CADTH

CADTH COMMON DRUG REVIEW

Clinical Review Report

Lixisenatide (Adlyxine)

(Sanofi-aventis Canada Inc.)

Indication: As an adjunct to diet and exercise to improve glycemic control in adult patients with type 2 diabetes mellitus in combination with:

- metformin
- a sulfonylurea (alone or with metformin)
- pioglitazone (alone or with metformin)
- a basal insulin (alone or with metformin)

when the therapy listed above does not provide adequate glycemic control.

Service Line:	CADTH Common Drug Review
Version:	1.0
Publication Date:	December 2017
Report Length:	164 Pages

CADTH

About CADTH: CADTH is an independent, not-for-profit organization responsible for providing Canada's health care decision-makers with objective evidence to help make informed decisions about the optimal use of drugs, medical devices, diagnostics, and procedures in our health care system.

Funding: CADTH receives funding from Canada's federal, provincial, and territorial governments, with the exception of Quebec.

CADTH

Table of Contents

Tables

Figures

Abbreviations

A1C	glycated hemoglobin
ACS	acute coronary syndrome
AE	adverse event
ANCOVA	analysis of covariance
BNP	B-type brain natriuretic peptide
CDR	CADTH Common Drug Review
CI	confidence interval
CM	cardiac marker
DPP-4	dipeptidyl peptidase-4
eGFR	estimated glomerular filtration rate
FPG	fasting plasma glucose
GLP-1	glucagon-like peptide-1
HF	heart failure
HRQoL	health-related quality of life
ITT	intention-to-treat
IWQOL-Lite	Impact of Weight on Quality of Life–Lite questionnaire
LOCF	last observation carried forward
LS	least squares
MI	myocardial infarction
mITT	modified intention-to-treat
MMRM	mixed-effects models for repeated measures
NICE	National Institute for Health and Care Excellence
NT-proBNP	N-terminal pro b-type natriuretic peptide
PPG	postprandial glucose
RCT	randomized controlled trial
SAE	serious adverse event
SC	subcutaneous
SE	standard error
SGLT2	sodium-glucose cotransporter-2
SMPG	self-monitored plasma glucose
UA	unstable angina
ULN	upper limit of normal
WDAE	withdrawal due to adverse event

Drug	Lixisenatide (Adlyxine)
Indication	As an adjunct to diet and exercise to improve glycemic control in adult patients with type 2 diabetes mellitus in combination with the following therapies when they do not provide adequate glycemic control: • metformin • a sulfonylurea (alone or with metformin) • pioglitazone (alone or with metformin) • a basal insulin (alone or with metformin)
Reimbursement Request	As an adjunct to diet and exercise to improve glycemic control in adult patients with type 2 diabetes mellitus in combination with a basal insulin (alone or with metformin)
Manufacturer	Sanofi-aventis Canada Inc.

Executive Summary

Introduction

Diabetes mellitus is a metabolic disorder characterized by persistent elevations in blood glucose (hyperglycemia) as well as impaired glycemic control, which, if prolonged, may result in damage to blood vessels, consequently causing dysfunction and failure of various organs including heart, brain, kidneys, retina, and lower limbs. Diabetes is one of the most common chronic diseases in Canada, of which type 2 diabetes mellitus accounts for approximately 90% of cases. Diabetes Canada estimated that there were 3.4 million people (9.3% of the population) with diabetes in 2015, and that by 2025 this number will increase to five million people (12.1%). The economic burden of diabetes in Canada is heavy.

Lixisenatide is a potent and selective prandial glucagon-like peptide-1 (GLP-1) receptor agonist that mimics the effect of endogenous GLP-1, thereby stimulating glucose-dependent insulin secretion thus limiting hypoglycemia, decreasing glucagon output, slowing gastric emptying, and inducing satiety, providing beneficial effects on weight. It is believed glycated hemoglobin (A1C) targets are achieved through control of both the fasting plasma glucose (FPG) and the postprandial glucose (PPG). Unlike some other antidiabetic therapies (e.g., basal insulin), lixisenatide mainly reduces the PPG, which provides a complementary mechanism of action when used in conjunction with basal insulin, which acts primarily on FPG.[1,2] GLP-1 receptor agonists are also generally associated with gastrointestinal adverse events (AEs) such as nausea, diarrhea, and vomiting. Lixisenatide is available as pre-filled pens in strengths of 0.05 mg/mL and 0.1 mg/mL to deliver 14 doses of 10 mcg per dose or 20 mcg per dose, respectively.

The reimbursement request for lixisenatide is as an adjunct to diet and exercise to improve glycemic control in adult patients with type 2 diabetes mellitus in combination with a basal insulin (alone or with metformin).3 According to the Health Canada–approved product monograph, lixisenatide should be used as an adjunct to diet and exercise to improve glycemic control in adult patients with type 2 diabetes mellitus in combination with metformin, a sulfonylurea (alone or with metformin), pioglitazone (alone or with metformin),

or a basal insulin (alone or with metformin) when those therapies do not provide adequate glycemic control.

The objective of this review was to perform a systematic review of the beneficial and harmful effects of lixisenatide (Adlyxine) for the treatment of adults with type 2 diabetes in combination with a basal insulin (alone or with metformin).

Included Studies

Placebo-Controlled Trials

The evidence for this review as it pertains to the use of lixisenatide for the treatment of adults with type 2 diabetes mellitus in combination with a basal insulin (with or without metformin) was drawn from four similarly designed double-blind, phase III multi-centre, multinational, placebo-controlled randomized controlled trials (RCTs). GETGOAL – L (N = 495), GETGOAL – DUO 1 (N = 446), and GETGOAL – L – C (N = 447) randomized patients treated with a basal insulin with or without metformin; GETGOAL – L Asia (N = 311) randomized patients treated with a basal insulin with or without sulfonylurea. All placebo-controlled trials were designed to assess the efficacy and safety of treatment with 20 mcg lixisenatide in addition to permitted background therapy compared with placebo in addition to permitted background therapy over 24 weeks. In each trial, the primary efficacy outcome was the absolute change from baseline in A1C at week 24. Other outcomes of interest that were collected across all placebo-controlled trials include the percentage of patients achieving target A1C, change from baseline in two-hour PPG, FPG, glucose excursion, average seven-point self-monitored plasma glucose (SMPG), body weight and total daily basal insulin, and need for rescue therapy as well as mortality, AEs, serious adverse events (SAEs), withdrawal due to adverse events (WDAEs), and notable harms. Investigators and patients were blinded to the treatment arm assignment; however, study drug treatment volumes in the injection pens were not concealed.

Key limitations of the trials include randomization potentially being compromised due to study withdrawals; concerns with the statistical testing across secondary end points; concerns with the imputation model and the definitions of intention-to-treat (ITT) analysis and hypoglycemia; lack of control for multiple statistical testing across subgroups of interest and sensitivity analyses; large placebo response; and differences in patient and practice characteristics between the study centres included in the placebo-controlled trials and what would be seen in a Canadian setting (e.g., the mean age of patients, racial group, and use of optimal standard antidiabetic practices).

Active-Controlled Trial

The evidence for this review as it pertains to the use of lixisenatide for the treatment of adults with type 2 diabetes mellitus in combination with a basal insulin (with or without metformin) was also drawn from one open-label, phase III, noninferiority, multi-centre, multinational, active-controlled RCT. GETGOAL – DUO 2 (N = 893) randomized patients treated with a basal insulin (with or without metformin) in a 1:1:1 ratio to assess the efficacy and safety of treatment with 20 mcg lixisenatide in addition to permitted background therapy compared with insulin glulisine once daily and insulin glulisine three times daily in addition to permitted background therapy over 26 weeks. In GETGOAL – DUO 2, the primary analysis was based on the three co-primary end points: 1) noninferiority of lixisenatide versus insulin glulisine once daily in the change from baseline in A1C at week 26 using a noninferiority margin of 0.4%; 2a) noninferiority of lixisenatide versus insulin glulisine three times daily in the change from baseline in A1C at week 26 using a noninferiority margin of 0.4%; and 2b)

superiority of lixisenatide versus insulin glulisine three times daily in the change from baseline in body weight at week 26. Other outcomes of interest were collected and include the percentage of patients achieving target A1C, change from baseline in two-hour PPG, FPG, glucose excursion, average seven-point SMPG, body weight, change from baseline in total daily basal insulin and health-related quality of life (HRQoL) using the Impact of Weight on Quality of Life–Lite questionnaire (IWQOL-Lite), as well as mortality, AEs, SAEs, WDAEs, and notable harms.

Key limitations of the trial include its open-label design; concerns with the titration regimen of insulin (basal and prandial), the imputation model, and the definitions of ITT analysis and hypoglycemia; lack of per-protocol analysis for noninferiority tests; randomization potentially being compromised due to study withdrawal; the lack of control for multiple statistical testing across all secondary end points, subgroups of interest, and sensitivity analyses; and the differences in patient and practice characteristics between the study centres included in GETGOAL – DUO 2 and what would be seen in a Canadian setting (e.g., the mean age of patients, racial group, and the use of optimal standard antidiabetic practices).

Results and Interpretation

Efficacy

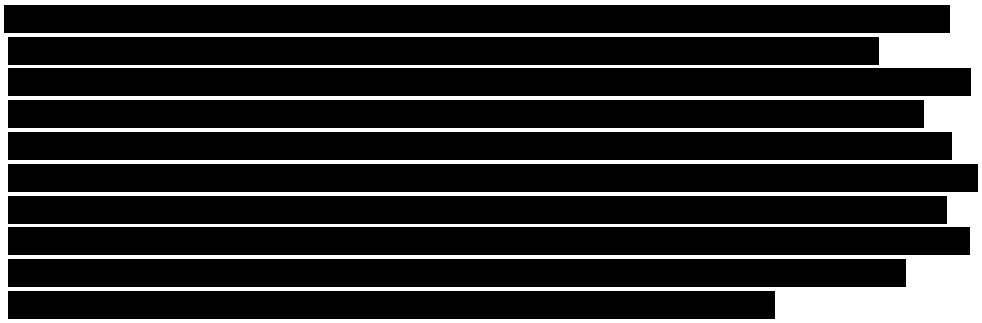
Placebo-Controlled Trials

Patients treated with lixisenatide experienced a statistically significantly greater reduction in the primary end point of absolute change in A1C compared with placebo at week 24 in all placebo-controlled trials. The adjusted mean differences were –0.36% (95% confidence interval [CI], –0.55% to –0.17%), $P = 0.0002$; –0.88% (95% CI, –1.12% to –0.65%), $P < 0.0001$; –0.32 (95% CI, –0.46% to –0.17%), $P < 0.0001$; and –0.51% (95% CI, –0.69% to –0.34%), $P < 0.0001$ in GETGOAL – L, GETGOAL – L Asia, GETGOAL – DUO 1, and GETGOAL – L – C, respectively. The primary end point (absolute change from baseline in A1C at week 24) was also analyzed in numerous pre-specified subgroups; however, no formal statistical tests were performed. Overall, no consistent trends could be identified in any of the subgroup data. Given that subgroups typically do not maintain randomization (unless used as stratification variables for randomization, which was true of the A1C [less than 8.0%, ≥ 8.0%] and metformin [yes, no] subgroups only), are likely underpowered (small sample size) to detect a statistically significant difference, and have an increased likelihood of type I error, these analyses should be treated as exploratory. Sensitivity analyses to assess the impact of rescue medication were performed based on all scheduled A1C measurements during the main 24-week double-blind treatment period for the primary end point in all placebo-controlled trials. A sensitivity analysis with 24-week completers (patients who completed the 24 weeks of treatment) was also conducted. The results of all sensitivity analyses were similar in magnitude, direction, statistical significance, and in support of the primary analyses in all placebo-controlled trials; however, the validity of the sensitivity analyses on these end points may be biased given that patients were assumed to be missing at random.

Overall, numerically more patients in the lixisenatide groups had an A1C less than 7% compared with placebo groups in all placebo-controlled trials (range 28% to 56% compared with 5% to 39%, respectively). Similar trends were noted for the proportion of patients with an A1C less than 6.5% (range 14% to 32% compared with 1% to 16%). The results for A1C responders were not part of the statistical testing hierarchy and should be considered exploratory; therefore, no statistical interpretations should be made.

Patients treated with lixisenatide also experienced a statistically significantly greater reduction in two-hour PPG (adjusted mean differences were similar in all of the placebo-controlled trials: –3.81 mmol/L [95% CI, –4.70 to –2.93], *P* < 0.0001; –7.83 mmol/L [95% CI, –8.89 to –6.77], *P* < 0.0001; –3.16 mmol/L [95% CI, –3.95 to –2.38], *P* < 0.0001; and –3.45 mmol/L [95% CI, –4.23 to −2.67], *P* < 0.0001 in GETGOAL – L, GETGOAL – L Asia, GETGOAL – DUO 1, and GETGOAL – L – C, respectively) compared with placebo at week 24. Patients treated with lixisenatide also experienced a statistically significantly greater reduction in average seven-point SMPG (adjusted mean differences –0.88 mmol/L [95% CI, –1.31 to –0.45], *P* < 0.0001; –0.39 mmol/L [95% CI, –0.68 to –0.11], *P* = 0.0071; and –0.54 mmol/L [95% CI –0.87 to –0.21], *P* = 0.0014 in GETGOAL – L, GETGOAL – DUO 1, and GETGOAL – L – C, respectively) compared with placebo at week 24. However, numerical differences were observed in the average seven-point SMPG in GETGOAL – L Asia (–1.35 mmol/L [95% CI, –1.84 to –0.86]) given that an end point in the statistical testing order failed before the testing for significance in average seven-point SMPG (statistical significance of this end point should not have been tested and should be considered exploratory). Glucose excursion was not part of the statistical testing hierarchy and therefore should be considered exploratory given the increased risk of type I error; patients treated in the lixisenatide group reported numerically greater reductions (adjusted mean differences –3.80 mmol/L [95% CI, –4.57 to –3.03], –7.22 mmol/L [95% CI, –8.25 to –6.20], –3.09 mmol/L [95% CI, –3.84 to –2.33], and –3.13 mmol/L [95% CI, –3.83 to –2.43] in GETGOAL – L, GETGOAL – L Asia, GETGOAL – DUO 1, and GETGOAL – L – C, respectively) when compared with placebo at week 24.

No statistically significant change in FPG was reported with lixisenatide compared with placebo at week 24 in all placebo-controlled trials with the exception of GETGOAL – L Asia. The adjusted mean differences were similar in all of the placebo-controlled trials (–0.08 mmol/L [95% CI, –0.59 to 0.43], *P* = 0.7579; –0.12 mmol/L [95% CI, –0.46 to 0.23], *P* = 0.5142; and –0.38 mmol/L [95% CI, –0.79 to 0.02], *P* = 0.0650 in GETGOAL – L, GETGOAL – DUO 1, and GETGOAL – L – C, respectively). A numerically greater reduction in FPG in GETGOAL – L Asia was observed compared with placebo (–0.67 mmol/L [95% CI, –1.23 to –0.11]; however, results should be considered exploratory given that an end point in the statistical testing order failed before the testing for significance in FPG (statistical significance of this end point should not have been tested).



The changes in body weight ranged between –1.80 kg to 0.28 kg in the lixisenatide groups and –0.52 kg to 1.16 kg in the placebo groups, respectively, at week 24. The adjusted mean differences were similar in GETGOAL – DUO 1 and GETGOAL – L – C, and were statistically significantly in favour of lixisenatide compared with placebo (–0.89 kg [95% CI, –1.42 to –0.35], *P* = 0.0012, and –1.17 kg [95% CI, –1.60 to –0.74], *P* < 0.0001,

respectively). No statistically significant difference in body weight was observed in GETGOAL – L Asia (–0.43 kg [–0.93 to 0.06], *P* = 0.0857), whereas a numerically greater reduction in body weight was observed in GETGOAL – L (–1.28 kg [95% CI, –1.80 to –0.75]); however, results should be considered exploratory given that an end point in the statistical testing order failed before the testing for significance in body weight (statistical significance of this end point should not have been tested). [redacted]

[redacted]No data were provided for weight loss responders in GETGOAL – DUO 1 and GETGOAL – L – C. The results for weight loss responders were not part of the statistical testing hierarchy and should be considered exploratory; therefore, no statistical interpretations should be made.

All placebo-controlled trials reported the need for rescue therapy, with the exception of GETGOAL – L – C. Overall, a numerically similar number of patients received rescue therapy in the placebo group compared with the lixisenatide group in GETGOAL – L, GETGOAL – L Asia, and GETGOAL – DUO 1 (7%, 3%, and less than 1% compared with 6%, 1% and less than 1%, respectively) during the double-blind treatment phase. No statistically significant differences in the need for rescue therapy were observed in any of the placebo-controlled trials. [redacted]

Overall, patients treated with lixisenatide required statistically significantly less total daily basal insulin compared with placebo at week 24 in GETGOAL – DUO 1 and GETGOAL – L – C. The adjusted mean differences were –2.24 units per day (95% CI, –4.26 to –0.22), *P* = 0.0300, and –1.11 units per day (95% CI, –1.86 to –0.37), *P* = 0.0033 in GETGOAL – DUO 1 and GETGOAL – L – C, respectively. The results for change in total daily basal insulin were not part of the statistical testing hierarchy in GETGOAL – L and GETGOAL – L Asia, and their adjusted mean differences were –3.69 units per day (95% CI, –6.57 to –0.82) and –1.29 units per day (95% CI, –2.10 to –0.48), respectively. These results should be considered exploratory; therefore, no statistical interpretations should be made. [redacted]

Active-Controlled Trial

Patients treated with lixisenatide insulin glulisine once daily and insulin glulisine three times daily all experienced numerical reductions in A1C at week 26 (adjusted mean differences were –0.05% [95% CI, –0.17% to 0.06%] and 0.21% [95% CI, 0.1% to 0.33%], respectively). Based on the adjusted mean differences and the pre-specified noninferiority margin for change in A1C (0.4%), lixisenatide is noninferior to both insulin glulisine once daily and insulin glulisine three times daily in terms of the primary end point of absolute change from baseline in A1C at week 26 given that the upper bounds of the 95% CIs did not exceed the noninferiority margin of 0.4%. The primary end points (absolute change from baseline in A1C at week 26) were also analyzed in numerous pre-specified subgroups; however, no formal statistical tests were performed. Overall, no numerical differences were observed in the adjusted mean differences in any of the subgroups between lixisenatide and insulin glulisine once daily for the change from baseline in A1C at week 26. Contrarily, a numerically smaller reduction in the change from baseline in A1C at week 26 was reported between lixisenatide and insulin glulisine three times daily in all subgroups with the exception of the A1C ≥ 8.0% (0.17% [95% CI, –0.03% to 0.36%]), no metformin use (0.17% [95% CI, –0.15% to 0.50%]), duration of diabetes ≤ 10 years (0.06% [95% CI, 0.12% to 0.24%]), total daily basal insulin dose < 45 units per day (0.18% [95% CI, –0.06% to 0.41%]), and duration of basal insulin dose ≥ three years (0.38% [95% CI, 0.18% to 0.58%]). Given that subgroups typically do not maintain randomization (unless used as stratification variables for randomization, which was true of the A1C [less than 8.0%, ≥ 8.0%] and metformin [yes, no] subgroups only) and are likely underpowered (small sample size) to detect a statistically significant difference, as well as the increased likelihood of type I error, these analyses should be treated as exploratory.

A sensitivity analysis to support the primary analyses was performed using a mixed-effects models for repeated measures. Another sensitivity analysis with 26-week completers (patients who completed the 26 weeks of treatment) was also conducted. The results of all sensitivity analyses were similar in magnitude, direction, statistical significance, and in support of the primary analyses in all treatment groups; however, the validity of the sensitivity analyses on these end points may be biased given that patients were assumed to be missing at random.

No numerical differences were observed in the adjusted mean differences between lixisenatide and insulin glulisine once daily or insulin glulisine three times daily for patients who achieved an A1C < 7% (3.7% [95% CI, –4.0% to 11.5%] and –7.3% [95% CI, –15.1% to 0.6%], respectively). No numerical difference was reported in the adjusted mean difference between lixisenatide and insulin glulisine once daily for patients who achieved an A1C ≤ 6.5% (2.7% [95% CI, –3.6% to 9.01%]). Numerically fewer patients achieved an A1C ≤ 6.5% with an adjusted mean of –10.5% (95% CI, –17.3% to –3.6%) between lixisenatide and insulin glulisine three times daily. The results for A1C responders were not adjusted for multiple statistical testing and should be considered exploratory; therefore, no statistical interpretations should be made.

Overall, patients treated with lixisenatide also experienced a numerically greater reduction in some secondary end points such as two-hour PPG (adjusted mean differences were –2.07 mmol/L [95% CI, –3.29 to –0.85] and –2.23 mmol/L [95% CI, –3.39 to –1.07]) and glucose excursion (adjusted mean differences were –1.61 mmol/L [95% CI, –2.76 to –0.45] and –2.08 mmol/L [95% CI, –3.19 to –0.97]) compared with both insulin glulisine once daily and insulin glulisine three times daily at week 26, respectively. However, the clinical importance

of such differences remains unclear. The results for two-hour PPG and glucose excursion were not adjusted for multiple statistical testing and should be considered exploratory; therefore, no statistical interpretations should be made.

No numerical differences in FPG were observed in patients treated with lixisenatide compared with both insulin glulisine once daily and insulin glulisine three times daily at week 26. The adjusted mean differences in both the treatment group taking insulin glulisine once daily and the treatment group taking insulin glulisine three times daily were –0.01 mmol/L (95% CI, –0.32 to 0.30) and –0.17 mmol/L (95% CI, –0.48 to 0.143), respectively. The results for FPG were not adjusted for multiple statistical testing and should be considered exploratory; therefore, no statistical interpretations should be made.

Generally, no numerical differences in average seven-point SMPG were observed in patients treated with lixisenatide compared with insulin glulisine once daily at week 26 (adjusted mean difference –0.002 mmol/L [95% CI, –0.245 to 0.240]). The reduction in average seven-point SMPG was numerically smaller in the treatment group taking insulin glulisine three times daily compared with lixisenatide (0.269 mmol/L [95% CI, 0.028 to 0.510]). The results for average seven-point SMPG were not adjusted for multiple statistical testing and should be considered exploratory; therefore, no statistical interpretations should be made.

Patients treated with lixisenatide experienced a reduction in body weight, whereas patients in both the treatment group taking insulin glulisine once daily and the treatment group taking insulin glulisine three times daily experienced an increase in body weight at week 26. The adjusted mean differences were similar in both insulin glulisine once daily and insulin glulisine three times daily treatment groups and were statistically significantly in favour of lixisenatide (–1.66 kg [95% CI, –2.26 to –1.06] and –1.99 kg [95% CI, –2.59 to –1.40], respectively). Lixisenatide was found to be superior to insulin glulisine three times daily in the co-primary end point of change in body weight at week 26. The primary end point (change from baseline in body weight at week 26) was also analyzed in numerous pre-specified subgroups; however, no formal statistical tests were performed. Overall, patients treated with lixisenatide experienced a numerically greater reduction in body weight compared with insulin glulisine once daily and insulin glulisine three times daily in all subgroups at week 26, with the exception of the mean difference in body weight between lixisenatide and insulin glulisine three times daily in the age < 50 years subgroup (–1.49 kg [95% CI, –3.05 to 0.07]). Given that subgroups typically do not maintain randomization (unless used as stratification variables for randomization, which was true of the A1C [< 8.0%, ≥ 8.0%] and metformin [yes, no] subgroups only), are likely underpowered (small sample size) to detect a statistically significant difference, and have an increased likelihood of type I error, these analyses should be treated as exploratory.

