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

FOR THE TREATMENT OF TYPE 2 DIABETES MELLITUS

BRIEFING DOCUMENT FOR THE ENDOCRINOLOGIC AND METABOLIC DRUGS ADVISORY COMMITTEE

MEETING DATE: 25 May 2016

ADVISORY COMMITTEE BRIEFING MATERIALS:
AVAILABLE FOR PUBLIC RELEASE

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ABBREVIATIONS

ACS	Acute coronary syndrome
ADA	Anti-drug antibody
AE	Adverse event
ANCOVA	Analysis of covariance
ARAC	Allergic reaction assessment committee
AUC	Area under the curve
BI	Basal insulin
BID	Twice daily
BMI	Body mass index
BOCF	Baseline observation carried forward
CAC	Cardiovascular Events Adjudication Committee
CI	Confidence interval
Cmax	Maximal plasma concentration
CMH	Cochran-Mantel-Haenszel
CV	Cardiovascular
EAIR	Exposure-adjusted incidence rate
FDA	Food And Drug Administration
FPG	Fasting plasma glucose
eGFR	Estimated glomerular filtration rate
GI	Gastrointestinal
GLP-1	Glucagon-like peptide-1
HbA1c	Glycosylated hemoglobin
HLT	High level term
IMP	Investigational medicinal product
ITT	Intent-to-treat
LLOQ	Lower limit of quantification
LOCF	Last observation carried forward
LS	Least square
MAR	Missing at random
MedDRA	Medical Dictionary of Regulatory Activities
mITT	Modified intent-to-treat
MMRM	Mixed-effect model with repeated measures
MNAR	Missing not at random
NDA	New Drug Application
nmol	Nanomole
OAD	Oral antidiabetic drug
PCSA	Potentially clinically significant abnormality
PK	Pharmacokinetic
PPG	Postprandial plasma glucose
PY	Patient-years
QD	Once daily
SD	Standard deviation
SE	Standard error
SMPG	Self-monitored plasma glucose
SU	Sulfonylurea

T2DM	Type 2 diabetes mellitus
TEAE	Treatment-emergent adverse event
TID	Thrice-daily
Tmax	Time to maximal concentration
TZD	Thiazolidinedione
ULN	Upper limits of normal
US	United States
WHO	World Health Organization

1 READERS GUIDE TO THE BRIEFING BOOK

This Briefing Book will provide information on the lixisenatide and iGlarLixi clinical development programs, which will be assessed at the Endocrinologic and Metabolic Drugs Advisory Committee Meeting on 25 May 2016.

Lixisenatide and iGlarLixi are being reviewed for approval in patients with type 2 diabetes mellitus (T2DM).

- Lixisenatide is a glucagon-like peptide-1(GLP-1) receptor agonist that has been studied as monotherapy and as add-on therapy to oral antidiabetic drugs (OADs) and basal insulin.
- iGlarLixi is a fixed-ratio combination of lixisenatide and basal insulin glargine (Lantus®, 100 U/mL); it has been studied in patients who would benefit from initiation or intensification of insulin therapy. iGlarLixi has also been nicknamed "LixiLan" and in publicly available information, the reader will primarily find references to LixiLan. In its regulatory submission, the Sponsor referred to iGlarLixi as the Fixed-Ratio Combination or FRC.

The primary reason for the Advisory Committee meeting is to discuss certain aspects of iGlarLixi. Since lixisenatide is currently under review, the Food and Drug Administration (FDA) has asked the Sponsor to provide an overview of the benefits and risks of lixisenatide, in addition to a discussion of the combination product. Lantus, the other component of the combination is a well known product with an established safety profile including a large cardiovascular (CV) outcomes study (ORIGIN) and will be only briefly discussed in this document.

The Executive Summary is a concise review of both clinical development programs and should provide the reader with the relevant efficacy and safety data. Furthermore, results of additional analyses that address topics the Agency has raised in their review of the NDAs are presented in this section. The benefit/risk conclusions are presented at the end of the Executive Summary.

More detailed efficacy and safety data are provided in the subsequent sections of the Briefing Book and the reader is advised to use the table of contents as a guide to select sections of interest. The lixisenatide efficacy information focuses on the studies of lixisenatide in combination with basal insulin, as they are most relevant to iGlarLixi.

The majority of the safety presented in the Briefing Book is from the lixisenatide development program, which has assessed the larger number of patients and has greater patient-years of exposure as compared to iGlarLixi. The recently completed ELIXA study demonstrated the CV safety of lixisenatide in patients with T2DM who had recently experienced an acute coronary syndrome (Section 6.5) (1). Due to the differing types of comparators, the safety data are presented separately for lixisenatide, the ELIXA study, and iGlarLixi.

Whenever insulin glargine is mentioned in this Briefing Book, the product referred to is insulin glargine (100 U/mL, Lantus). Insulin glargine (300 U/mL, Toujeo) was not used in the development programs of lixisenatide or iGlarLixi.

2 EXECUTIVE SUMMARY

2.1 MANAGEMENT OF T2DM IN 2016

The risk of micro- and macrovascular complications of diabetes is directly related to the duration and magnitude of hyperglycemia. Achieving glycemic control early and maintaining glycemic control despite the progressive nature of the disease is therefore the cornerstone of the professional guidelines for the treatment of T2DM. Despite the availability of many oral and injectable therapies, the management of patients with T2DM remains challenging. In particular, the management of patients uncontrolled on OADs is a challenge for physicians. Due to concerns about the potentially unfavorable consequences associated with initiation and intensification of insulin therapy, including weight gain and an increased risk of hypoglycemia, glycemic control is left unchecked in a substantial proportion of patients (2, 3, 4). The median time to treatment intensification with basal insulin in patients with HbA1c ≥7.0% taking 2 or 3 OADs was >7 years (2). Even after initiation of basal insulin many patients remain uncontrolled because insulin only affects one of the contributors to elevated glycosylated hemoglobin (HbA1c) levels, i.e., fasting plasma glucose (FPG).

Patients already treated with basal insulin who remain suboptimally controlled represent an additional unmet need as noted in current treatment guidelines (5, 6). Even after initiation of insulin therapy, periodic intensification, including the use of more complex regimens (e.g., basal-bolus insulin) will be required for a substantial proportion of patients.

With the availability of today's numerous glucose-lowering tools, and the recognition of the importance of an individualized, patient-centered approach to diabetes care, many factors will need to be considered before making a therapeutic decision. For instance, whether a therapeutic option has an effect on fasting glucose, or postprandial glucose, or even both is a logical consideration. Other aspects such as mitigation of unfavorable side effects have to be considered as they are important for patient acceptance and adherence. Therefore, a physician faced with a patient needing treatment intensification will incorporate considerations with respect to improvements in glycemic control, beneficial effects on weight, and the expectation that these benefits will be achieved without the costs of an increased risk of hypoglycemia or adverse events (AEs) that may lead to permanent treatment discontinuation. Given the multiple medications many patients with T2DM are using, therapeutic simplicity should be another important consideration for physicians when intensifying therapy.

2.2 INTRODUCTION TO LIXISENATIDE AND IGLARLIXI

2.2.1 Lixisenatide

The role of lixisenatide in T2DM

Patients requiring management of postprandial glycemic excursions are in need of a simple solution that primarily addresses the prandial component of hyperglycemia.

A large body of clinical trial data demonstrates that lixisenatide is safe and effective in the treatment of T2DM and provides:

- Clinically relevant reductions in HbA1c that are primarily mediated by
- Robust reductions in postprandial glucose (PPG) levels, with
- A beneficial effect on body weight, including in patients receiving concomitant basal insulin, and
- A low risk of hypoglycemia as monotherapy or in combination with metformin or a thiazolidinedione and a limited additional risk in combination with a SU or basal insulin

Lixisenatide, due to its pronounced prandial effects, has been shown to provide an effective add-on to basal insulin therapy.

Lixisenatide is a once-daily (QD) GLP-1 receptor agonist that was approved in 2013 in the European Union (EU) for the treatment of adults with T2DM to achieve glycemic control in combination with oral glucose-lowering medicinal products and/or basal insulin. Lixisenatide is currently approved in over 60 countries worldwide.

The proposed indication in the United States is as an adjunct to diet and exercise to improve glycemic control in adults with T2DM.

The lixisenatide Phase 3 clinical trial program has shown that lixisenatide was effective in improving glycemic control when given as monotherapy, as an add-on to OADs, or as an add-on to basal insulin. Lixisenatide significantly reduces HbA1c by providing robust reductions in PPG levels with less of an effect on FPG. As the PPG-lowering effect of lixisenatide is associated with the slowing of gastric emptying (Section 2.5.1.3) and the insulinotropic effect is glucose-dependent, it is associated with a low risk of hypoglycemia.

A tabular summary of studies in the lixisenatide clinical development program is provided in Section 8.1.

2.2.2 Insulin glargine (100 U/mL)

Insulin glargine (100 U/mL, Lantus) was approved in the United States and Europe in 2000 and has been marketed worldwide. Extensive safety and exposure data are currently available for this product including a large CV outcomes study, the ORIGIN (Outcome Reduction with Initial Glargine INtervention) study (7). A total of 12,537 adult patients (mean age, 63.5 years) with high

CV risk plus impaired fasting glucose, impaired glucose tolerance, or T2DM were randomized 1:1 to receive insulin glargine 100 U/mL (titrated to a FPG of 95 mg/dL or less) or standard of care. The first co-primary outcome was the composite of death from CV causes, nonfatal myocardial infarction, or nonfatal stroke; the second co-primary outcome was the composite of any of these events, a revascularization procedure, or hospitalization for heart failure.

The median follow-up was 6.2 years. Rates of incident CV outcomes were similar in the insulin glargine and standard care groups: 2.94 and 2.85 per 100 person-years, respectively, for the first co-primary outcome (hazard ratio, 1.02; 95% confidence interval [CI], 0.94 to 1.11; p=0.63) and 5.52 and 5.28 per 100 person-years, respectively, for the second co-primary outcome (hazard ratio, 1.04; 95% CI, 0.97 to 1.11; p=0.27). There were no differences between insulin glargine and standard care for the two co-primary outcomes, for any component endpoint comprising these outcomes, or for all-cause mortality. In addition, the incidence of cancer was similar between the two treatment groups.

Because Lantus has been approved for many years and has a well-established benefit-risk profile, it will not be discussed further in this Briefing Book.

2.2.3 iGlarLixi

The role of iGlarLixi in T2DM

- There is a need for new therapies that provide greater reductions in HbA1c, addressing both elevated fasting and PPG levels, the two components of elevated HbA1c levels. The current step-wise approach faces challenges related to treatment complexity (i.e., number of injection), weight gain, and fear of hypoglycemia.
- iGlarLixi was developed to combine the complementary actions of insulin glargine (100 U/mL) which primarily targets FPG, and lixisenatide which primarily reduces PPG levels. The development program demonstrated that iGlarLixi provides:
  - A significantly larger effect on both HbA1c and PPG as compared to treatment with insulin glargine
  - A reduction or mitigation of the weight gain typically associated with insulin glargine, and fewer gastrointestinal (GI) side effects compared to treatment with a GLP-1 receptor agonist alone
  - No additional risk of hypoglycemia compared to insulin glargine alone
- iGlarLixi offers an advantage over existing modalities of treatment intensification by improving glycemic control with a once-daily dual antihyperglycemic therapy delivered in a single pen-injector. This treatment has been shown to benefit patients uncontrolled with OADs in whom initiation of insulin is desirable, as well as patients already on basal insulin ± OAD(s) who are not meeting glycemic goals.

iGlarLixi is a titratable fixed ratio-combination of long-acting insulin glargine (100 U/mL) (Lantus®) and the GLP-1 receptor agonist lixisenatide.

The proposed indication is as an adjunct to diet and exercise to improve glycemic control in adults with T2DM when treatment with both insulin glargine and lixisenatide is appropriate. The daily dose-range for insulin glargine is 10 to 60 U corresponding to a lixisenatide dose-range of 5 to 20 µg.

A tabular summary of studies in the iGlarLixi clinical development program is provided in Section 8.2.

2.3 REGULATORY HISTORY

Lantus® was approved in the United States (US) and Europe in 2000 and has been marketed worldwide. Extensive safety and exposure data are currently available for this product including a large CV outcomes study (7).

Lixisenatide was granted marketing authorization in the European Union in February 2013 as an add-on treatment to OADs and/or basal insulin in adults with T2DM. Lixisenatide is currently approved in more than 60 countries worldwide.

The New Drug Application (NDA) for lixisenatide was submitted on 20 December 2012 followed by the submission of the interim analysis data from the ELIXA CV outcomes trial by a fire-walled group at Sanofi on the same day. During the review of the application, the FDA notified the sponsor of the intent to hold an Advisory Committee meeting.

The NDA was withdrawn on 10 September 2013 in advance of the scheduled Advisory Committee due to concerns that any public disclosure of interim data could jeopardize completion of the trial. The lixisenatide NDA was resubmitted to the FDA on 27 July 2015 with the inclusion of final results from ELIXA.

Based on experience with Lantus and lixisenatide, Sanofi began investigating the combination of a fixed-ratio for both insulin-naïve patients and those needing intensification of insulin therapy. Since 2013, Sanofi has had extensive communications with the FDA, including written advice on the fixed-ratio program that confirmed the pivotal study endpoints as well as the clinical, quality, and regulatory strategy for iGlarLixi.

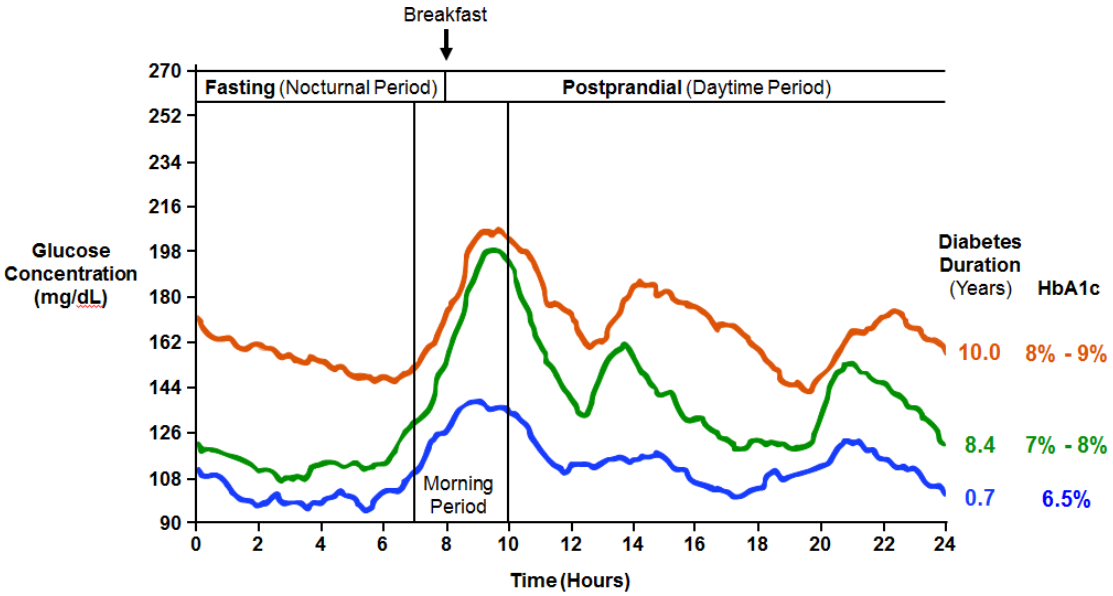
2.4 UNMET NEED IN T2DM - RELATIVE ROLES OF FPG AND PPG

Pathophysiologically, T2DM is characterized by a gradual and progressive deterioration in β cell function together with a reduced sensitivity to insulin (8, 9). As insulin levels decline, suppression of hepatic glucose output is reduced, contributing to the hyperglycemic burden. Early in disease development when patients are typically on one or more OADs, postprandial hyperglycemia predominates, with FPG levels in the near-normal range (10, 11). Gradually, basal glycemic levels increase over time and in most patients a dual deficit develops that encompasses both PPG and FPG (Figure 1) (11, 12, 13).

As seen in the continuous glucose monitoring of patients with T2DM at various phases in the evolution of the disease (13), the largest blood glucose excursions occur in the morning

(Figure 1), partly due to diurnal variations in insulin sensitivity, and must be considered in the choice of treatment.

Figure 1 – The relative roles of FPG and PPG over the course of T2DM

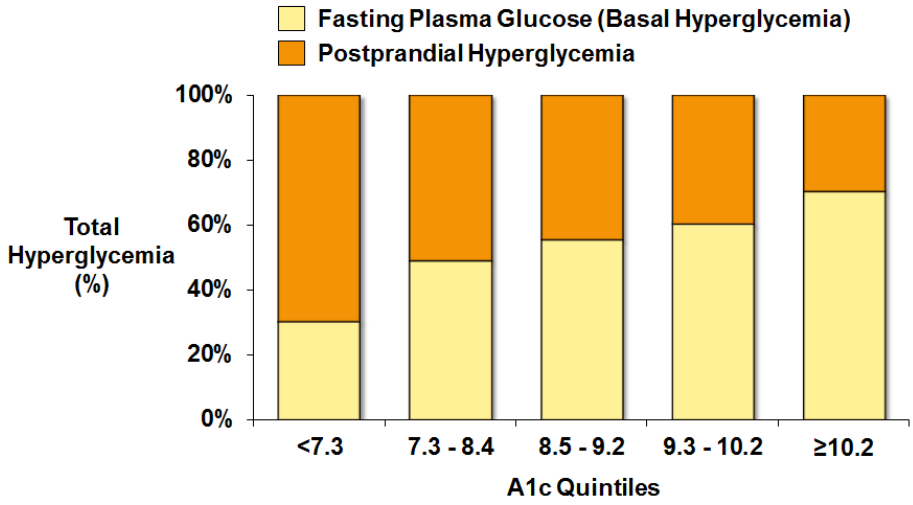


Based on 24-hour recordings of continuous glucose monitoring in 3 groups of patients with T2DM at various phases in the evolution of the disease.
Monnier et al. Diabetes Care. 2007 Feb;30(2):263-9.

Early therapeutic strategies tend to target basal hyperglycemia, but this approach eventually fails to provide sufficient glycemic control because of a residual postprandial deficit (Figure 1). A survey of 2208 patients with T2DM from a United States (US) Health Care provider (GE Centricity) found that 36.2% of patients did not meet a treatment goal of HbA1c <7.0%. Of these, approximately two-thirds had a fasting glucose <140 mg/dL.

Monnier et al (Figure 2) showed that at all levels of elevated HbA1c, PPG excursions contribute to hyperglycemia and that the closer a patient is to goal, the more dominant is the PPG contribution (10, 11). In this context, a therapy that can lower PPG or a combination treatment that addresses both FPG and PPG would be a rational choice.

Figure 2 - Relative contribution of fasting and postprandial hyperglycemia to HbA1c levels



Monnier L et al. Diabetes Care. 2003;26:881-885.

Patients uncontrolled on OADs

Patients suboptimally controlled on one or more oral antidiabetic therapies now have the choice per current treatment guidelines (5, 6) of adding either insulin, which carries the risks of weight gain and hypoglycemia, or a GLP-1 receptor agonist, which carries a low risk of hypoglycemia and the potential for weight loss/neutrality but with GI side effects early in the treatment period. Lixisenatide provides an attractive option for those patients who primarily need improved PPG control (Section 2.8]). For those patients needing both improved FPG and PPG control, iGlarLixi is an effective option (Section 2.9).

Patients uncontrolled on basal insulin

Patients with suboptimal control already receiving basal insulin have limited treatment options: adding rapid-acting mealtime insulin 1 to 3 times per day, transferring to twice-daily (BID) injected insulin mix products, or adding a separately administered non-titratable GLP-1 receptor agonist. The prandial addition of rapid-acting insulin up to 3 times a day to prevent PPG excursions is frequently employed. Although this approach can be effective, it has several drawbacks, including treatment complexity, frequent blood glucose monitoring and carbohydrate counting, an increased risk of hypoglycemia, and weight gain.

Lixisenatide is an alternative to prandial insulin because it can improve and simplify the overall management of patients who need intensification of basal insulin. A randomized, controlled trial (N=894) compared the effects of the addition of lixisenatide or prandial regimens of a rapid-acting insulin (once daily [QD] or thrice daily [TID]) to patients suboptimally controlled on basal insulin ± OADs (Section 2.8.4). In this trial, lixisenatide provided comparable reductions in HbA1c over 26 weeks versus both prandial insulin regimens, but with less symptomatic hypoglycemia. Lixisenatide was also associated with significant weight loss as compared to weight gain for both prandial insulin regimens.

As shown in the Phase 3 program, iGlarLixi can further simplify treatment intensification. As a once-daily dual combination therapy delivered simultaneously in a single pen-injector, iGlarLixi offers:

- More robust glycemic control, as evinced by lower HbA1c levels, than with insulin glargine or lixisenatide alone
- Attenuation of common side effects such as weight gain as compared to insulin glargine and GI side effects as compared to lixisenatide
- No additional risk of hypoglycemia, despite better glycemic control compared to insulin glargine
- A simpler regimen with fewer injections than prandial insulin, making it easier for patients to take the next step to improved glycemic control earlier in the treatment course

2.5 MECHANISM OF ACTION

2.5.1 Mechanism of action: lixisenatide

The broad therapeutic potential of lixisenatide is based on 3 well-defined mechanisms that lower blood glucose:

- stimulation of insulin secretion when blood glucose levels rise (14)
- inhibition of postprandial glucagon secretion (15)
- delayed gastric emptying leading to decreased glucose absorption post-meal with a resultant reduction in PPG excursions (16, 17, 18).

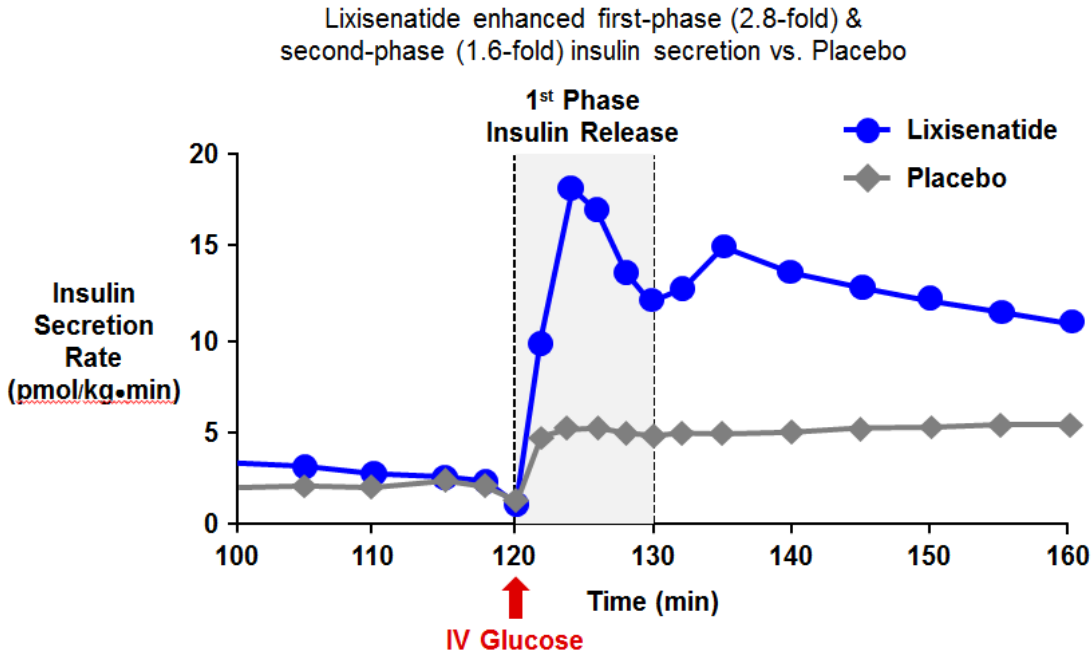
As these effects are meal/glucose-dependent, lixisenatide is associated with a low risk of hypoglycemia.

2.5.1.1 Lixisenatide stimulates insulin secretion

The effect of lixisenatide on insulin secretion was evaluated in patients with T2DM who had fasted overnight. Two hours after subcutaneous lixisenatide (20 µg) or placebo injection, participants received an intravenous bolus of glucose (14).

Lixisenatide enhanced first-phase insulin release by 2.8-fold and second-phase insulin release 1.6-fold versus placebo (Figure 3).

Figure 3 – Effect of lixisenatide on insulin secretion following an intravenous glucose challenge

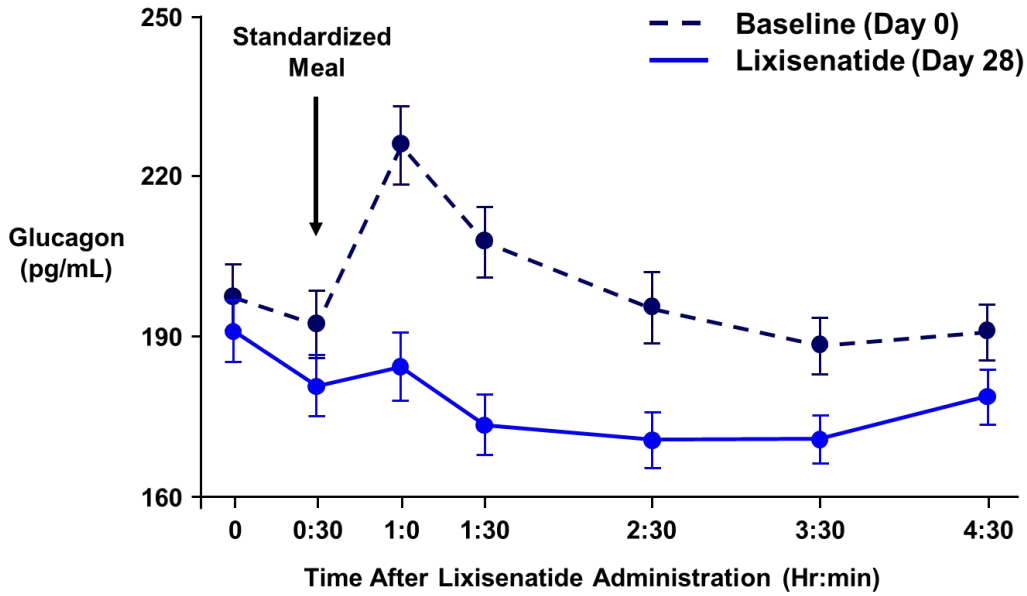


Becker R, et al. Diabetes Obes Metab. 2014 Sep;16(9):793-800.

2.5.1.2 Lixisenatide regulates postprandial glucagon levels

In normal subjects, as glucose arrives from a meal, hepatic glucose output is reduced due to the suppression of glucagon release. In T2DM, postprandial hyperglucagonemia contributes to increased PPG levels. Lixisenatide prevents the postprandial increase in glucagon secretion in patients with T2DM, thereby providing an additional mechanism of PPG-lowering post meal (15) (Figure 4).

Figure 4 – Effect of lixisenatide on postprandial glucagon level in patients with T2DM



Ahrén B, et al, Diabetes Obes Metab. 2014 Sep;16(9):861-8.

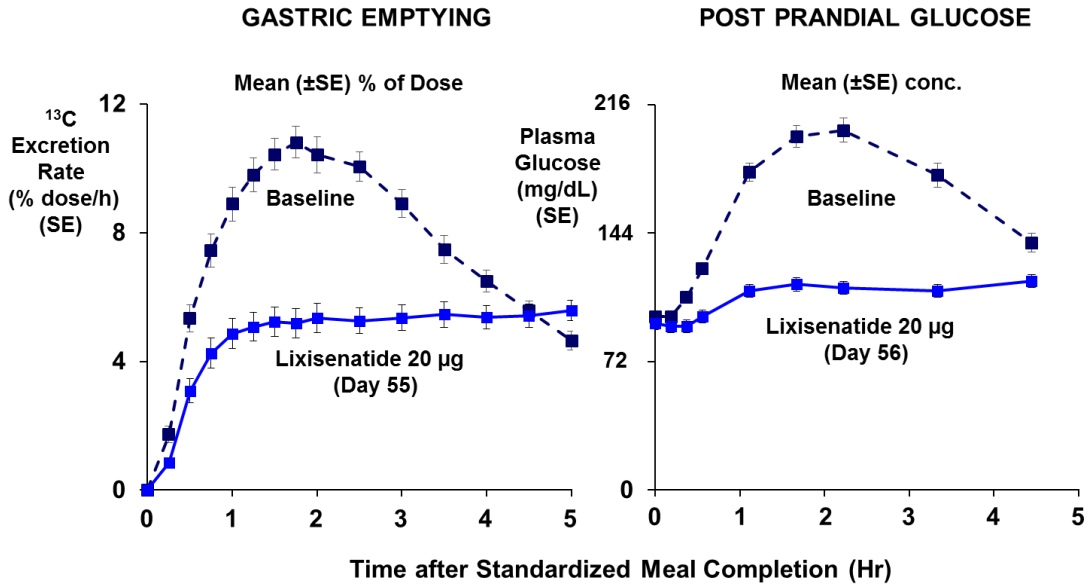
2.5.1.3 Lixisenatide slows gastric emptying and suppresses PPG excursions

Lixisenatide has a profound effect on gastric emptying. Figure 5 shows the effect of lixisenatide on gastric emptying after 55 days of administration (20 µg once-daily) in patients with T2DM using insulin glargine ± metformin. Gastric emptying was measured by 13C excretion rates, following 13C octanoic acid administration, using a breath test. Lixisenatide produced a profound reduction in 13C excretion rates when compared to pre-drug baseline values, demonstrating a significant delay in gastric emptying post meal.

Consistent with the delay in gastric emptying, lixisenatide produced a near-complete suppression of PPG excursions in the same patients following a standardized meal at Day 56 of lixisenatide administration (20 µg once-daily).

These data demonstrate the correlation between the impact of lixisenatide on delayed gastric emptying and the reduction of PPG excursions. Furthermore, the profound impact of lixisenatide on PPG levels after repeated administration over nearly 8 weeks demonstrates that this effect is durable and provides evidence of a lack of tachyphylaxis (attenuation of the pharmacodynamic effect over time).

Figure 5 - Effect of lixisenatide on gastric emptying and postprandial glucose after a standardized meal test

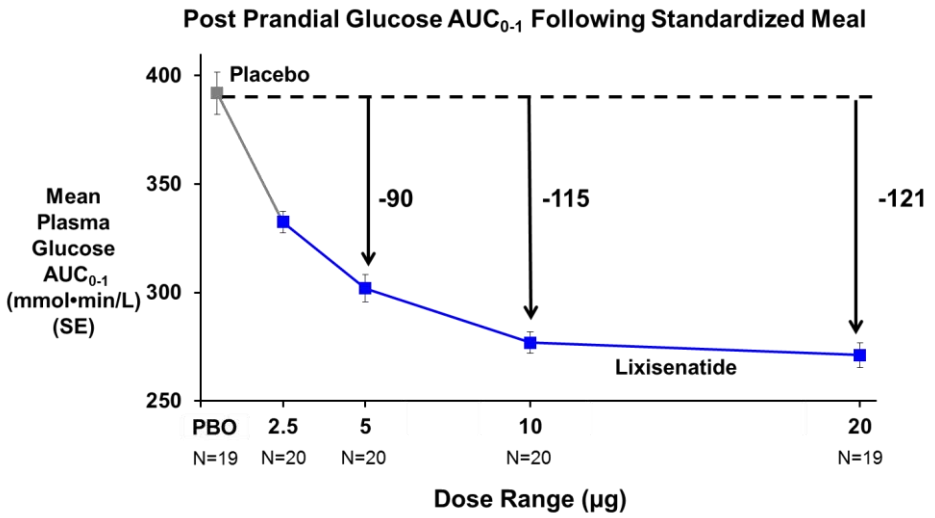


Patients with T2DM, repeated daily doses of 20 µg, Study PDY12625

Effect of lixisenatide dose on PPG-lowering

Lixisenatide reduces PPG exposure at doses as low as 5 µg once-daily. The relationship between dose and PPG exposure is depicted in Figure 6; a standardized meal test was administered one hour after lixisenatide injection in healthy normal volunteers. Maximal reductions in the area under the PPG time-concentration curve ($AUC_{0\text{-}1h}$) were achieved at 10 to 20 µg lixisenatide once-daily. At 5 µg QD, nearly 75% of the PPG reduction obtained with 20 µg lixisenatide once-daily was observed.

Figure 6 - Relationship of lixisenatide dose to reduction of postprandial glucose $AUC_{0\text{-}1h}$ after a standardized meal



Single doses of lixisenatide administered once daily in healthy volunteers, Study PDY12545

Duration of postprandial effect of lixisenatide

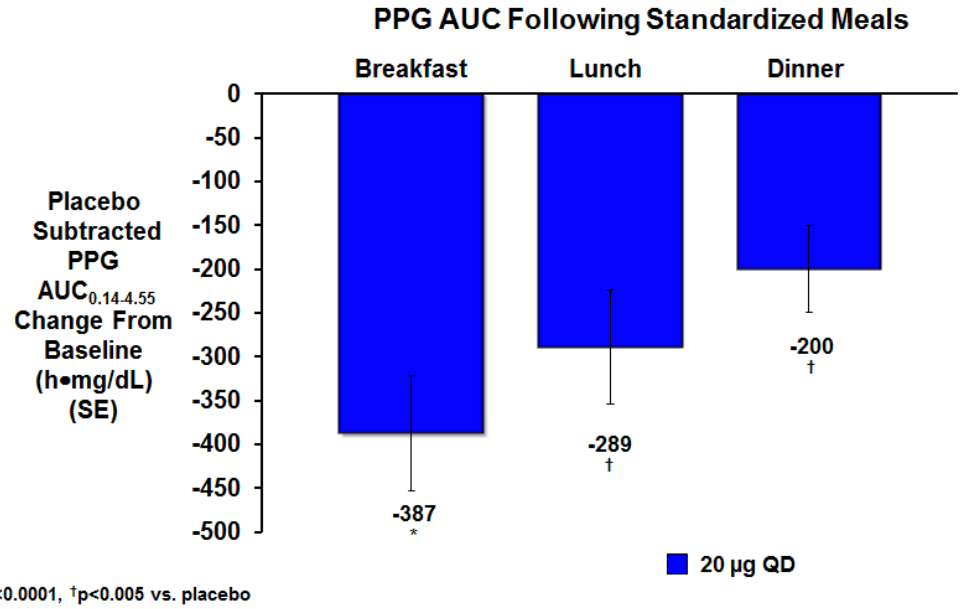
A number of studies have been conducted to evaluate the duration of action of lixisenatide including assessing the effect of alternative dosing regimens.

One such study (ACT6011) evaluated the effect of a 20 µg once-daily dose as part of a 4-week ascending-dose study in patients with T2DM. In subjects who received lixisenatide once-daily before breakfast, PPG $AUC_{0.14\text{-}4.55h}$ was measured following standardized meals at breakfast, lunch, and dinner. Postprandial glucose $AUC_{0.14\text{-}4.55h}$ values were compared with baseline values taken prior to drug administration. Lixisenatide produced significant glucose-lowering after all three meals and the greatest effect was observed after breakfast, just after drug administration (Figure 7).

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 1).

The once-daily results from Study ACT6011 are also supported by 7-point self-monitored plasma glucose (SMPG) data from a number of Phase 2 and 3 studies that demonstrated reduction of plasma glucose throughout the day following a 20 µg once-daily dose of lixisenatide.

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



*p<0.0001, †p<0.005 vs. placebo

Patients with T2DM, ascending doses for 4 weeks, Study ACT6011

Effect of once-daily versus twice-daily dosing

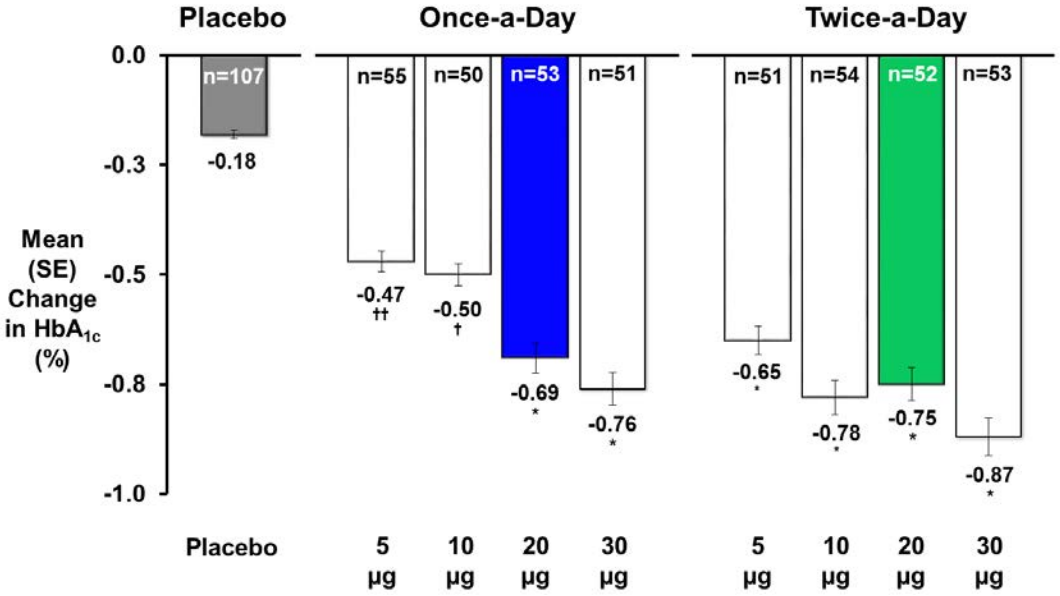
An alternative approach to evaluating the duration of action of lixisenatide was to assess the impact of dosing regimen (QD vs. BID) on the safety and efficacy of lixisenatide. This was evaluated in a Phase 2 13-week, randomized, double-blind, placebo-controlled, dose-response study where patients (52 to 55 per group) with T2DM were given various doses of lixisenatide (ranging from 5 to 30 µg) in combination with metformin, using a QD or BID dosing regimen. For doses above 10 µg, patient dosing was initiated at 10 µg and then escalated by 5 µg/week until the final dose level of 20 or 30 µg was achieved.

Figure 8 shows the impact of lixisenatide doses ranging from 5 to 30 µg QD or BID. Near-maximal effects on HbA1c reduction were evident at 20 µg daily doses or above, regardless of the dosing regimen (QD or BID). Importantly, the placebo-subtracted mean reduction in HbA1c for 5 µg QD was nearly 60% of the response at 20 µg QD. The responder rate (i.e., the percentage of patients reaching HbA1c levels <7.0%) also showed a similar dose- response relationship. Again, the maximal effect was observed at daily doses of 20 µg lixisenatide, regardless of dosing regimen. As with the change from baseline in HbA1c, responder rates at 5 µg QD were approximately half of the maximal effect observed at 20 µg QD.

In the comparison of equivalent daily doses using a once-daily 20 µg regimen versus a twice-daily 10 µg regimen, similar reductions from baseline in HbA1c and HbA1c responder rates were seen.

The data demonstrate that near maximal effects on HbA1c reduction were seen at once-daily 20 µg doses of lixisenatide and above. At these doses, limited further effectiveness is observed with twice-daily dosing as side effects increase with higher doses or with a BID regimen (Figure 9).

Figure 8 – Effect of lixisenatide on HbA1c after 13 weeks: once-daily versus twice-daily regimens



*p<0.0001, †p<0.005, ††p<0.05 vs. placebo
Patients with T2DM, dose-ranging study for 13 weeks, DRI6012

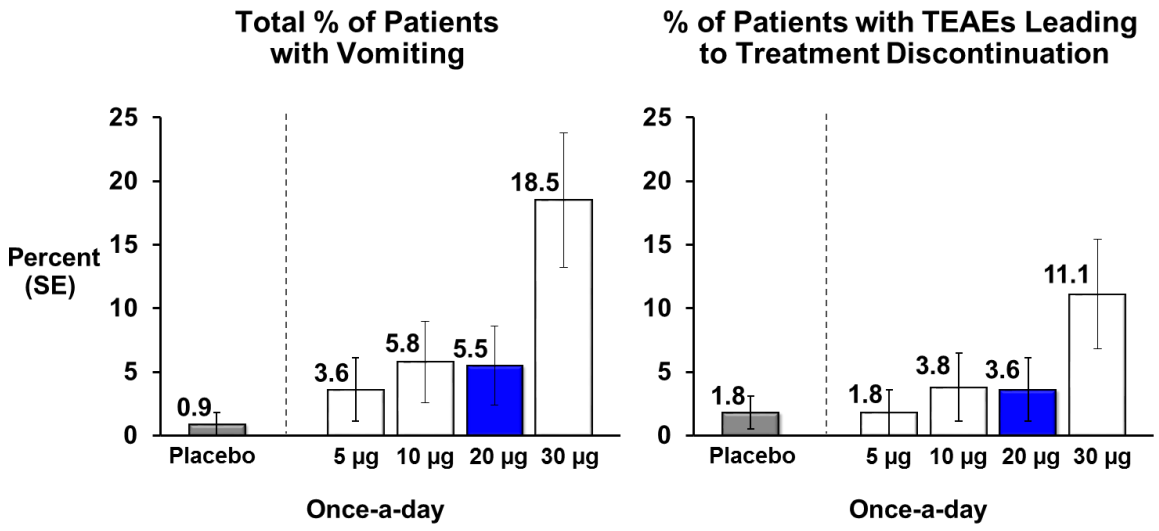
Effect of lixisenatide dose and regimen on tolerability

In order to understand the tolerability associated with increasing doses of lixisenatide, the impact of dose on vomiting (a known GI side effect of the GLP-1 receptor agonist class), on treatment discontinuation due to treatment-emergent adverse events (TEAEs), and on injection site reactions was assessed for the Phase 2 dose-ranging study described in the previous section. The lowest rate of vomiting was observed in the 5 µg QD group (Figure 9). In the 10 and 20 µg QD groups, the rate was higher and comparable between groups, while the rate of vomiting was substantially higher in the 30 µg QD group. A similar dose relationship was also observed with BID dosing, with no significant impact of dose regimen at equivalent daily doses.

The impact of dose on permanent treatment discontinuation due to TEAEs showed a similar pattern (Figure 9). The lowest rate of discontinuation was seen at 5 µg once-daily, higher and comparable rates were seen at 10 and 20 µg once-daily, and the highest rate was observed at 30 µg once-daily. A similar dose relationship was also observed with twice-daily dosing. As with vomiting, the dose regimen, at equivalent daily doses, did not appear to impact permanent treatment discontinuation due to TEAEs.

The relationship of dose to injection site reactions was less evident than those described above, but the events occurred more frequently at higher doses of lixisenatide. However, injection site reactions at equivalent daily doses of lixisenatide, were observed more often in the twice-daily groups than in the once-daily dosing groups. In the 20 µg once-daily group, 3.6% of patients had an injection site reaction compared to 10.7% in the 10 µg twice-daily group.

Figure 9 – Effect of lixisenatide, once-daily, on rates of vomiting and permanent treatment discontinuation due to adverse events



Patients with T2DM, dose ranging for 13 weeks, Study DRI6012

2.5.1.4 Rationale for dose and regimen selection for lixisenatide and iGlarLixi

For further development as a single agent, the dose and regimen selected for lixisenatide was 20 µg once-daily. The basis for this decision was multifactorial, balancing maximal efficacy and patient adherence with acceptable tolerability, related to the following observations:

- Daily doses above 20 µg did not provide a clinically meaningful improvement in efficacy as measured by change from baseline in HbA1c or HbA1c responder rates. This could not be further improved using a twice-daily regimen. Daily doses above 20 µg resulted in higher rates of vomiting, permanent treatment discontinuation due to TEAEs, and injection site reactions.
- Twice-daily dosing resulted in nearly three-fold higher rates of injection site reactions.
- Adherence to injectable treatment regimens has been shown to increase with fewer injections per day (19).

The dose-range of lixisenatide selected for further development of iGlarLixi was 5 to 20 µg. The basis for this decision was as follows:

- Daily doses as low as 5 µg provided a clinically meaningful improvement in efficacy as measured by change from baseline in HbA1c or HbA1c responder rates. Doses above 20 µg did not offer further clinical improvement.
- Daily doses as low as 5 µg produced significant reductions in PPG levels. Doses above 20 µg did not offer any additional improvement. This effect is evident when lixisenatide is administered alone or in combination with insulin glargine. Insulin glargine given alone has been shown to have little effect on PPG levels (Figure 21 and Figure 24).

2.5.1.5 Summary of lixisenatide pharmacodynamics

Lixisenatide lowers blood glucose through 3 different mechanisms: stimulation of insulin secretion when blood glucose levels rise (14), inhibition of postprandial glucagon secretion (15) and delayed gastric emptying leading to decreased glucose absorption post-meal with a resultant reduction in PPG excursions (16, 17, 18).

- Near maximal effects of lixisenatide on the reduction of HbA1c levels and PPG exposure were observed at 20 µg once-daily but substantial effects were seen as low as 5 µg once-daily.
- The PPG-lowering was evident after all meals of the day with 20 µg once-daily dosing; the greatest effect was observed after the first meal after drug administration.
- A twice-daily dosing regimen did not offer increased benefits with respect to the reduction of HbA1c levels and PPG excursions.
- As a stand-alone product, the 20 µg QD lixisenatide dose provided maximal efficacy balanced with acceptable tolerability.
- The combined data provide the basis for the selection of the 5 to 20 µg dose-range of lixisenatide for the development of the iGlarLixi combination product.

2.5.2 Complementary actions of iGlarLixi

The mechanisms of action of lixisenatide and insulin glargine are complementary: insulin glargine lowers basal glucose levels throughout the day while lixisenatide primarily targets PPG excursions. As patients with T2DM often experience elevations in both components of hyperglycemia, the combination of insulin glargine and lixisenatide provides a rational therapy.

Due to large variations in insulin sensitivity and the risk of inducing hypoglycemia with insulin, insulin glargine requires precise titration. Lixisenatide has shown clinically meaningful effects on HbA1c and PPG across the dose range from 5 to 20 µg and can therefore be combined with insulin glargine in a fixed-ratio combination. The combination is titrated based on the patient's insulin glargine requirement and delivers lixisenatide across the 5 to 20 µg dose-range.

2.6 CLINICAL PHARMACOLOGY

2.6.1 Lixisenatide

Lixisenatide demonstrated rapid absorption, achieved maximum plasma concentrations after approximately 2 hours, and had a plasma half-life of 2 to 5 hours. After multiple dosing, exposure to lixisenatide was approximately dose proportional between doses of 5 and 30 µg QD or BID in patients with T2DM. There was no need for dose adjustment by gender, race, or age. Pharmacokinetic (PK) variability was driven largely by renal clearance and body weight although dose adjustment is not required in patients with mild (creatinine clearance: 60 to 90 mL/min) or moderate (creatinine clearance: 30 to <60 mL/min) renal impairment. Elderly subjects, many with mild renal impairment, had only modest increases in lixisenatide exposure compared to younger subjects. There is limited data in patients with severe renal impairment.

Lixisenatide did not demonstrate any clinically relevant effects on overall exposure (AUC) to warfarin, acetaminophen, ramipril, digoxin, atorvastatin, and oral contraceptives; no dose adjustment is needed for these drugs when taken concomitantly with lixisenatide.

The delay in gastric emptying induced by lixisenatide reduced the rate of absorption (maximal plasma concentration [Cmax], time to maximal concentration [Tmax]) of a model drug (acetaminophen). Oral drugs that may depend on threshold concentrations for their efficacy, such as antibiotics, OCs or atorvastatin, should be taken at least 1 hour before or 11 hours after lixisenatide injection.

In 2 thorough QT/QTc studies, the lixisenatide 20 µg QD and 30 µg BID regimens were not associated with increases in QTcF intervals. Transient increases in PR intervals and heart rate were observed in the larger-scale thorough QT/QTc study; these are considered to be a class effect of GLP-1 receptor agonists.

Lixisenatide showed insulinotropic and glucagonostatic properties consistent with a GLP-1 receptor agonist (Section 2.5.1). The counterregulatory hormone response (glucagon, cortisol, epinephrine, norepinephrine, growth hormone) and hypoglycemia awareness are preserved during provoked hypoglycemia in the presence of lixisenatide (20).

Anti-drug antibody formation resulted in increases in lixisenatide concentrations of 10-fold or more as well as increases in inter-individual PK variability, but had no relevant effect on the efficacy of lixisenatide except at the very highest concentrations of antibody (<3% of the population).

2.6.2 iGlarLixi

Pharmacokinetics of insulin glargine

Administration of the combination had no relevant impact on the PK of insulin glargine based on single-dose studies. Following single-dose administration of the combination at ratios of 1.5 U/1 µg and 4 U/1 µg, the relative bioavailability of insulin glargine was generally comparable in the fixed-ratio combination versus separate simultaneous injections, with AUC0-24h ratios of 0.86 and 0.88, respectively.

The PK of insulin glargine itself is dependent on the insulin glargine concentration in the injection solution and is well-characterized for the 100 U/mL solution.

Steady state - accumulation ratio:

- No accumulation was observed following repeated administration of insulin glargine alone.
- Since lixisenatide has no relevant impact on the PK of insulin glargine when administered in combination, accumulation of insulin glargine when administered as a combination was not investigated.
- Dose proportionality: AUC of insulin glargine administered as a combination or separate simultaneous injections increased with increasing body weight-adjusted dose of insulin glargine (0.4 U/kg in one study and 0.6 U/kg in another study).

Pharmacokinetics of lixisenatide

The AUC of lixisenatide was comparable regardless of whether it was administered in combination or administered alone. There was a small decrease in Cmax of lixisenatide of 22% to 34% compared with separate simultaneous administration of insulin glargine and lixisenatide.

Suitability of insulin glargine and lixisenatide for a fixed-ratio combination product

In summary, the clinical pharmacology data demonstrate that combining the two products in a fixed-ratio combination allows the combination product to provide the complementary benefits of insulin glargine (predominantly FPG) and lixisenatide (predominantly PPG) on both components of hyperglycemia as a therapeutic principle.

2.7 DOSING AND ADMINISTRATION

2.7.1 Lixisenatide

Lixisenatide is administered subcutaneously QD using a pen-type injector. In most Phase 3 studies, it was injected in the morning within 1 hour before breakfast.

All Phase 3 studies evaluated lixisenatide at a dose of 20 µg QD as the maintenance dose. The Phase 3 studies included a 2-week stepwise dose increase of lixisenatide (or volume-matched placebo when applicable) consisting of either:

- a 2-step dose-increase regimen (10 µg QD for 1 week, then 15 µg QD for 1 week, followed by 20 µg QD as a maintenance dose; "2-step regimen") or
- a 1-step dose-increase regimen (10 µg for 2 weeks followed by 20 µg QD as a maintenance dose; "1-step regimen").

A 1-step dose-increase regimen resulted in changes from baseline in HbA1c in the same range as a 2-step regimen (Section 3.2.3). Furthermore, the tolerability profile of the 1-step and 2-step regimen were the same. The 1-step dose increase regimen was therefore chosen as the final dosing regimen.

Patients were permitted to reduce their lixisenatide maintenance dose if they experienced poor GI tolerability.

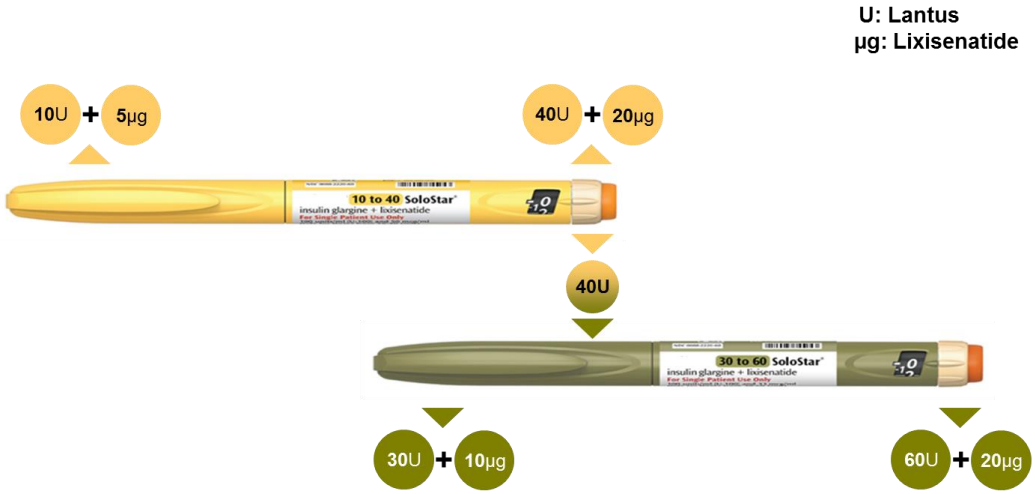
In the proposed US label, lixisenatide dosing is initiated at 10 µg QD for 14 days and then increased to 20 µg QD as the maintenance dose.

2.7.2 iGlarLixi

To maintain the lixisenatide dose within a clinically effective range that did not exceed 20 µg and simultaneously provide a wide range of insulin glargine doses, iGlarLixi is provided in 2 different ratios in 2 different pens.

The pens are based on the established SoloStar® platform that is used with Lantus (insulin glargine) (Figure 10).

Figure 10 – iGlarLixi commercial pens



Two pens are proposed for commercial use (Figure 10). The availability of 2 titratable pens allows:

- Insulin-naïve patients to initiate treatment at a recommended daily insulin glargine (100 U/mL) dose of 10 U with a corresponding dose of 5 µg of lixisenatide (yellow/peach pen). Effectiveness of the 5 µg lixisenatide dose is described in Figure 6 and Figure 8.
- In patients switching from basal insulin to iGlarLixi, 2 different starting doses are available depending on previous insulin need: either the yellow/peach pen (20 U/10 µg) or the green/olive pen (30 U/10 µg) (Figure 11), thereby avoiding a major decrease in their current insulin dose.

The dose of iGlarLixi is adjusted based on the need for basal insulin, i.e., primarily on the basis of fasting SMPG levels. After initiation of iGlarLixi and during titration, the yellow/peach pen is used for total daily insulin glargine doses of 10 to 40 U, and the green/olive pen for total daily doses of 41 to 60 U, thereby not exceeding the maximum lixisenatide starting dose of 10 µg (Figure 11). Thus, for patients using the yellow/peach pen and requiring >40 U, a switch to the green/olive pen (41 to 60 U) can be made. The flexibility of iGlarLixi dosing allows patients to titrate based on their individual responses to treatment.

Based on a United States payer database of basal insulin use, the vast majority of insulin glargine users received a dose between 10 and 60 U/day (21).

Figure 11 - iGlarLixi pens allow titration of insulin glargine and lixisenatide

	Lantus (U)	Lixisenatide (µg)
0	0	0
	Safety Test	
10	10	5.0
11	11	5.5
12	12	6.0
13	13	6.5
14	14	7.0
15	15	7.5
16	16	8.0
17	17	8.5
18	18	9.0
19	19	9.5
20	20	10.0
21	21	10.5
22	22	11.0
23	23	11.5
24	24	12.0
25	25	12.5
26	26	13.0
27	27	13.5
28	28	14.0
29	29	14.5
30	30	15.0
31	31	15.5
32	32	16.0
33	33	16.5
34	34	17.0
35	35	17.5
36	36	18.0
37	37	18.5
38	38	19.0
39	39	19.5
40	40	20.0

	Lantus (U)	Lixisenatide (µg)
0	0	0
	Safety Test	
30	30	10.0
31	31	10.3
32	32	10.7
33	33	11.0
34	34	11.3
35	35	11.7
36	36	12.0
37	37	12.3
38	38	12.7
39	39	13.0
40	40	13.3
41	41	13.7
42	42	14.0
43	43	14.3
44	44	14.7
45	45	15.0
46	46	15.3
47	47	15.7
48	48	16.0
49	49	16.3
50	50	16.7
51	51	17.0
52	52	17.3
53	53	17.7
54	54	18.0
55	55	18.3
56	56	18.7
57	57	19.0
58	58	19.3
59	59	19.7
60	60	20.0

Thus, 2 titratable pens with 2 different fixed-ratio combinations and 2 different dose-ranges allow:

- Lower insulin glargine doses to be paired with effective lixisenatide doses, and
- Higher insulin glargine doses to be paired with no more than the maximum lixisenatide dose of 20 µg.

2.8 OVERVIEW OF EFFICACY IN THE LIXISENATIDE PROGRAM

2.8.1 Introduction

A total of 13,433 patients were enrolled in the lixisenatide Phase 2/3 program, of which 7,874 were exposed to lixisenatide. Exposure to lixisenatide was >10,000 patient-years (PY) with 56.8% of patients treated for ≥1 year.

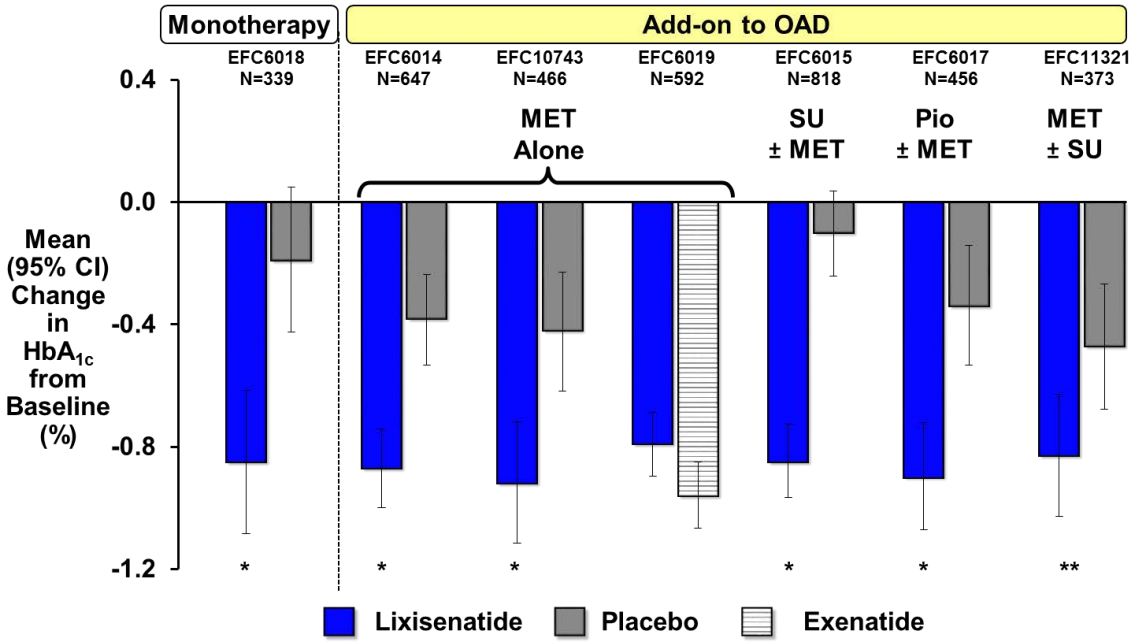
Change in HbA1c from baseline to the primary efficacy time point was the primary endpoint in the Phase 3 studies including nine double-blind placebo-controlled studies and two active-controlled studies (versus exenatide BID and versus insulin glulisine).

The primary efficacy time point is defined as Week 24 in all studies except 2 studies (one with Week 12 and another with Week 26).

2.8.2 Efficacy in placebo-controlled trials

Lixisenatide produced clinically relevant reductions in HbA1c, showing superiority over placebo in all 9 placebo-controlled studies, with a consistent reduction in HbA1c of approximately 0.9% (treatment differences from placebo ranged between 0.3% and 0.9%) (Figure 12). Lixisenatide was also non-inferior to exenatide BID with a pre-specified non-inferiority margin of 0.4% (upper bound of the 2-sided 95% CI=0.297%).

Figure 12 – Lixisenatide produces consistent and clinically relevant reductions in HbA1c

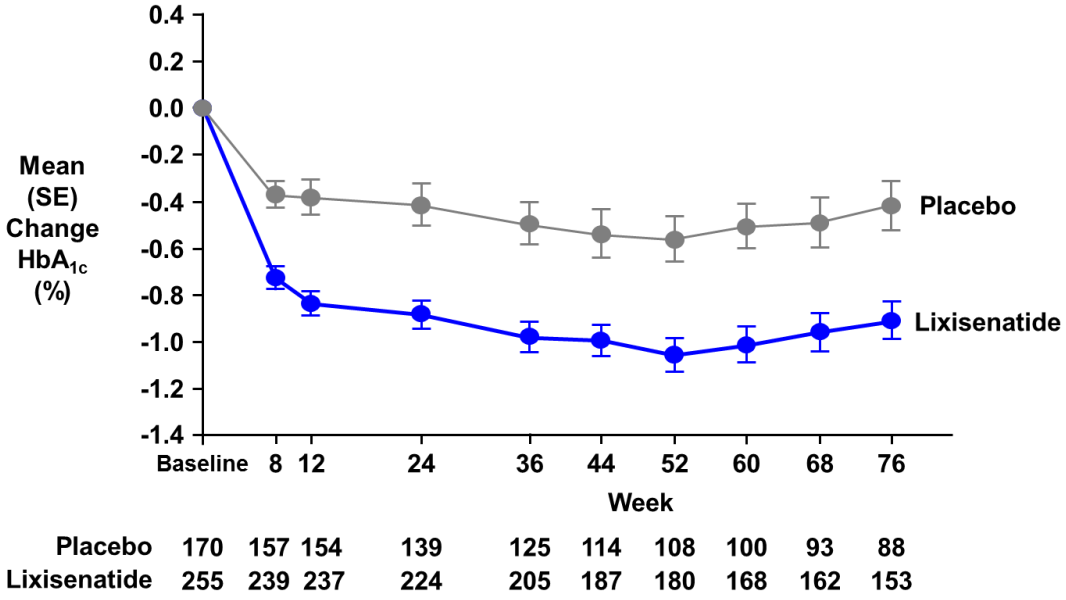


*p<0.0001; **p<0.001
mITT population, 24-week data (12-week for monotherapy), LOCF
MET, metformin; Pio, pioglitazone; SU, sulfonylurea

Importantly, the reduction in HbA1c began early in the course of treatment and persisted over 76 weeks. In the trial illustrated in Figure 13, lixisenatide or placebo were added to ongoing treatment with metformin in patients with T2DM. The study ended when the last randomized patient completed 76 weeks of treatment.

Overall, across the lixisenatide Phase 3 program, approximately 80% of the HbA1c-lowering effect was achieved during the first 8 weeks of treatment.

Figure 13 – Glucose-lowering efficacy (±SE) of lixisenatide was maintained over 76 weeks of treatment



Add-on to MET EFC6014

While lixisenatide had modest effects on FPG, it provided profound PPG-lowering, with greater reductions in 2-hour PPG compared to placebo when measured after the first meal post-injection, with a statistically significant difference in all studies in which it was measured ($p<0.0001$).

A beneficial effect on body weight was seen in all studies. When lixisenatide was administered alone or in combination with metformin and/or a SU, a clinically relevant mean reduction in body weight was observed in the lixisenatide groups. The reduction from baseline to Week 24 ranged from 1.50 to 2.68 kg and was generally greater than seen in the placebo groups (ranging from 0.93 to 1.98 kg). A beneficial effect on body weight was also seen in the studies with insulin as background therapy. Although the magnitude of the effect on body weight depended on the concomitant background therapy, treatment with lixisenatide has been shown to attenuate the weight gain seen with many T2DM treatment regimens.

2.8.3 Efficacy of lixisenatide versus placebo added on to basal insulin

Lixisenatide added-on to newly initiated insulin glargine is effective in overweight/obese patients with a long duration of T2DM while also attenuating the effect of insulin on weight gain. Whenever insulin glargine is mentioned in this Briefing Book, the product referred to is insulin glargine (100 U/mL, Lantus).

