.

**Research Design and Methods:** When added to oral antidiabetes drugs (OADs) in a 26-week randomized trial (LEAD-6), liraglutide more effectively improved A1C, FPG, and HOMA-B than exenatide, with less persistent nausea and hypoglycemia. In this 14-week extension of LEAD-6, patients switched from twice-daily exenatide 10 µg to once-daily liraglutide 1.8 mg or continued liraglutide.

**Results:** Switching from exenatide to liraglutide further and significantly reduced A1C (0.32%), FPG (0.9 mmol/L), bodyweight (0.9 kg), and SBP (3.8 mmHg) with minimal minor hypoglycemia (1.30 episodes/patient-year) or nausea (3.2%). Among patients continuing liraglutide, further significant decreases in bodyweight (0.4 kg) and SBP (2.2 mmHg) occurred with 0.74 episodes/patient-year of minor hypoglycemia and 1.5% experiencing nausea.

**Conclusion:** Conversion from exenatide to liraglutide is well-tolerated and provides additional glycemic control and cardiometabolic benefits.
Glucagon-like peptide-1 (GLP-1) receptor agonists improve glycemic control and reduce weight with minimal risk of hypoglycemia (1,2). The first randomized head-to-head comparison of two GLP-1 receptor agonists added to oral antidiabetes agents (OAD) (Liraglutide Effect and Action in Diabetes [LEAD]-6) showed that once-daily liraglutide 1.8 mg provided greater improvements in A1C and fasting plasma glucose (FPG) with lower hypoglycemia and less persistent nausea compared with twice-daily exenatide 10 µg after 26 weeks; similar decreases in weight (≈3 kg) and systolic blood pressure (SBP; 2.0 to 2.5 mmHg) occurred with both drugs (3).

The objectives of this 14-week extension were to assess the safety and efficacy of switching from exenatide to liraglutide, or continuing liraglutide for up to 40 weeks.

RESEARCH DESIGN AND METHODS
The LEAD-6 design has been reported (3). Adults with type 2 diabetes inadequately controlled (A1C 7–11%) with maximally tolerated stable doses of metformin, sulfonylurea, or both for ≥3 months were randomized (1:1) to liraglutide 1.8 mg once-daily or exenatide 10 µg twice-daily. After 26 weeks, patients continued into a nonrandomized 14-week extension: all exenatide patients were switched to liraglutide 0.6 mg once-daily for 1 week, then escalated to 1.2 mg for another week, and then a final maintenance dose of 1.8 mg. Patients originally randomized to liraglutide 1.8 mg continued. Background OADs remained unchanged, although sulfonylurea doses could be decreased by 50% if unacceptable hypoglycemia occurred.

Visits occurred at weeks -2 (screening), 0 (randomization), 4, 8, 12, 20, 26, 34, and 40 for both groups. Efficacy and safety assessments during the extension phase (week 26 to 40) were identical to those previously described (3). Extension intention-to-treat (ITT) (all randomized patients exposed to trial product who entered the extension) and extension safety (all patients exposed to trial product who entered the extension) populations were used for efficacy and safety analyses, respectively. Changes from baseline (last available observation up to 26 weeks) to week 40 within each treatment group were analyzed by paired t-tests. Treatment groups were not compared. Post-baseline missing values were imputed using last observation carried forward (LOCF). Unless noted, mean (SE) values are presented. Significance was P<0.05.

RESULTS
All 389 patients completing 26 weeks entered the extension. Three patients that were not formally randomized were excluded from the extension ITT population. Demographics were well-matched between groups and similar to those previously reported (3). Overall, 376/389 patients (97%) completed the extension: 10/187 (5.3%) with exenatide→liraglutide and 3/202 (1.5%) continuing liraglutide withdrew. Withdrawals (n [%]) in the exenatide→liraglutide and liraglutide groups, respectively, were due to either adverse events (AEs) (6 [3.2%] and 0), ineffective therapy (0 and 2 [1.0%]), protocol noncompliance (0 and 1 [0.5%]), meeting withdrawal criteria (1 [0.5%] and 0), or other reasons (3 [1.6%] and 0). Demographic and screening characteristics were similar between patients who withdrew during the extension and those who completed, with the exception of mean duration of diabetes that was longer for those withdrawing (12.2 years) than completers (7.9 years).

Efficacy: Mean A1C further decreased from 7.2% at week 26 to 6.9% at week 40 (-0.32±0.043%; P<0.0001) after switching from exenatide to liraglutide, but remained similar with continued liraglutide (7.0% to 6.9%; -
0.06±0.041%, \( P=0.1222 \) (Figure 1A). Additional patients reached A1C targets after switching from exenatide to liraglutide (Figure 1B).