Numerically more patients in the lixisenatide groups compared with both the insulin glulisine once daily and insulin glulisine three times daily groups achieved no weight gain (65% compared with 37% and 31%, respectively), weight loss of ≥ 2% body weight (33% compared with 11% and 11%, respectively), weight loss of ≥ 3% body weight (23% compared with 7% and 6%, respectively) and weight loss ≥ 5% body weight (12% compared with 4% and 2%, respectively). The results for weight loss responders were not adjusted for multiple statistical testing and should be interpreted with caution.

In general, patients treated with lixisenatide required a numerical increase in total daily basal insulin (0.70 units per day), whereas patients treated with insulin glulisine once daily and insulin glulisine three times daily required a numerical reduction in their total daily basal

insulin dose at week 26 (–0.06 units per day and –3.13 units per day, respectively). No numerical difference was observed in the adjusted mean difference between lixisenatide and insulin glulisine once daily (0.76 units per day [95% CI, –1.41 to 2.92]). Patients in the lixisenatide group required numerically more basal insulin than the insulin glulisine three times daily group with an adjusted mean difference of 3.83 units per day (95% CI, 1.66 to 6.00). The results for change in daily basal insulin were not adjusted for multiple statistical testing and should be considered exploratory; therefore, no statistical interpretations should be made.

Mean total daily insulin glulisine doses were [redacted] compared with 9.97 units per day and 20.24 units per day in the insulin glulisine once daily and insulin glulisine three times daily groups, respectively, [redacted] and week 26. Mean total daily insulin doses were [redacted] compared with 73.61 units per day and 81.05 units per day in the insulin glulisine once daily and insulin glulisine three times daily groups, respectively, [redacted] and week 26. The results for all changes in insulin were not adjusted for multiple statistical testing and should be considered exploratory; therefore, no statistical interpretations should be made.

[redacted]

Harms

Placebo-Controlled Trials

A numerically greater percentage of patients in the lixisenatide group experienced AEs compared with the placebo group in all placebo-controlled trials (range between 64% and 89% versus 41% and 86%, respectively). The most commonly reported AEs that occurred more frequently in the lixisenatide treatment groups compared with the placebo groups were hypoglycemia (ranged between 25% and 44% compared with 19% and 41%, respectively), nausea (ranged between 23% and 40% compared with 5% and 10%, respectively), headache (ranged between 2% and 13% compared with 0% and 10%, respectively), diarrhea (ranged between 3% and 11% compared with 2% and 6%, respectively), vomiting (ranged between 9% and 18% compared with 1% and 2%, respectively), and decreased appetite (ranged between 2% and 7% compared with 0% and 1%, respectively). Overall, the frequencies of AEs were relatively similar across trials; however, the difference in frequency of hypoglycemia in the lixisenatide group compared with the placebo group in GETGOAL –

L Asia was greater than those observed in the other placebo-controlled-trials (44% in the lixisenatide group compared with 24% in the placebo group). [redacted] SAEs were reported more frequently in the lixisenatide group compared with the placebo group (5% to 14% compared with 1% to 10%, respectively), with a similar frequency across all placebo-controlled trials.

A numerically greater percentage of patients in the lixisenatide group withdrew due to AEs compared with the placebo group in all trials (range between 4% and 11% versus 2% and 7%, respectively). The most commonly reported AEs leading to withdrawals that occurred more frequently in the lixisenatide treatment groups compared with the placebo groups were hypoglycemia, nausea, and vomiting. Overall, the frequency of WDAEs was relatively similar across trials.

[redacted] one death in GETGOAL – L Asia and two deaths in GETGOAL – DUO 1; however, none of the deaths were considered to be related to study treatment by the investigators and adjudication committee. No deaths were reported in GETGOAL – L – C.

For some of the notable harms, a numerically greater percentage of patients experienced an event in the lixisenatide group compared with the placebo group in all the placebo-controlled trials: hypoglycemia ([redacted] 44% versus 24%, 27% versus 19%, and 25% versus 20% for the lixisenatide versus the placebo groups in GETGOAL – L, GETGOAL – L Asia, GETGOAL – DUO 1, and GETGOAL – L – C, respectively), nausea ([redacted] 40% versus 5%, 27% versus 5%, and 23% versus 5% for the lixisenatide versus the placebo groups in GETGOAL – L, GETGOAL – L Asia, GETGOAL – DUO 1, and GETGOAL – L – C, respectively), diarrhea ([redacted] 7% versus 3%, 7% versus 3%, and [redacted] for the lixisenatide versus the placebo groups in GETGOAL – L, GETGOAL – L Asia, GETGOAL – DUO 1, and GETGOAL – L – C, respectively), vomiting ([redacted] 18% versus 2%, 9% versus 1%, and 11% versus 1% for the lixisenatide versus the placebo groups in GETGOAL – L, GETGOAL – L Asia, GETGOAL – DUO 1, and GETGOAL – L – C, respectively). The occurrence of the remaining notable harms — specifically allergic reaction, pancreatitis, injection site reaction and severe hypoglycemia — was approximately equal in both treatment groups across all the placebo-controlled trials, with the exception of injection site reaction in GETGOAL – DUO 1 (7% in the lixisenatide group compared with 2% in the placebo group).

Active-Controlled Trial

A similar percentage of patients in the lixisenatide group experienced AEs compared with the insulin glulisine once daily group and a numerically smaller percentage reported AEs when compared with insulin glulisine three times daily (74% versus 74% and 80%, respectively). The most commonly reported AEs that occurred more frequently in the lixisenatide treatment group compared with the insulin glulisine once daily and insulin glulisine three times daily groups were nausea (25% versus 2% and 1%, respectively), diarrhea (7% versus 3% and 1%, respectively), and vomiting (9% versus 2% and 2%, respectively). Contrarily, one commonly reported AE occurred more frequently in the insulin glulisine once daily and insulin glulisine three times groups compared with the lixisenatide group: hypoglycemia (47% and 52% versus 36%, respectively). SAEs were reported by 4% to 5% of patients, with a similar frequency between treatment groups.

A numerically greater percentage of patients in the lixisenatide group withdrew due to AEs compared with the insulin glulisine once daily and insulin glulisine three times daily groups (5% versus 1% and 1%, respectively). The most commonly reported AEs leading to withdrawal that occurred more frequently in the lixisenatide treatment groups compared with the insulin glulisine once daily and insulin glulisine three times daily groups were nausea and vomiting.

A total of three deaths occurred in GETGOAL – DUO 2; however, none of the deaths were considered to be related to study treatment by the investigators and adjudication committee.

For some of the notable harms, a numerically greater percentage of patients experienced an event in the lixisenatide group compared with the insulin glulisine once daily and insulin glulisine three times daily groups: nausea (25% versus 2% and 1%, respectively), diarrhea (7% versus 3% and 1%, respectively), and vomiting (9% versus 2% and 2%, respectively). Contrarily, one commonly reported AE occurred more frequently in the insulin glulisine once daily and insulin glulisine three times daily groups compared with the lixisenatide group: hypoglycemia (47% and 52% versus 36%, respectively). The occurrence of the remaining notable harms — specifically allergic reaction, pancreatitis, injection site reaction, and severe hypoglycemia — was approximately equal in all treatment groups.

Potential Place in Therapy[a]

In patients with type 2 diabetes mellitus who are managed with oral diabetes agents in combination with basal insulin but A1C is not at target, there are limited options for improving glycemic control. In these cases, the fasting blood glucose is typically at target due to the use of basal insulin, but postprandial blood glucose remains elevated. A switch to a more intensive insulin regimen is required in most cases, such as the addition of prandial insulin injections (multiple daily injections) or a switch to twice-daily, pre-mixed insulin. Both of these alternative regimens are more work intensive, less convenient for patients, and have the potential to increase hypoglycemia. For some patients, the addition of a GLP-1 receptor agonist such as lixisenatide is a reasonable alternative; however, the use of this medication class for many patients is currently limited by cost. According to the clinical expert consulted for this CADTH Common Drug Review (CDR), the manufacturer's reimbursement request for lixisenatide appears to be clinically appropriate, given that the use of a GLP-1 receptor agonist is an appealing alternative to intensifying a patient's insulin regimen. The same clinical expert noted that the evidence reviewed for this CDR submission suggests that lixisenatide can reduce postprandial blood glucose in a clinically meaningful way when added to basal insulin with or without oral antidiabetic therapies. However, in patients with significantly elevated A1C (e.g., greater than 2.0% above target), it is less likely that the addition of lixisenatide alone could optimize glycemic control, and intensification of insulin therapy would likely still be required. The evidence also suggests that the risk of hypoglycemia is lower with lixisenatide compared with the addition of prandial insulin.

The clinical expert consulted for this CDR review noted that lixisenatide could be particularly useful in patients with lower health literacy who may struggle with complex insulin regimens, as well as elderly patients and patients who are frail in whom hypoglycemia is avoided. Similarly, lixisenatide may also be preferred in patients who are overweight and obese, in whom the addition of short-acting insulin could predispose to weight gain. The same clinical expert noted that no specialized diagnostic testing would be required to identify patients in whom the addition of lixisenatide may be appropriate and that clinicians would likely base

their decision on A1C results as well as fasting and postprandial blood glucose testing, which would be routinely requested in this patient population.

The clinical expert highlighted one potential issue in the prescribing of lixisenatide. Given that there is a separate pen for each of the two drug doses (i.e., 10 mcg and 20 mcg), unlike other GLP-1 agonists where one pen can administer different doses, this implies that patients taking lixisenatide will be unable to self-titrate their dose based on tolerability per their physician's instructions, which could result in increased pharmacy faxes or physician visits for any changes in doses.

The clinical expert also highlighted that lixisenatide was found to be noninferior to placebo in terms of cardiovascular outcome in the ELIXA trial, which is reassuring for clinicians and patients. However, it should also be noted that other GLP-1 agonists have been shown to have cardiovascular benefit and that clinicians may prefer to use these agents, particularly in patients with high cardiovascular risk.

Conclusions

The CDR systematic review included four double-blind, phase III, placebo-controlled RCTs and one open-label, active-controlled RCT designed to assess the benefits of lixisenatide as an adjunct to diet and exercise to improve glycemic control in adult patients with type 2 diabetes mellitus in combination with a basal insulin (alone or with metformin).

Statistically significant differences in favour of lixisenatide compared with placebo were reported for the primary outcome (absolute change from baseline in A1C at week 24) in all placebo-controlled trials (GETGOAL – L [N = 495], GETGOAL – L Asia [N = 311], GETGOAL – DUO 1 [N = 446], and GETGOAL – L – C [N = 447]). Lixisenatide was also associated with benefits in some but not all secondary outcomes, including change in two-hour PPG and change in body weight. Key limitations of the placebo-controlled trials include randomization potentially being compromised due to study withdrawals; concerns with the statistical testing across secondary end points; concerns with the imputation model and the definitions of ITT analysis and hypoglycemia; lack of control for multiple statistical testing across subgroups of interest and sensitivity analyses; large placebo response; and the differences in patient and practice characteristics between the study centres included in the placebo-controlled trials and what would be seen in a Canadian setting (e.g., A1C and FPG near target, the mean age of patients, racial group, and the use of optimal standard antidiabetic practices). More patients in the lixisenatide group experienced AEs compared with the placebo group in all trials. The most commonly reported AEs that occurred more frequently in the lixisenatide treatment groups compared with the placebo groups were hypoglycemia, nausea, headache, diarrhea, vomiting, and decreased appetite, which is consistent with the gastrointestinal risk profile of GLP-1 agonists.

In addition, in GETGOAL – DUO 2, lixisenatide demonstrated noninferiority in the absolute change from baseline in A1C compared with insulin glulisine once daily and insulin glulisine three times daily using a noninferiority margin of 0.4% in three co-primary outcomes: 1) noninferiority of lixisenatide versus insulin glulisine once daily in the change from baseline in A1C at week 26 using a noninferiority margin of 0.4%; 2a) noninferiority of lixisenatide versus insulin glulisine three times daily in the change from baseline in A1C at week 26 using a noninferiority margin of 0.4%; and 2b) superiority of lixisenatide versus insulin glulisine three times daily in the change from baseline in body weight at week 26. Lixisenatide was also associated with benefits in some but not all secondary outcomes, including change in two-hour PPG. Key limitations of the trial include its open-label design,

concerns with the titration regimen of insulin, the imputation model, and the definitions of ITT analysis and hypoglycemia; lack of per-protocol analysis for noninferiority tests; randomization potentially being compromised due to study withdrawals; the lack of control for multiple statistical testing across all secondary end points, subgroups of interest, and sensitivity analyses; and the differences in patient and practice characteristics between the study centres included in GETGOAL – DUO 2 and what would be seen in a Canadian setting (e.g., A1C and FPG near target, the mean age of patients, racial group, and the use of optimal standard antidiabetic practices). The most commonly reported AEs that occurred more frequently in the lixisenatide treatment groups compared with the placebo groups were nausea, diarrhea, and vomiting, which is consistent with the gastrointestinal risk profile of GLP-1 agonists. However, more hypoglycemic events were reported in patients treated with insulin glulisine once daily and insulin glulisine three times daily compared with lixisenatide.

Overall, it is important to note that lixisenatide was found to be noninferior to placebo in terms of cardiovascular outcome in the ELIXA trial.

Table 1: Summary of Results for the Placebo-Controlled Trials

End Point	GETGOAL							
	– L		– L (Asia)		– DUO 1		– L – C	
	PLB N = 167	LIXI N = 328	PLB N = 157	LIXI N = 154	PLB N = 223	LIXI N = 223	PLB N = 224	LIXI N = 224
A1C (%)								
Baseline, n (%)	158 (95)	304 (93)	154 (98)	146 (95)	221 (99)	215 (96)	221 (99)	220 (98)
Baseline, mean (SD)	8.38 (0.83)	8.39 (0.86)	8.53 (0.78)	8.53 (0.73)	7.60 (0.54)	7.56 (0.54)	7.93 (0.69)	7.90 (0.66)
Adjusted LS mean change from baseline at week 24 (SE)	–0.38 (0.11)	–0.74 (0.09)	0.11 (0.13)	–0.77 (0.14)	–0.40 (0.09)	–0.71 (0.09)	–0.11 (0.09)	–0.62 (0.09)
Adjusted LS MD versus placebo (95% CI)	–0.36 (–0.55, –0.17) *P* = 0.0002		-0.88 (–1.12, –0.65) *P* < 0.0001		–0.32 (–0.46, –0.17) *P* < 0.0001		–0.51 (–0.69, –0.34) *P* < 0.0001	
Mean change from baseline at last visit[a] (SE)	[redacted]	[redacted]	NA	NA	NA	NA	NA	NA
A1C responders,[b] n (%)								
≤ 6.5%	6 (4)	44 (14)	2 (1)	26 (18)	36 (16)	69 (32)	13 (6)	49 (22)
> 6.5%	152 (96)	260 (86)	152 (99)	120 (82)	[redacted]	[redacted]	16.3% (10.2, 22.5)[d]	
P value	NA[c]		NA[c]		NA[c]		NA[c]	
< 7.0%	19 (12)	86 (28)	8 (5)	52 (36)	85 (39)	121 (56)	30 (14)	82 (37)
≥ 7.0%	139 (88)	218 (72)	146 (95)	94 (64)	[redacted]	[redacted]	23.6% (16.1, 31.1)[d]	
P value	NA[c]		NA[c]		NA[c]		NA[c]	
Two-hour PPG (mmol/L)								
Baseline, n (%)	123 (74)	235 (72)	142 (90)	131 (85)	204 (91)	194 (87)	199 (89)	200 (89)
Baseline, mean (SD)	15.85 (3.71)	16.44 (4.29)	17.99 (3.66)	17.88 (3.27)	12.85 (3.75)	13.02 (3.83)	14.07 (3.62)	13.71 (4.26)
Adjusted LS mean change from baseline at week 24 (SE)	–1.72 (0.54)	–5.54 (0.47)	–0.14 (0.56)	–7.96 (0.60)	0.08 (0.48)	–3.09 (0.48)	–0.61 (0.42)	–4.06 (0.41)
Adjusted LS MD versus placebo (95% CI)	–3.81 (–4.70, –2.93) *P* < 0.0001		–7.83 (–8.89, –6.77) *P* < 0.0001		–3.16 (–3.95, –2.38) *P* < 0.0001		–3.45 (–4.23, –2.67) *P* < 0.0001	
Mean change from baseline at last visit[a] (SE)	[redacted]	[redacted]	NA	NA	NA	NA	NA	NA
Glucose excursion								

End Point	GETGOAL							
	– L		– L (Asia)		– DUO 1		– L – C	
	PLB N = 167	LIXI N = 328	PLB N = 157	LIXI N = 154	PLB N = 223	LIXI N = 223	PLB N = 224	LIXI N = 224
(mmol/L)								
Baseline, n (%)	123 (74)	233 (71)	142 (90)	131 (85)	204 (91)	194 (87)	NR	NR
Baseline, mean (SD)	7.21 (3.44)	7.69 (3.47)	9.94 (4.00)	9.72 (3.22)	6.37 (3.61)	6.40 (4.21)	NR	NR
Adjusted LS mean change from baseline at week 24 (SE)	–0.34 (0.47)	–4.14 (0.41)	0.14 (0.54)	–7.09 (0.58)	–0.33 (0.46)	–3.42 (0.46)	–0.74 (NR)	–3.87 (NR)
Adjusted LS MD versus placebo (95% CI)	–3.80 (–4.57, –3.03) NA[c]		–7.22 (–8.25, –6.20) NA[c]		–3.09 (–3.84, –2.33) NA[c]		–3.13 (–3.83, –2.43) NA[c]	
Mean change from baseline at last visit[a] (SE)	[redacted]	[redacted]	NA	NA	NA	NA	NA	NA
Average seven-point SMPG (mmol/L)								
Baseline, n (%)	153 (92)	294 (90)	138 (88)	142 (92)	214 (96)	210 (94)	214 (96)	213 (95)
Baseline, mean (SD)	10.57 (2.69)	10.74 (2.57)	11.44 (2.45)	11.56 (2.54)	8.29 (1.52)	8.20 (1.45)	9.30 (1.86)	9.22 (1.87)
Adjusted LS mean change from baseline at week 24 (SE)	–0.61 (0.24)	–1.49 (0.20)	–0.56 (0.27)	–1.91 (0.27)	–0.08 (0.18)	–0.47 (0.18)	0.06 (0.17)	–0.48 (0.17)
Adjusted LS MD versus placebo (95% CI)	–0.88 (–1.31, –0.45) *P* < 0.0001		–1.35 (–1.84, –0.86) NA[c]		–0.39 (–0.68, –0.11) *P* = 0.0071		–0.54 (–0.87, –0.21) *P* = 0.0014	
Mean change from baseline at last visit[a] (SE)	[redacted]	[redacted]	NA	NA	NA	NA	NA	NA
FPG (mmol/L)								
Baseline, n (%)	163 (98)	317 (97)	157 (100)	148 (96)	220 (99)	214 (96)	219 (98)	219 (98)
Baseline, mean (SD)	8.03 (2.65)	8.11 (2.84)	7.75 (2.25)	7.64 (2.31)	6.69 (1.98)	6.56 (1.74)	6.92 (1.79)	7.05 (2.06)
Adjusted LS mean change from baseline at week 24 (SE)	–0.55 (0.28)	–0.63 (0.23)	0.25 (0.30)	–0.42 (0.31)	0.46 (0.21)	0.34 (0.21)	0.55 (0.21)	0.17 (0.21)
Adjusted LS MD versus placebo (95% CI)	–0.08 (–0.59, 0.43) *P* = 0.7579		–0.67 (–1.23, –0.11) NA[c]		–0.12 (–0.46, 0.23) *P* = 0.5142		–0.38 (–0.79, 0.02) *P* = 0.0650	
Mean change from baseline at last visit[a] (SE)	[redacted]	[redacted]	NA	NA	NA	NA	NA	NA
Body weight (kg)								
Baseline, n (%)	161 (96)	311 (95)	157 (100)	150 (97)	220 (99)	217 (97)	220 (98)	219 (98)
Baseline, mean (SD)	89.11 (21.00)	87.39 (20.00)	65.60 (12.47)	65.99 (12.94)	86.74 (20.54)	87.47 (21.98)	74.59 (13.29)	74.19 (14.05)
Adjusted LS mean change from baseline at week 24 (SE)	–0.52 (0.29)	–1.80 (0.25)	0.06 (0.27)	–0.38 (0.28)	1.16 (0.33)	0.28 (0.33)	–0.07 (0.22)	–1.24 (0.22)
Adjusted LS MD versus placebo (95% CI)	–1.28 (–1.80, –0.75) NA[c]		–0.43 (–0.93, 0.06) *P* = 0.0857		–0.89 (–1.42, –0.35) *P* = 0.0012		–1.17 (–1.60, –0.74) *P* < 0.0001	
Mean change from baseline at last visit[a] (SE)	[redacted]	[redacted]	NA	NA	NA	NA	NA	NA
Weight loss responders, n (%)	[redacted]	[redacted]	157 (100)	150 (97)	NR	NR	NR	NR

End Point	GETGOAL							
	– L		– L (Asia)		– DUO 1		– L – C	
	PLB N = 167	LIXI N = 328	PLB N = 157	LIXI N = 154	PLB N = 223	LIXI N = 223	PLB N = 224	LIXI N = 224
≥ 5% body weight lost	[redacted]	[redacted]	7 (5)	11 (7)	NR	NR	NR	NR
< 5% body weight lost	[redacted]	[redacted]	150 (95)	139 (93)	NR	NR	NR	NR
Rescue therapy, n (%)								
During 24-week DB phase								
Yes	12 (7)	19 (6)	5 (3)	2 (1)	1 (< 1)	1 (< 1)	NR	NR
P value	NA[c]		NA[c]		NA[c]		NR	
During whole DB phase[e]								
Yes	[redacted]	[redacted]	NA	NA	NA	NA	NA	NA
Change in total daily basal insulin (U)								
Baseline, n (%)	165 (99)	325 (99)	157 (100)	151 (98)	223 (100)	222 (100)	215 (96)	213 (95)
Baseline, mean dose (SD)	57.65 (34.73)	53.62 (33.97)	24.11 (14.18)	24.87 (14.02)	44.24 (19.86)	43.41 (18.87)	37.51 (16.07)	39.85 (19.15)
Adjusted LS mean change from baseline at week 24 (SE)	–1.93 (1.59)	–5.62 (1.32)	–0.11 (0.44)	–1.39 (0.46)	5.34 (1.26)	3.10 (1.26)	–1.87 (0.39)	–2.98 (0.39)
Adjusted LS MD versus placebo (95% CI)	–3.69 (–6.57, –0.82) NA[c]		–1.29 (–2.10, –0.48) NA[c]		–2.24 (–4.26 to –0.22) *P* = 0.0300		–1.11 (–1.86, –0.37) *P* = 0.0033	
Mean change from baseline at last visit[a] (SE)	[redacted]	[redacted]	NA	NA	NA	NA	NA	NA
Patients with > 0 AEs, n (%)	[redacted]	[redacted]	110 (70)	137 (89)	152 (68)	178 (80)	91 (41)	143 (64)
Most common AEs[f]								
Hypoglycemia	[redacted]	[redacted]	37 (24)	67 (44)	[redacted]	[redacted]	[redacted]	[redacted]
Nausea	[redacted]	[redacted]	7 (5)	61 (40)	11 (5)	61 (27)	12 (5)	51 (23)
Headache	[redacted]	[redacted]	3 (2)	16 (10)	[redacted]	[redacted]	0	5 (2)
Diarrhea	[redacted]	[redacted]	4 (3)	10 (7)	7 (3)	15 (7)	[redacted]	[redacted]
Nasopharyngitis	[redacted]	[redacted]	20 (13)	21 (14)	[redacted]	[redacted]	[redacted]	[redacted]
Vomiting	[redacted]	[redacted]	3 (2)	28 (18)	3 (1)	21 (9)	2 (1)	25 (11)
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Dizziness	[redacted]	[redacted]	8 (5)	13 (8)	[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Upper respiratory tract infection	[redacted]	[redacted]	1 (1)	7 (5)	[redacted]	[redacted]	[redacted]	[redacted]
Bronchitis	[redacted]	[redacted]	2 (1)	0	[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Asthenia	[redacted]	[redacted]	12 (8)	10 (7)	[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Dyspepsia	[redacted]	[redacted]	0	11 (7)	[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Abdominal discomfort	[redacted]	[redacted]	1 (1)	11 (7)	[redacted]	[redacted]	[redacted]	[redacted]
Decreased appetite	[redacted]	[redacted]	0	10 (7)	[redacted]	[redacted]	[redacted]	[redacted]

End Point	GETGOAL							
	– L		– L (Asia)		– DUO 1		– L – C	
	PLB N = 167	LIXI N = 328	PLB N = 157	LIXI N = 154	PLB N = 223	LIXI N = 223	PLB N = 224	LIXI N = 224
Constipation	[redacted]	[redacted]	4 (3)	8 (5)	[redacted]	[redacted]	[redacted]	[redacted]
Patients with > 0 SAEs, n (%)	[redacted]	[redacted]	9 (6)	10 (7)	10 (5)	17 (8)	2 (1)	11 (5)
Most common reasons[g]								
Coronary artery disease	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
WDAEs, n (%)	[redacted]	[redacted]	5 (3)	14 (9)	8 (4)	19 (9)	[redacted]	[redacted]
Most common reasons								
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Number of deaths, n (%)	[redacted]	[redacted]	1 (1)	0	2 (1)	0	0	0
Notable harms, n (%)								
Hypoglycemia	[redacted]	[redacted]	37 (24)	67 (44)	[redacted]	[redacted]	[redacted]	[redacted]
Nausea	[redacted]	[redacted]	7 (5)	61 (40)	11 (5)	61 (27)	12 (5)	51 (23)
Diarrhea	[redacted]	[redacted]	4 (3)	10 (7)	7 (3)	15 (7)	[redacted]	[redacted]
Vomiting	[redacted]	[redacted]	3 (2)	28 (18)	3 (1)	21 (9)	2 (1)	25 (11)
Allergic reaction	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Pancreatitis	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Injection site reaction	[redacted]	[redacted]	2 (1)	2 (1)	5 (2)	15 (7)	[redacted]	[redacted]
Severe hypoglycemia	[redacted]	[redacted]	0	0	0	1 (< 1)	NR	NR

A1C = glycated hemoglobin; AE = adverse event; ANCOVA = analysis of covariance; CI = confidence interval; CSR = Clinical Study Report; DB = double-blind; FPG = fasting plasma glucose; LIXI = lixisenatide; LS = least squares; MD = mean difference; NA = not applicable; NR = not reported; PLB = placebo; PPG = postprandial glucose; RCT = randomized controlled trial; SMPG = self-monitored plasma glucose; SAE = serious adverse event; SD = standard deviation; SE = standard error; WDAE = withdrawal due to adverse event.