In patients suboptimally controlled despite oral therapy, insulin glargine was added to OADs and systematically titrated during a 12-week run-in, after which patients (N=466) with HbA1c 7.0 to 9.0% were randomized to lixisenatide 20 µg QD or placebo for 24 weeks with ongoing insulin and OAD(s) (Study EFC10781) (22). The primary end point was HbA1c change from baseline to Week 24.

Randomized patients had a mean diabetes duration of 9.2 years, body mass index (BMI) 31.8 kg/m^2, and daily insulin glargine dosage of 44 units. HbA1c decreased during the run-in from 8.6 to 7.6%. Adding lixisenatide further reduced HbA1c to 7.0% at Week 24 versus 7.3% for placebo (least squares [LS] mean difference, –0.32%; 95% CI, –0.46 to –0.17; p<0.0001). Lixisenatide also had a favorable effect on body weight with a difference versus placebo of -0.89 kg (p=0.0012).

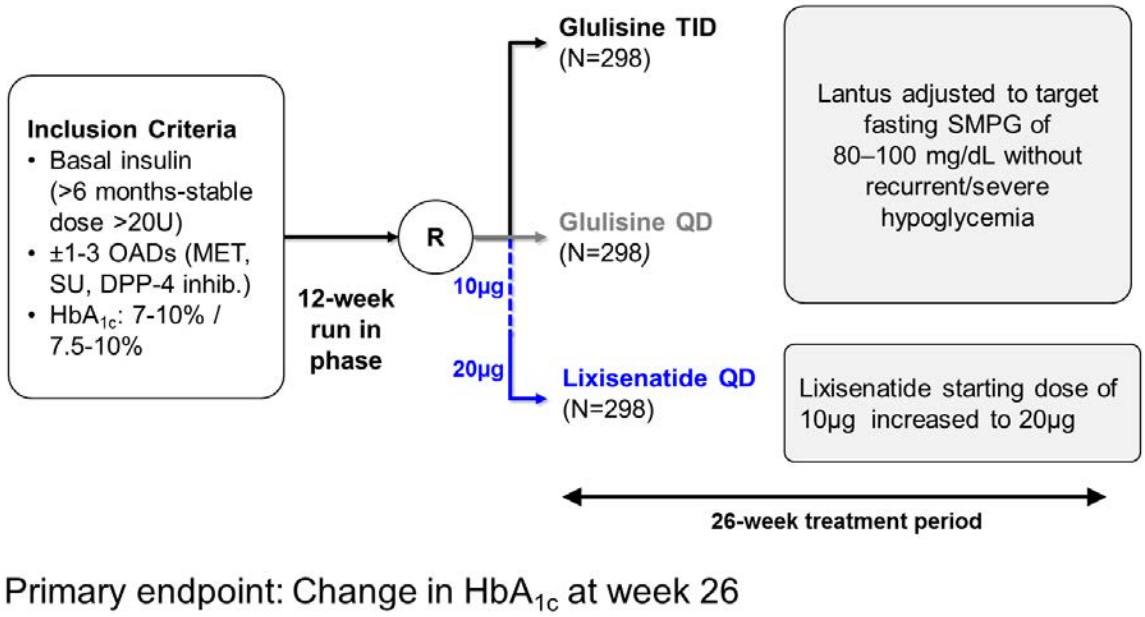
2.8.4 Efficacy of lixisenatide versus prandial insulin added on to insulin glargine

In patients who are insufficiently controlled on basal insulin, a standard treatment has been to add a mealtime insulin, either with the largest meal (basal-plus) or with all meals (basal-bolus).

A randomized, controlled study demonstrated that in patients who have exhausted multiple treatment options and are uncontrolled on basal insulin, lixisenatide can minimize hypoglycemia and weight gain while normalizing glycemia, in comparison to adding mealtime insulin QD or TID. A more complete description of the study is provided in Section 3.4.

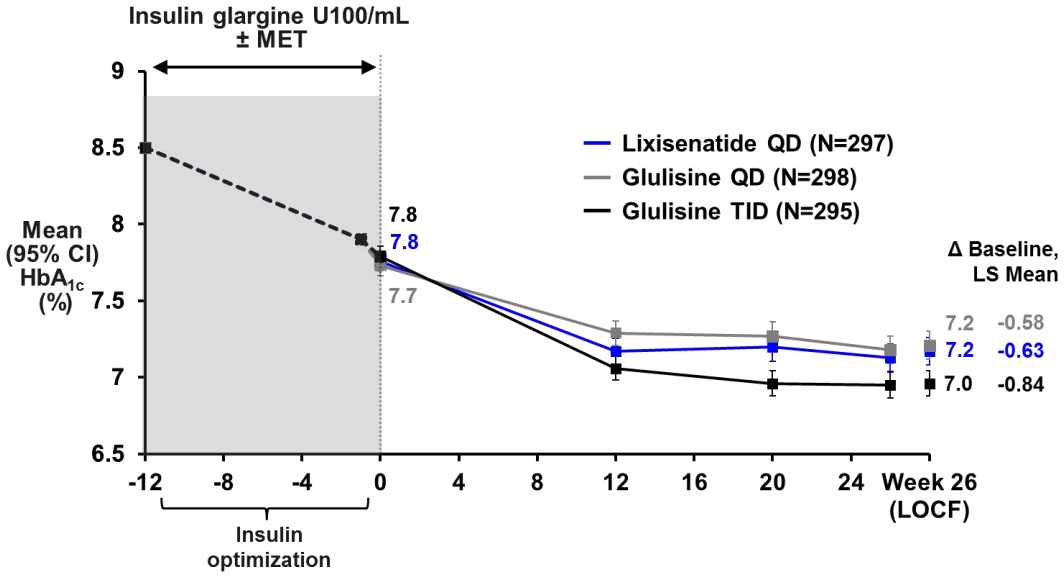
Lixisenatide was studied in patients who were insufficiently controlled with basal insulin ± OADs (Study EFC12626). In a 12-week run-in period, insulin glargine therapy was optimized and OADs other than metformin were discontinued. Patients who met the post run-in inclusion and exclusion criteria (N=894) were randomized 1:1 to lixisenatide 20 µg QD or to prandial insulin glulisine (QD or TID) (all arms ± metformin) for 26 weeks of treatment (Figure 14).

Figure 14 – Study EFC12626: Lixisenatide versus prandial insulin as a treatment for T2DM



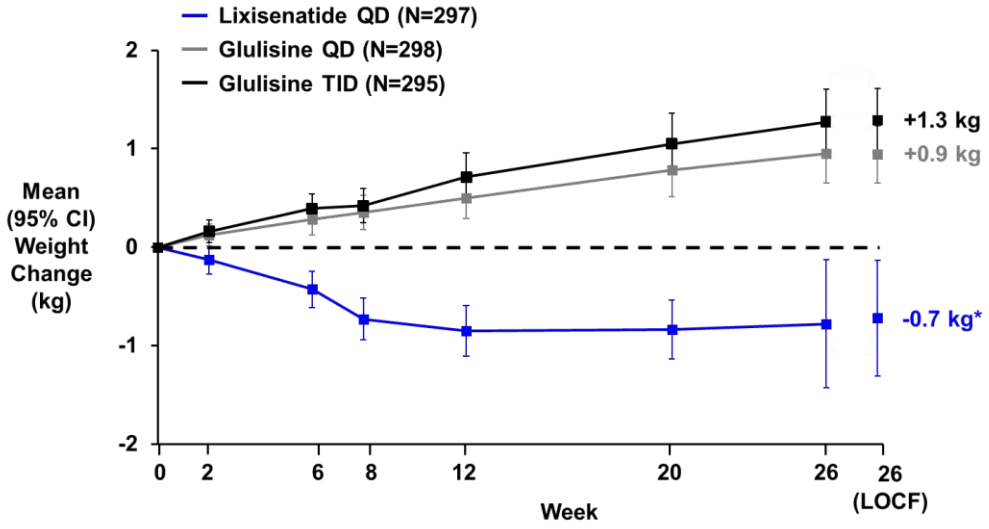
The trial met all co-primary endpoints comparing lixisenatide as a once-daily add-on to basal insulin versus the addition of rapid-acting insulin injected once each day at the main meal (basal-plus) or TID at each meal (basal-bolus). Lixisenatide was shown to be non-inferior to both comparator insulin regimens for reduction in HbA1c (Figure 15) and statistically superior to basal-bolus for body weight change as the co-primary endpoints for the study (Figure 16). Mean end-of-treatment HbA1c values were low and comparable across the treatment groups, 7.2% for both lixisenatide QD and glulisine QD and 7.0% for glulisine TID.

Figure 15 –Study EFC12626: Once-daily lixisenatide is non-inferior to prandial insulin for HbA1c reduction (mITT populations)



As is common with intensification of insulin therapy, patients receiving prandial insulin regimens experienced an increase in body weight, while patients receiving lixisenatide in combination with basal insulin had a reduction in weight (Figure 16).

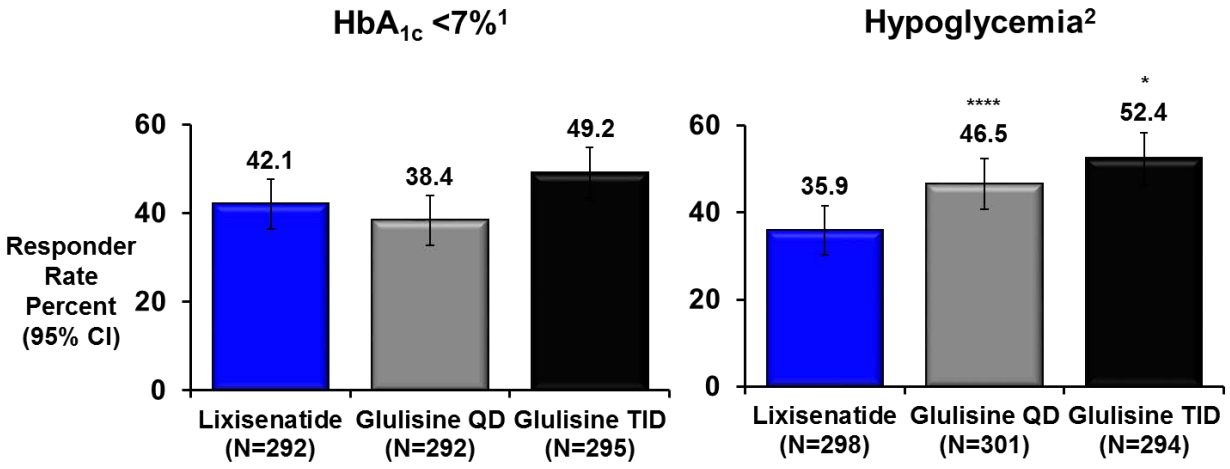
Figure 16 – Study EFC12626: Lixisenatide QD provided a beneficial effect on body weight vs. prandial insulin QD and TID (mITT population)



*Mean change is statistically significant vs TID Glulisine

As a measure of treatment success for lixisenatide versus the two prandial insulin regimens, the proportion of patients with HbA1c <7.0% was comparable across treatment groups, but the incidence of symptomatic hypoglycemia was significantly lower in the lixisenatide group (Figure 17).

Figure 17 – Study EFC12626: Once-daily lixisenatide demonstrates a clinical advantage over prandial insulin QD and TID

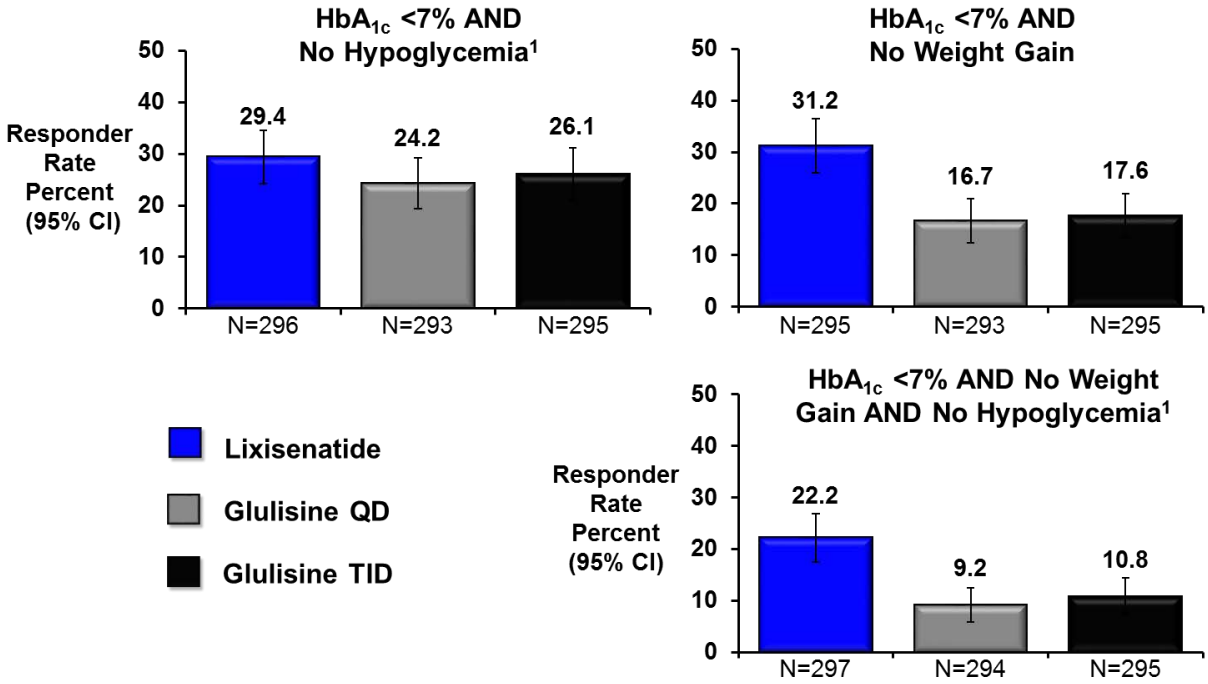


*p<0.0001; ****p=0.01
1. mITT population was used to assess change in HbA1c.
2. Safety population was used to assess symptomatic hypoglycemia (as reported by Investigator).

The goal of intensification of treatment is not only to obtain a reduction in HbA1c, but also to achieve this with a minimum of undesirable effects, such as hypoglycemia or weight gain. Lixisenatide QD offered a clinical advantage over prandial insulin QD or TID with respect to change in body weight and incidence of documented symptomatic hypoglycemia (plasma glucose <60 mg/dL) in a setting of comparable HbA1c control (Figure 18).

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



Safety population was used to assess documented symptomatic hypoglycemia (PG <60 mg/dL). The mITT population was used to assess change in HbA1c.

2.8.5 Anti-lixisenatide antibodies and efficacy

Anti-lixisenatide antibody status had minimal effect on the efficacy of lixisenatide (Section 3.2.3.2). Changes in HbA1c from baseline were similar regardless of anti-drug antibody (ADA) status (positive or negative). A small number of lixisenatide-treated patients (45, 2.4%) with very high ADA concentrations (>100 nanomole [nmol]/L) had a smaller decrease in HbA1c.

2.8.6 Efficacy conclusions for lixisenatide

Lixisenatide is effective in the treatment of T2DM as either monotherapy or add-on to OADs and/or basal insulin. Lixisenatide provides:

- Clinically relevant reductions in HbA1c
- Robust reductions in PPG levels
- A beneficial effect on body weight
- A minimal risk of hypoglycemia as monotherapy or in combination with metformin or a thiazolidinedione, and a limited additional risk in combination with a SU or basal insulin

Additionally, in patients treated with optimally titrated insulin glargine, lixisenatide treatment achieved non-inferiority with respect to glycemic control versus insulin glulisine QD and TID, accompanied by body weight loss and a reduced risk of hypoglycemia.

Taken together, these results support lixisenatide as an effective glucose-lowering agent including in patients not achieving target glycemic control despite basal insulin therapy, for whom lixisenatide could be a valuable alternative therapeutic option to mealtime insulin.

2.9 OVERVIEW OF EFFICACY IN THE IGLARLIXI DEVELOPMENT PROGRAM

The efficacy of iGlarLixi in patients with T2DM was assessed in 2229 randomized patients in one Phase 2 proof-of-concept study and two pivotal Phase 3 studies. Exposure to iGlarLixi in the Phase 2/3 program was 533.6 patient-years (Table 73).

The two pivotal trials were in T2DM patients suboptimally controlled on metformin ± a second OAD in EFC12404, and patients suboptimally controlled on basal insulin ± OADs in EFC12405. In both populations, iGlarLixi has demonstrated statistically significantly superior glycemic control versus its monocomponents as comparator(s).

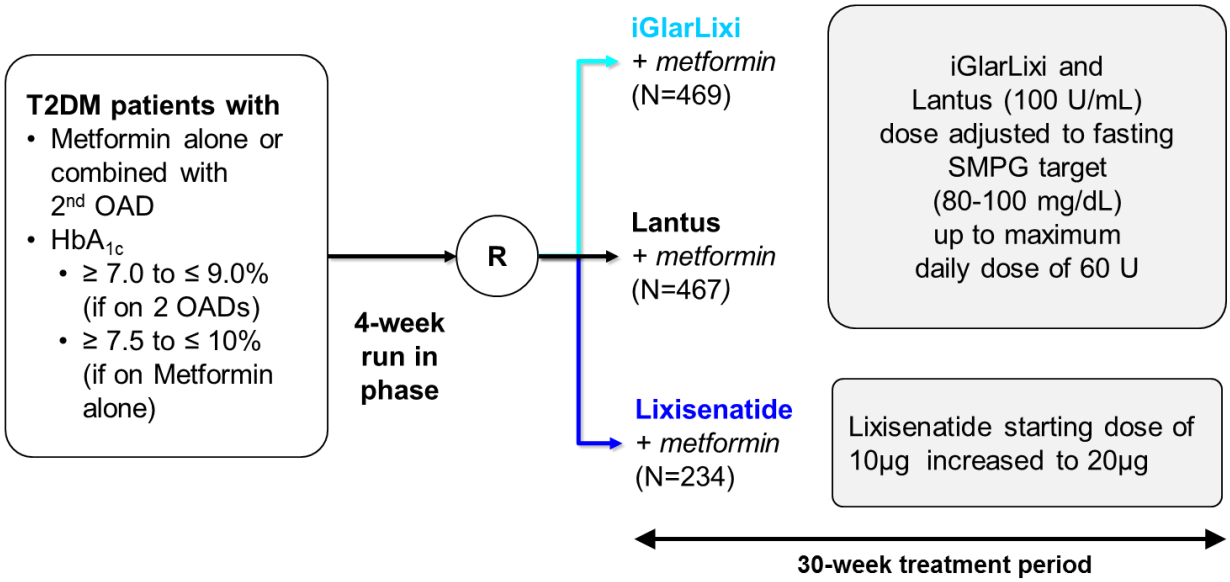
2.9.1 Study EFC12404 (insulin-naïve)

Patients who were inadequately controlled on metformin ± a second OAD were enrolled in a 4-week run-in period during which only metformin therapy was continued and was optimized. If at the end of the run-in, patients met the inclusion and exclusion criteria they were randomized 2:2:1 to iGlarLixi, insulin glargine, and lixisenatide (Figure 19). During the treatment period, patients in the insulin-based treatment groups were titrated to the same fasting SMPG targets (80 to 100 mg/dL, inclusive) and daily insulin glargine doses were capped at 60 U. 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. Lixisenatide was self-administered QD in the hour before breakfast or the evening meal.

The primary endpoint was change from baseline in HbA1c at Week 30 and the co-primary efficacy hypotheses were statistical superiority of iGlarLixi versus lixisenatide and non-inferiority of iGlarLixi versus insulin glargine. The primary efficacy analysis was a mixed-effect model with

repeated measures (MMRM) using all post baseline data including those collected after treatment discontinuation or initiation of rescue therapy.

Figure 19 – EFC12404: Study design



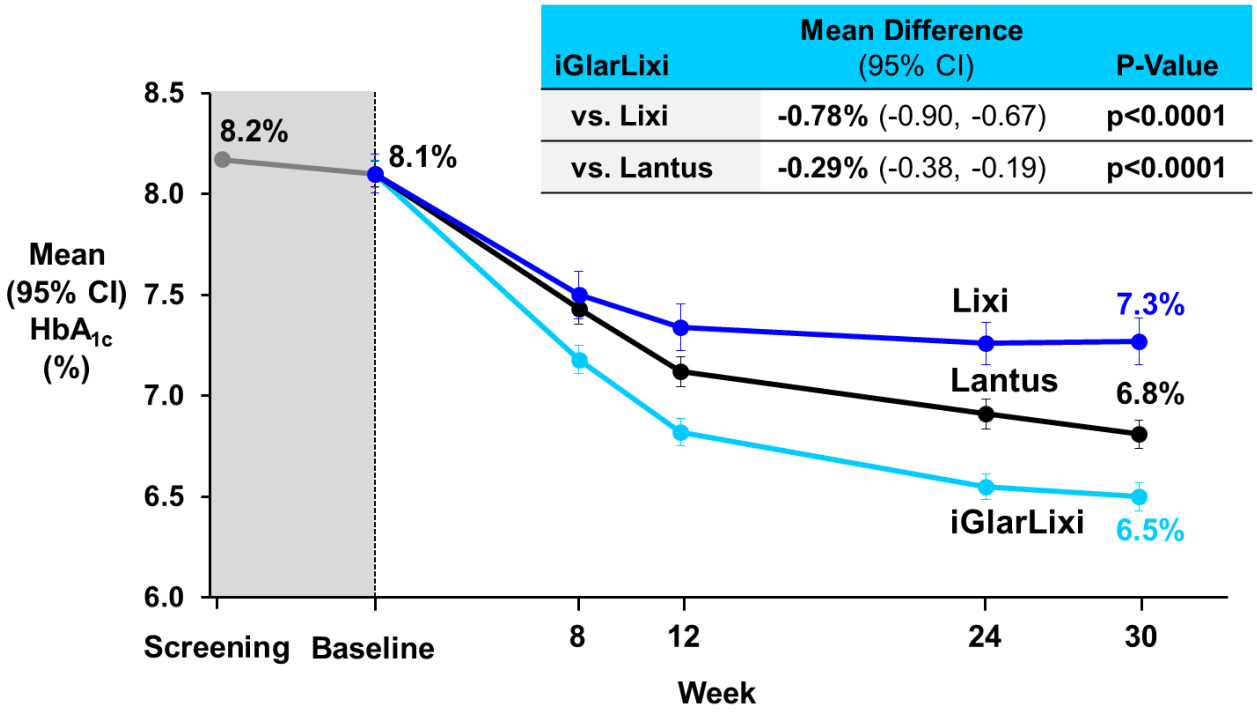
Primary endpoint: Change in HbA_{1c}, at week 30

Baseline demographics were well-balanced across treatment groups. Most patients had a baseline BMI >30 indicating that the majority of the population was obese. Baseline disease characteristics were well-balanced with an overall mean duration of diabetes of ~9 years with a mean HbA1c of 8.2% at screening (Section 4.2.1 [Table 11]). The percentage of patients using 2 OADs at screening was 57.9% overall; for those patients, the overall mean duration of use was 4.2 years.

Both co-primary endpoints were met by the demonstration of superiority over lixisenatide and non-inferiority versus insulin. Importantly, iGlarLixi demonstrated a statistically significant greater reduction in HbA1c than insulin glargine as specified in the hierarchical testing order (Table 62).

From a mean baseline HbA1c of 8.1% in all 3 treatment groups, (Section 4.2.3 [Table 12]), mean end-of-treatment HbA1c levels of 6.5% (iGlarLixi), 6.8% (insulin glargine), and 7.3% (lixisenatide) were reached (Figure 20).

Figure 20 - Study EFC12404: Mean HbA1c (%) by visit during the study period (mITT population)



The plot includes all scheduled measurements obtained during the study, including those obtained after study drug discontinuation or introduction of rescue therapy.

A higher proportion of patients in the iGlarLixi group achieved multiple measures of treatment success compared to the insulin glargine group as assessed by responder rates:

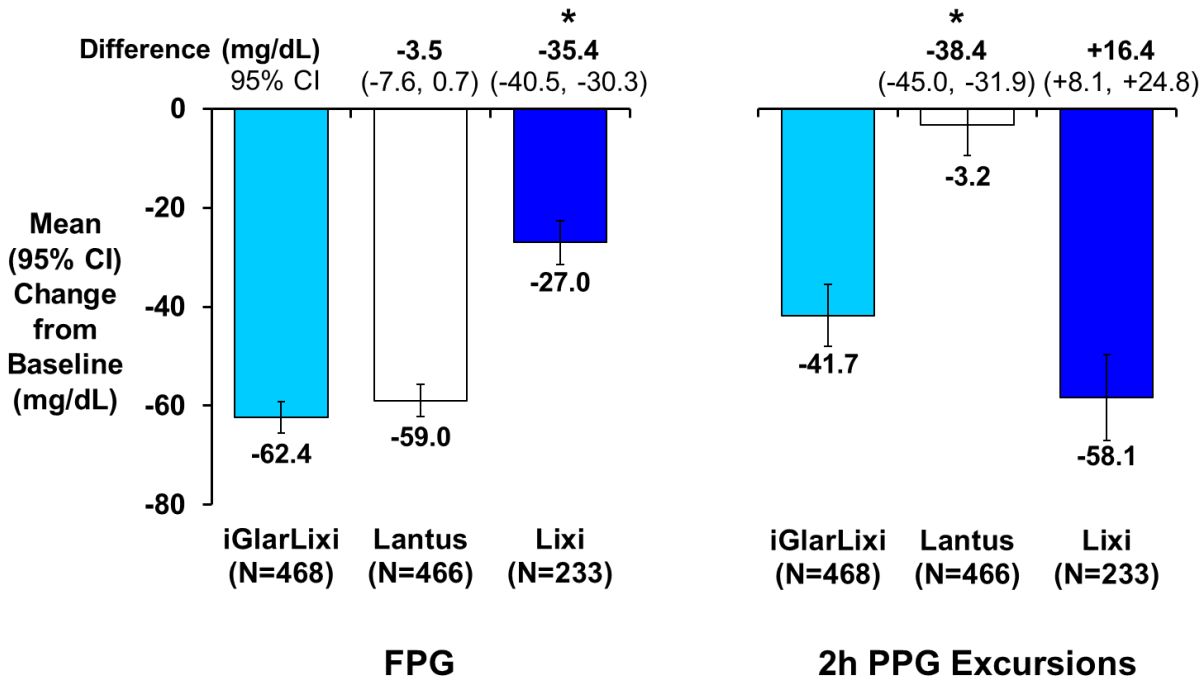
- Most patients in the iGlarLixi group (73.7%) reached an HbA1c target <7.0% at the end of the 30-week treatment period versus a smaller proportion for insulin glargine (59.4%) and lixisenatide (33.0%) (Figure 41). The 95% CI for the treatment difference vs. insulin glargine was 8.37% to 20.25%; for the treatment difference vs. lixisenatide it was 33.63% to 47.59%.
- The proportion of patients achieving an HbA1c <7.0% without weight gain also shows that iGlarLixi compares favorably with insulin glargine, with a statistically significantly higher proportion of patients reaching this endpoint at Week 30 in the iGlarLixi group (43.2%) than in the insulin glargine group (25.1%) (p<0.0001).
- The proportion of patients with an HbA1c <7.0%, without weight gain, and without documented symptomatic hypoglycemia (plasma glucose ≤70 mg/dL) was highest in the iGlarLixi group, 31.8% versus 18.9% for insulin glargine. The treatment difference was statistically significant (p<0.0001).

The differences in responder rates between iGlarLixi and insulin glargine are clinically meaningful for patients with T2DM.

The secondary endpoints of FPG and PPG are informative with respect to the contribution of lixisenatide and insulin glargine to the greater HbA1c benefit provided by the combination (iGlarLixi) compared to its individual components (Figure 21).

- There is a robust change in FPG levels from baseline in both the iGlarLixi and insulin glargine groups, with a negligible difference between the two arms, indicating the predominant contribution of insulin glargine to FPG levels.
- The opposite results were seen with 2-hour PPG excursions (calculated by subtracting the 30 minute pre-meal glucose values from the 2-hour post meal values after a standardized breakfast). The effects of lixisenatide on PPG excursions are robust and clearly evident in the iGlarLixi group. The increase in PPG control provided by lixisenatide thus provides the basis for the superior overall glycemic control observed with iGlarLixi versus insulin glargine.

Figure 21 – Study EFC12404: Insulin glargine affects FPG levels, lixisenatide affects PPG excursions (mITT population)



*p<0.0001

Insulin glargine and lixisenatide have opposing effects on body weight (Figure 42). Thus, body weight increased with insulin glargine by 1.1 kg and decreased with iGlarLixi by 0.3 kg, with a statistically significant mean treatment difference of -1.40 kg (95% CI, -1.89 to -0.91; p<0.0001). This observation highlights the contribution of the lixisenatide component in iGlarLixi, which mitigates the weight gain typically seen with initiation of insulin glargine.

2.9.2 Study EFC12405 (previously insulin-treated)

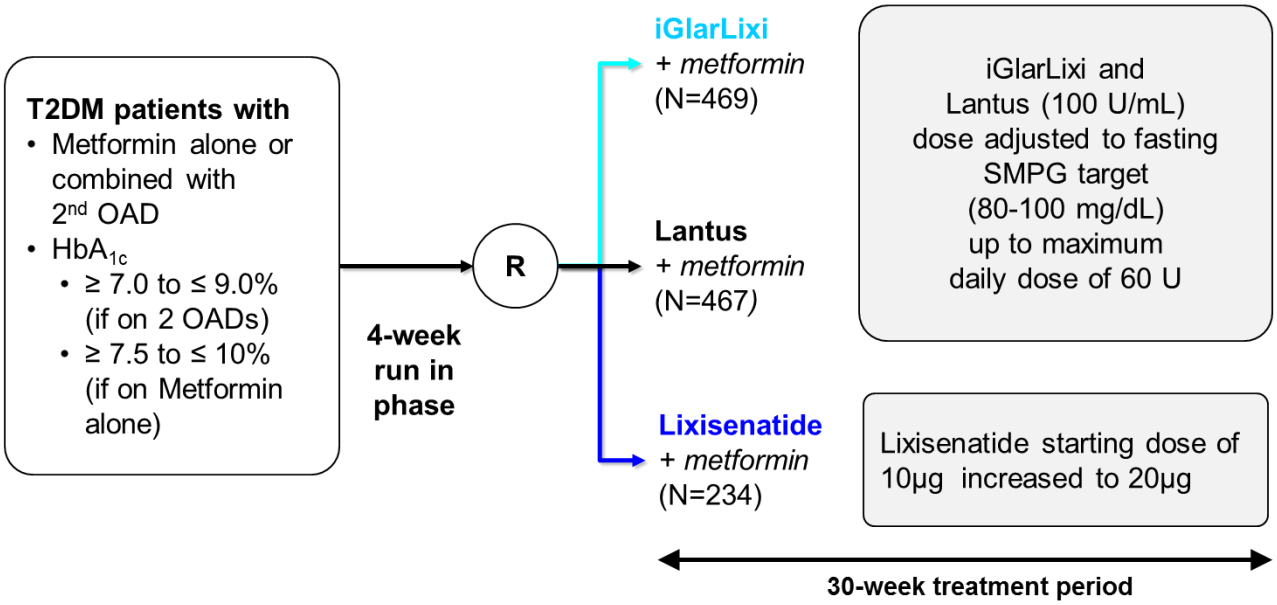
Patients who were suboptimally controlled on basal insulin ± 1 or 2 OADs were enrolled in a 6-week run-in to introduce and/or titrate insulin glargine while continuing metformin (if previously taken) and discontinuing other OADs. If at the end of the run-in, patients met the inclusion and exclusion criteria (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 22).

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 22 – EFC12405: Study design



Primary endpoint: Change in HbA_{1c}, at week 30

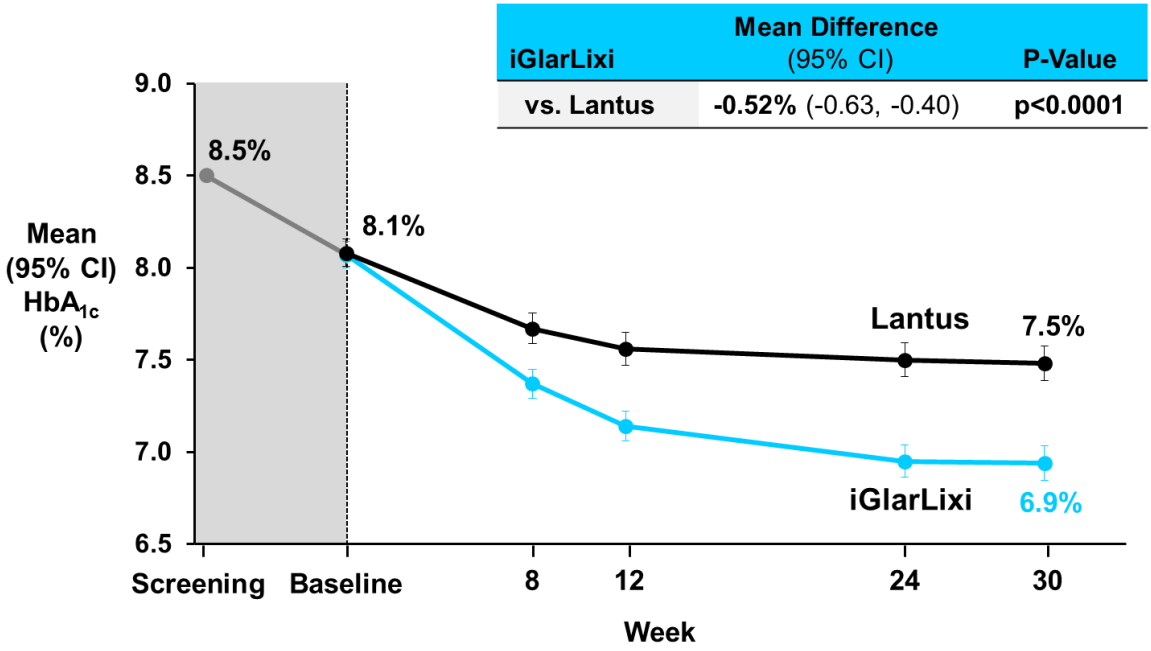
Baseline demographics were well-balanced across treatment groups. The overall population was balanced by gender and was primarily Caucasian (91.7%) with a mean age of 60 years. The mean screening BMI was 31.3 kg/m^2 with 58.6% of patients having a mean BMI ≥30 kg/m^2, indicating that the majority of patients were obese.

Baseline characteristics related to diabetes were comparable in the 2 treatment groups and indicative of a population in poor glycemic control despite concurrent use of basal insulin ± 1 to 2 OADs over a period of several years (Section 4.3.1 [Table 16]). At screening, the mean duration of diabetes was 12.1 years with a mean HbA1c of 8.5% in both groups.

iGlarLixi met its primary objective by demonstrating statistical superiority over insulin glargine for change in HbA1c from baseline to Week 30.

At the end of run-in, the mean screening HbA1c of 8.5% had decreased to 8.1%. During the 30-week treatment period, LS mean HbA1c level further decreased by 1.1% to a mean of 6.9% with iGlarLixi and by 0.6% to a mean of 7.5% with insulin glargine (Figure 23).

Figure 23 – Study EFC12405 primary endpoint: iGlarLixi achieved superior HbA1c reduction versus insulin glargine (mITT population)



The analysis included all scheduled measurements obtained during the study, including those obtained after study drug discontinuation or introduction of rescue therapy.

A higher proportion of patients in the iGlarLixi group achieved multiple measures of treatment success compared to the insulin glargine group as assessed by responder rates:

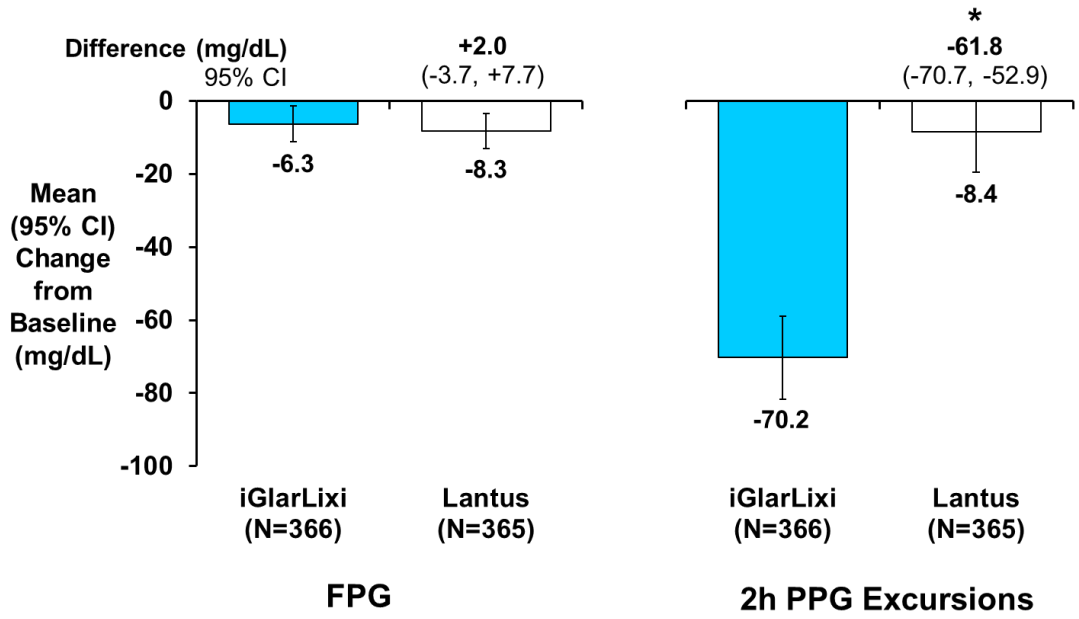
- A higher proportion of patients in the iGlarLixi group (54.9%) reached an HbA1c target <7.0% at the end of the 30-week treatment period vs. insulin glargine (29.6%). The 95% CI for the treatment difference vs. insulin glargine was 18.9% to 32.1%.
- The proportion of patients achieving an HbA1c <7.0% without weight gain also shows that iGlarLixi compares favorably with insulin glargine, with a statistically significantly higher proportion of patients reaching this endpoint at Week 30 in the iGlarLixi group (34.2%) than in the insulin glargine group (13.4%) (p<0.0001).
- More than twice as many patients in the iGlarLixi group (19.9%) reached the triple composite endpoint of HbA1c <7.0% with no body weight gain at Week 30 and with no documented symptomatic hypoglycemia (plasma glucose ≤70 mg/dL) during the study as compared to patients in the insulin glargine group (9.0%) with a treatment difference of 10.94% (95% CI: 5.93% to 15.96%).

The differences in responder rates between iGlarLixi and insulin glargine are clinically meaningful for patients with T2DM.

The differing effects of insulin glargine and iGlarLixi on the secondary endpoints of FPG and PPG were again demonstrated (Figure 24). A small reduction from baseline in FPG was seen in both treatment groups, with a negligible difference between groups. The small reduction from baseline in FPG is a consequence of the improvement in FPG during the insulin glargine run-in period: only patients who had achieved a mean fasting SMPG level of ≤140 mg/dL were eligible for randomization.

With respect to the robust improvement in PPG excursions, the contribution of lixisenatide is evident: the reductions in mean 2-hour PPG excursions at Week 30 were 70.2 mg/dL for iGlarLixi and 8.4 mg/dL for insulin glargine (p<0.0001).

Figure 24 – Study EFC12405: Insulin glargine affects FPG, lixisenatide affects PPG (mITT population)



*p<0.0001

The opposing effects of insulin glargine and lixisenatide on body weight were also seen in this study. Mean body weight decreased by 0.7 kg in the iGlarLixi group and increased by 0.7 kg in the insulin glargine group with a statistically significant treatment difference of -1.4 kg (p<0.0001).

2.9.3 iGlarLixi: Consistency of findings across subgroups

A pre-specified meta-analysis of change from baseline to Week 30 in HbA1c using pooled data from the 2 pivotal Phase 3 studies was performed by subgroup (Figure 25). Change from baseline was consistent across baseline categories including race, ethnicity, gender, age, baseline BMI, and baseline HbA1c.

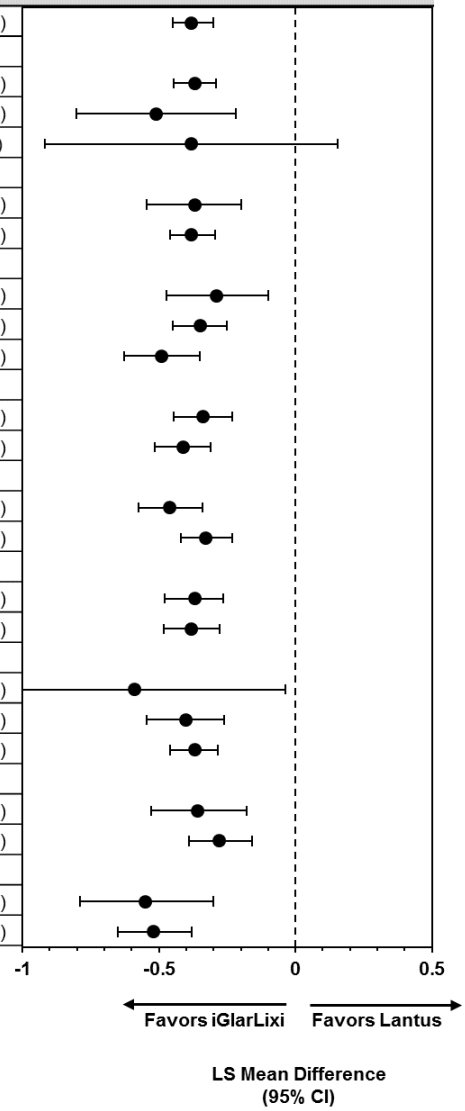
Change from baseline by country was not included in the meta-analysis of pooled studies. However, the change by country was pre-specified in the analysis of change in HbA1c for each of

the individual pivotal studies. The results of the analysis by country for the US were consistent with the overall results:

- In Study EFC12404, the US was the highest enrolling country; the iGlarLixi group had a LS mean reduction from baseline in HbA1c of 1.54% versus 1.63% for the entire study population.
- In Study EFC12405, the US was also the highest enrolling country; the iGlarLixi group had a LS mean reduction from baseline in HbA1c of 1.10% versus 1.13% for the entire study population.

Figure 25 - Forest plot of meta-analysis of change in HbA1c (%) from baseline to Week 30 by baseline factors using pooled data from Studies EFC12404 and EFC12405 (mITT populations)

	iGlarLixi (N)	Lantus (N)	LS Mean Difference (95% CI)
Overall	831	828	-0.38 (-0.45, -0.30)
Race			
Caucasian/White	750	751	-0.37 (-0.45, -0.29)
Black	50	54	-0.51 (-0.80, -0.22)
Asian/Oriental	20	15	-0.38 (-0.92, 0.15)
Ethnicity			
Hispanic	149	151	-0.37 (-0.55, -0.20)
Non Hispanic	682	677	-0.38 (-0.46, -0.30)
Age			
<50	135	122	-0.29 (-0.47, -0.10)
≥50 to <65	454	474	-0.35 (-0.45, -0.25)
≥65	242	232	-0.49 (-0.63, -0.35)
Gender			
Male	386	410	-0.34 (-0.45, -0.23)
Female	445	418	-0.41 (-0.52, -0.31)
Baseline BMI (kg/m^2)			
<30	328	334	-0.46 (-0.57, -0.34)
≥30	503	494	-0.33 (-0.42, -0.23)
Baseline HbA1c (%)			
<8.0	387	386	-0.37 (-0.48, -0.26)
≥8.0	444	442	-0.38 (-0.48, -0.28)
Creatinine Clearance (Screening)			
≥30 to <60 (Moderate)	22	12	-0.59 (-1.15, -0.04)
≥60 to <60 (Mild)	219	243	-0.40 (-0.54, -0.26)
≥90 (Normal)	586	568	-0.37 (-0.46, -0.28)
Study 404			
US	132	148	-0.36 (-0.53, -0.18)
Non US	335	316	-0.28 (-0.39, -0.16)
Study 405			
US	90	84	-0.55 (-0.79, -0.30)
Non US	274	280	-0.52 (-0.65, -0.38)



2.9.4 Efficacy of iGlarLixi by daily insulin glargine dose levels

Insulin requirements vary among patients with T2DM and thus a broad range of daily insulin dosing was used across the 2 pivotal studies (EFC12404 and EFC12405). In order to determine the contribution of each component to iGlarLixi, the pharmacodynamic effects across final daily insulin dose-categories were examined.

Because it was not feasible to randomly assign patients into predefined fixed-dose insulin groups, the data was analyzed based on the end-of-study daily insulin doses. The following efficacy measures were assessed by dose-range: effects on HbA1c as the overall measure of clinical efficacy, effects on FPG as a measure of the insulin glargine effect, and effects on PPG excursions, which are uniquely affected by lixisenatide. Additionally, whether the mitigation of weight gain could be observed across the entire daily dose-range was also evaluated.

Patient distribution across end-of-study insulin glargine daily dose-categories

The distribution of patients across the end-of-study dose-categories for both the iGlarLixi and insulin glargine (Lantus) groups was evaluated for both studies (see Section 5 for data on Study EFC12405).

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 42 (9%) 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 patients in this lowest daily dose category.

Table 1 – Study EFC12404: Patient distribution across final daily insulin glargine dose-range

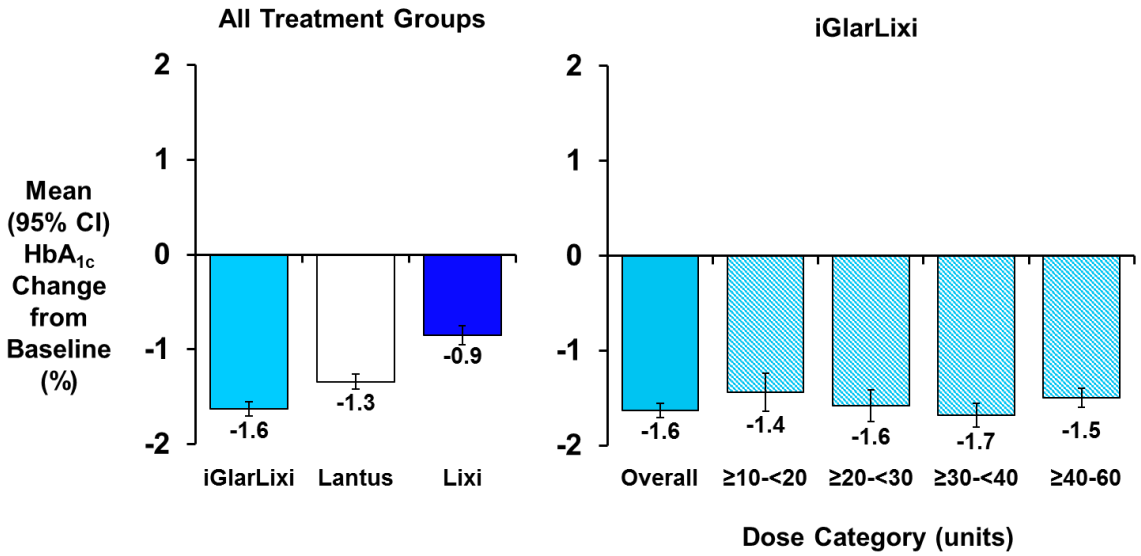
	Study 404			
Final Insulin Dose (U)	**iGlarLixi (N=468)**		**Lantus (N=466)**	
<10	0	0	3	<1%
≥10 to <20	58	12%	39	8%
≥20 to <30	76	16%	96	21%
≥30 to <40	126	27%	117	25%
≥40 to ≤60	208	44%	209	45%
>60	0	0	2	<1%

Reduction from baseline to Week 30 in HbA1c

In the overall results for reduction from baseline in HbA1c in EFC12404, iGlarLixi showed superiority over insulin glargine and lixisenatide, demonstrating a positive contribution of both components to the overall treatment effect (Table 12).

The treatment effect across end-of-study daily insulin dose categories is consistent with the overall effect, even at the lower dose categories (Figure 26). This is suggestive of a contribution of the lixisenatide component across the entire daily dose range.

Figure 26 - Study EFC12404: Mean change in HbA1c from baseline to Week 30 for iGlarLixi by final daily insulin dose category (mITT population)

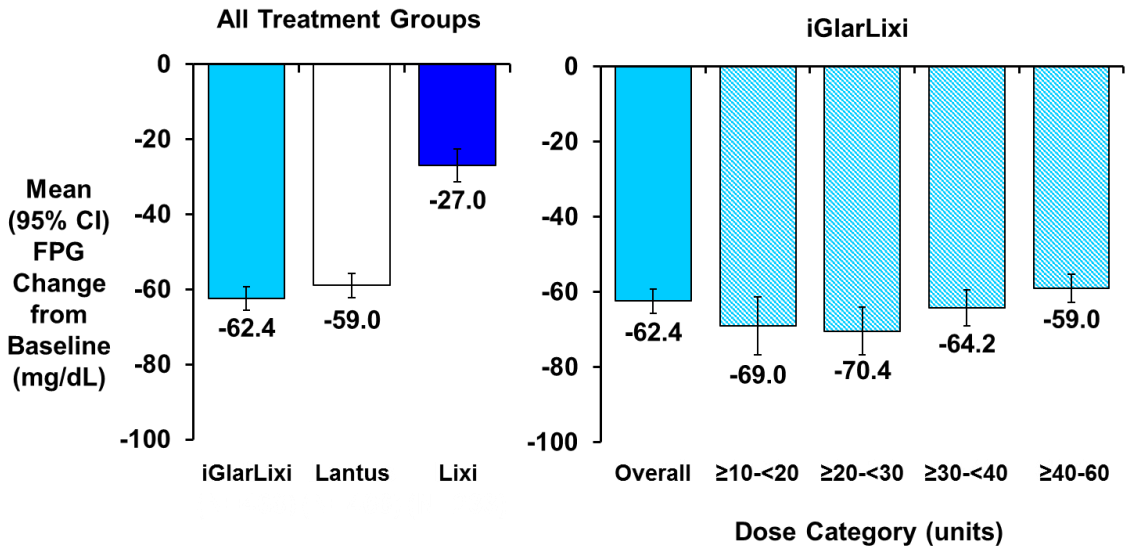


Change from baseline to Week 30 in FPG

The overall study results in EFC12404 indicated that insulin glargine primarily affects FPG levels while lixisenatide primarily affects PPG levels (Figure 21).

The FPG-lowering effect at Week 30 was consistent across the entire insulin glargine final daily dose range, indicating that the titration of iGlarLixi was effective across the entirety of that range (Figure 27).

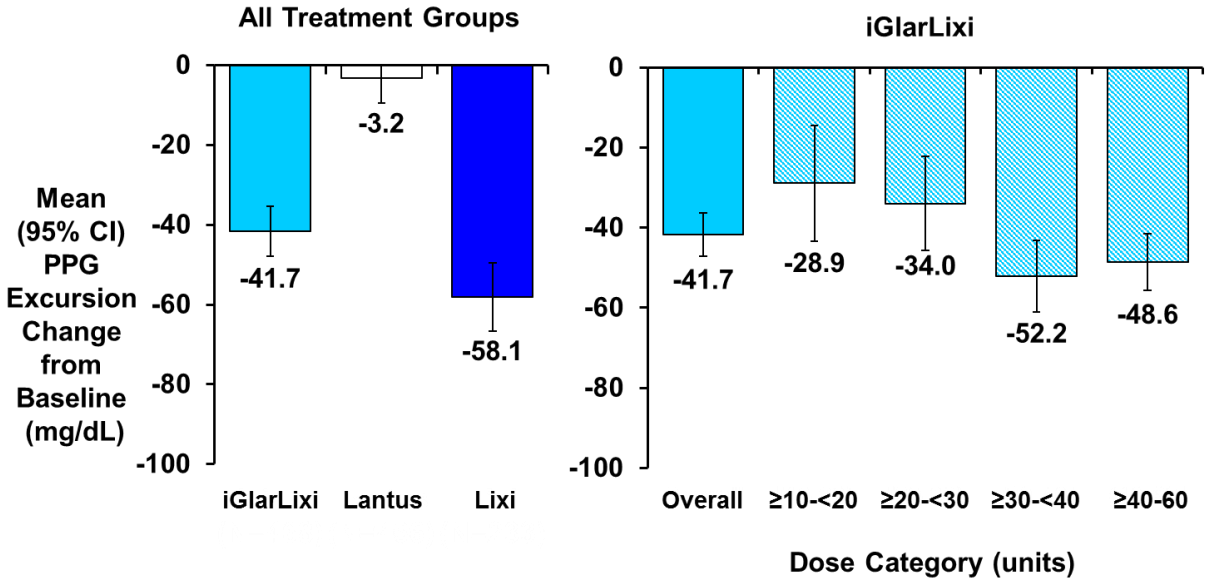
Figure 27 - Study EFC12404: Mean change in FPG from baseline to Week 30 for iGlarLixi by final daily insulin dose category (mITT population)



Change from baseline to Week 30 in 2-hour PPG excursions

The overall study results in EFC12404 indicated no contribution from insulin glargine on 2-hour PPG excursions after a standardized breakfast meal (Figure 21 and Figure 28). The PPG-lowering effect of iGlarLixi was evident across all daily insulin dose categories.

Figure 28 – Study EFC12404: Mean change from baseline in PPG excursions for iGlarLixi by final daily insulin dose category (mITT population)



Change from baseline to Week 30 in body weight

The overall study results in EFC12404 showed minimal weight reduction in the iGlarLixi group while there was a clear weight increase in the insulin glargine group (Figure 42).

Across final daily insulin dose-categories in the iGlarLixi group, weight reductions were observed at all but the highest daily dose (Figure 29). In contrast to the iGlarLixi group where predominantly weight reductions were observed, weight gain was observed in the insulin glargine group at all but the lowest final daily dose-category (Figure 30).

The aggregate results support the conclusion that lixisenatide contributes to the mitigation of insulin therapy-associated weight gain across the entire end-of-study daily insulin dose range.

Figure 29 – Study EFC12404: Mean change in weight from baseline to Week 30 with iGlarLixi treatment by final daily insulin dose category (mITT population)

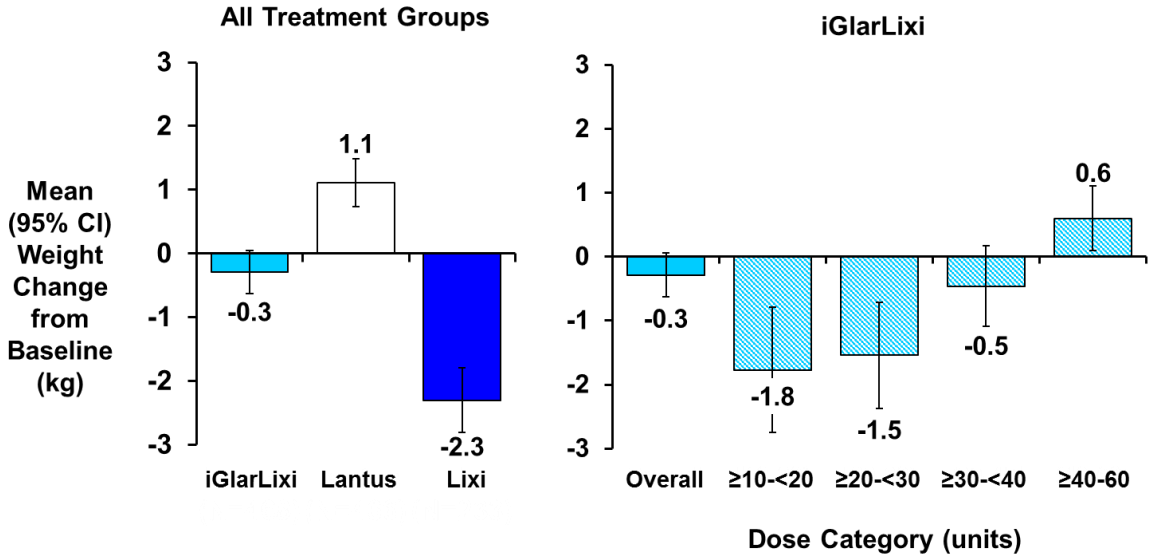
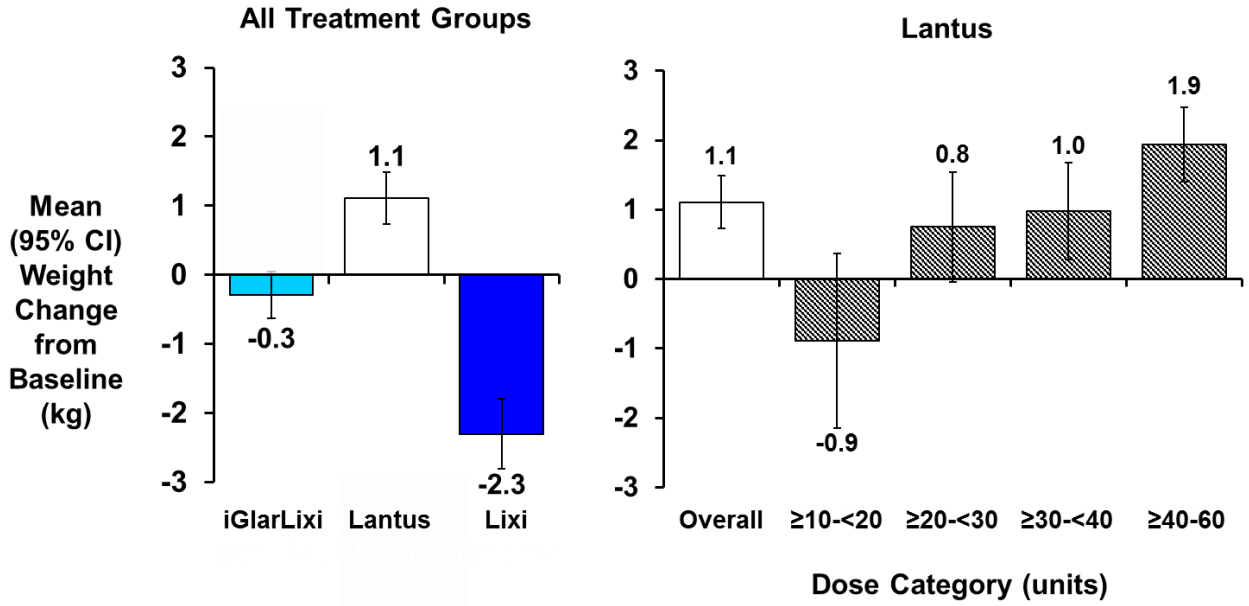


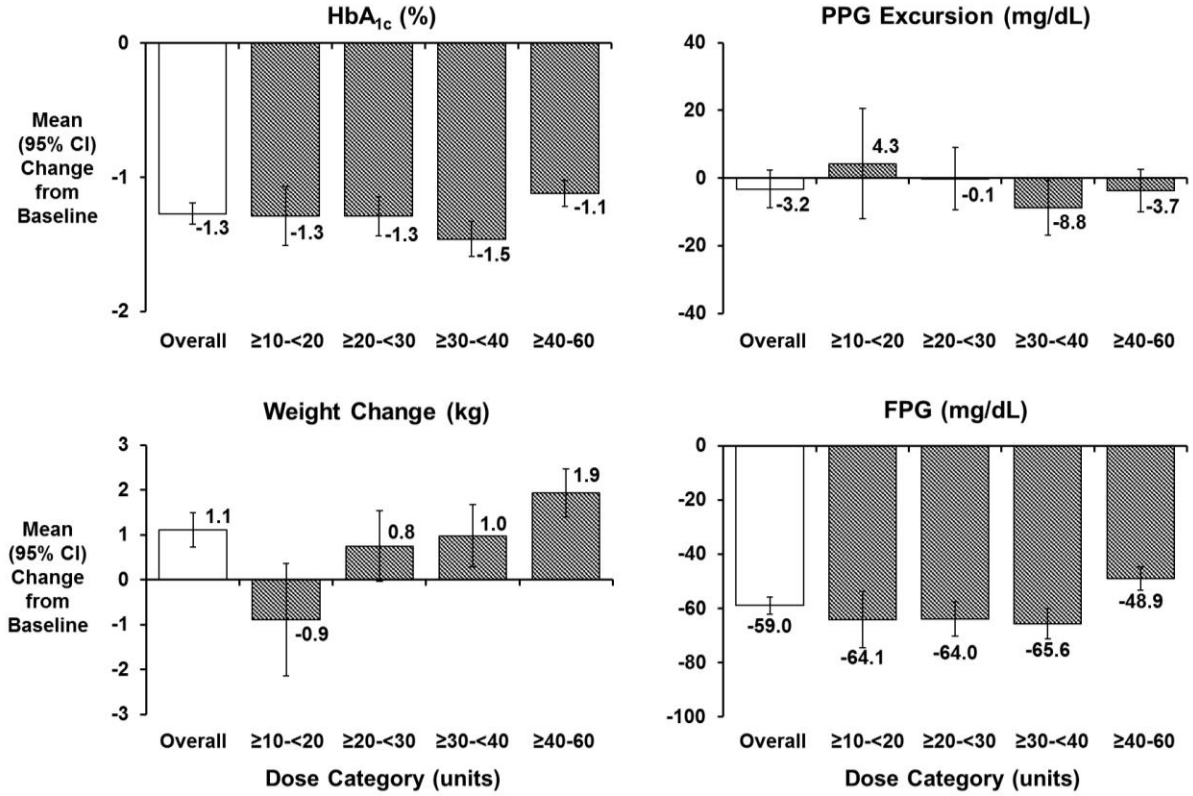
Figure 30 – Study EFC12404: Mean change in weight from baseline to Week 30 with insulin glargine treatment by final daily insulin dose category (mITT population)



Overall, the results demonstrate that both components (insulin glargine and lixisenatide) contribute to the efficacy of iGlarLixi across the lixisenatide and insulin glargine dose-ranges in EFC12404. Further, these analyses showed a positive benefit-risk balance at all dose levels of iGlarLixi, similar to the balance observed in the overall individual study results.

The mean changes in HbA1c and FPG from baseline to Week 30 were also comparable across final daily insulin dose-categories within the insulin glargine arm; the results by dose category were similar to the overall treatment group results (Figure 31). Across final daily insulin dose-categories in the insulin glargine arm, weight gain was observed at all but the lowest dose-category.

Figure 31 – Study EFC12404: Mean change in HbA1c, FPG, PPG, and body weight from baseline to Week 30 with insulin glargine treatment by final daily insulin dose category (mITT population)



Efficacy results for EFC12405 across the final insulin glargine dose range are similar and presented in Section 5.

The safety of iGlarLixi was also evaluated across the entire daily dose range. The results of these analyses showed consistency with the overall safety results and can be found in Section 5.

2.9.5 Robustness of efficacy findings

Sensitivity analyses with respect to missing data and rescue medication

Several sensitivity analyses were performed to investigate the potential impact of rescue medication and missing data (Section 8.3.2). The overall rate of missing data was low and the results of the sensitivity analyses are consistent with the main findings of the 2 pivotal studies.

Sensitivity analyses of study results with respect to insulin dosing

Sensitivity analyses to assess the effect of dose-capping the insulin glargine comparator at a daily dose of 60 U were performed. A "tipping point" analysis estimated the additional HbA1c benefit that would have been needed in the insulin glargine comparator group in order to make the treatment differences in HbA1c change from baseline no longer statistically significant.

