LIXISENATIDE and iGlarLixi (insulin glargine/lixisenatide fixed-ratio combination)

FOR THE TREATMENT OF TYPE 2 DIABETES MELLITUS

ERRATUM TO THE BRIEFING DOCUMENT FOR THE ENDOCRINOLOGIC AND METABOLIC DRUGS ADVISORY COMMITTEE

MEETING DATE: 25 May 2016

AVAILABLE FOR PUBLIC RELEASE

This document is an erratum for the following sections of the Advisory Committee briefing document.

Page 46: Study design figure for EFC12405 found in Section 2.9.2 Study EFC12405 (previously insulin-treated)

The original Advisory Committee briefing document includes a figure of the study design for Study EFC12404 instead of Study EFC405 (Figure 1). The correct figure is provided below with accompanying text.

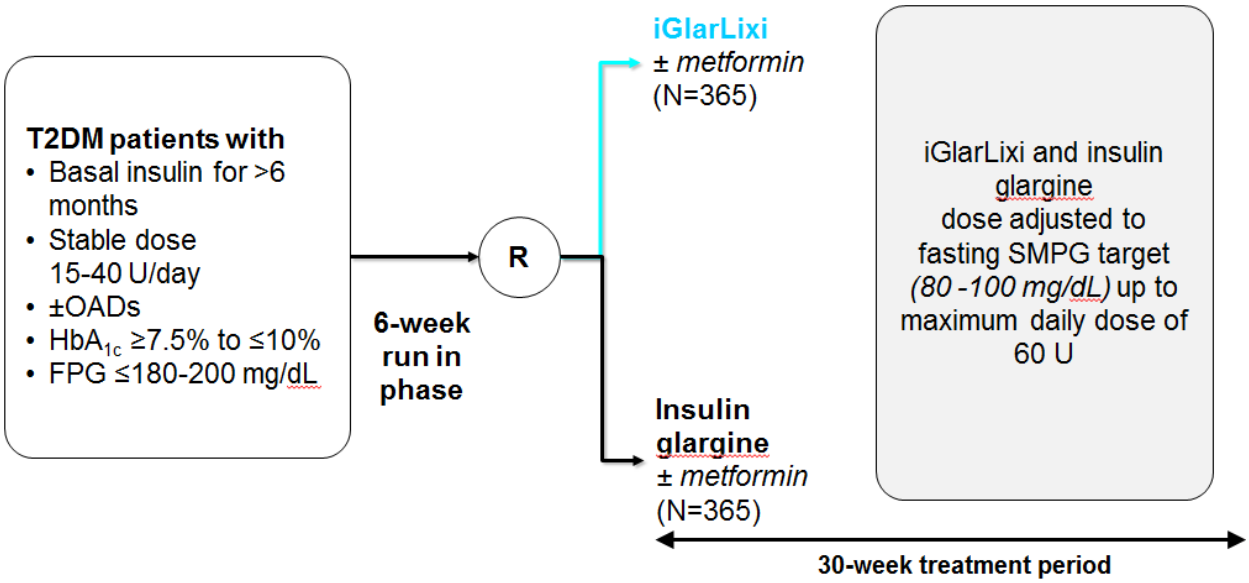
Study EFC12405 (previously insulin-treated)

Patients who were suboptimally controlled on basal insulin ± 1 or 2 OADs were enrolled in a 6-week run-in to introduce and/or titrate insulin glargine while continuing metformin (if previously taken) and discontinuing other OADs. If at the end of the run-in, patients met the inclusion and exclusion criteria (fasting SMPG ≤140 mg/dL, HbA1c ≥7% and ≤10%, daily average insulin glargine dose ≥20 U or ≤50 U), they were randomized 1:1 to iGlarLixi or insulin glargine (Figure 1).

During the treatment period, patients were titrated to the same fasting SMPG targets in each arm (80 to 100 mg/dL, inclusive); daily insulin glargine doses were capped at 60 U in both arms. iGlarLixi was self-administered QD in the morning, in the hour before breakfast. Insulin glargine was self-administered QD at any time of the day but at about the same time every day.

The primary endpoint was change from baseline in HbA1c at Week 30 and the primary efficacy hypothesis was statistical superiority of iGlarLixi versus insulin glargine.