Note: All efficacy outcomes are based on the modified intention-to-treat population and do not include patients requiring rescue therapy.

Harms analyses are based on the safety population.

Last observation carried forward was used to impute missing data.

Means and mean differences were analyzed using an ANCOVA model with treatment groups (lixisenatide and placebo), randomization strata of screening A1C (< 8.0, ≥ 8.0%), randomization strata of metformin use at screening (yes, no), country as fixed effects, and baseline A1C value as a covariate in GETGOAL – L and GETGOAL – L – C. Instead of randomization strata of metformin use at screening (yes, no) as fixed effects in the ANCOVA model, randomization strata of sulfonylurea use at screening (yes, no) and randomization strata of thiazolidinedione use at screening (yes, no) were used in GETGOAL – L Asia and GETGOAL – DUO 1, respectively.

[a] "Last visit" refers to the final visit conducted in the extension phase of GETGOAL – L.

[b] A1C responder analysis was not part of the statistical testing hierarchy and is therefore considered exploratory.

[c] Previous end point in the statistical testing order failed before the testing for significance in this end point (statistical significance of this end point should not have been tested and should be considered exploratory).

[d] Difference between lixisenatide and comparator.

[e] Includes rescue therapy administered during the extension phase of GETGOAL – L.

[f] Frequency ≥ 5%.

[g] Frequency ≥ 2%.

Source: Riddle 2013,[4] GETGOAL – L CSR,[5] Riddle 2013,[6] GETGOAL – DUO 1 CSR,[7] Seino 2012,[8] GETGOAL – L Asia CSR,[9] and GETGOAL – L – C CSR.[10]

Table 2: Summary of Results for the Active-Controlled Trial

End Point[a]	GETGOAL – DUO 2		
	LIXI N = 298	IG Once Daily N = 298	IG Three Times Daily N = 298
A1C (%)			
Baseline, n (%)	292 (98)	292 (98)	295 (99)
Baseline, mean (SD)	7.76 (0.56)	7.72 (0.58)	7.79 (0.60)
Adjusted LS mean change from baseline at week 26 (SE)	–0.63 (0.05)	–0.58 (0.05)	–0.84 (0.05)
Adjusted LS MD versus comparator (95% CI)		–0.05 (–0.17, 0.06)	0.21 (0.1, 0.33)
A1C responders, n (%)			
≤ 6.5	60 (21)	52 (18)	91 (31)
Difference versus comparator (95% CI)		2.7% (–3.6, 9.0)	–10.5% (–17.3, –3.6)
< 7.0	123 (42)	112 (38)	145 (49)
Difference versus comparator (95% CI)		3.7% (–4.0, 11.5)	–7.3% (–15.1, 0.6)
Two-hour PPG (mmol/L)			
Baseline, n (%)	69 (23)	55 (18)	68 (23)
Baseline, mean (SD)	14.12 (3.62)	13.82 (3.52)	14.56 (3.48)
Adjusted LS mean change from baseline at week 26 (SE)	–3.64 (0.59)	–1.57 (0.60)	–1.41 (0.58)
Adjusted LS MD versus comparator (95% CI)		–2.07 (–3.29, –0.85)	–2.23 (–3.39, –1.07)
Glucose excursion (mmol/L)			
Baseline, n (%)	[redacted]	[redacted]	[redacted]
Baseline, mean (SD)	[redacted]	[redacted]	[redacted]
Adjusted LS mean change from baseline at week 26 (SE)	[redacted]	[redacted]	[redacted]
Adjusted LS MD versus comparator (95% CI)		[redacted]	[redacted]
Average seven-point SMPG (mmol/L)			
Baseline, n (%)	270 (91)	268 (90)	278 (93)
Baseline, mean (SD)	9.010 (1.746)	9.052 (1.743)	8.941 (1.545)
Adjusted LS mean change from baseline at week 26 (SE)	–0.784 (0.114)	–0.782 (0.113)	–1.053 (0.111)
Adjusted LS MD versus comparator (95% CI)		–0.002 (–0.245, 0.240)	0.269 (0.0283, 0.510)
FPG (mmol/L)			
Baseline, n (%)	295 (99)	295 (99)	294 (99)
Baseline, mean (SD)	6.58 (1.83)	6.85 (1.99)	6.65 (1.89)
Adjusted LS mean change from baseline at week 26 (SE)	–0.23 (0.14)	–0.21 (0.14)	–0.06 (0.14)
Adjusted LS MD versus comparator (95% CI)		–0.01 (–0.32 to 0.30)	–0.17 (–0.48 to 0.14)
Body weight (kg)			
Baseline, n (%)	295 (99)	295 (99)	295 (99)
Baseline, mean (SD)	90.10 (17.39)	88.37 (15.88)	90.00 (17.21)
Adjusted LS mean change from baseline at week 26 (SE)	–0.63 (0.28)	1.03 (0.28)	1.37 (0.27)
Adjusted LS MD versus comparator (95% CI)		–1.66 (–2.26, -1.06) *P* value NR	–1.99 (–2.59, –1.40) *P* < 0.0001
Patients with no weight gain, n (%)			
Responders	191 (65)	108 (37)	90 (31)
Lixisenatide versus comparator response (95% CI)		28.1% (20.5, 35.8)	34.2% (26.7, 41.7)

End Point[a]	GETGOAL – DUO 2		
	LIXI N = 298	**IG Once Daily N = 298**	**IG Three Times Daily N = 298**
Weight loss responders, n (%)			
≥ 2% weight reduction	97 (33)	33 (11)	32 (11)
Lixisenatide versus comparator response (95% CI)		21.7% (15.3, 28.1)	22.0% (15.6, 28.4)
≥ 3% weight reduction	69 (23)	21 (7)	18 (6)
Lixisenatide versus comparator response (95% CI)		16.3% (10.7, 22.0)	17.3% (11.8, 22.9)
≥ 5% weight reduction	36 (12)	11 (4)	7 (2)
Lixisenatide versus comparator response (95% CI)		8.5% (4.1, 12.9)	9.8% (5.7, 14.0)
Change in total daily basal (glargine) insulin (U)			
Baseline, n (%)	292 (98)	294 (99)	294 (99)
Baseline, mean (SD)	67.45 (31.68)	64.79 (32.09)	65.05 (27.01)
Adjusted LS mean change from baseline at week 26 (SE)	0.70 (1.00)	–0.06 (1.00)	–3.13 (0.98)
Adjusted LS MD versus comparator (95% CI)		0.76 (–1.41, 2.92)	3.83 (1.66, 6.00)
Mean total daily insulin glulisine dose (U)			
Week 2 (SD)	NA	[redacted]	[redacted]
Week 26 (SD)	NA	10.44 (8.10)	21.53 (13.43)
Week 26 LOCF (SD)	NA	9.97 (7.80)	20.24 (13.04)
Mean total daily insulin dose (U)			
Week 2 (SD)	NA	[redacted]	[redacted]
Week 26 (SD)	NA	75.14 (40.48)	83.61 (33.52)
Week 26 LOCF (SD)	NA	73.61 (39.13)	81.05 (33.55)
[redacted]			
[redacted]			
[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]
[redacted]		[redacted]	[redacted]
[redacted]			
[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]
[redacted]		[redacted]	[redacted]
[redacted]			
[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]
[redacted]		[redacted]	[redacted]
[redacted]			
[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]

End Point[a]	GETGOAL – DUO 2		
	LIXI N = 298	IG Once Daily N = 298	IG Three Times Daily N = 298
[redacted]			
[redacted]			
[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]
[redacted]			
[redacted]			
[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]
[redacted]			
Patients with > 0 AEs, n (%)	221 (74)	222 (74)	236 (80)
Most common AEs[b]			
[redacted]	[redacted]	[redacted]	[redacted]
Nausea	75 (25)	5 (2)	3 (1)
[redacted]	[redacted]	[redacted]	[redacted]
Diarrhea	20 (7)	10 (3)	4 (1)
[redacted]	[redacted]	[redacted]	[redacted]
Vomiting	26 (9)	5 (2)	6 (2)
[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]
Patients with > 0 SAEs, n (%)	11 (4)	11 (4)	14 (5)
Most common reasons[d]			
[redacted]	[redacted]	[redacted]	[redacted]
WDAEs, n (%)	15 (5)	2 (1)	3 (1)
Most common reasons			
[redacted]	[redacted]	[redacted]	[redacted]

End Point[a]	GETGOAL – DUO 2		
	LIXI N = 298	IG Once Daily N = 298	IG Three Times Daily N = 298
[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]
Number of deaths, n (%)	1 (< 1)	0	2 (1)
Notable harms, n (%)			
Hypoglycemia	[redacted]	[redacted]	[redacted]
Nausea	75 (25)	5 (2)	3 (1)
Diarrhea	20 (7)	10 (3)	4 (1)
Vomiting	26 (9)	5 (2)	6 (2)
Allergic reaction	[redacted]	[redacted]	[redacted]
Pancreatitis	[redacted]	[redacted]	[redacted]
Injection site reaction	[redacted]	[redacted]	[redacted]
Severe hypoglycemia	0	2 (1)	0

A1C = glycated hemoglobin; AE = adverse event; ANCOVA = analysis of covariance; CI = confidence interval; FPG = fasting plasma glucose; IG = insulin glulisine; IWQOL-Lite = Impact of Weight on Quality of Life–Lite; LIXI = lixisenatide; LOCF = last observation carried forward; LS = least squares; MD = mean difference; NA = not applicable; NR = not reported; PPG = postprandial glucose; RCT = randomized controlled trial; SAE = serious adverse event; SMPG = self-monitored plasma glucose; t.i.d. = three time daily; SD = standard deviation; SE = standard error; WDAE = withdrawal due to adverse event.

Note: All efficacy outcomes are based on the modified intention-to-treat population.

Harms analyses are based on the safety population.

LOCF was used to impute missing data.

P values not reported for any end point in GETGOAL – DUO 2.

Lixisenatide met the noninferiority margin of 0.4% when compared with both insulin glulisine once daily and insulin glulisine t.i.d. in terms of absolute change from baseline in A1C at week 26, and was superior when compared with insulin glulisine t.i.d. in terms of change from baseline in body weight at week 26.

Means and mean differences were analyzed using an ANCOVA model with treatment groups (lixisenatide, insulin glulisine once daily, and insulin glulisine t.i.d.), randomization strata of screening A1C (< 8.0, ≥ 8.0%), randomization strata of metformin use at screening (yes, no), country as fixed effects, and baseline A1C value as a covariate.

[a] End points other than the co-primary end points (absolute change from baseline in A1C for lixisenatide compared with insulin glulisine once daily and insulin glulisine t.i.d., and change from baseline in body weight for lixisenatide compared with insulin glulisine t.i.d. at week 26) were not part of the statistical testing hierarchy and are therefore considered exploratory.

[b] Frequency ≥ 5%.

[c] Asymptomatic hypoglycemia.

[d] Frequency ≥ 2%.

Source: Rosenstock 2016[11] and GETGOAL – DUO 2 Clinical Study Report.[12]

Introduction

Disease Prevalence and Incidence

Diabetes mellitus is a metabolic disease that is characterized by persistent elevations in blood glucose (hyperglycemia). This persistent elevated blood glucose causes damage to blood vessels on a microvascular (retinopathy, nephropathy, neuropathy) and macrovascular (peripheral artery disease, cardiovascular disease) level. There are two main subtypes of diabetes mellitus: type 1 diabetes mellitus, in which the primary problem is a lack of adequate insulin secretion from pancreatic beta cells, and type 2 diabetes mellitus, in which cells are unresponsive to insulin. Type 2 diabetes mellitus is more common than type 1 diabetes mellitus, accounting for approximately 90% of cases of diabetes mellitus.[13] The etiology of type 1 diabetes mellitus is unknown, although onset is typically early in life. In contrast, onset of type 2 diabetes mellitus is typically later in life, although this is changing with the current epidemic of childhood obesity in western societies. Poor diet and minimal exercise, and associated weight gain, are considered to be risk factors for type 2 diabetes mellitus.[14] There is overlap between the two conditions, most notably patients with type 2 diabetes mellitus — who in the initial stages of their disease are able to secrete insulin or may be hyperinsulinemic — progress to a stage where insulin secretion is reduced, similar to type 1 diabetes mellitus.

Diabetes has significant health impacts on individuals and societies. The prevalence of diabetes is increasing at a dramatic rate around the world. An estimated 422 million adults were living with diabetes globally in 2014, compared with 108 million in 1980; this number is projected to increase to 642 million by 2040.[15,16] Diabetes is one of the most common chronic diseases in Canada. Diabetes Canada estimated that there were 3.4 million people (9.3% of the population) with diabetes in 2015, and that by 2025 this number will increase to five million people (12.1%).[17] People with diabetes are more likely to be hospitalized and to experience complications requiring specialist care. By 2020, the diabetes-associated costs to the Canadian health care system are estimated to increase to C$16.9 billion per year.[18]

Standards of Therapy

Treatment regimens and therapeutic targets should be individualized in patients with type 2 diabetes mellitus. Treatment usually begins with lifestyle modification including exercise and diet. When lifestyle interventions are not sufficient to control blood glucose levels, pharmacological treatment becomes necessary.[19,20] There are many classes of antidiabetic drugs used in treating type 2 diabetes mellitus, including insulin. Metformin is indicated for most patients and is considered to be the first-line drug of choice. When initial therapy with lifestyle intervention and metformin monotherapy fails to achieve adequate glycemic control, a second or third agent can be added to metformin. Several oral antidiabetic agents can be used with metformin, such as sulfonylureas, meglitinides, thiazolidinediones, alpha-glucosidase inhibitors, dipeptidyl peptidase-4 (DPP-4) inhibitors, and sodium-glucose cotransporter-2 (SGLT2). Injectable agent (glucagon-like peptide-1 [GLP-1] receptor agonists; insulin and insulin analogues in rapid-acting, intermediate or longer-acting forms) can be added to metformin when metformin monotherapy fails, or patients are switched to insulin.[20] In deciding upon which agent to add after metformin, there must be consideration of multiple factors, for example: the agent's effectiveness at blood glucose and glycated hemoglobin (A1C) lowering, concerns regarding hypoglycemia, ability to reduce the risk of diabetic microvascular and/or macrovascular complications, and effect on body weight.[19]

Although there are currently numerous therapeutic options and combination therapy strategies available, many patients do not achieve adequate glycemic control on oral antidiabetic treatments alone and require the addition of basal insulin to restore A1C to target levels (i.e., < 7.0%).[21-23] Despite the use of a basal insulin, some patients will require further treatment to achieve or maintain this glycemic target.[4,6] The addition of one or more injections of a prandial insulin before mealtime is an effective option; however, this also has drawbacks, including complexity, increased testing, risk of hypoglycemia, and weight gain.[6]

Drug

Lixisenatide is a potent and selective prandial GLP-1 receptor agonist that mimics the effect of endogenous GLP-1, thereby stimulating glucose-dependent insulin secretion thus limiting hypoglycemia, decreasing glucagon output, slowing gastric emptying, and inducing satiety, providing beneficial effects on weight.[24] It is believed A1C targets are achieved through control of both the fasting plasma glucose (FPG) and the postprandial glucose (PPG). Unlike some other antidiabetic therapies (e.g., basal insulin), lixisenatide mainly reduces the PPG, which provides a complementary mechanism of action when used in conjunction with basal insulin, which acts primarily on FPG.[1,2] Furthermore, lixisenatide has been shown to have a robust and pronounced effect on PPG that is sustained throughout the day. The recommended starting dose of lixisenatide is 10 mcg once daily, administered subcutaneously (in the thigh, abdomen, or upper arm) within the hour before any meal. Lixisenatide should ideally be administered before the same meal every day. The dose should be increased and maintained at 20 mcg once daily for additional glycemic control. The maximum recommended dose is 20 mcg once daily. Lixisenatide is available in as a pre-filled pen in strengths of 0.05 mg/mL and 0.1 mg/mL to deliver 14 doses of 10 mcg per dose or 20 mcg per dose, respectively. Other GLP-1 receptor agonists currently approved in Canada are dulaglutide, albiglutide, exenatide, and liraglutide.

Lixisenatide is indicated as an adjunct to diet and exercise to improve glycemic control in adult patients with type 2 diabetes mellitus in combination with a basal insulin (alone or with metformin).[3] According to the Health Canada–approved product monograph, lixisenatide should be used as an adjunct to diet and exercise to improve glycemic control in adult patients with type 2 diabetes mellitus in combination with metformin, a sulfonylurea (alone or with metformin), pioglitazone (alone or with metformin), or a basal insulin (alone or with metformin) when these therapies do not provide adequate glycemic control.[3]

Table 3: Key Characteristics of GLP-1 Analogues, TZDs, DPP-4 Inhibitors, and Insulin

	GLP-1 Analogues	Thiazolidinediones	DPP-4 Inhibitors	Insulin/Insulin Analogues
Mechanism of Action	Mimic GLP-1, which: • leads to insulin secretion • inhibits glucagon release • delays gastric emptying • reduces food intake.	PPAR-γ agonists: • increase uptake of FFA • increase uptake of glucose • reduce glucose synthesis.	Increase GLP-1 by inhibiting the DPP-4 enzyme, which inactivates GLP-1 and: • leads to insulin secretion • inhibits glucagon release • delays gastric emptying • reduces food intake.	Substitute for endogenously secreted insulin.
Indication[a]	Liraglutide: T2DM in combination with metformin, or metformin and a sulfonylurea, when these drugs, with diet and exercise, do not provide adequate glycemic control; T2DM in combination with metformin and a basal insulin when liraglutide and metformin, with diet and exercise, do not provide adequate glycemic control. Albiglutide: T2DM that cannot be adequately controlled by diet and exercise alone. May be used as monotherapy or in combination with metformin, metformin and a sulfonylurea, or basal insulin with oral antidiabetic therapies. Exenatide (twice daily): T2DM that cannot be adequately controlled by diet and exercise alone. May be used as monotherapy or in combination with metformin, a sulfonylurea, or metformin and a sulfonylurea. Exenatide (extended-release, once weekly): T2DM that cannot be adequately controlled by diet and exercise alone.	T2DM that cannot be adequately controlled by diet and exercise alone. May be used as monotherapy or in combination with a sulfonylurea or metformin when monotherapy fails to adequately control blood glucose.	Saxagliptin: T2DM in combination with metformin, a sulfonylurea, insulin (with or without metformin), or metformin and a sulfonylurea when these drugs, used alone with diet and exercise, do not provide adequate glycemic control Sitagliptin: T2DM as monotherapy, in combination with metformin, a sulfonylurea and metformin, insulin (with or without metformin), pioglitazone, or metformin and pioglitazone when these drugs, with diet and exercise, do not provide adequate glycemic control. Linagliptin: T2DM as monotherapy, in combination with metformin, a sulfonylurea, or metformin and a sulfonylurea when these drugs, with diet and exercise, do not provide adequate glycemic control.	Patients with DM who require insulin for control of hyperglycemia.

	GLP-1 Analogues	Thiazolidinediones	DPP-4 Inhibitors	Insulin/Insulin Analogues
	May be used in combination with metformin, a sulfonylurea, metformin and a sulfonylurea, or insulin glargine. Dulaglutide: T2DM that cannot be adequately controlled by diet and exercise alone. May be used in combination with metformin, metformin and a sulfonylurea, or prandial insulin with metformin. Lixisenatide: T2DM that cannot be adequately controlled by diet and exercise alone in combination with a basal insulin alone or with metformin.			
Route of Administration	Subcutaneous	Oral	Oral	Subcutaneous
Recommended Dose	Varies by drug	15 mg to 30 mg once daily	Varies by drug	Titrated
Serious Side Effects and Safety Issues	Warnings/Precautions • Thyroid cancer • Prolonged PR interval • Hypoglycemia (when combined with sulfonylurea) • Pancreatitis • GI disorders Contraindications • Personal or family history of MTC and in patients with MEN2	Serious warning • Bone fractures in women • Fluid retention Warnings/Precautions • Bladder cancer • Heart failure • Hepatitis/hepatic failure	Contraindications • DKA Warnings/precautions • Heart failure • pancreatitis • immune suppression	Serious Warnings and Precautions • Hypoglycemia • Immune responses

DKA = diabetic ketoacidosis; DM = diabetes mellitus; DPP-4 = dipeptidyl peptidase-4; FFA = free fatty acid; GLP-1 = glucagon-like peptide-1; MEN2 = multiple endocrine neoplasia syndrome type 2; MTC = medullary thyroid carcinoma; PPAR = peroxisome proliferator-activated receptor; T2DM = type 2 diabetes mellitus; TZD = thiazolidinedione.

[a] Health Canada indication.