This analysis evaluates the potential impact on the treatment effect if insulin glargine comparator doses >60 U had been allowed.

The results of these tipping point analyses (Table 63 and Table 64) demonstrated that a further change in HbA1c values by as much as -0.5% in glargine patients at 60 U would result in only a modest (30 to 40%) reduction in the treatment effect in both studies.

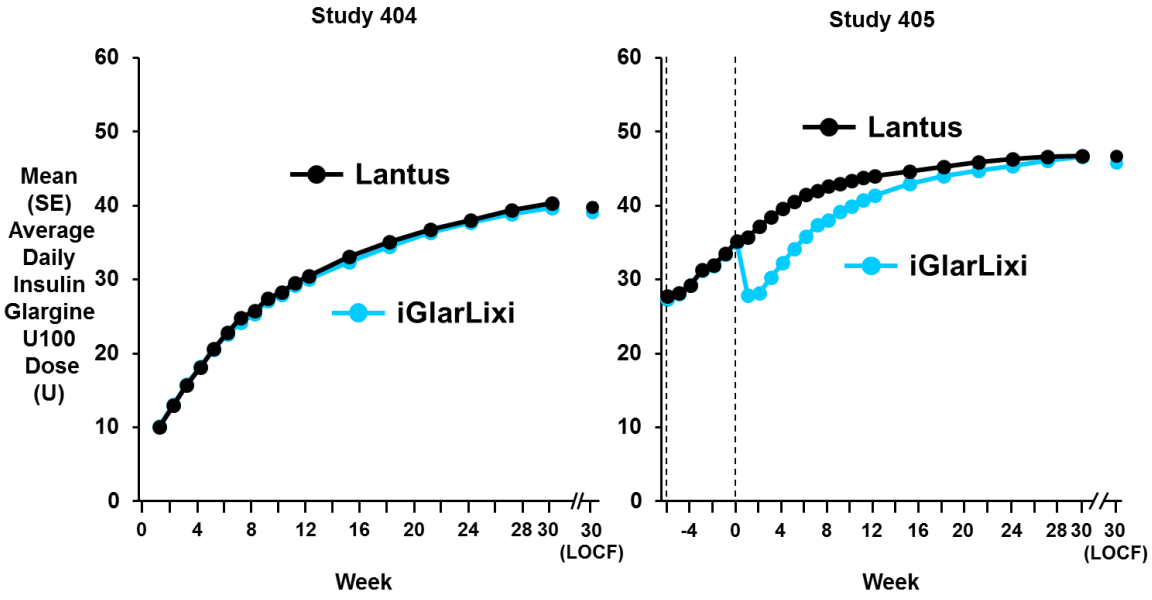
- For EFC12404, a >0.9% additional HbA1c reduction in these capped glargine patients would be required to lose the statistical significance for the treatment difference between the iGlarLixi and glargine treatment arms.
- For EFC12405, a -1.0% additional HbA1c change in these capped glargine patients would still keep the statistical significance between the iGlarLixi and glargine treatment arms.

The 60 U dose cap in the insulin glargine arms allowed for direct comparisons of the treatment effect between study arms. The results of the tipping point analysis indicate that the dose-capping had little impact on the study results and that allowing the insulin glargine comparator arm to rise beyond 60 U would have been unlikely to alter the observed treatment differences. The results of the tipping point analysis are not surprising from a clinical perspective since there is evidence that basal insulin doses >0.5 U/kg have limited additional glycemic efficacy while increasing the risks of hypoglycemia and weight gain in patients with T2DM (23, 24). Such observations are also reflected in the American Diabetes Association guidelines to consider additional therapies (e.g., meal time insulin or a GLP-1 receptor agonist) beyond just basal insulin when doses greater than 0.5 U/kg do not achieve glycemic control (5). Of note, for individuals in the insulin glargine arms who reached a final daily insulin dose of 60 U, the average daily insulin dose/body weight (U/kg) reached 0.60 and 0.66 U/kg at Week 30, in EFC12404 (insulin-naïve) and EFC12405 (previously insulin-treated), respectively.

Effect of titration on results

Because the trials were open-label, the Sponsor looked at insulin doses over time to confirm that differences in titration between the iGlarLixi and insulin glargine arms did not affect the results. It is important to recognize that lixisenatide has only a negligible effect on FPG (Figure 21 and Figure 24). Therefore, since titration decisions are based on fasting SMPG values, it is unlikely that dose titration would have varied significantly between the glargine and iGlarLixi arms in EFC12404 and EFC405. This is evident in Figure 32 which illustrates insulin dosing over the course of both studies. In EFC12404, insulin doses were titrated similarly in both arms as evidenced by the superimposed curves of the average daily insulin dose over time. Similarly, in EFC12405 after the first 12 weeks of treatment, curves for the average daily insulin doses are also superimposed. The initial insulin dose reduction observed in the iGlarLixi arm was mandated by the need to comply with the maximum lixisenatide starting dose of 10 µg. These data demonstrate that no bias was introduced by differential titration in the glargine and iGlarLixi arms. This was not unexpected given that lixisenatide in a fixed-ratio combination with insulin glargine provides a negligible effect on FPG levels.

Figure 32 – Studies EFC12404 and EFC12405: Similar titrations were performed in iGlarLixi and insulin glargine arms



2.10 OVERVIEW OF SAFETY

2.10.1 Safety findings: lixisenatide

As of 02 March 2015 (the cut-off date for lixisenatide safety data), a total of 7,874 patients were exposed to lixisenatide in the Phase 2/3 studies, 3,031 of them from the CV outcomes study (ELIXA). There were 6,000 patients exposed for ≥24 weeks, 4,474 for more than 1 year, and 1,661 for more than 2 years (Table 27).

2.10.1.1 Phase 3 placebo-controlled study pool

The Phase 3 placebo-controlled study pool (N=4508) during the main treatment period (24 weeks) was the primary basis for the assessment of frequent events.

- The percentage of patients with at least one TEAE was higher with lixisenatide (70.2%) than with placebo (62.3%), primarily due to TEAEs in the GI System Organ Class (SOC) (39.7% for lixisenatide and 18.4% for placebo).
- Nausea was the most frequently reported TEAE with lixisenatide (25.3% versus 6.0% with placebo) and vomiting was the third most frequent (9.8% versus 1.8% with placebo).
- Hypoglycemia was the second most commonly reported TEAE in patients treated with lixisenatide. Lixisenatide was associated with a low risk of hypoglycemia as monotherapy or in combination with metformin or a thiazolidinedione, and a limited additional risk in combination with a SU or basal insulin.
- The percentage of patients with injection site reactions was 4.0% in the lixisenatide group and 1.8% in the placebo group. The majority of injection site reactions were mild; there were no serious or severe events reported. Few patients (0.2%) discontinued treatment due to injection site reactions.
- To assess the impact of longer term treatment on the incidence of serious TEAEs, these were examined over the entire treatment period of 12 to 24 to ≥76 weeks. The incidence of serious TEAEs was similar in both treatment groups (8.5% with lixisenatide and 7.8% with placebo) in the Phase 3 placebo-controlled pool.
- TEAEs leading to death were reported by 0.1% and 0.2% of patients in the lixisenatide and placebo groups, respectively.
- The incidence of permanent treatment discontinuation in patients with any TEAE was 7.2% in the lixisenatide group and 3.2% in the placebo group. The most frequently reported TEAEs by preferred term (PT) that led to permanent treatment discontinuation in the lixisenatide group were (lixisenatide versus placebo): nausea (2.8% versus 0), vomiting (1.2% versus 0), dizziness (0.6% versus <0.1%), diarrhea (0.4% versus <0.1%), and hypoglycemia (0.3% versus 0).
- Immunogenicity based on anti-lixisenatide antibodies: The percentage of lixisenatide-treated patients with common TEAEs was similar in ADA-positive patients (71.2%) and ADA-negative patients (68.8%), compared with a percentage of 2.3% in the placebo group.
    - There was no relevant imbalance in the percentage of patients with common TEAEs when analyzed by ADA status for any SOC, PT, or High Level Term (HLT) apart from the injection site reactions HLT.
    - Injection site reactions at the HLT level (PTs coded from the Investigator verbatim term) were reported more frequently in the ADA-positive (84 [4.8%] patients) than in the ADA-negative (19 [1.9%] patients) and placebo groups (26 [1.6%] patients.

2.10.1.2 Phase 2/3 study pool

The Phase 2/3 study pool (N=13,433) was used to assess events of special interest to the GLP-1 receptor agonist class.

Pancreatitis events and any increase in amylase and/or lipase >2 x Upper Limit of Normal (ULN) confirmed by a repeat measurement, were to be specifically documented. In addition, an independent Pancreatic Safety Adjudication Committee (PSAC) was established in 2013 to review and assess, in a blinded manner, pancreatic TEAEs in the ongoing studies at the time, including ELIXA and EFC12626.

- In the Phase 2/3 placebo-controlled studies, the percentage of patients with any pancreatitis TEAEs in the acute and chronic pancreatitis HLT was 0.3% with both lixisenatide (20 patients) and placebo (13 patients). The EAIR of pancreatitis TEAEs per 100 patient-years was 0.22 with lixisenatide and 0.17 with placebo.
- In ELIXA, the percentage of patients with suspected pancreatitis sent for adjudication during the on-treatment period was comparable between lixisenatide and placebo (36 patients [1.2%] versus 32 patients [1.1%], respectively). Fewer patients in the lixisenatide group had TEAEs of any type of pancreatitis as confirmed by the PSAC (5 [0.2%] patients versus 8 [0.3%] patients, respectively).

For **malignant pancreatic neoplasms**, potential events were reviewed and adjudicated by the same PSAC that reviewed and adjudicated potential pancreatitis events. A total of 8 (0.1%) patients treated with lixisenatide and 11 (0.2%) patients treated with placebo had suspected pancreatic neoplasms that were sent to the PSAC during the on- and post-treatment period. Among them, 5 (<0.1%) patients treated with lixisenatide and 9 (0.2%) patients treated with placebo had pancreatic neoplasms adjudicated as pancreatic malignant. In all Phase 2/3 studies, 7 (<0.1%) patients treated with lixisenatide had malignant pancreatic neoplasm as adjudicated by the PSAC.

Allergic reactions, including anaphylaxis, have been reported with a variety of peptide medications, including the GLP-1 receptor agonists. During the lixisenatide development program, these events were actively solicited as an event of special interest, and thoroughly evaluated via independent, blinded expert case adjudication. Among the adjudicated allergic reactions, urticaria was the most common manifestation of allergy, accounting for more than one-third of all drug-related reactions (Table 54).

- Adverse events adjudicated as allergic reactions by the Allergic Reaction Assessment Committee (ARAC): Across the Phase 2/3 controlled trials, more than 400 suspected allergic events were referred to the ARAC for adjudication. The incidence of confirmed allergic reaction was low overall, with 1.4% of lixisenatide-treated and 0.8% of comparator-treated patients having positively-adjudicated allergic events. The majority of allergic events occurring in patients in either treatment group were attributed to causes other than study drug. However, possibly-related events were more common with lixisenatide than with control, giving an EAIR of 0.3 allergic reactions per 100 patient-years and an exposure-adjusted relative risk of 2.19.

- There were 9 events adjudicated as anaphylactic reaction and 1 event of anaphylactic shock for lixisenatide versus no such events in the control group. However, the majority of these events did not involve hypotension or severe multisystem manifestations, and most could be managed in the ambulatory care setting with antihistamines and/or corticosteroids. These events are described in Section 8.6.
- Review of the published literature for hypersensitivity and anaphylaxis, performed to provide some context for these events among the class of GLP-1 receptor agonists, revealed rates of hypersensitivity which were higher for both lixisenatide and placebo than described for the marketed GLP-1 receptor agonists. The difference in rates most likely reflects the active case ascertainment and adjudication processes employed in the lixisenatide development program rather than a material difference in incidence.
- Analysis of the comparative incidence of anaphylaxis was evaluable in a single pooled analysis for dulaglutide. The rate of anaphylaxis observed with dulaglutide in the pooled Phase 2 and 3 randomized controlled trials was 0.3%, a rate not dissimilar to the incidence for these events seen with lixisenatide. In the remaining published results, study sizes were too small (i.e., 150 to 500 patients per treatment group) to reliably assess this rare risk. In total, the published data suggest that the incidence of hypersensitivity and anaphylaxis seen with lixisenatide are not inconsistent with that seen with the marketed GLP-1 receptor agonists.

Cardiovascular Safety: The primary CV safety assessment is based on the results of the CV outcomes Study EFC11319 (ELIXA) which is discussed in the following section.

2.10.1.3 Cardiovascular safety in ELIXA

ELIXA was designed to fulfill the FDA requirement for the evaluation of the CV effects of new antidiabetic therapies in patients with T2DM issued in December 2008, i.e., to exclude an unacceptable increase (>30%) in CV risk (25).

Study design

ELIXA was a double-blind, placebo-controlled, 1:1 randomized, 2-arm, multinational Phase 3 study conducted in adult patients ≥30 years of age with T2DM. Patients had to have been admitted to an acute-care facility for a biomarker-proven, spontaneous acute coronary syndrome (ACS) event within 180 days before screening. The duration of the study was event driven. Approximately 844 positively-adjudicated CV events were planned for evaluation of the primary CV endpoint (i.e., 844 patients with at least one positively-adjudicated primary CV endpoint event).

Glycemic control during the study was managed by the investigators in accordance with local clinical practice guidelines by the adjustment of concomitant glucose-lowering agents or the addition of new antidiabetic medications with the exception of other incretin therapies (GLP-1 receptor agonists or DPP-IV inhibitors). This approach was expected to yield similar glycemic control in the two study groups.

The CV endpoints were adjudicated by a Cardiovascular Events Adjudication Committee (CAC) and was composed of experts in the field of CV or cerebrovascular diseases, independent from the sponsor and the investigators. The CAC was responsible for defining and validating the definitions of the components of the primary and secondary CV outcomes, and for classifying, in a blinded fashion, clinical events as satisfying these definitions, as well as validating the classification of the cause of all deaths.

Patient disposition

A total of 6,068 randomized patients were treated with lixisenatide or placebo; median exposure was 23.3 months for placebo and 22.4 months for lixisenatide.

More than 96% of patients in both treatment groups completed the study and vital status at the end of the study was known for >98% of patients in both treatment groups. Demographics and disease characteristics were well-balanced between groups as was the use of concomitant antidiabetic medications. A more detailed presentation of the ELIXA study is provided in Section 6.5.

CV safety results

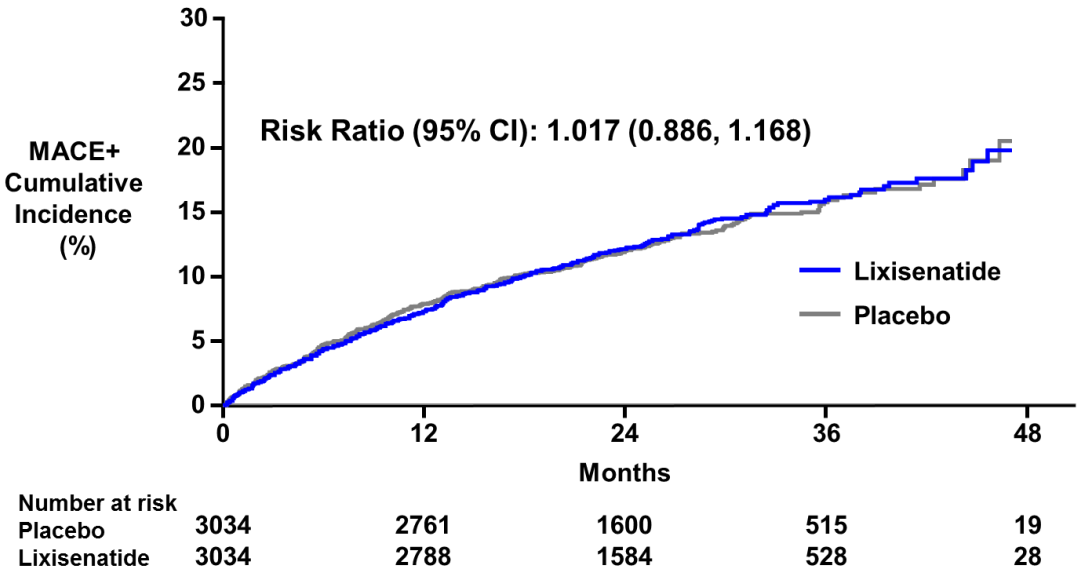
To exclude an unacceptable increase in CV risk, events of MACE and MACE+ composite outcomes were evaluated:

- MACE+: CV death, non-fatal MI, non-fatal stroke or hospitalization for unstable angina; these events comprised the primary composite endpoint.
- MACE: CV death, non-fatal MI, non-fatal stroke

There were 805 patients with at least one positively adjudicated primary CV endpoint during the study. The percentage of patients with a primary CV endpoint (13.4% and 13.2% for lixisenatide and placebo, respectively) was comparable between treatment groups with a HR of 1.017 (95% CI, 0.886 to 1.168). The upper bound of the 2-sided 95% CI was below the prespecified non-inferiority margin of 1.3 but above 1.0; thus, lixisenatide demonstrated non-inferiority but did not show superiority versus placebo for the primary CV endpoint.

The percentage of patients with each type of CV endpoint event included in the primary composite endpoint was comparable between treatment groups. Further, Kaplan-Meier cumulative curves of time from randomization to the first primary CV endpoint event for lixisenatide and placebo were superimposed for the majority of the study period (Figure 33).

Figure 33 – ELIXA: Kaplan-Meier cumulative curves of the primary CV endpoint (ITT population)



MACE+ = CV death, non-fatal MI, non-fatal stroke and hospitalization for unstable angina.

The results of the analyses of the primary composite CV endpoint were consistent between treatment groups by gender, age, race, ethnicity, and duration of time between the qualifying ACS event and randomization.

Consistent with the analyses of the primary CV endpoint, the event rates of composite secondary endpoints adding "hospitalization for heart failure" or both "hospitalization for heart failure" and "coronary revascularization" were comparable between treatments. There was no signal for increased risk of heart failure; rates of hospitalization for heart failure were 4.0% and 4.2% for lixisenatide and placebo, respectively.

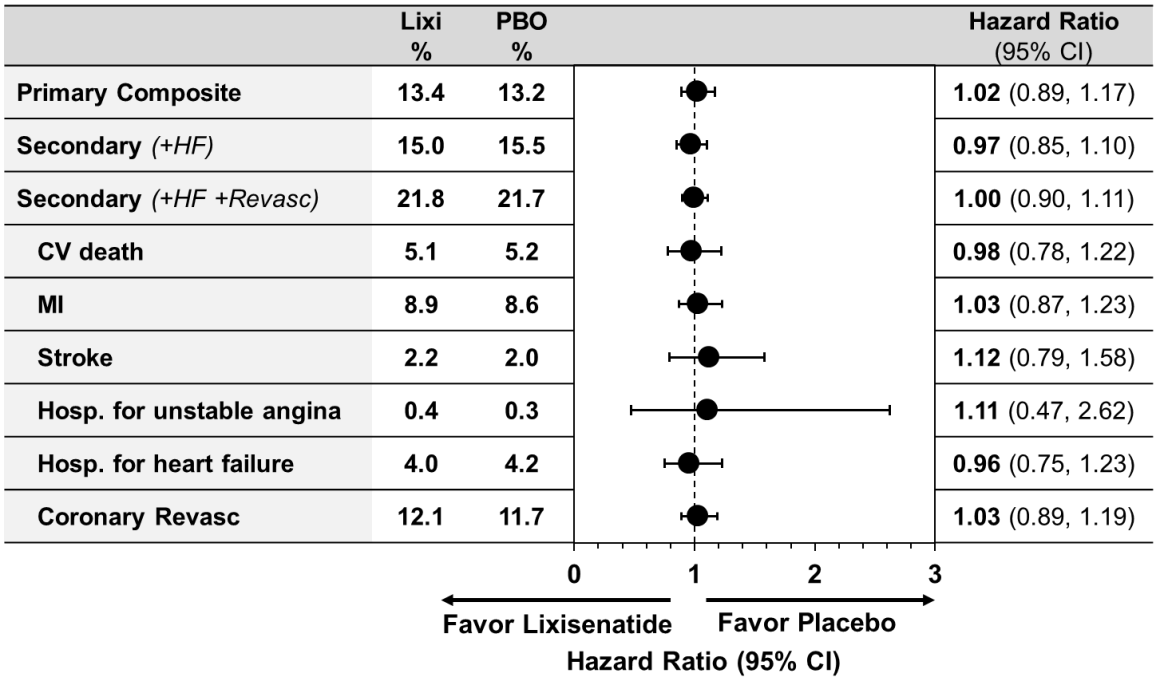
The results of the analysis of the composite MACE endpoint were consistent with the findings for the primary composite endpoint, with comparable event rates between treatment groups. The HR was 1.02 with an associated upper bound of the 2-sided 95% CI below 1.3.

In the analysis of time to death from any cause, there was no imbalance between lixisenatide and placebo; the HR for lixisenatide was 0.937 with a 2-sided 95% CI of 0.776 to 1.131.

In addition to non-inferiority on the CV indicators of macrovascular pathologies associated with T2DM, lixisenatide appeared to reduce the progression of albuminuria, an important microvascular complication of T2DM. The difference in percent change between lixisenatide and placebo on the secondary endpoint of urinary albumin/creatinine ratio from baseline to Week 108 was -0.10% (95% CI: -0.17, -0.03).

In conclusion, in the primary analysis of ELIXA, lixisenatide achieved non-inferiority versus placebo. Therefore, it was shown to have an acceptable CV safety profile when administered chronically to patients with T2DM at high CV risk. The CV safety of lixisenatide was demonstrated for all components of the composite primary and secondary CV endpoints (Figure 34).

Figure 34 – ELIXA: Consistent effects on all composite and individual components of the primary and secondary CV endpoints



2.10.2 Safety findings: iGlarLixi

The iGlarLixi clinical program provides a safety database with over 530 patient-years of exposure to iGlarLixi in combined Phase 2/3 studies. The CV safety of iGlarLixi is supported by 2 large CV outcome trials performed with each component alone, ORIGIN for insulin glargine (7) and ELIXA for lixisenatide (1).

In both populations studied (insulin-naïve and previously insulin-treated), iGlarLixi was well-tolerated and the safety profile was consistent with the profiles of its monocomponents.

The Phase 3 controlled study pool (N=1899) was used for the assessment of frequent events.

- The percentage of patients with at least one TEAE was 55.4% for iGlarLixi versus 50.2% for insulin glargine; the percentage for lixisenatide was 67.4%.
- The incidence of serious TEAEs was similar in the iGlarLixi, insulin glargine, and lixisenatide treatment groups: 4.6%, 4.4%, and 3.9%, respectively.
- The proportion of patients with a TEAE leading to death was comparable across treatment groups, 3 patients (0.4%) in the iGlarLixi group, 5 patients (0.6%) in the insulin glargine group, and 1 patient (0.4%) in the lixisenatide group.
- The proportion of patients permanently discontinuing due to TEAEs was low in the iGlarLixi (2.6%) and insulin glargine (1.4%) treatment groups, while in the lixisenatide group, the proportion was more than 3-fold higher at 9.0%.

  - The difference between the lixisenatide and iGlarLixi treatment groups was largely due to the higher frequency of TEAEs in the GI disorders SOC in the lixisenatide group of Study EFC12404, 12 patients (5.2%) versus 4 patients (0.9%) in the iGlarLixi group.
- The majority of TEAEs in all 3 treatment groups were mild to moderate. Severe events occurred in low numbers of patients, 20 patients (2.4%) in the iGlarLixi group, 26 patients (3.1%) in the insulin glargine group, and 11 patients (4.7%) in the lixisenatide group.

The frequency and types of on-treatment AEs, serious AEs, deaths, TEAEs leading to premature treatment discontinuation, and TEAEs of special interest for the GLP-1 receptor agonist class did not reveal any new safety signals in the iGlarLixi treatment group. The pooled safety data show that treatment with iGlarLixi was not associated with an increased risk of independently adjudicated CV events, pancreatitis, or malignant pancreatic neoplasm.

Initiation of insulin is typically associated with a risk of hypoglycemia. In patients failing metformin ± a second OAD in Study EFC12404, the number of events of documented symptomatic hypoglycemia per patient-year (plasma glucose ≤70 mg/dL) was comparable in the iGlarLixi (25.6%) and insulin glargine (23.6%) treatment groups. The number of events per patient-year was low and comparable between groups, 1.44 for iGlarLixi and 1.22 for insulin glargine. No events of severe or serious hypoglycemia were reported in the iGlarLixi group and no events of hypoglycemia led to permanent discontinuation. Thus, in this insulin-naïve population, initiation of iGlarLixi provided significant improvements in HbA1c levels relative to insulin glargine alone, in the absence of an increased risk of hypoglycemia.

In the previously insulin-treated population in Study EFC12405, the intensification of insulin with iGlarLixi provided a significant reduction in HbA1c versus insulin glargine alone without an additional risk of hypoglycemia. The incidence of documented symptomatic hypoglycemia was 40.0% and 42.5% in the iGlarLixi and insulin glargine groups, respectively. The number of events per patient-year was lower in the iGlarLixi group (3.03) compared to the insulin glargine group (4.22). Four patients (1.1%) in the iGlarLixi group and one patient (0.3%) in the insulin glargine group had events of severe hypoglycemia.

In both study populations, iGlarLixi mitigated the GI side effect profile that is typical of the GLP-1 receptor agonist class. Compared to lixisenatide, iGlarLixi had lower rates of nausea and vomiting, leading to fewer permanent treatment discontinuations. Whereas GI effects mainly occur during the initial dosing period with lixisenatide and with GLP-1 receptor agonists in general, a blunting of this phenomenon was observed during the initial iGlarLixi dosing period. The reduced incidence of GI TEAEs is most likely related to the gradual dose increase of the lixisenatide component occurring in parallel to the up-titration of insulin, which is a design feature of the fixed-ratio combination of insulin glargine and lixisenatide. In addition, in Study EFC12404, the lixisenatide initiation dose was 5 µg.

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 4.2.3.3.1and Section 4.3.3.3.1).

2.11 BENEFIT/RISK: LIXISENATIDE AND IGLARLIXI

The benefit/risk of lixisenatide and iGlarLixi is best discussed in the context of the profile of the patients for whom these products are most appropriate.

Benefits in patients who are inadequately controlled on OADs

The lixisenatide clinical development program demonstrated that lixisenatide is effective and well-tolerated at a maintenance dose of 20 µg QD in patients suboptimally controlled on OADs. Lixisenatide provides clinically relevant reductions in HbA1c, robust reductions in PPG levels, a beneficial effect on body weight, and a minimal risk of hypoglycemia. Monnier has shown that PPG is an important component of total hyperglycemia, and the closer a patient is to goal, the more dominant is the PPG contribution (Figure 2). Given the fact that lixisenatide primarily affects PPG levels, patients in whom FPG levels are close to target but who have not achieved HbA1c goal are the most appropriate population for lixisenatide treatment.

In all placebo-controlled efficacy and safety studies, the percentage of HbA1c responders was significantly higher for lixisenatide as compared to placebo. Up to 56.3% of lixisenatide-treated patients had an HbA1c <7.0% at the end of the main treatment period, depending on background treatment and baseline HbA1c.

In this patient population, lixisenatide offers an easy-to-use, once-daily subcutaneous injection from a single-dose pen-like injector with a 1-step dose escalation to the maintenance dose.

In patients uncontrolled on OADs who are in need of both FPG and PPG improvements, iGlarLixi may provide the better treatment option because the following benefits have been observed in the clinical development program:

- Improved glycemic control as compared to its individual components through complementary benefits on both FPG and PPG, while
- Avoiding the weight gain typically seen with the initiation of insulin therapy,
- Avoiding an increased risk of hypoglycemia compared to insulin glargine alone despite the better overall glycemic control,
- Blunting of the GI intolerability typically seen with the initiation of a GLP-1 receptor agonist used alone, a cause of permanent treatment discontinuation, and
- Offering a simple once-daily, titratable injection regimen based on the established SoloStar platform, without an increase in treatment complexity

Benefits in patients who are inadequately controlled on basal insulin

The PPG-lowering effect of lixisenatide complements the FPG-lowering effect of basal insulin, effectively addressing both components of hyperglycemia. The addition of lixisenatide once-daily to a basal insulin regimen was evaluated in four Phase 3 studies and showed reductions in HbA1c similar to those obtained with basal plus rapid-acting prandial insulin regimens. Additionally, better outcomes on body weight and hypoglycemia were achieved. These results demonstrate that

lixisenatide is an attractive alternative therapeutic option compared to prandial insulin in patients not achieving target glycemic control with basal insulin.

In patients uncontrolled on basal insulin, iGlarLixi led to a statistically significant and medically relevant improvement in HbA1c. The superior glycemic control can be ascribed to the complementary effects of lixisenatide and insulin glargine on glucose levels. It allowed more patients to reach HbA1c targets while preventing or minimizing the body weight gain usually observed at intensification of an insulin-based therapy, with no additional risk of hypoglycemia as compared to insulin glargine alone. iGlarLixi is therefore an attractive option for treatment intensification in patients already on basal insulin, without increasing treatment complexity by adding-on an additional injection (GLP-1 receptor agonist) or additional injection(s) with the need for increased glucose self-monitoring and carbohydrate counting (prandial insulin).

Risks of lixisenatide and iGlarLixi

In general, the data from the clinical program show that lixisenatide was safe and well-tolerated by the majority of patients. Nausea, hypoglycemia, and vomiting were the most commonly reported TEAEs. Reported events of nausea and vomiting were mostly mild in intensity, transient, and usually occurred within the first few weeks of treatment initiation.

The risk of hypoglycemia with lixisenatide monotherapy or in combination with metformin was low. There was a limited additional risk in combination with a SU or basal insulin.

There was no evidence that lixisenatide carries additional risks of pancreatitis, malignant pancreatic neoplasm, or thyroid malignancy beyond the background rates generally seen in patients with T2DM. Lixisenatide is associated with a potential for infrequent allergic reactions; however, clinically severe anaphylaxis or shock is rare. In total, the published data suggest that the incidence of hypersensitivity and anaphylaxis seen with lixisenatide are not inconsistent with that seen with marketed GLP-1 receptor agonists.

iGlarLixi was generally well tolerated. The aforementioned improvement in glycemic control was achieved with a safety profile that reflected that of the iGlarLixi components. Compared to lixisenatide (Section 6.4.1), iGlarLixi had markedly lower rates of nausea and vomiting (Section 6.8.1), leading to fewer permanent treatment discontinuations (Section 6.8.5). GI side effects are known to be among the main reasons for discontinuation of GLP-1 receptor agonists. Whereas GI effects mainly occur during the initial dosing period with lixisenatide and with GLP-1 receptor agonists in general, a blunting of this phenomenon was observed with introduction of iGlarLixi treatment. This is most likely related to the more gradual increase of the lixisenatide dose in parallel to the up-titration of insulin that is inherent to the concept of the iGlarLixi fixed-dose combination.

Cardiovascular safety

For both lixisenatide and insulin glargine, large, randomized, CV outcomes studies have been completed (1, 7). These studies unequivocally established the CV safety of each compound. In addition, these studies provided large placebo-controlled safety databases to better establish the risks of several other events of interest, such as the incidence of cancer, pancreatitis, and thyroid

tumors. Both studies confirmed the safety profiles of insulin glargine and lixisenatide that was established in clinical use and in the Phase 3 programs.

Lixisenatide dose

The 20 µg QD dose selection is supported by efficacy and safety results in 7874 patients with >10,000 patient-years of exposure. Across all Phase 3 studies, treatment with lixisenatide 20 µg QD either as monotherapy or as an add-on to ongoing treatment with metformin, SU, or basal insulin in various combinations was superior to placebo for reduction in HbA1c.

In addition, supportive data from the lixisenatide clinical development program have demonstrated clinically meaningful glycemic efficacy at doses starting at 5 µg (Section 2.5.1.3). The dose-range selected for iGlarLixi is therefore a logical choice for a product that is meant to be titrated according to patient's individual needs.

In order to confirm the choice of the dose-range for iGlarLixi, analyses were performed to address the question of whether the contribution of the components to both efficacy and safety was present across the entirety of the dose-range. These analyses have shown that the strategy of iGlarLixi titrated according to individual patients' needs was appropriate. While the trials were not designed to assess benefit/risk per dose level, these analyses indicated a positive benefit-risk balance at all dose levels of iGlarLixi, similar to the balance observed in the overall individual study results.

Durability of effect

Persistence of efficacy has already been demonstrated over extended periods of exposure for each component of the combination. Accordingly, the iGlarLixi Phase 2/3 studies, which ranged from 24 to 30 weeks of treatment, were considered as sufficient to assess benefit-risk. Based on the composite data from the stand-alone components and the iGlarLixi development program, iGlarLixi is expected to provide durable efficacy.

Benefit/Risk conclusions

Since 2013 lixisenatide has been marketed in Europe and subsequently around the world. The overall safety profile for lixisenatide has been well-characterized including a placebo-controlled CV outcomes trial (ELIXA) (1). Moreover, the safety profile of insulin glargine has also been well-established in over a decade and a half of global use. Its safety profile was confirmed in a large, randomized, controlled CV outcomes study (ORIGIN) (7). The data strongly suggest that these products when used individually, or in co-administration with other products as well as in a fixed-ratio combination with each other, have a well-grounded safety profile consistent with other marketed insulins and GLP-1 receptor agonists.

The pharmacodynamic profile of lixisenatide provides strong support for its use in patients who are in need of improvement of their postprandial hyperglycemia. Lixisenatide is appropriate both for patients who are close to HbA1c target on OADs but need treatment intensification or for patients on basal insulin whose HbA1c elevation is primarily driven by PPG excursions.

Combination therapies are generally considered as a more convenient alternative to taking the individual components separately. Once a patient is in need of intensification after failure on multiple oral therapies, the increased complexity of treatment will be daunting for patients and physicians alike. The iGlarLixi data indicate that initiation with the combination of insulin glargine and lixisenatide presents benefits to the patient that go beyond the convenience of two products in a titratable, single, QD injection. These benefits are encapsulated by the fact that each of the components complements the anti-hyperglycemic effects and mitigates the shortcomings of the other, and that there is simply no other way to achieve these benefits other than through the use of a combination product such as iGlarLixi. In particular, the gradual dose increase of lixisenatide, which results in better GI tolerability than with lixisenatide alone cannot be achieved in any other way. As the simultaneous initiation of two injectable therapies at the same time would be considered unacceptable by patients and physicians, iGlarLixi rises above the mere convenience factor common to most combination products. Thus from a practical patient and physician perspective, the efficacy, safety, and convenience of iGlarLixi's single-injection therapy is clinically relevant and addresses an unmet medical need.

In summary:

- iGlarLixi, given once-daily from a single pen-injector, provides simplicity in the initiation/intensification of basal insulin therapy based on titration to individualized patient needs.
- With a complementary mode of action that targets both FPG and PPG levels, iGlarLixi improves glycemic control more effectively than either component alone in the setting of improved tolerability and with mitigation of the weight gain typically seen with initiation and intensification of insulin therapy.

3 LIXISENATIDE EFFICACY IN 9 PHASE 3 PLACEBO-CONTROLLED STUDIES

3.1 STUDY DESIGN

The lixisenatide clinical program included 9 Phase 3 placebo-controlled efficacy and safety studies that were designed to demonstrate the superiority of lixisenatide versus placebo (Table 2).

The primary analysis of efficacy was conducted at the 24-week time point in all study protocols, except a monotherapy study that was conducted for 12 weeks. Additionally, 5 studies included long-term extensions to at least 76 weeks.

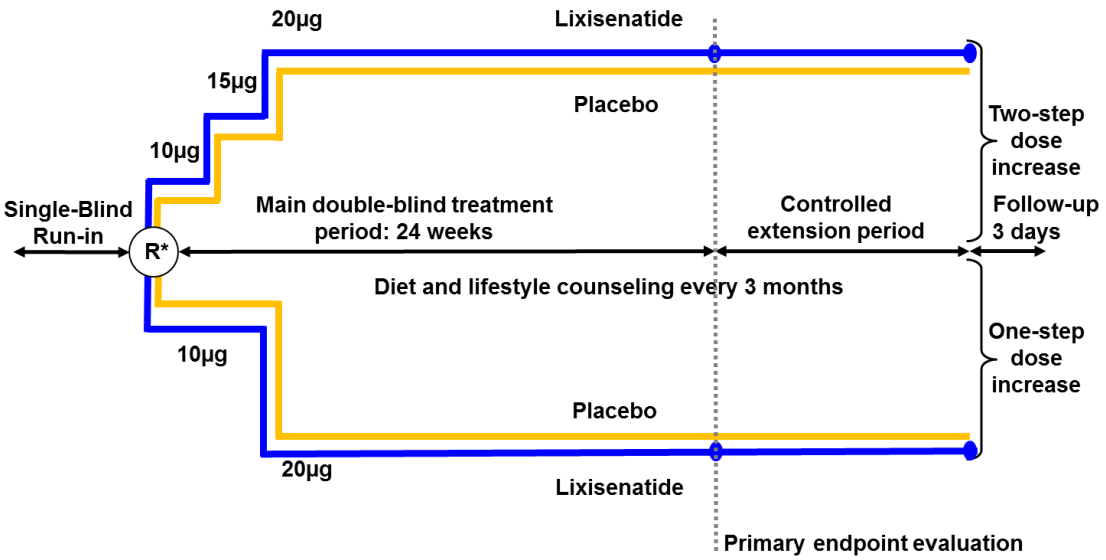
Table 2 – Phase 3 placebo-controlled studies of lixisenatide efficacy

Study Number	Treatment	Titration	Duration
EFC6014	Add-on to metformin alone	2-step	≥76 weeks
EFC6015	Add-on to a SU ± metformin	2-step	≥76 weeks
EFC6016	Add-on to basal insulin ± metformin	2-step	≥76 weeks
EFC6017	Add-on to pioglitazone ± metformin	2-step	≥76 weeks
EFC6018	Monotherapy	1-step and 2-step	12 weeks
EFC10743	Add-on to metformin alone	1-step and 2-step	≥76 weeks
EFC10781	Add-on to insulin glargine and metformin ± TZD	2-step	24 weeks
EFC10887[1]	Add-on to basal insulin ± SU	2-step	24 weeks
EFC11321[1]	Add-on to metformin ± SU	1-step	24 weeks

[1] Conducted in multinational Asian population.

Figure 35 presents a representative design of the 9 Phase 3 placebo-controlled efficacy and safety studies.

Figure 35: Representative design scheme for Phase 3 studies: Study EFC10743



*R=randomization

Key elements of the study design are as follows:

- Study drug was self-administered QD in the morning within 1 hour before breakfast.
- Lixisenatide was initiated with a 10 µg QD regimen, which was increased to the maintenance dose of 20 µg QD after 2 weeks (1-step titration). In the initial studies, a 2-step titration was used, starting with lixisenatide 10 µg QD for 1 week, followed by 15 µg QD for 1 week, and then 20 µg QD. The 2-step regimen did not provide an advantage with respect to glycemic efficacy or GI side effects (Section 3.2.3). The 1-step dose increase regimen was therefore chosen as the final dosing regimen.
- In all studies, the 20 µg maintenance dose could be decreased in case of poor GI tolerability. Another attempt to reach the 20 µg maintenance dose was made, but a patient was allowed to remain at the 10 or 15 µg dose if the maintenance dose of 20 µg could not be tolerated.
- In all Phase 3 trials, background antidiabetic medication had to be at a stable dose (generally for at least 3 months) before screening. In most of these studies, a 1-week single-blind placebo-controlled run-in period was performed, to fully assess baseline status and to train patients on self-injection. However, Study EFC10781, which enrolled insulin-naïve patients, included a 12-week run-in, in order to initiate and properly titrate insulin glargine and control FPG before randomization.
- Randomization was stratified by two factors in all Phase 3 studies: (1) screening values of HbA1c (<8 %, ≥8%) and (2) a second OAD at screening in studies that allowed more than 1 background OAD, or screening values of BMI (<30 kg/m^2, ≥ 30 kg/m^2) in monotherapy (EFC6018) or metformin alone studies (EFC6014 and EFC10743).

3.1.1 Inclusion and exclusion criteria

Inclusion and exclusion criteria were similar across the Phase 3 efficacy/safety studies. Patients were eligible for study entry if they met the following main criteria:

- Adult (i.e., >18 years old in most countries) male and female patients, with no upper age limit.
- T2DM as defined by World Health Organization (WHO) (i.e., FPG ≥126 mg/dL or 2-hour PPG ≥200 mg/dL) for at least 1 year. Slightly different criteria were used in some studies (i.e., T2DM for at least 2 months in Study EFC6018 since it was performed in patients who were not receiving antidiabetic medication).
- HbA1c between 7 and 10% inclusive and FPG ≤250 mg/dL at screening. In Study EFC10781 HbA1c had to be between 7 and 10% inclusive at screening and between 7 and 9% inclusive 1 week before randomization.
- BMI >20 kg/m² with no limit in Study EFC10887. Moreover, no patient with change in weight of more than 5 kg during the 3 months preceding the screening visit was allowed in most studies.

Patients were excluded if they had a recent (within 6 months of study entry) history of myocardial infarction, stroke, or heart failure; a history of unexplained pancreatitis, chronic pancreatitis, or pancreatectomy; clinically relevant history of GI disease associated with prolonged nausea and vomiting, including, but not limited to, gastroparesis and gastroesophageal reflux disease requiring medical treatment, within 6 months prior to the time of screening; or were experiencing uncontrolled hypertension.

3.1.2 Endpoints

The primary efficacy endpoint in the 9 Phase 3 placebo-controlled efficacy/ safety studies was the change from baseline in HbA1c at the primary efficacy time point (end of the main treatment period), which was Week 12 in Study EFC6018 and Week 24 in all others.

Main secondary endpoints included:

- Response rate defined as the percentage of patients with HbA1c <7% at the primary efficacy time point.
- Change in 2 hour PPG and glucose excursion (defined as 2 hour PPG minus plasma glucose 30 minutes prior to the prandial administration of study drug) from a standardized meal test, which was performed in Studies EFC6014, EFC6015, EFC6016, EFC6018, EFC10887, and EFC11321.
- Change from baseline in FPG and body weight at the primary efficacy time point.
- Percentage of patients requiring rescue therapy at the primary efficacy time point.
- Change in 7-point SMPG profiles (each time point and average) in basal insulin background studies EFC6016, EFC10781 and EFC10887.

Additional endpoints included:

- Change in basal insulin daily dose and total insulin daily dose from baseline/screening to Week 24 in Studies EFC6016 and EFC10887.
- Change in insulin glargine daily dose from baseline at Week 24 in Study EFC10781.

3.1.3 Statistical methodology

The primary efficacy analyses were conducted in a modified intent-to-treat (mITT) population defined as all randomized patients who received at least 1 dose of study drug and who had both a baseline assessment and at least one post-baseline assessment of any primary or secondary efficacy variable. Patient disposition by study and treatment group are provided in Appendix 8.4.1.

A parametric analysis of covariance (ANCOVA) model was the prespecified primary analysis of change from baseline in HbA1c to the primary efficacy time point. For the primary efficacy analysis, missing HbA1c values at the primary efficacy time point were imputed using the last observation carried forward (LOCF) procedure, as outlined in the FDA's guidance for the development of new drugs in T2DM (FDA 2008) that was available at the time the Phase 3 program was initiated in 2008. The ANCOVA model included treatment group, randomization strata, and country as fixed effects and the baseline HbA1c value as a covariate. The LS means and the 2-sided 95% CIs for the treatment difference were estimated from the ANCOVA model for each individual study, and the p-values for the LS mean difference were calculated for testing superiority of lixisenatide over placebo.

For the primary efficacy evaluation, data collected beyond the on-treatment period or obtained after the initiation of rescue therapy were excluded and imputed using LOCF. Section 8.4 summarizes patient disposition of the primary analysis of HbA1c change from baseline to the primary efficacy time point in the mITT population in 9 Phase 3 placebo-controlled studies. Multiple sensitivity analyses that handled missing data or data obtained after initiation of rescue therapy differently evaluated the robustness of the findings for the primary efficacy endpoint of HbA1c change from baseline.

Sensitivity analyses included a MMRM under the missing at random (MAR) framework and conservative methods under the missing not at random (MNAR) assumption based on recommendations from the National Research Council report on The Prevention and Treatment of Missing Data in Clinical Trials (NRC 2010): a pattern mixture model implemented with multiple imputation using jump to placebo (placebo-based imputation) and a baseline observation carried forward (BOCF)-like multiple imputation to account for uncertainty associated with missing data. In addition, a tipping point analysis was conducted by multiply imputing missing HbA1c values with a delta adjustment in the lixisenatide group. In the tipping point analysis, missing HbA1c values at each post baseline visit were imputed under the MAR assumption and a delta (HbA1c increase) was added to each imputed value in the lixisenatide group in the mITT population. These sensitivity analyses were based on all post baseline observations that included data collected after treatment discontinuation or initiation of rescue therapy.

For the primary analysis of HbA1c responders at 7%, the same approach of LOCF for handling the missing data in the HbA1c responder analysis was pre-specified and used. To assess the impact of missing data and imputation method on the responder analysis, sensitivity analyses were also performed by treating patients with missing HbA1c data at the primary efficacy time point as non-responders or by treating patients with missing HbA1c data or patients who initiated rescue therapy prior to the primary efficacy time point as non-responders in the mITT population. In addition, in order that no bias was introduced by using the mITT population instead of the true ITT population, an additional sensitivity analysis in all randomized patients was conducted by treating patients with missing HbA1c data at the primary efficacy time point in the ITT population as non-responders. These methods are described in Appendix 8.4.3.

All continuous secondary efficacy variables were analyzed using an ANCOVA model similar to that used for the primary efficacy endpoint. The categorical efficacy variables were analyzed using a Cochran-Mantel-Haenszel (CMH) method stratified by randomization strata.

The mean change in HbA1c from baseline to the primary efficacy time point was the only primary efficacy endpoint in the 9 placebo-controlled Phase 3 efficacy and safety studies. For each study, a step-down testing procedure was prespecified for assessment of the treatment differences of the primary and key secondary efficacy endpoints for controlling the Type 1 error rate at 5%.

For assessing the consistency of the HbA1c reduction at the primary efficacy time point by demography and baseline characteristics, a meta-analysis using the inverse of variance as weights was performed based on the pooled data of all 9 placebo-controlled studies in the mITT population.

The antibody effect on change in HbA1c to Week 24 was assessed based on the pooled data from the 8 Phase 3 placebo-controlled studies with at least 24-weeks of treatment (Studies EFC6014, EFC6015, EFC6016, EFC6017, EFC10743, EFC10781, EFC10887 and EFC11321) using the inverse of variance as weights across studies to estimate the weighted average of lixisenatide effect (LS mean) and associated 95% CI for the mITT population.

3.2 RESULTS

3.2.1 Patient disposition

The patient disposition by study and treatment group to the primary efficacy time point in these 9 studies is provided in Appendix 8.4.1.

3.2.2 Baseline demographics and disease characteristics

In each Phase 3 study, baseline demographics, HbA1c, and other efficacy variables were generally balanced across groups.

In the mITT population in each Phase 3 placebo controlled efficacy/safety study, baseline values of HbA1c and other efficacy variables were balanced across groups. Baseline HbA1c was between 7.96% to 8.12% in all groups with a mean of 8.0% in all studies in which lixisenatide

was used in monotherapy or add-on to metformin or pioglitazone, and ranged from 8.22% to 8.53% in studies in which lixisenatide was used as add-on to SU or basal insulin. Baseline HbA1c was approximately 7.6% in Study EFC10781 in which patients were optimally titrated with insulin glargine for 12 weeks prior to randomization, and mean baseline FPG was 119.17 mg/dL in this study.

3.2.3 Change in HbA1c from baseline to the primary efficacy time point

Across studies, the LS mean change in HbA1c from baseline to the primary efficacy time point (Week 12 or Week 24) in the lixisenatide treatment groups was approximately -0.8% (range of -0.71% to -0.92%) (Table 3). The difference between lixisenatide and placebo was statistically significant in all Phase 3 placebo-controlled studies based on the prespecified primary analysis ($p=0.0002$ for Study EFC6016; $p=0.0004$ for Study EFC11321; $p<0.0001$ in all other studies). The LS mean difference versus placebo ranged from -0.32% in Study EFC10781 to -0.88% in Study EFC10887.

Multiple sensitivity analyses that handled missing data or data obtained after initiation of rescue therapy differently evaluated the robustness of the findings for the primary efficacy endpoint as discussed in Section 3.1.3 and Section 8.4.3. The analyses showed consistent results, all demonstrating superiority over placebo. Results of the primary and the above sensitivity analyses are also provided in Section 8.4.3 for 3 studies (EFC6015, EFC6017 and EFC6016) that have a higher percentage of patients with missing HbA1c data at Week 24. In the tipping point analysis, an HbA1c increase of 3.6%, 1.2%, and 2.8% in Studies EFC6015, EFC6016 and EFC6017, respectively, to each imputed value in the lixisenatide group was required to tip the to lose a statistically significance treatment difference (Table 72).

3.2.3.1 Comparison of change in HbA1c between 1-step and 2-step dose titration regimens

There was no difference in HbA1c results between the 1- and 2-step dose titration regimens. In EFC6018 and EFC10743, separate statistical analyses were performed for the 1-step and 2-step dose titration groups and showed consistent results (LS mean changes: -0.73% for the 2-step group and -0.85% for the 1-step group in EFC6018; -0.83% for the 2-step group and -0.92% for the 1-step group in EFC10743). Clinically and statistically significant reductions in HbA1c vs. placebo ($p<0.0001$) occurred with both dose titration regimens in each study.

Table 3 - Mean change in HbA1c (%) from baseline to Week 24 in Phase 3 placebo-controlled efficacy/safety studies (mITT population)

		N	Baseline	LS Mean Change (SE)[a]	LS Mean Treatment Difference(SE)[ab]	95% CI[ab]	P-Value[ab]
Monotherapy	EFC6018						
	Placebo	112	8.07	-0.19 (0.121)			
	Lixisenatide 2-step dose increase	113	7.97	-0.73 (0.116)	-0.54 (0.123)	[-0.785, -0.300]	<.0001
	Lixisenatide 1-step dose increase	114	8.06	-0.85 (0.119)	-0.66 (0.122)	[-0.903, -0.423]	<.0001
Add-on Met alone	EFC6014						
	Placebo	164	8.02	-0.38 (0.075)			
	Lixisenatide morning	244	8.07	-0.87 (0.065)	-0.48 (0.088)	[-0.657, -0.312]	<.0001
	Lixisenatide evening	239	8.07	-0.75 (0.066)	-0.37 (0.088)	[-0.540, -0.193]	<.0001
	EFC10743						
	Placebo	158	8.03	-0.42 (0.099)			
	Lixisenatide 2-step dose increase	152	8.12	-0.83 (0.099)	-0.41 (0.089)	[-0.583, -0.232]	<.0001
	Lixisenatide 1-step dose increase	156	7.99	-0.92 (0.101)	-0.49 (0.090)	[-0.670, -0.317]	<.0001
Add-on to SU or SU+Met	EFC6015						
	Placebo	274	8.22	-0.10 (0.071)			
	Lixisenatide	544	8.28	-0.85 (0.061)	-0.74 (0.063)	[-0.867, -0.621]	<.0001
Add-on to Pio or Pio+Met	EFC6017						
	Placebo	148	8.05	-0.34 (0.100)			
	Lixisenatide	308	8.08	-0.90 (0.089)	-0.56 (0.088)	[-0.731, -0.386]	<.0001

		N	Baseline	LS Mean Change (SE)[a]	LS Mean Treatment Difference(SE)[ab]	95% CI[ab]	P-Value[ab]
Add-on to BI or BI+Met	EFC6016						
	Placebo	158	8.38	-0.38 (0.107)			
	Lixisenatide	304	8.39	-0.74 (0.090)	-0.36 (0.096)	[-0.550, -0.174]	0.0002
Add-on to IG+Met or IG+Met+TZD	EFC10781						
	Placebo	221	7.60	-0.40 (0.092)			
	Lixisenatide	215	7.56	-0.71 (0.091)	-0.32 (0.074)	[-0.463, -0.171]	<.0001
Asian studies							
Add-on to BI or BI+SU	EFC10887						
	Placebo	154	8.53	0.11 (0.131)			
	Lixisenatide	146	8.53	-0.77 (0.137)	-0.88 (0.118)	[-1.116, -0.650]	<.0001
Add-on to Met or Met+SU	EFC11321						
	Placebo	188	7.83	-0.47 (0.104)			
	Lixisenatide	185	7.95	-0.83 (0.102)	-0.36 (0.099)	[-0.551, -0.162]	0.0004

Met = Metformin, SU = Sulfonylurea, Pio = Pioglitazone, BI = Basal insulin, IG = Insulin glargine, TZD = Thiazolidinediones.
a Analysis of covariance (ANCOVA) model with treatment groups, randomization strata, and country as fixed effects and baseline HbA1c value as a covariate.
b Difference in LS Mean between lixisenatide and placebo.
Week 24 value is the last observation carried forward (LOCF) before initiation of rescue therapy on or before week 24 (week 12 for EFC6018).
Patients with both baseline and the Week 24 measurements are included.

3.2.3.2 Anti-lixisenatide antibody effect on change in HbA1c from baseline

At the end of the main treatment period in the 8 studies with at least 24 weeks of treatment (12-week study EFC6018 excluded) anti-lixisenatide antibody status with a concomitant HbA1c value was available in 1954 patients from the lixisenatide group, including 1333 (68.2%) assessed as antibody-positive in the mITT population and 621 (31.8%) assessed as antibody-negative. The LS mean change in HbA1c from baseline to Week 24 was similar regardless of the antibody status: -0.82% (95% CI: -0.895 to -0.755) in antibody-positive patients and -0.83% (95% CI: -0.920 to -0.746) in antibody-negative patients.

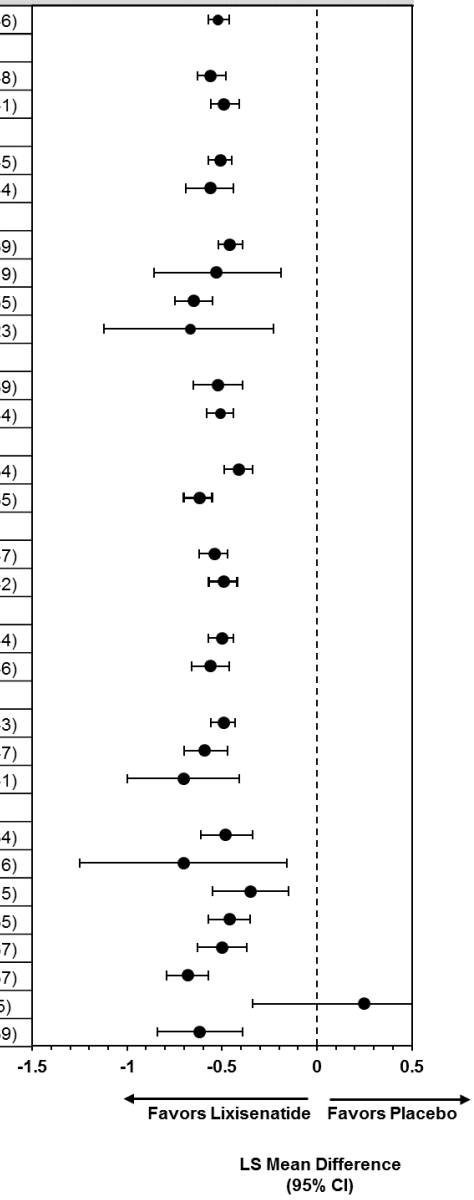
Additional analyses evaluated the effect of antibody concentration on efficacy at the end of the main treatment period (Week 24) in the same 8 studies. Most antibody-positive patients had antibody concentrations below the lower limit of quantification (LLOQ; 3.21 nmol/L) with a LS mean change in HbA1c of -0.88% at week 24. The LS mean change in HbA1c from baseline at Week 24 was -0.64% (95% CI: -0.751, -0.528) in the 370 lixisenatide-treated subjects with antibody concentration value between LLOQ and ≤100 nmol/L. In the 45 (2.4%) lixisenatide-treated subjects with antibody concentrations >100 nmol/L, the LS mean change in HbA1c from baseline at week 24 was -0.16 % (95% CI: -0.418, 0.096). A lower HbA1c reduction in patients with highest antibody concentrations is consistent with other GLP-1 agonists; however, antibody concentration is not predictive of individual response.

3.2.3.3 HbA1c change from baseline by patient subgroup

The findings for the LS mean difference in HbA1c were consistent by patient subgroup and region (Figure 36).

Figure 36 - Change In HbA1c (%) from baseline to Week 24 meta-analysis by baseline factors based on the pooled data of 9 Phase 3 placebo-controlled studies (mITT population)

	Lixi (N)	Lantus (N)	LS Mean Difference (95% CI)
Overall	2720	1577	-0.52 (-0.57, -0.46)
Gender			
Male	1296	778	-0.56 (-0.63, -0.48)
Female	1424	799	-0.49 (-0.56, -0.41)
Age			
<65	2239	1242	-0.51 (-0.57, -0.45)
≥65	481	335	-0.56 (-0.69, -0.44)
Race			
Caucasian/White	1808	928	-0.46 (-0.52, -0.39)
Black	69	41	-0.53 (-0.86, -0.19)
Asian/Oriental	792	587	-0.65 (-0.75, -0.55)
Other	51	21	-0.67 (-1.12, -0.23)
Ethnicity			
Hispanic	557	250	-0.52 (-0.65, -0.39)
Non Hispanic	1832	985	-0.51 (-0.58, -0.44)
Baseline HbA1c (%)			
<8.0	1316	785	-0.41 (-0.49, -0.34)
≥8.0	1404	792	-0.62 (-0.70, -0.55)
Baseline BMI (kg/m^2)			
<30	1294	802	-0.54 (-0.62, -0.47)
≥30	1426	775	-0.49 (-0.57, -0.42)
Duration of Diabetes (Years)			
<10	1896	1032	-0.50 (-0.57, -0.44)
≥10	824	545	-0.56 (-0.66, -0.46)
Baseline Renal Function (mL/min)			
>90	2002	1104	-0.49 (-0.56, -0.43)
≥60 - ≤90	592	404	-0.59 (-0.70, -0.47)
≥30 - <60	110	62	-0.70 (-1.00, -0.41)
Region			
North America	502	252	-0.48 (-0.61, -0.34)
Australia	28	15	-0.70 (-1.25, -0.16)
Western Europe	225	103	-0.35 (-0.55, -0.15)
Eastern Europe	661	368	-0.46 (-0.57, -0.35)
Central and South America	498	243	-0.50 (-0.63, -0.37)
Asia	613	476	-0.68 (-0.79, -0.57)
Middle East	16	17	0.25 (-0.34, 0.85)
India	138	90	-0.62 (-0.84, -0.39)



BMI = Body mass index, Studies included: EFC6014, EFC6015, EFC6016, EFC6017, EFC6018, EFC10743, EFC10781, EFC10887 and EFC11321.
A fixed-effect meta-analysis method with the inverse of variance as the weight was used.
Week 24 value is the last observation carried forward (LOCF) before initiation of rescue therapy on or before week 24 (week 12 for EFC6018).
Patients with both baseline and the Week 24 values are included. LS Mean difference were provided for categories with >=5 patients in each treatment group.

In the 3 Phase 3 studies with insulin as background therapy, lixisenatide 20 µg QD, whether as an established treatment or with newly initiated insulin, significantly reduced HbA1c by 0.63% to

0.77% from baseline, which is comparable to the reduction observed when up to 3 injections of rapid-acting insulin are used (26, 27, 28). In EFC10781, when lixisenatide was combined with optimal titration of insulin glargine, HbA1c decreased from screening by 1.64% and 56.3% of patients achieved HbA1c <7.0%.

3.2.4 HbA1c responder analysis

In the 9 Phase 3 placebo-controlled studies, the percentages of responders at the primary efficacy time point were statistically significantly higher in the lixisenatide groups than in the placebo groups (Table 4). Percentages of patients reaching HbA1c <7.0% in the lixisenatide groups ranged from 28.3% (EFC6016) to 56.3% (EFC10781) compared with 12.0% and 38.5% in the placebo groups.

All sensitivity analyses (patients with missing HbA1c data as non-responders in the mITT or in the ITT population; patients with missing HbA1c data or having received rescue therapy as non-responders in the mITT population) showed consistent results for all 9 studies, supporting the efficacy of lixisenatide. Results of these sensitivity analyses for Studies EFC6015, EFC6016, and EFC6017 are provided in Appendix 8.4.3.

Table 4 - HbA1c value <7.0% at Week 24 (Week 12 for Study EFC6018) from the Phase 3 placebo-controlled studies (mITT population)

			<7.0%	
		N	n(%)	P-value[a]
Monotherapy	**EFC6018**			
	Placebo	112	30 (26.8%)	
	Lixisenatide 2-step dose increase	113	59 (52.2%)	<.0001
	Lixisenatide 1-step dose increase	114	53 (46.5%)	0.0013
Add-on Met alone	**EFC6014**			
	Placebo	164	36 (22.0%)	
	Lixisenatide morning	244	105 (43.0%)	<.0001
	Lixisenatide evening	239	97 (40.6%)	<.0001
	EFC10743			
	Placebo	158	38 (24.1%)	
	Lixisenatide 2-step dose increase	152	64 (42.1%)	0.0005
	Lixisenatide 1-step dose increase	156	74 (47.4%)	<.0001
Add-on SU or SU+Met	**EFC6015**			
	Placebo	274	37 (13.5%)	
	Lixisenatide	544	198 (36.4%)	<.0001
Add-on Pio or Pio+Met	**EFC6017**			
	Placebo	148	39 (26.4%)	
	Lixisenatide	308	161 (52.3%)	<.0001
Add-on BI or BI+Met	**EFC6016**			
	Placebo	158	19 (12.0%)	
	Lixisenatide	304	86 (28.3%)	<.0001
Add-on IG+Met or IG+Met+TZD	**EFC10781**			
	Placebo	221	85 (38.5%)	
	Lixisenatide	215	121 (56.3%)	0.0001
Asian studies				
Add-on BI or BI+SU	**EFC10887**			
	Placebo	154	8 (5.2%)	
	Lixisenatide	146	52 (35.6%)	<.0001
Add-on Met or Met+SU	**EFC11321**			
	Placebo	188	73 (38.8%)	
	Lixisenatide	185	98 (53.0%)	0.0030

BI, basal insulin; IG, insulin glargine; Met, metformin; Pio, pioglitazone; TZD, thiazoledinedione; SU, sulfonylurea

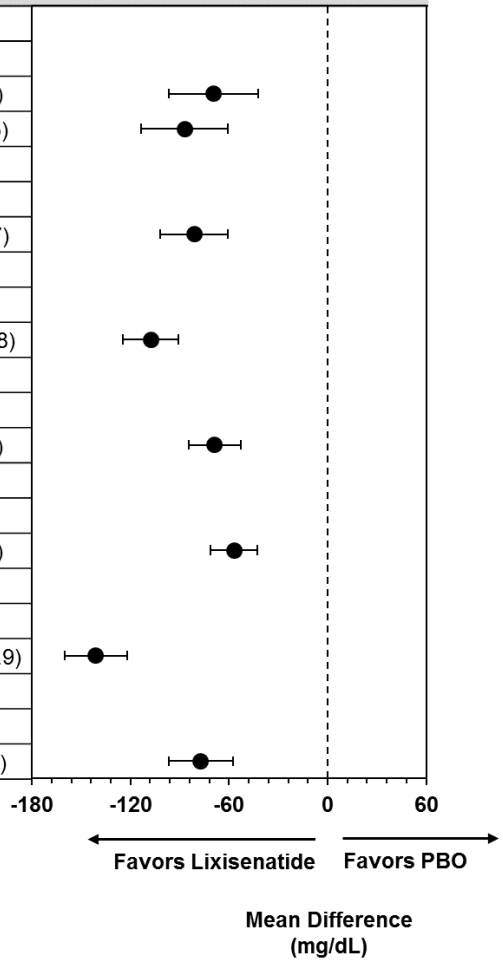
3.2.5 Mean change from baseline in 2-hour postprandial glucose

Meal tests were performed in a subset of subjects in EFC6015, EFC6016, EFC6018, EFC10781, EFC10887, EFC11321 and EFC6014. In these studies, 2-hour PPG and glucose excursion were assessed at baseline and Week 12/Week 24 after a standardized liquid breakfast (Ensure Plus® Drink, Abbott: 400 mL; 600 kcal; 53.8% carbohydrate, 16.7% protein and 29.5% fat).