Figure 1 – EFC12405: Study design

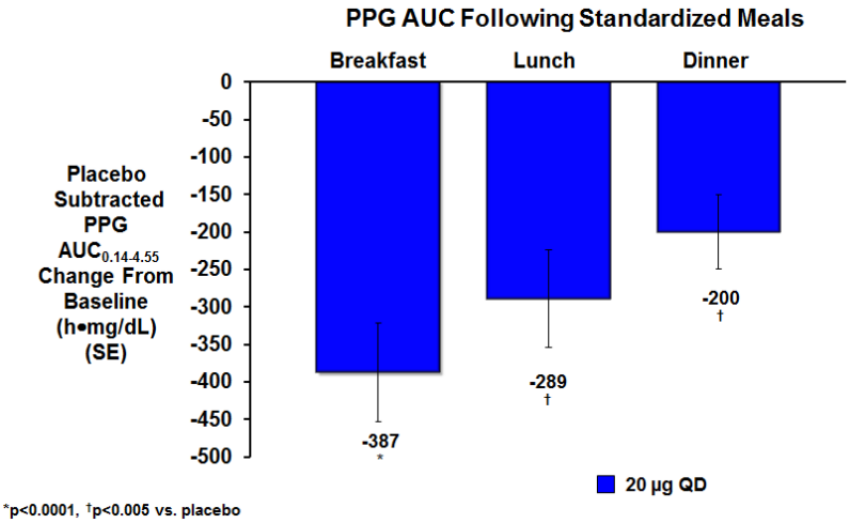


Corrections/revisions/additions for the following sections are provided in **bolded red text**.

- **Page 27 (third paragraph): Duration of postprandial effect of lixisenatide**

When lixisenatide was injected before breakfast, the reduction in PPG levels was due to a strong effect on gastric emptying. At later meals of the day, other mechanisms of glucose-lowering such as increased insulin secretion or decreased glucagon release, which are known for lixisenatide and other GLP-1 receptor agonists, likely contributed to the reduction in plasma glucose observed at lunch and especially, dinner (**Figure 7**).

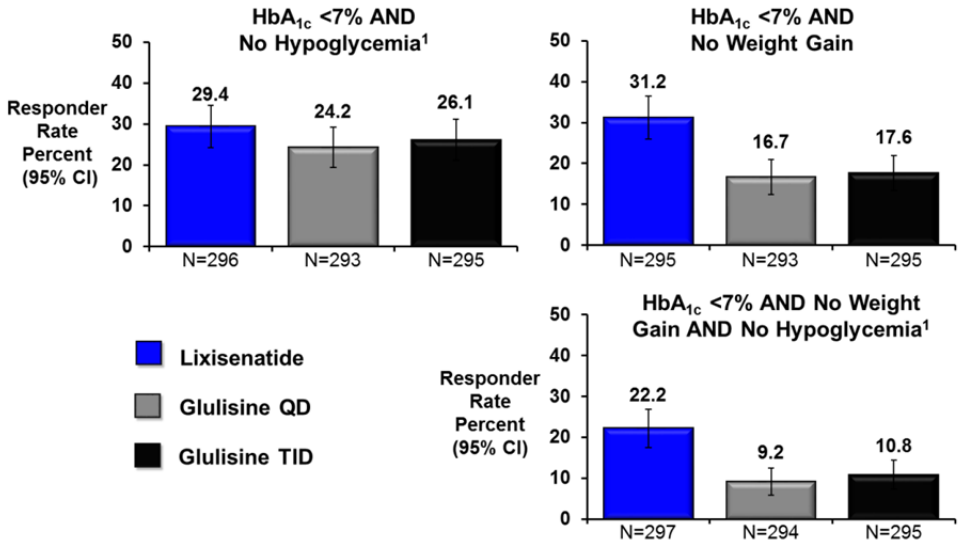
Figure 7 – Effect of lixisenatide (20 µg once-daily) injected before breakfast on postprandial glucose exposure throughout the day



- **Page 41 (second paragraph): Section 2.8.4 Efficacy of lixisenatide versus prandial insulin added on to insulin glargine**

The proportion of patients reaching HbA1c <7.0% without body weight gain was greater for lixisenatide (Figure 18). The proportion of patients reaching glycemic target without body weight gain and without documented symptomatic hypoglycemia (plasma glucose **<60 mg/dL**) was also greater for lixisenatide: twice as many patients achieved this endpoint with lixisenatide QD versus either prandial insulin regimen (Figure 18).

Figure 18 – Study EFC12626: Composite efficacy endpoints (change in HbA1c/body weight, incidence of documented symptomatic hypoglycemia)



- **Page 50 (fourth paragraph in Section 2.9.4): Efficacy of iGlarLixi by daily insulin glargine dose levels - Patient distribution across end-of-study insulin glargine daily dose-categories**

In Study EFC12404 (insulin-naïve), the majority of patients were using a final daily dose between 20 and 60 U of insulin in both the iGlarLixi and insulin glargine groups (Table 1). A total of 58 (12%) patients in the iGlarLixi group and **39 (8%)** patients in the insulin glargine group were using a final daily dose of insulin less than 20 U, which corresponded to a daily lixisenatide dose between 5 and 10 µg. Only Study EFC12404 **had a sufficient number of patients to evaluate** in this lowest daily dose category.

- **Page 58 (last primary bullet point): Safety in the lixisenatide Phase 3 placebo-controlled study pool**

Immunogenicity based on anti-lixisenatide antibodies: The percentage of lixisenatide-treated patients with common TEAEs was similar in anti-drug antibody-positive patients (71.2%) and anti-drug antibody-negative patients (68.8%), compared with a percentage of **62.3%** in the placebo group.