Source: Product monographs from e-CPS.[25]

Table 4: Key Characteristics of SGLT2 Inhibitors, Metformin, and Sulfonylureas

	SGLT2 Inhibitors	Biguanides (Metformin)	Sulfonylurea
Mechanism of Action	Inhibits the SGLT2 transporter in the kidney, leading to increased glucose excretion.	Reduces gluconeogenesis, increases conversion of glucose to glycogen, and increases degradation of glucose.	Promotes insulin secretion by binding to the sulfonylurea receptor (SUR-1).
Indication[a]	Canagliflozin: In T2DM: • as monotherapy in patients for whom metformin is inappropriate • in combination with metformin or a sulfonylurea when diet and exercise plus monotherapy with one of these agents does not provide adequate glycemic control • in combination with metformin and either a sulfonylurea or pioglitazone when diet, exercise, and dual therapy (with metformin plus either a sulfonylurea or pioglitazone) do not provide adequate glycemic control • in combination therapy with insulin (with or without metformin) when diet and exercise, and therapy with insulin (with or without metformin), do not provide adequate glycemic control.	T2DM that cannot be controlled by proper dietary management, exercise, and weight reduction, or when insulin therapy is not appropriate. Treatment of obese patients with diabetes.	T2DM in adults, alone or in combination with other antihyperglycemic agents, as an adjunct to exercise and diet.
Route of Administration	Oral	Oral	Oral
Recommended Dose	100 mg to 300 mg once daily	850 mg to 1000 mg twice daily	Varies by drug
Serious Side Effects and Safety Issues	Contraindications • Patients who experience renal impairment with eGFR less than 45 mL/min/1.73 m^2, end-stage renal disease or patients on dialysis Warnings/Precautions: • reduced intravascular volume • hypoglycemia when combined with antihyperglycemics • increase in LDL-C • hyperkalemia • impaired renal function.	Contraindications • Acute or chronic metabolic acidosis including diabetic ketoacidosis • Severe renal impairment Warnings • Lactic acidosis (rare)	Contraindications • Ketoacidosis • Severe liver or renal impairment Precautions • Hypoglycemia

DM = diabetes mellitus; DPP-4 = dipeptidyl peptidase-4; eGFR = estimated glomerular filtration rate; GLP-1 = glucagon-like peptide-1; LDL-C = low-density lipoprotein cholesterol; SGLT2 = sodium-glucose cotransporter-2; T2DM = type 2 diabetes mellitus.

[a] Health Canada indication.

[b] Health Canada–approved combination for canagliflozin and empagliflozin, but not dapagliflozin.

Source: Product monographs from e-CPS.[25]

Objectives and Methods

Objectives

To perform a systematic review of the beneficial and harmful effects of lixisenatide 20 mcg subcutaneous (SC) injections for the treatment of adults with type 2 diabetes mellitus who have experienced inadequate glycemic control on therapy with insulin (alone or in combination with metformin).

Methods

All manufacturer-provided trials considered pivotal by Health Canada were included in the systematic review. Phase III studies were selected for inclusion based on the selection criteria presented in Table 5.

Table 5: Inclusion Criteria for the Systematic Review

Patient Population	Adults with type 2 diabetes mellitus who have experienced inadequate glycemic control on therapy with insulin (alone or in combination with metformin) **Subgroups** • Age • Baseline A1C • Type 2 diabetes duration • BMI • Background diabetes therapy • History of heart failure • History of cerebrovascular or cardiovascular disease
Intervention	Lixisenatide 20 mcg once daily in insulin (alone or in combination with metformin)
Comparators	One of the following in combination with basal insulin: • Sulfonylureas • SGLT2 inhibitors • Incretin mimetics (DPP-4 inhibitors, GLP-1 analogues) • Thiazolidinediones • Insulin secretagogues (meglitinides) • Metformin • Insulin/insulin analogues (including basal and prandial regimens) • Alpha-glucosidase inhibitors or • Placebo
Outcomes	**Key Efficacy Outcomes** • Glycemic control (e.g., A1C, FPG, PPG, glucose excursion) • Mortality (all-cause, cardiovascular-related) • Myocardial infarction (fatal and nonfatal) • Stroke (fatal and nonfatal) • Heart failure • Peripheral vascular disease • Hospitalization (CV-related, all-cause) • Diabetes-related microvascular morbidity • Health-related quality of life

	Other Efficacy Outcomes • Blood pressure • Body weight • Health care resource utilization **Harms Outcomes** • AEs • SAEs • WDAEs • Mortality • Notable harms: medullary thyroid cancer, arrhythmia, pancreatitis, anaphylaxis, renal impairment, hypoglycemia (including severe hypoglycemia), angioedema, injection site reactions, gastrointestinal AEs
Study Design	Published and unpublished phase III RCTs

A1C = glycated hemoglobin; AE = adverse event; BMI = body mass index; CV = cardiovascular; DPP-4 = dipeptidyl peptidase-4; FPG = fasting plasma glucose; GLP-1 = glucagon-like peptide-1; PPG = postprandial glucose; RCT = randomized controlled trial; SAE = serious adverse event; SGLT2 = sodium-glucose cotransporter-2; WDAE = withdrawal due to adverse event.

The literature search was performed by an information specialist using a peer-reviewed search strategy.

Published literature was identified by searching the following bibliographic databases: MEDLINE (1946–) with in-process records and daily updates via Ovid, Embase (1974–) via Ovid, and PubMed. The search strategy consisted of both controlled vocabulary, such as the National Library of Medicine's MeSH (Medical Subject Headings), and keywords. The main search concept was Adlyxine (lixisenatide).

No methodological filters were applied to limit retrieval by study type. Where possible, retrieval was limited to the human population. Retrieval was not limited by publication year or by language. Conference abstracts were excluded from the search results.

The initial search was completed on June 23, 2017. Regular alerts were established to update the search until the meeting of the CADTH Canadian Drug Expert Committee on October 18, 2017. Regular search updates were performed on databases that do not provide alert services.

Grey literature (literature that is not commercially published) was identified by searching relevant websites from the following sections of the Grey Matters checklist (www.cadth.ca/resources/finding-evidence/grey-matters): Health Technology Assessment agencies, health economics, clinical practice guidelines, databases (free), Internet search, and open access journals. Google and other Internet search engines were used to search for additional Web-based materials. These searches were supplemented by reviewing the bibliographies of key papers and through contacts with appropriate experts. In addition, the manufacturer of the drug was contacted for information regarding unpublished studies.

Two CADTH Common Drug Review (CDR) clinical reviewers independently selected studies for inclusion in the review based on titles and abstracts, according to the predetermined protocol. Full-text articles of all citations considered potentially relevant by at least one reviewer were acquired. Reviewers independently made the final selection of studies to be included in the review, and differences were resolved through discussion. Included studies are presented in Table 6 and Table 7; excluded studies (with reasons) are presented in Appendix 3.

Results

Findings from the Literature

A total of five studies were identified from the literature for inclusion in the systematic review. The included studies are summarized in Table 6 and Table 7 and described in Included Studies. A list of excluded studies is presented in Appendix 3.

Figure 1: Flow Diagram for Inclusion and Exclusion of Studies

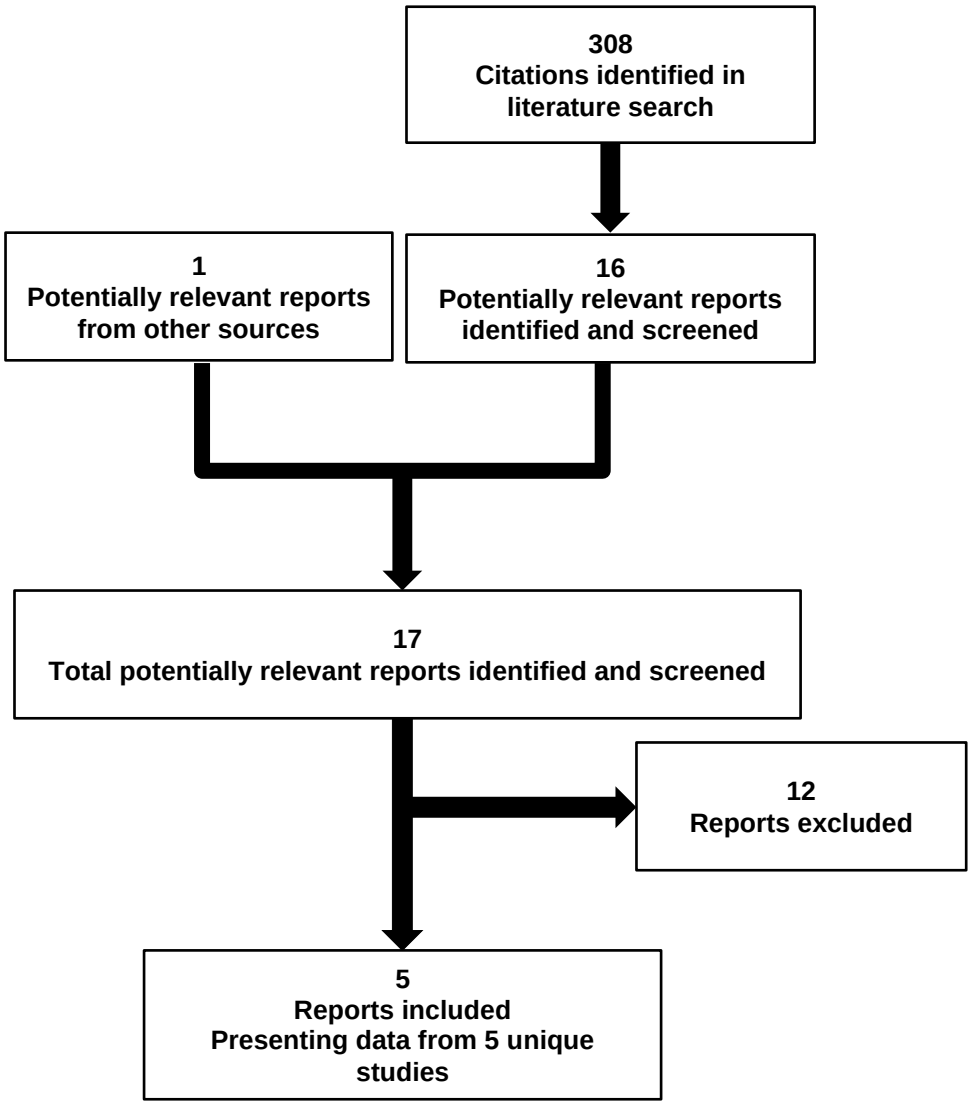


Table 6: Details of Included Studies (Placebo-Controlled Randomized Controlled Trials)

		GETGOAL			
		– L	– L Asia	– L – C	– DUO 1
Designs & Populations	**Study Design**	DB, MC, MN, PC, phase III RCT			
	Locations	111 centres in 15 countries: Canada, Egypt, India, Mexico, Puerto Rico, Republic of Korea, Russia, South America, Turkey, US, and Western Europe	57 centres in four countries: Japan, Philippines, Republic of Korea, and Taiwan	51 centres in four countries: China, India, Korea, and Russia	140 centres in 25 countries: Canada, Eastern Europe, India, Israel, Malaysia, Mexico, Puerto Rico, South Africa, South America, Taiwan, US, and Western Europe
	Randomized (N)	496	311	448	446
	Inclusion Criteria	• Adults with type 2 diabetes for a minimum of one year • Treated with BI for a minimum of three months (stable dose [±20%] ≥ 30 units/day for ≥ 2 months before screening) • Patients treated with basal insulin alone or with MET had to have A1C 7.0% to 10.0% at screening • Patients treated with MET required a stable dose 1,500 mg/day (or 1,000 mg/day for South Korea) for a minimum of three months before screening	• Adults (25 years of age to 81 years of age) with type 2 diabetes for a minimum of one year • Treated with BI for a minimum of three months (stable dose [±20%] ≥ 10 units/day for ≥ 2 months before screening) • Patients treated with basal insulin alone or with SU had to have A1C 7.0% to 10.0% at screening • Patients treated with SU required a stable dose for a minimum of three months before screening	• Adults with type 2 diabetes for a minimum of one year • Insufficiently controlled with basal insulin (alone or with MET) • Treated with BI for a minimum of three months (stable dose [±20%] ≥ 15 units/day for ≥ 2 months before screening) • Patients treated with basal insulin alone or with MET had to have A1C 7.0% to 10.5% at screening • Patients treated with MET required a stable dose 1,000 mg/day for a minimum of three months before screening	• Adults with type 2 diabetes for a minimum of one year • Patients treated with basal insulin alone or with MET had to have A1C 7.0% to 10.0% at screening • BMI > 20.0 kg/m^2 • Treated with MET (stable dose 1,500 mg/day) alone or in combination with a SU or glinide or a TZD or a combination of these for a minimum of three months before screening • Administration of insulin glargine was started at 10 units daily and was titrated weekly, targeting a fasting range of 4.4 mmol/L to 5.6 mmol/L
	Exclusion Criteria	Cardiovascular, hepatic, neurological, endocrine disease, active malignant tumour or other major systemic disease or patients with short life expectancy making implementation of the protocol or interpretation of the study results difficult, history or presence of clinically significant diabetic retinopathy, and history or presence of macular edema likely to require laser treatment within the study period			
		• FPG > 13.9 mmol/L • History of unexplained or chronic pancreatitis • History of GI disease associated with prolonged nausea and vomiting • Alcohol and substance abuse six months before screening • Uncontrolled hypertension (SBP > 180 mm Hg or DBP > 95 mm Hg)			

		GETGOAL			
		– L	– L Asia	– L – C	– DUO 1
		• Lipase > 3 × ULN • Prior experience with lixisenatide • History of hypoglycemia unawareness • History of allergic reactions to GLP-1			
		• End-stage renal disease (creatinine clearance < 15 mL/min) • Use of antidiabetic agents other than metformin or basal insulin within three months of screening • BMI ≤ 20.0 kg/m^2 • BW change > 5.0 kg three months before screening • AST, ALT, or ALP > 2 × ULN	• End-stage renal disease (creatinine clearance < 15 mL/min) • Use of antidiabetic agents other than SU or basal insulin within three months of screening • AST, ALT, or ALP > 2 × ULN	• Severe renal impairment or end-stage renal disease (creatinine clearance < 30 mL/min) • Use of antidiabetic agents other than metformin or basal insulin within three months of screening • BMI ≤ 20.0 kg/m^2 • BW change > 5.0 kg three months before screening • AST, ALT, or ALP > 3 × ULN • History of medullary thyroid cancer or genetic predisposition to MTC	• FPG > 13.3 mmol/L • History of unexplained or chronic pancreatitis • History of GI disease associated with prolonged nausea and vomiting • Alcohol and substance abuse six months before screening • Hypertension (SBP > 180 mm Hg or DBP > 110 mm Hg) • Lipase > 3 × ULN • Prior experience with lixisenatide • History of hypoglycemia unawareness • History of allergic reactions to GLP-1 • Use of antidiabetic agents other than MET, SU, glinides, TZDs, and basal insulin within three months of screening • ALT > 3 × ULN • History of medullary thyroid cancer or genetic predisposition to MTC
DRUGS	**Intervention**	Lixisenatide 10 mcg subcutaneous injection once daily for one week, followed by one week of 15 mcg and 20 mcg thereafter within one hour before breakfast Added to BI alone or in combination with other antidiabetic background therapies		Lixisenatide 20 mcg subcutaneous injection once daily following a 14-day titration period (10 mcg once daily) Added to BI alone or in combination with other antidiabetic background therapies	Lixisenatide 10 mcg subcutaneous injection once daily for one week, followed by one week of 15 mcg and 20 mcg thereafter within one hour before breakfast Added to BI alone or in combination with other antidiabetic background therapies

		GETGOAL			
		– L	– L Asia	– L – C	– DUO 1
	Comparator	Placebo subcutaneous injection once daily within one hour before breakfast Added to BI alone or in combination with other antidiabetic background therapies			
DURATION	**Phase**				
	Screening	2 weeks			
	Run-in	1 week		8 weeks	12 weeks
	Double-blind	24 weeks with up to 52-week extension	24 weeks		
	Follow-up	3 days			
OUTCOMES	**Primary End Point**	Absolute change from baseline in A1C			
	Other End Points	• Change from baseline in FPG, BW, in insulin dose • Two-hour PPG • A1C responders • Average seven-point SMPG • Rescue therapy[a]			
NOTES	**Publications**	Riddle 2013[4]	Seino 2012[8]	NA	Riddle 2013[6]

A1C = glycated hemoglobin; ALP = alkaline phosphatase; ALT = alanine transaminase; AST = aspartate transaminase; BI = basal insulin; BMI = body mass index; BW = body weight; CI = confidence interval; CSR = Clinical Study Report; CV = cardiovascular; DBP = diastolic blood pressure; DPP-4 = dipeptidyl peptidase-4; eGFR = estimated glomerular filtration rate; FPG = fasting plasma glucose; GI = gastrointestinal; GLP-1 = glucagon-like peptide-1; MET = metformin; MC = multi-centre; MN = multinational; NA = not available; OAD = oral antidiabetic drug; PPG = postprandial glucose; RCT = randomized controlled trial; SBP = systolic blood pressure; SMPG = self-monitored plasma glucose; SU = sulfonylurea; TZD = thiazolidinedione; ULN = upper limit of normal.

[a] Rescue therapy was not evaluated in GETGOAL – L – C.

Source: Riddle 2013,[4] GETGOAL – L CSR,[5] Riddle 2013,[6] GETGOAL – DUO 1 CSR,[7] Seino 2012,[8] GETGOAL – L Asia CSR,[9] GETGOAL – L – C CSR.[10]

Table 7: Details of Included Study (Active-Controlled Randomized Controlled Trial)

		GETGOAL – DUO 2
DESIGNS & POPULATIONS	**Study Design**	OL, MC, MN, AC, phase III, RCT
	Locations	199 centres in 18 countries: Canada, Chile, Mexico, Romania, Russia, Ukraine, US, and Western Europe
	Randomized (N)	894
	Inclusion Criteria	• Adults with type 2 diabetes mellitus for a minimum of one year • Treated with BI for a minimum of six months (stable dose ≥ 20 units/day for ≥ 2 months before screening) alone or in combination with one to three OADs (MET [≥ 1,500 mg/day or maximum tolerated dose], a DPP-4 inhibitor, an SU, or a glinide) • Patients treated with basal insulin alone or with MET had to have A1C 7.5% to 10.0% (58 mmol/mol to 86 mmol/mol) at screening; patients treated with basal insulin plus an SU and/or a DPP-4 inhibitor and/or a glinide had to have A1C 7.0% to 10.0% (53 mmol/mol to 86 mmol/mol) at screening • BMI > 20.0 kg/m^2 to 40.0 kg/m^2 • Administration of insulin glargine was started at 10 units daily and was titrated every three days, targeting a fasting range of 4.4 mmol/L to 5.6 mmol/L

		GETGOAL – DUO 2
	Exclusion Criteria	• Prior experience with lixisenatide • History of GI disease associated with prolonged nausea and vomiting • Alcohol and substance abuse six months before screening • History of unexplained or chronic pancreatitis • History of medullary thyroid cancer or genetic predisposition to MTC • Uncontrolled hypertension (SBP > 180 mm Hg or DBP > 95 mm Hg) • Alanine/aspartate aminotransferase, amylase, or lipase > 3 × ULN • Calcitonin > 20 pg/mL • Severe renal impairment or end-stage renal disease (creatinine clearance < 30 mL/min) • BW change > 5.0 kg three months before screening • Use of antidiabetic agents other than MET or basal insulin within three months of screening • History of hypoglycemia unawareness • Previous discontinuation of GLP-1 receptor agonists due to safety or lack of efficacy • Cardiovascular, hepatic, neurological, endocrine disease, active malignant tumour or other major systemic disease or patients with short life expectancy making implementation of the protocol or interpretation of the study results difficult, history or presence of clinically significant diabetic retinopathy, and history or presence of macular edema likely to require laser treatment within the study period
DRUGS	**Intervention**	Lixisenatide 20 mcg subcutaneous injection once daily following a 14-day titration period (10 mcg once daily) added to BI (insulin glargine) alone or in combination with MET
	Comparator(s)	Insulin glulisine once or three times daily added to BI (insulin glargine) alone or in combination with MET
DURATION	**Phase**	
	Screening	2 weeks
	Run-in	12 weeks
	OL treatment	26 weeks
	Follow-up	3 days
OUTCOMES	**Primary End Point**	Noninferiority (95% CI upper bound < 0.4%) absolute change in A1C from baseline for lixisenatide once daily versus insulin glulisine once daily, and either: • noninferiority for lixisenatide once daily versus insulin glulisine three times daily • superiority in change in body weight for lixisenatide once daily versus insulin glulisine three times daily
	Other End Points	• Change from baseline in FPG, BW, in insulin dose • Two-hour PPG • A1C responders • Average seven-point SMPG • Health care resource utilization
NOTES	**Publications**	Rosenstock 2016[11]

A1C = glycated hemoglobin; AC = active comparator; BI = basal insulin; BMI = body mass index; BW = body weight; CI = confidence interval; CSR = Clinical Study Report; DPP-4 = dipeptidyl peptidase-4; FPG = fasting plasma glucose; GI = gastrointestinal; MET = metformin; MC = multi-centre; MN = multinational; OAD = oral antidiabetic drug; OL = open-label; pg = picogram; PPG = postprandial glucose; RCT = randomized controlled trial; SMPG = self-monitored plasma glucose; SU = sulfonylurea; ULN = upper limit of normal.

Source: Rosenstock 2016[11] and GETGOAL – DUO 2 Clinical Study Report.[12]

Included Studies

Description of Studies

Five phase III randomized controlled trials (RCTs) met the inclusion criteria for the CDR systematic review of which four were placebo-controlled (Table 6) and one active-controlled (Table 7).

Placebo-Controlled Trials

GETGOAL – L (N = 496), GETGOAL – L Asia (N = 311), GETGOAL – L – C (N = 448), and GETGOAL – DUO 1 (N = 446) were similarly designed double-blind, placebo-controlled, phase III RCTs. All trials were multi-centre and multinational; however, only two trials (GETGOAL – L and GETGOAL – Duo 1) recruited patients from centres located in North America (including Canada), whereas both GETGOAL – L Asia and GETGOAL – L – C did not include any North American centres. Most placebo-controlled trials were designed to assess the efficacy and safety of treatment with lixisenatide compared with placebo over a 24-week double-blind treatment phase in patients with type 2 diabetes mellitus with inadequate glycemic control on basal insulin therapy (alone or in combination with metformin) with the exception of GETGOAL – L Asia, which included patients with type 2 diabetes mellitus with inadequate glycemic control on basal insulin therapy (alone or in combination with sulfonylurea). The intervention in all placebo-controlled trials consisted of lixisenatide in addition to permitted background therapy and was randomized (to a 1:1 ratio) against placebo with the exception of GETGOAL – L (randomized to a 2:1 ratio of lixisenatide to placebo). In all trials, randomization was conducted using an interactive voice response system and stratified by A1C (< 8.0%, ≥ 8.0%). Randomization was also stratified by concomitant background antidiabetic therapy and metformin use (yes, no) in both GETGOAL – L and GETGOAL – L – C, sulfonylurea (yes, no) in GETGOAL – L Asia, and thiazolidinedione (yes, no) in GETGOAL – DUO 1. In each trial, the primary efficacy outcome was the absolute change in A1C for from baseline at week 24. Investigators and patients were blinded to the treatment arm assignment; however, study drug treatment volumes in the injection pens were not concealed.

All trials comprised a two-week screening phase, a one- to 12-week placebo run-in phase (to ensure optimal basal insulin titration), and a 24-week double-blind treatment phase followed by three days of follow-up. Antidiabetic drugs other than metformin (in GETGOAL – L and GETGOAL – L – C), sulfonylurea (in GETGOAL – L Asia), and thiazolidinediones (in GETGOAL – DUO 1) were to be discontinued. In addition, the GETGOAL – L 24-week main double-blind treatment phase was followed by an up to 52–week extension phase in which patients continued treatment according to their original randomization.