The superiority of lixisenatide over placebo for 2-hour PPG was observed consistently across studies (Figure 37) regardless of background therapy, with a statistically significant ($p<0.0001$) LS mean treatment difference.

Figure 37 - Change in 2-hour PPG (mg/dL): Forest plot of LS mean difference between lixisenatide and placebo from baseline to Week 24 based on the Phase 3 placebo-controlled studies (mITT population)

	Study	N	Mean Difference vs PBO (95% CI)
Monotherapy	EFC6018		
	Placebo	54	
	Lixi two step	53	-69.6 (-96.8, -42.4)
	Lixi one step	62	-86.9 (-113.3, -60.5)
Add-on Met Alone	EFC6014		
	Placebo	64	
	Lixi morning	200	-81.3 (-101.8, -60.7)
Add-on SU or SU+Met	EFC6015		
	Placebo	120	
	Lixi	249	-107.7 (-124.5, -90.8)
Add-on BI or BI+Met	EFC6016		
	Placebo	123	
	Lixi	235	-68.7 (-84.6, -52.7)
Add-on IG+Met or IG+Met+TZD	EFC10781		
	Placebo	204	
	Lixi	194	-57.0 (-71.2, -42.8)
Add-on BI or BI+SU	EFC10887		
	Placebo	142	
	Lixi	131	-141.0 (-160.1, -121.9)
Add-on Met or Met+SU	EFC11321		
	Placebo	116	
	Lixi	107	-77.1 (-96.5 , -57.7)



PPG = Postprandial plasma glucose, Met = Metformin, SU = Sulfonylurea, BI = Basal insulin, IG = Insulin glargine, TZD = Thiazolidinediones, Lixi = Lixisenatide.
Week 24 value is the last observation carried forward (LOCF) before initiation of rescue therapy on or before Week 24 (Week 12 for EFC6018).

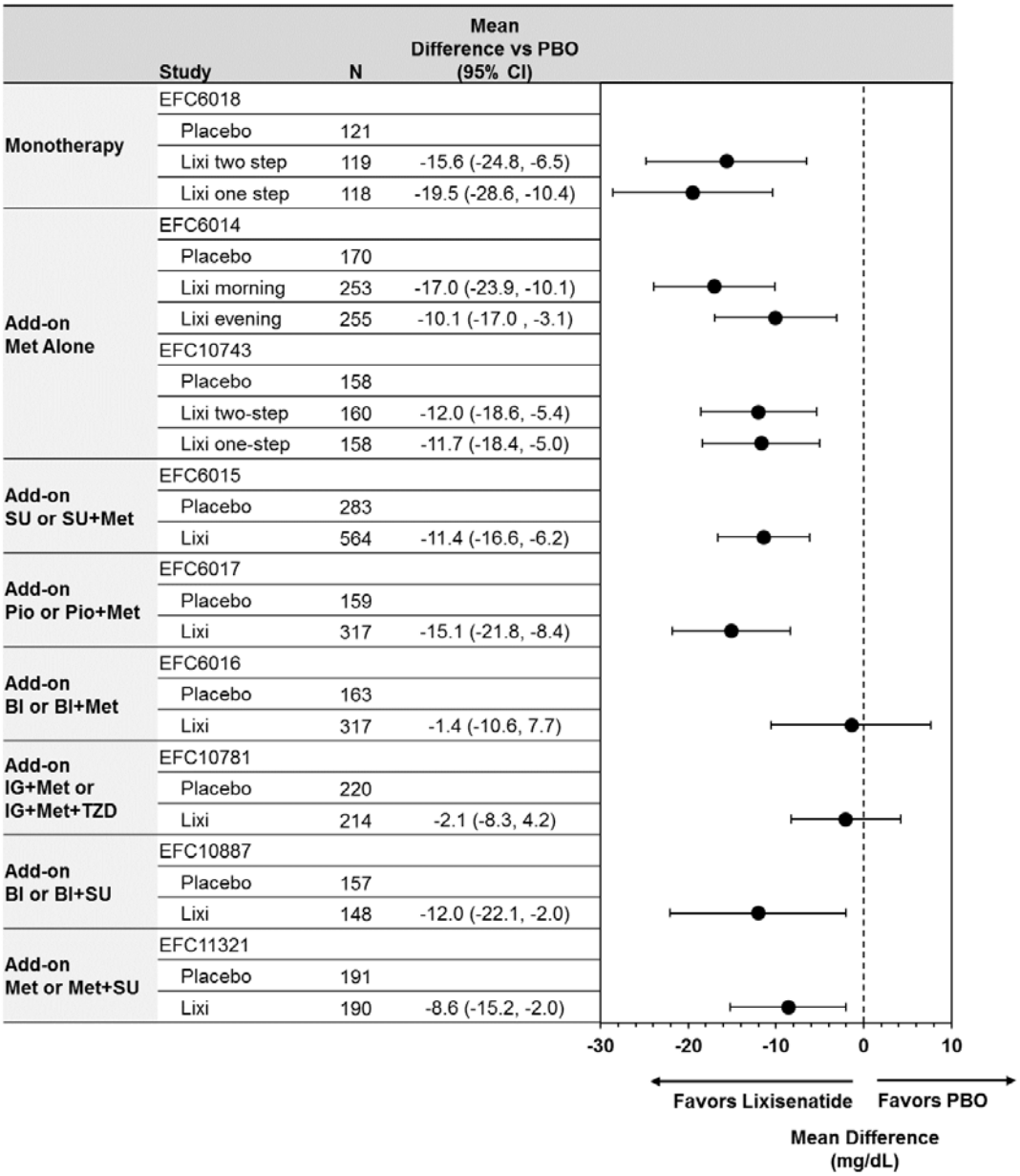
3.2.6 Mean change from baseline in fasting plasma glucose

Lixisenatide primarily affects PPG levels and had only modest effects on FPG.

Changes in FPG were small but consistently significantly different from control (except in EFC6016) (Figure 38). In EFC6016, a stable dose of basal insulin was used in both treatment groups and a similar reduction in FPG was expected.

In EFC10781, FPG was controlled by insulin glargine at baseline as patients were randomized into this study only if their FPG was <140 mg/dL. Consequently, a significant change from baseline or a difference between treatment groups was not expected or observed.

Figure 38 - Change in FPG (mg/dL): Forest plot of LS mean difference between lixisenatide and placebo for change from baseline to Week 24 based on the Phase 3 placebo-controlled studies (mITT population)



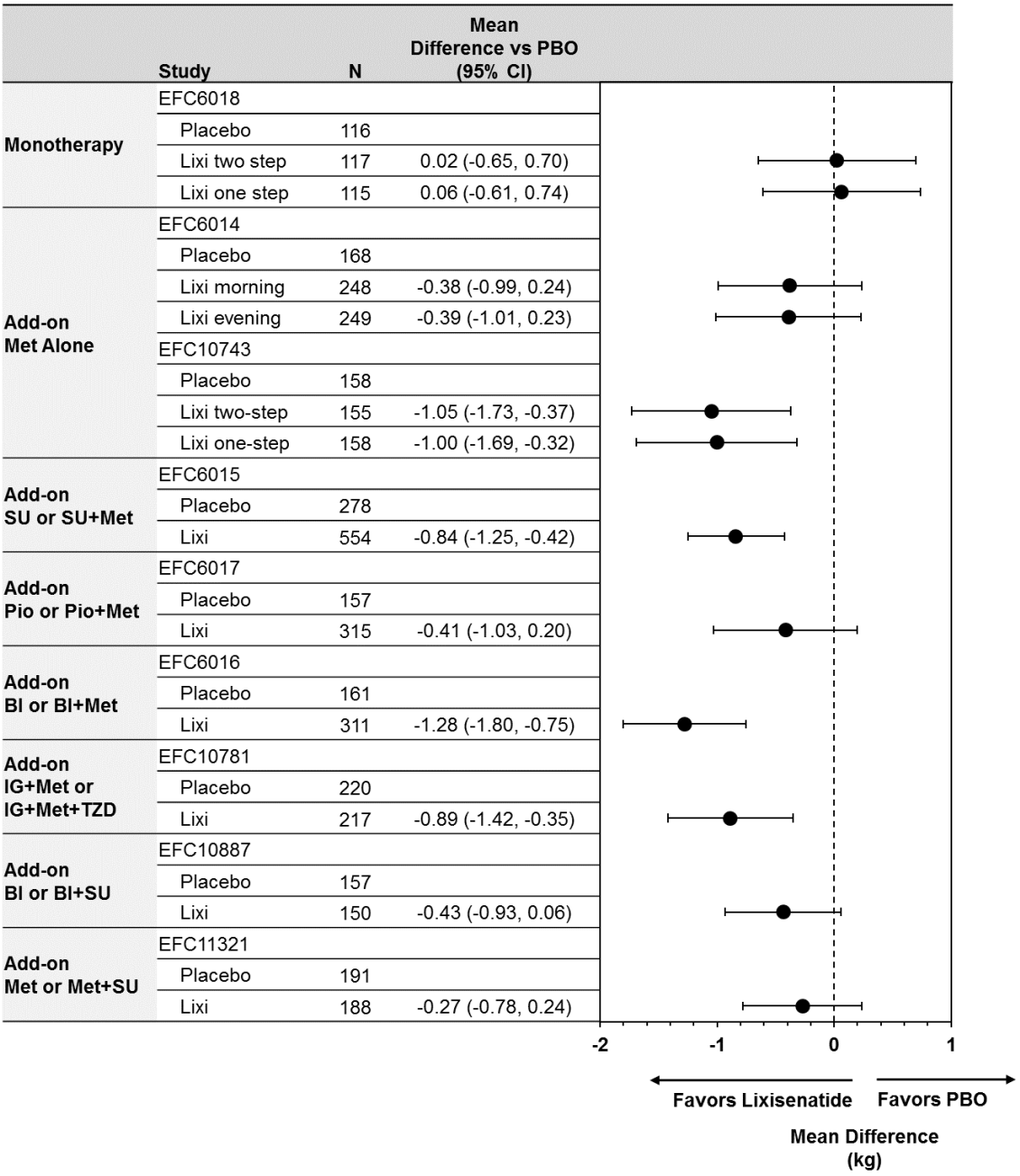
FPG = Fasting plasma glucose, Met = Metformin, SU = Sulfonylurea, Pio = Pioglitazone, BI = Basal insulin, IG = Insulin glargine, TZD = Thiazolidinediones, Lixi = Lixisenatide.
Week 24 value is the last observation carried forward (LOCF) before initiation of rescue therapy on or before week 24 (week 12 for EFC6018).

3.2.7 Mean change from baseline in body weight

A beneficial effect on body weight was seen in all studies. The reduction from baseline to Week 24 ranged from 1.50 to 2.68 kg and was generally greater than in the placebo groups (ranging from 0.93 to 1.98 kg) (Figure 39).

A beneficial effect on body weight is especially important when basal insulin is used, which typically leads to body weight gain. Lixisenatide produced a clinically and statistically significant reduction in body weight (1.80 kg) compared to placebo in Study EFC6016 in which subjects were treated with basal insulin. Similarly, in Study EFC10781 (add-on to optimally titrated insulin glargine), body weight remained stable in the lixisenatide group (LS mean change of 0.28 kg) as compared with a LS mean increase of 1.16 kg in the placebo group. The difference with placebo (-0.89 kg) was statistically significant.

Figure 39 - Change in body weight (kg): Forest plot of LS mean difference between lixisenatide and placebo from baseline to Week 24 based on the Phase 3 placebo-controlled studies (mITT population)



Met = Metformin, SU = Sulfonylurea, Pio = Pioglitazone, BI = Basal insulin, IG = Insulin glargine, TZD = Thiazolidinediones, Lixi = Lixisenatide.
Week 24 value is the last observation carried forward (LOCF) before initiation of rescue therapy on or before week 24 (week 12 for EFC6018).

3.3 DURABILITY OF EFFECT

After the main treatment period, HbA1c was measured at Week 36 then every 8 weeks and at the end-of-treatment visit (≥76 weeks) in 5 studies (EFC6014, EFC6015, EFC6016, EFC6017, and EFC10743). The reduction in mean HbA1c over the primary period was maintained over 76 weeks of treatment in the lixisenatide groups in all studies.

The percentages of responders (patients with HbA1c <7% or ≤6.5%) at Week 52 and at the end of treatment visit remained similar to those obtained at Week 24 for most groups, including placebo.

The mean changes in 2-hour PPG at Week 76 were similar to those at Week 24. Across studies, the mean reduction in FPG observed after the primary study period continued over 76 weeks of treatment while maintaining the difference from placebo.

Most of the effect on body weight occurred during the initial 24-week treatment period, after which mean body weight remained relatively stable over 76 weeks or continued to decrease slightly in all studies.

3.4 STUDY EFC12626: EFFICACY OF LIXISENATIDE VERSUS PRANDIAL INSULIN ADDED ON TO INSULIN GLARGINE

EFC12626 was an active-comparator, Phase 3 Study which successfully demonstrated that lixisenatide 20 µg QD was non-inferior to insulin glulisine QD or TID for HbA1c reduction from baseline when each treatment was added on to insulin glargine. Lixisenatide also significantly reduced body weight while both prandial insulin-based regimens led to weight gain. Importantly, fewer patients treated with lixisenatide experienced hypoglycemic events as reported by their investigators compared to the prandial insulin-based regimens. Overall, this study showed that lixisenatide combined with insulin glargine offers an effective and well-tolerated add-on therapy for patients not controlled with basal insulin alone.

3.4.1 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 to lixisenatide 20 µg QD or to prandial insulin glulisine (QD or TID) (all arms ± metformin) for 26 weeks of treatment (Figure 14).

3.4.1.1 Endpoints

The co-primary endpoints were:

1. Non-inferiority of lixisenatide versus insulin glulisine QD in HbA1c reduction at Week 26.
2. Non-inferiority of lixisenatide versus insulin glulisine TID in HbA1c reduction *or* superiority of lixisenatide in body-weight change at Week 26.

The predefined non-inferiority margin of 0.4% was chosen based on clinical input and is in accordance with the FDA draft guidance for industry: "Diabetes mellitus: developing drugs and therapeutic biologics for treatment and prevention" (29).

Secondary endpoints included the percentage of patients who reached target HbA1c <7.0% at Week 26, change from baseline in body weight at Week 26, change from baseline in PPG and glucose excursions during a standardized meal test at Week 26, change from baseline in seven-point SMPG profile at Week 26, the percentage of patients who reached target HbA1c <7.0% at Week 26 and did not experience documented (plasma glucose <60 mg/dL) symptomatic hypoglycemia during the 26-week treatment period, the percentage of patients who reached target HbA1c <7.0% and had no weight gain at Week 26, and the percentage of patients who reached target HbA1c <7.0%, had no weight gain at Week 26, and did not experience symptomatic hypoglycemia during the 26-week treatment period.

3.4.1.2 Statistical methodology

For the primary efficacy analysis, the same ANCOVA model and LOCF method for imputing missing values at Week 26 was the pre-specified analysis method as used in other Phase 3 studies (see Section 3.1.3).

Section 8.4.2 summarizes patient disposition of the primary analysis of HbA1c change from baseline at Week 26 in the mITT population. Sensitivity analyses of MMRM under the MAR assumption and 26-week completer analyses were also conducted for HbA1c change from baseline to Week 26.

In the primary analysis of responders (HbA1c <7.0% and three composite endpoints of responders), the same approach of LOCF for handling the missing data in the HbA1c responder analysis was pre-specified and used. To assess the robustness of the data, sensitivity analyses were performed by treating patients with missing HbA1c data at Week 26 as non-responders in the mITT population as well as in the ITT population. Detailed information on these analyses is provided in Section 8.4.4.

The Type 1 error for the primary endpoints was controlled at the 5% level. The co-primary endpoint 1 and 2 were assessed separately at α=0.025 (1-sided) so that the study was to be declared positive when both 1 and 2 are met. For the co-primary endpoint 2, the Hochberg procedure was used to control the Type 1 error as follows: If both non-inferiority in HbA1c and superiority in body weight comparing lixisenatide to insulin glulisine TID were met at α=0.025 (1-sided), then both would be declared significant. If only one endpoint was met at α=0.025 (1-sided), then the test/comparison that was met would be tested at α=0.0125 (1-sided).

3.4.2 Patient disposition

The incidence of treatment discontinuation was higher in the lixisenatide group than in the insulin glulisine QD and insulin glulisine TID groups (Table 5), mainly related to GI AEs.

Table 5 - Study EFC12626: Patient disposition

	Lixisenatide (N=298)	Insulin Glulisine QD (N=298)	Insulin Glulisine TID (N=298)
Randomized and not treated	0	0	1 (0.3%)
Randomized and treated	298 (100%)	298 (100%)	297 (99.7%)
Completed study treatment period	268 (89.9%)	281 (94.3%)	285 (95.6%)
Did not complete study treatment period	30 (10.1%)	17 (5.7%)	12 (4.0%)
Subject's decision for treatment discontinuation	18 (6.0%)	11 (3.7%)	8 (2.7%)
Reason for treatment discontinuation			
Adverse event	14 (4.7%)	2 (0.7%)	5 (1.7%)
Lack of efficacy[a]	6 (2.0%)	4 (1.3%)	0
Poor compliance to protocol	0	3 (1.0%)	2 (0.7%)
Lost to follow-up	0	0	0
Other reasons	9 (3.0%)	8 (2.7%)	5 (1.7%)

a: No rescue therapy was planned for the study, instead discontinuation was recommended if HbA1c value was above 8.5% at Week 12 or later on, and if appropriate corrective action failed and the repeated HbA1c 4 weeks later remained above 8.5%.
Note: Percentages are calculated using the number of patients randomized as denominator.
Subject 840120004 (lixisenatide arm) was diagnosed with breast cancer soon after randomization and was discontinued from study, subject did not respond to any more request from the site, no end of treatment information is available for the subject

3.4.3 Demographics and baseline characteristics

The demographic and baseline characteristics were generally similar across treatment groups in the mITT population (Table 6).

All baseline disease characteristics including median duration of diabetes, median age at onset of diabetes, and categories of creatinine clearance were generally similar between treatment groups.

Table 6 – Study EFC12626: Demographics and baseline characteristics

	Lixisenatide (N=298)	Insulin Glulisine QD (N=298)	Insulin Glulisine TID (N=298)
Age (years)			
Mean (SD)	59.8 (8.6)	60.2 (8.6)	59.4 (9.5)
Age group (years) [n (%)]			
< 50	39 (13.1%)	33 (11.1%)	48 (16.1%)
≥ 50 to < 65	170 (57.0%)	172 (57.7%)	154 (51.7%)
≥ 65 to < 75	76 (25.5%)	76 (25.5%)	85 (28.5%)
≥ 75	13 (4.4%)	17 (5.7%)	11 (3.7%)
Gender [n (%)]			
Male	138 (46.3%)	135 (45.3%)	132 (44.3%)
Female	160 (53.7%)	163 (54.7%)	166 (55.7%)
Race [n (%)]			
Caucasian/White	276 (92.6%)	280 (94.0%)	272 (91.3%)
Black	13 (4.4%)	11 (3.7%)	12 (4.0%)
Asian/Oriental	9 (3.0%)	7 (2.3%)	13 (4.4%)
Other	0	0	1 (0.3%)
Ethnicity [n (%)]			
Hispanic	63 (21.1%)	58 (19.5%)	68 (22.8%)
Non-Hispanic	235 (78.9%)	240 (80.5%)	230 (77.2%)
Baseline BMI (kg/m2)			
Mean (SD)	32.27 (4.57)	31.86 (4.39)	32.50 (4.60)
Baseline BMI Categories (kg/m2) [n(%)]			
< 30	97 (32.6%)	118 (39.6%)	97 (32.7%)
≥ 30	201 (67.4%)	180 (60.4%)	200 (67.3%)
HbA1c (%)			
Mean (SD)	7.77 (0.55)	7.73 (0.59)	7.79 (0.60)
2-hour PPG (mg/dL)			
Mean (SD)	254.75 (65.53)	255.90 (63.67)	256.73 (60.33)
2-hour glucose excursion (mg/dL)			
Mean (SD)	135.66 (56.97)	137.56 (63.29)	132.41 (60.08)
FPG (mg/dL)			
Mean (SD)	118.55 (32.87)	123.21 (35.73)	119.80 (34.06)
7-point SMPG (mg/dL)			
Mean (SD)	162.42 (31.46)	163.33 (31.33)	162.00 (28.20)

BMI = Body Mass Index.

3.4.4 Primary endpoint: change from baseline in HbA1c

Lixisenatide 20 µg QD was non-inferior to each insulin glulisine regimen, as the upper bound of the 2-sided 95% CI was below the prespecified non-inferiority margin of 0.4% (Table 7).

Table 7 – Study EFC12626: Mean change in HbA1c (%) from baseline to Week 26 (mITT population)

HbA1c (%)	Lixisenatide (N=297)	Insulin Glulisine QD (N=298)	Insulin Glulisine TID (N=295)
Baseline			
Mean (SD)	7.76 (0.56)	7.72 (0.58)	7.79 (0.60)
Week 26 (LOCF)			
Mean (SD)	7.17 (0.77)	7.21 (0.79)	6.96 (0.73)
Change from baseline to Week 26 (LOCF)			
Mean (SD)	-0.59 (0.79)	-0.51 (0.80)	-0.82 (0.78)
LS Mean (SE) [a]	-0.63 (0.054)	-0.58 (0.054)	-0.84 (0.053)
LS Mean difference (SE) of lixisenatide vs. [ab]	-	-0.05 (0.059)	0.21 (0.059)
95% CI	-	(-0.170 to 0.064)	(0.095 to 0.328)

LOCF = Last observation carried forward.
[a] Analysis of covariance (ANCOVA) model with treatment groups (lixisenatide, insulin glulisine QD, and insulin glulisine TID), Visit 7 (Week -1) strata of HbA1c [<8.0, ≥8.0%], randomization strata of metformin use, and country as fixed effects and baseline HbA1c value as a covariate.
[b] Difference in LS Mean between lixisenatide vs. insulin glulisine QD, or lixisenatide vs. insulin glulisine TID.
The analysis included measurements obtained up to 14 days after the last injection of the investigational medicinal product.
Patients with both baseline and Week 26 (LOCF) measurements are included.

Sensitivity analyses showed results, all demonstrating non-inferiority versus comparators (Appendix 8.4.4).

Percentage of patients with HbA1c <7.0% at Week 26

At Week 26, the percentage of patients reaching target HbA1c <7.0% was higher in the lixisenatide group than in the insulin glulisine QD group but lower with lixisenatide than with insulin glulisine TID. Results of sensitivity analyses of treating patients with missing HbA1c data at Week 26 as non-responders in the mITT and ITT populations are provided in Section 8.4.4.

Table 8 - Study EFC12626: Number (%) of patients with HbA1c <7.0% at Week 26 (mITT population)

HbA1c (%)	Lixisenatide (N=297)	Insulin Glulisine QD (N=298)	Insulin Glulisine TID (N=295)
Number	292	292	295
<7.0%	123 (42.1%)	112 (38.4%)	145 (49.2%)
Proportion difference (95% CI) of Lixisenatide vs. [a,b]	-	3.7% (-4.03% to 11.49%)	-7.3% (-15.07% to 0.56%)

a Weighted average of proportion difference between treatment groups (lixisenatide vs insulin glulisine QD, or lixisenatide vs. insulin glulisine TID) from each strata (Visit 7 (Week -1) strata of HbA1c [<8.0, ≥8.0%], randomization strata of metformin use) using Cochran-Mantel-Haenszel (CMH) weights.
b Proportion difference and associated CI between lixisenatide vs. insulin glulisine QD, or lixisenatide vs. insulin glulisine TID.
Proportion difference = difference of the proportions of patients achieving HbA1c value ≤6.5% or <7% respectively.
The analysis included measurements obtained up to 14 days after the last injection of the investigational medicinal product.

3.4.5 Secondary endpoints

Postprandial plasma glucose and glucose excursions after a standardized breakfast meal

All three treatment groups showed improvement in postprandial glycemic control over the 26-week treatment period. The decrease in mean PPG was greater with lixisenatide than with insulin glulisine QD or TID (Table 9). Similarly, PPG excursion decreased from baseline to Week 26 in all three treatment groups, the decrease being greater with lixisenatide as compared to insulin glulisine QD or TID.

Table 9 - Study EFC12626: Mean change in postprandial glucose from baseline to Week 26 (mITT population)

Postprandial plasma glucose (PPG) (mg/dL)	Lixisenatide (N=90)	Insulin Glulisine QD (N=88)	Insulin Glulisine TID (N=295)
2-hour PPG change from baseline to Week 26 (LOCF)			
Number	69	55	68
Mean (SD)	-70.83 (77.20)	-29.18 (72.30)	-33.62 (57.24)
Median	-68.46	-36.03	-37.83
Min : Max	-381.9 : 84.7	-207.2 : 142.3	-156.7 : 145.9
LS Mean (SE)	-65.50 (10.761)	-28.25 (10.748)	-25.35 (10.517)
LS Mean difference (SE) of lixisenatide vs.	-	-37.25 (11.131)	-40.15 (10.621)
95% CI	-	(-59.225 to -15.279)	(-61.113 to -19.178)

LOCF = Last observation carried forward.
Analysis of covariance (ANCOVA) model with treatment groups (lixisenatide, insulin glulisine QD, insulin glulisine TID), Visit 7 (Week -1) strata of HbA1c [<8.0, ≥8.0%], randomization strata of metformin use, and country as fixed effects and baseline post-prandial plasma glucose as a covariate.
Difference in LS Mean between lixisenatide vs. insulin glulisine QD, or lixisenatide vs. insulin glulisine TID.
The analysis included measurements obtained up to the date of last injection of the investigational medicinal product.
Patients with injection of study drug before breakfast and with both baseline and Week 26 (LOCF) measurements are included.

Body weight at Week 26

The changes in body weight were -0.63 kg for the lixisenatide group, +1.03 kg for the insulin glulisine QD group (between-group difference of -1.66 kg) and +1.37 kg for the insulin glulisine TID group (difference of -1.99 kg, p-value<0.0001). The percentage of patients with no weight gain was 64.7% in the lixisenatide group versus 36.6% in the insulin glulisine QD group and 30.5% in the insulin glulisine TID group.

Clinically relevant composite endpoints

The percentage of patients reaching HbA1c <7.0% at Week 26 and not experiencing documented symptomatic hypoglycemia (plasma glucose <60 mg/dL) during the treatment period was 29.4%, 24.2% and 26.1% in the lixisenatide, insulin glulisine QD and insulin glulisine TID groups, respectively.

The percentage of patients reaching HbA1c <7.0% and having no weight gain at Week 26 was higher in the lixisenatide group than in the two other treatment groups: 31.2% versus 16.7% in the insulin glulisine QD group and 17.6% in the insulin glulisine TID group. The response rate difference of lixisenatide versus insulin glulisine QD was 14.5% (95% CI: 7.77% to 21.14%) and versus insulin glulisine TID was 13.5% (95% CI: 6.73% to 20.17%).

The percentage of patients reaching HbA1c <7.0%, having no weight gain, and not experiencing documented symptomatic hypoglycemia at Week 26 was also higher in the lixisenatide group than in the 2 other treatment groups: 22.2% versus 9.2% in the insulin glulisine QD and 10.8% in the insulin glulisine TID group. The response rate difference versus insulin glulisine QD was 13.0% (95% CI: 7.32% to 18.78%) and versus insulin glulisine TID was 11.4% (95% CI: 5.5% to 17.2%).

Sensitivity analyses of treating patients with missing data at Week 26 as non-responders in the mITT population showed consistent results and they are provided in Section 8.4.4.

3.5 LIXISENATIDE EFFICACY CONCLUSIONS

Lixisenatide 20 µg QD is effective in achieving statistically significant, clinically relevant, and durable reductions in HbA1c compared with placebo, regardless of whether it is given as monotherapy or as an add-on to one or more OADs and/or basal insulin, in various combinations.

Changes in HbA1c from baseline were similar regardless of anti-lixisenatide antibody status (positive or negative). In a small number of patients (2.4%) with antibody concentrations >100 nmol/L, a smaller decrease in HbA1c was observed.

Lixisenatide has a modest effect on FPG. Overall in the Phase 3 placebo-controlled studies, the reduction from baseline in FPG ranged from 7.6 mg/dL to 21.5 mg/dL in the lixisenatide groups.

The glycemic efficacy of lixisenatide is largely driven via robust reductions in 2-hour PPG, ranging from 57.0 to 141.0 mg/dL. Lixisenatide provided greater reductions in 2-hour PPG

compared to placebo when measured after the first meal post-injection, with a statistically significant difference in all studies ($p<0.0001$).

In the four Phase 3 studies with concomitant administration of insulin, lixisenatide QD significantly reduced HbA1c from baseline, demonstrating a complementary effect to basal insulin (which primarily targets FPG).

In patients treated with optimally titrated insulin glargine, addition of lixisenatide achieved non-inferiority in change in HbA1c versus addition of insulin glulisine QD and TID. Lixisenatide was accompanied by body weight loss and a reduced risk of hypoglycemia compared to the prandial insulin regimens. Mean end-of-treatment HbA1c values were low and comparable across the treatment groups, 7.2% for both lixisenatide QD and glulisine QD and 7.0% for glulisine TID.

A beneficial effect on body weight was seen in all studies. Clinically relevant weight loss (with changes from baseline ranging from -1.50 to -2.68 kg) was observed at the end of the main treatment period in most Phase 3 studies in which lixisenatide was administered as monotherapy or add-on to OADs. A beneficial effect on body weight was also seen in studies where lixisenatide was concomitantly administered with basal insulin.

Taken together, these results support lixisenatide as an effective glucose-lowering agent at various stages of T2DM progression, including patients not achieving glycemic targets despite use of basal insulin, for whom lixisenatide could be a valuable alternative therapeutic option to mealtime insulin.

4 EFFICACY OF IGLARLIXI – STUDIES EFC12404 AND EFC12405

4.1 OVERVIEW OF STUDY DESIGN

Both of the trials were open-label because of differences in the type and number of pens used to administer iGlarLixi, insulin glargine, and lixisenatide.

Two pens (A with 2 U/1 µg ratio and B with 3 U/1 µg ratio) were used for iGlarLixi (Figure 11). Pen A delivered 10 to 40 U; Pen B delivered 30 to 60 U. Patients were allowed to switch pens during the study based on insulin requirements.

Subjects above 65 years of age were eligible for inclusion in the studies and accounted for 28.1% of all randomized subjects. Subjects were excluded from the pivotal trials if they had significant medical conditions including renal, hepatic, or CV problems, uncontrolled hypertension, cancer, a history of medullary thyroid carcinoma or elevated calcitonin levels, a history of pancreatitis, or amylase and/or lipase levels >3 times the upper limit of the normal laboratory range. Any contraindication to metformin use, according to local labeling (eg, renal impairment defined as creatinine >1.4 mg/dL in women, >1.5 mg/dL in men, or creatinine clearance <60 mL/min) was exclusionary for all patients in Study EFC12404 where metformin was a mandatory background therapy and for those patients taking metformin in Study EFC12405. For patients not treated with metformin in EFC12405, renal impairment with creatinine clearance <30 mL/min (using the Cockcroft and Gault formula) or end-stage renal disease was exclusionary.

In both trials, insulin doses were adjusted once weekly to achieve a fasting SMPG target of 80 to 100 mg/dL, inclusive, using the same protocol-specified algorithm (Table 10).

Table 10 - Dose adjustment algorithm for iGlarLixi and insulin glargine

Median of fasting SMPG values from the last 3 days	Dose change (U/day)
>140 mg/dL	+4
>100 and ≤140 mg/dL	+2
80 to 100 mg/dL	No change
≥60 and <80 mg/dL	-2
<60 mg/dL or occurrence of ≥ 2 symptomatic hypoglycemia or one severe hypoglycemia in the preceding week	-2 to -4 or at the discretion of the investigator or medically qualified designee

SMPG = self-monitored plasma glucose

As the maximum daily dose of iGlarLixi was 60 U (60 U/20 µg), the insulin glargine stand-alone dose was also capped at 60 U in order to best assess the contribution of the lixisenatide component to glycemic control.

4.1.1 Endpoints

In both studies, the primary efficacy endpoint was the change in HbA1c from baseline to Week 30.

Key secondary efficacy endpoints were percentage of patients reaching HbA1c targets, changes from baseline to Week 30 in 2-hr PPG excursions during a standardized breakfast meal, body weight, FPG, the daily average of the 7-point SMPG, patients reaching HbA1c <7.0% with no body weight gain at Week 30, percent of patients reaching HbA1c <7.0% with no body weight gain at Week 30 and with no documented symptomatic hypoglycemia (PG ≤70 mg/dL) during the study, and mean daily insulin dose at Week 30 (EFC12404) or change from baseline to Week 30 in the insulin dose (EFC12405).

Other endpoints included:

- Categories of symptomatic hypoglycemia
  - Documented symptomatic hypoglycemia was defined by the protocol as an event during which typical symptoms of hypoglycemia were accompanied by a measured plasma glucose (PG) of ≤70 mg/dL.
  - Severe symptomatic hypoglycemia was defined as an event requiring assistance of another person to actively administer carbohydrate, glucagon, or other resuscitative actions.
- Percent of patients receiving rescue therapy
- Safety and tolerability in each treatment group
- Immunogenicity (antibody variables): anti-lixisenatide antibody status and concentration and/or anti-insulin antibody status and titer (depending on the treatment group)

4.1.2 Statistical methodology

Efficacy analyses were based on the mITT population defined as all randomized patients who had a baseline and one post baseline assessment of any primary or secondary endpoint.

In both studies, the primary efficacy analysis was a MMRM under MAR framework, using all post baseline data including those collected after treatment discontinuation or initiation of rescue therapy. The model included treatment group, randomization strata, visit, treatment-by-visit interaction and country as fixed effects, and baseline HbA1c value-by-visit interaction as a covariate.

The summary of patient disposition for the primary analysis of HbA1c change from baseline at Week 30 in the mITT population is provided in Table 65 for both studies.

In both studies, multiple sensitivity analyses were conducted to investigate the potential impact of rescue medication and missing data on the primary endpoint of HbA1c change from baseline to Week 30. They included a MMRM model using data prior to initiation of rescue therapy for assessing the impact of rescue therapy and conservative methods under the MNAR assumption

based on recommendations from the National Research Council's report on The Prevention and Treatment of Missing Data in Clinical Trials (NRC 2010): a pattern mixture model implemented with multiple imputation using jump to control (control based imputation) and a BOCF-like multiple imputation to account for uncertainty associated with missing data. In addition, a tipping point analysis was conducted by multiply imputed missing HbA1c values with a delta adjustment in the iGlarLixi group. In the tipping point analysis, missing HbA1c values at each post baseline visit were imputed under the MAR assumption and an additional HbA1c increase (delta) was added to each imputed value in the iGlarLixi group in the mITT population. Results of the primary sensitivity analyses are presented in Figure 57 and Table 66 (iGlarLixi versus insulin glargine) and Figure 58 and Table 67 (iGlarLixi versus lixisenatide).

For the analysis of HbA1c <7.0%, sensitivity analyses were also performed by treating patients with missing HbA1c data at Week 30 or initiation of rescue therapy prior to Week 30 as non-responders in the mITT population. In addition, in order to ensure no bias was introduced by using the mITT population instead of the true ITT population, an additional sensitivity analysis was conducted in all randomized patients. Lastly, a sensitivity analysis that further penalized the iGlarLixi group by treating the patients with missing data in the control group as responders while patients with missing data in the iGlarLixi group were treated as non-responders was also performed. Patients who received rescue therapy were considered as non-responders in this analysis. Detailed information is provided in Section 8.3.

In EFC12404, the co-primary efficacy hypotheses were statistical superiority of iGlarLixi vs. lixisenatide and non-inferiority of iGlarLixi vs. insulin glargine.

- Statistical superiority of iGlarLixi vs. lixisenatide was tested at a 2-sided 5% significance level. Non-inferiority of iGlarLixi vs. insulin glargine was demonstrated if the upper bound of the 2-sided 95% CI of the difference between iGlarLixi and insulin glargine was ≤0.3%. For the co-primary hypotheses, superiority and non-inferiority were claimed only when both were demonstrated at the given statistical significance level.
- Once the co-primary hypotheses were both established for the primary efficacy endpoint, a step-down testing procedure for the key secondary efficacy endpoints, including a test of superiority of iGlarLixi over insulin glargine alone on the primary endpoint (see Table 62), was performed at 2-sided alpha level of 0.05.

In EFC12405, superiority of iGlarLixi vs. insulin glargine in change in HbA1C was tested at a 2-sided 0.05 significance level.

In both studies, the key secondary endpoints were tested in a hierarchical order as specified in the protocols and statistical analysis plans in order to control the overall Type 1 error. The statistical testing order is presented in Table 62 in the Appendix. An MMRM method similar to that used for analysis of the primary endpoint or ANCOVA was applied to continuous secondary efficacy endpoints, and the CMH method stratified by randomization strata was applied for categorical efficacy endpoints.

A pre-specified meta-analysis of change from baseline to Week 30 in HbA1c using pooled data from Study EFC12404 and EFC12405 was performed by subgroup.

4.2 STUDY EFC12404: PATIENTS INSUFFICIENTLY CONTROLLED ON METFORMIN WITH OR WITHOUT A SECOND OAD

The study design is shown in Figure 19. Patients included in the trial had T2DM diagnosed for at least 1 year before screening, had been treated for at least 3 months prior to screening with metformin alone ± a second OAD (a SU, a glinide, a SGLT-2 inhibitor, or a DPP-4 inhibitor), and were suboptimally controlled with this treatment.

Key exclusion criteria were previous treatment with insulin except for short-term treatment due to intercurrent illness and a screening HbA1c of <7.5% or >10% for patients previously treated with metformin alone and <7.0% or >9% for patients previously treated with metformin and a second OAD.

Eligible patients entered a 4-week run-in phase for optimization of metformin dosing while other OADs were discontinued.

- Metformin was titrated to at least 2000 mg/day or maximum tolerated dose (MTD), which had to be ≥1500 mg/day at randomization.

- At the end of the run-in phase, patients with an HbA1c ≥7.0% and ≤10.0%, an FPG ≤250 mg/dL, and a metformin MTD ≥1500 mg/day were randomized into the trial.

A total of 1170 patients were randomized 2:2:1 to iGlarLixi, insulin glargine, and lixisenatide.

iGlarLixi was initiated with Pen A. The initial daily dose was 10 U (10 U of insulin glargine combined with 5 µg of lixisenatide). Doses were then individually titrated throughout the study to reach and maintain a fasting SMPG of 80 to 100 mg/dL, inclusive, while avoiding hypoglycemia. Pen A was used for daily doses up to 40 U. If doses above 40 U were needed, patients switched to Pen B.

Insulin glargine was initiated at 10 U during the first week and then optimized and individually titrated throughout the study to reach and maintain fasting SMPG of 80 to 100 mg/dL, inclusive, without hypoglycemia. In both insulin-based groups, the maximum daily dose was capped at 60 U.

Lixisenatide was initiated at 10 µg for 2 weeks, and a maintenance dose of 20 µg was to be used for the duration of the trial if tolerated.

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. Lixisenatide was self-administered QD in the hour before breakfast or the evening meal.

4.2.1 Description of study population

Baseline demographics were well-balanced across treatment groups. The overall population was balanced by gender and was predominantly Caucasian (90.1%) with a mean age of 58.4 years. The population was generally overweight or obese with a mean baseline BMI of 31.7 kg/m^2 overall; 63.4% of all patients had a baseline BMI ≥30 kg/m^2.

Baseline characteristics related to diabetes were comparable in the 3 treatment groups and indicative of a population in poor glycemic control that would benefit from insulin initiation (Table 11). Overall, the mean duration of diabetes was approximately 9 years with a mean HbA1c of 8.2% at screening. The percentage of patients using 2 OADs at screening (metformin plus one of a sulfonylurea [SU], a glinide, a SGLT2-inhibitor, or a DPP-4 inhibitor) was 57.9% overall, with a SU having been used by the largest percentage (53.9%) of patients. For patients using 2 OADs, the overall mean duration of use was 4.2 years.

Table 11 - Study EFC12404: Disease characteristics at screening or baseline (randomized population)

Disease characteristics at baseline or screening	iGlarLixi (N=469)	Insulin Glargine (N=467)	Lixisenatide (N=234)	All (N=1170)
Duration of diabetes (years)				
Number	469	467	234	1170
Mean (SD)	8.89 (5.51)	8.66 (5.59)	8.89 (6.26)	8.80 (5.69)
Median	8.14	7.60	7.65	7.69
Min : Max	1.0 : 34.2	1.0 : 39.7	1.0 : 44.5	1.0 : 44.5
Duration of metformin treatment (years)				
Number	466	466	232	1164
Mean (SD)	6.42 (4.85)	6.46 (4.70)	6.12 (4.45)	6.38 (4.71)
Median	5.25	5.45	5.45	5.37
Min : Max	0.3 : 34.2	0.3 : 26.4	0.2 : 24.7	0.2 : 34.2
Daily dose of metformin at baseline (mg)				
Number	469	467	234	1170
Mean (SD)	2246.1 (456.8)	2244.7 (444.7)	2267.3 (427.4)	2249.8 (445.9)
Median	2000.0	2000.0	2000.0	2000.0
Min : Max	1000 : 3000	1000 : 3000	1000 : 3000	1000 : 3000
Second OAD use at screening by class [n (%)]				
Number (Yes)	274 (58.4%)	270 (57.8%)	133 (56.8%)	677 (57.9%)
Sulfonylurea	259 (55.2%)	249 (53.3%)	123 (52.6%)	631 (53.9%)
Glinide	3 (0.6%)	10 (2.1%)	5 (2.1%)	18 (1.5%)
SGLT-2 inhibitor	2 (0.4%)	2 (0.4%)	0	4 (0.3%)
DPP-4 inhibitor	12 (2.6%)	11 (2.4%)	5 (2.1%)	28 (2.4%)
Duration of second OAD treatment (years)				
Number	274	269	133	676
Mean (SD)	3.98 (4.07)	4.61 (4.67)	3.94 (3.54)	4.22 (4.23)
Median	2.59	3.26	2.49	2.82
Min : Max	0.3 : 21.3	0.3 : 25.4	0.3 : 16.0	0.3 : 25.4

OAD = Oral anti-diabetic drug, SGLT-2 = Sodium glucose co-transporter 2, DPP-4 = Dipeptidyl-peptidase 4, GLP-1 = Glucagon like peptide-1

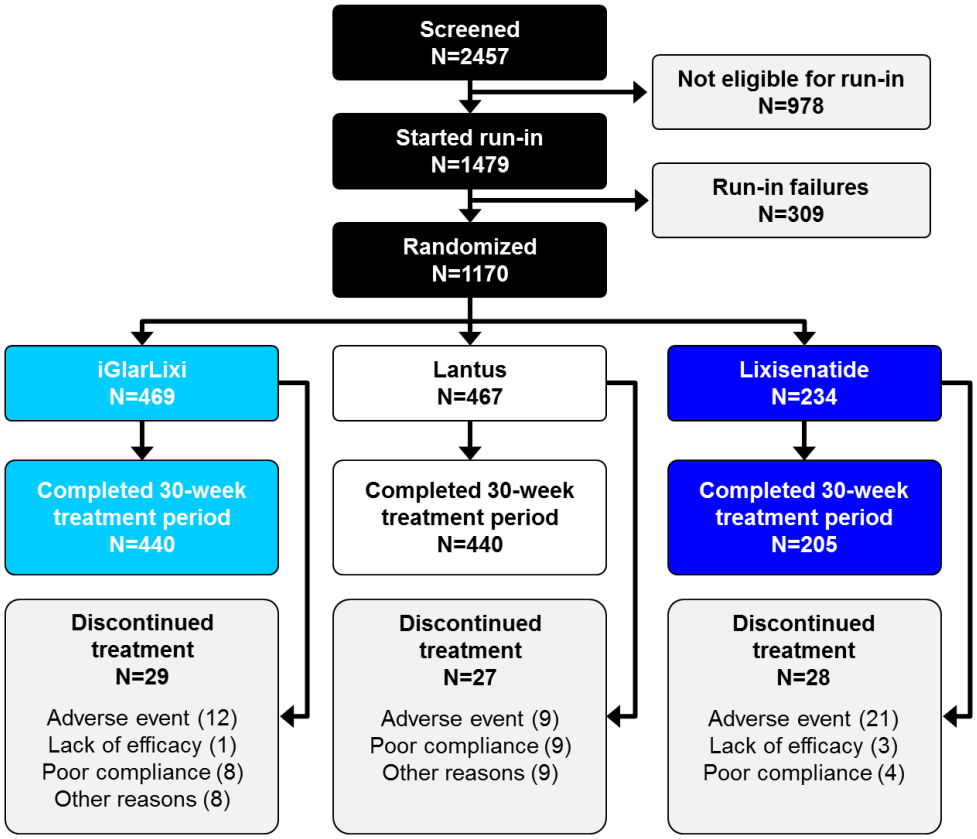
4.2.2 Patient disposition

Of the 2457 patients screened, 653 (26.6%) had an HbA1c value out of the protocol-defined range (Figure 40), and were therefore not eligible for run-in.

Of the 1479 patients who entered the run-in phase, 1170 were randomized (469 patients to the iGlarLixi group, 467 to the insulin glargine group, and 234 to the lixisenatide group). The main reasons for run-in failure were FPG value >250 mg/dL (100 patients) and HbA1c value <7.0% or >10% (95 patients), both measured at Visit 4 (Week -1) (Figure 40).

The percentage of patients completing the on-treatment period in the iGlarLixi group (93.8%) was comparable to the insulin glargine group (94.2%). The percentage completing the treatment period was lowest in the lixisenatide group (87.6%). The percentages of patients permanently discontinuing study medication due to AEs were lower in the iGlarLixi (2.6%) and insulin glargine groups (1.9%) compared to the lixisenatide group (9.0%). Less than 2% of patients in each treatment group discontinued in the categories of lack of efficacy, poor compliance to study protocol, or "other" reasons. "Other" reasons for discontinuation were not reported as being safety-related.

Figure 40 - Study EFC12404: Patient disposition (randomized population)



4.2.3 Efficacy findings

4.2.3.1 Primary endpoint: Change in HbA1c at Week 30

The co-primary efficacy hypotheses were statistical non-inferiority of iGlarLixi versus insulin glargine and superiority of iGlarLixi versus lixisenatide in HbA1c change from baseline to Week 30; both were demonstrated (Table 12). The mean difference for iGlarLixi versus insulin glargine was -0.29% ($p<0.0001$), and thus, according to the predefined hierarchical testing order, superiority of iGlarLixi over insulin glargine was also achieved (Table 62).

From a mean baseline HbA1c (post run-in) of 8.1% in all 3 treatment groups, LS mean HbA1c decreased by 1.63% for iGlarLixi, 1.34% for insulin glargine, and 0.85% for lixisenatide, reaching mean HbA1c levels of 6.5%, 6.8%, and 7.3%, respectively.

Table 12 - Study EFC12404: Mean change in HbA1c (%) from baseline to Week 30 using MMRM (mITT population)

HbA1c (%)	iGlarLixi (N=468)	Insulin Glargine (N=466)	Lixisenatide (N=233)
Baseline			
Number	467	464	233
Mean (SD)	8.08 (0.71)	8.08 (0.69)	8.13 (0.72)
Median	8.00	8.00	8.00
Min : Max	4.5 : 10.2	5.9 : 10.4	6.7 : 10.3
Week 30			
Number	443	446	221
Mean (SD)	6.50 (0.75)	6.81 (0.76)	7.31 (0.87)
Median	6.30	6.70	7.20
Min : Max	4.9 : 9.6	4.6 : 10.7	5.2 : 11.0
Change from baseline to Week 30			
Number	467	464	233
LS Mean (SE) [a]	-1.63 (0.038)	-1.34 (0.039)	-0.85 (0.052)
LS mean difference (SE) vs insulin glargine [a]	-0.29 (0.048)	-	-
95% CI	(-0.384 to -0.194)	-	-
p-value	<0.0001	-	-
LS mean difference (SE) vs lixisenatide [a]	-0.78 (0.059)	-	-
95% CI	(-0.898 to -0.665)	-	-
p-value	<0.0001	-	-

a. Mixed-effect model with repeated measures with treatment groups (fixed ratio combination, insulin glargine alone, lixisenatide alone), randomization strata of HbA1c (<8.0%, ≥ 8.0%) at Visit 4 (Week -1), randomization strata of second OAD use at screening (Yes, No), visit (Week 8, 12, 24, and 30), treatment-by-visit interaction, and country as fixed effects, and baseline HbA1c value-by-visit interaction as a covariate. Countries with fewer than 5 patients were grouped with the country with the lowest number of patients that was 5 or more.

The analysis included all scheduled measurements obtained during the study, including those obtained after study drug discontinuation or introduction of rescue therapy. Patients are included who had measurements at baseline and post-baseline.

The results of sensitivity analyses of the primary endpoint were fully consistent with the results of the primary analysis (Figure 58 and Figure 57).

Tipping point analyses were also conducted as described in Section 4.1.2). An additional HbA1c increase of 3.6% to each imputed value in the iGlarLixi group was required to tip the results to lose statistical significance for the iGlarLixi versus insulin glargine comparison. For the iGlarLixi versus lixisenatide comparison, the results remained statistically significant with even very conservative imputations up to an HbA1c increase of 4.0% to each imputed value in the iGlarLixi group (Table 66 and Table 67).

4.2.3.2 Key secondary endpoints

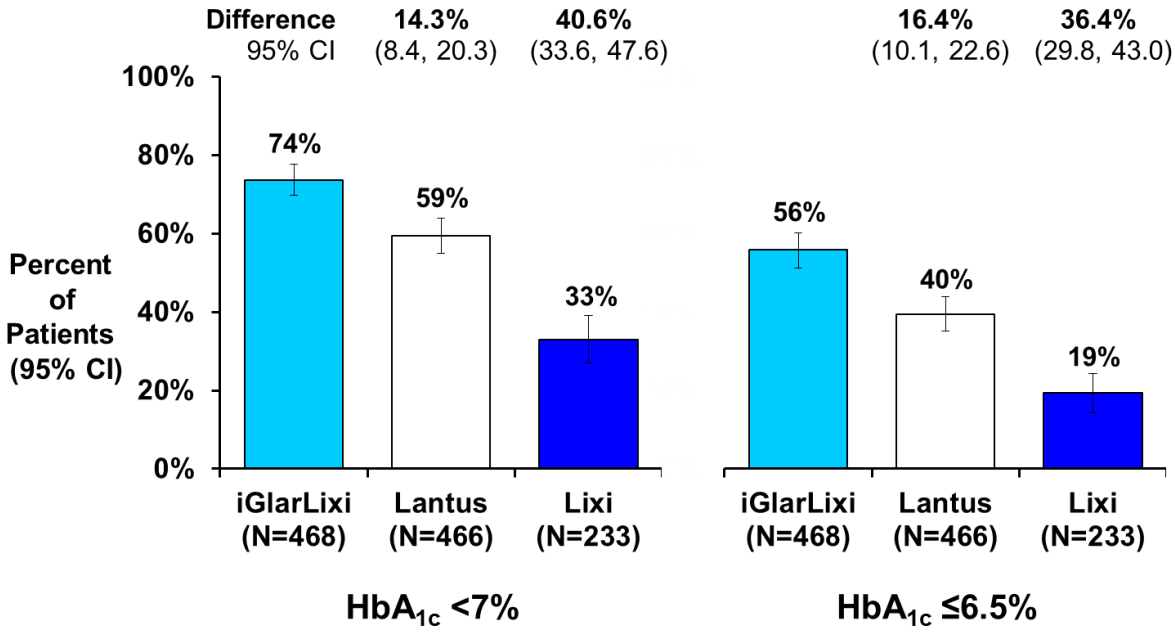
4.2.3.2.1 Proportion of responders with HbA1c <7.0% and ≤6.5% at Week 30

Most patients in the iGlarLixi group (73.7%) reached an HbA1c target <7.0% at the end of the 30-week treatment period versus a smaller proportion for insulin glargine (59.4%) and lixisenatide (33.0%). The 95% CI for the treatment difference vs. insulin glargine was 8.4% to 20.3%; for the treatment difference vs. lixisenatide it was 33.6% to 47.6%.

More than half of patients (55.8%) treated with iGlarLixi reached an HbA1c ≤6.5% compared to insulin glargine (39.5%) and lixisenatide (19.3%). The 95% CI for the treatment difference vs. insulin glargine was 10.1% to 22.6%; for the treatment difference vs. lixisenatide it was 29.8% to 43.0%.

Sensitivity analyses were fully consistent with the results of the primary HbA1c responder analyses (Figure 59 and Figure 60).

Figure 41 – Study EFC12404: Proportion of responders with HbA1c <7.0% and ≤6.5% at Week 30



4.2.3.2.2 Postprandial glucose control during a standardized meal test vs. insulin glargine at Week 30

The key secondary endpoints were tested in a hierarchical order as specified in the protocol and statistical analysis plan for controlling the overall Type 1 error (Table 62) and the testing order is noted in the text for each tested endpoint.

Elevated PPG concentrations can contribute substantially to suboptimal glycemic control. iGlarLixi improved PPG control after a standardized breakfast as compared to insulin glargine,

with a statistically significant and clinically relevant improvement from baseline in mealtime excursions (Figure 21).

At Week 30, the mean 2-hour PPG excursions were 50.7 mg/dL for iGlarLixi, 86.5 mg/dL for insulin glargine, and 30.6 mg/dL for lixisenatide. The LS mean treatment difference was statistically significant for the comparison of iGlarLixi with insulin glargine (-38.4 mg/dL; 95% CI: -44.995 to -31.883; p<0.0001; Test 1 in the step-down testing order).

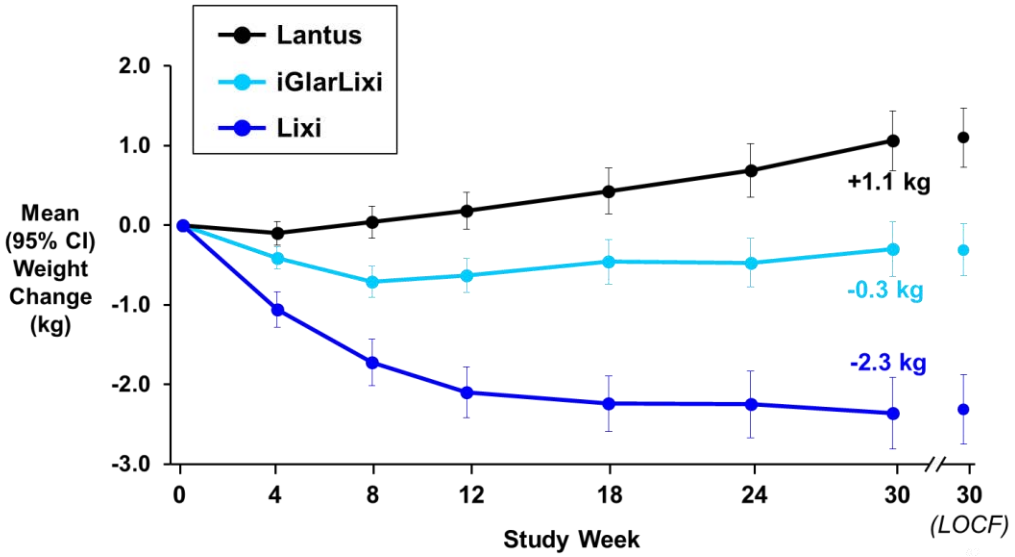
4.2.3.2.3 Change in body weight vs. insulin glargine at Week 30

Body weight decreased in the iGlarLixi and lixisenatide groups and increased in the insulin glargine group with a statistically significant difference between iGlarLixi and insulin glargine (mean treatment difference of -1.40 kg [95% CI, -1.89 to -0.91; p<0.0001; Test 2 in the testing order]). This observation highlights the contribution of the lixisenatide component to the beneficial body weight effect of iGlarLixi.

A post hoc evaluation of the percentage of patients with no body weight gain at Week 30 showed that more patients in the iGlarLixi group than in the insulin glargine group had no weight gain during the treatment period: more than half (52.1%) in the iGlarLixi group and about a third (34.3%) in the insulin glargine group.

While iGlarLixi attenuated the weight gain typically associated with initiation of insulin therapy, in the insulin glargine group there was a mean increase in body weight that progressed steadily over the 30-week treatment period, without evidence of a plateau (Figure 42).

Figure 42 - Study EFC12404: Mean change from baseline in body weight (kg) by visit (mITT population)



The analysis included all scheduled measurements obtained during the study, including those obtained after study drug discontinuation or introduction of rescue therapy.

4.2.3.2.4 Change in FPG vs. lixisenatide from baseline to Week 30

The reduction in FPG was statistically significantly greater in the iGlarLixi group (62.4 mg/dL) compared to the lixisenatide group (27.0 mg/dL]) with a treatment difference of -35.4 mg/dL ($p<0.0001$; Test 3 in the testing order). Mean FPG values at Week 30 were 113.9 mg/dL for iGlarLixi and 148.9 mg/dL for lixisenatide. At end of treatment, the mean FPG for iGlarLixi was well within the 2015 ADA-recommended target range for pre-prandial glucose (80 to 130 mg/dL).

At Week 30, the mean FPG value was 117.6 mg/dL in the insulin glargine group, with a treatment difference of -3.5 mg/dL versus iGlarLixi (this endpoint was not included in the testing order). Patients in both groups were titrated once weekly to the same fasting SMPG target of 80 to 100 mg/dL, inclusive, explaining the similar FPG values at Week 30.

4.2.3.2.5 Change in daily average 7-point SMPG vs. lixisenatide from baseline to Week 30

The reduction in daily average SMPG values was statistically significantly greater in the iGlarLixi group compared to lixisenatide. The iGlarLixi group reported a decrease of 60.4 mg/dL compared to 35.1 mg/dL for the lixisenatide group. The treatment difference was -25.2 mg/dL ($p<0.0001$; Test 4 in the testing order). At Week 30 there was a clear improvement in glycemic control both from baseline and across the day with iGlarLixi versus lixisenatide.

4.2.3.2.6 HbA1c <7.0% and no body weight gain at Week 30

The advantage of using a composite endpoint is that it allows a more comprehensive definition of efficacy, particularly when more than one response to therapy is important. A statistically significantly higher proportion of patients reached this composite endpoint at Week 30 in the iGlarLixi group (43.2%) than in the insulin glargine group (25.1%), ($p<0.0001$; Test 5 in the testing order).

4.2.3.2.7 Change in daily average 7-point SMPG vs. insulin glargine from baseline to Week 30

The reduction in daily average SMPG was statistically significantly greater in the iGlarLixi group as compared to insulin glargine: 60.4 mg/dL versus 47.9 mg/dL with a treatment difference of -12.5 mg/dL ($p<0.0001$; Test 7 in the testing order).

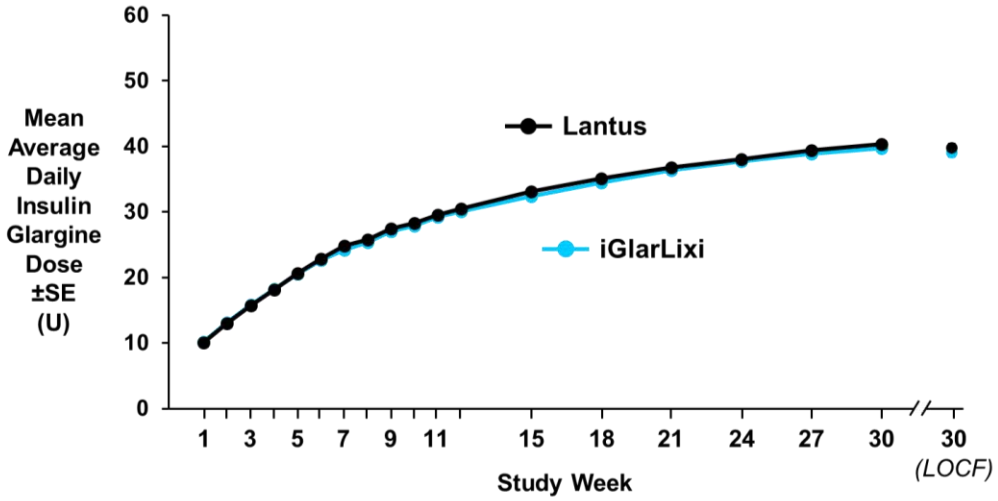
4.2.3.2.8 HbA1c <7.0%, no body weight gain, and no documented hypoglycemia (PG ≤70 mg/dL) vs. insulin glargine

Significantly more patients in the iGlarLixi group reached the triple composite endpoint than did patients in the insulin glargine group (31.8% versus 18.9% respectively), with a treatment difference of 12.98% ($p<0.0001$; Test 8 in the testing order). The proportion of patients reaching this triple composite endpoint was also numerically higher in the iGlarLixi group compared to the lixisenatide group (26.2%).

4.2.3.2.9 Change in daily insulin dose at Week 30

At Week 30, the mean average daily insulin glargine dose was comparable in the iGlarLixi (39.8 U) and insulin glargine groups (40.3 U) (Test 9 in the testing order). In both groups, the average mean daily dose of insulin glargine rose steadily and concordantly over the treatment period (Figure 43).

Figure 43 - Study EFC12404: Mean average daily insulin glargine dose (U) by visit (mITT population)



Final insulin dose

At the end of the treatment period, the proportion of patients taking doses ≥30 U was comparable between groups, 71.2% for iGlarLixi and 70.2% for insulin glargine (Table 13). The maximum allowed dose of 60 U was taken by 15.6% of patients in the iGlarLixi group and 20.1% in the insulin glargine group.

In the iGlarLixi group, 240 (51.2%) patients were using Pen A, and 227 (48.4%) had switched and were using Pen B at the end of the treatment period.