- **Page 59 (first bullet point): Safety in the lixisenatide Phase 2/3 study pool**

In the Phase 2/3 all-controlled studies, the percentage of patients with any pancreatitis TEAE in the High Level Term of acute and chronic pancreatitis was 0.3% (21 patients) for lixisenatide and 0.2% (14 patients) for all comparators. The exposure adjusted incidence rate per 100 patient-years was 0.21 for lixisenatide and 0.17 for all comparators.

- **Page 64 (last paragraph): Safety findings for iGlarLixi**

Thus iGlarLixi provides benefits for the management of T2DM: no additional risk of hypoglycemia compared to insulin glargine alone (Section 6.9.1.2), attenuation of the GI effects typical of the GLP-1 receptor agonist class (Section 6.8.1), and mitigation of the body weight gain that can accompany insulin use (**Section 4.2.3.2.3** and **Section 4.3.3.2.3**).

- **Page 86 (second paragraph in Section 3.4): Study EFC12626 - Efficacy of lixisenatide versus prandial insulin added on to insulin glargine**

Study design and methods: Patients that had exhausted most therapeutic options and were insufficiently controlled with basal insulin ± OADs underwent a 12-week run-in period; insulin glargine therapy was optimized and OADs other than metformin were discontinued. Patients who met the post run-in inclusion and exclusion criteria (N=894) were randomized **1:1:1** to lixisenatide 20 µg QD or to prandial insulin glulisine (QD or TID) (all arms ± metformin) for 26 weeks of treatment (Figure 14).

- **Page 152 (second paragraph in Section 6.8.2): Common TEAEs by baseline characteristics (iGlarLixi program)**

The incidence of common TEAEs in the iGlarLixi and insulin glargine treatment groups were similar in patients with normal renal function (53.8% versus 48.5%, respectively; combined N=1177) and in patients with mild renal impairment (56.5% versus 54.0%, respectively; combined N=433). The incidence was numerically higher in patients with **moderate** renal impairment but the combined number of patients was low (N=56).

- **Page 156 (first paragraph): Pancreatic enzymes (iGlarLixi program)**

There were no events of pancreatitis in the Phase 2/3 iGlarLixi program (**Section 6.9.4.2**).

- **Page 159 (second paragraph): Symptomatic hypoglycemia (lixisenatide program) - Basal insulin +/- metformin as background therapy (EFC6016, ~~EFC10887~~)**

The incidence of symptomatic hypoglycemia over the entire treatment period (EFC6016 only) was 42.1% with lixisenatide and 38.9% with placebo, with a relative risk of lixisenatide versus placebo of 1.08 (95% CI: 0.86, 1.36). **Over the entire treatment period, 7 patients (2.1%) in the lixisenatide group and 1 patient (0.6%) in the placebo group experienced severe symptomatic hypoglycemia.**

~~There were 5 (3.6%) patients in the lixisenatide group and 3 (4.6%) patients in the placebo group with >25 events.~~ ~~There were 3 additional patients on lixisenatide who had severe symptomatic hypoglycemia (1 of whom was receiving rapid acting insulin as rescue therapy) and 1 patient on placebo.~~

- **Page 161 (second paragraph): Symptomatic hypoglycemia (lixisenatide program) - Basal insulin (insulin glargine optimally titrated) +/- metformin (EFC12626).**

In this 26-week study, patients previously treated with basal insulin were randomized to lixisenatide or insulin glulisine QD or insulin glulisine TID added to insulin glargine optimally titrated, with or without metformin. Symptomatic hypoglycemia **defined per the protocol** was reported for 98 (32.9%) patients on lixisenatide, 117 (38.9%) patients on insulin glulisine QD, and 132 (44.9%) patients on insulin glulisine TID (Table 46). The relative risk for lixisenatide was 0.85 (95% CI: 0.68, 1.05) versus insulin glulisine QD and 0.73 (95% CI: 0.60, 0.90) versus insulin glulisine TID (Figure 56). There were 2 (0.7%) patients in the insulin glulisine QD group with severe symptomatic hypoglycemia. The majority of symptomatic hypoglycemic events in all 3 groups occurred between 23:00 and <10:00: 217/332 (65.4%) events in the lixisenatide group, 247/395 (62.5%) events in the insulin glulisine QD, and 300/600 (50.0%) in the insulin

glulisine TID group. There were 5 patients who had > 25 events: 1 (0.3%) patient on lixisenatide, 1 (0.3%) patient on insulin glulisine QD, and 3 (1.0%) patients on insulin glulisine TID.

Page 178 (third paragraph of Section 6.9.6.2): iGlarLixi program

The integrated analysis of anti-lixisenatide antibody data was based on the Phase 3 study pool and on EFC12404. **In all patients treated with lixisenatide (including as part of iGlarLixi),** the proportion of antibody-positive patients increased from baseline over 30 weeks (from 4-5.1% to 42.8-56.8%).