Active-Controlled Trial

GETGOAL – DUO 2 (N = 894) was a three-arm, multi-centre, multinational, open-label, active-controlled RCT and recruited patients from centres located in North America (including Canada). GETGOAL – DUO 2 directly compared once daily lixisenatide with two prandial insulin regimens — insulin glulisine once daily and insulin glulisine three times daily — in overweight patients with type 2 diabetes mellitus with inadequate glycemic control on insulin glargine therapy (alone or in combination with oral antidiabetic drugs). The active-controlled trial was designed to assess the efficacy and safety of treatment with lixisenatide compared with placebo over a 26-week open-label treatment phase. The intervention consisted of lixisenatide in addition to permitted background therapy and was randomized

(to a 1:1:1 ratio) against insulin glulisine once daily and insulin glulisine three times daily. Randomization was conducted using an interactive voice response system and stratified by A1C (< 8.0%, ≥ 8.0%) and by concomitant background antidiabetic therapy and metformin use (yes, no). In GETGOAL – DUO 2, the primary analysis was based on the three co-primary end points: 1) noninferiority of lixisenatide versus insulin glulisine once daily in the change from baseline in A1C at week 26 using a noninferiority margin of 0.4%; 2a) noninferiority of lixisenatide versus insulin glulisine three times daily in the change from baseline in A1C at week 26 using a noninferiority margin of 0.4%; and 2b) superiority of lixisenatide versus insulin glulisine three times daily in the change from baseline in body weight at week 26. Investigators and patients were not blinded to the treatment arm assignment.

GETGOAL – DUO 2 comprised a two-week screening phase, a 12-week run-in phase used to switch and optimize basal insulin (insulin glargine), and a 26-week open-label treatment phase followed by three days of follow-up. Antidiabetic drugs other than metformin were to be discontinued at the start of the run-in phase. Patients treated with another type of basal insulin were to switch to insulin glargine (titrated every three days to achieve target fasting SMPG between 4.4 mmol/L and 5.6 mmol/L) without recurrent or severe hypoglycemia.

Populations

Inclusion and Exclusion Criteria

Refer to Table 6 and Table 7 for a detailed list of inclusion and exclusion criteria in the placebo-controlled and active-controlled trials, respectively.

Placebo-Controlled Trials

The inclusion criteria across placebo-controlled trials were relatively variable. All placebo-controlled trials required a stable dose of basal insulin for a minimum of three months. Most placebo-controlled trials enrolled adult patients with a diagnosis of type 2 diabetes mellitus for a minimum of one year. GETGOAL – L restricted the age requirement to adults between age 25 and age 81. Eligible patients in most placebo-controlled trials required basal insulin therapy alone or in combination with other antidiabetic therapies (metformin, sulfonylurea, thiazolidinedione) and had to have A1C between 7.0% and 10.0% at screening. GETGOAL – L – C enrolled patients with A1C up to 10.5% at screening. Patients were required to be treated with a stable dose of antidiabetic therapies for a minimum of three months before screening (metformin between 1,000 mg/day and 1,500 mg/day).

All placebo-controlled trials prohibited the inclusion of patients with a history of: pancreatitis, end-stage renal disease (including severe renal disease in GETGOAL – L – C), gastrointestinal disease, hypoglycemia unawareness, and allergic reaction. Patients were also excluded from the placebo-controlled trials for alcohol and substance abuse six months before screening, hypertension, and BMI ≤ 20 kg/m^2 with the exception of GETGOAL – L Asia, which did not have any BMI restrictions. The use of antidiabetic therapies other than those permitted in each trial (metformin in GETGOAL – L and GETGOAL – L – C, sulfonylurea in GETGOAL – L Asia, and metformin, sulfonylurea, glinides, and thiazolidinedione in GETGOAL – DUO 1) was prohibited as well as any prior exposure to lixisenatide. Also excluded from all placebo-controlled trials were patients with cardiovascular, hepatic, neurological, endocrine disease, active malignant tumour, or other major systemic disease; short life expectancy making implementation of the protocol or interpretation of the study results difficult; history or presence of clinically significant diabetic

retinopathy; and history or presence of macular edema likely to require laser treatment within the study period.

Active-Controlled Trial

The GETGOAL – DUO 2 trial required a stable dose of basal insulin for a minimum of six months and enrolled adult patients with a diagnosis of type 2 diabetes mellitus for a minimum of one year. Eligible patients required basal insulin therapy alone or in combination with other antidiabetic therapies (metformin, sulfonylurea, DPP-4, and GLP-1). Patients treated with basal insulin alone or in combination with metformin were required to have had A1C between 7.5% and 10.0%, inclusive at screening, whereas those treated with basal insulin with a sulfonylurea or DPP-4 were required to have had A1C between 7.0% and 10.0%, inclusive. Patients were required to be treated with a stable dose of antidiabetic therapies for a minimum of three months before screening (metformin > 1,500 mg/day or maximally tolerated).

GETGOAL – DUO 2 prohibited the inclusion of patients with a history of: pancreatitis, end-stage renal disease (including severe renal impairment), gastrointestinal disease, and hypoglycemia unawareness. Patients were also excluded from the active-controlled trial for alcohol and substance abuse six months before screening, hypertension, and BMI ≤ 20 kg/m^2 and > 40 kg/m^2. The use of antidiabetic therapies other than metformin was prohibited as well as any prior exposure to lixisenatide. Also excluded were patients with cardiovascular, hepatic, neurological, endocrine disease, active malignant tumour, or other major systemic disease; short life expectancy making implementation of the protocol or interpretation of the study results difficult; history or presence of clinically significant diabetic retinopathy; and history or presence of macular edema likely to require laser treatment within the study period.

Baseline Characteristics

Placebo-Controlled Trials

The placebo-controlled trials enrolled patients with type 2 diabetes mellitus treated with basal insulin with a mean age that ranged between 54 years and 59 years (standard deviation ranged between nine and 10), of whom 73% to 79% were between age 50 and age 75. Gender was relatively well balanced between treatment arms and trials (44% male and 51% male). The majority of patients in GETGOAL – L and GETGOAL – DUO 1 were Caucasian (75% to 78%), whereas the majority of patients were Asian (86%) in GETGOAL – L – C. GETGOAL – L Asia only recruited Asian patients. Mean duration of diabetes ranged between 8.7 years and 14.1 years (standard deviation ranged between 5.8 and 7.7). All patients enrolled in the placebo-controlled trials had been receiving treatment with insulin therapy for at least two years (mean range: 2.1 years to 3.2 years, [standard deviation range: 2.1 to 4.3]) and were treated with basal insulin with a mean dose that ranged between 24 units per day and 58 units per day (standard deviation ranged between 14 and 35). The majority of patients in most of the placebo-controlled trials were treated with metformin (78% to 100%) at a mean dose that ranged between 1,622 mg per day and 2,058 mg per day (standard deviation ranged between 405 and 480). As well, most patients were treated within the ≥ 1,500 mg to < 2,500 mg category (73% to 75%) with the exception of the patients enrolled in the GETGOAL – L Asia trial, wherein treatment with metformin was prohibited.

Overall, no trial reported use of sulfonylureas as concomitant background therapies with the exception of GETGOAL – L Asia, wherein approximately 70% of patients were treated.

Concomitant treatment with thiazolidinediones was permitted only in GETGOAL – DUO 1 and only reported in the minority of patients (12%). Mean body weight and mean BMI ranged between 65.6 kg and 88.9 kg (standard deviation ranged between 12.5 and 21.8) and 25.2 kg/m^2 and 32.6 kg/m^2 (standard deviation ranged between 3.7 and 6.6), respectively. Overall the proportion of patients with BMI < 30 kg/m^2 and those with BMI ≥ 30 kg/m^2 was relatively variable. The majority of patients in GETGOAL – L and GETGOAL – DUO 1 had a BMI ≥ 30 kg/m^2 (nearly 60% and 54%, respectively), whereas the majority of patients in GETGOAL – L Asia and GETGOAL – L – C had a BMI < 30 kg/m^2 (nearly 90% and 76%, respectively).

Mean A1C ranged between 7.69% and 8.54% (standard deviation ranged between 0.52 and 0.81). The majority of patients enrolled in all placebo-controlled trials had A1C ≥ 8.0% (51% to 77%) with the exception of GETGOAL – DUO 1, wherein the majority of patients had A1C < 8.0% (70%). Mean FPG, two-hour PPG, glucose excursion and seven-point SMPG ranged between 6.55 mmol/L and 8.13 mmol/L (standard deviation ranged between 1.72 and 2.83), 12.79 mmol/L and 17.81 mmol/L (standard deviation ranged between 3.36 and 4.30), 6.24 mmol/L and 9.72 mmol/L (standard deviation ranged between 3.19 and 4.35), and 8.20 mmol/L and 11.58 mmol/L (standard deviation ranged between 1.47 and 2.69), respectively. Most patients had normal renal function with creatinine clearance ≥ 80 mL per minute (54% to 85%) and had history of cardiovascular risk factors (74% to 88%). Generally, the distribution of patient characteristics was similar across treatment groups but varied considerably across trials. Details of patients' baseline characteristics and concomitant treatment in the placebo-controlled trials are presented in Table 8.

Table 8: Summary of Baseline Characteristics (Placebo-Controlled RCTs)

Characteristics	GETGOAL							
	– L		– L Asia		– DUO 1		– L – C	
	PLB N = 167	LIXI N = 328	PLB N = 157	LIXI N = 154	PLB N = 223	LIXI N = 223	PLB N = 224	LIXI N = 224
Age, mean years (SD)	57 (10)	57 (10)	59 (10)	58 (10)	56 (10)	56 (10)	56 (9)	54 (10)
< 50 years, n (%)	[redacted]	[redacted]	32 (20)	25 (16)	[redacted]	[redacted]	48 (21)	66 (30)
≥ 75 years, n (%)	[redacted]	[redacted]	4 (3)	8 (5)	[redacted]	[redacted]	NR	NR
Male, n (%)	82 (49)	146 (45)	80 (51)	69 (45)	113 (51)	109 (49)	98 (44)	105 (47)
Ethnic origin, n (%)								
Caucasian	130 (78)	254 (77)	0	0	167 (75)	165 (74)	34 (15)	29 (13)
Black	6 (4)	14 (4)	0	0	11 (5)	9 (4)	0	0
Asian	30 (18)	53 (16)	157 (100)	154 (100)	43 (19)	44 (20)	190 (85)	195 (87)
Other	1 (1)	7 (2)	0	0	2 (1)	5 (2)	0	0
Mean duration of diabetes, years (SD)	12.4 (6.3)	12.5 (7.0)	14.1 (7.7)	13.7 (7.7)	8.7 (5.8)	9.6 (6.0)	10.2 (6.2)	10.3 (6.1)
Insulin								
Mean treatment duration, years (SD)	3.2 (4.0)	3.1 (3.4)	3.0 (4.3)	2.9 (3.7)	NR	NR	2.1 (2.1)	2.3 (2.4)
Mean dose, units/day (SD)	58 (35)	54 (34)	24 (14)	25 (14)	44 (20)	43 (19)	37 (16)	40 (19)
Range (min, max)	0, 200	0, 400	10, 90	10, 100	4, 128	10, 168	15, 114	15, 120
Glargine, n (%)	83 (50)	165 (50)	92 (59)	95 (62)	NR	NR	188 (84)	182 (81)
Detemir, n (%)	19 (11)	24 (7)	42 (27)	41 (27)	NR	NR	12 (5)	15 (7)
NPH, n (%)	64 (38)	134 (41)	21 (13)	18 (12)	NR	NR	23 (10)	27 (12)
Premix, n (%)	3 (2)	5 (2)	2 (1)	0	NR	NR	0	0

Characteristics	GETGOAL							
	– L		– L Asia		– DUO 1		– L – C	
	PLB N = 167	LIXI N = 328	PLB N = 157	LIXI N = 154	PLB N = 223	LIXI N = 223	PLB N = 224	LIXI N = 224
Any, n (%)	167 (100)	328 (100)	157 (100)	154 (100)	223 (100)	223 (100)	224 (100)	224 (100)
Metformin								
Yes, n (%)	130 (78)	262 (80)	0	0	223 (100)	223 (100)	199 (89)	198 (88)
Mean dose, mg/day (SD)	2,008 (442)	1,961 (459)	NA	NA	2,058 (431)	2,039 (405)	1,622 (428)	1,665 (480)
Range (min, max)	1,000, 3,000	850, 4,200	NA	NA	1,500, 3,400	1,500, 3,400	1,000, 3,000	1,000, 3,000
Category of metformin use at baseline, n (%)								
< 1,500 mg	[redacted]	[redacted]	NA	NA	[redacted]	[redacted]	37 (19)	35 (18)
≥ 1,500 mg to < 2,500 mg	[redacted]	[redacted]	NA	NA	[redacted]	[redacted]	146 (74)	144 (73)
≥ 2,500 mg to < 3,000 mg	[redacted]	[redacted]	NA	NA	[redacted]	[redacted]	12 (6)	10 (5)
≥ 3,000 mg	[redacted]	[redacted]	NA	NA	[redacted]	[redacted]	3 (2)	9 (5)
Sulfonylurea								
Yes, n (%)	0	0	111 (71)	108 (70)	NR	NR	0	0
Glibenclamide mean dose ≥ 5 mg/day	NA	NA	15 (14)	5 (5)	NA	NA	NA	NA
Gliclazide mean dose ≥ 80 mg/day	NA	NA	3 (3)	3 (3)	NA	NA	NA	NA
Glimepiride mean dose ≥ 3 mg/day	NA	NA	45 (41)	56 (52)	NA	NA	NA	NA
TZD								
Yes, n (%)	0	0	0	0	27 (12)	27 (12)	0	0
Mean body weight, kg (SD)	88.9 (20.8)	87.1 (20.0)	65.6 (12.5)	65.9 (13.0)	86.8 (20.4)	87.3 (21.8)	74.6 (13.3)	73.9 (14.1)
Mean BMI, kg/m^2 (SD)	32.6 (6.3)	31.9 (6.2)	25.2 (3.9)	25.4 (3.7)	31.7 (6.0)	32.0 (6.6)	27.9 (4.5)	27.5 (4.5)
< 30 kg/m^2, n (%)	61 (37)	137 (42)	140 (89)	141 (92)	103 (46)	103 (46)	172 (77)	169 (75)
≥ 30 kg/m^2, n (%)	106 (63)	191 (58)	17 (11)	13 (8)	120 (54)	120 (54)	51 (23)	55 (25)
A1C								
Mean, % (SD)	8.46 (0.81)	8.49 (0.83)	8.52 (0.78)	8.54 (0.73)	7.70 (0.54)	7.69 (0.52)	7.94 (0.70)	7.90 (0.66)
< 8.0, n (%)	[redacted]	[redacted]	36 (23)	35 (23)	[redacted]	[redacted]	110 (49)	111 (50)
≥ 8.0, n (%)	[redacted]	[redacted]	121 (77)	119 (77)	[redacted]	[redacted]	114 (51)	113 (50)
Mean FPG, mmol/L (SD)	8.05 (2.65)	8.13 (2.83)	7.75 (2.25)	7.67 (2.32)	6.70 (1.97)	6.55 (1.72)	6.94 (1.79)	7.06 (2.06)
Mean two-hour PPG, mmol/L (SD)	16.11 (3.86)	16.47 (4.30)	17.75 (3.94)	17.81 (3.36)	12.79 (3.69)	12.90 (3.94)	14.19 (3.64)	13.78 (4.18)
Mean glucose excursion, mmol/L (SD)	[redacted]	[redacted]	9.70 (4.19)	9.72 (3.27)	[redacted]	[redacted]	6.94 (3.19)	6.50 (3.44))
Mean average seven-point SMPG, mmol/L (SD)	10.58 (2.69)	10.76 (2.61)	11.42 (2.46)	11.58 (2.51)	8.26 (1.52)	8.20 (1.47)	9.30 (1.85)	9.20 (1.85)
Mean creatinine clearance, mL/min (SD)	[redacted]	[redacted]	88.45 (30.45)	90.09 (34.88)	[redacted]	[redacted]	105.65 (31.77)	109.09 (31.80)
Range (min, max)	[redacted]	[redacted]	22, 203	29, 243	[redacted]	[redacted]	37, 257	46, 214

Characteristics	GETGOAL							
	– L		– L Asia		– DUO 1		– L – C	
	PLB N = 167	LIXI N = 328	PLB N = 157	LIXI N = 154	PLB N = 223	LIXI N = 223	PLB N = 224	LIXI N = 224
< 15							0	0
≥ 15 to < 30							0	0
< 30	[redacted]	[redacted]	1 (1)	1 (1)	[redacted]	[redacted]		
≥ 30 to < 50	[redacted]	[redacted]	10 (6)	11 (7)	[redacted]	[redacted]		
≥ 30 to < 60							7 (3)	9 (4)
≥ 50 to ≤ 80	[redacted]	[redacted]	55 (35)	59 (38)	[redacted]	[redacted]		
≥ 60 to <90							70 (31)	57 (25)
> 80	[redacted]	[redacted]	91 (58)	83 (54)	[redacted]	[redacted]		
≥ 90							146 (66)	158 (71)
History of CV risk factors	[redacted]	[redacted]	126 (80)	134 (87)	[redacted]	[redacted]	330 (74)	

A1C = glycated hemoglobin; BMI = body mass index; CV = cardiovascular; CSR = Clinical Study Report; FPG = fasting plasma glucose; LIXI = lixisenatide; max = maximum; min = minimum; NPH = neutral protamine Hagedorn; NR = not reported; PLB = placebo; PPG = postprandial glucose; RCT = randomized controlled trial; SMPG = self-monitored plasma glucose; TZD = thiazolidinedione; SD = standard deviation.

Source: Riddle 2013,[4] GETGOAL – L CSR,[5] Riddle 2013,[6] GETGOAL – DUO 1 CSR,[7] Seino 2012,[8] GETGOAL – L Asia CSR,[9] and GETGOAL – L – C CSR.[10]

Active-Controlled Trial

GETGOAL – DUO 2 enrolled patients with type 2 diabetes mellitus treated with basal insulin with a mean age of nearly 60 years (standard deviation of 9), of whom approximately [redacted] were between ages ≥ 50 years old and < 75 years old. The majority of patients enrolled were female (55%) and Caucasian (93%) and had a BMI ≥ 30 kg/m^2 (64%). Patients were diagnosed with diabetes for a mean of nearly 12 years (standard deviation of 6.7). All patients enrolled in the active-controlled trial had been receiving treatment with insulin therapy for at least three years (standard deviation of 3.1) and were treated with basal insulin with a mean dose of 66 units per day (standard deviation of 30). The majority of patients were treated with metformin (87%) at a mean dose of 2,090 mg per day (standard deviation of 470) and [redacted] were treated within the ≥ 1,500 mg to < 2,500 mg category [redacted] Concomitant treatment with sulfonylureas, DPP-4 and GLP-1 were permitted in GETGOAL – DUO 2 and reported [redacted], respectively). Mean body weight and mean BMI were 89.0 kg (standard deviation of 17) and 32.0 kg/m^2 (standard deviation of 5), respectively. Mean A1C was 7.86% (standard deviation of 0.53). [redacted] of patients enrolled in GETGOAL – DUO 2 had A1C ≥ 8.0% [redacted]. Mean FPG, two-hour PPG, glucose excursion, and seven-point SMPG were 6.77 mmol/L (standard deviation of 1.91), 14.18 mmol/L (standard deviation of 3.47), 7.33 mmol/L (standard deviation of 3.37), and 9.02 mmol/L (standard deviation of 1.68), respectively. [redacted] had normal renal function with creatinine clearance ≥ 90 mL per minute [redacted] and had history of cardiovascular risk factors (90% to 94%). Generally, the distribution of patient characteristics was similar across treatment groups. Details of patients' baseline characteristics and concomitant treatment in GETGOAL – DUO 2 are presented in Table 9.

Table 9: Summary of Baseline Characteristics (Active-Controlled RCT)

Characteristics	GETGOAL – DUO 2		
	LIXI N = 298	IG Once Daily N = 298	IG Three Times Daily N = 298
Age, mean years (SD)	60 (9)	60 (9)	59 (10)
< 50 years, n (%)	[redacted]	[redacted]	[redacted]
≥ 75 years, n (%)	[redacted]	[redacted]	[redacted]
Male, n (%)	138 (46)	135 (45)	132 (44)
Ethnic origin, n (%)			
Caucasian	276 (93)	280 (94)	272 (91)
Black	13 (4)	11 (4)	12 (4)
Asian	9 (3)	7 (2)	13 (4)
Other	0	0	1 (< 1)
Mean duration of diabetes, years (SD)	11.9 (6.4)	12.3 (6.8)	12.4 (6.8)
Insulin			
Mean treatment duration, years (SD)	3.1 (2.6)	3.3 (3.5)	3.2 (3.1)
Mean dose, units/day (SD)	68 (32)	65 (32)	65 (27)
Range (min, max)	13, 192	14, 205	18, 204
Glargine, n (%)	199 (67)	203 (68)	191 (64)
Detemir, n (%)	25 (8)	32 (11)	30 (10)
NPH, n (%)	74 (25)	63 (21)	77 (26)
Any, n (%)	298 (100)	298 (100)	298 (100)
Metformin			
Yes, n (%)	262 (88)	260 (87)	259 (87)
Mean dose, mg/day (SD)	2,069 (486)	2,089 (477)	2,114 (447)
Range (min, max)	500, 3,000	750, 3,400	850, 3,000
Category of metformin use at baseline, n	[redacted]	[redacted]	[redacted]
< 1,500 mg, n (%)	[redacted]	[redacted]	[redacted]
≥ 1,500 mg to < 2,500 mg, n (%)	[redacted]	[redacted]	[redacted]
≥ 2,500 mg to < 3,000 mg, n (%)	[redacted]	[redacted]	[redacted]
≥ 3,000 mg, n (%)	[redacted]	[redacted]	[redacted]
Sulfonylurea			
Yes, n (%)	141 (47)	129 (43)	142 (48)
DPP-4			
Yes, n (%)	37 (12)	29 (10)	42 (14)
GLP-1			
Yes, n (%)	[redacted]	[redacted]	[redacted]
Mean body weight, kg (SD)[a]	90.2 (17.5)	88.4 (15.8)	90.1 (17.3)
Mean BMI, kg/m^2 (SD)[a]	32.3 (4.6)	31.9 (4.4)	32.5 (4.6)
< 30 kg/m^2, n (%)	97 (33)	118 (40)	97 (33)
≥ 30 kg/m^2, n (%)	201 (67)	180 (60)	200 (67)
A1C			
Mean, % (SD)	7.77 (0.55)	7.73 (0.59)	7.79 (0.60)
< 8.0, n (%)	[redacted]	[redacted]	[redacted]
≥ 8.0, n (%)	[redacted]	[redacted]	[redacted]
Mean FPG, mmol/L (SD)	6.58 (1.82)	6.84 (1.98)	6.65 (1.89)
Mean two-hour PPG, mmol/L (SD)	14.26 (3.55)	14.02 (3.59)	14.25 (3.35)

Characteristics	GETGOAL – DUO 2		
	LIXI N = 298	IG Once Daily N = 298	IG Three Times Daily N = 298
Mean glucose excursion, mmol/L (SD)	7.31 (3.19)	7.31 (3.63)	7.35 (3.34)
Mean average seven-point SMPG, mmol/L (SD)	9.02 (1.75)	9.07 (1.74)	8.99 (1.57)
Mean creatinine clearance, mL/min (SD)	[redacted]	[redacted]	[redacted]
Range (min, max)	[redacted]	[redacted]	[redacted]
< 15	[redacted]	[redacted]	[redacted]
≥ 15 to < 30	[redacted]	[redacted]	[redacted]
≥ 30 to < 60	[redacted]	[redacted]	[redacted]
≥ 60 to < 90	[redacted]	[redacted]	[redacted]
≥ 90	[redacted]	[redacted]	[redacted]
History of CV risk factors	269 (90)	280 (94)	272 (91)

A1C = glycated hemoglobin; BMI = body mass index; CV = cardiovascular; DPP-4 = dipeptidyl peptidase-4; FPG = fasting plasma glucose; GLP-1 = glucagon-like peptide-1; IG = insulin glulisine; LIXI = lixisenatide; max = maximum; min = minimum; NPH = neutral protamine Hagedorn; NR = not reported; PLB = placebo; PPG = postprandial glucose; RCT = randomized controlled trial; SMPG = self-monitored plasma glucose; TZD = thiazolidinedione; SD = standard deviation.