Table 13 - Study EFC12404: Number (%) of patients by final insulin dose at the end of the treatment period (safety population)

Final Insulin Dose	iGlarLixi (N=469)	Insulin Glargine (N=467)
<20 U	59 (12.6%)	43 (9.2%)
≥20 U to <30 U	76 (16.2%)	96 (20.6%)
≥30 U to ≤40 U	126 (26.9%)	117 (25.1%)
>40 U to ≤60 U	208 (44.3%)	209 (44.8%)
>60 U	0	2 (0.4%)
=60 U	73 (15.6%)	94 (20.1%)
Pen A[a]		
<20 U	59 (12.6%)	
≥20 U to <30 U	75 (16.0%)	
≥30 U to ≤40 U	104 (22.2%)	
>40 U to ≤60 U	2 (0.4%)	
>60 U	0	
Pen B [b]		
<20 U	0	
≥20 U to <30 U	0	
≥30 U to ≤40 U	21 (4.5%)	
>40 U to ≤60 U	206 (43.9%)	
>60 U	0	

a 2U/1µg fixed ratio for insulin glargine/lixisenatide intended to administer daily doses between 10 and 40U (10 U/5µg and 40U/20µg)
b 3U/1µg fixed ratio for insulin glargine/lixisenatide intended to administer daily doses between 41 and 60U (≈41U/14µg and 60U/20µg)
Note: Percentages are calculated using the number of safety patients as the denominator.

Final lixisenatide dose

In the iGlarLixi group, the mean daily dose of the lixisenatide component at Week 30 was 15.5 µg, and the majority of treated patients (58.6%) were receiving ≥15 µg to ≤20 µg of lixisenatide at the end of the treatment period. In the lixisenatide group, the majority of patients (88.8%) used a final daily lixisenatide dose of 20 µg.

4.2.3.3 Other endpoints

4.2.3.3.1 Hypoglycemia

iGlarLixi decreased HbA1c significantly in comparison to insulin glargine (Table 12) without a concomitant increase in hypoglycemia.

Comparable proportions of patients in the iGlarLixi (25.6%) and insulin glargine groups (23.6%) reported at least one event of documented symptomatic hypoglycemia (plasma glucose ≤70 mg/dL) as defined in the protocol (Table 14).

There was a single case of severe hypoglycemia in a patient in the insulin glargine group compared to none in the iGlarLixi and lixisenatide groups. There were no serious TEAEs of symptomatic hypoglycemia and no hypoglycemia events leading to treatment discontinuation in Study EFC12404.

Table 14 - Study EC12404: Summary of symptomatic hypoglycemia (PG ≤70 mg/dL) meeting the protocol definition during the on-treatment period (safety population)

Symptomatic hypoglycemia	iGlarLixi (N=469)	Insulin Glargine (N=467)	Lixisenatide (N=233)
Total patient years of exposure	263.1	262.5	125.2
Documented symptomatic hypoglycemia (plasma glucose ≤70 mg/dL)			
Number of patients with events, n (%)	120 (25.6%)	110 (23.6%)	15 (6.4%)
Number of events	378	321	43
Number of events per patient-year [a]	1.44	1.22	0.34
Severe symptomatic hypoglycemia			
Number of patients with events, n (%)	0	1 (0.2%)	0
Number of events	0	1	0
Number of events per patient-year [a]	0	<0.01	0

eCRF: electronic Case Report Form.
Patient years of exposure: calculated as time from the first to the last injection of study drug plus 1 day.
a Calculated as number of events divided by total patient years of exposure.
Symptomatic hypoglycemia was recorded on the dedicated eCRF and met the protocol definition for severe or documented symptomatic hypoglycemia.
On-treatment period is defined as the time from the first injection of study drug up to 1 day after the last injection of study drug, regardless of the introduction of rescue therapy.

4.2.3.3.2 Percent of patients receiving rescue therapy

Rescue therapy was to be initiated according to predefined criteria of glycemic control given in the clinical study protocol. A low and comparable proportion of patients received rescue therapy in the iGlarLixi (3.6%, 17 patients) and insulin glargine groups (3.4%, 16 patients). In the lixisenatide group, 29 patients (12.4%) received rescue therapy.

4.3 Study EFC12405: Patients Insufficiently Controlled on Basal Insulin ± 1 or 2 OADs

The 2-arm study design is depicted in Figure 22.

At screening, patients had been treated with a basal insulin for at least 6 months before screening. The total daily basal insulin dose was to have been stable (±20%) and between 15 and 40 U/day for at least 2 months. The dose(s) of any oral glucose-lowering therapies (if taken) must have been stable during the 3 months before the screening visit. The permitted oral glucose-lowering therapies were metformin (≥1500 mg/day or maximal tolerated dose), a SU, glinide, sodium-glucose co-transporter-2 (SGLT-2) inhibitor, or dipeptidyl peptide 4 (DPP-4) inhibitor.

Table 15 - Study EFC12405: HbA1c and FPG requirements for patients at screening

	Basal Insulin + 2 OADs or 1 OAD Other than Metformin	Basal Insulin Only or Basal Insulin + Metformin
HbA1c	7.5-10%	7.5-10%
FPG	≤180 mg/dL	≤200 mg/dL

During the 6-week run-in, patients remained on or switched to insulin glargine with optimization/stabilization of dose while continuing metformin (if previously used) and discontinuing other OADs. Metformin, if used, was to be maintained at a stable dose throughout the study unless safety issues developed.

At end of the 6-week run-in, patients with an HbA1c ≥7.0% and ≤10.0%, fasting SMPG ≤140 mg/dL, and a daily insulin glargine dose of 20-50 U were randomized 1:1 to iGlarLixi or insulin glargine.

During the treatment period, patients were titrated to the same fasting SMPG targets in each arm (80 to 100 mg/dL, inclusive); 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 iGlarLixi starting dose was 20 U/10 µg (Pen A) if the insulin glargine dose on the day before randomization was <30 U and 30 U/10 µg (Pen B) if the insulin glargine dose on the day before randomization was ≥30 U. The dose was to remain stable for 2 weeks. The starting dose of 20 U or 30 U was chosen in order not to exceed the recommended starting lixisenatide dose of 10 µg while at the same time avoiding a major decrease in the patient's current insulin dose.

The insulin glargine starting dose was the same dose as the day before randomization.

4.3.1 Description of study population

The overall population was balanced by gender and was primarily Caucasian (91.7%) with a mean age of 60 years. The study population had a mean screening BMI of 31.3 kg/m^2 with 58.6% of patients having a mean BMI ≥30 kg/m^2, indicating that the majority of patients were obese.

Baseline characteristics related to diabetes were comparable in the 2 treatment groups and indicative of a population in poor glycemic control despite concurrent use of basal insulin with or without one or more OADs over a period of several years (Table 16). At screening, the mean duration of diabetes was 12.1 years with a mean HbA1c of 8.5% in both groups. After the run-in period, mean HbA1c had decreased to 8.1% in both groups, with 61.7% of all patients having a value ≥8.0%.

The duration of basal insulin use was approximately 3 years in the iGlarLixi and insulin glargine groups. The percentage of patients using metformin at screening was comparable between groups, with metformin used by 89.4% of all patients. The percentage of patients using 2 OADs at screening was 43.6% and 37.9% in the iGlarLixi and insulin glargine groups, respectively, with

the most frequent combination overall being metformin plus a SU (34.6%). Of patients using 2 OADs, the mean duration of use was 4.4 and 4.8 years in each group, respectively.

The overall mean daily dose of insulin glargine was approximately 29 U at the start of run-in and had increased to approximately 35 U at the time of randomization. The overall mean FPG was 143.9 mg/dL at screening and was reduced to 132.4 mg/dL at the end of run-in.

Table 16 - Study EFC12405: Disease characteristics at screening or baseline (randomized population)

	iGlarLixi (N=367)	Insulin Glargine (N=369)	All (N=736)
Duration of diabetes (years)			
Number	367	368	735
Mean (SD)	12.02 (6.64)	12.13 (6.85)	12.08 (6.74)
Median	10.49	11.32	10.75
Min : Max	1.1 : 36.7	1.0 : 42.7	1.0 : 42.7
Duration of prior basal insulin treatment (years)			
Number	367	369	736
Mean (SD)	3.12 (3.06)	3.31 (3.08)	3.22 (3.07)
Median	2.15	2.29	2.20
Min : Max	0.4 : 20.6	0.2 : 24.8	0.2 : 24.8
Daily dose of prior basal insulin (U) at run-in (Visit 2)			
Number	367	369	736
Mean (SD)	28.36 (8.22)	29.00 (8.14)	28.68 (8.18)
Median	30.00	28.00	28.00
Min : Max	10.0 : 44.0	12.0 : 50.0	10.0 : 50.0
Average daily dose of insulin glargine (U) at randomization (Visit 6) [a]			
Number	366	369	735
Mean (SD)	35.04 (9.22)	35.23 (8.63)	35.13 (8.92)
Median	35.00	36.00	36.00
Min : Max	15.0 : 58.0	12.0 : 52.0	12.0 : 58.0
Metformin use at screening recorded in eCRF [n (%)]			
Number	367	369	736
Yes	329 (89.6%)	329 (89.2%)	658 (89.4%)
No	38 (10.4%)	40 (10.8%)	78 (10.6%)
Daily dose of metformin at baseline (mg) [b]			
Number	329	329	658
Mean (SD)	2082.8 (499.2)	2042.0 (455.9)	2062.4 (478.1)
Median	2000.0	2000.0	2000.0
Min : Max	850 : 3500	500 : 4000	500 : 4000
Number of OAD use at screening [n (%)]			
Number	367	369	736
No OAD	18 (4.9%)	19 (5.1%)	37 (5.0%)
1 OAD	189 (51.5%)	210 (56.9%)	399 (54.2%)
2 OADs	160 (43.6%)	140 (37.9%)	300 (40.8%)

	iGlarLixi (N=367)	Insulin Glargine (N=369)	All (N=736)
OAD use by drug class at screening [n (%)]			
Number	367	369	736
No OAD	18 (4.9%)	19 (5.1%)	37 (5.0%)
1 OAD	189 (51.5%)	210 (56.9%)	399 (54.2%)
Metformin only	170 (46.3%)	190 (51.5%)	360 (48.9%)
Sulfonylurea only	16 (4.4%)	14 (3.8%)	30 (4.1%)
DPP-4 inhibitor only	2 (0.5%)	4 (1.1%)	6 (0.8%)
SGLT-2 inhibitor only	0	1 (0.3%)	1 (0.1%)
Glinide only	1 (0.3%)	1 (0.3%)	2 (0.3%)
Combination of 2 OADs	160 (43.6%)	140 (37.9%)	300 (40.8%)
Metformin plus Sulfonylurea	137 (37.3%)	118 (32.0%)	255 (34.6%)
Metformin plus DPP-4 inhibitor	20 (5.4%)	18 (4.9%)	38 (5.2%)
Metformin plus Glinide	2 (0.5%)	3 (0.8%)	5 (0.7%)
Sulfonylurea plus DPP-4 inhibitor	1 (0.3%)	1 (0.3%)	2 (0.3%)
Duration of second OAD use (years) [c]			
Number	161	141	302
Mean (SD)	4.35 (3.53)	4.75 (4.95)	4.53 (4.25)
Median	3.55	3.05	3.32
Min : Max	0.3 : 23.6	0.2 : 29.7	0.2 : 29.7

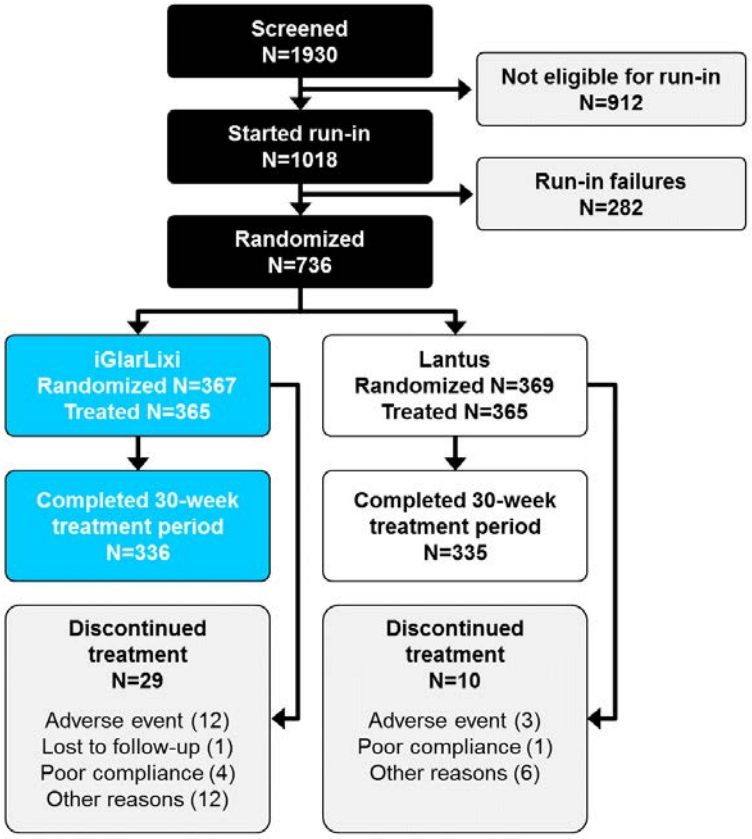
a Averaged daily dose of insulin glargine recorded in eCRF for the 3 days before randomization.
b For patients who took metformin at screening
c For patients who took a 2nd OAD at screening
The baseline value is defined as the last available value before the first injection of study drug or the last available value on or before the date of randomization if not treated with study drug.

4.3.2 Patient disposition

Of the 1930 patients screened, 912 were not eligible for run-in primarily due to an HbA1c value out of the protocol-defined range. Of the 1018 patients who entered the run-in phase, 736 were randomized to 1 of the 2 treatment groups. The 2 main reasons for run-in failure were a mean fasting SMPG value or HbA1c value out of the protocol-defined range at Week -1 (108 and 67 patients out of the 1018 patients who entered the run in phase, respectively).

The percentage of patients completing the treatment period was comparable in both groups (91.6% in the iGlarLixi group and 96.2% in the insulin glargine group). A total of 29 patients (7.9%) permanently discontinued study medication in the iGlarLixi group and 10 patients (2.7%) discontinued in the insulin glargine group. The main reasons for permanent discontinuation were due to AEs (3.3% in the iGlarLixi group and 0.8% in the insulin glargine group) and "other" reasons (3.3% in the iGlarLixi group and 1.6% in the insulin glargine group). "Other" reasons for discontinuation were not reported as being safety-related with the exception of one "hypoglycemia" in the iGlarLixi group.

Figure 44 - Study EFC12405: Patient disposition (randomized population)



4.3.3 Efficacy findings

4.3.3.1 Primary endpoint: Change in HbA1c at Week 30

iGlarLixi met its primary objective by demonstrating statistical superiority over insulin glargine for change in HbA1c from baseline to Week 30. After 30 weeks of treatment, LS mean HbA1c had decreased by 1.13% to a mean of 6.94% with iGlarLixi and by 0.62% to a mean of 7.48% with insulin glargine (Table 17). In this difficult to treat population with advanced T2DM of long duration, the attainment of an HbA1c <7.0% is clinically important.

Superiority was demonstrated with a LS mean treatment difference of –0.52%, which is noteworthy given that the 2 groups were titrated to an identical fasting SMPG target and were both capped at a daily dose of 60 U.

Table 17 - Study EFC12405: Mean change in HbA1c (%) from baseline to Week 30 using MMRM (mITT population)

HbA1c (%)	iGlarLixi (N=366)	Insulin Glargine (N=365)
Baseline		
Number	364	364
Mean (SD)	8.07 (0.68)	8.08 (0.73)
Median	8.00	8.00
Min : Max	6.6 : 10.2	5.9 : 10.0
Week 30		
Number	346	355
Mean (SD)	6.94 (0.87)	7.48 (0.91)
Median	6.80	7.40
Min : Max	5.0 : 9.8	5.6 : 11.2
Change from baseline to Week 30		
Number	364	364
LS Mean (SE)[a]	-1.13 (0.057)	-0.62 (0.055)
LS mean difference (SE) vs insulin glargine	-0.52 (0.060)	-
95% CI	(-0.633 to -0.397)	-
p-value	<0.0001	-

The analysis included all scheduled measurements obtained during the study, including those obtained after study drug discontinuation or introduction of rescue therapy. Patients are included who had measurements at baseline and post-baseline.

The results of prespecified sensitivity analyses of the primary endpoint were fully consistent with the results of the primary analysis including the key sensitivity analysis for the on-treatment period (Figure 57). Tipping point analyses were also conducted (described in Section 4.1.2). For the iGlarLixi vs. insulin glargine comparison, the results remained statistically significant with even very conservative imputations up to a HbA1c increase of 4.0% to each imputed value in the iGlarLixi group (Table 66 and Table 67.

4.3.3.2 Key secondary endpoints

4.3.3.2.1 Proportion of responders with HbA1c <7.0% at Week 30

A higher proportion of patients in the iGlarLixi group (54.9%) reached an HbA1c target <7.0% at the end of the 30-week treatment period vs. insulin glargine (29.6%). The 95% CI for the treatment difference vs. insulin glargine was 18.94% to 32.10%.

4.3.3.2.2 Postprandial glucose control during a standardized meal test vs. insulin glargine at Week 30

The key secondary endpoints were tested in a hierarchical order as specified in the protocol and statistical analysis plan (Table 62) and the testing order is noted in the text for each tested endpoint.

iGlarLixi improved PPG control after a standardized breakfast as compared to insulin glargine with a statistically significant and clinically relevant improvement in mealtime excursions (Figure 24). Mean 2-hour PPG excursions at Week 30 were 56.0 mg/dL for iGlarLixi and 120.8 mg/dL for insulin glargine. LS mean changes from baseline were -70.2 mg/dL for iGlarLixi and -8.4 mg/dL for insulin glargine with a LS mean treatment difference of -61.8 mg/dL (95% CI: -70.700 to -52.946; p<0.0001; Test 1 in the step-down testing order).

4.3.3.2.3 Change in body weight vs. insulin glargine at Week 30

Body weight decreased in the iGlarLixi group and increased in the insulin glargine group, demonstrating the ability of lixisenatide in a fixed-ratio combination with glargine to minimize the weight gain associated with initiation of insulin-based regimens. The LS mean changes from baseline to Week 30 were -0.7 kg and +0.7 kg, respectively. The treatment difference of -1.4 kg was statistically significant (95% CI:-1.808 to -0.930; p<0.0001; Test 2 in the testing order).

A post hoc evaluation of the percentage of patients with no body weight gain at Week 30 showed that more than half of patients in the iGlarLixi group (54.4%) had no weight gain during the treatment period while 61.9% of patients in the insulin glargine group gained weight.

4.3.3.2.4 Change in daily average 7-point SMPG vs. insulin glargine at Week 30

Patients treated with iGlarLixi had a statistically significantly greater reduction in average 7-point SMPG (27.1 mg/dL) compared to patients treated with insulin glargine (10.9 mg/dL). The LS mean difference between the two groups was -16.2 mg/dL (p<0.0001; Test 3 in the testing order).

4.3.3.2.5 HbA1c <7.0% and no body weight gain vs. insulin glargine at Week 30

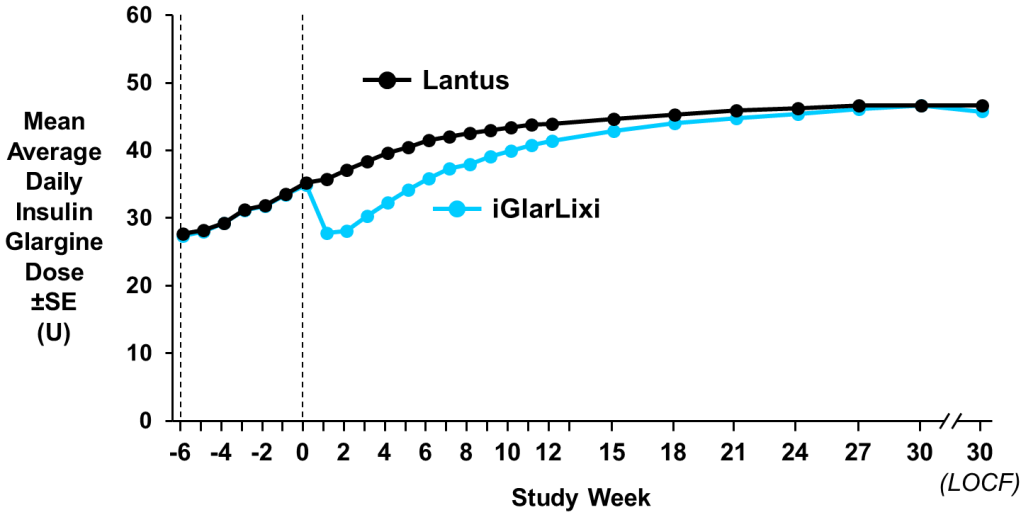
A significantly higher percentage of patients reached this composite endpoint in the iGlarLixi group (34.2%) compared to the insulin glargine group (13.4%), with a treatment difference of 20.8% (p<0.0001; Test 4 in the testing order).

4.3.3.2.6 Change in daily insulin dose at Week 30

A comparable increase from baseline in the LS mean daily dose of insulin glargine was observed in both treatment groups (10.6 U for iGlarLixi and 10.9 U for insulin glargine) with an equivalent mean daily dose at Week 30 of approximately 47 U (Test 5 in the testing order). In both treatment groups, the daily dose was capped at 60 U and patients were titrated once weekly to a fasting SMPG target of 80 to 100 mg/dL, inclusive, using the same protocol-specified algorithm.

As specified by the protocol, the initiation dose of iGlarLixi had to be either 20 U/10 µg with Pen A or 30 U/10 µg with Pen B (depending on the insulin glargine dose received on the day before randomization) and was to be kept stable for 2 weeks. This was reflected in a transient drop in the mean daily insulin glargine dose, followed by a steady rise (Figure 45). Beginning at Week 20, the mean daily dose began to plateau in both groups reaching the same level by Week 30.

Figure 45 - Study EFC12405: Mean average daily insulin glargine dose (U) by visit (mITT population)



Final insulin dose

At the end of the treatment period, the largest proportion of patients in any one dose-range were those taking >40 U to ≤60 U of insulin glargine, 60.8% in the iGlarLixi group and 64.7% in the insulin glargine group (Table 18). The maximum allowed dose of 60 U was taken by comparable proportions of patients in the iGlarLixi (27.1%) and insulin glargine (30.7%) groups.

In the iGlarLixi group, 100 (27.4%) patients were using Pen A and 264 (72.3%) were using Pen B at the end of the treatment period.

Final lixisenatide dose

In the iGlarLixi group, the mean average daily dose of lixisenatide at Week 30 was 16.9 µg/day. The majority of treated patients (68.8%) had a final lixisenatide dose ≥15 to ≤20 µg/day.

Table 18 - Study EFC12405: Number (%) of patients by final insulin dose at the end of the treatment period (Safety population)

Final Insulin Dose	iGlarLixi (N=365)	Insulin Glargine (N=365)
<20 U	2 (0.5%)	3 (0.8%)
≥20 U to <30 U	44 (12.1%)	39 (10.7%)
≥30 U to ≤40 U	97 (26.6%)	87 (23.8%)
>40 U to ≤60 U	222 (60.8%)	236 (64.7%)
>60 U	0	0
=60 U	99 (27.1%)	112 (30.7%)
Pen A [a]		
<20 U	2 (0.5%)	
≥20 U to <30 U	43 (11.8%)	
≥30 U to ≤40 U	53 (14.5%)	
>40 U to ≤60 U	2 (0.5%)	
Pen B [b]		
<20 U	0	
≥20 U to <30 U	1 (0.3%)	
≥30 U to ≤40 U	44 (12.1%)	
>40 U to ≤60 U	219 (60.0%)	

a 2U/1µg fixed ratio for insulin glargine/lixisenatide.
b 3U/1µg fixed ratio for insulin glargine/lixisenatide.
Note: Percentages are calculated using the number of safety patients as the denominator.

4.3.3.2.7 HbA1c <7.0%, no body weight gain, and no documented hypoglycemia (PG ≤70 mg/dL) vs. insulin glargine at Week 30

Inferential statistics were exploratory for this endpoint because the preceding test in the hierarchical testing order (change from baseline in dose of insulin glargine) was not significant.

However, more than twice as many patients in the iGlarLixi group (19.9%) reached the triple composite endpoint as compared to patients in the insulin glargine group (9.0%). The treatment difference was 10.94% (Test 6 in the testing order).

4.3.3.2.8 Change in FPG vs. insulin glargine at Week 30

Both treatment groups had an initial mean decrease in FPG from approximately 143.9 mg/dL at screening to approximately 132.0 mg/dL at baseline (post run-in).

The reduction from baseline in FPG was comparable in the iGlarLixi and insulin glargine groups with mean values at Week 30 of 122.1 mg/dL and 120.5 mg/dL, respectively, both within the 2015 ADA-recommended target range for pre-prandial glucose (80 to 130 mg/dL). Patients were titrated once weekly to the same fasting SMPG target of 80 to 100 mg/dL, inclusive, explaining the similar FPG values at Week 30.

4.3.3.3 Other endpoints

4.3.3.3.1 Hypoglycemia

In this 30-week study, treatment with iGlarLixi significantly decreased HbA1c in comparison to insulin glargine (Table 17) without a concomitant increase in documented symptomatic hypoglycemia. Comparable proportions of patients in each group reported at least one event of documented symptomatic hypoglycemia (plasma glucose ≤70 mg/dL): 40.0% and 42.5% in the iGlarLixi and insulin glargine groups, respectively (Table 19). The number of events per patient-year was lower in the iGlarLixi group compared to the insulin glargine group (3.03 versus 4.22).

Four patients (1.1%) in the iGlarLixi group had a total of 5 severe hypoglycemic events that were also considered as serious (preferred terms [PT]: hypoglycemia, hypoglycemic unconsciousness, and hypoglycemic seizure). Of these, 3 patients had confounding factors that may have contributed to the episodes of severe hypoglycemia, including dementia, an unusual amount of physical activity, and lack of food intake prior to the event. One patient (0.3%) in the insulin glargine group had a severe event of hypoglycemia (PT: hypoglycemic seizure) that was also serious; the event was precipitated by a lack of dietary compliance.

Table 19 - Study EFC12405: Summary of symptomatic hypoglycemia (PG ≤70 mg/dL) meeting protocol definition during the on-treatment period (safety population)

Symptomatic hypoglycemia	iGlarLixi (N=365)	Insulin Glargine (N=365)
Total patient years of exposure	201.9	208.6
Documented symptomatic hypoglycemia (plasma glucose ≤70 mg/dL)		
Number of patients with events, n (%)	146 (40.0%)	155 (42.5%)
Number of events	612	880
Number of events per patient-year [a]	3.03	4.22
Severe symptomatic hypoglycemia		
Number of patients with events, n (%)	4 (1.1%)	1 (0.3%)
Number of events	5	1
Number of events per patient-year [a]	0.02	<0.01

eCRF: electronic Case Report Form.
Patient years of exposure: calculated as time from the first to the last injection of open label study drug plus 1 day.
a Calculated as number of events divided by total patient years of exposure.
Symptomatic hypoglycemia = symptomatic hypoglycemia recorded on the dedicated eCRF and meeting protocol definition for severe, or documented, or probable symptomatic hypoglycemia.
For symptomatic hypoglycemia, the on-treatment period is defined as the time from the first injection of open label study drug up to 1 day after the last injection of study drug, regardless of the introduction of rescue therapy.

4.3.3.3.2 Percent receiving rescue therapy

Rescue therapy was to be initiated according to predefined criteria of glycemic control given in the clinical study protocol. The percentage of patients requiring rescue therapy in the iGlarLixi group was 2.7% (10 patients) compared to 6.0% (22 patients) in the insulin glargine group.

5 EFFICACY OF LOW-DOSE IGLARLIXI

When lixisenatide is given alone, the starting dose is 10 µg for 2 weeks and the maintenance dose is 20 µg. As part of iGlarLixi, lixisenatide can be used across a dose range of 5 to 20 µg. Post hoc analyses were performed to address the question of whether the contribution of each component was present across the entirety of this dose range.

Overall, the results of these studies demonstrate that both components of iGlarLixi contribute to the efficacy and safety profile. In particular, the improvement in HbA1c levels achieved with iGlarLixi versus insulin glargine establishes that iGlarLixi provides glycemic benefits via both the insulin glargine and the lixisenatide components.

Additional details are provided in Section 2.9.4.

5.1 METHODOLOGY

Post hoc descriptive analyses were performed to evaluate the contribution of each component of iGlarLixi to efficacy and safety across the full daily dose range using the final dose at the end of the treatment period.

Pre-randomization assignment into predefined fixed-dose groups that limit dose adjustment is not feasible for a product that is titrated according to individual patients' needs in order to achieve glycemic control. Therefore, a post-randomization approach was used based on patient dose or final daily dose category at the end of treatment. Since these categories were identified based on post-randomization parameters at Week 30, post hoc statistical comparisons would not be valid.

Analyses were performed by final daily insulin dose category for both the iGlarLixi and insulin glargine groups and by final daily lixisenatide dose category for the iGlarLixi group. As demonstrated in this section, in both iGlarLixi pivotal studies, there was a significant and clinically relevant effect at all final daily dose-categories, including patients who received 10 to 20 U of insulin glargine.

5.2 DESCRIPTION OF STUDY POPULATION

Patients were distributed over the full range of daily insulin glargine (Table 20) and lixisenatide (Table 21) dose-categories at the end of the treatment period.

Table 20 - Number (%) of patients by final insulin daily dose category at the end of the treatment period (mITT population)

	EFC12404		EFC12405	
Final Insulin Dose	**iGlarLixi**	**Insulin Glargine**	**iGlarLixi**	**Insulin Glargine**
	(N=468)	**(N=466)**	**(N=366)**	**(N=365)**
<10 U	0	3 (0.6%)	0	0
≥10 U to <20 U	58 (12.4%)	39 (8.4%)	2 (0.5%)	3 (0.8%)
≥20 U to <30 U	76 (16.2%)	96 (20.6%)	44 (12.0%)	39 (10.7%)
≥30 U to ≤40 U	126 (26.9%)	117 (25.1%)	97 (26.5%)	87 (23.8%)
>40 U to ≤60 U	208 (44.4%)	209 (44.8%)	222 (60.7%)	236 (64.7%)
>60 U	0	2 (0.4%)	0	0

Note: Percentages are calculated using the number of mITT patients as the denominator.

Table 21 - Number (%) of patients by final lixisenatide daily dose category at the end of the treatment period (mITT population)

	EFC12404	EFC12405
Final Lixisenatide Dose	**iGlarLixi (N=468)**	**iGlarLixi (N=366)**
<5 µg	0	0
≥5 µg to <10 µg	58 (12.4%)	3 (0.8%)
≥10 µg to <15 µg	131 (28.0%)	108 (29.5%)
≥15 µg to ≤20 µg	275 (58.8%)	251 (68.6%)
>20 µg	2 (0.4%)	2 (0.5%)

Note: Percentages are calculated using the number of mITT patients as the denominator.

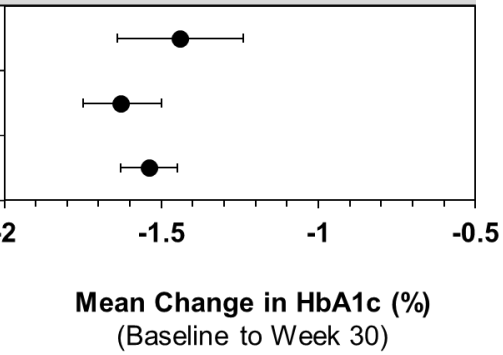
5.3 HBA1C

5.3.1 Study EFC12404

The change in HbA1c from baseline to Week 30 was consistent across final daily insulin dose-categories (Figure 26) and by final daily lixisenatide dose-categories within the iGlarLixi treatment group (Figure 46). This was also the case by final daily insulin dose-category within the insulin glargine treatment group. The results by dose-category were similar to that of the overall treatment group results.

Figure 46 – Study EFC12404: Forest plot of mean change in HbA1c (%) from baseline to Week 30 by final daily lixisenatide dose category for the iGlarLixi group (mITT population)

Final Lixisenatide Dose (µg)	iGlarLixi (N)	Mean Difference (95% CI)
≥5 to <10	57	**-1.44** (-1.64, -1.24)
≥10 to <15	131	**-1.63** (-1.76, -1.51)
≥15 to ≤20	275	**-1.54** (-1.63, -1.45)

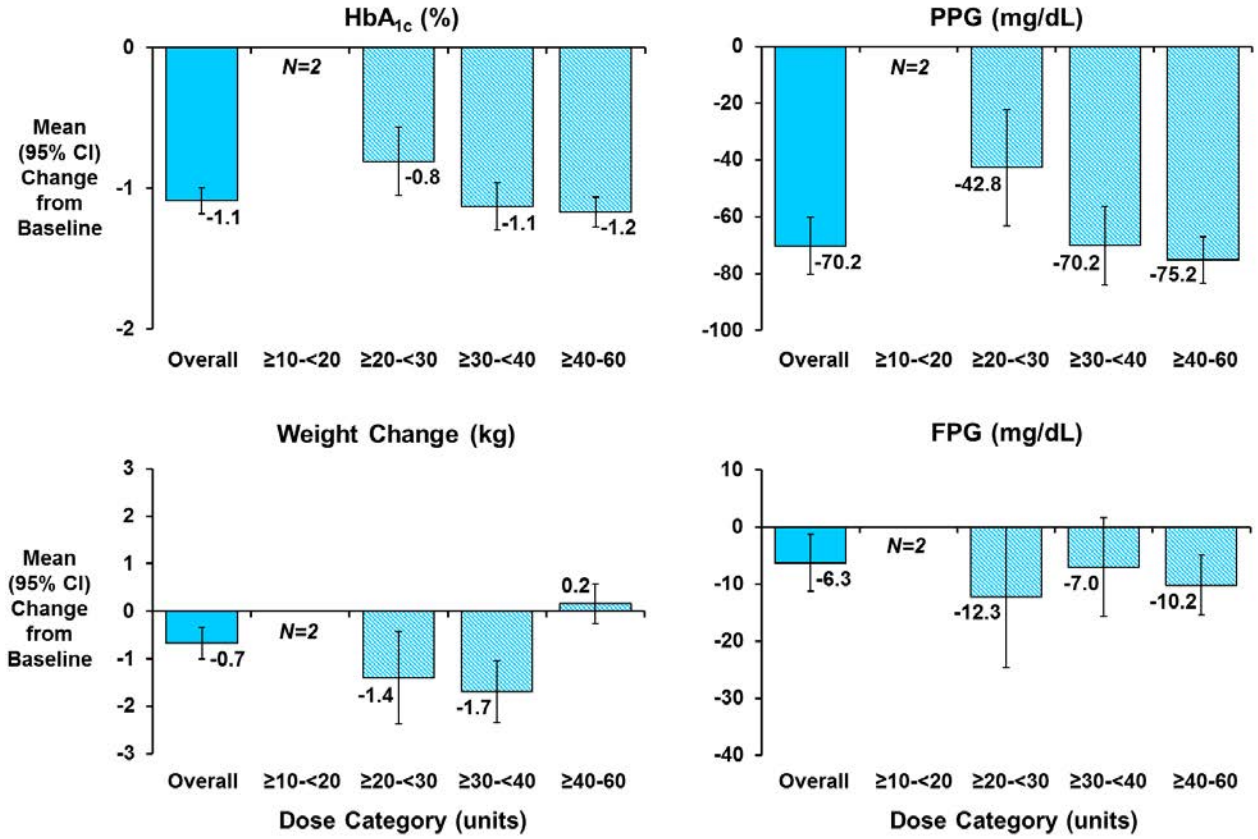


The analysis included all scheduled measurements obtained during the study, including those obtained after study drug discontinuation or introduction of rescue therapy. Categories with ≥5 patients were presented.

5.3.2 Study EFC12405

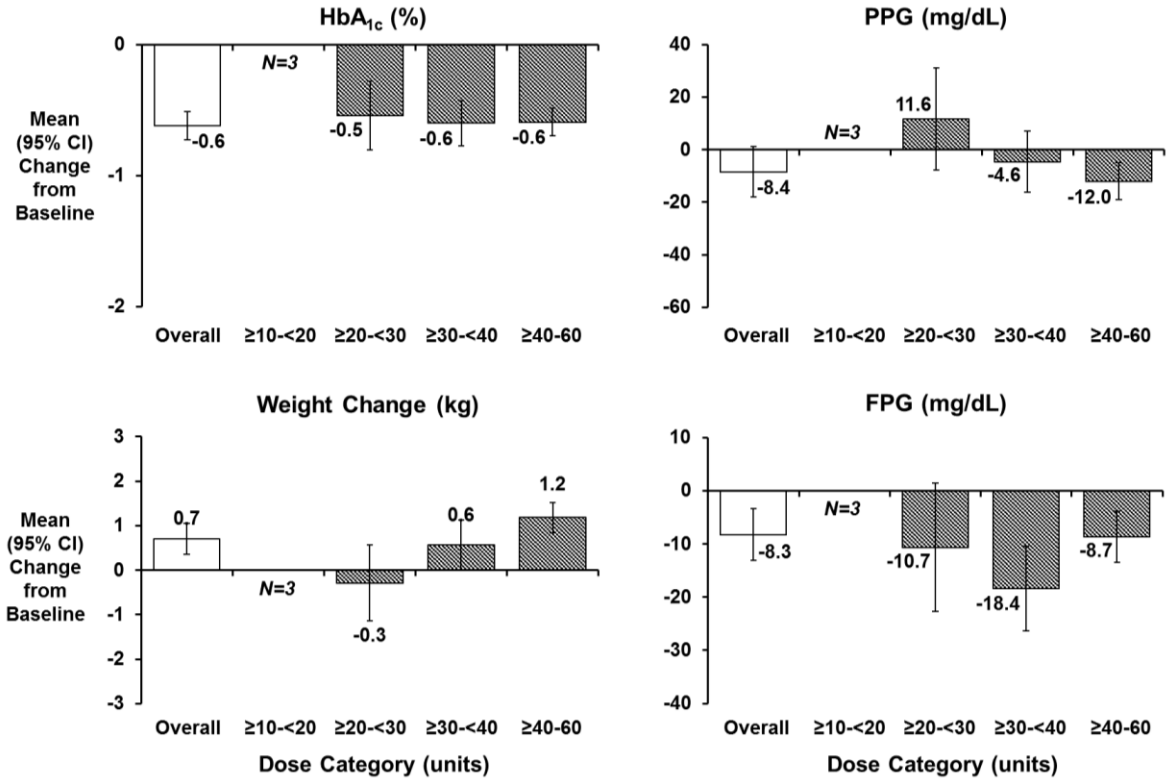
The changes in HbA1c and FPG from baseline to Week 30 were comparable across final daily insulin dose-categories within the iGlarLixi group; the results by dose-category were similar to the overall treatment group results (Figure 47). Across final daily insulin dose-categories in the iGlarLixi group, robust weight reductions were observed at all but the highest dose-category.

Figure 47 – Study EFC12405: Mean change in HbA1c, FPG, PPG, and body weight from baseline to Week 30 for the iGlarLixi group by final daily insulin glargine dose category (mITT population)



The changes in HbA1c and FPG from baseline to Week 30 were comparable across final daily insulin dose-categories within the insulin glargine group; the results by dose-category were similar to the overall treatment group results (Figure 48). Across final daily insulin dose-categories in the insulin glargine group, weight gain was observed at all but the lowest daily dose-category.

Figure 48 - Study EFC12405: Mean change in HbA1c, FPG, PPG, and body weight from baseline to Week 30 for the insulin glargine arm by final daily insulin glargine dose category (mITT population)



5.4 OVERALL SAFETY EXPERIENCE

Post hoc analyses by final daily insulin dose-categories focused on the assessment of safety evaluations at the low insulin and low lixisenatide dose-levels. Since the incidence of the key safety parameters (nausea/vomiting, diarrhea, documented symptomatic hypoglycemia [≤70 mg/dL]) was generally low, these analyses were performed using a cut-off of <20 U and ≥20 U in EFC12404 where a relevant number of patients were using <20 U/day (corresponding to a lixisenatide dose of <10 µg).

In EFC12404, within each treatment group, the incidence of overall TEAEs, serious TEAEs, and TEAEs leading to treatment discontinuation was consistent across all final daily dose-categories (Table 22).

Table 22 – Study EFC12404: Overall summary of TEAEs by final daily insulin dose categories (<20 U, ≥20 U) (safety population)

	iGlarLixi (N=469)		Insulin Glargine (N=467)	
n(%)	<20 U (N=59)	>=20 U (N=410)	<20 U (N=43)	>=20 U (N=424)

n(%)	iGlarLixi (N=469)		Insulin Glargine (N=467)	
	<20 U (N=59)	>=20 U (N=410)	<20 U (N=43)	>=20 U (N=424)
Patients with any TEAE	35 (59.3%)	232 (56.6%)	16 (37.2%)	211 (49.8%)
Patients with any serious TEAE	3 (5.1%)	15 (3.7%)	4 (9.3%)	15 (3.5%)
Patients with any TEAE leading to death	2 (3.4%)	0	1 (2.3%)	2 (0.5%)
Patients with any TEAE leading to permanent treatment discontinuation	6 (10.2%)	6 (1.5%)	3 (7.0%)	6 (1.4%)

TEAE: Treatment-Emergent Adverse Event
n (%) = number and percentage of patients with at least one TEAE.

5.5 GASTROINTESTINAL TOLERABILITY

Post hoc analyses were performed on the incidence of GI disorders (nausea, vomiting, and diarrhea) by final daily insulin and final daily lixisenatide dose-categories.

In EFC12404, results were consistent across final daily insulin (Table 23) and final daily lixisenatide dose-categories in the iGlarLixi group (Table 24).

Table 23 – Study EFC12404: Summary of GI TEAEs by final daily insulin dose categories (<20 U, ≥20 U) (safety population)

	iGlarLixi (N=469)		Insulin Glargine (N=467)	
	<20 U (N=59)	≥20 U (N=410)	<20 U (N=43)	≥20 U (N=424)
Gastrointestinal disorders	10 (16.9%)	72 (17.6%)	2 (4.7%)	33 (7.8%)
Diarrhea				
Number of patients with events, n(%)	5 (8.5%)	37 (9.0%)	1 (2.3%)	19 (4.5%)
Number of events per patient year	0.27	0.19	0.15	0.09
Nausea				
Number of patients with events, n(%)	4 (6.8%)	41 (10.0%)	0	17 (4.0%)
Number of events per patient year	0.2	0.24	0	0.07
Vomiting				
Number of patients with events, n(%)	1 (1.7%)	14 (3.4%)	1 (2.3%)	6 (1.4%)
Number of events per patient year	0.03	0.07	0.1	0.03

GI: Gastrointestinal, TEAE: Treatment-Emergent Adverse Event
Patient years of exposure: calculated as time from the first to the last injection of study drug plus 3 days.
[a] Calculated as number of events divided by total patient years of exposure.
MedDRA Version: 18.0.

Table 24 – Study EFC12404: Summary of GI TEAEs by final daily lixisenatide dose categories (<10 µg, ≥10 µg - <15 µg, ≥15 µg - ≤20 µg) (safety population)

	iGlarLixi (N=469)		
	<10 µg (N=59)	≥10 µg -<15 µg (N=131)	≥15 µg - ≤20 µg (N=275)
Gastrointestinal disorders	10 (16.9%)	30 (22.9%)	42 (15.3%)
Diarrhea			
Number of patients with events, n(%)	5 (8.5%)	16 (12.2%)	21 (7.6%)
Number of events per patient year	0.27	0.23	0.18
Nausea			
Number of patients with events, n(%)	4 (6.8%)	17 (13.0%)	24 (8.7%)
Number of events per patient year	0.2	0.35	0.19
Vomiting			
Number of patients with events, n(%)	1 (1.7%)	7 (5.3%)	7 (2.5%)
Number of events per patient year	0.03	0.12	0.05

GI: Gastrointestinal, TEAE: Treatment-Emergent Adverse Event
Patient years of exposure: calculated as time from the first to the last injection of study drug plus 3 days.
[a] Calculated as number of events divided by total patient-years of exposure.
MedDRA Version: 18.0.

5.6 DOCUMENTED SYMPTOMATIC HYPOGLYCEMIA

Since documented symptomatic hypoglycemia with SMPG ≤70 mg/dL is considered a key safety parameter with regard to iGlarLixi treatment, post hoc analyses by final daily insulin and lixisenatide dose-categories were performed.

In EFC12404, analyses of documented symptomatic hypoglycemia by categories of final daily insulin dose (<20 U; ≥20 U) (Table 25) and final daily lixisenatide dose (Table 26) revealed a similar number of events per patient-year in each dose category in the iGlarLixi group. In the insulin glargine group, there was a higher incidence at <20 U (41.9%) compared to ≥20 U (21.7%).

Table 25 – Study EFC12404: Summary of documented symptomatic hypoglycemia during the on-treatment period by final daily insulin dose categories (<20 U, ≥20 U) (safety population)

	iGlarLixi (N=469)		Insulin Glargine (N=467)	
Events	**<20 U (N=59)**	**≥20 U (N=410)**	**<20 U (N=43)**	**≥20 U (N=424)**
Total patient years of exposure	29.3	233.8	20.2	242.2
Documented symptomatic hypoglycemia (plasma glucose ≤70 mg/dL)				
Number of patients with events, n (%)	13 (22.0%)	107 (26.1%)	18 (41.9%)	92 (21.7%)
Number of events	49	329	94	227
Number of events per patient years[a]	1.67	1.41	4.64	0.94

eCRF: electronic Case Report Form.
Patient years of exposure: calculated as time from the first to the last injection of study drug plus 1 day.
[a] Calculated as number of events divided by total patient-years of exposure.
Documented symptomatic hypoglycemia = symptomatic hypoglycemia recorded on the dedicated eCRF and meeting protocol definition for documented symptomatic hypoglycemia.
On-treatment period is defined as the time from the first injection of study drug up to 1 day for symptomatic hypoglycemia after the last injection of study drug, regardless of the introduction of rescue therapy.

Table 26 – Study EFC12404: Summary of documented symptomatic hypoglycemia during the on-treatment period by final daily lixisenatide dose categories (<10 µg, ≥10 µg - <15 µg, ≥15 µg - ≤20 µg) (Safety population)

	iGlarLixi (N=469)		
Events	**<10 µg (N=59)**	**≥10 µg-<15 µg (N=131)**	**≥15 µg-≤20 µg (N=275)**
Total patient years of exposure	29.3	73.4	158.0
Documented symptomatic hypoglycemia (plasma glucose ≤70 mg/dL)			
Number of patients with events, n (%)	13 (22.0%)	41 (31.3%)	66 (24.0%)
Number of events	49	130	199
Number of events per patient years[a]	1.67	1.77	1.26

eCRF: electronic Case Report Form.
Patient years of exposure: calculated as time from the first to the last injection of study drug plus 1 day.
[a] Calculated as number of events divided by total patient-years of exposure.
Documented symptomatic hypoglycemia = symptomatic hypoglycemia recorded on the dedicated eCRF and meeting protocol definition for documented symptomatic hypoglycemia.
On-treatment period is defined as the time from the first injection of study drug up to 1 day for symptomatic hypoglycemia after the last injection of study drug, regardless of the introduction of rescue therapy.

5.7 CONCLUSIONS

Overall, the results demonstrate that both components (insulin glargine and lixisenatide) contribute to the efficacy of iGlarLixi across the lixisenatide and insulin glargine daily dose-ranges. These analyses further indicated a positive benefit-risk balance at all daily dose-levels of iGlarLixi, similar to the balance observed in the overall individual study results.

6 LIXISENATIDE AND IGLARLIXI SAFETY FINDINGS

6.1 LIXISENATIDE SAFETY ANALYSIS POPULATIONS

The clinical development program consisted of 42 clinical studies including 20 Phase 2/3 and 22 Phase 1 studies. The lixisenatide NDA showed AEs separately analyzed in the Phase 1 and Phase 2/3 studies. Since the experience in Phase 1 was consistent with the mechanism of action of lixisenatide with no unique safety issues detected, this briefing document presents the safety experience with lixisenatide for the Phase 2/3 experience.

All safety analyses from the Phase 2/3 integrated safety database are based on the safety population, defined as all patients randomized and exposed to at least one dose of study treatment.

To examine the safety experience with lixisenatide in Phase 2/3, safety data from the following pooled datasets were examined:

- **Data Pool 1 placebo comparison (N=4508)**: 9 Phase 3, randomized, double blind, placebo controlled, efficacy/safety studies.
  - 5 studies were long-term studies with a main treatment period of 24 weeks and an entire treatment period to ≥76 weeks.
  - 4 studies had a main treatment period only (24 weeks except for 1 study with 12 weeks).
  - Analyses were performed for the main treatment period and the entire treatment period (≥76 weeks).
- **Data Pool 2 all safety data (N=13,433)**: 20 Phase 2/3 studies, including ELIXA
  - Safety analyses are presented for lixisenatide versus placebo (13 placebo-controlled studies), for lixisenatide versus all comparators (5 active-controlled studies), and for all patients receiving lixisenatide (20 studies).
  - ELIXA contributed 3031 patients and 5732.2 PY of the total exposure to lixisenatide, as well as 3032 patients exposed to placebo for 5917.8 PY (Table 28).
  - Analyses were performed for the entire treatment period.

Pooling across studies with different randomization ratios may distort the comparability between treatment groups. Some studies have different randomization ratios that affect the interpretation of the between-group comparison when the analysis is not adjusted for study. For AEs of interest that are discussed in this document, the relative risk or risk difference with corresponding 95% CIs was calculated from analysis stratified by study, addressing the concern of varying randomization ratios.

6.2 LIXISENATIDE EXTENT OF EXPOSURE IN PHASE 3 PLACEBO-CONTROLLED STUDIES AND PHASE 2/3 STUDIES

Patient exposure to lixisenatide and placebo in the 9 Phase 3 placebo-controlled studies and in all Phase 2/3 studies is detailed in Table 27.

9 Phase 3 placebo-controlled efficacy/safety studies (Data Pool 1). Common AEs, SAEs and AEs leading to treatment discontinuation were assessed using pooled data from the main treatment periods (12 or 24 weeks, Data Pool 1a) of these studies. The median treatment duration for Data Pool 1a was 169 days for both the lixisenatide and placebo groups. The median treatment duration for the entire treatment period (Data Pool 1b) was longer with lixisenatide than placebo due to differing randomization ratios between the 76- and 24-week studies.

Phase 2/3 studies (Data Pool 2). Data Pool 2 was used to assess uncommon/infrequently occurring AEs. A total of 7874 patients (6455 from placebo controlled studies) were exposed to lixisenatide in all Phase 2/3 studies (Table 27). Of these, 6000 (76.2%) patients (4958 from placebo-controlled studies) were exposed for ≥24 weeks, 4474 (56.8%) (4166 from placebo controlled studies) for ≥52 weeks, and 1661 (21.1%) (1648 from placebo controlled studies) for ≥104 weeks.

Table 27 - Exposure to study medication in Phase 2/3 placebo-controlled and all lixisenatide studies (safety population)

	Controlled				
	Phase 3[a]		Phase 2/3[b]		All Phase 2/3[c]
	Lixisenatide (N=2869)	Placebo (N=1639)	Lixisenatide (N=6455)	Placebo (N=4842)	Lixisenatide (N=7874)
Cumulative exposure (patient-years)	3258.7	1642.4	9104.7	7592.7	10035.9
Duration of study treatment (days)					
Number	2869	1639	6455	4842	7874
Mean (SD)	414.9 (255.8)	366.0 (246.3)	515.2 (348.9)	572.7 (353.8)	465.5 (342.6)
Median	533.0	196.0	556.0	586.5	526.0
Min : Max	1 : 875	1 : 925	1 : 1572	1 : 1548	1 : 1572
Number of patients with duration of study treatment by category [n (%)]					
≥ 12 weeks	2622 (91.4%)	1533 (93.5%)	5843 (90.5%)	4530 (93.6%)	7043 (89.4%)
≥ 24 weeks	2248 (78.4%)	1306 (79.7%)	4958 (76.8%)	4100 (84.7%)	6000 (76.2%)
≥ 52 weeks	1653 (57.6%)	759 (46.3%)	4166 (64.5%)	3365 (69.5%)	4474 (56.8%)
≥ 78 weeks	1260 (43.9%)	586 (35.8%)	3281 (50.8%)	2691 (55.6%)	3457 (43.9%)
≥ 104 weeks	272 (9.5%)	111 (6.8%)	1648 (25.5%)	1536 (31.7%)	1661 (21.1%)
≥ 130 weeks			828 (12.8%)	861 (17.8%)	828 (10.5%)
≥ 156 weeks			419 (6.5%)	422 (8.7%)	419 (5.3%)
≥ 182 weeks			163 (2.5%)	160 (3.3%)	163 (2.1%)
≥ 208 weeks			18 (0.3%)	11 (0.2%)	18 (0.2%)

a Data Pool 1: EFC6014, EFC6015, EFC6016, EFC6017, EFC6018, EFC10743, EFC10781, EFC10887, and EFC11321.
b Data Pool 1 plus ACT6011, PDY6797, DRI6012, and EFC11319 (ELIXA).
c Data Pool 2: 20 Phase 2/3 studies; 18 all-controlled (13 placebo, 5 active) studies and 2 lixisenatide only.
A total of 100 patients (38 in the placebo group, 3 in the active comparator group and 59 in the lixisenatide group) did not have an End of treatment (EOT) date collected on the EOT case report form. In the calculation of treatment duration, the EOT date was imputed with the last available dose date.

6.2.1 Exposure in ELIXA

ELIXA (Study EFC11319) contributed 3031 patients and 5732.2 PY of the total exposure to lixisenatide, as well as 3032 patients exposed to placebo for 5917.8 PY (Table 28). More than 80% of patients on lixisenatide were treated for ≥52 weeks, more than 66% were treated for ≥78 weeks, and more than 45% were treated for ≥104 weeks (≥2 years).

Table 28 – ELIXA: Exposure to study medication (Safety population)

	Placebo (N=3032)	Lixisenatide (N=3031)
Cumulative exposure (patient-years)	5917.8	5732.2
Duration of study treatment (days)		
Number	3032	3031
Mean (SD)	712.9 (331.7)	690.8 (348.4)
Median	693.5	672.0
Min : Max	1 : 1548	1 : 1572
Number of patients with duration of study treatment by category [n (%)]		
≥ 24 weeks	2794 (92.2%)	2710 (89.4%)
≥ 52 weeks	2606 (85.9%)	2513 (82.9%)
≥ 78 weeks	2105 (69.4%)	2021 (66.7%)
≥ 104 weeks	1425 (47.0%)	1376 (45.4%)

A total of 51 patients (25 in the placebo group and 26 in the lixisenatide group) did not have an End of treatment (EOT) date collected on the EOT case report form. In the calculation of treatment duration, the EOT date was imputed with the last available dose date.

6.3 LIXISENATIDE DEMOGRAPHIC AND OTHER BASELINE CHARACTERISTICS

Overall, the demographic and baseline characteristics of patients in the integrated Phase 2/3 studies were similar between the lixisenatide and placebo groups.

6.3.1 Demographics

Data Pool 1: 9 Phase 3 placebo-controlled efficacy/safety studies. The demographic and baseline characteristics of this safety population were generally comparable between the lixisenatide and placebo groups (Table 29). The median age was approximately 56 years. Approximately half of the patients were male, and the majority were Caucasian/White. The median BMI was approximately 30.0 kg/m^2.

Data Pool 2: Phase 2/3 Studies. The demographic and baseline characteristics of the safety population were generally comparable between the lixisenatide and placebo groups. The higher median age and larger proportion of males compared with Data Pool 1 reflects the contribution of ELIXA (EFC11319), which included higher proportions of elderly and male patients than the other Phase 2/3 placebo controlled studies (Table 29). The greater number of patients with renal impairment seen in the combined Phase 2/3 studies reflects the higher enrollment of these patients in ELIXA, where more than 75% of patients had some degree of renal impairment and more than 20% had moderate impairment (Table 31).

Table 29 – Demographic and baseline characteristics in Phase 2/3 placebo-controlled and all lixisenatide studies (Safety population)

	Placebo-controlled studies				
	Phase 3[a]		Phase 2/3[b]		All Phase 2/3[c]
	Lixisenatide (N=2869)	Placebo (N=1639)	Lixisenatide (N=6455)	Placebo (N=4842)	Lixisenatide (N=7874)
Age (years)					
Mean (SD)	55.9 (9.8)	56.4 (10.1)	57.9 (9.9)	59.1 (10.0)	57.6 (9.9)
Age Group (years) [n (%)]					
<50	719 (25.1%)	389 (23.7%)	1299 (20.1%)	802 (16.6%)	1675 (21.3%)
≥50 to <65	1633 (56.9%)	897 (54.7%)	3518 (54.5%)	2611 (53.9%)	4234 (53.8%)
≥65 to <75	453 (15.8%)	314 (19.2%)	1375 (21.3%)	1143 (23.6%)	1666 (21.2%)
≥75	64 (2.2%)	39 (2.4%)	263 (4.1%)	286 (5.9%)	299 (3.8%)
Sex [n(%)]					
Male	1362 (47.5%)	811 (49.5%)	3769 (58.4%)	3012 (62.2%)	4451 (56.5%)
Female	1507 (52.5%)	828 (50.5%)	2686 (41.6%)	1830 (37.8%)	3423 (43.5%)
Race [n(%)]					
Caucasian/White	1898 (66.2%)	973 (59.4%)	4536 (70.3%)	3400 (70.2%)	5786 (73.5%)
Black	73 (2.5%)	43 (2.6%)	243 (3.8%)	170 (3.5%)	285 (3.6%)
Asian/Oriental	843 (29.4%)	601 (36.7%)	1297 (20.1%)	988 (20.4%)	1396 (17.7%)
Other	55 (1.9%)	22 (1.3%)	379 (5.9%)	284 (5.9%)	407 (5.2%)
Ethnicity[d] [n(%)]					
Number	2673	1445	6126	4584	7420
Hispanic	591 (22.1%)	261 (18.1%)	1485 (24.2%)	1172 (25.6%)	1731 (23.3%)
Non Hispanic	2082 (77.9%)	1184 (81.9%)	4641 (75.8%)	3412 (74.4%)	5689 (76.7%)
Region [n(%)]					
US	401 (14.0%)	206 (12.6%)	884 (13.7%)	586 (12.1%)	1073 (13.6%)
Non US	2468 (86.0%)	1433 (87.4%)	5571 (86.3%)	4256 (87.9%)	6801 (86.4%)
Baseline BMI (kg/m^2)					
Number	2869	1639	6455	4839	7874
Mean (SD)	31.28 (6.49)	30.86 (6.50)	30.71 (5.97)	30.42 (6.01)	31.11 (5.99)
Median	30.33	29.86	29.91	29.48	30.46
Min : Max	17.9 : 64.4	18.2 : 64.7	17.1 : 68.9	16.9 : 64.7	17.1 : 69.4
Baseline BMI (kg/m^2) category [n(%)]					
<30	1379 (48.1%)	833 (50.8%)	3254 (50.4%)	2597 (53.6%)	3682 (46.8%)
≥30	1490 (51.9%)	806 (49.2%)	3201 (49.6%)	2242 (46.3%)	4192 (53.2%)

a Data Pool 1: EFC6014, EFC6015, EFC6016, EFC6017, EFC6018, EFC10743, EFC10781, EFC10887, and EFC11321.
b Data Pool 1 plus ACT6011, PDY6797, DRI6012, and EFC11319 (ELIXA).
c Data Pool 2: 20 Phase 2/3 studies; 18 all controlled (13 placebo, 5 active) studies and 2 lixisenatide only.
d Studies ACT6011, PDY6797, PDY10931, PDY12625, and EFC11321 did not collect ethnicity.

6.3.2 Renal status at baseline

Phase 3 placebo-controlled efficacy/safety studies (Data Pool 1). Fewer than 30% of the patients had impaired renal function.

Phase 2/3 studies (Data Pool 2). The proportion of patients with renal impairment was lower with lixisenatide (approximately 50%) than placebo (approximately 60%) (Table 30). The greater number of patients with renal disease seen in the combined Phase 2/3 studies reflects the higher enrollment of these patients in ELIXA, where more than 75% of patients had some degree of renal impairment and more that 20% had moderate impairment.

Table 30 - Baseline renal function status in Phase 2/3 placebo-controlled and all lixisenatide studies (Safety population)

	Placebo-controlled studies				
	Phase 3[a]		Phase 2/3[b]		All Phase 2/3[c]
N(%)	Lixisenatide (N=2869)	Placebo (N=1639)	Lixisenatide (N=6455)	Placebo (N=4842)	Lixisenatide (N=7874)
Renal function status at baseline[d]					
Number	2853	1636	6434	4831	7852
≥ 90 (normal)	2094 (73.4%)	1150 (70.3%)	3227 (50.2%)	1946 (40.3%)	4337 (55.2%)
60 to < 90 (mild)	637 (22.3%)	414 (25.3%)	2417 (37.6%)	2061 (42.7%)	2690 (34.3%)
30 to < 60 (moderate)	122 (4.3%)	68 (4.2%)	786 (12.2%)	816 (16.9%)	820 (10.4%)
45 to <60	105 (3.7%)	57 (3.5%)	569 (8.8%)	586 (12.1%)	597 (7.6%)
30 to <45	17 (0.6%)	11 (0.7%)	217 (3.4%)	230 (4.8%)	223 (2.8%)
15 to < 30 (severe)	0	4 (0.2%)	4 (<0.1%)	8 (0.2%)	5 (<0.1%)

[a] Data Pool 1: EFC6014, EFC6015, EFC6016, EFC6017, EFC6018, EFC10743, EFC10781, EFC10887, and EFC11321.
[b] Data Pool 1 plus ACT6011, PDY6797, DRI6012, and EFC11319 (ELIXA).
[c] Data Pool 2: 20 Phase 2/3 studies; 18 all controlled (13 placebo, 5 active) studies and 2 lixisenatide only.
[d] Renal function status is defined from estimated glomerular filtration rate (eGFR) (mL/min/1.73m^2) for EFC11319. For other studies, it is defined from creatinine clearance value (ml/min) using the equation of Cockcroft and Gault.

ELIXA CV outcomes study. Based on the estimated glomerular filtration rate (eGFR), categories of baseline renal status were balanced across treatment groups (Table 31). More than 75% of patients in each group had impaired renal function and more than 20% had an eGFR <60 mL/min/1.73 m^2.

Table 31 – ELIXA: Baseline renal status

Baseline estimated glomerular filtration rate (eGFR), n (%)	Placebo	Lixisenatide
Number	3026	3029
≥15 to <30 mL/min/1.73 m^2 (severe renal impairment)	4 (0.1%)	4 (0.1%)
≥30 to <60 mL/min/1.73 m^2 (moderate renal impairment)	744 (24.6%)	655 (21.6%)
≥60 to <90 mL/min/1.73 m^2 (mild renal impairment)	1603 (53.0%)	1632 (53.9%)
≥90 mL/min/1.73 m^2 (normal)	675 (22.3%)	738 (24.4%)

eGFR: estimated glomerular filtration rate, calculated by the 4-variable modification of diet in renal disease (MDRD) formula using the serum creatinine, race, age, and gender of the patient: GFR (mL/min/1.73 m2) = 175 × serum creatinine (mg/dL)-1.154 × age (years)-0.203 × 1.212 [if black] × 0.742 [if female]

6.4 LIXISENATIDE TREATMENT-EMERGENT ADVERSE EVENTS

The main treatment periods of the 9 Phase 3 placebo controlled efficacy/safety studies (Data Pool 1) are the primary basis for the overview of TEAEs. The percentage of patients with at least one TEAE was higher with lixisenatide (70.2%) than with placebo (62.3%), primarily due to TEAEs in the gastrointestinal SOC (39.7% vs. 18.4% for lixisenatide and placebo, respectively) (Table 32).