After switching from exenatide to liraglutide, further reductions in FPG (Figure 1C; -0.9±0.16 mmol/L, \( P<0.0001 \)), bodyweight (Figure 1D; -0.9±0.15 kg, \( P<0.0001 \)), and SBP (Figure 1E; -3.8±0.84 mmHg \( P<0.0001 \)) occurred while the homeostasis model of beta-cell function (HOMA-B) assessment increased (14.5±4.4%, \( P=0.001 \)), consistent with the FPG reductions. In those continuing liraglutide, reductions in FPG (Figure 1C; -0.2±0.11 mmol/L, \( P=0.0973 \)), bodyweight (Figure 1D; -0.4±0.15 kg, \( P=0.0089 \)) and SBP (Figure 1E; -2.2±0.88 mmHg, \( P=0.0128 \)) occurred. No significant changes in postprandial glucose (except after lunch with exenatide\( \rightarrow \)liraglutide \(-0.64±0.21 \) mmol/L, \( P=0.0032 \)), DBP, fasting insulin, fasting C-peptide, proinsulin:insulin ratio, or HOMA-IR occurred in either group.

**Safety** Similar numbers of patients reported \( \geq 1 \) AEs during the extension (exenatide\( \rightarrow \)liraglutide: 70 [37.4%] and liraglutide: 76 [37.6%]). Most AEs were mild in severity (exenatide\( \rightarrow \)liraglutide: 79/117 events, liraglutide: 81/120 events); investigators assessed most as unrelated to trial drug (exenatide\( \rightarrow \)liraglutide: 72/117 events, liraglutide: 94/120 events). Nausea and diarrhea occurred in 3.2% of patients switching from exenatide\( \rightarrow \)liraglutide and 1.5% for continuing liraglutide while vomiting was 0.5% with exenatide\( \rightarrow \)liraglutide and 2.0% for continuing liraglutide. One major hypoglycemic episode occurred in a patient continuing liraglutide while extension rates (episodes/patient-year) of minor hypoglycemia were 1.30 (exenatide\( \rightarrow \)liraglutide), down from 2.60 with exenatide at week 26 (3), and 0.74 (liraglutide). Thirteen AEs associated with withdrawal from the extension of six patients in the exenatide\( \rightarrow \)liraglutide group were myocardial infarction, diarrhea (three events), impaired gastric emptying, eructation, nausea, lethargy, paraesthesia, anxiety, depressed mood, depression, and dyspnea. For two of these six patients, the AEs associated with their withdrawal from the extension (nausea and diarrhea) had been previously reported as separate events during the 26-week exenatide treatment period.

Four patients in the exenatide\( \rightarrow \)liraglutide group had seven SAEs (cardiac failure, myocardial infarction, cataract, chest discomfort, chronic obstructive pulmonary disease [two events], dyspnea). Five patients continuing liraglutide had eight SAEs (cerebral infarction, cerebrovascular accident, transient ischemic attack, acute coronary syndrome, coronary artery occlusion, portal vein thrombosis, rectal cancer, depression). Two deaths occurred (exenatide\( \rightarrow \)liraglutide: myocardial infarction after 198 days of treatment; liraglutide: cerebral infarction [patient completed the study but died shortly after]). Investigators assessed all events as ‘unlikely’ to be related to trial product. Calcitonin levels remained at the lower level of the normal range (<1 pg/mL) and did not differ between groups. No medullary thyroid carcinoma or pancreatitis cases were reported during the extension.

**CONCLUSIONS** This extension shows that patients can be simply and safely switched from twice-daily pre-meal exenatide to meal-independent, once-daily liraglutide using weekly dose escalation from 0.6 mg to 1.2 mg to 1.8 mg. Conversion to liraglutide from exenatide was well-tolerated and further improved glycemic control. Additional reductions in bodyweight and SBP occurred in both groups. Over 40 weeks, liraglutide reduced A1C by 1.3%. The magnitude of these changes and differences between liraglutide and exenatide
are consistent with results reported in phase 3 LEAD (liraglutide) (3–8) and exenatide (9–11) trials. The greater efficacy of liraglutide may be due to sustained levels achieved over 24 hours by once-daily dosing compared with biphasic levels achieved during the 2.4-hour half-life of exenatide after dosing within 1 hour of breakfast and dinner (12).

Further studies are required to investigate the durability of these responses. Given the likely preference for once-daily, meal-independent dosing, liraglutide appears to be a useful addition to the diabetes treatment armamentarium.

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REFERENCES


Figure 1. Effect of switching from exenatide to liraglutide or continuing liraglutide on various measures of efficacy (extension ITT population). A. A1C over time; B. Percentage of patients reaching A1C targets at week 26 (after the main part of the trial) and week 40 (after the exenatide group switched to liraglutide for 14 weeks); C. Fasting plasma glucose (FPG) over time; D. Bodyweight over time; and E. Systolic blood pressure (SBP) over time. All patients originally in the exenatide group switched to liraglutide at week 26, whereas the liraglutide group continued liraglutide. Maroon represents liraglutide and blue exenatide. In panel B, the white line within each bar indicates the percentage of patients reaching A1C targets at week 26 and the top of the bar indicates the percentage reaching A1C targets at week 40. In panels A and C-E, dotted maroon lines indicate patients who switched from exenatide to liraglutide at week 26. Values are mean (± SE) with last observation carried forward imputation for post-baseline timepoints.