[a] Assessed 12 weeks before open-label treatment phase.

Source: Rosenstock 2016[11] and GETGOAL – DUO 2 Clinical Study Report.[12]

Interventions

Lifestyle and diet therapy undertaken before screening was to be continued during the trial. Lixisenatide studied in the GETGOAL trials were available in 10 mcg or 20 mcg doses for SC injection. Patients enrolled in the GETGOAL – L, GETGOAL – L Asia, and GETGOAL – DUO 1 self-administered volume-matched placebo or an initial dose of lixisenatide 10 mcg once daily in the morning, within the hour preceding breakfast, in a single-blind manner for one week followed by one week of 15 mcg, and then 20 mcg (maintenance dose) once daily thereafter. Patients enrolled in GETGOAL – L – C self-administered volume-matched placebo or an initial dose of lixisenatide 10 mcg once daily in the morning, within the hour preceding breakfast, and in a single-blind manner for 14 days followed by 20 mcg (maintenance dose) once daily on day 15 and thereafter. GETGOAL – DUO 2 utilized a similar dosage regimen as GETGOAL – L – C, with an initial dose of lixisenatide 10 mcg once daily in the morning, within the hour preceding breakfast for 14 days, followed by 20 mcg (maintenance dose) once daily on day 15 and thereafter. If the 20 mcg once daily maintenance dose was not tolerated, the dosage could be temporarily reduced to 15 mcg or 10 mcg once daily. Increasing the dose back to the maintenance dose (20 mcg once daily) should be considered within four weeks. If the patient could not tolerate the 10 mcg dose, the study treatment would have been permanently discontinued. Lixisenatide dose titrations occurred during the main double-blind treatment phase in the placebo-controlled trials and during the open-label treatment phase in GETGOAL – DUO 2.

Placebo-Controlled Trials

Throughout the study and for at least two months before screening, patients were to be treated with a stable dose of basal insulin for at least three months before screening in the placebo-controlled trials: ±20% of basal insulin (≥ 30 units per day) in GETGOAL – L, ±20% of basal insulin (≥ 10 units/day) in GETGOAL – L Asia, and ±20% of basal insulin (≥ 15 units per day) in GETGOAL – L – C. Daily basal insulin doses were titrated weekly based on target fasting SMPG between 4.4 mmol/L and 5.6 mmol/L, inclusive. Insulin glargine doses were adjusted throughout the study to maintain the patient at the fasting SMPG target

levels. Patients with A1C ≤ 7.5% at randomization were to reduce daily basal insulin dose by 20% to reduce the risk of hypoglycemia. Daily doses of basal insulin where then to be increased gradually between week 4 and week 12 in the absence of hypoglycemia, whereas daily doses of basal insulin in patients with A1C > 7.5% were to remain stable. Daily basal insulin doses were then to remain relatively stable throughout the study, not exceeding ±20% of the daily dose at screening. Overall, a reduction in the daily basal insulin dose was to be considered if a patient had two or more symptomatic hypoglycemic episodes or one severe hypoglycemic episode.

Patients treated with metformin at screening were to remain on a stable dose of at least 1,500 mg per day throughout the trial in both GETGOAL – L and GETGOAL – DUO 1, whereas patients enrolled in GETGOAL – L – C were to remain on a stable dose of 1,000 mg/day. The dose of sulfonylurea was to be reduced by at least 25% (or stopped in case of minimum dose) at randomization to reduce the risk of hypoglycemia in patients with A1C < 8.0% in GETGOAL – L Asia. In the absence of hypoglycemia, the sulfonylurea dose was to be gradually increased (or restarted if discontinued) between week 4 and week 12 to the dose received at screening. In addition to metformin, thiazolidinediones was also a permitted concomitant background antidiabetic therapy in GETGOAL – DUO 1, whereas concomitant use of sulfonylureas and glinides were to be discontinued before the double-blind treatment phase. All concomitant background antidiabetic therapies were to be discontinued during the double-blind treatment phase of the placebo-controlled trials other than those specified (e.g., basal insulin, metformin, sulfonylurea, and thiazolidinediones), and the doses of all permitted concomitant antidiabetic therapies (other than insulin) were to be kept unchanged throughout the study.

Active-Controlled Trial

In GETGOAL – DUO 2, patients were required to have had been treated with a stable dose of daily basal insulin background therapy for at least six months (stable dose ≥ 20 units per day for ≥ 2 months before screening) alone or in combination with metformin (≥ 1,500 mg/day), a DPP-4 inhibitor, a sulfonylurea, or a glinide. All concomitant background antidiabetic therapies were to be discontinued during the open-label treatment phase other than daily basal insulin and metformin, if previously taken. Basal insulin (insulin glargine) was optimally titrated every three days based on target fasting SMPG between 4.4 mmol/L and 5.6 mmol/L, inclusive. Patients with A1C ≥ 7.0%, ≤ 9.0%, and a mean fasting SMPG ≤ 7.8 mmol/L continued into the 26-week open-label treatment phase. To avoid hypoglycemia when treated with lixisenatide or insulin glulisine, the insulin glargine dose was to be reduced during the open-label treatment period in patients with A1C ≥ 7.0% and ≤ 8.0%. Patients who were receiving any basal insulin other than insulin glargine before screening switched to insulin glargine during the run-in phase. The starting dose of insulin glargine was the total dose of the previous insulin (or initial dose minus 20% if treated with more than one daily injection or with insulin detemir). Insulin glargine was subcutaneously injected once daily at breakfast or dinner based on preference.

SC insulin glulisine was the comparator in the GETGOAL – DUO 2. It administered within 15 minutes before breakfast or dinner in the insulin glulisine once daily group and within 15 minutes before each meal in the insulin glulisine three times daily group. The initial insulin glulisine dose was three units to five units per injection and subsequently titrated to obtain a SMPG value between > 5.6 mmol/L and ≤ 7.8 mmol/L while avoiding hypoglycemia at every visit. The titration procedure to achieve and maintain target doses of insulin glulisine were at the discretion of the investigator; however, small decreases to doses were permitted in case of hypoglycemia. If A1C remained above 8.5% at week 12 and thereafter, corrective actions

were required to ensure optimally titrated insulin (basal insulin and insulin glulisine), optimal lixisenatide titration, and treatment adherence. In such cases, a study visit was planned four weeks later to evaluate the impact of the corrective actions. If A1C levels above 8.5% persisted, final assessments were performed and the patient was discontinued from treatment and the study. In addition to the scheduled visits, titrations were permitted through phone calls as often as deemed necessary by the investigator.

Outcomes

Efficacy

Placebo-Controlled Trials

In the placebo-controlled trials, the primary efficacy outcomes were the absolute change from baseline in A1C at week 24. Other efficacy outcomes included the percentage of patients achieving A1C < 7.0% and ≥ 7.0%, or ≤ 6.5% and > 6.5% at week 24; changes in two-hour PPG (after a standardized meal), glucose excursion, average seven-point SMPG profiles (average SMPG for measurements before and two hours after breakfast, before and two hours after lunch, before and two hours after dinner, and at bedtime), FPG, and body weight; weight loss of < 5% body weight or > 5% body weight; and change from baseline in daily basal insulin dose and total insulin dose at week 24. The need for rescue therapy was also evaluated in GETGOAL – L, GETGOAL – L Asia, and GETGOAL – DUO 1. GETGOAL – L continued to evaluate these outcomes beyond week 24 in a variable extension phase (up to 52 weeks of treatment).

In addition, GETGOAL – L – C also evaluated the percentage of patients achieving three composite end points defined as: A1C < 7.0% with no confirmed symptomatic hypoglycemia, A1C < 7.0% with no weight gain, and A1C < 7.0% with no weight gain and no confirmed symptomatic hypoglycemia

The need for rescue therapy in GETGOAL – L and GETGOAL – L Asia was defined as a fasting SMPG value (on three consecutive days), or an FPG level (analyzed by the central laboratory) that exceeded the threshold values defined as:

- from baseline visit to week 8: FPG > 15.0 mmol/L
- from week 8 to week 12: FPG > 13.3 mmol/L
- from week 12 up to week 24: FPG > 11.1 mmol/L or A1C > 8.5%

[redacted]

Similarly, GETGOAL – DUO 1 defined the need for rescue therapy as:

- during the run-in phase: FPG > 13.3 mmol/L
- from week 0 to week 8: FPG > 11.1 mmol/L or A1C > 9.0%
- from week 8 to week 24: FPG > 10.0 mmol/L or A1C > 8.5%.

Active-Controlled Trial

In GETGOAL – DUO 2, the primary analysis was based on the three co-primary end points: 1) noninferiority of lixisenatide versus insulin glulisine once daily in the change from baseline in A1C at week 26 using a noninferiority margin of 0.4%; 2a) noninferiority of lixisenatide versus insulin glulisine three times daily in the change from baseline in A1C at week 26 using a noninferiority margin of 0.4%; and 2b) superiority of lixisenatide versus insulin glulisine three times daily in the change from baseline in body weight at week 26. Other efficacy outcomes included the percentage of patients achieving A1C < 7.0% or ≤ 6.5% at week 24; changes in two-hour PPG (after a standardized meal), glucose excursion,

average seven-point SMPG profiles (average SMPG for measurements before and two hours after breakfast, before and two hours after lunch, before and two hours after dinner, and at bedtime), FPG, and body weight; the percentage of patients with weight loss < 5% body weight or > 5% body weight; and change from baseline in daily basal insulin dose and total insulin dose at week 24.

In addition, GETGOAL – DUO 2 evaluated the percentage of patients with achieving three composite end points defined as: A1C < 7.0% with no confirmed symptomatic hypoglycemia, A1C < 7.0% with no weight gain, and A1C < 7.0% with no weight gain and no confirmed symptomatic hypoglycemia. [redacted]

Harms

All trials (placebo-controlled and active-controlled) collected safety data, including the occurrence of adverse events (AEs), serious adverse events (SAEs), withdrawal due to adverse events (WDAEs), and notable harms. The safety outcomes that follow apply to both placebo-controlled and active-controlled trials.

AEs were defined as any untoward medical occurrence or clinical investigation in a patient administered the pharmaceutical product and which does not need to have a causal relationship with this treatment.

SAEs were defined as an event that resulted in death, was life-threatening, required in-patient hospitalization or prolongation of existing hospitalization, resulted in persistent or significant disability or incapacity, was a congenital anomaly or birth defect, or was medically important.

Symptomatic hypoglycemia was defined as an event with clinical symptoms that were considered to result from a hypoglycemic episode (e.g., sweating, palpitations, hunger, restlessness, anxiety, fatigue, irritability, headache, loss of concentration, somnolence, psychiatric or visual disorders, transient sensory or motor defects, confusion, convulsions, or coma) with an accompanying plasma glucose < 3.3 mmol/L or associated with prompt recovery after oral carbohydrate administration if no plasma glucose value was available. Symptoms with an associated plasma glucose ≥ 3.3 mmol/L were not to be reported as hypoglycemia.

Severe symptomatic hypoglycemia was defined as an event with clinical symptoms that were considered to result from hypoglycemia in which the patient required the assistance of another person, because the patient could not treat him/herself due to acute neurological impairment directly resulting from the hypoglycemic event, and one of the following:

- the event was associated with a plasma glucose level below 2.0 mmol/L
- if no plasma glucose value was available, then the event was associated with prompt recovery after oral carbohydrate, intravenous glucose, or glucagon administration.

An allergic reaction assessment committee comprising independent experts in the field of allergy was used to assess and adjudicate allergic reactions that may occur during the study. The allergic reaction assessment committee was blinded regarding to study treatment. Examples of AEs that may constitute an allergic reaction were generalized itch, nasal itch, swelling at injection site, flushing, hives, swelling at lips, eyes, face, tongue, hands, feet, lump in throat, difficulty swallowing, hoarseness, change in pitch of voice, incapacity to speak, wheezing, chest tightness, and stridor, among others. Local injection site reactions were not considered as allergic reactions.

Suspicions of pancreatitis included cases of severe and persistent abdominal pain, which can radiate to the back, often with characteristic positional features, and with possible occurrence of nausea, vomiting, fever, and leukocytosis. Under suspicions of pancreatitis, further measurement of amylase and lipase should be performed. The diagnosis of pancreatitis may also be considered if other causes of abdominal pain are excluded (i.e., gallbladder disease, etc.) accompanied by elevated amylase or lipase, pancreatic changes on ultrasound, and CT, MRI (with contrast, as appropriate), or both. Amylase and lipase values greater than the two-fold upper limit of normal (ULN) should be repeated within seven days, whereas values greater than the three-fold ULN should be repeated within 48 hours. Amylase and lipase elevations without associated clinical symptoms should receive a gastroenterologic evaluation with additional imaging, as appropriate.

Statistical Analysis

Overall, no interim analyses were planned or conducted in any of the placebo-controlled or active-controlled trials.

Placebo-Controlled Trials

The primary analysis of the efficacy in the placebo-controlled trials was performed based on measurements obtained at week 24 of the double-blind treatment phase. The last observation carried forward (LOCF) procedure was used to impute missing data. [redacted] The primary efficacy end point in all placebo-controlled trials was the change from baseline in A1C at week 24 and was analyzed using an analysis of covariance (ANCOVA) model stratified by A1C at screening (< 8.0%, ≥ 8.0%), metformin use at screening (yes, no), and country as fixed effects, using baseline A1C value as a covariate. In GETGOAL – L Asia and GETGOAL – DUO 1, background therapies were stratified by sulfonylurea (yes, no) and by thiazolidinediones (yes, no) instead of metformin, respectively. Those that required rescue therapy were not included in the A1C analysis and all efficacy outcomes were analyzed in the modified intention-to-treat (mITT) population. Data are presented as the least squares (LS) mean change from baseline with corresponding standard errors and LS mean difference from placebo with corresponding 95% confidence intervals (CIs).

Shapiro–Wilk statistics for normality and Levene's test for the homogeneity of variances between the treatment groups were used to examine the underlying assumptions for the ANCOVA model. If significant deviations from the assumptions were observed, normalized (using Tukey's) rank transformation to the same ANCOVA model (without Tukey's rank transformation for the baseline covariate) was evaluated as a sensitivity analysis. Sensitivity analyses to assess the impact of rescue medication were performed based on all scheduled A1C measurements during the main 24-week double-blind treatment period using a multi-level model with random slopes and intercepts and mixed-effects models for repeated measures (MMRM) for the primary end point (absolute change from baseline in A1C at week 24) under the missing at random framework to adjust for the effect of rescue medication in all placebo-controlled trials. The MMRM included the fixed-effects factors for treatment (lixisenatide or placebo), visit, the treatment-by-visit interaction, randomization strata of visit 12 A1C (< 8.0%, ≥ 8.0%), and country, as well as the covariate, baseline A1C value-by-visit interaction. Randomization strata of thiazolidinedione use (yes, no) was also included in GETGOAL – DUO 1 only. The factor visit had three levels (week 8, week 16, and week 24). A sensitivity analysis with 24-week completers (patients who completed the 24 weeks of treatment) using the observed week-24 values and the same ANCOVA model described for the primary analysis above was also conducted.

All continuous secondary variables were assessed with a similar ANCOVA method, whereas secondary categorical data were analyzed using a Cochran–Mantel–Haenszel method. Both crude means and adjusted means for lixisenatide and placebo were provided with a 95% two-sided CI at a significance level of alpha = 0.05. Subsequent to the statistical significance (at alpha = 0.05) of the primary efficacy variable, a testing hierarchy was performed on the secondary efficacy variables using the mITT population. The statistical testing hierarchy stopped when an end point was found to be statistically insignificant at alpha = 0.05. No adjustments for type I error were made for any other secondary efficacy end points.

The statistical testing order in GETGOAL – L was:

- change from baseline in two-hour PPG after a standardized meal at week 24
- change from baseline in the average seven-point SMPG at week 24
- change from baseline in FPG at week 24
- change from baseline in body weight at week 24
- percentage of patients requiring rescue therapy during the main 24-week double-blind treatment period.

The statistical testing order in GETGOAL – L Asia was:

- change from baseline in two-hour PPG after a standardized meal at week 24
- change from baseline in body weight at week 24
- change from baseline in the average seven-point SMPG at week 24
- change from baseline in FPG at week 24
- percentage of patients requiring rescue therapy during the main 24-week double-blind treatment period.

The statistical testing order in GETGOAL – DUO 1 was:

- change from baseline in two-hour PPG after the standardized meal test at week 24
- change from baseline in the daily average seven-point SMPG at week 24
- change from baseline in body weight at week 24
- change from baseline in average daily insulin glargine dose at week 24

- change from baseline in FPG at week 24
- percentage of patients requiring rescue therapy during the on-treatment period.

The statistical testing order in GETGOAL – L – C was:

- change from baseline in two-hour PPG after the standardized meal test at week 24
- change from baseline in the daily average seven-point SMPG at week 24
- change from baseline in body weight at week 24
- change from baseline in average daily insulin glargine dose at week 24
- change from baseline in FPG at week 24.

Pre-specified subgroups were evaluated in a similar manner using an ANCOVA model, with the addition of the subgroup factor interaction as fixed effects; however, no type I error corrections were applied. Subgroup analyses also did not include patients who required rescue in the A1C analysis and were analyzed in the mITT population. Analyses were performed using the A1C data in order to assess consistency of treatment effect across the following baseline factors:

- country
- race (Caucasian, Black, Asian, other)
- ethnicity (Hispanic, not Hispanic)
- age group (< 50 years, ≥ 50 years to < 65 years, ≥ 65 years)
- gender
- baseline BMI (< 30 kg/m2, ≥ 30 kg/m2)
- baseline A1C (< 8.0%, ≥ 8.0%)
- metformin use at screening (yes, no) (GETGOAL – L and GETGOAL – L – C only)
- sulfonylurea use at screening (yes, no) (GETGOAL – L Asia only)
- thiazolidinedione use at screening (yes, no) (GETGOAL – DUO 1 only).

Safety results were presented by treatment group (lixisenatide and placebo) for the on-treatment period of the whole study and the 24-week treatment period (time from the first dose of the double-blind investigational product up to three days after the last dose of the investigational product injection) and analyzed using the safety population.

A sample size calculation based on the primary efficacy end point (absolute change from baseline in A1C at week 24) was conducted for all placebo-controlled trials using a common standard deviation of 1.3% in A1C with a two-sided test at the 5% significance level. Of note, there were no specific power calculations conducted for the pre-specified subgroups of interest for this CDR review.

In GETGOAL – L, a sample size of 450 patients was required (300 patients in the lixisenatide arm; 150 patients in the placebo arm) to detect a difference of 0.5% (or 0.4%) in the absolute change from baseline in A1C at week 24 between lixisenatide and placebo, with a power of 96% (or 86%).

In GETGOAL – L Asia, a sample size of 300 patients (150 patients per group) was considered sufficient to detect a difference of 0.5% in the absolute change from baseline in A1C at week 24 between lixisenatide and placebo, with a power of 90%.

In GETGOAL – DUO 1, a sample size of 450 patients (225 patients per group) provided a power of 98% to detect differences of 0.5% and a power of 90% to detect differences of 0.4% in the absolute change from baseline in A1C at week 24 between lixisenatide and placebo. To achieve a total of 450 randomized patients, approximately 950 patients were included in the run-in phase.

In GETGOAL – L – C, a sample size of 432 patients (216 patients per group) provided a power of 97% to detect differences of 0.5% in the absolute change from baseline in A1C at week 24 between lixisenatide and placebo. To achieve a total of 432 randomized patients, approximately 750 patients were included in the run-in phase.

Active-Controlled Trial

In GETGOAL – DUO 2, the primary analysis was based on the following co-primary end points analyzed using a similar ANCOVA model as the placebo-controlled trials (stratified by A1C at screening [< 8.0%, ≥ 8.0%], metformin use at screening [yes, no], and country as fixed effects, using baseline A1C value as a covariate), and LOCF procedure was used to impute missing data:

1. noninferiority of lixisenatide versus insulin glulisine once daily in the change from baseline in A1C at week 26
2a. noninferiority of lixisenatide versus insulin glulisine three times daily in the change from baseline in A1C at week 26
2b. superiority of lixisenatide versus insulin glulisine three times daily in the change from baseline in body weight at week 26.

The primary co-primary end points 1 and 2 (either 2a or 2b) were assessed separately and data are presented as the LS mean change from baseline with corresponding standard errors, and LS mean differences from insulin glulisine once daily and insulin glulisine three times daily with corresponding 95% CI. Lixisenatide was to be declared noninferior to insulin glulisine once daily if: 1) the upper bound of the two-sided 95% CI for the treatment difference in the absolute change from baseline in A1C at week 26 was < 0.4%; and either 2a) noninferior to insulin glulisine three times daily if the upper bound of the two-sided 95% CI for the treatment difference in the absolute change from baseline in A1C at week 26 was < 0.4%, or 2b) superior to insulin glulisine three times daily in the absolute change from baseline in body weight at week 26.

The predefined noninferiority margin for A1C (0.4%) was determined based on regulatory recommendations in force at the time of the protocol preparation and based on other studies with similar compounds. For the co-primary end point 2 (both 2a and 2b), a Hochberg procedure was used in order to control the type I error at alpha = 0.025 level (one-sided). The Hochberg procedure was as follows: if noninferiority of 2a and superiority of 2b were both met at alpha = 0.025 level (one-sided), then end point 2 was met at alpha = 0.025 level (one-sided). If only one (either 2a or 2b) co-primary end point was satisfied, then that end point should be tested at alpha = 0.0125 level (one-sided). No control for type I error was made for any secondary end points in GETGOAL – DUO 2.

Sensitivity analyses to support the primary analysis using MMRM for the primary end points (absolute change from baseline in A1C and body weight at week 26) under the missing at random framework were conducted. The MMRM model used treatment group (lixisenatide, insulin glulisine once daily, and insulin glulisine three times daily), stratum of A1C week 1 (< 8%, ≥ 8 %), randomization stratum of metformin use (yes, no), visit (week 12, week 20, and week 26 for A1C; week 2, week 6, week 12, week 20, and week 26 for body weight), treatment-by-visit interaction, and country as fixed effects, using the corresponding baseline (A1C or body weight) value-by-visit interaction as covariate. A sensitivity analysis with 26-week completers (patients who completed the 26 weeks of treatment) using the observed week 26 values and the same ANCOVA model described for the primary analysis above was also conducted.

In GETGOAL – DUO 2, a sample size of 285 patients per group ensured that the upper confidence limit of the two-sided 95% CI for the adjusted mean difference between lixisenatide and insulin glulisine once daily in the absolute change from baseline in A1C at week 26 would not exceed 0.4% with at least 94% power, and ensured the upper confidence limit of the two-sided 97.5% CI for the adjusted mean difference between lixisenatide and insulin glulisine three times daily in the absolute change from baseline in A1C at week 26 would not exceed 0.4% with at least 90% power. The sample size calculation assumed a common standard deviation of 1.2% in A1C, a true difference in A1C between the treatment groups of zero, and a 20% dropout rate. The sample size also ensured at least 90% power to detect a difference of 1 kg in absolute change from baseline in body weight at week 26 between lixisenatide and insulin glulisine three times daily and assumed a common standard deviation of 2.75 kg at the 2.5% significance level (two-sided).