Table 32 – Overall TEAE summary in Phase 3 placebo-controlled studies: main treatment period (Safety population)

	Lixisenatide (N=2869)	Placebo (N=1639)
Patients with any TEAE	2013 (70.2%)	1021 (62.3%)
Patients with any serious TEAE	96 (3.3%)	60 (3.7%)
Patients with any TEAE leading to death	3 (0.1%)	4 (0.2%)
Patients with any TEAE leading to permanent treatment discontinuation	208 (7.2%)	53 (3.2%)

Main treatment period: 12 weeks for EFC6018 and 24 weeks for other studies.
TEAE: Treatment-Emergent Adverse Event.
Studies included: EFC6014, EFC6015, EFC6016, EFC6017, EFC6018, EFC10743, EFC10781, EFC10887 and EFC11321.

TEAEs occurring in at least 2% of patients in the lixisenatide group in the main treatment period for Data Pool 1 are shown by PT and SOC for lixisenatide versus placebo (Table 33).

Table 33 – TEAEs in the main treatment period in 9 Phase 3 placebo-controlled studies (≥2% in the lixisenatide treatment group)

PRIMARY SYSTEM ORGAN CLASS Preferred Term n (%)	Lixisenatide (N=2869)	Placebo (N=1639)
INFECTIONS AND INFESTATIONS	664 (23.1%)	398 (24.3%)
Upper respiratory tract infections	341 (11.9%)	203 (12.4%)
Nasopharyngitis	163 (5.7%)	112 (6.8%)
Influenza	92 (3.2%)	52 (3.2%)
Urinary tract infection	59 (2.1%)	29 (1.8%)
METABOLISM AND NUTRITION DISORDERS	533 (18.6%)	254 (15.5%)
Hypoglycemia	392 (13.7%)	174 (10.6%)
Decreased appetite	101 (3.5%)	20 (1.2%)
NERVOUS SYSTEM DISORDERS	543 (18.9%)	223 (13.6%)
Headache	244 (8.5%)	99 (6.0%)
Dizziness	193 (6.7%)	71 (4.3%)
Tremor	64 (2.2%)	18 (1.1%)
Vascular hypertensive disorders	56 (2.0%)	48 (2.9%)
GASTROINTESTINAL DISORDERS	1138 (39.7%)	302 (18.4%)
Nausea	725 (25.3%)	99 (6.0%)
Vomiting	282 (9.8%)	30 (1.8%)
Diarrhea	221 (7.7%)	90 (5.5%)
Abdominal pain upper	62 (2.2%)	14 (0.9%)
Abdominal pain	56 (2.0%)	24 (1.5%)
Constipation	79 (2.8%)	30 (1.8%)
Dyspepsia	92 (3.2%)	4 (0.2%)
Abdominal distension	64 (2.2%)	14 (0.9%)
MUSCULOSKELETAL AND CONNECTIVE TISSUE DISORDERS	340 (11.9%)	162 (9.9%)
Back pain	86 (3.0%)	32 (2.0%)
Arthralgia	55 (1.9%)	33 (2.0%)
GENERAL DISORDERS AND ADMINISTRATION SITE CONDITIONS	371 (12.9%)	149 (9.1%)
Asthenia	85 (3.0%)	30 (1.8%)
Fatigue	76 (2.6%)	23 (1.4%)
Injection site reactions	108 (3.8%)	26 (1.6%)

Main treatment period: 12 weeks for EFC6018 and 24 weeks for the other studies.
TEAE: Treatment-Emergent Adverse Event.
Data Pool 1: EFC6014, EFC6015, EFC6016, EFC6017, EFC6018, EFC10743, EFC10781, EFC10887, and EFC11321.

GI events including nausea, vomiting, dyspepsia, diarrhea, and abdominal pain occurred at a higher incidence with lixisenatide, which is consistent with the GLP-1 receptor agonist class. Adverse events reported as hypoglycemia are included in a separate analysis of symptomatic

hypoglycemia, which evaluated risk of the event by background diabetes treatment (Section 6.9.1). Injection site reactions are discussed in more detail in Section 6.9.2.1.

6.4.1 GI tolerability

As expected for the GLP-1 receptor agonist class, GI TEAEs were commonly reported in the lixisenatide treatment groups.

In the main treatment period of the Phase 3 placebo-controlled studies:

- The incidence of treatment-emergent nausea was 25.3% in the lixisenatide group and 6.0% in the placebo group.
- Of 725 patients with nausea in the lixisenatide group, 16 reported a severe event giving an incidence of severe nausea of 0.6%. The rest of the nausea events were mostly mild in intensity (Table 34).
- The incidence of vomiting was 9.8% with lixisenatide and 1.8% with placebo.
- The incidence of severe vomiting was 0.3% with lixisenatide and <0.1% with placebo.

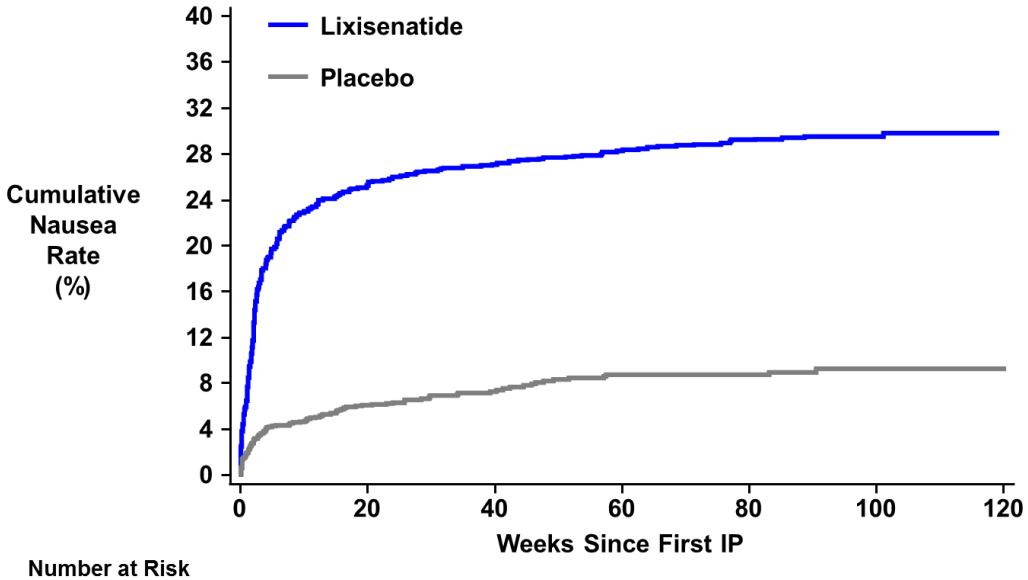
Table 34 – Summary of nausea and vomiting by maximum severity in Phase 3 placebo-controlled studies: main treatment period (Safety population)

	Lixisenatide (N=2869)	Placebo (N=1639)
Nausea	725 (25.3%)	99 (6.0%)
Mild	496 (17.3%)	84 (5.1%)
Moderate	212 (7.4%)	12 (0.7%)
Severe	16 (0.6%)	3 (0.2%)
Missing	1 (<0.1%)	0
Vomiting	282 (9.8%)	30 (1.8%)
Mild	173 (6.0%)	21 (1.3%)
Moderate	100 (3.5%)	8 (0.5%)
Severe	9 (0.3%)	1 (<0.1%)

Studies included: EFC6014, EFC6015, EFC6016, EFC6017, EFC6018, EFC10743, EFC10781, EFC10887 and EFC11321. *Main treatment period*: 12 weeks for EFC6018 and 24 weeks for other studies.

Figure 49 provides a Kaplan-Meier plot for nausea showing that the events primarily occurred shortly after initiation of lixisenatide treatment. After the first 8 weeks of treatment, the incidence of new events of nausea was similar in the lixisenatide and placebo groups.

Figure 49 – Kaplan-Meier Plot of time to first onset of nausea (PT) in Phase 3 placebo-controlled studies: entire treatment period (Safety population)



Number at Risk

Placebo	1639	1316	719	669	520	150	7
Lixisenatide	2869	1812	1312	1216	942	290	14

Studies included: EFC6014, EFC6015, EFC6016, EFC6017, EFC6018, EFC10743, EFC10781, EFC10887 and EFC11321
IP, investigational product (study drug)

6.4.2 Safety in subgroups by age, race, and renal function

Treatment differences in the incidence of common TEAEs and the pattern of common TEAEs that were seen in the overall population were also seen in most of the subgroups analyzed. Treatment differences favoring placebo were generally more pronounced in elderly patients (≥65 years), in Asian/Oriental and Black patients, and in patients with BMI <30 kg/m^2. This was primarily due to treatment differences in the GI disorders SOC (and the PTs of nausea and vomiting) and to some extent in the metabolism and nutrition disorders SOC. The imbalance observed in the metabolism and nutrition disorders SOC is confounded by the fact that the Asian population included in these studies had either used basal insulin and/or SU as background therapy. Relative to the corresponding subgroups being compared, higher incidences of common TEAEs were generally observed with both lixisenatide and placebo in female patients, Black patients, Hispanic patients, patients with a medical history of dyslipidemia, and patients with concomitant use of statins/statin combinations.

In the safety population of Study EFC11319 (ELIXA), there were 3,235 patients with mild renal impairment, 1,399 patients with moderate renal impairment, and 8 patients (4 treated with lixisenatide) with severe renal impairment, based on the eGFR at baseline (Table 31). In general, a higher incidence of common TEAEs (≥2% HLT in any treatment group) was seen in patients with moderate renal impairment than in patients with mild renal impairment or with normal renal function. This was observed with both lixisenatide and placebo.

6.4.3 Mortality

Overall, deaths were balanced between lixisenatide and placebo. The majority of deaths in the Phase 2/3 studies occurred in the high risk population of the CV outcomes study EFC11319. The overall mortality rates per 100 PY across all Phase 2/3 placebo-controlled studies (2.8 for placebo, 2.2 for lixisenatide) also reflect the effect of EFC11319 on mortality in the lixisenatide development program. Mortality rates per 100 PY in the 9 Phase 3 placebo-controlled studies of Data Pool 1 were 0.4 for lixisenatide and 0.6 for placebo (Table 35).

Table 35 - Mortality in Phase 2/3 studies (safety population)

	Number of Patients	Number of Deaths[a]	Crude Mortality rate	Patient Years[b]	Mortality per 100 Patient-years
Phase 3 placebo-controlled studies[c]					
Placebo	1639	11	0.7%	1727.7	0.6
Lixisenatide	2869	13	0.5%	3446.5	0.4
EFC11319					
Placebo	3032	223	7.4%	6690.8	3.3
Lixisenatide	3031	212	7.0%	6727.6	3.2
All placebo-controlled studies[d]					
Placebo	4842	234	4.8%	8453.2	2.8
Lixisenatide	6455	225	3.5%	10295.8	2.2
All controlled studies[e]					
Lixisenatide	7354	230	3.1%	10983.9	2.1
All comparators[f]	6079	240	3.9%	9289.7	2.6
All Phase 2/3 studies[g]					
Lixisenatide	7874	231	2.9%	11280.2	2.0

a All deaths occurred during a study.
b Calculated as time from the first IP injection to the last contact date for patients with no event or to the time of death for patients with event.
c Data Pool 1: EFC6014, EFC6015, EFC6016, EFC6017, EFC6018, EFC10743, EFC10781, EFC10887, and EFC11321.
d Data Pool 1 plus ACT6011, PDY6797, DRI6012, and EFC11319 (ELIXA).
e Data Pool 2 excluding 2 lixisenatide only studies
f All comparators: placebo, exenatide, liraglutide, sitagliptin and insulin glulisine.
g Data Pool 2: 20 Phase 2/3 studies; 18 all-controlled (13 placebo, 5 active) studies and 2 lixisenatide only.

No deaths were reported in the Phase 2 studies. Deaths in all 15 Phase 3 studies were adjudicated by the CAC. About two-thirds of all reported deaths were adjudicated as CV deaths. The rates of CV death per 100 PY were 1.62 with lixisenatide and 1.92 with placebo. Most CV deaths were adjudicated as sudden death (1.2% with lixisenatide and 1.3% with placebo) and fatal MI (0.6% with lixisenatide and 0.5% with placebo).

The incidence of non-CV deaths was 0.8% with lixisenatide versus 1.4% with placebo; the rate per 100 PY was 0.49 and 0.77, respectively. Non-CV deaths primarily included infections (0.2%

with lixisenatide and 0.4% with placebo) and malignancies (0.4% with lixisenatide and 0.5% with placebo).

6.4.4 Serious adverse events

To assess the impact of longer term treatment on the incidence of serious TEAEs, these were examined over the entire treatment period of 12 to 24 to ≥76 weeks (Table 36).

Over the entire treatment period for Phase 3 placebo-controlled studies, the incidence of serious TEAEs was similar in both treatment groups (8.5% with lixisenatide and 7.8% with placebo). The overall rate per 100 patient-years was also similar between treatment groups (7.43 with lixisenatide and 7.73 with placebo).

Table 36 – Serious TEAEs (PTs with 3 or more patients in any treatment group) in Phase 3 placebo-controlled efficacy/safety studies: entire treatment period (Data Pool 1) (safety population)

	Lixisenatide (N=2869)		Placebo (N=1639)	
Preferred Term n(%)	**n (%)**	**Rate per 100 PY[a]**	**n (%)**	**Rate per 100 PY[a]**
Any event	244 (8.5%)	7.43	128 (7.8%)	7.73
Acute myocardial infarction	8 (0.3%)	0.24	7 (0.4%)	0.42
Cerebral infarction	8 (0.3%)	0.24	1 (<0.1%)	0.06
Pneumonia	8 (0.3%)	0.24	10 (0.6%)	0.60
Angina unstable	7 (0.2%)	0.21	5 (0.3%)	0.30
Coronary artery disease	7 (0.2%)	0.21	6 (0.4%)	0.36
Non-cardiac chest pain	7 (0.2%)	0.21	1 (<0.1%)	0.06
Osteoarthritis	7 (0.2%)	0.21	2 (0.1%)	0.12
Transient ischaemic attack	5 (0.2%)	0.15	1 (<0.1%)	0.06
Urinary tract infection	5 (0.2%)	0.15	1 (<0.1%)	0.06
Hypertensive crisis	4 (0.1%)	0.12	0	0.00
Percutaneous coronary intervention	4 (0.1%)	0.12	2 (0.1%)	0.12
Atrial fibrillation	3 (0.1%)	0.09	2 (0.1%)	0.12
Cardiac failure congestive	3 (0.1%)	0.09	1 (<0.1%)	0.06
Coronary arterial stent insertion	3 (0.1%)	0.09	3 (0.2%)	0.18
Goiter	3 (0.1%)	0.09	0	0.00
Hemorrhoids	3 (0.1%)	0.09	0	0.00
Myocardial infarction	3 (0.1%)	0.09	4 (0.2%)	0.24
Pancreatic carcinoma	3 (0.1%)	0.09	0	0.00
Rib fracture	3 (0.1%)	0.09	0	0.00
Road traffic accident	3 (0.1%)	0.09	0	0.00
Vitreous haemorrhage	3 (0.1%)	0.09	0	0.00
Angina pectoris	2 (<0.1%)	0.06	4 (0.2%)	0.24
Coronary artery bypass	2 (<0.1%)	0.06	4 (0.2%)	0.24
Bronchitis	1 (<0.1%)	0.03	3 (0.2%)	0.18
Cellulitis	1 (<0.1%)	0.03	3 (0.2%)	0.18
Cholecystitis acute	1 (<0.1%)	0.03	4 (0.2%)	0.24

a Rate per 100 PY (patient years) calculated as 100*(n/total patient years of exposure). Each patient's years of exposure is calculated as time from the first to the last injection of IP plus 3 days. Total patient years of exposure is 1655.84 years for placebo and 3282.3 years for lixisenatide.

TEAE: Treatment-Emergent adverse event.

Five of the studies were long-term studies with a main treatment period of 24 weeks and an entire treatment period to ≥76 weeks. The remaining 4 studies had a main treatment period only (24 weeks except for 1 study with 12 weeks).

Data Pool 1: EFC6014, EFC6015, EFC6016, EFC6017, EFC6018, EFC10743, EFC10781, EFC10887, and EFC11321

6.4.5 Adverse events associated with permanent treatment discontinuation

In the main treatment period of the 9 Phase 3 placebo controlled studies, the proportion of patients with TEAEs leading to permanent treatment discontinuation was greater with lixisenatide than placebo (7.2% compared to 3.2%, respectively) (Table 37). The difference between lixisenatide and placebo was largely due to discontinuations for GI events. Nausea (2.8%) and vomiting (1.2%) accounted for most of the GI TEAEs that were associated with permanent discontinuation from treatment for lixisenatide.

Table 37 – TEAEs leading to treatment discontinuation in Phase 3 placebo-controlled studies: (main treatment period - safety population - 3 or more patients in either treatment group)

System Organ Class Preferred Term n(%)	Lixisenatide (N=2869)	Placebo (N=1639)
ANY EVENT	208 (7.2%)	53 (3.2%)
Nausea	80 (2.8%)	0
Vomiting	35 (1.2%)	0
Dizziness	16 (0.6%)	1 (<0.1%)
Diarrhea	12 (0.4%)	1 (<0.1%)
Hypoglycemia	9 (0.3%)	0
Asthenia	6 (0.2%)	0
Decreased appetite	5 (0.2%)	1 (<0.1%)
Headache	5 (0.2%)	1 (<0.1%)
Dyspepsia	5 (0.2%)	0
Blood calcitonin increased	5 (0.2%)	2 (0.1%)
Abdominal pain upper	4 (0.1%)	0
Dermatitis allergic	4 (0.1%)	0
Fatigue	4 (0.1%)	0
Lipase increased	4 (0.1%)	1 (<0.1%)
Cerebral infarction	3 (0.1%)	0
Abdominal distension	3 (0.1%)	1 (<0.1%)
Acute myocardial infarction	1 (<0.1%)	3 (0.2%)
Pancreatic enzymes increased	1 (<0.1%)	3 (0.2%)

Main treatment period: 12 weeks for EFC6018 and 24 weeks for other studies. TEAE: Treatment-Emergent adverse event. Studies included: EFC6014, EFC6015, EFC6016, EFC6017, EFC6018, EFC10743, EFC10781, EFC10887 and EFC11321.

6.4.6 Laboratory evaluations

No clinically relevant differences between the lixisenatide and comparator groups were identified for the laboratory parameters of hematology, biochemistry, and urinalyses.

Pancreatic Enzymes (Amylase/Lipase)

- In the 9 Phase 3 placebo-controlled efficacy/safety studies, mean amylase and lipase values were similar between the lixisenatide and placebo groups and remained constant over the entire study period.
- In the Phase 2/3 placebo-controlled studies, the percent of patients with elevations in lipase or amylase considered as a potentially clinically significant abnormality (PCSA) (≥3 x ULN) regardless of baseline status were the same in both treatment groups, 2.1% for lipase and 0.3% for amylase. Corresponding exposure-adjusted incidence rates (EAIRs)

per 100 PY were 1.39 in the lixisenatide group and 1.26 in the placebo group for lipase, and 0.22 and 0.16, respectively, for amylase.

- In ELIXA, baseline amylase and lipase values were similar in the 2 treatment groups. Mean amylase and lipase values remained generally constant over the course of the study in both treatment groups. Incidences of PCSAs for amylase (≥3 x ULN) and lipase (≥3 x ULN) during the on-treatment period were low and similar in the lixisenatide and placebo groups: amylase (0.4% versus 0.3%, respectively) and lipase (2.3% versus 2.1%, respectively).

Calcitonin

- In the 9 Phase 3 placebo-controlled efficacy/safety studies, mean calcitonin values remained relatively constant over time in both treatment groups.
- In the Phase 2/3 placebo controlled studies, a total of 85 (1.6%) patients on lixisenatide and 63 (1.5%) patients on placebo reported on-treatment calcitonin values in the range ≥20 to <50 pg/mL regardless of baseline status, resulting in corresponding EAIRs per 100 PY of 1.08 and 0.95, respectively. Twenty-two (0.4%) lixisenatide patients (EAIR: 0.28) compared to 4 (<0.1%) placebo patients (EAIR: 0.06) reported calcitonin values ≥50 pg/mL. Incidences were similar in the Phase 2/3 all controlled studies, as well as in all patients treated with lixisenatide in the Phase 2/3 studies.
- In ELIXA, mean calcitonin values remained relatively constant over the course of the on-treatment period, without relevant differences between lixisenatide and placebo. The incidence of PCSAs for calcitonin reported during the on-treatment period was low and similar between treatment groups. Calcitonin ≥20 to 50 pg/mL was reported in 52 (1.8%) patients in the lixisenatide group and 42 (1.5%) patients in the placebo group; calcitonin ≥50 pg/mL was reported in 12 (0.4%) and 2 (<0.1%) patients, respectively.

Liver function

- In the Phase 3 placebo-controlled efficacy safety studies, no relevant mean changes from baseline were observed for LFT parameters (ALT, AST, ALP, GGT, and total bilirubin) over time in either treatment group.
- A similar pattern was observed in the Phase 2/3 all-controlled studies, as well as in all patients treated with lixisenatide in the Phase 2/3 studies.
- In ELIXA, no relevant changes were observed in mean values for ALT, AST, ALP, and total bilirubin from baseline to the last on-treatment assessment in either treatment group. The incidences of PCSAs for LFT parameters (i.e., ALT, AST, ALP, and total bilirubin) reported during the on-treatment period were low and similar between treatment groups.
- Seven lixisenatide-treated and 10 placebo-treated patients were identified as cases with concurrent elevations of ALT or AST >3 x ULN and total bilirubin ≥2 x ULN. The EAIR per 100 PY for these cases was 0.08 for lixisenatide and 0.14 for placebo. Of the 7 cases in the lixisenatide group, only 1 case met Hy's Law criteria (i.e., hepatocellular jaundice without cholestasis). In this case which occurred in the ELIXA study, the patient developed acute hepatitis and acute pancreatitis in the days following amiodarone infusion for new onset paroxysmal atrial fibrillation.

Other laboratory parameters

- There were no clinically significant differences in mean change or shift to possibly clinically significant values between treatment groups for hematology parameters (hemoglobin, hematocrit, red blood cells, and platelets) or white blood cell parameters (white blood cell count, neutrophils, lymphocytes, monocytes, basophils, and eosinophils).
- There were no clinically significant differences between groups for renal function (creatinine, creatinine clearance), or for uric acid or serum lipids.

6.5 LIXISENATIDE CARDIOVASCULAR OUTCOME STUDY EFC11319 (ELIXA)

The completed CV outcome study, ELIXA, was a double blind, placebo-controlled study in more than 6000 patients with T2DM who recently experienced a spontaneous, biomarker-positive ACS event and received either lixisenatide or placebo in combination with standard-of-care treatment. The ELIXA study demonstrated the safety of lixisenatide in terms of CV morbidity and mortality compared to placebo in T2DM patients at high CV risk (1). The results from ELIXA provide the CV safety assessment for lixisenatide.

6.5.1 Endpoints

The primary endpoint was the time to first occurrence, from randomization to the end of study, of any of the following events positively adjudicated by the CAC: CV death, non-fatal MI, non-fatal stroke, and hospitalization for unstable angina.

The secondary endpoints were:

- Composite endpoint of CV death, non-fatal MI, non-fatal stroke, hospitalization for unstable angina, or hospitalization for heart failure
- Composite endpoint of CV death, non-fatal MI, non-fatal stroke, hospitalization for unstable angina, hospitalization for heart failure, or coronary revascularization procedure (as per protocol amendment 2)
- Urinary albumin excretion (based on the urinary albumin/creatinine ratio [UACR]) at 108 weeks (i.e., approximately 2 years)

6.5.2 Study design, patient population, and statistical considerations

ELIXA was a multicenter, randomized (1:1), double-blind, placebo-controlled, 2-arm, parallel-group Phase 3 study in patients ≥30 years of age with T2DM and a recent (<180 days) bio-marker positive ACS event requiring hospitalization. The duration of the study was event driven.

The analyses of the primary and secondary endpoints (composite CV endpoints and changes in urinary albumin excretion) were performed on the ITT population.

For the primary endpoint, non-inferiority of lixisenatide versus placebo was to be claimed if the upper bound of the 2-sided 95% CI of the hazard ratio was <1.3, as required by the FDA for the demonstration of acceptable CV safety. Superiority of lixisenatide versus placebo was to be

claimed if the upper bound of the 2-sided 95% CI of the hazard ratio was <1.0. The analyses of the CV endpoints were based on the positively-adjudicated CV endpoint events occurring from randomization to the study end date, inclusive for each patient, even after the patient had discontinued study treatment. Cardiovascular endpoint events that occurred after the study end date for a patient were not included in the primary analyses, regardless of adjudication status, unless otherwise specified. The primary endpoint was analyzed using a Cox proportional hazards model with treatment (lixisenatide, placebo), and region (North America, South and Central America, Western Europe, Eastern Europe, Africa/Near East, and Asia/pacific) as the factors. The hazard ratio between lixisenatide and placebo were estimated along with the associated two-sided 95% CI. Patients who did not experience any of the primary CV outcomes as positively adjudicated by the CAC were considered as right-censored observations. The censoring time was the time from randomization to the last contact date on or before the study end date for a patient. A sensitivity analysis of the time to first occurrence of any of the primary composite CV events occurring during the on-treatment period were analyzed using the same Cox model. The on-treatment period for efficacy CV endpoints was defined as the time from randomization up to 30 days after the last injection of double-blind study drug.

All AE analyses and other safety assessments, including overall mortality, allergic reactions, pancreatitis, and pancreatic cancer were performed on the safety population, which included all randomized patients who received at least one dose of study treatment. The on-treatment period for most safety analyses was defined as the time from the first administration of study treatment up to 3 days after the last administration.

Glycemic control during the study was managed by the investigators in accordance with local clinical practice guidelines with the exception that other incretin therapies (GLP-1 receptor agonists or DPP-IV inhibitors) were not allowed. This approach was expected to yield similar glycemic control in the two study groups and was done to prevent a high rate of premature discontinuation due to lack of glycemic control, which would have adversely affected the primary ITT analysis and interpretation of the CV endpoints.

6.5.3 Results

6.5.3.1 Patient disposition and baseline characteristics

A total of 6068 patients were randomized 1:1 to lixisenatide or placebo and entered the double-blind treatment phase (Table 38). More than 96% of patients in both treatment groups completed the study and vital status at the end of the study was known for >98% of patients in both treatment groups.

The duration of study follow-up was comparable between treatment groups, with medians of 25.8 and 25.7 months, respectively, for lixisenatide and placebo.

Table 38 – ELIXA: Patient disposition (randomized population)

Patient disposition	Placebo (N=3034)	Lixisenatide (N=3034)

Patient disposition	Placebo (N=3034)	Lixisenatide (N=3034)
Completed the study	2924 (96.4%)	2929 (96.5%)
Completed the final visit	2702 (89.1%)	2722 (89.7%)
Death	222 (7.3%)	207 (6.8%)
Did not complete the study	110 (3.6%)	105 (3.5%)
Site termination by sponsor	13 (0.4%)	5 (0.2%)
Withdrawal by patient	83 (2.7%)	88 (2.9%)
Patient lost to follow-up	14 (0.5%)	11 (0.4%)
Other	0	1 (<0.1%)
Vital status known at the global study end	2992 (98.6%)	3005 (99.0%)
Alive	2769 (91.3%)	2794 (92.1%)
Dead	223 (7.4%)	211 (7.0%)

Note: Percentages are calculated using the number of randomized patients as denominator.

Demographics were well-balanced between treatment groups as were the diabetes characteristics at baseline (Table 39). The median age at study entry was 60 years, and approximately one third (33.7%) of the study population was 65 years or older. More male (69.3%) and Caucasian (75.4%) patients were enrolled in the study. The majority of patients were either obese or overweight with a median BMI of 29.4 kg/m^2. Mean duration of diabetes was 9.3 years and the mean HbA1c at baseline was 7.68%.

Table 39 - ELIXA: Demographics and patient characteristics at screening or baseline

Patient demographics	Placebo (N=3034)	Lixisenatide (N=3034)	All (N=6068)
Age (years)			
Number	3034	3034	6068
Mean (SD)	60.6 (9.6)	59.9 (9.7)	60.3 (9.7)
Age group (years) [n (%)]			
Number	3034	3034	6068
≥65 to <75	792 (26.1%)	805 (26.5%)	1597 (26.3%)
≥75	248 (8.2%)	198 (6.5%)	446 (7.4%)
Gender [n (%)]			
Number	3034	3034	6068
Male	2096 (69.1%)	2111 (69.6%)	4207 (69.3%)
Female	938 (30.9%)	923 (30.4%)	1861 (30.7%)
Race [n (%)]			
Number	3034	3034	6068
Caucasian/White	2318 (76.4%)	2258 (74.4%)	4576 (75.4%)
Black	103 (3.4%)	118 (3.9%)	221 (3.6%)
Asian/Oriental	367 (12.1%)	404 (13.3%)	771 (12.7%)
Other	246 (8.1%)	254 (8.4%)	500 (8.2%)
Baseline BMI (kg/m^2)			
Number	3032	3033	6065
Mean (SD)	30.20 (5.79)	30.12 (5.60)	30.16 (5.69)
Baseline BMI Categories (kg/m^2) [n (%)]			
Number	3032	3033	6065
<30	1681 (55.4%)	1649 (54.4%)	3330 (54.9%)
≥30	1351 (44.6%)	1384 (45.6%)	2735 (45.1%)
Duration of diabetes (years)			
Number	3034	3031	6065
Mean (SD)	9.38 (8.32)	9.20 (8.19)	9.29 (8.25)
Baseline HbA1c (%)			
Number	3033	3034	6067
Mean (SD)	7.64 (1.28)	7.72 (1.32)	7.68 (1.30)

SD: standard deviation, BMI: body mass index.

The use of specific classes of concomitant antidiabetic medications was balanced between treatment groups (Table 40). The percentage of patients using concomitant insulin was 46.1% and 48.3% in the lixisenatide and placebo groups, respectively.

Table 40 – ELIXA: On-study medications: Antidiabetic medications – number (%) of patients by pre-specified categories – Randomized population

On-study antidiabetic medications	Placebo (N=3034)	Lixisenatide (N=3034)
Any glucose lowering medications	2919 (96.2%)	2895 (95.4%)
Any metformin	2339 (77.1%)	2317 (76.4%)
Any sulfonylureas	1299 (42.8%)	1249 (41.2%)
Any thiazolidinediones	98 (3.2%)	72 (2.4%)
Any insulin	1466 (48.3%)	1398 (46.1%)
Other	270 (8.9%)	275 (9.1%)

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Note: On-study anti-diabetics medications are those that the patient continued or started on or after the day of randomization up to the following: (1) the date of death from any cause if patients died during the study; (2) the date of last successful contact performed as reported in the CRF.

6.5.3.2 Primary Composite Cardiovascular Endpoint

The proportions of patients with primary CV endpoint events (13.4% with lixisenatide and 13.2% with placebo) as well as the incidence rate per 100 PY (6.39 with lixisenatide and 6.31 with placebo) were comparable between treatment groups, with a hazard ratio of 1.017 (95% CI: 0.886, 1.168) (Table 41). The upper bound of the 2-sided 95% CI estimated from the Cox model was below the pre specified non-inferiority margin of 1.3, demonstrating non-inferiority versus placebo. Results of the sensitivity analysis for the on-treatment period were fully consistent with the results of the primary analysis; the HR was 1.002 with an upper bound of the 2-sided 95% CI <1.3 (Section 8.4.6).

Table 41 – ELIXA: Analysis of the primary cardiovascular endpoint (ITT population)

	Placebo (N=3034)	Lixisenatide (N=3034)	Hazard ratio (95% CI)[c]	Log-rank test p-value
Composite of CV death, non-fatal MI, non-fatal stroke, or hospitalization for unstable angina*			1.017 (0.886, 1.168)	0.8542
Number of patients with event (%)	399 (13.2%)	406 (13.4%)	-	-
Total patient years for the event[a]	6328.2	6356.8	-	-
Incidence rate per 100 patient years[b]	6.31	6.39	-	-

*Only CAC positively adjudicated events are included.

CV: cardiovascular, MI: myocardial infarction, CI: confidence interval. CAC: Cardiovascular Events Adjudication Committee.

a Calculated as time from randomization date to the first event date or censoring date (the end of study date) for patients who had no events.

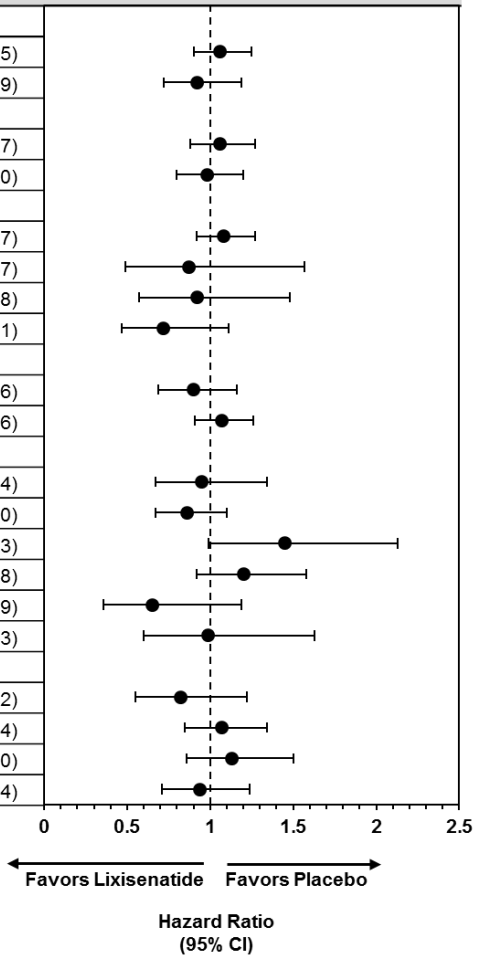
b Calculated as number of patients with an event divided by total patient years for the event and multiplied by 100.

c In case of multiple events occurring on the same date, event is counted in the categories following the order of CV death, non-fatal MI, non-fatal stroke, hospitalization for unstable angina.

The results of the analyses of the primary composite CV endpoint were consistent between treatment groups by gender, age, race, ethnicity, and duration of time between the qualifying ACS event and randomization, and showed some heterogeneity across regions, although the 95% CIs were overlapping and included unity (Figure 50).

Figure 50 – ELIXA: Subgroup analyses of the primary cardiovascular endpoint (ITT population)

	Lixisenatide N (%)	Placebo (N)	Hazard Ratio (95% CI)
Gender			
Male	292 (13.8%)	272 (13.0%)	1.06 (0.90, 1.25)
Female	114 (12.4%)	127 (13.5%)	0.92 (0.72, 1.19)
Age Group (Years)			
<65	227 (11.2%)	212 (10.6%)	1.06 (0.88, 1.27)
≥65	179 (17.8%)	187 (18.0%)	0.98 (0.80, 1.20)
Race			
Caucasian	313 (13.9%)	297 (12.8%)	1.08 (0.92, 1.27)
Black	23 (19.5%)	22 (21.4%)	0.87 (0.49, 1.57)
Asian/Oriental	34 (8.4%)	33 (9.0%)	0.92 (0.57, 1.48)
Other	36 (14.2%)	47 (19.1%)	0.72 (0.47, 1.11)
Ethnicity			
Hispanic	106 (12.3%)	122 (13.5%)	0.90 (0.69, 1.16)
Not Hispanic	300 (13.8%)	277 (13.0%)	1.07 (0.91, 1.26)
Region			
North America	62 (15.3%)	64 (15.9%)	0.95 (0.67, 1.34)
South and Central America	119 (12.2%)	137 (14.1%)	0.86 (0.67, 1.10)
Western Europe	61 (17.2%)	46 (12.2%)	1.45 (0.99, 2.13)
Eastern Europe	112 (14.4%)	98 (12.1%)	1.20 (0.92, 1.58)
Africa/Near East	19 (12.3%)	25 (17.6%)	0.65 (0.36, 1.19)
Asia/Pacific	33 (8.8%)	29 (8.8%)	0.99 (0.60, 1.63)
Days Between ACS and Randomization			
<30	45 (11.3%)	54 (13.5%)	0.82 (0.55, 1.22)
≥30 to <60	154 (14.2%)	148 (13.5%)	1.07 (0.85, 1.34)
≥60 to <90	110 (15.2%)	90 (13.3%)	1.13 (0.86, 1.50)
≥90	97 (11.7%)	107 (12.5%)	0.94 (0.71, 1.24)

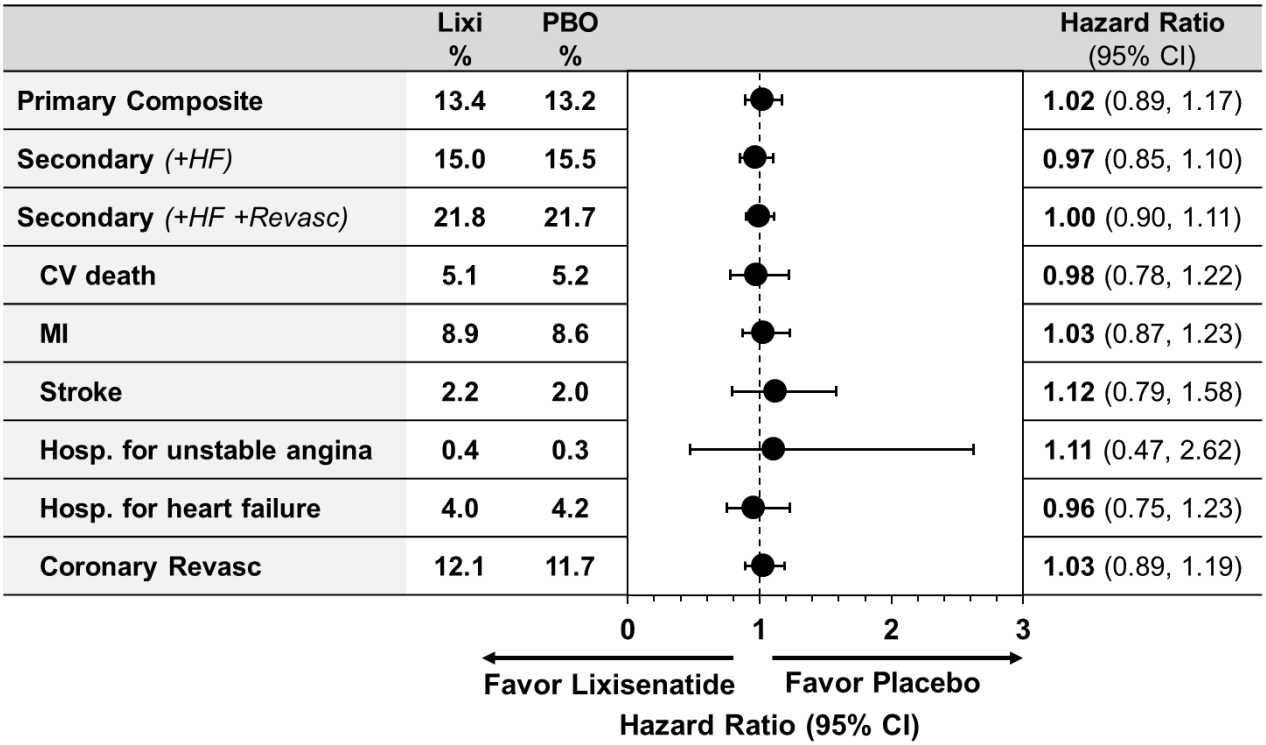


HR: hazard ratio, CI: confidence interval, CAC: Cardiovascular Events Adjudication Committee.
Only CAC positively adjudicated events are included.

6.5.3.3 Secondary cardiovascular endpoints

A Forest plot of secondary CV endpoints is shown in Figure 51. Consistent with the analyses of the primary CV endpoint, the event rates of composite secondary endpoints adding "hospitalization for heart failure" or both "hospitalization for heart failure" and "coronary revascularization" were comparable between treatments. The hazard ratio for the composite secondary endpoint of MACE+ or hospitalization for heart failure was 0.968 (95% CI: 0.851, 1.102), and the hazard ratio for the composite secondary endpoint of MACE+ or hospitalization for heart failure, or coronary revascularization was 0.997 (95% CI: 0.895, 1.111).

Figure 51 – ELIXA: Forest plot of each individual cardiovascular event of the secondary endpoints (ITT population)



CV: cardiovascular, MI: myocardial infarction, HR: hazard ratio, CI: confidence interval.
Only CAC positively adjudicated events are included.

6.5.3.4 Change from baseline in urinary albumin/creatinine ratio (UACR)

Progression of albuminuria is a marker of nephropathy, an important microvascular complication of diabetes. Therefore, the percentage changes in UACR from baseline to Week 108 (~2 years) was a pre-specified secondary endpoint. Geometric mean values at baseline were similar between treatment groups. Geometric mean UACR increased from baseline to Week 108 in both groups, consistent with progression of the underlying disease. However, treatment with lixisenatide was associated with a smaller increase (24%) compared to the increase (34%) seen with placebo. The difference in percent change between lixisenatide and placebo from baseline to Week 108 was -0.10% (95% CI: -0.17, -0.03).

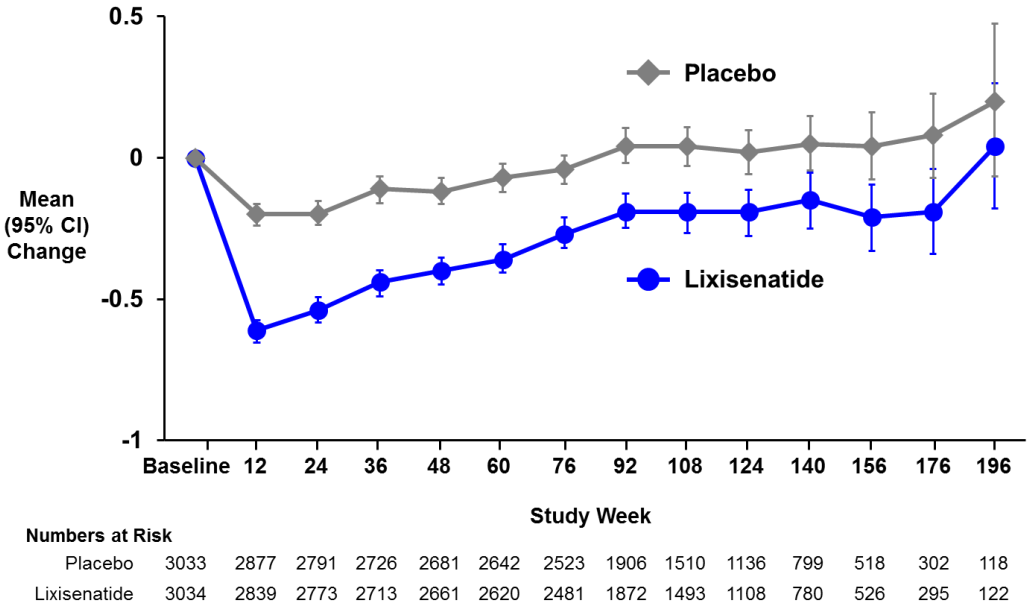
6.5.3.5 Glycemic control

The primary objective of the ELIXA study was to assess the CV safety of lixisenatide. Glycemic and metabolic parameters, including HbA1c, FPG, and body weight, were summarized descriptively.

Baseline mean HbA1c was comparable between treatment groups (7.72% for lixisenatide and 7.64% for placebo). Based on the study design, a major difference in HbA1c change was not expected between treatment groups. Mean HbA1c was reduced from baseline in both treatment

groups, but a greater reduction was observed in the lixisenatide group at each observation point (Figure 52).

Figure 52 - ELIXA: Mean change in HbA1c (%) from baseline by scheduled visit (ITT population)



Numbers at Risk

Placebo	3033	2877	2791	2726	2681	2642	2523	1906	1510	1136	799	518	302	118
Lixisenatide	3034	2839	2773	2713	2661	2620	2481	1872	1493	1108	780	526	295	122

Only visits with at least 30 patients with measurements in each group are presented.

6.6 IGLARLIXI SAFETY ANALYSIS POPULATIONS

To examine the safety experience with iGlarLixi in the Phase 2/3 program, safety data from the following pooled datasets were examined:

- **Phase 3 Controlled Study Pool (N=1899)** included Studies EFC12404 and EFC12405. This pool was the primary basis for the assessment of overall TEAEs, serious TEAEs, TEAEs leading to treatment discontinuation, clinical laboratory values, vital signs, and pancreatic events adjudicated by the Pancreatic Safety Assessment Committee (PSAC).
- **Phase 2/3 Controlled Study Pool (N=2222)** included Studies ACT12374 [Phase 2, active-controlled, efficacy and safety study of iGlarLixi in T2DM uncontrolled on metformin], EFC12404, and EFC12405. This pool was used for the assessment of deaths, malignancies, hepatic and renal AEs, and AEs adjudicated as allergic reactions by the ARAC, AEs adjudicated by the CAC as major CV events, local tolerability at injection site, and benign thyroid disorders.

6.7 IGLARLIXI EXTENT OF EXPOSURE IN PHASE 2/3 STUDIES

In the Phase 2/3 study pool, median duration of exposure was similar in the iGlarLixi and insulin glargine treatment groups (211 and 210 days, respectively) (Table 73). The proportion of patients

with an exposure ≥169 days was comparable between groups, 91.0% for iGlarLixi and 92.6% for insulin glargine.

6.8 IGLARLIXI TREATMENT-EMERGENT ADVERSE EVENTS

An overall summary of treatment-emergent AEs (TEAEs) was based on the Phase 3 study pool for the comparison of iGlarLixi versus insulin glargine and based on Study EFC12404 for the comparison of iGlarLixi with lixisenatide (Table 42).

- The percentage of patients with at least one TEAE was 55.4% for iGlarLixi versus 50.2% for insulin glargine. In Study EFC12404, the percentage for lixisenatide was 67.4%.
- The proportion of patients with a serious TEAE was comparable across treatment groups, with an incidence no higher than 4.6% in any one group.
- The proportion of patients with a TEAE leading to death was low and comparable across treatment groups.
- The percentage of patients that permanently discontinued treatment due to a TEAE was substantially lower in the iGlarLixi group versus the lixisenatide group (2.6% versus 9.0%, respectively). The difference between the two groups was largely due to the higher frequency of TEAEs in the GI disorders SOC in the lixisenatide group (12 patients [5.2%] versus 4 patients [0.9%] in the iGlarLixi group) of Study EFC12404 (Table 45). The incidence of permanent discontinuation was lowest in the insulin glargine group (1.4%).
- The majority of TEAEs in all 3 treatment groups were mild to moderate. Severe events occurred in low numbers of patients, 20 patients (2.4%) in the iGlarLixi group, 26 patients (3.1%) in the insulin glargine group, and 11 patients (4.7%) in the lixisenatide group.

Table 42 - Overall summary of TEAEs in the iGlarLixi pivotal Phase 3 studies (Safety population)

	Phase 3 controlled study pool[1]		EFC12404	
	iGlarLixi (N=834) n (%)	Insulin Glargine (N=832) n (%)	iGlarLixi (N=469) n (%)	Lixisenatide (N=233) n (%)
Patients with any TEAE	462 (55.4%)	418 (50.2%)	267 (56.9%)	157 (67.4%)
Patients with any serious TEAE	38 (4.6%)	37 (4.4%)	18 (3.8%)	9 (3.9%)
Patients with any TEAE leading to death	3 (0.4%)	5 (0.6%)	2 (0.4%)	1 (0.4%)
Patients with any TEAE leading to permanent treatment discontinuation	22 (2.6%)	12 (1.4%)	12 (2.6%)	21 (9.0%)

[1] Studies included: EFC12404 and EFC12405.
TEAE: Treatment-Emergent Adverse Event
n (%) = number and percentage of patients with at least one TEAE.

6.8.1 GI tolerability

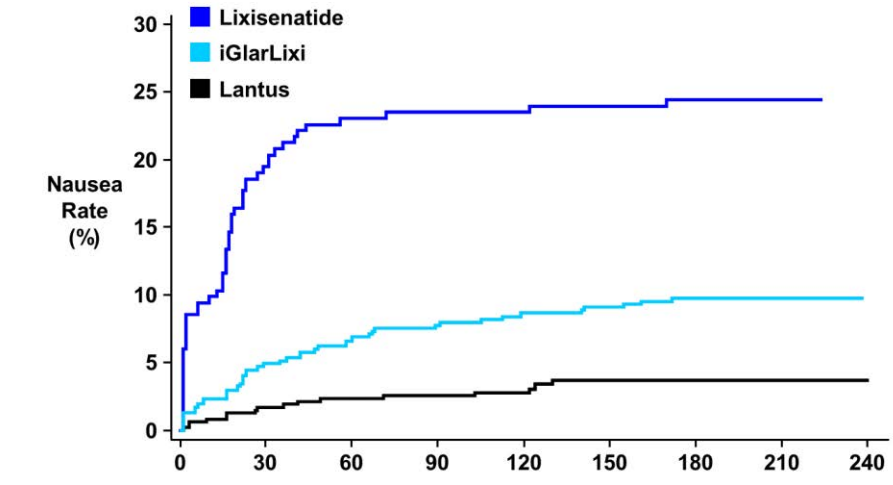
The most frequently reported drug-related TEAEs with an incidence ≥3% in any treatment group were primarily GI-related events of nausea, diarrhea, and vomiting. The highest incidence for these drug-related TEAEs occurred in the lixisenatide group.

Data from the Phase 3 study pool show that lixisenatide given in a fixed-ratio combination with insulin glargine provides better GI tolerability than when used alone.

- The incidence of TEAEs of nausea in the iGlarLixi group (10.0%) was less than half that of the lixisenatide group (24.0%) in EFC12404.
- The incidence of vomiting was 2-fold lower in the iGlarLixi group (3.2%) as compared to the lixisenatide group (6.4%) in EFC12404.
- The majority of patients in the iGlarLixi group had only 1 episode of nausea (66/83 patients) and 1 episode of vomiting (23/28 patients).
- In the iGlarLixi group, all but one of the events of nausea, vomiting, and diarrhea were of mild to moderate severity; none of the events were reported as SAEs. Nausea was reported as severe by 1 (0.1%] patient in the iGlarLixi group and 4 (1.7%) patients in the lixisenatide treatment group.
- The incidence of TEAEs in the GI disorders system organ class (SOC) in the iGlarLixi group (19.7%) was lower than with lixisenatide (36.9%) but higher than with insulin glargine (10.6%).

The outcome of the pivotal Phase 3 Study EFC12404 clearly demonstrates that the common GI TEAE of nausea occurs less frequently with iGlarLixi than with lixisenatide alone as shown in (Figure 53).

Figure 53 – Study EFC12404: Kaplan-Meier cumulative incidence curve for time to first onset of nausea during the on-treatment period (Safety population)



Number at Risk

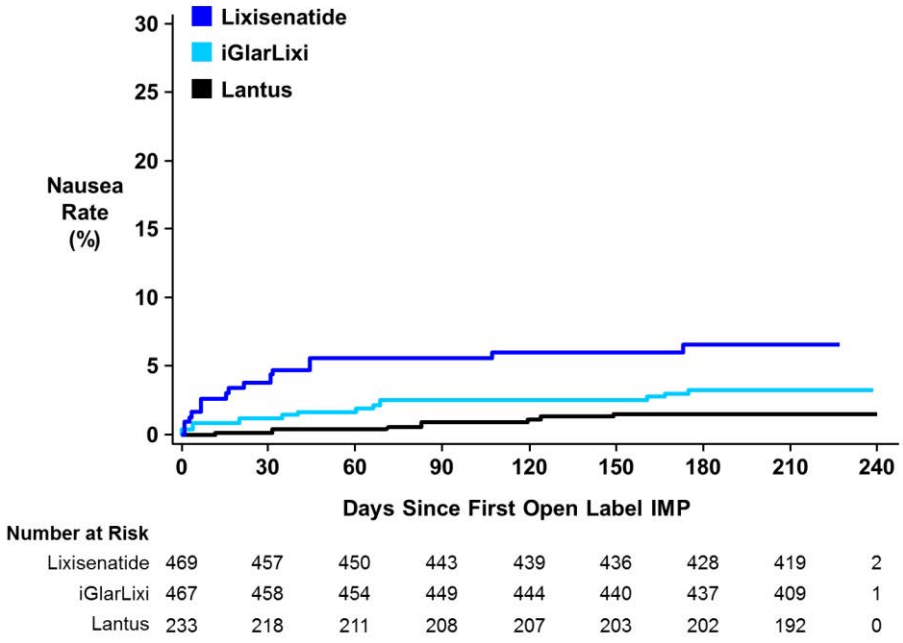
Lixisenatide	233	182	172	170	170	165	164	158	0
iGlarLixi	469	441	429	421	414	408	400	390	2
Lantus	467	452	446	442	437	431	428	401	1

INS/LIXI = iGlarLixi, LIXI = lixisenatide
The on-treatment period is defined as the time from the first injection of open-label investigational medicinal product (IMP) up to 3 days after the last injection of IMP, regardless of the introduction of rescue therapy.

Whereas adverse GI effects mainly occur during the initial dosing period with lixisenatide (as with GLP-1 receptor agonists in general), a blunting of this phenomenon was observed with the introduction of iGlarLixi, where fewer nausea events occurred over the first 6 to 8 weeks of treatment (Figure 53).

A similar pattern was seen for TEAEs of vomiting, with most events occurring over the first weeks of treatment (Figure 54). The reduced incidence of GI TEAEs is most likely related to the gradual dose increase of the lixisenatide component occurring in parallel to the up-titration of insulin, which is a design feature of the fixed-ratio combination of insulin glargine and lixisenatide.

Figure 54 – Study EFC12404: Kaplan-Meier cumulative incidence curve for time to first onset of vomiting during the on-treatment period (Safety population)



INS/LIXI = iGlarLixi, LIXI = lixisenatide
The on-treatment period is defined as the time from the first injection of open-label investigational medicinal product (IMP) up to 3 days after the last injection of IMP, regardless of the introduction of rescue therapy.

6.8.2 Common TEAEs by baseline characteristics

Subgroup analyses were conducted to explore the potential differences of common TEAEs (HLTs ≥2% in any treatment group) by baseline characteristics using data from the Phase 3 study pool. There was no difference in the incidence of TEAEs based on baseline values for gender, age, BMI, and various categories of medical history in either treatment group.

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 severe renal impairment but the combined number of patients was low (N=56).

6.8.3 Mortality

The analyses of deaths were based on the Phase 2/3 controlled study pool. No deaths were reported in the 6 Phase 1 studies.

A total of 10 deaths were reported in the two Phase 3 studies (EFC12404 and EFC12405): 3 patients (0.3%) in the iGlarLixi group, 6 patients (0.6%) in the insulin glargine group, and 1 patient (0.4%) in the lixisenatide group. None of the 10 deaths were judged by the Investigators to be treatment-related. No deaths were reported in Phase 2 Study ACT12374.

Table 43 - Summary of overall mortality in the Phase 2/3 controlled studies (Safety population)

	Phase 2/3 controlled study pool[1]		EFC12404	
	iGlarLixi	Insulin Glargine	iGlarLixi	Lixisenatide
	(N=995)	(N=994)	(N=469)	(N=233)
Number of deaths [2], n (%)	3 (0.3%)	6 (0.6%)	2 (0.4%)	1 (0.4%)
Total patient years at risk [3]	555.8	560.2	270.7	134.8
Mortality per 100 patient-years	0.54	1.07	0.74	0.74

1 Studies included: ACT12374, EFC12404 and EFC12405.
2 All deaths that occurred during the study, including on-treatment period and post-treatment period, were counted.
3 Calculated as the time from the first injection of study drug to the end of study date for patients with no event or to the time of death for patients with an event.
All randomized and treated patients were included.

6.8.4 Serious adverse events

In the Phase 3 study pool, the incidence of serious TEAEs was similar in the iGlarLixi and insulin glargine treatment groups: 4.6% (38 patients) and 4.4% (37 patients), respectively (Table 44).

The incidence of individual serious events in any one treatment group was distributed across a variety of PTs and SOCs. No specific SAE was frequently reported.

In the Phase 3 study pool, post-treatment SAEs were reported in 3 (0.4%) patients in the insulin glargine group and 1 (0.4%) patient in the lixisenatide group in Study EFC12404.

Table 44 - Serious TEAEs (PTs with 2 or more patients in any treatment group) by primary SOC and PT in the Phase 3 controlled studies (Safety population)

	Phase 3 controlled study pool		EFC12404	
	iGlarLixi (N=834)	Insulin Glargine (N=832)	iGlarLixi (N=469)	Lixisenatide (N=233)
PRIMARY SYSTEM ORGAN CLASS **Preferred Term, n (%)**	**n (%)**	**n (%)**	**n (%)**	**n (%)**
Any TEAE	38 (4.6%)	37 (4.4%)	18 (3.8%)	9 (3.9%)
INFECTIONS AND INFESTATIONS	5 (0.6%)	5 (0.6%)	4 (0.9%)	2 (0.9%)
Urinary tract infection	2 (0.2%)	0	2 (0.4%)	0
Pneumonia	1 (0.1%)	2 (0.2%)	0	0
METABOLISM AND NUTRITION DISORDERS	2 (0.2%)	1 (0.1%)	0	2 (0.9%)
Hypoglycemia	2 (0.2%)	1 (0.1%)	0	0
NERVOUS SYSTEM DISORDERS	4 (0.5%)	1 (0.1%)	1 (0.2%)	2 (0.9%)
Hypoglycemic unconsciousness	2 (0.2%)	0	0	0
CARDIAC DISORDERS	9 (1.1%)	8 (1.0%)	2 (0.4%)	0
Acute myocardial infarction	2 (0.2%)	1 (0.1%)	0	0
Angina unstable	2 (0.2%)	0	0	0
Cardiac failure congestive	1 (0.1%)	2 (0.2%)	1 (0.2%)	0
VASCULAR DISORDERS	1 (0.1%)	2 (0.2%)	1 (0.2%)	0
Hypertension	1 (0.1%)	2 (0.2%)	1 (0.2%)	0
HEPATOBILIARY DISORDERS	2 (0.2%)	1 (0.1%)	1 (0.2%)	0
Cholecystitis chronic	2 (0.2%)	0	1 (0.2%)	0
GENERAL DISORDERS AND ADMINISTRATION SITE CONDITIONS	0	4 (0.5%)	0	1 (0.4%)
Non-cardiac chest pain	0	3 (0.4%)	0	0

Phase 3 study pool included: EFC12404 and EFC12405.
MedDRA Version: 18.0.
Note: Table was sorted by the internationally agreed order for SOCs and then by decreasing frequency of PT within a SOC by the fixed ratio combination group based on the pooled data. Adverse Events Associated with Permanent Treatment Discontinuation

6.8.5 Adverse events associated with permanent treatment discontinuation

The proportion of patients permanently discontinuing due to TEAEs was low in the iGlarLixi (2.6%) and insulin glargine (1.4%) treatment groups, while in the lixisenatide group, the proportion was more than 3-fold higher at 9.0% (Table 45). The difference between the lixisenatide and iGlarLixi treatment groups was largely due to the higher frequency of TEAEs in the gastrointestinal disorders SOC in the lixisenatide group of Study EFC12404, 12 patients (5.2%) versus 4 patients (0.9%) in the iGlarLixi group.

- In the Phase 3 study pool, the most frequently reported TEAE by PT that led to permanent treatment discontinuation in the iGlarLixi group was nausea (0.7% [6 patients]); there were 3 patients (0.4%) who discontinued due to urticaria.
- In the lixisenatide group of Study EFC12404, the most frequently reported TEAEs leading to permanent treatment discontinuation were nausea (2.6% [6 patients]) and vomiting (1.7% [4 patients]).
- There were no frequently reported TEAEs (PT with 2 or more patients) that led to permanent discontinuation in the insulin glargine group.

Table 45 - iGlarlixi: TEAEs leading to treatment discontinuation (PTs with 2 or more patients in any treatment group) by primary SOC and PT in the Phase 3 controlled studies (Safety population)

	Phase 3 controlled study pool [1]		EFC12404	
PRIMARY SYSTEM ORGAN CLASS Preferred Term, n (%)	iGlarLixi (N=834)	Insulin Glargine (N=832)	iGlarLixi (N=469)	Lixisenatide (N=233)
Any TEAE	22 (2.6%)	12 (1.4%)	12 (2.6%)	21 (9.0%)
GASTROINTESTINAL DISORDERS	8 (1.0%)	1 (0.1%)	4 (0.9%)	12 (5.2%)
Nausea	6 (0.7%)	0	2 (0.4%)	6 (2.6%)
Vomiting	2 (0.2%)	0	2 (0.4%)	4 (1.7%)
Diarrhea	1 (0.1%)	0	1 (0.2%)	2 (0.9%)
SKIN AND SUBCUTANEOUS TISSUE DISORDERS	4 (0.5%)	1 (0.1%)	4 (0.9%)	1 (0.4%)
Urticaria	3 (0.4%)	0	3 (0.6%)	1 (0.4%)

[1] Studies included: EFC12404 and EFC12405.
TEAE: Treatment-Emergent Adverse Event, SOC: System Organ Class, PT: Preferred Term.
MedDRA Version: 18.0.
Note: Table was sorted by the internationally agreed order for SOCs and then by decreasing frequency of PT within a SOC by the iGlarLixi group based on the pooled data.

6.8.6 Laboratory evaluations

No clinically relevant differences between the iGlarLixi and comparator groups were identified for the laboratory parameters of hematology, biochemistry (including calcitonin), and urinalyses.

Pancreatic enzymes

There were no events of pancreatitis in the Phase 2/3 iGlarLixi program (Section 6.9.2.2). The incidence of on-treatment elevations of pancreatic enzymes considered a PCSA (≥3 x ULN) was also low across all treatment groups.

- In the Phase 3 study pool, the percentage of patients with elevations in lipase or amylase considered PCSA (≥3 x ULN) regardless of baseline status were similar between the iGlarLixi and insulin glargine groups: lipase (0.8% versus 1.2%) and amylase (0.1% versus 0.2%).
- In Study EFC12404, the percentages in the iGlarLixi group versus the lixisenatide group were 0.9% versus 2.2% for lipase, and 0.2% versus 0.4% for amylase.

Liver function

The percentage of patients with PCSAs for ALT, AST, ALP, and total bilirubin and with out-of-normal range values for gamma glutamyl transferase (G-GT) reported during the on-treatment period in the iGlarLixi, insulin glargine, and lixisenatide treatment groups was low and similar across treatment groups.

Renal function

The percentage of patients with abnormalities of mild or moderate renal impairment based on creatinine clearance during the on-treatment period was comparable in the iGlarLixi and insulin glargine groups (28.6% and 28.2%, respectively, for mild; 5.0% and 3.7%, respectively, for moderate). Percentages were lower in the lixisenatide group: 23.3% for mild renal impairment and 1.8% for moderate. Severe renal impairment was reported in 2 patients (0.2%) in the insulin glargine group and none in the iGlarLixi and lixisenatide groups.

6.9 SPECIAL SAFETY TOPICS

6.9.1 Symptomatic hypoglycemia

Lixisenatide was associated with a low risk of hypoglycemia as monotherapy or in combination with metformin or a thiazolidinedione, and a limited additional risk in combination with a SU or basal insulin.

6.9.1.1 Lixisenatide

In the lixisenatide Phase 3 studies, symptomatic hypoglycemia was defined as symptoms considered to result from hypoglycemia, with a plasma glucose <60 mg/dL or prompt recovery after carbohydrates or glucagon in the absence of plasma glucose measurement. Severe symptomatic hypoglycemia was defined as a hypoglycemia event where the assistance of another was required to administer corrective treatment associated with a plasma glucose ≤36 mg/dl (or with prompt recovery in the absence of glucose measurement). The analyses include events of symptomatic hypoglycemia reported during the main and entire treatment periods of the studies.

The analyses are shown by background antidiabetic treatment; background antidiabetic therapy is further considered as being without or with basal insulin.

No background treatment (EFC6018). During this 12-week monotherapy study, 4 (1.7%) patients treated with lixisenatide and 2 (1.6%) patients treated with placebo experienced symptomatic hypoglycemia. The relative risk for lixisenatide versus placebo was 1.02 (95% CI: 0.19, 5.50) (Figure 55). No events of severe symptomatic hypoglycemia were reported.

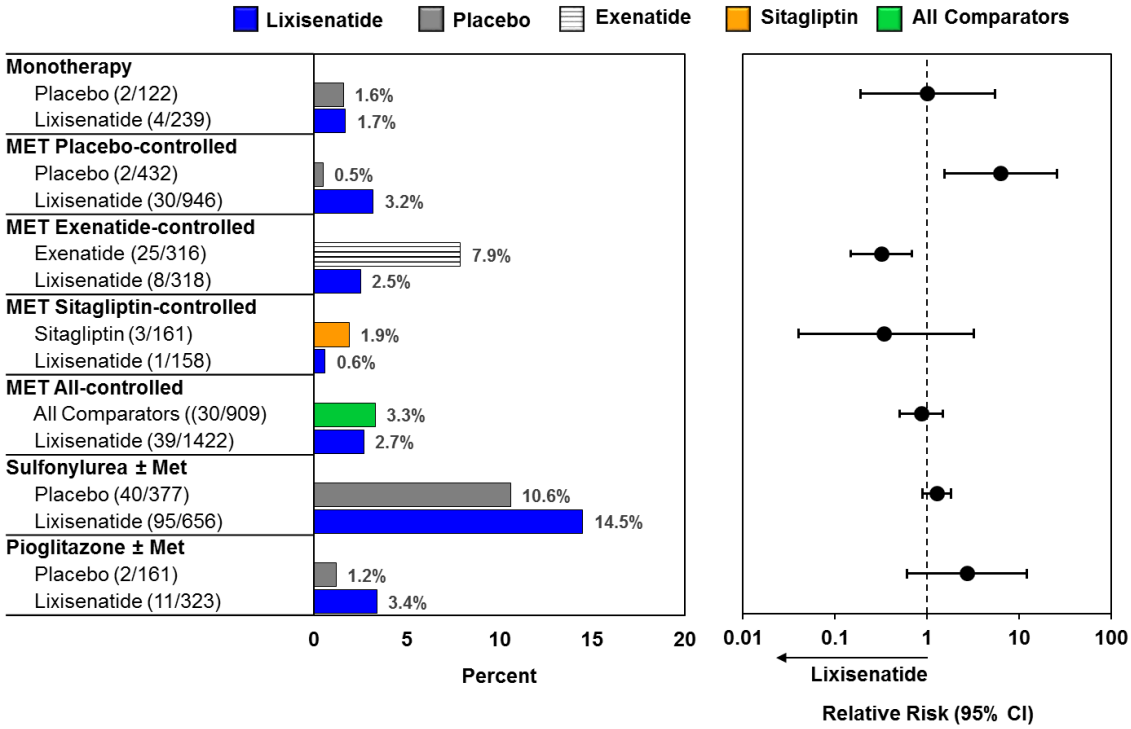
Metformin alone as background therapy, placebo-controlled studies (EFC6014, EFC10743, EFC11321).

In patients treated concomitantly with lixisenatide and metformin, the incidence of symptomatic hypoglycemia was higher than with placebo. No events of severe symptomatic hypoglycemia were reported.

During the main treatment period in the placebo-controlled studies EFC6014, EFC10743, and the subpopulation in EFC11321 with metformin alone as background therapy, 30 (3.2%) patients on lixisenatide versus 2 (0.5%) patients on placebo experienced symptomatic hypoglycemia. The relative risk for lixisenatide versus placebo stratified by study was 6.32 (95% CI: 1.56, 25.61) (Figure 55).

During the entire treatment period in EFC6014 and EFC10743, 7.0% of patients on lixisenatide compared to 4.8% of patients on placebo experienced symptomatic hypoglycemia. The EAIR per 100 PY of symptomatic hypoglycemia was 5.02 with lixisenatide and 3.30 with placebo; the event rate per 100 PY was 9.2 and 4.6, respectively.

Figure 55 - Symptomatic hypoglycemia: Forest plot (relative risk) on non-insulin background therapy in Phase 3 controlled efficacy/safety studies: main treatment period (safety population)



Studies: EFC6014, EFC6015, EFC6017, EFC6018, EFC6019, EFC10743, EFC10780 and EFC11321.
MET=Metformin, Monotherapy included: EFC6018, MET Placebo-controlled included: EFC6014, EFC10743 and EFC11321 (patients on metformin alone),
MET Exenatide-controlled included: EFC6019,
Pioglitazone +/- MET included: EFC6017, MET All-controlled included: EFC6014, EFC6019, EFC10743, EFC10780 and EFC11321 (patients on metformin only).
Main treatment period: 12 weeks for EFC6018 and 24 weeks for other studies. All comparators included placebo, exenatide and sitagliptin.
Relative risk and 95% CI: calculated using CMH method stratified by study for the analysis with more than one study.

Sulfonylurea +/- metformin as background therapy (EFC6015, EFC11321). During the main treatment period of the 2 studies with SU ± metformin as background therapy, (EFC6015 and the subpopulation in EFC11321 with metformin + SU as background therapy), 95 (14.5%) patients on lixisenatide and 40 (10.6%) patients on placebo experienced symptomatic hypoglycemia. The relative risk for lixisenatide versus placebo stratified by study was 1.28 (95% CI: 0.90, 1.81).

Pioglitazone +/- metformin as background therapy (EFC6017). During the main treatment period of this study, 11 (3.4%) patients on lixisenatide and 2 (1.2%) patients on placebo experienced symptomatic hypoglycemia. The relative risk for lixisenatide versus placebo was 2.74 (95% CI: 0.61, 12.22). During the entire treatment period, the incidence of symptomatic hypoglycemia was 7.1% with lixisenatide and 4.3% with placebo, with a relative risk (lixisenatide versus placebo) of 1.64 (95% CI: 0.72, 3.74). No events of severe symptomatic hypoglycemia were reported.

Basal insulin +/- metformin as background therapy (EFC6016, EFC10887). During the main treatment period in study EFC6016 and the subpopulation of patients [all Asians] who had basal

insulin only as background therapy in Study EFC10887, 106 (28.3%) patients on lixisenatide and 49 (23.0%) patients on placebo experienced symptomatic hypoglycemia (Table 46). The relative risk for lixisenatide versus placebo stratified by study was 1.26 (95% CI: 0.93, 1.69) (Figure 56). Events of severe symptomatic hypoglycemia were experienced by 4 (1.1%) patients with lixisenatide (all in EFC6016) and no patients with placebo.

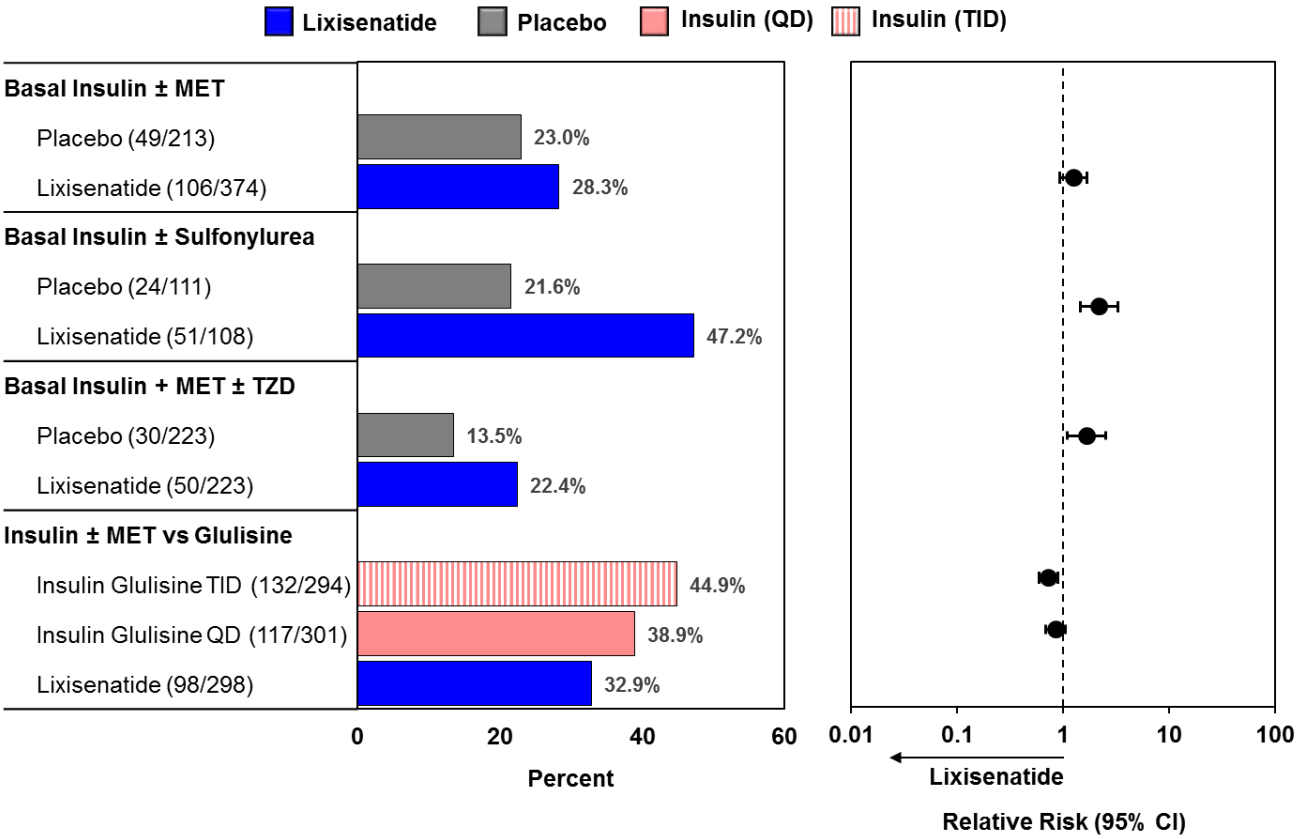
The incidence of symptomatic hypoglycemia over the entire treatment period (EFC6016 only) was 42.1% with lixisenatide and 38.9% with placebo, with a relative risk of lixisenatide versus placebo of 1.08 (95% CI: 0.86, 1.36). There were 5 (3.6%) patients in the lixisenatide group and 3 (4.6%) patients 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.

Table 46 - Number (%) of patients with symptomatic hypoglycemia on basal insulin background therapy in Phase 3 controlled efficacy/safety studies: main treatment period (safety population)

	Symptomatic hypoglycemia			Severe symptomatic hypoglycemia		
Background therapy Treatment	**Any symptomatic hypoglycemia**	**Blood glucose <60 mg/dL**	**No blood glucose reported**	**Any severe symptomatic hypoglycemia**	**Blood glucose <36 mg/dL**	**No blood glucose reported**
Basal insulin ± metformin[a]						
Placebo (N=213)	49 (23.0%)	46 (21.6%)	3 (1.4%)	0	0	0
Lixisenatide (N=374)	106 (28.3%)	100 (26.7%)	12 (3.2%)	4 (1.1%)	3 (0.8%)	1 (0.3%)
Basal insulin + sulfonylurea[b]						
Placebo (N=111)	24 (21.6%)	21 (18.9%)	9 (8.1%)	0	0	0
Lixisenatide (N=108)	51 (47.2%)	46 (42.6%)	12 (11.1%)	0	0	0
Basal insulin[c] + metformin ± TZD[d]						
Placebo (N=223)	30 (13.5%)	26 (11.7%)	6 (2.7%)	0	0	0
Lixisenatide (N=223)	50 (22.4%)	45 (20.2%)	8 (3.6%)	1 (0.4%)	0	1 (0.4%)
Basal insulin[c] ± metformin[e]						
Lixisenatide (N=298)	98 (32.9%)	94 (31.5%)	6 (2.0%)	0	0	0
Insulin Glulisine QD (N=301)	117 (38.9%)	113 (37.5%)	8 (2.7%)	2 (0.7%)	1 (0.3%)	1 (0.3%)
Insulin Glulisine TID (N=294)	132 (44.9%)	131 (44.6%)	4 (1.4%)	0	0	0

[a] EFC6016 and EFC10887 (patients on basal insulin only). [b] EFC10887 (patients on basal insulin + sulfonylurea). [c] Insulin glargine optimally titrated. [d] EFC10781. [e] EFC12626. Main treatment period is 24 weeks or 26 weeks (EFC12626).

Figure 56 - Forest plot of patients with symptomatic hypoglycemia (relative risk) on basal insulin background therapy in Phase 3 controlled efficacy/safety studies: main treatment period (safety population)



*Insulin glargine optimally titrated.
Studies included: EFC6016, EFC10781, EFC10887 and EFC12626.
MET=Metformin, Basal insulin +/- MET included: EFC6016 and EFC10887 (patients on basal insulin alone), Basal insulin + sulfonylurea included: EFC10887 (patients on basal insulin + sulfonylurea), Basal insulin + MET +/-TZD: EFC10781, Basal insulin +/- MET vs. Insulin glulisine included: EFC12626
Main treatment period is 24 weeks or 26 weeks (EFC12626).
Relative risk and 95% CI: calculated using CMH method stratified by study for the analysis with more than one study.

Basal insulin + SU as background therapy (EFC10887). In this 24-week study in Asian patients, in the subpopulation of patients that used basal insulin + SU as background therapy, 51 (47.2%) patients on lixisenatide and 24 (21.6%) patients on placebo experienced symptomatic hypoglycemia (Table 46). The relative risk for lixisenatide versus placebo was 2.18 (95% CI: 1.45, 3.28) (Figure 56). No events of severe symptomatic hypoglycemia (per protocol definition) were reported. The majority of patients in both groups had ≤5 events (88.2% on lixisenatide and 87.5% on placebo).

Basal insulin (insulin glargine optimally titrated) + metformin +/- TZD (EFC10781). In this 24-week study in insulin-naïve patients optimally titrated to insulin glargine + metformin with or without TZD as background therapy, 50 (22.4%) patients on lixisenatide and 30 (13.5%) patients on placebo experienced symptomatic hypoglycemia (Table 46). The relative risk for lixisenatide versus placebo was 1.67 (95% CI: 1.10, 2.52) (Figure 56). There was 1 (0.4%) patient on

lixisenatide with severe symptomatic hypoglycemia. The majority of patients in both groups had ≤5 events (98.0% on lixisenatide and 96.7% on placebo); 1 (2.0%) patient on lixisenatide had between 11 and 15 events and 1 (3.3%) patient on placebo had between 6 and 10 events.

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 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.

ELIXA

In ELIXA, standard-of-care was the background therapy. During the on-treatment period, the incidence of symptomatic hypoglycemia was comparable between groups: 16.6% versus 15.2%, respectively, for lixisenatide and placebo. The EAIR of symptomatic hypoglycemia per 100 patient-years was 10.2 with lixisenatide and 8.83 with placebo; the event rate per 100 patient-years was 28.4 with lixisenatide and 25.9 with placebo. The incidence of symptomatic hypoglycemia in subgroups according to gender, age, or race showed a distribution pattern similar to that of the entire population. The incidence of severe symptomatic hypoglycemia was low in both treatment groups. Fewer patients treated with lixisenatide than with placebo experienced severe symptomatic hypoglycemia; event rates per 100 patient-years were 0.3 and 0.6 in the lixisenatide and placebo group, respectively.

6.9.1.2 iGlarLixi

Study EFC12404 (insulin-naïve)

In Study EFC12404 (Table 47), the percentages of patients with at least 1 documented symptomatic hypoglycemic event (plasma glucose value ≤70 mg/dL) and the corresponding event rates per patient-year were low and similar for the iGlarLixi (25.6%; 1.44 events per patient-year) and insulin glargine groups (23.6%; 1.22 events per patient-year). As expected, the incidence (6.4%) and event-rate of documented symptomatic hypoglycemia per patient-year (0.34) were lowest in the lixisenatide group.

There was 1 patient with severe symptomatic hypoglycemia in the insulin glargine group compared to none in the iGlarLixi and lixisenatide groups. There were no serious TEAEs of symptomatic hypoglycemia and no hypoglycemia events leading to permanent treatment discontinuation.

Table 47 – Study EFC12404: Symptomatic hypoglycemia recorded on the dedicated eCRF page and meeting protocol definition during the on-treatment period (Safety population)

Symptomatic hypoglycemia	iGlarLixi (N=469)	Insulin Glargine (N=467)	Lixisenatide (N=233)
Total patient years of exposure	263.1	262.5	125.2
Symptomatic hypoglycemia			
Number of patients with events, n (%)	128 (27.3%)	119 (25.5%)	15 (6.4%)
Number of patients with events per patient year[a]	0.49	0.45	0.12
Number of events	409	338	46
Number of events per patient year[b]	1.55	1.29	0.37
Documented symptomatic hypoglycemia (plasma glucose ≤70 mg/dL [3.9 mmol/L])			
Number of patients with events, n (%)	120 (25.6%)	110 (23.6%)	15 (6.4%)
Number of patients with events per patient year[a]	0.46	0.42	0.12
Number of events	378	321	43
Number of events per patient year[b]	1.44	1.22	0.34
Documented symptomatic hypoglycemia (plasma glucose <60 mg/dL [3.3 mmol/L])			
Number of patients with events, n (%)	66 (14.1%)	50 (10.7%)	6 (2.6%)
Number of patients with events per patient year[a]	0.25	0.19	0.05
Number of events	128	75	13
Number of events per patient year[b]	0.49	0.29	0.10
Severe symptomatic hypoglycemia			
Number of patients with events, n (%)	0	1 (0.2%)	0
Number of patients with events per patient year[a]	0	<0.01	0
Number of events	0	1	0
Number of events per patient year[b]	0	<0.01	0

eCRF: electronic Case Report Form.

Patient years of exposure: calculated as time from the first to the last injection of study drug plus 1 day.

a Calculated as number of patients with events divided by total patient-years of exposure.

b Calculated as number of events divided by total patient-years of exposure.

Symptomatic hypoglycemia = symptomatic hypoglycemia recorded on the dedicated eCRF and meeting protocol definition for severe, or documented, or probable symptomatic hypoglycemia.

On-treatment period is defined as the time from the first injection of study drug up to 1 day for symptomatic hypoglycemia after the last injection of study drug, regardless of the introduction of rescue therapy.

Study EFC12405 (previously insulin-treated)

In Study EFC12405 (Table 48), the percentages of patients with at least 1 documented symptomatic hypoglycemia event (plasma glucose value ≤70 mg/dL) were similar for the iGlarLixi (40.0%) and insulin glargine groups (42.5%) but with lower number of events per patient year for iGlarLixi (3.03) versus insulin glargine (4.22).

Four patients (1.1%) in the iGlarLixi group had a total of 5 severe hypoglycemic events that were also considered as serious (PTs: hypoglycemia, hypoglycemic unconsciousness, and hypoglycemic seizure). Of these, 3 patients had confounding factors that may have contributed to

the episodes of severe hypoglycemia, including dementia, an unusual amount of physical activity, and lack of food intake prior to the event. One patient (0.3%) in the insulin glargine group had a severe event of hypoglycemia that was also serious (PT: hypoglycemic seizure); the event was precipitated by a lack of dietary compliance. Two patients in the iGlarLixi group discontinued treatment due to hypoglycemia versus none in the insulin glargine group.

Table 48 – Study EFC12405: Symptomatic hypoglycemia recorded on the dedicated eCRF page and meeting protocol definition during the on-treatment period (Safety population)

Symptomatic hypoglycemia	iGlarLixi (N=365)	Insulin Glargine (N=365)
Total patient years of exposure	201.9	208.6
Symptomatic hypoglycemia		
Number of patients with events, n (%)	152 (41.6%)	161 (44.1%)
Number of patients with events per patient year [a]	0.75	0.77
Number of events	639	910
Number of events per patient year [b]	3.17	4.36
Documented symptomatic hypoglycemia (plasma glucose ≤70 mg/dL [3.9 mmol/L])		
Number of patients with events, n (%)	146 (40.0%)	155 (42.5%)
Number of patients with events per patient year [a]	0.72	0.74
Number of events	612	880
Number of events per patient year [b]	3.03	4.22
Documented symptomatic hypoglycemia (plasma glucose <60 mg/dL [3.3 mmol/L])		
Number of patients with events, n (%)	89 (24.4%)	83 (22.7%)
Number of patients with events per patient year [a]	0.44	0.40
Number of events	229	235
Number of events per patient year [b]	1.13	1.13
Severe symptomatic hypoglycemia		
Number of patients with events, n (%)	4 (1.1%)	1 (0.3%)
Number of patients with events per patient year [a]	0.02	<0.01
Number of events	5	1
Number of events per patient year [b]	0.02	<0.01

eCRF: electronic Case Report Form.

Patient-years of exposure: calculated as time from the first to the last injection of open label study drug plus 1 day.

a Calculated as number of patients with events divided by total patient-years of exposure.

b Calculated as number of events divided by total patient-years of exposure.

Symptomatic hypoglycemia = symptomatic hypoglycemia recorded on the dedicated eCRF and meeting protocol definition for severe, or documented, or probable symptomatic hypoglycemia.

On-treatment period is defined as the time from the first injection of open label study drug up to 1 day for symptomatic hypoglycemia after the last injection of study drug, regardless of the introduction of rescue therapy.

6.9.2 Injection site reactions

6.9.2.1 Lixisenatide

A TEAE was counted as an injection site reaction when the PT coded from either the Investigator-reported (verbatim) term or the ARAC assessment, contained the wording "injection site." The evaluation of injection site reactions focuses on the Phase 3 placebo-controlled efficacy/safety studies where the incidence was 4.0% for lixisenatide and 1.8% for placebo (Table 49). The EAIR per 100 patient-years was 4.54 for lixisenatide and 2.15 for placebo. Across the all-controlled Phase 2/3 studies (Data Pool 2), the EAIR per 100 patient-years was similar to the Phase 3 placebo-controlled data: 3.12 for lixisenatide versus 1.15 for all comparators.

In the Phase 3 placebo-controlled efficacy/safety studies, no severe or serious injection site reactions were reported, and most events were mild in intensity. Five patients (0.2%) discontinued lixisenatide treatment due to an injection site reaction. Most patients had their first injection site reaction during the first 10 weeks of treatment with lixisenatide.

The role of antibody formation in the occurrence of injection site reaction is discussed in Section 6.9.6.

Table 49 - Number (%) of patients with injection site reaction in Phase 3 placebo-controlled studies: *main treatment period* (safety population)

Preferred Term n (%)	Lixisenatide (N=2869)	Placebo (N=1639)
Any injection site reaction	**116 (4.0%)**	**29 (1.8%)**
Investigator reported Preferred Terms	108 (3.8%)	26 (1.6%)
Injection site pain	25 (0.9%)	13 (0.8%)
Injection site pruritus	25 (0.9%)	0
Injection site erythema	17 (0.6%)	1 (<0.1%)
Injection site hematoma	16 (0.6%)	7 (0.4%)
Injection site reaction	13 (0.5%)	2 (0.1%)
Injection site rash	8 (0.3%)	0
Injection site hemorrhage	5 (0.2%)	2 (0.1%)
Injection site irritation	4 (0.1%)	1 (<0.1%)
Injection site swelling	4 (0.1%)	1 (<0.1%)
Injection site hypersensitivity	2 (<0.1%)	0
Injection site induration	2 (<0.1%)	1 (<0.1%)
Injection site inflammation	2 (<0.1%)	0
Injection site macule	2 (<0.1%)	0
Injection site nodule	2 (<0.1%)	0
Injection site discomfort	1 (<0.1%)	0
Injection site urticaria	1 (<0.1%)	0
Injection site vesicles	1 (<0.1%)	0

Studies included: EFC6014, EFC6015, EFC6016, EFC6017, EFC6018, EFC10743, EFC10781, EFC10887 and EFC11321.
Main treatment period: 12 weeks for EFC6018 and 24 weeks for other studies.
ARAC: allergic reaction assessment committee.

ELIXA

In this trial, an AE was considered an injection site reaction when the PT coded from either the investigator-reported term or from an ARAC diagnosis, contained the wording “injection site”. On-treatment injection site reactions were reported in 65 (2.1%) patients in the lixisenatide group and 43 (1.4%) patients in the placebo group. For injection site reactions identified from investigator-reported events, the majority of events were of mild intensity. Injection site pain was reported as severe in intensity and related to study drug in 1 lixisenatide-treated patient. No patients in the lixisenatide or placebo group reported a serious injection site reaction.

6.9.2.2 iGlarLixi

In the Phase 2/3 study pool, the percentage of patients with injection site reactions was higher for the iGlarLixi than the insulin glargine group (1.7% and 1.1%, respectively). Events were generally mild with one patient in each of the iGlarLixi and insulin glargine treatment groups reporting an event of moderate severity.

6.9.3 Allergic reactions

During the lixisenatide and iGlarLixi Phase 3 programs, allergic AEs were to be reported on a specific AE form to thoroughly describe the potential allergic event and allow prospective evaluation via independent, blinded expert case adjudication.

6.9.3.1 Lixisenatide

An ARAC was formed in April 2007 to adjudicate all potential allergic-like TEAEs reported by investigators. This external panel of three allergy experts performed a blinded review of all potential allergic events to determine if an allergic reaction had occurred. For those events adjudicated as an allergic reaction, the ARAC also proposed a diagnosis, evaluated severity, and assessed the possible relationship with study drug. Pre-specified diagnoses were based on Sampson's criteria as follows (30):

Table 50 – ARAC Allergic Reaction Diagnoses

Term	Definition
Urticaria (hives)	papillary or dermal lesion, strictly located to skin, transitory (<24 hours)
Angioedema	papillary or dermal lesion possibly involving mucosae, transitory (24 to 48 hours)
Anaphylactic Reaction	skin or mucosal lesion of acute onset associated with at least 1 other organ involved (respiratory, GI, vascular, etc.)
Anaphylactic Shock	a diagnosis of anaphylaxis had been made and a symptomatic drop in blood pressure had occurred
Other	allergic diagnosis not meeting other diagnoses (to be given as free text)

Severity was classified based on treatment received, on a pre-specified scale:

Table 51 – ARAC Allergic Reaction Grading

Grade	Classification
Grade 1	No systemic treatment administered or only antihistamines administered
Grade 2	Treatment with systemic catecholamines or systemic corticosteroids
Grade 3	Treatment with both systemic catecholamines and systemic corticosteroids
Grade 4	Hospitalization without airway compromise (no mechanical airway protection)
Grade 5	Hospitalization and airway compromise (no mechanical airway protection)
Grade 6	Airway protection or death

Overall incidence. The evaluation of allergic AEs focused on the Phase 2/3 all-comparator pool. A total of 283 (3.9%) patients treated with lixisenatide and 146 (2.4%) patients treated with comparator had suspected allergic events that were sent to the ARAC for adjudication (Table 52). Of the events sent to ARAC, 99 (1.4%) patients treated with lixisenatide and 50 (0.8%) patients treated with comparator had events adjudicated as allergic by the ARAC. The EAIR per 100 patient-years for all allergic events (regardless of relationship to study drug) was 1.02 with lixisenatide and 0.60 with comparators.

Those events not assessed as hypersensitivity were primarily non-allergic injection site reactions that were typically transient, non-serious, and did not require drug discontinuation.

Summary by PT as coded from the ARAC diagnosis. The most frequent PTs coded from the ARAC diagnosis in the lixisenatide group, irrespective of relationship to study drug, were (lixisenatide versus comparator): urticaria (24 [0.3%] versus 14 [0.2%]), rhinitis allergic (17 [0.2%] versus 8 [0.1%]), anaphylactic reaction (10 [0.1%] versus 4 [<0.1%]), angioedema (8 [0.1%] versus 7 [0.1%]), and dermatitis contact (8 [0.1%] versus 2 [<0.1%])(Table 53).

Allergic events adjudicated as possibly related to study drug. Among the adjudicated allergic reactions, urticaria was the most common manifestation of allergy, accounting for more than one-third of all drug-related reactions (Table 54). The incidence of TEAEs adjudicated as possibly related allergic reactions was 0.4% (29 patients) for lixisenatide and 0.1% (9 patients) for comparator . The EAIR per 100 patient-years was 0.30 with lixisenatide and 0.11 with comparators. The most frequent PTs assessed as possibly related to study drug in the lixisenatide group were (lixisenatide versus comparator): urticaria (11 [0.2%] versus 6 [<0.1%]), anaphylactic reaction (9 [0.1%] versus 0), and angioedema (5 [<0.1%] versus 2 [<0.1%]).

Severity assessed by the ARAC. The majority of TEAEs adjudicated by the ARAC as allergic reactions (for both possibly related and not related to study drug) were classified as mild (severity grade 1 or grade 2) by the ARAC.

Table 52 - Summary of suspected allergic reaction AEs sent to ARAC for adjudication in Phase 2/3 studies: entire treatment period (safety population)

	All controlled[a]	
	Lixisenatide (N=7312)	**All comparators (N=6057)**
Total patient years of exposure	9813.98	8440.50
Suspected allergic reaction events sent to ARAC for adjudication		
Number of patients (%)	283 (3.9%)	146 (2.4%)
Number of events	351	183
Adjudicated as an allergic reaction by ARAC		
Number of patients (%)	99 (1.4%)	50 (0.8%)
EAIR per 100 patient years	1.02	0.60
Number of events (Rate per 100 PY)	114 (1.16)	59 (0.70)
Adjudicated as an allergic reaction possibly related to study drug by ARAC		
Number of patients (%)	29 (0.4%)	9 (0.1%)
EAIR per 100 patient years	0.30	0.11
Number of events (Rate per 100 PY)	32 (0.33)	12 (0.14)

a Data Pool 2 excluding ACT6011 and 2 lixisenatide only studies. All comparators included placebo, exenatide, liraglutide, sitagliptin and insulin glulisine.

Patient-years of exposure: calculated as time from the first to the last injection of study drug plus 3 days.

EAIR: exposure-adjusted incidence rate.

Rate per 100 PY (patient-years) calculated as 100*(number of events/total patient years of exposure).

ARAC: Allergic Reaction Assessment Committee. PY: Patient year

Table 53 – Number (%) of patients with AEs adjudicated by ARAC as allergic reaction by PT in Phase 2/3 studies: entire treatment period (safety population)

		All controlled[a]	
ARAC diagnosis category	**MedDRA coded term (PT) for ARAC diagnosis**	**Lixisenatide (N=7312)**	**All comparators (N=6057)**
Total patient years of exposure		9813.98	8440.50
All	Any event	99 (1.4%)	50 (0.8%)
Urticaria (Hives)	Urticaria	24 (0.3%)	14 (0.2%)
Anaphylactic Reaction	Anaphylactic reaction	10 (0.1%)	4 (<0.1%)
Angioedema	Angioedema	8 (0.1%)	7 (0.1%)
Anaphylactic Shock	Anaphylactic shock	6 (<0.1%)	1 (<0.1%)
Other	Any event	54 (0.7%)	26 (0.4%)
	Rhinitis allergic	17 (0.2%)	8 (0.1%)
	Dermatitis contact	8 (0.1%)	2 (<0.1%)
	Conjunctivitis allergic	7 (<0.1%)	1 (<0.1%)
	Asthma	2 (<0.1%)	2 (<0.1%)
	Pruritus generalized	4 (<0.1%)	1 (<0.1%)
	Dermatitis allergic	3 (<0.1%)	1 (<0.1%)
	Pruritus	3 (<0.1%)	1 (<0.1%)
	Drug eruption	2 (<0.1%)	0
	Allergy to arthropod sting	1 (<0.1%)	0
	Allergy to venom	1 (<0.1%)	0
	Arthropod sting	1 (<0.1%)	0
	Conjunctivitis	1 (<0.1%)	0
	Dermatitis atopic	1 (<0.1%)	1 (<0.1%)
	Erythema multiform	1 (<0.1%)	0
	Food allergy	1 (<0.1%)	2 (<0.1%)
	Injection site reaction	1 (<0.1%)	0
	Local reaction	1 (<0.1%)	0
	Rhinitis	1 (<0.1%)	0
	Type IV hypersensitivity reaction	1 (<0.1%)	0
	Contrast media allergy	0	1 (<0.1%)
	Dermatitis	0	2 (<0.1%)
	Eczema	0	1 (<0.1%)
	Rash pruritic	0	1 (<0.1%)
	Rash	0	1 (<0.1%)
	Seasonal allergy	0	1 (<0.1%)

a Data Pool 2 excluding ACT6011 and 2 lixisenatide only studies. All comparators included placebo, exenatide, liraglutide, sitagliptin and insulin glulisine.

Patient years of exposure: calculated as time from the first to the last injection of study drug plus 3 days.

ARAC: Allergic Reaction Assessment Committee.

Table 54 - Number (%) of patients with AEs adjudicated as allergic reaction possibly related to study drug by ARAC-Phase 2/3 studies: entire treatment period (safety population)

		All controlled[a]	
ARAC diagnosis category	MedDRA coded term (PT) for ARAC diagnosis	Lixisenatide (N=7312)	All comparators (N=6057)
Total patient years of exposure		9813.98	8440.50
Possibly related to study drug	Any event	29 (0.4%)	9 (0.1%)
Urticaria (Hives)	Urticaria	11 (0.2%)	6 (<0.1%)
Anaphylactic Reaction	Anaphylactic reaction	9 (0.1%)	0
Angioedema	Angioedema	5 (<0.1%)	2 (<0.1%)
Anaphylactic Shock	Anaphylactic shock	1 (<0.1%)	0
Other	Any event	6 (<0.1%)	2 (<0.1%)
	Conjunctivitis allergic	1 (<0.1%)	0
	Dermatitis allergic	1 (<0.1%)	0
	Injection site reaction	1 (<0.1%)	0
	Local reaction	1 (<0.1%)	0
	Pruritus generalized	1 (<0.1%)	0
	Type IV hypersensitivity reaction	1 (<0.1%)	0
	Dermatitis	0	1 (<0.1%)
	Rash pruritic	0	1 (<0.1%)

a Data Pool 2 excluding ACT6011 and 2 lixisenatide only studies. All comparators included placebo, exenatide, liraglutide, sitagliptin and insulin glulisine.

Patient-years of exposure: calculated as time from the first to the last injection of study drug plus 3 days.

ARAC: Allergic Reaction Assessment Committee. PT: Preferred term.

6.9.3.1.1 Anaphylactic reaction or shock

A total of 21 patients in the Phase 2/3 studies (16 treated with lixisenatide and 5 treated with placebo) had TEAEs adjudicated by the ARAC as anaphylactic reaction or anaphylactic shock. The EAIR of TEAEs adjudicated as anaphylactic reaction or anaphylactic shock by the ARAC per 100 patient-years was 0.16 with lixisenatide and 0.07 with placebo; the exposure-adjusted relative risk stratified by study for lixisenatide versus placebo was 2.23 (95% CI: 0.82, 6.97).

A total of 10 patients treated with lixisenatide and none treated with placebo experienced TEAEs adjudicated as anaphylactic reaction or anaphylactic shock possibly related to study drug by the ARAC. The 10 events with lixisenatide consisted of 9 anaphylactic reactions and 1 anaphylactic shock (later considered by the ARAC to be an anaphylactoid reaction). Among the 9 anaphylactic reactions, most events were adjudicated as low in severity, between grades 1 through 3 (four grade 1 events, three grade 2 events, two grade 3 events). The single case of anaphylactic shock was adjudicated as grade 5 (i.e., hospitalization with airway compromise). In addition, one patient each in the lixisenatide and placebo arms had grade 4 (i.e., requiring hospitalization) angioedema. Full recovery was noted in all patients.

Most of the cases did not exhibit hypotension, laryngeal edema, or severe asthma, the hallmark symptoms generally associated with a clinical diagnosis of anaphylaxis. The majority of cases

were largely mild urticaria/angioedema requiring no treatment or antihistamines/corticosteroids (catecholamines were used in 1 case). Recovery occurred within hours and the majority of patients were treated in an ambulatory care setting, rather than the emergency department or being hospitalized.

The event onset ranged from Day 1 (30 minutes after the first administration of study drug), to Days 2, 13, 22, 23, 27, 26, 165, and 170 following the first administration of study drug.

One event was adjudicated by the ARAC as anaphylactic shock possibly related to study drug (see Appendix 8.6 for details). This reaction occurred 20 minutes after the first injection of lixisenatide. The assessment provided by the ARAC indicated that allergic reactions typically occur only after previous exposure to a specific agent, but not at first exposure. A rare exception could be cross reactivity with other agents, which is highly unlikely since this patient did not report prior GLP-1 receptor agonist intake. No specific anti-lixisenatide immunoglobulin E (IgE) antibodies were found, and the patient's total IgE was within the normal range. Therefore, this event was not consistent with a "true" anaphylactic reaction linked to an IgE-mediated mechanism and was considered by the ARAC to be an anaphylactoid reaction or idiosyncratic reaction, which may be considered as exceptional, specific for a single patient, and unpredictable.

Each event of anaphylactic reaction or shock is summarized in Appendix 8.6.

ELIXA

In ELIXA, allergic events as adjudicated by the ARAC were infrequent and numerically balanced by treatment group (Table 55). One grade 3 event of anaphylaxis and one grade 4 event of angioedema were reported in the lixisenatide treatment group as related to study drug. The remainder of events in both treatment groups were grade 1 urticaria and other mild skin reactions. Note that ELIXA allergic events were also included in the preceding discussion of Phase 2/3 all-comparator allergic events.

Table 55 – ELIXA: On-treatment allergic reactions as adjudicated by the ARAC

	All patients	
n (%)	**Lixisenatide N=3034**	**Placebo N=3034**
Any allergic event	27 (0.9)	25 (0.8)
Drug-related allergic events	5 (0.2)	5 (0.2)
Urticaria	2 (<0.1)	4 (0.1)
Anaphylactic reaction	1 (<0.1)	0
Angioedema	1 (<0.1)	0
Other allergic reaction	1 (<0.1)	1 (<0.1)

Data shown are from the entire study period.

6.9.3.2 iGlarLixi

The same ARAC performed blinded adjudications for iGlarLixi studies. In the Phase 2/3 study pool, 13 (1.3%) patients in the iGlarLixi group, 9 (0.9%) patients in the insulin glargine group, and 5 (2.1%) patients in the lixisenatide group had suspected allergic events that were sent to the ARAC for adjudication.

The percentage of patients with TEAEs adjudicated as an allergic event was low across treatment groups: 7 (0.7%) patients in the iGlarLixi group, 5 (0.5%) patients in the insulin glargine group, and 2 (0.9%) patients in the lixisenatide group. The majority of patients (9/14) had events that were assessed as not related to study drug. There were 2 (0.9%) patients with events adjudicated as an allergic reaction possibly related to study drug in the lixisenatide group of EFC12404 (PTs of anaphylactic reaction [grade 2] and urticaria). Three (0.3%) patients had events adjudicated as an allergic reaction possibly related to study drug in the iGlarLixi group (all with a PT of urticaria, one event of which was reported as serious); all were considered moderate in intensity. There were no adjudicated events considered related to study drug in the insulin glargine group. Study drug was permanently discontinued in the 5 patients with possibly related events and all 5 patients recovered.

A summary of anaphylaxis adjudicated as possibly related to lixisenatide is found in Section 8.6.

6.9.3.3 Hypersensitivity with marketed GLP-1 receptor agonists

The potential for severe hypersensitivity reactions is included in the prescribing information for the four GLP-1 agonists currently marketed in the United States.

In order to further evaluate the observed hypersensitivity seen with lixisenatide during clinical development, and to place it into the context of these other marketed GLP-1 agonists, Sanofi has performed a review of the literature to identify the incidence rates for anaphylaxis and general hypersensitivity among the class. The search included a review of the Medline and Embase

databases for the period 2000-2016 citing clinical trial or registry data pertaining to hypersensitivity incidence for exenatide, liraglutide, albiglutide, and dulaglutide.

As shown in Table 56, the rate of anaphylaxis observed with dulaglutide in the pooled Phase 2 and 3 randomized controlled trials was 0.3%, a rate not dissimilar to the incidence for these events seen with lixisenatide. While no anaphylaxis events were observed in the other published trials, this finding is not unexpected given the small numbers of patients studied (approximately 150 to 500 patients per treatment arm) and the generally low frequency of anaphylaxis.

The observed incidence of general hypersensitivity in the published trials ranged from 0.2% to 1.5%, which was generally lower than that seen with lixisenatide (irrespective of relationship to drug). However, as the incidence of hypersensitivity in the placebo arms of the lixisenatide trials (0.8%) was also higher than the marketed GLP-1 receptor agonists, this would seem more likely an effect of the stimulated reporting of these events as a targeted event of special interest in the Sanofi program, rather than a true difference in incidence between lixisenatide and the class.

In summary, these data support a general risk for hypersensitivity and anaphylaxis with lixisenatide that is not inconsistent with the other members of the class.

Table 56 - Literature review of hypersensitivity with marketed GLP-1 receptor agonists: clinical trial data

Generic Name of Drug	Reference	Name of Trial (or study design)	Follow-up Period	Incidence of Anaphylaxis Events/Patients (%)	Incidence of Hypersensitivity Reactions Events/Patients (%)
Exenatide	Rosenstock et al 2013	T-Emerge 2	24 weeks	N/A	3/385 (0.8)
Liraglutide	Pratley et al 2014	HARMONY-7	32 weeks	0/408 (0)	1/408 (0.2)
Albiglutide	Nauck et al 2016	HARMONY-2	52 weeks	0/200 (0)	1/200 (0.5)
	Leiter et al 2014	RCT	52 weeks	0/249 (0)	Angioedema: 1/249 (0.4); Face edema: 1/249 (0.4); Lip swelling: 1/249 (0.4); Exfoliative rash: 0/249 (0)
	Pratley et al 2014	HARMONY-7	32 weeks	0/404 (0)	6/404 (1.5)
	Weissman et al 2014	HARMONY-4	52 weeks	0/504 (0)	0/504 (0)
	Reusch et al 2014	HARMONY-1	52 weeks	0/155 (0)	0/155 (0)
Dulaglutide	Milicevic 2016	9 phase 2 and 3 RCTs	Not specified	6/2213 (0.3)	7/2213 (0.3)
	Umpierrez et al 2014	AWARD-3	52 weeks	N/A	1.5 mg: 0/269 (0); 0.75 mg: 0/270 (0)
	Wysham et al 2014	AWARD-1	52 weeks	N/A	1.5 mg: 0/279 (0) 0.75 mg: 0/280 (0)

6.9.4 Pancreatitis

6.9.4.1 Lixisenatide

An independent Pancreatic Safety Adjudication Committee (PSAC) was established in 2013 to review and assess, in a blinded manner, pancreatic AEs in the ongoing studies at the time (ELIXA and Study EFC12626). In addition, specific cases with high elevations of amylase and/or lipase (>5 x ULN) or confirmed elevations (>3 x ULN) at 2 or more separate visits could be sent for adjudication based on the Investigator's judgment.

The PSAC reviewed and adjudicated the suspected events as pancreatitis ("yes" or "no"), or insufficient documentation for event determination. Events adjudicated as pancreatitis were further categorized as acute pancreatitis, chronic pancreatitis, acute on chronic pancreatitis, or unknown.

As assessed by the PSAC adjudication in Study EFC12626, pancreatitis occurred infrequently. In Study EFC12626, only 1 patient, who was treated with lixisenatide, had an event adjudicated as acute pancreatitis. The event was mild in intensity and resolved in 4 days without complications.

ELIXA

Pancreatitis occurred infrequently in both treatment groups. The percentage of patients with suspected pancreatitis sent for adjudication during the on-treatment period was comparable between lixisenatide and placebo (36 patients [1.2%] vs. 32 patients [1.1%], respectively). Fewer patients in the lixisenatide group had TEAEs of any type of pancreatitis as confirmed by the PSAC (5 [0.2%] patients vs. 8 [0.3%] patients, respectively).

6.9.4.2 iGlarLxi

The same PSAC performed blinded adjudications for iGlarLixi studies. No events were adjudicated as pancreatitis by the PSAC or reported by the investigator using the PT of pancreatitis.

Phase 2 Study ACT12374 was completed before the establishment of the PSAC. Events of pancreatitis were to be reported as TEAEs defined in the HLT of Acute and Chronic Pancreatitis. However, no TEAEs of pancreatitis were reported in Study ACT12374.

6.9.5 Pancreatic cancer and thyroid tumors

6.9.5.1 Lixisenatide

For malignant pancreatic neoplasms, potential events were reviewed and adjudicated by the same PSAC that reviewed and adjudicated potential pancreatitis events. There was no indication of an increased risk of malignant pancreatic neoplasm as adjudicated by the PSAC. In the Phase 2/3

controlled pool, the incidence of adjudicated malignant pancreatic neoplasm was <0.1% (6 patients) for lixisenatide and 0.1% (9 patients) for all comparators.

There was no indication of an increased risk of malignant thyroid neoplasm. In the Phase 2/3 controlled pool, the incidence of thyroid tumors was 0.3% (24 patients) for lixisenatide and 0.2% (14 patients) for all comparators. Papillary thyroid cancer was reported for 1 patient treated with lixisenatide and 2 patients treated with comparators (1 placebo and 1 active comparator). Medullary thyroid cancer with elevated calcitonin values was reported for 1 patient treated with placebo.

Table 57 - Incidence of pancreatic and thyroid cancer in the lixisenatide clinical program: on-treatment and post treatment period (safety population)

		Phase 2/3 controlled pool [b]		ELIXA		Phase 2/3 pool	
		Lixisenatide (N=7354)	All comparators (N=6079)	Lixisenatide (N=3031)	Placebo (N=3032)	IGlarLixi (N=995)	Insulin glargine (N=994)
Adjudicated malignant pancreatic neoplasm [a]	Incidence	6 (<0.1%)	9 (0.1%)	3 (<0.1%)	9 (0.3%)	0	1 (0.1%)
	EAIR per 100 PY	0.05	0.10	-	-	-	-
Thyroid [a]	Incidence	24 (0.3%)	14 (0.2%)	11 (0.4%)	8 (0.3%)	0	0
	EAIR per 100 PY	0.22	0.15	-	-	-	-

a Malignant and unspecified SMQ was used (MedDRA 17.1 SMQ(#20000091) for the analyses.
b Data Pool 2 excluding 2 lixisenatide only studies. All comparators included placebo, exenatide, liraglutide, sitagliptin, and insulin glulisine

There were no clinically relevant differences in laboratory parameters (amylase, lipase, and calcitonin), see Section 6.4.6 (Lixisenatide and ELIXA) and Section 6.8.6 (iGlarLixi).

ELIXA

Malignant pancreatic neoplasm adjudicated by the PSAC occurred infrequently during the combined on-treatment and post-treatment periods. The incidence was lower in the lixisenatide than in the placebo group (3 patients versus 9 patients, respectively).

The incidence of thyroid malignancy during the combined on-treatment and post-treatment periods was balanced between groups, 8 patients for placebo and 11 patients for lixisenatide. No events of thyroid C-cell tumor or hyperplasia were reported in the study.

6.9.5.2 iGlarLixi

In the iGlarLixi program, all events of potential pancreatic neoplasm were sent to the PSAC for blinded prospective adjudication. One patient (0.1%) in the insulin glargine group had a positively adjudicated malignant pancreatic neoplasm that resulted in permanent treatment discontinuation;

the event was not considered related to study drug. There were no observed events of pancreatic neoplasm in Phase 2 Study ACT12374.

There were no thyroid malignancies in the iGlarLixi or lixisenatide treatment groups.

6.9.6 Immunogenicity

6.9.6.1 Lixisenatide

The proportion of ADA positive lixisenatide patients increased from baseline over the first 24 weeks (from 5.1% to 69.6%) and plateaued thereafter, with 71.5% at Week 76 and 70.2% at Week 100 (Table 58). Among these antibody positive patients, approximately 70% had an antidrug antibody concentration below the LLOQ.

Table 58 - Number (%) of patients with positive anti-lixisenatide antibody status by visit in Phase 3 placebo-controlled efficacy/safety studies: Entire Treatment Period (Safety population)

Visit	Lixisenatide (N=2869) N/N1 (%)	Placebo (N=1639) N/N1 (%)
Baseline	129/2515 (5.1%)	52/1484 (3.5%)
Week 2	232/2406 (9.6%)	59/1419 (4.2%)
Week 4	879/2354 (37.3%)	67/1409 (4.8%)
Week 12	101/175 (57.7%)	3/93 (3.2%)
Week 24	1370/1968 (69.6%)	103/1318 (7.8%)
Week 76	913/1277 (71.5%)	29/596 (4.9%)
Week 100	226/322 (70.2%)	3/133 (2.3%)

N = the number of patients in the safety population.
N1 = the number of patients with evaluable anti-lixisenatide antibody status in the safety population at the respective visit.
Data Pool 1: EFC6014, EFC6015, EFC6016, EFC6017, EFC6018, EFC10743, EFC10781, EFC10887, and EFC11321.

In the Phase 3 placebo-controlled study dataset, the overall incidence of TEAEs with lixisenatide was similar in antibody-positive patients (71.2%) and antibody-negative patients (68.8%) during the main treatment period. There was no imbalance in the incidence of common TEAEs, including GI events, when analyzed by antibody status. For injection site reactions, the risk was greater in antibody positive subjects compared to the antibody negative group (4.8% compared to 1.9%, respectively).

Overall, the incidence of AEs adjudicated by the ARAC as allergic reaction was 2.0% in lixisenatide antibody-positive group (at any time during study) and 1.4% in the antibody-negative group in the entire treatment period of the Phase 3 placebo-controlled dataset. Allergic reaction risk was also examined by antibody concentration. For patients with antibody concentrations <LLOQ, 1.3% had an AE adjudicated as an allergic reaction by the ARAC, compared to 2.3% of patients with antibody concentrations ≥LLOQ to ≤100 nmol/L, and 6.7% of patients with concentrations >100 nmol/L. However, there were few patients (n=8/135) with higher concentrations that had allergic reactions.

To evaluate the role of antibody formation and timing of an allergic reaction, an analysis evaluated allergic reaction events and antibody measurements within ± 90 days from the onset date of the allergic reaction. Overall, 39% (18/46) of patients with an allergic reaction were antibody negative and 61% (28/46) of patients with an allergic reaction were antibody positive within 90 days of the event.

Overall, across all lixisenatide subjects, about 70% were antibody positive suggesting that the risk of allergic reaction was unrelated to antibody status.

6.9.6.2 iGlarLixi

The summary and analysis of anti-insulin glargine antibody and anti-lixisenatide antibody data from the Phase 3 study pool are based on the data collected during the on-treatment period for antibody analysis.

In EFC12404, a higher percentage of insulin-naïve patients in the iGlarLixi groups became insulin glargine antibody-positive compared to placebo patients (21.0% vs. 8.9%). In EFC12405, there was no relevant difference between treatment groups (26.2% for iGlarLixi and 24.8% for insulin glargine).

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

The analysis of common on-treatment TEAEs (≥2.0% by High Level Term), allergic events adjudicated as an allergic reaction, and of symptomatic hypoglycemia (plasma glucose ≤70 mg/dL) by anti-insulin and anti-lixisenatide antibody status revealed no substantive differences between antibody-positive and antibody-negative patients treated with iGlarLixi.

6.9.7 Pen-related events: iGlarLixi

Pen-related events were proactively collected in the iGlarLixi program. Pen-related events were defined as any problem the patient had with the pen-injectors used in the study. A specific questionnaire was completed by the Investigator to provide a description of the issue and assess whether this was associated with a clinical event.

Pen-related events occurred across both studies in all treatment groups. None of the pen- related events that occurred during the Phase 3 studies were associated with a clinical event (i.e., hypoglycemia, hyperglycemic event, GI or other AE) (Table 59).

Table 59 - Number (%) of patients with events reported in pen-related event questionnaire during the on-treatment period (iGlarLixi safety population)

	EFC12404 (N=1169)			EFC12405 (N=730)	
	iGlarLixi (N=469)	Insulin glargine (N=467)	Lixisenatide (N=233)	iGlarLixi (N=365)	Insulin glargine (N=365)
Any pen-related event	25 (5.3%)	10 (2.1%)	9 (3.9%)	11 (3.0%)	15 (4.1%)
-Associated with a clinical event	0	0	0	0	0

Clinical event = symptomatic hypoglycemic event, hyperglycemic adverse event or other adverse event collected in pen-related questionnaire.
Note: The on-treatment period is defined as the time from the first injection of open label study drug up to 3 days after the last injection of study drug, regardless of the introduction of rescue therapy.

All events were further categorized as potential device technical issues, pen handling issues, or use of the pen outside its intended dose range. Very few patients (13 in Study EFC12404 and 4 in Study EFC12405) reported events in the third category (use of the pen outside its intended dose range) which was considered specific to the iGlarLixi pens.

To minimize the occurrence of these events, mitigations were subsequently implemented in the design of the commercial pens (compared to the clinical pens) and in the labeling (i.e., Instructions for Use, pen label, and pen package): a mechanical stop was added to prevent users from dialing doses greater than the maximum dose for each pen, and the section of the number sleeve below the intended dose range was printed in reverse colors (i.e., white numbers on a black background).

6.10 POSTMARKETING EXPERIENCE WITH LIXISENATIDE

Sanofi has a robust system for signal detection in the post marketing setting. Reports of AEs such as anaphylaxis, pancreatitis, pancreatic cancer, and thyroid cancer are and will continue to be monitored using this system. Appropriate actions, including changes to the labeling, will be undertaken if needed.

Lixisenatide has been approved since in 2013 in the EU and is currently approved in over 60 countries worldwide. Based on IMS bulk sales data available through 31 March 2015, the estimated worldwide lixisenatide post-marketing exposure to lixisenatide was 40,971 PY.

A search of the Sanofi Pharmacovigilance database was conducted to retrieve AEs reported with lixisenatide treatment. Cumulatively through 07 July 2015, a total of 3,259 spontaneous adverse reactions in 1,507 unique cases were retrieved. There were a cumulative 387 SAEs reported in 156 cases. The 10 most commonly reported spontaneous serious adverse events were: Nausea (23 events), Vomiting (20 events), Hypoglycemia (17 events), Diarrhea (14 events), Pancreatitis and/ or Pancreatitis acute (11 events), Dizziness (8 events), Hypersensitivity (8 events), Abdominal pain (8 events), Decreased appetite (7 events), Urticaria (7 events), and Dyspnea (7 events).

Systemic hypersensitivity reactions, defined as Medical Dictionary of Regulatory Activities (MedDRA) anaphylactic reaction (SMQ Narrow) and angioedema (SMQ Narrow) were reported in a total of 47 cases, with a reporting rate of 11.5 per 10,000 PY.

Pancreatitis defined as MedDRA acute pancreatitis (SMQ Narrow) was reported in 11 cases, with a reporting rate of 2.7 per 10,000 patient-years.

There were no reports of medullary thyroid cancer.

These data revealed no new safety concerns with marketed drug use.

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8 APPENDICES

8.1 SUMMARY OF STUDIES IN THE LIXISENATIDE DEVELOPMENT PROGRAM

Table 60 - Summary of Studies in the Lixisenatide Development Program

Study	Patients randomized	Type of control	Lixisenatide treatment combination	Main objectives
Phase 1				
AVE0010/ 01-016	28	Placebo	Monotherapy	Safety
BEQ11094	90	Uncontrolled	Monotherapy	Pharmacokinetics (bioequivalence)
BDR6864	43	Uncontrolled	Monotherapy	Pharmacokinetics (bioavailability)
BDR12546	15	Uncontrolled	Monotherapy	Pharmacokinetics (bioavailability)
INT6052	25	Placebo	Monotherapy	Pharmacokinetics (drug interaction with oral contraceptive)
INT6863	15	Placebo	Monotherapy	Pharmacokinetics (drug interaction with acetaminophen)
INT10408	16	Uncontrolled	Monotherapy	Pharmacokinetics (drug interaction with warfarin)
INT10409	36	Uncontrolled	Monotherapy	Pharmacokinetics (drug interaction with atorvastatin)
INT10782	30	Uncontrolled	Monotherapy	Pharmacokinetics (drug interaction with ramipril)
INT10783	24	Uncontrolled	Monotherapy	Pharmacokinetics (drug interaction with digoxin)
PDY10433	22	Placebo	Monotherapy	Pharmacodynamics (first- and second phase insulin release in T2DM)
PDY11431	24	Placebo	Monotherapy	Pharmacodynamics (gallbladder motility)
PDY11824	20	Placebo	Monotherapy	Pharmacodynamics (first- and second phase insulin release in healthy subjects)
PDY11941	18	Placebo	Monotherapy	Pharmacodynamics (response to hypoglycemia)
PDY12545	20	Placebo	Monotherapy	Pharmacodynamics (glucose profiles and gastric emptying

Study	Patients randomized	Type of control	Lixisenatide treatment combination	Main objectives
PKD11475	12 pediatric, 12 adults	Placebo	Monotherapy	Pharmacodynamics / Pharmacokinetics (bioavailability)
POP6053	32	No renal impairment	Monotherapy	Pharmacokinetics and safety (renal impairment)
POP11320	22	Uncontrolled	Monotherapy	Pharmacokinetics in Chinese subjects
POP11814	36	Young subjects	Monotherapy	Pharmacokinetics (elderly subjects)
TDR11215	275	Placebo	Monotherapy	Safety (sperm concentration)
TES6865	91	Placebo and active (moxifloxacin)	Monotherapy	Safety (thorough QTc)
TES11807	264	Placebo and active (moxifloxacin)	Monotherapy	Safety (thorough QTc)
DRI6012	542	Placebo	Add-on to metformin	Dose response
ACT6011	65	Placebo	Add-on to SU or metformin or SU+metformin	Pharmacodynamics
PDY6797	120	Placebo	Add-on to SU or SU+metformin	Pharmacokinetics, pharmacodynamics and safety
PDY10931	148	Active (liraglutide)	Add-on to metformin	Pharmacodynamics
PDY12625	142	Active (liraglutide)	Add-on to insulin glargine or insulin glargine+metformin	Pharmacodynamics
Phase 3				
EFC6018	361	Placebo	Monotherapy	Efficacy at 12 weeks and safety
EFC6014	680	Placebo	Add-on to metformin	Efficacy at 24 weeks and safety
EFC10743	484	Placebo	Add-on to metformin	Efficacy at 24 weeks and safety
EFC11321	391	Placebo	Add-on to metformin or metformin+SU	Efficacy at 24 weeks and safety in Asian patients
EFC6015	859	Placebo	Add-on to SU or SU+metformin	Efficacy at 24 weeks and safety
EFC6017	484	Placebo	Add-on to pioglitazone or pioglitazone+metformin	Efficacy at 24 weeks and safety
EFC6016	496	Placebo	Add-on to basal insulin or basal insulin+metformin	Efficacy at 24 weeks and safety
EFC10887	311	Placebo	Add-on to basal insulin or basal insulin+SU	Efficacy at 24 weeks and safety in Asian patients

Study	Patients randomized	Type of control	Lixisenatide treatment combination	Main objectives
EFC10781	446	Placebo	Add-on to insulin glargine and metformin (+/- TZD)	Efficacy at 24 weeks and safety
EFC6019	639	Active (exenatide)	Add-on to metformin	Efficacy at 24 weeks and safety
EFC12626	894	Active (insulin glulisine QD and TID)	Add-on to insulin glargine or insulin glargine+metformin	Efficacy at 26 weeks and safety
EFC12261	451	Active (lixisenatide prior to main meal)	Add-on to metformin	Efficacy and safety relative to timing of the lixisenatide dose
EFC10780	319	Active (sitagliptin)	Add-on to metformin	Efficacy at 24 and safety
EFC11319	6068	Placebo	Add-on to standard of care	Cardiovascular outcomes
LTS10888	69	Uncontrolled	Monotherapy	Safety in Japanese patients

8.2 SUMMARY OF STUDIES IN IGLARLIXI CLINICAL DEVELOPMENT PROGRAM

Table 61 - Summary of studies in the iGlarLixi clinical development program

Study	Number of subjects/patients randomized	Type of control [a]	Population	Ratios of insulin glargine/lixisenatide	Main objective
Phase 1					
BDR10880	43	Controlled by separate injections	T1DM	1.5, 4.0 U/1 µg	PK + PD
BDR11038	16	Controlled by separate injections	T1DM	0.25, 1.3 – 1.9 U/1 µg	PK + PD
BDR11540	24	Lixisenatide-controlled	Healthy	0.25, 0.5 U/1 µg	PK
BDR11578	23	Controlled by separate injections	T1DM	1.7 – 2.8 U/1 µg	PK + PD
BDR12547	16	Uncontrolled	Healthy	0.5, 1.0, 2.0 U/1 µg	PK
PKD12406	20	Lixisenatide-controlled	Healthy	1.0, 2.0, 4.0 U/1 µg	PK
Phase 2					
ACT12374	323	Active-controlled vs. insulin glargine	T2DM uncontrolled on metformin	2 U:1µ g	Efficacy and safety
Phase 3					
EFC12404	1170	Active-controlled vs. insulin glargine and lixisenatide	T2DM uncontrolled on metformin ± 2nd OAD	2 U:1 µg and 3 U:1µg	Efficacy and safety
EFC12405	736	Active-controlled vs. insulin glargine	T2DM uncontrolled on basal insulin ± OAD(s)	2 U:1 µg and 3U:1 µg	Efficacy and safety

PD, pharmacodynamics; PK, pharmacokinetics; T1DM, type 1 diabetes mellitus
a Cross-over design in all Phase 1studies: separate injections of insulin glargine and lixisenatide

8.3 STATISTICAL METHODOLOGY IGLARLIXI

8.3.1 Step-down testing order for key secondary efficacy endpoints

In both pivotal studies, key secondary efficacy endpoints were tested in a hierarchical order as specified in the protocols and statistical analysis plans.

The endpoints in bold were statistically significant for iGlarLixi in each stated comparison within the hierarchical testing order.

Table 62 - Step-down testing of key secondary efficacy endpoints in Studies EFC12404 and EFC12405

Study EFC12404	Study EFC12405 (all tests compared iGlarLixi to insulin glargine)
Change in 2hr-PPG excursion vs. insulin glargine	**Change in 2hr-PPG excursion**
Change in body weight vs. insulin glargine	**Change in body weight**
Change in FPG vs. lixisenatide	**Change in daily average 7-point SMPG**
Change in daily average 7-point SMPG vs. lixisenatide	**HbA1c <7.0% and no body weight gain**
HbA1c <7.0% and no body weight gain vs insulin glargine	Change in daily insulin dose at Week 30
HbA1c superiority of iGlarLixi vs. insulin glargine	HbA1c <7.0%, no body weight gain, and no documented symptomatic hypoglycemia*
Change in daily average 7-point SMPG vs. insulin glargine	Change in FPG
HbA1c <7.0%, no body weight gain, and no documented symptomatic hypoglycemia* vs. insulin glargine	
Daily insulin dose at Week 30 vs. insulin glargine	
Change in FPG vs. insulin glargine	

All changes were measured from baseline to Week 30.
*Symptomatic hypoglycemia with plasma glucose ≤70 mg/dL
FPG=fasting plasma glucose; PPG=postprandial plasma glucose; SMPG=self-monitored plasma glucose

8.3.2 Robustness of efficacy findings

Sensitivity analyses to assess the effect of dose-capping the insulin glargine comparator at a daily dose of 60 U were performed. A "tipping point" analysis estimated the additional HbA1c benefit that would have been needed in the insulin glargine comparator group in order to make the treatment differences in HbA1c change from baseline no longer statistically significant.