Pre-specified subgroups were evaluated in a similar manner using an ANCOVA model, with the addition of the subgroup factor interaction as fixed effects; however, no type I error corrections were applied. Subgroup analyses were also analyzed in the mITT population. Analyses were performed using the A1C and body weight data in order to assess consistency of treatment effect across the following baseline factors:

- country
- race (Caucasian, Black, Asian, other)
- ethnicity (Hispanic, not Hispanic)
- age group (< 50 years, ≥ 50 years to < 65 years, ≥ 65 years)
- gender
- baseline BMI (< 30 kg/m2, ≥ 30 kg/m2)
- baseline A1C (< 8.0%, ≥ 8.0%)
- metformin use at screening (yes, no)
- duration of diabetes at screening (< 10 years, ≥ 10 years)
- daily total insulin glargine dose at screening (< 45 units per day, ≥ 45 units per day)
- duration of basal insulin treatment at screening (< 3 years, ≥ 3 years).

Analysis Populations

The mITT population was defined as all patients who were randomized, took at least one dose of double-blind investigational product, and had both a baseline assessment and at least one post-baseline efficacy assessment of any primary or secondary efficacy variables, irrespective of compliance with the study protocol and procedures. Patients were analyzed for efficacy in the treatment group to which they were randomized.

The safety population was defined as all patients who were randomized and exposed to at least one dose of double-blind investigational product, regardless of the amount of treatment administered. In the event patients received treatments that differed from those assigned according to the randomization schedule, the safety analyses were conducted according to the treatment received rather than according to the randomization groups. If a patient was exposed to both lixisenatide and placebo, the patient would be analyzed in the treatment group (lixisenatide or placebo) to which he or she was treated for longer duration.

Patient Disposition

Placebo-Controlled Trials

[redacted]No information on patient study withdrawals were provided; however, treatment discontinuation ranged between 5% and 16% in all placebo-controlled trials. Generally, more patients discontinued study treatment in the lixisenatide groups compared with the placebo groups with the exception of GETGOAL – L – C (8% versus 14%). The most common reason for discontinuing study treatment in all placebo-controlled trials was AEs, ranging between 2% and 9%. Contrarily, in GETGOAL – L – C, the most common reason for discontinuing study treatment was lack of efficacy (7% in the placebo group and 2% in the lixisenatide group). Overall, more patients discontinued study treatment due to AEs in the lixisenatide group compared with the placebo group. Details in regard to patient disposition in the placebo-controlled trials are provided in Table 10.

Table 10: Patient Disposition (Placebo-Controlled Randomized Controlled Trials)

Characteristics	GETGOAL							
	– L		– L Asia		– DUO 1		– L – C	
	PLB	LIXI	PLB	LIXI	PLB	LIXI	PLB	LIXI
Screened, N	879		437		1,470		789	
Randomized and treated, N (%)	495 (56)		311 (71)		446 (30)		447 (57)	
	167	328[a]	157	154	223	223	223[a]	224
Discontinued 24-week DB treatment, n (%)	20 (12)	53 (16)	13 (8)	21 (14)	12 (5)	29 (13)	32 (14)	18 (8)
Adverse event	4 (2)	26 (8)	5 (3)	14 (9)	9 (4)	19 (9)	6 (3)	8 (4)
Lack of efficacy	3 (2)	3 (1)	2 (1)	1 (1)	0	0	16 (7)	4 (2)
Poor compliance to protocol	4 (2)	6 (2)	0	0	0	2 (1)	2 (1)	2 (1)
Lost to follow-up	1 (1)	0	0	0	0	0	0	0
Other	8 (5)	18 (5)	6 (4)	6 (4)	3 (1)	8 (4)	8 (4)	4 (2)
Discontinued DB treatment, n (%)	[redacted]	[redacted]	NA	NA	NA	NA	NA	NA
Adverse event	[redacted]	[redacted]	NA	NA	NA	NA	NA	NA
Lack of efficacy	[redacted]	[redacted]	NA	NA	NA	NA	NA	NA
Poor compliance to protocol	[redacted]	[redacted]	NA	NA	NA	NA	NA	NA
Lost to follow-up	[redacted]	[redacted]	NA	NA	NA	NA	NA	NA
Other	[redacted]	[redacted]	NA	NA	NA	NA	NA	NA
RS, N (%)	167 (100)	329 (100)	157 (100)	154 (100)	223 (100)	223 (100)	224 (100)	224 (100)

Characteristics	GETGOAL							
	– L		– L Asia		– DUO 1		– L – C	
	PLB	LIXI	PLB	LIXI	PLB	LIXI	PLB	LIXI
mITT, N (%)	166 (99)	327 (99)	157 (100)	154 (100)	223 (100)	223 (100)	223 (100)	223 (100)
Safety, N (%)	167 (100)	328 (100)	157 (100)	154 (100)	223 (100)	223 (100)	223 (100)	224 (100)

CSR = Clinical Study Report; DB = double-blind; LIXI = lixisenatide; mITT = modified intention-to-treat; NA = not applicable; PLB = placebo; RCT = randomized controlled trial; RS = randomized set.

[a] One patient did not receive treatment.

Source: Riddle 2013,[4] GETGOAL – L CSR,[5] Riddle 2013,[6] GETGOAL – DUO 1 CSR,[7] Seino 2012,[8] GETGOAL – L Asia CSR,[9] and GETGOAL – L – C CSR.[10]

Active-Controlled Trial

[redacted] Details in regard to patient disposition in GETGOAL – DUO 2 are provided in Table 11.

Table 11: Patient Disposition (Active-Controlled Randomized Controlled Trial)

Characteristics	GETGOAL – DUO 2		
	LIXI	IG Once Daily	IG t.i.d.
Screened, N			
Randomized and treated, N (%)			
Discontinued 26-week OL treatment phase, n (%)			
Adverse event			
Lack of efficacy			
Poor compliance to protocol			
Lost to follow-up			
Other			
RS, N (%)			
mITT, N (%)			
Safety, N (%)			

IG = insulin glulisine; LIXI = lixisenatide; mITT = modified intention-to-treat; NR = not reported; OL = open-label; PLB = placebo; RCT = randomized controlled trial; RS = randomized set; t.i.d. = three times daily.

[a] One patient did not receive treatment.

[b] Four patients were randomized to insulin glulisine three times daily group, but took an insulin glulisine dose once a day for more than 50% of the treatment period; therefore, these patients were analyzed in the insulin glulisine once daily group for the safety analysis. One patient was randomized to the insulin glulisine once daily group, but took an insulin glulisine dose at least twice a day for more than 50% of the treatment period; therefore, this patient was analyzed in the insulin glulisine three times daily group for the safety analysis.

Source: Rosenstock 2016[11] and GETGOAL – DUO 2 Clinical Study Report.[12]

Exposure to Study Treatments

Placebo-Controlled Trials

[redacted]

Details in regards to exposure in the placebo-controlled trials are provided in Table 12.

Table 12: Exposure (Placebo-Controlled Randomized Controlled Trials)

Exposure	GETGOAL							
	– L		– L Asia		– DUO 1		– L – C	
	PLB	LIXI	PLB	LIXI	PLB	LIXI	PLB	LIXI
Final dose of DB treatment, n (%)								
10 mcg	[redacted]							
15 mcg	[redacted]							
20 mcg	[redacted]							
> 20 mcg	[redacted]							
Duration of study treatment								
Mean, days (SD)	[redacted]							
Median, days (range; min, max)	[redacted]							

CSR = Clinical Study Report; DB = double-blind; LIXI = lixisenatide; max = maximum; min = minimum; NR = not reported; PLB = placebo; RCT = randomized controlled trial; SD = standard deviation.

[a] Includes exposure in double-blind extension phase.

Source: Riddle 2013,[4] GETGOAL – L CSR,[5] Riddle 2013,[6] GETGOAL – DUO 1 CSR,[7] Seino 2012,[8] GETGOAL – L Asia CSR,[9] and GETGOAL – L – C CSR.[10]

Active-Controlled Trials

[redacted]Details on patients' treatment duration and exposure in GETGOAL – DUO 2 are provided in Table 13.

Table 13: Exposure (Active-Controlled Randomized Controlled Trial)

Exposure	GETGOAL – DUO 2		
	LIXI	IG Once Daily	IG Three Times Daily
Final dose of DB treatment, n (%)			
10 mcg	[redacted]	[redacted]	[redacted]
20 mcg	[redacted]	[redacted]	[redacted]
> 20 mcg		[redacted]	[redacted]
Mean duration of study treatment, days (SD)	[redacted]	[redacted]	[redacted]
Median duration of study treatment, days (range; min, max)	[redacted]	[redacted]	[redacted]

CSR = Clinical Study Report; DB = double-blind; IG = insulin glulisine; LIXI = lixisenatide; max = maximum; min = minimum; NA = not applicable; PLB = placebo; RCT = randomized controlled trial; SD = standard deviation.

Source: Riddle 2013,[4] GETGOAL – L CSR,[5] Riddle 2013,[6] GETGOAL – DUO 1 CSR,[7] Seino 2012,[8] GETGOAL – L Asia CSR,[9] and GETGOAL – L – C CSR.[10]

Critical Appraisal

Internal Validity

Placebo-Controlled Trials

The GETGOAL – L, GETGOAL – L Asia, GETGOAL – DUO 1, and GETGOAL – L – C trials were all double-blind, placebo-controlled RCTs that used accepted methods to conceal allocation and randomize patients (interactive voice/Web response system). In addition, the use of the ANCOVA method of analysis would have ensured that the results were adjusted for variables including concomitant treatment with specified oral hypoglycemic drugs, baseline A1C, and country. The National Institute for Health and Care Excellence (NICE) also noted the robustness of the statistical model in their evidence review.[26] Baseline patient characteristics were relatively similar between treatment groups; therefore, randomization appears to be successful. Although the placebo-controlled trials were double-blind RCTs, the AE profile associated with GLP-1 analogues (i.e., gastrointestinal AEs) is well known; therefore, some unblinding may have occurred. Furthermore, syringe-injection volume was not concealed and may have caused some unblinding. Given that prior GLP-1 analogue experience was not an exclusion criterion in any of the trials, some patients with prior experience may have surmised that the allocated treatment was lixisenatide; however, considering that the end points of the placebo-controlled trials are relatively objective (e.g., absolute change in A1C), the potential for bias is of lesser concern. Unblinding may, however, lead to biases such as under- or over-reporting of subjective outcomes (i.e., AEs), which can affect the overall impression of harms with lixisenatide treatment.

Overall, the placebo-controlled trials did not address morbidity, mortality or HRQoL outcomes that are greatly important to patients; however, the ELIXA trial provides evidence for longer-term outcomes.[27] Complete study withdrawals were not reported in any of the placebo-controlled trials. Overall, there were numerically more WDAEs in the lixisenatide group compared with the placebo group; therefore, if the frequency of complete study withdrawals were greater in one group compared with the other group, randomization may have been compromised and the study results could be biased in favour of either treatment. NICE also reported that the treatment discontinuation rates ranged from 8% to 16% among patients randomized to lixisenatide, and 5% to 14% among those randomized to placebo. The European Medicines Agency's guideline on missing data in confirmatory clinical trials

suggests that patients who do not complete a clinical trial may be more likely to have extreme values than patients who complete a trial. Therefore, excluding these patients could underestimate the variability and artificially narrow the CI for the treatment effect and neither the LOCF method nor sensitivity analysis using the MMRM would have overcome this potential limitation.[26] All placebo-controlled trials included a run-in period to train patients on treatment administration, study protocol and management of symptoms, which was likely to have led to high treatment compliance and, consequently, a potential overestimation of the study drug's effectiveness.

The definition of hypoglycemia used in all of the placebo-controlled trials was an event with clinical symptoms that were considered to result from a hypoglycemic episode with an accompanying plasma glucose < 3.3 mmol/L, or associated with prompt recovery after oral carbohydrate administration if no plasma glucose value was available. Symptoms with an associated plasma glucose ≥ 3.3 mmol/L were not to be reported as hypoglycemia. This definition differs from that used by Diabetes Canada, which defines hypoglycemia as the development of autonomic or neuroglycopenic symptoms accompanied by a low plasma glucose level (< 4.0 mmol/L for patients treated with insulin or an insulin secretagogue) and symptoms responding to the administration of carbohydrate. [21] Misclassification of events (hypoglycemia) may not bias the study in favour of one treatment (assuming that blinding was maintained), but may overestimate or underestimate the true incidence of events.

Placebo responses varied considerably within and across placebo-controlled trials (ranging from an improvement of –0.4% to a worsening of 0.11% in A1C). The large placebo response rate may be due to suboptimal basal insulin therapy that was optimized during the run-in phase, given that A1C is an outcome with latent response. Such a confounding factor may prevent an accurate estimation of comparative efficacy, though the direction of bias is unclear. NICE also made similar comments on the variability of the placebo response and suggested that the variability in placebo response somewhat hampers assessment of lixisenatide's effects.[26]

All placebo-controlled trials found that lixisenatide was statistically significantly superior to placebo after 24 weeks of treatment in terms of absolute change from baseline in A1C. However, the use of the LOCF method for handling missing data is a potential source of bias. [redacted] By using a LOCF method, the benefits of lixisenatide may be overestimated and result in a larger treatment effect; this limitation would not have been overcome in the sensitivity analysis using the MMRM analysis. A similar observation was also noted by NICE.[26] A more appropriate method, such as the best case worst case method, may have been more suitable in these trials.

All efficacy analyses were conducted using a mITT population defined as all patients who were randomized, took at least one dose of double-blind investigational product, and had both a baseline assessment and at least one post-baseline efficacy assessment of any primary or secondary efficacy variables, irrespective of compliance with the study protocol and procedures. In the ANCOVA model, missing data were imputed using the LOCF approach, specifically using post-baseline data; patients for whom data after the date of randomization were missing were excluded from the analyses. Excluding these patients is inconsistent with the true definition of an intention-to-treat (ITT) analysis, in which all patients are included, and may not preserve the integrity of randomization. This can potentially raise concerns given the number of missing patients in the primary A1C analysis,

especially in the GETGOAL – L trial, in which 7% of patients were excluded. Furthermore, patients were excluded from the primary A1C analysis post-rescue treatment. Excluding these patients can artificially inflate the benefit of lixisenatide and bias the results by overestimating the treatment effect. However, sensitivity analyses to assess the impact of rescue medication were performed based on all scheduled A1C measurements during the main 24-week double-blind treatment period. Sensitivity analyses with 24-week completers using the observed week 24 values and the same ANCOVA model described for the primary analysis were also conducted. The results of all sensitivity analyses were similar in magnitude, direction, and statistical significance, and were in support of the primary analyses in all placebo-controlled trials, thereby lessening the concerns with the exclusion of patients requiring rescue therapy; however, the validity of the sensitivity analyses on these end points may be biased given that patients were assumed to be missing at random.

All placebo-controlled trials used a statistical testing hierarchy to examine secondary outcomes to control for type I error. Subsequent to the statistical significance (at alpha = 0.05 level) of the primary efficacy variable, a testing hierarchy was performed on the secondary efficacy variables. The statistical testing hierarchy stopped when an end point was found to not be statistically significant at alpha = 0.05 level. This is a common and appropriate strategy to account for multiplicity; however, the manufacturer does not appear to have adhered to its pre-specified testing strategy by continuing statistical testing for superiority after statistical insignificance was established. Overall, statistical testing should have stopped after the change in the FPG end point (third in the order of secondary analyses) in GETGOAL – L, change in the body weight end point (second in the order of secondary analyses) in GETGOAL – L Asia, change in the FPG end point (fifth in the order of secondary analyses) in GETGOAL – DUO 1, and change in the FPG end point (fifth in the order of secondary analyses) in GETGOAL – L – C. It is important to note that only the outcomes considered in the testing strategy and that met statistical significance can be considered acceptable, which implies that the results of the outcomes outside of the testing strategy (including all subgroup analyses) should be considered as exploratory and be interpreted with caution, since they were not appropriately adjusted for multiplicity, which increases the risk of making a type I error. Further, although subgroup analyses were presented for a number of relevant baseline factors, which were pre-specified, formal interaction tests and adjustments for multiple comparisons did not appear to have been made for these analyses. These analyses should be treated as exploratory given that subgroups typically do not maintain randomization (unless used as stratification variables for randomization, which was true of the A1C [< 8.0%, ≥ 8.0%] and metformin [yes, no] subgroups only, are likely underpowered (small sample size) to detect a statistically significant difference, and have an increased likelihood of type I error due to the lack of adjustment for multiple statistical testing.

Active-Controlled Trial

The GETGOAL – DUO 2 trial was an open-label, active-controlled RCT that also used accepted methods to randomize patients (interactive voice/Web response system). In addition, use of a similar ANCOVA method of analysis would have ensured that the results were adjusted for variables including concomitant treatment with specified oral hypoglycemic drugs, baseline A1C, and country. The robustness of the method of analysis was also noted by NICE.[26] Baseline patient characteristics were relatively similar between treatment groups; therefore, randomization appears to be successful. The open-label study design necessitates caution when interpreting the results of analyses of all end points. Unblinding may lead to biases such as under- or over-reporting of subjective outcomes (i.e.,

AEs and HRQoL), which can impact the overall impression with lixisenatide treatment. Although A1C is an objective outcome due to the open-label nature of the trial, basal insulin can be modified based on active treatment, which can be a potential confounder. More importantly, the open-label design raises concerns of the extent to which insulin glulisine was optimally administered during the trial, especially since patients who were assigned to receive insulin glulisine were asked to self-adjust their dose until their FPG had reached targets of < 5.6 mmol/L. Figure 3 indicates that patients may not have reached stable doses of insulin glulisine by the end of the study, indicating that the full effect of insulin glulisine may not be observed in the reported A1C due to the latent response of the measure. Suboptimal dosage of a direct comparator can lead to underestimation of the comparator's benefit, and therefore artificially inflate the treatment effect of lixisenatide.

Overall, the GETGOAL – DUO 2 trial did evaluate HRQoL but did not address morbidity and mortality outcomes that are greatly important to patients; however, the ELIXA trial provides evidence for longer-term outcomes.[27] Complete study withdrawals were not reported in GETGOAL – DUO 2. Overall, there were numerically more WDAEs in the lixisenatide group compared with the placebo group; therefore, if the frequency of complete study withdrawals were greater in one group compared with the other group, randomization may have been compromised and the study results could be biased in favour of either treatment. NICE reports that the European Medicines Agency's guideline on missing data in confirmatory clinical trials suggests that patients who do not complete a clinical trial may be more likely to have extreme values than patients who complete a trial. Therefore, excluding these patients could underestimate the variability and artificially narrow the CI for the treatment effect.[26] GETGOAL – DUO 2 also included a run-in period to train patients on treatment administration, study protocol, and management of symptoms, which was likely to have led to high treatment compliance and, consequently, a potential overestimation of the study drug's effectiveness.

The definition of hypoglycemia used in the GETGOAL – DUO 2 trial was an event with clinical symptoms that were considered to result from a hypoglycemic episode with an accompanying plasma glucose < 3.3 mmol/L, or associated with prompt recovery after oral carbohydrate administration if no plasma glucose value was available. Symptoms with an associated plasma glucose ≥ 3.3 mmol/L were not to be reported as hypoglycemia. This definition differs from that used by Diabetes Canada, which defines hypoglycemia as the development of autonomic or neuroglycopenic symptoms accompanied by a low plasma glucose level (< 4.0 mmol/L for patients treated with insulin or an insulin secretagogue) and symptoms responding to the administration of carbohydrate.[21] Given that GETGOAL – DUO 2 was open-label in design, misclassification of subjective outcomes (e.g., AEs) may bias the study in favour of one treatment due to over- or under-reporting of harms.

GETGOAL – DUO 2 was designed as a noninferiority trial to compare lixisenatide with insulin glulisine once daily and insulin glulisine three times daily using a noninferiority margin of 0.4%. This margin is similar to margins used in previous type 2 diabetes mellitus trials, and consistent with the 2008 FDA draft guidance for diabetes mellitus, which accepts a noninferiority margin of 0.3% or 0.4% A1C percentage units; however, the selection of the 0.4% margin is considered less conservative.[28] Even though GETGOAL – DUO 2 was designed as a noninferiority trial, the primary efficacy outcomes were tested using data from the mITT population, which could potentially bias the results in favour of a finding of noninferiority. Furthermore, no secondary analyses using data from the more appropriate per-protocol population was conducted to corroborate the primary findings; therefore, results

should be interpreted with caution. Overall, the trial length may not be of sufficient duration to determine the long-term effects of lixisenatide on body weight.

All efficacy analyses were conducted using a mITT population defined as all patients who were randomized, took at least one dose of double-blind investigational product, and had both a baseline assessment and at least one post-baseline efficacy assessment of any primary or secondary efficacy variables, irrespective of compliance with the study protocol and procedures. In the ANCOVA model, missing data were imputed using the LOCF approach, specifically using post-baseline data; in other words, patients for whom data after the date of randomization was missing were excluded from the analyses. Excluding these patients is inconsistent with the true definition of an ITT analysis, in which all patients are included, and may not preserve the integrity of randomization. However, this concern is minimized in GETGOAL – DUO 2, in which only 2% of patients were excluded from the primary analysis. Sensitivity analyses to support the primary analysis were performed using a MMRM and 26-week completers using the observed week 26 values and the same ANCOVA model described for the primary analysis. The results of all sensitivity analyses were similar in magnitude, direction, and statistical significance, and were in support of the primary analyses, therefore reaffirming the results of the primary analysis. Similarly to the placebo-controlled trials, the validity of the sensitivity analyses on these end points may be biased given that patients were assumed to be missing at random.

In GETGOAL – DUO 2, the co-primary analyses were appropriately corrected for multiple statistical testing; however, it is important to note that only the co-primary outcomes were controlled for multiple statistical testing, which implies that the results of all other outcomes (including all subgroup analyses) should be considered as exploratory and should be interpreted with caution since they were not appropriately adjusted for multiplicity, which increases the risk of making a type I error. Further, although subgroup analyses were presented for a number of relevant baseline factors, which were pre-specified, formal interaction tests and adjustments for multiple comparisons did not appear to have been made for these analyses. These analyses should be treated as exploratory given that subgroups typically do not maintain randomization (unless used as stratification variables for randomization, which was true of the A1C [< 8.0%, ≥ 8.0%] and metformin [yes, no] subgroups only), are likely underpowered (small sample size) to detect a statistically significant difference, and have an increased likelihood of type I error due to the lack of adjustment for multiple statistical testing.

External Validity

Placebo-Controlled Trials

In the placebo-controlled trials, 39% to 70% of patients were screening failures mostly due to A1C requirements. Stringent inclusion and exclusion criteria can result in large screening failures, and it can potentially lead to the inclusion of a highly enriched population that may not be completely representative of the type 2 diabetes mellitus population in Canada, potentially limiting the generalizability of the trial results. The clinical expert CDR consulted for this review highlighted that the placebo-controlled trials appear to have recruited patients with A1C that are near target and with FPG at target, which is atypical of the type 2 diabetes mellitus population in Canada also potentially limit the generalizability of the trial results. Overall, the placebo-controlled trials did not recruit many patients aged ≥ 75 years (2% to 5%). This is important to note since the prevalence of diagnosed diabetes generally increases with age. The Public Health Agency of Canada estimates that in 2008/09, individuals aged 75 to 79 years had the highest proportion of people with diagnosed

diabetes (23.1% of females, 28.5% of males); however, only the GETGOAL – O trial provides evidence in this subgroup of patients.[29,30] The clinical expert CDR consulted for this review highlighted that the placebo-controlled trials appear to have also recruited patients with lower body weight and BMI compared with the type 2 diabetes mellitus population in Canada (approximately 87 kg and 32 kg/m^2, respectively), also potentially limiting the generalizability of the trial results.