This analysis evaluates the potential impact on the treatment effect if insulin glargine comparator doses >60 U had been allowed.

- Tipping point analysis: –Δ (delta) was added to the observed post baseline HbA1c values for those patients in the glargine arm who had reached a 60 U dose of insulin glargine at the end of the study. The primary MMRM analyses were then conducted to find the largest Δ* that would make the treatment difference between iGlarLixi and insulin glargine statistically not significant.

Table 63 – Study EFC12404: Sensitivity analysis - mean change in HbA1c from baseline to Week 30 using MMRM assuming additional HbA1c reduction for insulin glargine patients with final insulin dose of 60 U (mITT population)

	iGlarLixi versus insulin glargine		
Additional HbA1c reduction (%)[a]	**LS Mean Difference (SE)[b]**	**95% CI[b]**	**P-value[b]**

Additional HbA1c reduction (%)[a]	iGlarLixi versus insulin glargine		
	LS Mean Difference (SE)[b]	95% CI[b]	P-value[b]
0.0	-0.2887 (0.04832)	(-0.384, -0.194)	<.0001
-0.1	-0.2687 (0.04822)	(-0.363, -0.174)	<.0001
-0.2	-0.2487 (0.04817)	(-0.343, -0.154)	<.0001
-0.3	-0.2286 (0.04818)	(-0.323, -0.134)	<.0001
-0.4	-0.2085 (0.04826)	(-0.303, -0.114)	<.0001
-0.5	-0.1885 (0.04839)	(-0.283, -0.094)	0.0001
-0.6	-0.1684 (0.04858)	(-0.264, -0.073)	0.0005
-0.7	-0.1484 (0.04883)	(-0.244, -0.053)	0.0024
-0.8	-0.1283 (0.04914)	(-0.225, -0.032)	0.0091
-0.9	-0.1083 (0.04950)	(-0.205, -0.011)	0.0289
-1.0	-0.0882 (0.04991)	(-0.186, 0.010)	0.0773

a Additional HbA1c reduction added to each post-baseline scheduled visit for insulin glargine patients with final insulin dose of 60 U.

b Mixed-effect model with repeated measures (MMRM) with treatment groups (fixed ratio combination, insulin glargine alone, lixisenatide alone), randomization strata of HbA1c (<8.0%, ≥ 8.0%) at Visit 4 (Week -1), randomization strata of second OAD use at screening (Yes, No), visit (Week 8, 12, 24, and 30), treatment-by-visit interaction, and country as fixed effects, and baseline HbA1c value-by-visit interaction as a covariate.

Countries with fewer than 5 randomized patients were grouped with the country with the lowest number of randomized patients that is 5 or more.

The analysis included all scheduled measurements obtained during the study, including those obtained after study drug discontinuation or introduction of rescue therapy.

Included are patients who have measurements at baseline and post-baseline.

Table 64 – Study EFC12405: Sensitivity analysis - mean change in HbA1c from baseline to Week 30 using MMRM assuming additional HbA1c reduction for insulin glargine patients with final insulin dose of 60 U (mITT population)

	iGlarLixi versus insulin glargine		
Additional HbA1c reduction (%)[a]	LS Mean Difference (SE)[b]	95% CI[b]	P-value[b]
0.0	-0.5151 (0.06026)	(-0.633, -0.397)	<.0001
-0.1	-0.4832 (0.06013)	(-0.601, -0.365)	<.0001
-0.2	-0.4512 (0.06011)	(-0.569, -0.333)	<.0001
-0.3	-0.4192 (0.06018)	(-0.537, -0.301)	<.0001
-0.4	-0.3872 (0.06036)	(-0.506, -0.269)	<.0001
-0.5	-0.3552 (0.06063)	(-0.474, -0.236)	<.0001
-0.6	-0.3231 (0.06101)	(-0.443, -0.203)	<.0001
-0.7	-0.2910 (0.06148)	(-0.412, -0.170)	<.0001
-0.8	-0.2590 (0.06205)	(-0.381, -0.137)	<.0001
-0.9	-0.2269 (0.06271)	(-0.350, -0.104)	0.0003
-1.0	-0.1948 (0.06346)	(-0.319, -0.070)	0.0022

a Additional HbA1c reduction added to each post-baseline scheduled visit for insulin glargine patients with final insulin dose of 60 U.

b Mixed-effect model with repeated measures (MMRM) with treatment groups (fixed ratio combination and insulin glargine), randomization strata of HbA1c (<8.0%, ≥ 8.0%) at Visit 5 (Week -1), randomization strata of metformin use at screening (Yes, No), visit (Week 8, 12, 24, and 30), treatment-by-visit interaction, and country as fixed effects, and baseline HbA1c value-by-visit interaction as covariates.

Countries with fewer than 5 randomized patients were grouped with the country with the lowest number of randomized patients that is 5 or more.

The analysis included all scheduled measurements obtained during the study, including those obtained after study drug discontinuation or introduction of rescue therapy.

Included are patients who have measurements at baseline and post-baseline.

8.3.3 Patient disposition for the primary analysis of HbA1c

Table 65 - iGlarLixi: Patient disposition of the primary endpoint of HbA1c change from baseline at Week 30 versus mITT population in 2 Phase 3 studies

Phase 3 study	Randomized	mITT	Patients without post-baseline HbA1c[a]	Patients with post-baseline HbA1c but no HbA1c at Week 30[b]	Patients included in the primary MMRM analysis of HbA1c[c]
EFC12404					
iGlarLixi	469	468	1 (0.2%)	24 (5.1%)	467 (99.8%)
Insulin glargine	467	466	2 (0.4%)	18 (3.9%)	464 (99.6%)
Lixisenatide	234	233	0	12 (5.2%)	233 (100.0%)
EFC12405					
iGlarLixi	367	366	2 (0.5%)	18 (4.9%)	364 (99.5%)
Insulin glargine	369	365	1 (0.3%)	9 (2.5%)	364 (99.7%)

MMRM = Mixed-effect model with repeated measures.
[a]Patients did not have any post-baseline HbA1c data in the mITT population.
[b] Patients had a post-baseline HbA1c data but did not have the HbA1c value at the primary time point in the mITT population.
[c] The primary efficacy analysis method was MMRM using all post-baseline HbA1c data at scheduled visits regardless of treatment discontinuation or initiation of rescue therapy.
Percentages are calculated using the number of mITT patients as denominator. The mITT population is defined as randomized patients with at least one post-baseline primary or secondary efficacy measurement.

8.3.4 Summaries of primary and sensitivity analyses for Phase 3 studies

Sensitivity analyses were performed for the primary efficacy endpoint to investigate the potential impact of rescue medication and missing data and include:

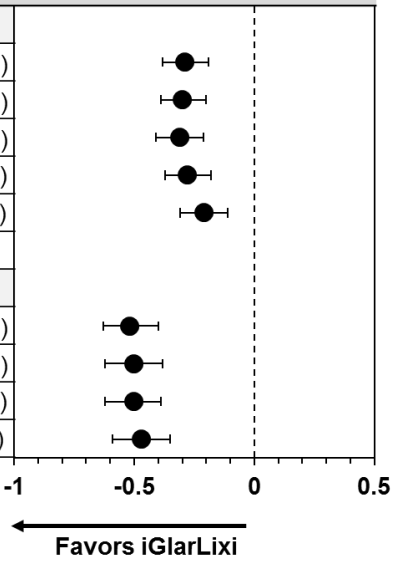
- MMRM under the MAR assumption using post baseline observations before being rescued in the mITT population in order to assess the impact of rescue therapy
- Pattern-mixture model that multiply imputed missing HbA1c values based on the observed data from discontinued patents in the same treatment group and the same randomization strata for missing data that occurred after study treatment discontinuation (MNAR) in the mITT population. Missing data that occurred while on-treatment were multiply imputed under MAR, as patients would still benefit from the study treatment. This was done in Study EFC12404 only, as there was insufficient data to build a reliable model in Study EFF12405.
- Pattern-mixture model that multiply imputed missing HbA1c values in the iGlarLixi group based on their baseline values and parameters from the imputation model for the control (insulin glargine) group plus an error (e.g., jump to control; imputation in the iGlarLixi under MNAR). Missing data in the control group were multiply imputed under MAR using control data in the mITT population.

- Pattern-mixture model with BOCF-like multiple imputation that multiply imputed missing HbA1c values in the iGlarLixi group based on distributions of the baseline HbA1c (imputation in the iGlarLixi group under MNAR). Missing data in the control group were multiply imputed under MAR using control data in the mITT population.
- Tipping point analysis that multiply imputed missing HbA1c values with a delta adjustment in the iGlarLixi group. Missing HbA1c values at each post-baseline visit were imputed under the MAR assumption and an additional HbA1c increase (delta) was added to each imputed value in the iGlarLixi group in the mITT population. The tipping point analysis was performed to find the change in HbA1c needed for patients in the iGlarLixi group with missing Week 30 values that would tip the results to not statistically significant in the mITT population.

The results of the sensitivity analyses are consistent with the primary endpoint in both studies (Figure 58 and Figure 57). In study EFC12404, an additional HbA1c increase of 3.6% to each imputed value in the iGlarLixi group was required to tip the results to lose statistical significance for the insulin glargine vs iGlarLixi comparison. In study EFC12405 for the iGlarLixi vs insulin glargine comparison and in EFC12404 for the iGlarLixi vs Lixisenatide comparison, results remained statistically significant with even very conservative imputations adding an additional HbA1c increase of 4% (Table 66 and Table 67).

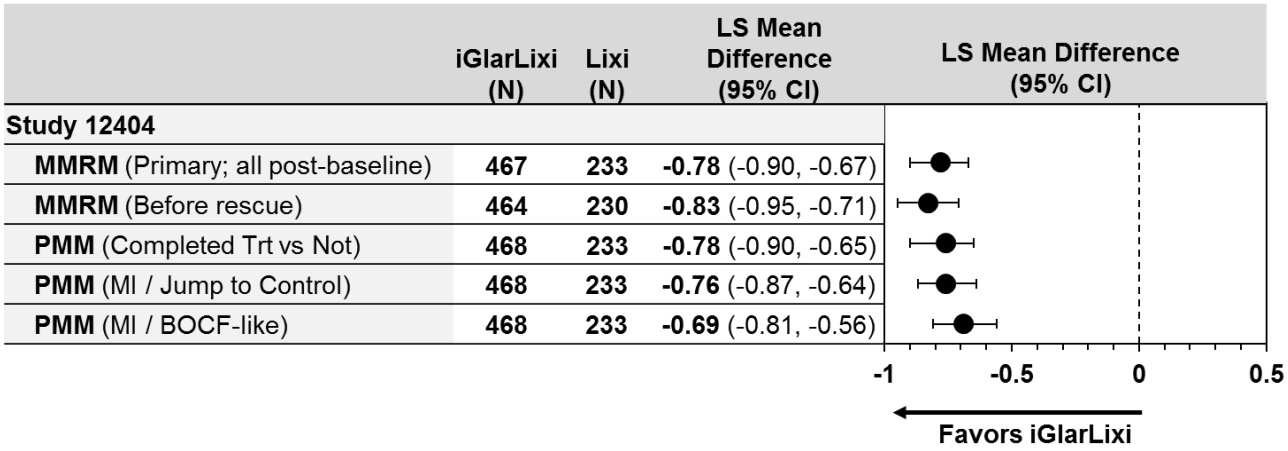
Figure 57 - iGlarLixi sensitivity analysis of primary endpoint (iGlarLixi versus insulin glargine)

	iGlarLixi (N)	Lantus (N)	LS Mean Difference (95% CI)
Study 12404			
MMRM (Primary; all post-baseline)	**467**	**464**	**-0.29** (-0.38, -0.19)
MMRM (Before rescue)	**464**	**459**	**-0.30** (-0.39, -0.20)
PMM (Completed Trt vs Not)	**468**	**466**	**-0.31** (-0.41, -0.21)
PMM (MI / Jump to Control)	**468**	**466**	**-0.28** (-0.37, -0.18)
PMM (MI / BOCF-like)	**468**	**466**	**-0.21** (-0.31, -0.11)
Study 12405			
MMRM (Primary; all post-baseline)	**364**	**364**	**-0.52** (-0.63, -0.40)
MMRM (Before rescue)	**362**	**360**	**-0.50** (-0.62, -0.38)
PMM (MI / Jump to Control)	**366**	**365**	**-0.50** (-0.62, -0.39)
PMM (BOCF-like)	**366**	**365**	**-0.47**(-0.59, -0.35)



MMRM: mixed-effect model with repeated measures, PMM: pattern-mixture model, MI: multiple imputation, BOCF: baseline observation carried forward, mITT: modified intent-to-treat

Figure 58 - iGlarLixi sensitivity analysis of primary endpoint (iGlarLixi versus lixisenatide)



MMRM: mixed-effect model with repeated measures, PMM: pattern-mixture model, MI: multiple imputation, BOCF: baseline observation carried forward, mITT: modified intent-to-treat

Table 66 – iGlarLixi sensitivity analysis of primary endpoint – an additional HbA1c increase (delta adjustment) to each imputed value in the iGlarLixi group: iGlarLixi versus insulin glargine (mITT population)

	Study (iGlarLixi versus insulin glargine)			
	EFC12404		EFC12405	
HbA1c increase (%)[a]	LS Mean Difference (95% CI)[b]	P-value[b]	LS Mean Difference (95% CI)[b]	P-value[b]
0	-0.2885 (-0.383, -0.194)	<.0001	-0.5158(-0.634, -0.398)	<.0001
0.4	-0.2677(-0.363, -0.172)	<.0001	-0.4942 (-0.613, -0.376)	<.0001
0.8	-0.2470 (-0.344, -0.151)	<.0001	-0.4725 (-0.592, -0.353)	<.0001
1.2	-0.2264 (-0.324, -0.128)	<.0001	-0.4507 (-0.573, -0.329)	<.0001
1.6	-0.2058 (-0.306, -0.106)	<.0001	-0.4289 (-0.554, -0.304)	<.0001
2	-0.1853 (-0.288, -0.083)	0.0004	-0.4070 (-0.535, -0.279)	<.0001
2.4	-0.1648 (-0.270, -0.059)	0.0022	-0.3851 (-0.517, -0.253)	<.0001
2.8	-0.1443 (-0.253, -0.035)	0.0095	-0.3631 (-0.500, -0.226)	<.0001
3.2	-0.1239 (-0.237, -0.011)	0.0312	-0.3411 (-0.483, -0.199)	<.0001
3.6	-0.1035 (-0.220, 0.013)	**0.0824**	-0.3191 (-0.466, -0.172)	<.0001
4	-0.0832 (-0.204, 0.038)	**0.1786**	-0.2970 (-0.450, -0.144)	0.0001

a Missing HbA1c values at each post-baseline scheduled visits up to Week 30 were multiply imputed assuming MAR 100 times to generate 100 datasets with complete HbA1c values. Additional HbA1c increases (delta) were added to each imputed value for patients in the iGlarLixi group.

b The completed datasets were analyzed using Mixed-effect model with repeated measures (MMRM) with treatment groups, randomization strata, treatment-by-visit interaction, and country as fixed effects, and baseline HbA1c value-by-visit interaction as a covariate. The results from the 100 analyses were combined.

The analysis included all measurements obtained during the study in the mITT population, including those obtained after IMP discontinuation or introduction of rescue therapy.

Table 67 – iGlarLixi sensitivity analysis of primary endpoint – an additional HbA1c increase (delta adjustment) to each imputed value in the iGlarLixi group: iGlarLixi versus lixisenatide (mITT population)

	Study 404 (iGlarLixi versus Lixisenatide)	
HbA1c increase (%)[a]	LS Mean Difference (95% CI)[b]	P-value[b]
0	-0.7788 (-0.895, -0.662)	<.0001
0.4	-0.7579 (-0.875, -0.641)	<.0001
0.8	-0.7372 (-0.856, -0.619)	<.0001
1.2	-0.7164 (-0.837, -0.596)	<.0001
1.6	-0.6958 (-0.819, -0.573)	<.0001
2	-0.6752 (-0.801, -0.549)	<.0001
2.4	-0.6546 (-0.784, -0.525)	<.0001
2.8	-0.6341 (-0.768, -0.500)	<.0001
3.2	-0.6136 (-0.752, -0.475)	<.0001
3.6	-0.5932 (-0.736, -0.450)	<.0001
4	-0.5727 (-0.721, -0.424)	<.0001

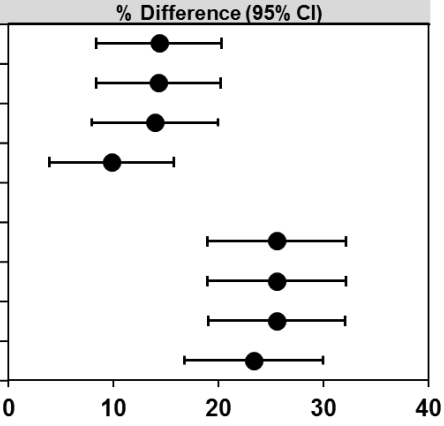
a Missing HbA1c values at each post-baseline scheduled visits up to Week 30 were multiply imputed assuming MAR 100 times to generate 100 datasets with complete HbA1c values. Additional HbA1c increases (delta) were added to each imputed value for patients in the iGlarLixi group.
b The completed datasets were analyzed using Mixed-effect model with repeated measures (MMRM) with treatment groups, randomization strata, treatment-by-visit interaction, and country as fixed effects, and baseline HbA1c value-by-visit interaction as a covariate. The results from the 100 analyses were combined.
The analysis included all measurements obtained during the study in the mITT population, including those obtained after IMP discontinuation or introduction of rescue therapy

The following sensitivity analyses were performed for the responder analysis of HbA1c <7% to investigate the potential impact of rescue medication and missing data:

- Missing + rescue as non-responders (NR) in mITT: patients with missing HbA1c data at Week 30 or initiation of rescue therapy prior to Week 30 were non-responders in the mITT population
- Missing as NR in ITT: responder analysis including all randomized patients (non-responder imputation used for missing data) to ensure no bias was introduced by using the mITT population instead of the true ITT population
- Worst case scenario in mITT: patients who were rescued were non-responders. Patients who discontinued treatment with missing Week 30 data were non-responders in the iGlarLixi group and responders in the control group in the mITT population.

Figure 59 – iGlarLixi: Results of primary and sensitivity analyses for HbA1c responders <7.0% at Week 30 (iGlarLixi versus insulin glargine)

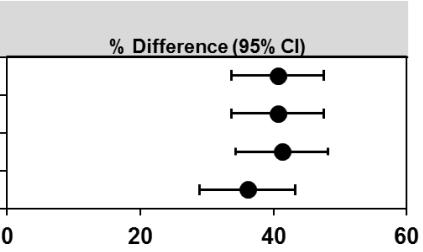
Study	Statistical Analysis	iGlarLixi (%)	Lantus (%)
Study 12404	Primary (Missing as NR in mITT)	73.7%	59.4%
	Missing as NR in ITT	73.6%	59.3%
	Missing + Rescue as NR in mITT	72.2%	58.4%
	Worst Case Scenario in mITT[1]	72.2%	62.4%
Study 12405	Primary (Missing as NR in mITT)	54.9%	29.6%
	Missing as NR in ITT	54.8%	29.3%
	Missing + Rescue as NR in mITT	54.1%	28.8%
	Worst Case Scenario in mITT[1]	54.1%	31.0%



1 Data after initiation of rescue was treated as non-responders. In patients without rescue therapy, missing data due to treatment discontinuation were treated as responders in the control group (Lantus) but as non-responders in the iGlarLixi group.
NR: non-responders, mITT: modified intent-to-treat

Figure 60 – Results of primary and sensitivity analyses for HbA1c responders <7.0% at Week 30 (iGlarLixi versus lixisenatide)

Study	Statistical Analysis	iGlarLixi (%)	Lixi (%)
Study 12404	Primary (Missing as NR in mITT)	73.7%	33.0%
	Missing as NR in ITT	73.6%	32.9%
	Missing + Rescue as NR in mITT	72.2%	30.9%
	Worst Case Scenario in mITT[1]	72.2%	36.1%



1 Data after initiation of rescue was treated as non-responders. In patients without rescue therapy, missing data due to treatment discontinuation were treated as responders in the control group (Lixisenatide) but as non-responders in the iGlarLixi group.
NR: non-responders, mITT: modified intent-to-treat

8.4 STATISTICAL METHODOLOGY LIXISENATIDE

8.4.1 Patient Disposition by Study in 9 Phase 3 placebo-controlled studies

Table 68 – Patient disposition to the primary efficacy time point (main treatment period) in 9 Phase 3 placebo-controlled studies (randomized population)

Background therapy	Phase 3 study	Randomized	mITT	Completed main treatment period	Discontinued during main treatment period[a]
Monotherapy	EFC6018				
	Placebo	122	121 (99.2%)	113 (92.6%)	9 (7.4%)
	Lixisenatide 2-step dose increase	120	120 (100.0%)	110 (91.7%)	10 (8.3%)
	Lixisenatide 1-step dose increase	119	118 (99.2%)	108 (90.8%)	11 (9.2%)
Add-on Met alone	EFC6014				
	Placebo	170	170 (100.0%)	158 (92.9%)	12 (7.1%)
	Lixisenatide morning	255	255 (100.0%)	233 (91.4%)	22 (8.6%)
	Lixisenatide evening	255	255 (100.0%)	224 (87.8%)	31 (12.2%)
	EFC10743				
	Placebo	162	159 (98.1%)	151 (93.2%)	11 (6.8%)
	Lixisenatide 2-step dose increase	161	160 (99.4%)	144 (89.4%)	17 (10.6%)
	Lixisenatide 1-step dose increase	161	160 (99.4%)	147 (91.3%)	14 (8.7%)
Add-on SU or SU+Met	EFC6015				
	Placebo	286	286 (100.0%)	255 (89.2%)	31 (10.8%)
	Lixisenatide	573	570 (99.5%)	499 (87.1%)	74 (12.9%)
Add-on Pio or Pio+Met	EFC6017				
	Placebo	161	159 (98.8%)	137 (85.1%)	24 (14.9%)
	Lixisenatide	323	320 (99.1%)	288 (89.2%)	35 (10.8%)
Add-on Met or Met+SU	EFC11321				
	Placebo	195	193 (99.0%)	184 (94.4%)	11 (5.6%)
	Lixisenatide	196	195 (99.5%)	179 (91.3%)	17 (8.7%)
Add-on BI or BI+Met	EFC6016				
	Placebo	167	166 (99.4%)	147 (88.0%)	20 (12.0%)
	Lixisenatide	329	327 (99.4%)	275 (83.6%)	54 (16.4%)
Add-on BI or BI+SU	EFC10887				

Background therapy	Phase 3 study	Randomized	mITT	Completed main treatment period	Discontinued during main treatment period[a]
Add-on IG+Met or IG+Met+TZD	Placebo	157	157 (100.0%)	144 (91.7%)	13 (8.3%)
	Lixisenatide	154	154 (100.0%)	133 (86.4%)	21 (13.6%)
	EFC10781				
	Placebo	223	223 (100.0%)	211 (94.6%)	12 (5.4%)
	Lixisenatide	223	223 (100.0%)	194 (87.0%)	29 (13.0%)

Met = Metformin, SU = Sulfonylurea, Pio = Pioglitazone, BI = Basal insulin, IG = Insulin glargine, TZD = Thiazolidinediones.
a Also includes randomized but not exposed patients. Primary Time point (main treatment period): 24 weeks for all studies except EFC6018 (12 weeks). Percentages are calculated using the number of randomized patients as denominator. The mITT population is defined as randomized and exposed patients with at least one post-baseline efficacy primary or secondary measurement.

Table 69 – Patient disposition for the entire treatment period in 5 Phase 3 placebo-controlled studies with long-term treatment of at least 76 weeks (randomized population)

Background therapy	Phase 3 study	Randomized	mITT	Completed entire treatment period	Discontinued during entire treatment period[a]
Add-on Met alone	EFC6014				
	Placebo	170	170 (100.0%)	128 (75.3%)	42 (24.7%)
	Lixisenatide morning	255	255 (100.0%)	198 (77.6%)	57 (22.4%)
	Lixisenatide evening	255	255 (100.0%)	185 (72.5%)	70 (27.5%)
	EFC10743				
	Placebo	162	159 (98.1%)	127 (78.4%)	35 (21.6%)
	Lixisenatide 2-step dose increase	161	160 (99.4%)	121 (75.2%)	40 (24.8%)
	Lixisenatide 1-step dose increase	161	160 (99.4%)	131 (81.4%)	30 (18.6%)
Add-on SU or SU+Met	EFC6015				
	Placebo	286	286 (100.0%)	204 (71.3%)	82 (28.7%)
	Lixisenatide	573	570 (99.5%)	396 (69.1%)	177 (30.9%)
Add-on Pio or Pio+Met	EFC6017				
	Placebo	161	159 (98.8%)	109 (67.7%)	52 (32.3%)
	Lixisenatide	323	320 (99.1%)	239 (74.0%)	84 (26.0%)
Add-on BI or BI+Met	EFC6016				
	Placebo	167	166 (99.4%)	115 (68.9%)	52 (31.1%)
	Lixisenatide	329	327 (99.4%)	213 (64.7%)	116 (35.3%)

Met = Metformin, SU = Sulfonylurea, Pio = Pioglitazone, BI = Basal insulin, IG = Insulin glargine, TZD = Thiazolidinediones.
a Also includes randomized but not exposed patients. Percentages are calculated using the number of randomized patients as denominator. The mITT population is defined as randomized and exposed patients with at least one post-baseline efficacy primary or secondary measurement.

8.4.2 Patient Disposition for the Primary Analysis of HbA1c Change at Week 24 (Week 12 for EFC6018 and Week 26 for EFC12626)

Table 70 – Patient disposition of the primary endpoint of HbA1c change from baseline at Week 24 versus mITT Population in 9 Phase 3 Placebo-Controlled Studies

Background therapy	Phase 3 study	Randomized	mITT	Patients without post-baseline HbA1c[a]	Patients with post-baseline HbA1c but no HbA1c at Week 24[b,c]	Received rescue therapy prior to Week 24[b]	Patients included in the primary HbA1c analysis at Week 24[b,d]
Monotherapy	EFC6018						
	Placebo	122	121	5 (4.1%)	6 (4.9%)	3 (2.5%)	112 (92.6%)
	Lixisenatide 2-step dose increase	120	120	2 (1.7%)	11 (9.2%)	2 (1.7%)	113 (94.2%)
	Lixisenatide 1-step dose increase	119	118	0	11 (9.3%)	1 (0.8%)	114 (96.6%)
Add-on Met alone	EFC6014						
	Placebo	170	170	2 (1.2%)	13 (7.6%)	18 (10.6%)	164 (96.5%)
	Lixisenatide morning	255	255	4 (1.6%)	18 (7.1%)	7 (2.7%)	244 (95.7%)
	Lixisenatide evening	255	255	4 (1.6%)	24 (9.4%)	10 (3.9%)	239 (93.7%)
	EFC10743						
	Placebo	162	159	1 (0.6%)	5 (3.1%)	7 (4.4%)	158 (99.4%)
	Lixisenatide 2-step dose increase	161	160	2 (1.3%)	12 (7.5%)	5 (3.1%)	152 (95.0%)
	Lixisenatide 1-step dose increase	161	160	0	17 (10.6%)	2 (1.3%)	156 (97.5%)
Add-on SU or SU+Met	EFC6015						
	Placebo	286	286	3 (1.0%)	33 (11.5%)	36 (12.6%)	274 (95.8%)
	Lixisenatide	573	570	9 (1.6%)	63 (11.1%)	23 (4.0%)	544 (95.4%)

Background therapy	Phase 3 study	Randomized	mITT	Patients without post-baseline HbA1c[a]	Patients with post-baseline HbA1c but no HbA1c at Week 24[b,c]	Received rescue therapy prior to Week 24[b]	Patients included in the primary HbA1c analysis at Week 24[b,d]
Add-on Pio or Pio+Met	EFC6017						
	Placebo	161	159	1 (0.6%)	16 (10.1%)	18 (11.3%)	148 (93.1%)
	Lixisenatide	323	320	4 (1.3%)	23 (7.2%)	12 (3.8%)	308 (96.3%)
Add-on Met or Met+SU	EFC11321						
	Placebo	195	193	2 (1.0%)	7 (3.6%)	13 (6.7%)	188 (97.4%)
	Lixisenatide	196	195	2 (1.0%)	11 (5.6%)	7 (3.6%)	185 (94.9%)
Add-on BI or BI+Met	EFC6016						
	Placebo	167	166	2 (1.2%)	19 (11.4%)	12 (7.2%)	158 (95.2%)
	Lixisenatide	329	327	6 (1.8%)	46 (14.1%)	19 (5.8%)	304 (93.0%)
Add-on BI or BI+SU	EFC10887						
	Placebo	157	157	1 (0.6%)	9 (5.7%)	5 (3.2%)	154 (98.1%)
	Lixisenatide	154	154	1 (0.6%)	12 (7.8%)	2 (1.3%)	146 (94.8%)
Add-on IG+Met or IG+Met+TZD	EFC10781						
	Placebo	223	223	2 (0.9%)	8 (3.6%)	1 (0.4%)	221 (99.1%)
	Lixisenatide	223	223	4 (1.8%)	15 (6.7%)	1 (0.4%)	215 (96.4%)

Met = Metformin, SU = Sulfonylurea, Pio = Pioglitazone, BI = Basal insulin, IG = Insulin glargine, TZD = Thiazolidinediones.
a Patients did not have any post-baseline HbA1c data in the mITT population.
b Primary time point (main treatment period) at Week 24 for all studies except EFC6018 (Week 12) and EFC12626 (Week 26).
c Patients had a post-baseline HbA1c data but did not have the HbA1c value at the primary time point in the mITT population.
d For the primary analysis, last observation carried forward was pre-specified and used. Data collected after initiation of rescue therapy or beyond the on-treatment period were not used and imputed using the last on-treatment, pre-rescue observation carried forward.
The mITT population is defined as randomized and exposed patients with at least one post-baseline primary or secondary efficacy measurement.
Percentages are calculated using the number of mITT patients as denominator. The mITT population is defined as randomized and exposed patients with at least one post-baseline primary or secondary efficacy measurement.

Table 71 – Patient disposition of the primary endpoint of HbA1c change from baseline at Week 26 versus mITT population in Study EFC12626

Background therapy	Phase 3 study	Randomized	mITT	Patients without post-baseline HbA1c[a]	Patients with post-baseline HbA1c but no HbA1c at Week 26[b]	Patients included in the primary HbA1c analysis at Week 26[c]
Add-on IG or IG+Met	EFC12626					
	Lixisenatide	298	297	4 (1.3%)	30 (10.1%)	292 (98.3%)
	Insulin glulisine QD	298	298	3 (1.0%)	20 (6.7%)	292 (98.0%)
	Insulin glulisine TID	298	295	0	12 (4.1%)	295 (100.0%)

a Patients did not have any post-baseline HbA1c data in the mITT population.
b Patients had a post-baseline HbA1c data but did not have the HbA1c value at Week 26 in the mITT population.
c For the primary analysis, last observation carried forward was pre-specified and used. Data collected after initiation of rescue therapy or beyond the on-treatment period were not used and imputed using the last on-treatment, pre-rescue observation carried forward.
Percentages are calculated using the number of mITT patients as denominator. The mITT population is defined as randomized and exposed patients with at least one post-baseline primary or secondary efficacy measurement.
No rescue therapy was planned for EFC12626, instead discontinuation was recommended if HbA1c value was above 8.5% at Week 12 or later on, and if appropriate corrective action failed and the repeated HbA1c 4 weeks later remained above 8.5%.

8.4.3 Sensitivity Analyses in 9 Phase 3 Placebo-Controlled Studies

HbA1c change from baseline to Week 24 (Week 12 for EFC6018, monotherapy study)

Multiple sensitivity analyses that differently handled missing data or data obtained after initiation of rescue therapy evaluated the robustness of the findings for primary efficacy endpoint of HbA1c change from baseline. They include the following analyses:

- MMRM ITT using all post-baseline observations including those after treatment discontinuation or initiation of rescue therapy in the mITT population
- Pattern-mixture model that multiply imputed missing HbA1c values in the lixisenatide group based on their baseline values and parameters from the imputation model for the placebo group plus an error (e.g. jump to placebo; imputation in the lixisenatide group under MNAR). Missing data in the placebo group was multiply imputed under MAR using placebo data in the randomized and exposed population
- Pattern-mixture model with BOCF-like multiple imputation that multiply imputed missing HbA1c values in the lixisenatide group based on distributions of the baseline HbA1c (imputation in the lixisenatide group under MNAR). Missing data in the placebo group were multiply imputed under MAR using placebo data in the mITT population
- Tipping point analysis that multiply imputed missing HbA1c values with a delta adjustment in the lixisenatide group. Missing HbA1c values at each post-baseline visit were imputed under the MAR assumption and an additional HbA1c increase (delta) was added to each imputed value in the lixisenatide group in the mITT population. The tipping point analysis was performed to find the change in HbA1c needed for patients in the lixisenatide group with missing Week 24 values that would tip the results to not statistically significant in the mITT population

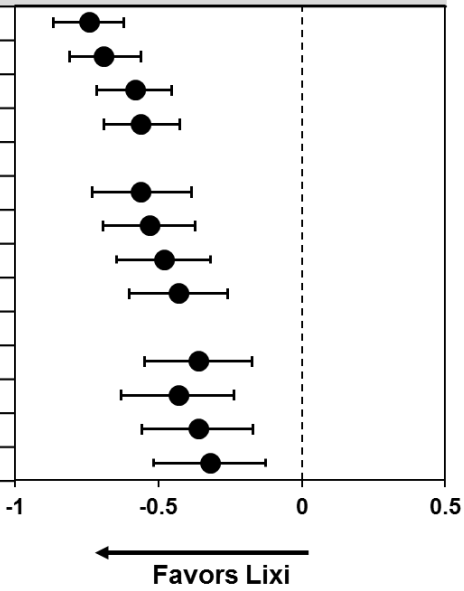
The sensitivity analyses showed consistent results, demonstrating superiority over placebo and confirming the efficacy of lixisenatide.

Of these 9 studies, results of the primary and the above sensitivity analyses are summarized in 3 studies (EFC6015, EFC6017 and EFC6016) that have a higher percentage of patients with missing HbA1c data at Week 24 (Figure 61 and Table 72).

In the tipping point analysis, a delta adjustment (HbA1c increase) of 3.6%, 1.2% and 2.8% in Studies EFC6015, EFC6016 and EFC6017, respectively, to each imputed value in the lixisenatide group was required to tip the results to lose statistical significance for the treatment difference (Table 72).

Figure 61 – Primary and Sensitivity Analyses of HbA1c Change from Baseline to Week 24

Study	Statistical Analysis	LS Mean Difference (95% CI)
Add-on SU or SU+Met *Lixi vs PBO* EFC6015	**ANCOVA LOCF** *(On-treatment / Primary)*	-0.74 (-0.87, -0.62)
	MMRM *(all post-baseline data)*	-0.69 (-0.81, -0.56)
	PMM *(MI / jump to Placebo)*	-0.58 (-0.72, -0.45)
	PMM *(MI / BOCF-like)*	-0.56 (-0.69, -0.43)
Add-on Pio or Pio+Met *Lixi vs PBO* EFC6017	**ANCOVA LOCF** *(On-treatment / Primary)*	-0.56 (-0.73, -0.39)
	MMRM *(all post-baseline data)*	-0.53 (-0.69, -0.37)
	PMM *(MI / jump to Placebo)*	-0.48 (-0.65, -0.32)
	PMM *(MI / BOCF-like)*	-0.43 (-0.60, -0.26)
Add-on BI or BI+Met *Lixi vs PBO* EFC6016	**ANCOVA LOCF** *(On-treatment / Primary)*	-0.36 (-0.55, -0.17)
	MMRM *(all post-baseline data)*	-0.43 (-0.63, -0.24)
	PMM *(MI / jump Placebo)*	-0.36 (-0.56, -0.17)
	PMM *(MI / BOCF-like)*	-0.32 (-0.52, -0.13)



LOCF: last observation carried forward, MMRM: mixed-effect model with repeated measures, PMM: pattern-mixture model, MI: multiple imputation, BOCF: baseline observation carried forward, Lixi: Lixisenatide, PBO: Placebo, BI: basal insulin, MET: metformin, SU: sulfonylurea, PIO: pioglitazone

Table 72 – Lixisenatide sensitivity (tipping point) analysis of HbA1c change from baseline to Week 24 – an additional HbA1c to each imputed value in the lixisenatide group) – mITT population

	Study					
	EFC6015		EFC6016		EFC6017	
HbA1c increase (%)[a]	LS Mean (95% CI)[b]	P-value[b]	LS Mean Difference (95% CI)[b]	P-value[b]	LS Mean Difference (95% CI)[b]	P-value[b]
0	-0.6885(-0.816, -0.561)	<.0001	-0.434(-0.634, -0.234)	<.0001	-0.5048(-0.666, -0.343)	<.0001
0.4	-0.6313(-0.760, -0.503)	<.0001	-0.3611(-0.564, -0.158)	0.0005	-0.4621(-0.626, -0.299)	<.0001
0.8	-0.5742(-0.706, -0.443)	<.0001	-0.2879(-0.497, -0.079)	0.007	-0.4196(-0.587, -0.252)	<.0001
1.2	-0.5171(-0.654, -0.380)	<.0001	-0.2145(-0.432, 0.003)	**0.0532**	-0.3771(-0.551, -0.203)	<.0001
1.6	-0.4601(-0.604, -0.317)	<.0001	-0.1412(-0.369, 0.086)	**0.2241**	-0.3348(-0.517, -0.153)	0.0003
2	-0.4032(-0.555, -0.251)	<.0001	-0.0681(-0.308, 0.172)	**0.5779**	-0.2926(-0.484, -0.101)	0.0028
2.4	-0.3463(-0.508, -0.185)	<.0001	0.005(-0.249, 0.258)	**0.9695**	-0.2505(-0.453, -0.048)	0.0153
2.8	-0.2894(-0.461, -0.117)	0.001	0.0779(-0.191, 0.346)	**0.5697**	-0.2084(-0.423, 0.006)	**0.0568**
3.2	-0.2325(-0.416, -0.049)	0.0129	0.1507(-0.134, 0.435)	**0.2994**	-0.1663(-0.394, 0.061)	**0.1515**
3.6	-0.1756(-0.371, 0.020)	**0.0782**	0.2235(-0.078, 0.525)	**0.1466**	-0.1242(-0.365, 0.117)	**0.3123**

a Missing HbA1c values at each post-baseline scheduled visits up to Week 24 were multiply imputed assuming MAR 100 times to generate 100 datasets with complete HbA1c values. Additional HbA1c increases (delta) were added to each imputed HbA1c value for patients in the lixisenatide group.
b The completed datasets were analyzed using Mixed-effect model with repeated measures (MMRM) with treatment groups, randomization strata, treatment-by-visit interaction, and country as fixed effects, and baseline HbA1c value-by-visit interaction as a covariate. The results from the 100 analyses were combined.
The analysis included all measurements obtained during the study up to Week 24 in the mITT population, including those obtained after IMP discontinuation or introduction of rescue therapy.

HbA1c responder analyses at Week 24 (Week 12 for EFC6018)

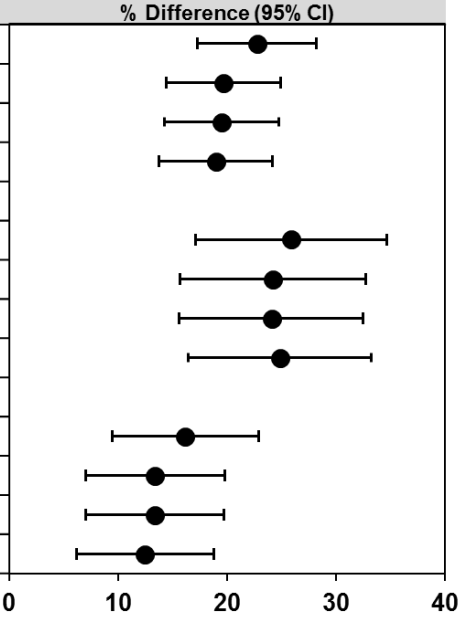
The same approach of LOCF for handling the missing data in the HbA1c responder analysis was pre-specified and used as the primary analysis method. The following sensitivity analyses were performed:

- Missing as non-responders (NR) in mITT: patients with missing HbA1c values at the primary time point were non-responders in the mITT population
- Missing as NR in ITT: responder analysis including all randomized patients (non-responder imputation used for missing data) to ensure no bias was introduced by using the mITT population instead of the true ITT population
- Missing + rescue as NR in mITT: patients with missing HbA1c values or patients who initiated rescue therapy prior to the primary time point were non-responders in the mITT population

They all showed consistent results and robustness of the data, supporting the efficacy of lixisenatide. Of 9 studies, results of the primary and the above sensitivity analyses are summarized for the 3 studies with the highest missing values (EFC6015, EFC6017 and EFC6016) (Figure 62).

Figure 62 – Results of Primary and Sensitivity Analyses of HbA1c <7% at Week 24 in EFC6015, EGC6017, and EFC6016

Study	Statistical Analysis	Lixisenatide (%)	Placebo (%)
Add-on SU or SU+Met EFC6015	Primary (LOCF)	36.4%	13.5%
	Missing as NR in mITT	32.6%	12.9%
	Missing as NR in ITT	32.5%	12.9%
	Missing + Rescue as NR in mITT	31.6%	12.6%
Add-on Pio or Pio+Met EFC6017	Primary (LOCF)	52.3%	26.4%
	Missing as NR in mITT	49.4%	25.2%
	Missing as NR in ITT	48.9%	24.8%
	Missing + Rescue as NR in mITT	48.8%	23.9%
Add-on BI or BI+Met EFC6016	Primary (LOCF)	28.3%	12.0%
	Missing as NR in mITT	24.8%	11.4%
	Missing as NR in ITT	24.6%	11.4%
	Missing + Rescue as NR in mITT	23.9%	11.4%



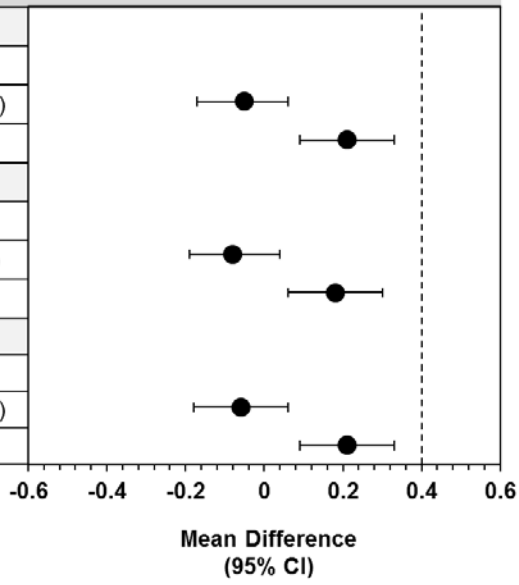
NR: non-responders, LOCF: last observation carried forward, mITT: modified intent-to-treat, BI: basal insulin, MET: metformin, SU: sulfonylurea, PIO: pioglitazone

8.4.4 Sensitivity Analyses in Study EFC12626

Sensitivity analyses that include MMRM using all post-baseline observations at scheduled visits and 26-week completer analyses were conducted for HbA1c change from baseline to Week 26. The forest plots of the primary and sensitivity analyses are presented below (Figure 63).

Figure 63 – Forest Plot – Sensitivity Analyses for Change in HbA1c from Baseline to Week 26 in Study EFC12626

EFC12626	N	Change from Baseline	LS Mean Difference (95% CI)
ANCOVA *(Primary-LOCF)*			
Lixisenatide	292	**-0.63**	
Insulin Glulisine QD	292	**-0.58**	**-0.05** (-0.17, 0.06)
Insulin Glulisine TID	295	**-0.84**	**0.21** (0.10, 0.33)
26-Week Completers			
Lixisenatide	262	**-0.66**	
Insulin Glulisine QD	275	**-0.59**	**-0.08** (-0.2, 0.04)
Insulin Glulisine TID	282	**-0.84**	**0.18** (0.06, 0.30)
MMRM *(All post-baseline data)*[1]			
Lixisenatide	284	**-0.63**	
Insulin Glulisine QD	290	**-0.57**	**-0.06** (-0.18, 0.06)
Insulin Glulisine TID	291	**-0.84**	**0.21** (0.09, 0.33)



LOCF: last observation carried forward, mITT: modified intent-to-treat,
1. There were a few patients who had post-baseline HbA1c data at unscheduled visits only. Note that MMRM method is based on all post-baseline data from scheduled visits.

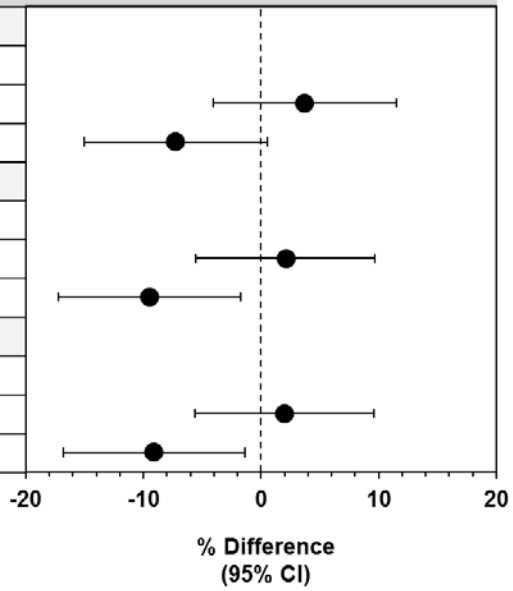
8.4.5 Responder analyses (HbA1c <7% and 3 composite endpoint responders at Week 26)

In the primary analysis of responders (HbA1c <7% and three composite endpoints of responders), the same approach of LOCF for handling the missing HbA1c data at Week 26 was pre-specified and used. To assess the robustness of the data, sensitivity analyses were performed by treating patients with missing HbA1c data at Week 26 as non-responders in the mITT population. In addition, an additional sensitivity analysis was also conducted in the all randomized patients for the HbA1c 7% responders in order to ensure no bias was introduced by using the mITT population instead of true ITT population.

Results of the primary and sensitivity analyses of above responders at Week 26 are presented in Figure 64 (HbA1c <7%) and Figure 65 (3 composite endpoint responders).

Figure 64 – Forest Plot: Sensitivity Analyses for HbA1c <7% at Week 26 in Study EFC12626 (mITT Population)

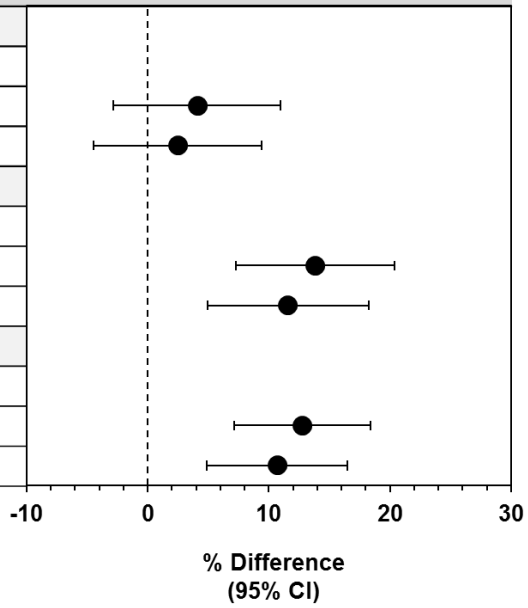
EFC12626	Responders (%)	% Difference (95% CI)
Primary as LOCF		
Lixisenatide	**42.1%**	
Insulin Glulisine QD	**38.4%**	**3.7%** (-4.03, 11.49)
Insulin Glulisine TID	**49.2%**	**-7.3%** (-15.07, 0.56)
Missing as NR in mITT		
Lixisenatide	**38.7%**	
Insulin Glulisine QD	**36.6%**	**2.1%** (-5.52, 9.68)
Insulin Glulisine TID	**48.1%**	**-9.5%** (-17.25, -1.75)
Missing as NR in ITT		
Lixisenatide	**38.6%**	
Insulin Glulisine QD	**36.6%**	**2.0%** (-5.61, 9.57)
Insulin Glulisine TID	**47.7%**	**-9.1%** (-16.78, -1.34)



LOCF: last observation carried forward, mITT: modified intent-to-treat, NR: non-responders

Figure 65 – Forest Plot: Sensitivity Analyses for Composite Responder Analyses at Week 26 in Study EFC12626 (mITT Population)

EFC12626	Responders (%)	% Difference (95% CI)
HbA_{1c} <7% and No Hypo		
Lixisenatide	**27.6%**	
Insulin Glulisine QD	**23.5%**	**4.1%** (-2.85, 10.99)
Insulin Glulisine TID	**25.1%**	**2.5%** (-4.50, 9.43)
HbA_{1c} <7% and No Weight Gain		
Lixisenatide	**29.6%**	
Insulin Glulisine QD	**15.8%**	**13.8%** (7.27, 20.35)
Insulin Glulisine TID	**18.0%**	**11.6%** (4.93, 18.28)
HbA_{1c} <7% and No Weight Gain and No Hypo		
Lixisenatide	**21.5%**	
Insulin Glulisine QD	**8.7%**	**12.8%** (7.16, 18.43)
Insulin Glulisine TID	**10.8%**	**10.7%** (4.85, 16.49)



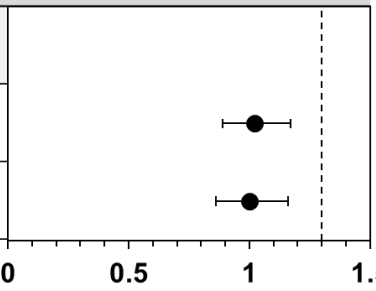
Documented symptomatic hypoglycemia with plasma glucose <60 mg/dL

8.4.6 Sensitivity Analyses in ELIXA

Results of the primary ITT and supportive on-treatment results (including events up to 30 days after end of treatment date) for the primary CV composite endpoint and MACE are provided below (Figure 66 and Figure 67).

Figure 66 – Primary CV Composite Endpoint On-treatment Analysis in ELIXA (ITT Population)

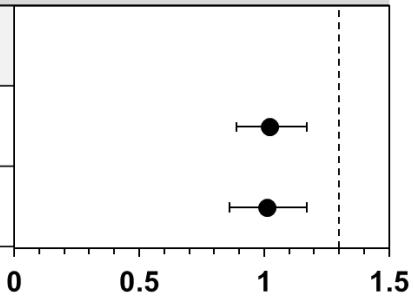
	Patients with Events n (%)		
	Lixisenatide (N=3034)	Placebo (N=3034)	Hazard Ratio (95% CI)
Primary CV Endpoint			
ITT	**406 (13.4%)**	**399 (13.2%)**	**1.02** (0.89, 1.17)
On-Treatment	**339 (11.2%)**	**348 (11.5%)**	**1.00** (0.86, 1.16)



ITT = intent-to-treat.
ITT analysis is based on all events from randomization to the study end date for each patient.
On-treatment analysis is based on all events from randomization up to 30 days after the last injection of double-blind study drug.

Figure 67 – MACE On-Treatment Analysis in ELIXA (ITT Population)

	Patients with Events n (%)		
	Lixisenatide (N=3034)	Placebo (N=3034)	Hazard Ratio (95% CI)
MACE			
ITT	**400 (13.2%)**	**392 (12.9%)**	**1.02** (0.89, 1.17)
On-Treatment	**334 (11.0%)**	**342 (11.3%)**	**1.01** (0.86, 1.17)



ITT = intent-to-treat.
ITT analysis is based on all events from randomization to the study end date for each patient.
On-treatment analysis is based on all events from randomization up to 30 days after the last injection of double-blind study drug.

8.5 OVERALL EXPOSURE: IGLARLIXI

Table 73 - Overall exposure to study medication in Phase 2/3 IGlarLixi studies (safety population)

	Phase 2/3 controlled study pool		Phase 3 controlled study pool		EFC12404	
	iGlarLixi (N=995)	Insulin Glargine (N=994)	iGlarLixi (N=834)	Insulin Glargine (N=832)	iGlarLixi (N=469)	Lixisenatide (N=233)
Cumulative exposure (patient-years)	533.6	542.5	461.8	468.2	261.5	124.6
Duration of study treatment (days)						
Number	992	992	831	830	468	232
Mean (SD)	196.5 (37.6)	199.8 (29.7)	203.0 (35.7)	206.1 (27.3)	204.1 (33.9)	196.1 (48.2)
Median	211.0	210.0	211.0	210.0	211.0	211.0
Min : Max	1 : 252	1 : 249	1 : 252	1 : 249	2 : 252	6 : 224
Cumulative duration of study treatment by category [n (%)]						
≥ 85 days	956 (96.1%)	975 (98.1%)	801 (96.0%)	815 (98.0%)	453 (96.6%)	215 (92.3%)
≥ 169 days	905 (91.0%)	920 (92.6%)	781 (93.6%)	802 (96.4%)	441 (94.0%)	209 (89.7%)
≥ 211 days	515 (51.8%)	401 (40.3%)	515 (61.8%)	400 (48.1%)	328 (69.9%)	143 (61.4%)

8.6 SUMMARY OF CASES OF ANAPHYLAXIS ADJUDICATED AS POSSIBLY RELATED TO LIXISENATIDE

Patients with drug-related anaphylactic reaction or anaphylactic shock (as adjudicated by ARAC)[1]

Case 1: Anaphylactic Shock (Study EFC11321, Patient 156029017)

This case involves a 66 year-old male with a history of T2DM, hypertension and dyslipidemia who experienced **anaphylactic shock** (serious criteria: life-threatening, requiring hospitalization) after the first administration of lixisenatide. He had no prior history of allergy or of GLP-1 agonist use. Ten minutes after dosing, the patient developed generalized pruritus, followed by flushing, rhinorrhea, nausea and vomiting, and loss of consciousness. Examination revealed tachycardia (HR 118 bpm), hypotension (BP 60/40 mmHg) and tachypnea (RR 22 per minute). Immediate treatment given in the doctor's office included IV fluids, IV dexamethasone 5 mg, and IM promethazine 12.5 mg. Stabilization of vital signs was noted in the ER (blood pressure 150/90 mmHg), but admission electrocardiogram revealed left anterior fascicular block with anterior ST-segment elevations. **Acute myocardial infarction** was ruled in on serial CK-MB values (CAC assessment- spontaneous MI). Lixisenatide was permanently discontinued and the patient treated with dopamine, aspirin, clopidogrel, LMWH, and metoprolol. Outcome was listed as recovered for both events. Testing performed in hospital for this patient as part of the diagnostic work-up revealed normal IgE levels. **ARAC Assessment: Grade 5 Anaphylactoid Shock**

ADA Testing- Patient 156029017

Time point	**Baseline**	**Day 29**	**Day 171**
ADA	Negative	Positive (<LLOQ)	Negative

Case 2: Anaphylactic Reaction (Study EFC10780, Patient 320001015)

A 45 year-old female with no reported allergy history developed **anaphylactic reaction** on Day 2 of treatment with lixisenatide. Ten minutes after drug administration, she developed generalized pruritus, flushing, hives, swelling of her eyelids, face, hands and feet, chest tightness and injection site swelling. She was diagnosed with an anaphylactic reaction (serious criterion: life threatening)

[1] Reporter terms are presented in bold font, with the ARAC adjudicated diagnosis given at the end of the narrative.

which was treated with chlorphenamine 4 mg. As minimal improvement was observed after 30 minutes, she was transferred to the ER and given epinephrine, dexamethasone 8 mg, and nasal cannula oxygen. The event resolved after approximately 2 hours, and the patient was discharged from the ER. Lixisenatide was permanently discontinued. The investigator considered the event possibly related to study drug. **ARAC Assessment: Grade 3 Anaphylactic Reaction**

ADA Testing – Patient 320001015

Time point	**Baseline**	**Day 7**
ADA	Negative	Negative

Case 3: Pruritus Generalized (ELIXA Study, Patient 076018043)

On Days 20 and 21 of treatment, a 62 year-old male with relevant medical history of CHF and COPD and experienced episodes of mild injection site pruritus 5 minutes after lixisenatide injection. The events resolved spontaneously after each episode and study drug was continued. On Day 27, the patient developed severe **generalized pruritus** (serious criterion: medically important) with facial swelling, nasal itching, wheezing, cough, dyspnea, nausea, vomiting and dizziness (blood pressure was not reported) requiring treatment in the ER with loratadine, salbutamol, saline and oxygen. Following treatment in the ER, he was discharged to home. The following day, he had recurrence of symptoms after another dose of lixisenatide, and was again treated in the ER. Lixisenatide was discontinued following the second episode and resolution of all symptoms was noted after 4 days. **ARAC Assessment: Grade 3 Anaphylactic Reaction**

ADA Testing – Patient 076018043

Baseline	**Day 36**	**Day 169**
Negative	Positive, 2560 (titer)	Positive, 160 (titer)

Case 4: Anaphylactic reaction (Study EFC12404, Patient 484006011)

A 60 year-old female with no allergy history developed **anaphylactic reaction** (serious criterion: (medically important) with symptoms of respiratory distress, throat burning, nausea, dizziness, anxiety, and generalized pruritic erythematous rash, 1 hour after lixisenatide administration on Day 25. Physical examination revealed a conscious and oriented female with normal ambulation, mild eyelid and lip edema with mild stridor and blood pressure of 88/57 mmHg. She was treated in the emergency department with IM dexamethasone 8 mg, with resolution of symptoms after 30 minutes. Study drug was discontinued. **ARAC Assessment: Grade 2 Anaphylactic Reaction**

ADA Testing (lixisenatide) - Patient 484006011

Baseline	**Day 31**
Negative	Positive, Concentration <3.21 nmol/L

Case 5: Angioedema, Maculopapular Rash (Study EFC6014, Patient 124411018)

A 53 year-old male with a history of drug allergy and prior GLP-1 agonist use developed injection site swelling, lip numbness, generalized pruritus and maculopapular rash on Day 13 of treatment with lixisenatide. The events recurred with worsening severity the following day after drug administration. The patient presented to the ER with increased lip swelling and dizziness (blood pressure normal), and was diagnosed with **angioedema** and **maculopapular rash** (serious criterion: medically important). He was treated with IV diphenhydramine, prednisone, ranitidine, cetirizine and IV fluids with symptom improvement, and was discharged from the ER. All symptoms fully resolved after several days. **ARAC Assessment: Grade 2 Anaphylactic Reaction**

ADA Testing- Patient 124411018

Baseline	**Day**
Negative	Positive, concentration 25.10 nmol/L

Case 6: Dermatitis Allergic (Study EFC10743, Patient 276303004)

A 52 year-old female with no allergy history developed **dermatitis allergic** (serious criterion-medically important) on Day 1 of treatment with lixisenatide. Thirty minutes after dose administration, the patient developed localized itching, flush and swelling under one arm which progressed to the other arm. This was followed by headache, dizziness, and a "lump" in the throat with hoarseness; vital signs were normal. She was treated with IV hydrocortisone 250 mg, IV clemastine 2 mg, and saline. Study drug was permanently discontinued and the patient recovered. **ARAC Assessment: Grade 2 Anaphylactic Reaction**

ADA Testing – Patient 276303004

Baseline
Negative

Case 7: Dermatitis Allergic (Study EFC10743, Patient 642307010)

A 53 year-old female with no allergy history developed nausea, dizziness, generalized pruritus, injection site swelling and palmar redness "a few seconds" after administration of lixisenatide on treatment Day 165. Thirty minutes later, she was noted to have blood pressure of 90/60 mmHg with borderline tachycardia (100 bpm) and tachypnea (26 breaths per minute). She was treated for the **allergic dermatitis** (non-serious event) with IV hydrocortisone 100 mg and loratadine with normalization of vital signs (BP 110/70, HR 78 bpm, respirations 16/min). Study drug was discontinued and the patient recovered fully the following day. **ARAC Assessment: Grade 2 Anaphylactic Reaction**

ADA Testing – Patient 642307010

Baseline	**Day 29**	**Day 170**
Negative	Positive , <LLOQ	Positive, concentration not evaluable

Case 8: Dermatitis allergic (2 episodes), Hypersensitivity (EFC6017, Patient 642701006)

A 54 year-old female with no allergy history developed mild generalized itching and eye redness, reported as **hypersensitivity** (non-serious event) on Day 163 of treatment and 30 minutes after dosing, which resolved the same day without corrective treatment. Study drug was continued. On Day 169, 25 minutes after drug administration, she developed generalized itching and rash, swelling of the eyes and tongue, and injection site swelling (reported as **allergic dermatitis**, non-serious event). Subsequent treatment the following day resulted in recurrence of the same muco-cutaneous symptoms plus nausea and abdominal pain (**allergic dermatitis**, non-serious event). Treatment with loratadine was given and study drug was discontinued, with recovery later the

same day. **ARAC Assessment: Grade 1 Allergic Conjunctivitis, drug related (1st episode); Grade 1 Angioedema, possible related (2nd episode); Grade 1 Anaphylactic Reaction**

Anti-Drug Antibody Testing – Patient 642701006

Baseline	Day 15	Day 169
Negative	Negative	Positive, concentration not evaluable

Case 9: Anaphylactic Reaction (Study DRI6012, Patient 840020001)

A 52 year-old male developed moderate generalized pruritus 10 minutes after study drug administration that lasted for approximately 30 minutes before resolving spontaneously on Day 20. As a result of the event, study drug was held by the patient for 3 days, then restarted study drug. Within 1 minutes of re-administration on Day 23, pruritus recurred, associated with swollen lips and tongue, lip numbness, a lump in the throat and difficulty breathing, diagnosed as an **anaphylactic reaction** (serious criterion: medically important). The patient self-administered 2 tablespoons of diphenhydramine and called for an ambulance; no further treatment was administered by the emergency medical staff. Study drug was discontinued, and the patient recovered fully within 1 hour. Antibody data are unavailable for this patient. **ARAC Assessment: Grade 1 Anaphylactic Reaction**

Case 10: Hypersensitivity (Study EFC6016, Patient 840635031)

A 52 year-old female with a medical history of drug allergy, urticaria and angioedema developed **hypersensitivity** (non-serious event) with generalized itching, injection site erythema and pruritus, hoarseness, wheeze, and chest tightness on Day 22. The patient was successfully treated with diphenhydramine. On Day 31, the events recurred with re-administration in the physician's office; vital signs were normal. The event resolved with diphenhydramine administration, and study drug was permanently discontinued. **ARAC Assessment: Grade 1 Anaphylactic Reaction**

ADA Testing Patient 840635031

Baseline	Day 15	Day 30
Negative	Negative	Positive, Concentration 223 nmol/L

Case 11: Hypersensitivity (Study EFC6016, Patient 840635033)

A 58 year-old female with a history of drug allergies and allergic rhinitis developed **hypersensitivity** (non-serious event) on Day 26 with symptoms of pruritus, generalized urticaria,

nausea and nasal congestion. The patient was treated with diphenhydramine and recovered rapidly. **ARAC Assessment: Grade 1 Anaphylactic Reaction**

ADA Testing – Patient 840635033

Baseline	**Day 30**	**Day 83**	**Day 169**	**Day 197**
Positive, <LLOQ	Positive, Concentration 41.7 nmol/L	Positive, Concentration 13.9 nmol/L	Positive, Concentration 5.39 nmol/L	Positive, Concentration 6.81 nmol/L