The GETGOAL – L Asia trial consisted of an entirely Asian population, and the majority of the GETGOAL – L – C trial consisted of Asian patients (87% Asian). The racial distribution in these trials would therefore not be entirely representative of the type 2 diabetes mellitus population in Canada and can potentially limit the generalizability of the trial results. NICE also noted generalizability issues from the GETGOAL – L Asia trial, which does not reflect the majority of the population in the UK.[26] Overall, no patients recruited in GETGOAL – L Asia were treated with metformin, which is widely considered to be the first-line drug therapy in patients with type 2 diabetes mellitus who are unable to achieve glycemic control with diet and exercise alone.[31]

The discrepancies in body weight and BMI compared with the type 2 diabetes mellitus population in Canada were especially apparent in the GETGOAL – L and GETGOAL – L – C trials (approximately 64 kg and 25 kg/m^2, and approximately 74 kg and 28 kg/m^2, respectively). The clinical expert CDR consulted for this review noted that patients with higher weight and BMI would be considered ideal candidates for GLP-1 receptor agonist treatment for the fear of potential weight gain with other antidiabetic treatments; therefore, conducting studies with mostly Asian patients who tend to have lower BMI and body weight may not reflect the target population for the drug. The same clinical expert also highlighted that the patients recruited in the GETGOAL – L Asia and GETGOAL – L – C trials were treated with lower doses of total daily basal insulin at baseline compared with the type 2 diabetes mellitus population in Canada, also potentially limiting the generalizability of the trial results. It is important to note that the lower body weights and BMI in the Asian population may potentially explain the discrepancies in total daily basal insulin. Furthermore, incretin-based therapies, such as GLP-1 mimetics, are believed to be particularly effective in people of Asian or Japanese decent because of the underlying pathophysiology of diabetes in these groups.[32,33] Therefore, the effects of lixisenatide may have been overestimated in the GETGOAL – L Asia and GETGOAL – L – C trials. NICE also highlighted the possibility of improved efficacy of GLP-1 receptor agonists in Asian populations in their evidence review. [26]

[redacted]

Daily basal insulin doses were titrated weekly based on target fasting SMPG between 4.4 mmol/L and 5.6 mmol/L, inclusive, which is inconsistent with Diabetes Canada, which recommends a target of 4.0 mmol/L to 7.0 mmol/L.[21] These discrepancies further limit the generalizability of the results to the type 2 diabetes mellitus population in Canada.

Active-Controlled Trial

In GETGOAL – DUO 2, 59% of patients were screening failures mostly due to A1C requirements. Similarly to the placebo-controlled trials, stringent inclusion and exclusion criteria can result in large screening failures and can potentially lead to the inclusion of a

highly enriched population that may not be completely representative of the type 2 diabetes mellitus population in Canada, potentially limiting the generalizability of the trial results. The clinical expert CDR consulted for this review highlighted that the active-controlled trial also appears to have recruited patients with A1C that are near target and with FPG at target, which is atypical of the type 2 diabetes mellitus population in Canada, also potentially limiting the generalizability of the trial results. Overall, GETGOAL – DUO 2 also did not recruit many patients aged ≥ 75 years (4% to 6%). This may be significant, as the prevalence of diagnosed diabetes generally increases with age. The Public Health Agency of Canada estimates that in 2008 and 2009, individuals ages 75 years to 79 years had the highest proportion of people with diagnosed diabetes (23.1% of females, 28.5% of males); however, only the GETGOAL – O trial provides evidence in this subgroup of patients.[29,30] The same clinical expert also highlighted that the GETGOAL – DUO 2 trial appears to have also recruited patients with lower body weight and BMI compared with the type 2 diabetes mellitus population in Canada (approximately 89 kg and 32 kg/m^2, respectively), also potentially limiting the generalizability of the trial results.

[redacted]Daily basal insulin and daily insulin glulisine doses were titrated weekly and every three days, respectively, based on target fasting SMPG between 4.4 mmol/L and 5.6 mmol/L, inclusive, which is inconsistent with Diabetes Canada, which recommends a target of 4.0 mmol/L to 7.0 mmol/L.[21] These discrepancies further limit the generalizability of the results to the type 2 diabetes mellitus population in Canada.

Efficacy

Only those efficacy outcomes identified in the review protocol are reported in Table 5. See Appendix 4 for detailed efficacy data.

Placebo-Controlled Trials

Glycemic Control

Details pertaining to glycemic control outcomes in the placebo-controlled trials are provided in Table 14.

In general, baseline A1C was similar between treatment groups in all placebo-controlled trials, and patients treated with lixisenatide experienced a greater reduction in A1C compared with placebo at week 24. The reductions in A1C were similar in GETGOAL – L and GETGOAL – DUO 1 (–0.74% and –0.71% in the lixisenatide groups, and –0.38% and –0.40% in the placebo groups, respectively, at week 24). The adjusted mean differences were –0.36% (95% CI, –0.55% to –0.17%), $P = 0.0002$, and –0.32 (95% CI, –0.46% to –0.17%), $P < 0.0001$ in GETGOAL – L and GETGOAL – DUO 1, respectively, which were statistically significantly in favour of lixisenatide compared with placebo. The A1C reductions in patients treated with lixisenatide in GETGOAL – L Asia and GETGOAL – L – C were similar to the other placebo-controlled trials (–0.77% and –0.62%); however, the A1C changes in patients treated with placebo were dissimilar (increase of 0.11% and decrease by –0.11%). The adjusted mean differences were –0.88% (95% CI, –1.12% to –0.65%), $P < 0.0001$; and –0.51% (95% CI, –0.69% to –0.34%), $P < 0.0001$, in GETGOAL – L Asia and

GETGOAL – L – C, respectively, which were also statistically significantly in favour of lixisenatide compared with placebo.

Numerically more patients in the lixisenatide groups had an A1C < 7% compared with placebo groups in all placebo-controlled trials (range 28% to 56% compared with 5% to 39%, respectively). Similar trends were noted for the proportion of patients with an A1C < 6.5% (range 14% to 32% compared with 1% to 16%). The results for A1C responders were not part of the statistical testing hierarchy and should be considered exploratory; therefore, no statistical interpretations should be made.

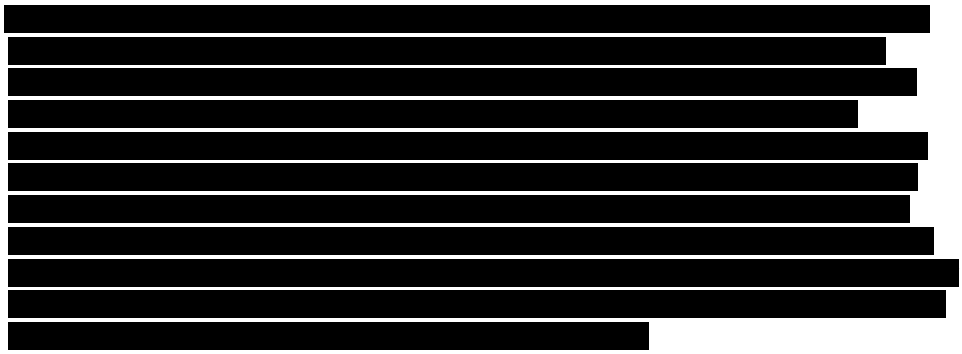
Overall, baseline two-hour PPG was similar between treatment groups in all placebo-controlled trials, and patients treated with lixisenatide experienced a greater reduction in two-hour PPG compared with placebo at week 24. The reductions in two-hour PPG were relatively variable across all placebo-controlled trials and ranged between –7.96 mmol/L and –3.09 mmol/L in the lixisenatide groups and –1.72 mmol/L to 0.08 mmol/L in the placebo groups, respectively, at week 24. The adjusted mean differences were similar in all of the placebo-controlled trials (with the exception of GETGOAL – L Asia) and were statistically significantly in favour of lixisenatide compared with placebo (–3.81 mmol/L [95% CI, –4.70 to –2.93], $P < 0.0001$; –3.16 mmol/L [95% CI, –3.95 to –2.38], $P < 0.0001$; and –3.45 mmol/L [95% CI, –4.23 to –2.67], $P < 0.0001$ in GETGOAL – L, GETGOAL – DUO 1, and GETGOAL – L – C, respectively). The reduction in two-hour PPG was greater in GETGOAL – L Asia compared with the other placebo-controlled trials and was also statistically significantly in favour of lixisenatide compared with placebo (–7.83 mmol/L [95% CI, –8.89 to –6.77], $P < 0.0001$).

Baseline FPG was similar between treatment groups in all placebo-controlled trials. Overall, no statistically significant differences were observed with lixisenatide treatment compared with placebo at week 24. The changes in FPG were relatively variable across all placebo-controlled trials and ranged between –0.63 mmol/L and 0.34 mmol/L in the lixisenatide groups, and between –0.55 mmol/L and 0.55 mmol/L in the placebo groups, respectively, at week 24. The adjusted mean differences were similar in all of the placebo-controlled trials (with the exception of GETGOAL – L Asia): –0.08 mmol/L (95% CI, –0.59 to 0.43), $P = 0.7579$; –0.12 mmol/L (95% CI, –0.46 to 0.23), $P = 0.5142$; and –0.38 mmol/L (95% CI, –0.79 to 0.02), $P = 0.0650$ in GETGOAL – L, GETGOAL – DUO 1, and GETGOAL – L – C, respectively. A numerically greater reduction in FPG in GETGOAL – L Asia was observed compared with placebo (–0.67 mmol/L [95% CI, –1.23 to –0.11]; however, results should be considered exploratory given that an end point in the statistical testing order failed before the testing for significance in FPG (statistical significance of this end point should not have been tested).

In terms of glucose excursion, baseline values were similar between treatment groups in all placebo-controlled trials. Patients treated with lixisenatide experienced a greater numerical reduction in glucose excursion compared with placebo at week 24. The reductions in glucose excursion were relatively variable across all placebo-controlled trials and ranged between –7.09 mmol/L and –3.42 mmol/L in the lixisenatide groups and –0.74 mmol/L to 0.14 mmol/L in the placebo groups, respectively, at week 24. The adjusted mean differences were similar in all of the placebo-controlled trials (with the exception of GETGOAL – L Asia): –3.80 mmol/L (95% CI, –4.57 to –3.03), –3.09 mmol/L (95% CI, –3.84 to –2.33), and –3.13 mmol/L (95% CI, –3.83 to –2.43) in GETGOAL – L, GETGOAL – DUO 1, and GETGOAL – L – C, respectively. The reduction in glucose excursion was also numerically greater in GETGOAL – L Asia compared with the other placebo-controlled trials

(–7.22 mmol/L [95% CI, –8.25 to –6.20]). The results for glucose excursion were not part of the statistical testing hierarchy and should be considered exploratory; therefore, no statistical interpretations should be made.

Generally, baseline average seven-point SMPG was similar between treatment groups in all placebo-controlled trials (with the exception of GETGOAL – L Asia), and patients treated with lixisenatide experienced a greater reduction in average seven-point SMPG compared with placebo at week 24. The reductions in average seven-point SMPG were relatively variable across all placebo-controlled trials and ranged between –1.49 mmol/L and –0.47 mmol/L, and –0.61 mmol/L to 0.06 mmol/L in the lixisenatide and placebo groups, respectively, at week 24. The adjusted mean differences were similar in all of the placebo-controlled trials (with the exception of GETGOAL – L Asia) and statistically significantly in favour of lixisenatide compared with placebo (–0.88 mmol/L [95% CI, –1.31 to –0.45], $P < 0.0001$; –0.39 mmol/L [95% CI, –0.68 to –0.11], $P = 0.0071$; –0.54 mmol/L [95% CI, –0.87 to –0.21], $P = 0.0014$ in GETGOAL – L, GETGOAL – DUO 1, and GETGOAL – L – C, respectively). The reduction in average seven-point SMPG was numerically greater in GETGOAL – L Asia compared with the other placebo-controlled trials (–1.35 mmol/L [95% CI, –1.84 to –0.86]); however, given that an end point in the statistical testing order failed before the testing for significance in average seven-point SMPG, statistical significance of this end point should not have been tested and should be considered exploratory. The primary end point (absolute change from baseline in A1C at week 24) was also analyzed in numerous pre-specified subgroups, and those highlighted in the CDR review protocol have been presented in Appendix 4; however, no formal statistical tests were performed. Overall, no consistent trends could be identified in any of the subgroup data. Detailed subgroup data are provided in Table 24 to **Error! Reference source not found.** in Appendix 4. The results for subgroup analyses were not part of the statistical testing hierarchy and should be considered exploratory; therefore, no statistical interpretations should be made.



Sensitivity analyses to assess the impact of rescue medication were performed based on all scheduled A1C measurements during the main 24-week double-blind treatment period using a multi-level model with random slopes and intercepts, as well as a MMRM for the primary end point (change from baseline in A1C at week 24) under the missing at random framework to adjust for the effect of rescue medication in all placebo-controlled trials. A sensitivity analysis with 24-week completers (patients who completed the 24 weeks of treatment) using the observed week-24 values and the same ANCOVA model described for the primary analysis above was also conducted. The results of all sensitivity analyses were similar in magnitude, direction and statistical significance, and were in support of the primary analyses in all placebo-controlled trials. The results of the sensitivity analyses were

not part of the statistical testing hierarchy and should be considered exploratory; therefore, no statistical interpretations should be made.

Table 14: Glycemic Control Outcomes (Placebo-Controlled Randomized Controlled Trials)

End Point	GETGOAL							
	– L		– L Asia		– DUO 1		– L – C	
	PLB N = 167	LIXI N = 328	PLB N = 157	LIXI N = 154	PLB N = 223	LIXI N = 223	PLB N = 224	LIXI N = 224
A1C (%)								
Baseline, n (%)	158 (95)	304 (93)	154 (98)	146 (95)	221 (99)	215 (96)	221 (99)	220 (98)
Baseline, mean (SD)	8.38 (0.83)	8.39 (0.86)	8.53 (0.78)	8.53 (0.73)	7.60 (0.54)	7.56 (0.54)	7.93 (0.69)	7.90 (0.66)
Adjusted LS mean change from baseline at week 24 (SE)	–0.38 (0.11)	–0.74 (0.09)	0.11 (0.13)	–0.77 (0.14)	–0.40 (0.09)	–0.71 (0.09)	–0.11 (0.09)	–0.62 (0.09)
Adjusted LS MD versus placebo (95% CI)	–0.36 (–0.55, –0.17) *P* = 0.0002		–0.88 (–1.12, –0.65) *P* < 0.0001		–0.32 (–0.46, –0.17) *P* < 0.0001		–0.51 (–0.69, –0.34) *P* < 0.0001	
Mean change from baseline at last visit[a] (SE)	[redacted]	[redacted]	NA	NA	NA	NA	NA	NA
A1C responders,[b] n (%)								
≤ 6.5%	6 (4)	44 (14)	2 (1)	26 (18)	36 (16)	69 (32)	13 (6)	49 (22)
> 6.5%	152 (96)	260 (86)	152 (99)	120 (82)	[redacted]	[redacted]	16.3% (10.2, 22.5)	
P value	NA		NA		NA		NA	
< 7.0%	19 (12)	86 (28)	8 (5)	52 (36)	85 (39)	121 (56)	30 (14)	82 (37)
≥ 7.0%	139 (88)	218 (72)	146 (95)	94 (64)	[redacted]	[redacted]	23.6% (16.1, 31.1)	
P value	NA		NA		NA		NA	
Two-hour PPG (mmol/L)								
Baseline, n (%)	123 (74)	235 (72)	142 (90)	131 (85)	204 (91)	194 (87)	199 (89)	200 (89)
Baseline, mean (SD)	15.85 (3.71)	16.44 (4.29)	17.99 (3.66)	17.88 (3.27)	12.85 (3.75)	13.02 (3.83)	14.07 (3.62)	13.71 (4.26)
Adjusted LS mean change from baseline at week 24 (SE)	–1.72 (0.54)	–5.54 (0.47)	–0.14 (0.56)	–7.96 (0.60)	0.08 (0.48)	–3.09 (0.48)	–0.61 (0.42)	–4.06 (0.41)
Adjusted LS MD versus placebo (95% CI)	–3.81 (–4.70, –2.93) *P* < 0.0001		–7.83 (–8.89, –6.77) *P* < 0.0001		–3.16 (–3.95, –2.38) *P* < 0.0001		–3.45 (–4.23, –2.67) *P* < 0.0001	
Mean change from baseline at last visit[a] (SE)	[redacted]	[redacted]	NA	NA	NA	NA	NA	NA
Glucose excursion[b] (mmol/L)								
Baseline, n (%)	123 (74)	233 (71)	142 (90)	131 (85)	204 (91)	194 (87)	NR	NR
Baseline, mean (SD)	7.21 (3.44)	7.69 (3.47)	9.94 (4.00)	9.72 (3.22)	6.37 (3.61)	6.40 (4.21)	NR	NR
Adjusted LS mean change from baseline at week 24 (SE)	–0.34 (0.47)	–4.14 (0.41)	0.14 (0.54)	–7.09 (0.58)	–0.33 (0.46)	–3.42 (0.46)	–0.74 (NR)	–3.87 (NR)
Adjusted LS MD versus placebo (95% CI)	–3.80 (–4.57, –3.03) NA		–7.22 (–8.25, –6.20) NA		–3.09 (–3.84, –2.33) NA		–3.13 (–3.83, –2.43) NA	
Mean change from baseline at last visit[a] (SE)	[redacted]	[redacted]	NA	NA	NA	NA	NA	NA

End Point	GETGOAL							
	– L		– L Asia		– DUO 1		– L – C	
	PLB N = 167	LIXI N = 328	PLB N = 157	LIXI N = 154	PLB N = 223	LIXI N = 223	PLB N = 224	LIXI N = 224
Average seven-point SMPG (mmol/L)								
Baseline, n (%)	153 (92)	294 (90)	138 (88)	142 (92)	214 (96)	210 (94)	214 (96)	213 (95)
Baseline, mean (SD)	10.57 (2.69)	10.74 (2.57)	11.44 (2.45)	11.56 (2.54)	8.29 (1.52)	8.20 (1.45)	9.30 (1.86)	9.22 (1.87)
Adjusted LS mean change from baseline at week 24 (SE)	–0.61 (0.24)	–1.49 (0.20)	–0.56 (0.27)	–1.91 (0.27)	–0.08 (0.18)	–0.47 (0.18)	0.06 (0.17)	–0.48 (0.17)
Adjusted LS MD versus placebo (95% CI)	–0.88 (–1.31, –0.45) $P < 0.0001$		–1.35 (–1.84, –0.86) NA[c]		–0.39 (–0.68, –0.11) $P = 0.0071$		–0.54 (–0.87, –0.21) $P = 0.0014$	
Mean change from baseline at last visit[a] (SE)	[redacted]	[redacted]	NA	NA	NA	NA	NA	NA
FPG (mmol/L)								
Baseline, n (%)	163 (98)	317 (97)	157 (100)	148 (96)	220 (99)	214 (96)	219 (98)	219 (98)
Baseline, mean (SD)	8.03 (2.65)	8.11 (2.84)	7.75 (2.25)	7.64 (2.31)	6.69 (1.98)	6.56 (1.74)	6.92 (1.79)	7.05 (2.06)
Adjusted LS mean change from baseline at week 24 (SE)	–0.55 (0.28)	–0.63 (0.23)	0.25 (0.30)	–0.42 (0.31)	0.46 (0.21)	0.34 (0.21)	0.55 (0.21)	0.17 (0.21)
Adjusted LS MD versus placebo (95% CI)	–0.08 (–0.59, 0.43) $P = 0.7579$		–0.67 (–1.23, –0.11) NA[c]		–0.12 (–0.46, 0.23) $P = 0.5142$		–0.38 (–0.79, 0.02) $P = 0.0650$	
Mean change from baseline at last visit[a] (SE)	[redacted]	[redacted]	NA	NA	NA	NA	NA	NA

A1C = glycated hemoglobin; ANCOVA = analysis of covariance; CI = confidence interval; CSR = Clinical Study Report; FPG = fasting plasma glucose; LIXI = lixisenatide; LS = least squares; MD = mean difference; NA = not applicable; NR = not reported; PLB = placebo; PPG = postprandial glucose; RCT = randomized controlled trial; SMPG = self-monitored plasma glucose; SD = standard deviation; SE = standard error.

Note: All efficacy outcomes are based on the modified intention-to-treat population and do not include patients requiring rescue therapy.

Last observation carried forward was used to impute missing data.

Means and mean differences were analyzed using an ANCOVA model with treatment groups (lixisenatide and placebo), randomization strata of screening A1C (< 8.0, ≥ 8.0%), randomization strata of metformin use at screening (yes, no), country as fixed effects, and baseline A1C value as a covariate in GETGOAL – L and GETGOAL – L – C. Instead of randomization strata of metformin use at screening (yes, no) as fixed effects in the ANCOVA model, randomization strata of sulfonylurea use at screening (yes, no) and randomization strata of thiazolidinediones use at screening (yes, no) were used in GETGOAL – L Asia and GETGOAL – DUO 1, respectively.

[a] "Last visit" refers to the final visit conducted in the extension phase of GETGOAL – L.

[b] A1C responder and glucose excursion analyses were not part of the statistical testing hierarchy and are therefore considered exploratory.

[c] End point in the statistical testing order failed before the testing for significance in average seven-point SMPG and FPG (statistical significance of this end point should not have been tested and should be considered exploratory).

Source: Riddle 2013,[4] GETGOAL – L CSR,[5] Riddle 2013,[6] GETGOAL – DUO 1 CSR,[7] Seino 2012,[8] GETGOAL – L Asia CSR,[9] and GETGOAL – L – C CSR.[10]

Body Weight

Details on the change in body weight in the placebo-controlled trials are provided in Table 15.

At baseline, the mean weight for patients in the placebo-controlled trial ranged from 65.99 kg to 87.47 kg in the lixisenatide groups and 65.60 kg to 89.11 kg in the placebo groups. The changes in body weight ranged between –1.80 kg and 0.28 kg in the lixisenatide groups and –0.52 kg to 1.16 kg in the placebo groups, respectively, at week 24. The adjusted mean differences were similar in GETGOAL – DUO 1 and GETGOAL – L – C, and were statistically significantly in favour of lixisenatide compared with placebo (–0.89 kg [95% CI, –

1.42 to –0.35], *P* = 0.0012, and –1.17 kg [95% CI, –1.60 to –0.74], *P* < 0.0001, respectively). No statistically significant difference in body weight was observed in GETGOAL – L Asia (–0.43 kg [–0.93 to 0.06], *P* = 0.0857), whereas a numerically greater reduction in body weight was observed in GETGOAL – L (–1.28 kg [95% CI, –1.80 to –0.75]); however, results should be considered exploratory given that an end point in the statistical testing order failed before the testing for significance in FPG (statistical significance of this end point should not have been tested).

[redacted] No data were provided for weight loss responders in GETGOAL – DUO 1 and GETGOAL – L – C. The results for weight loss responders were not part of the statistical testing hierarchy and should be considered exploratory; therefore, no statistical interpretations should be made.

[redacted]

Table 15: Body Weight Outcomes (Placebo-Controlled Randomized Controlled Trials)

End Point	GETGOAL							
	– L		– L Asia		– DUO 1		– L – C	
	PLB N = 167	LIXI N = 328	PLB N = 157	LIXI N = 154	PLB N = 223	LIXI N = 223	PLB N = 224	LIXI N = 224
Body weight (kg)								
Baseline, n (%)	161 (96)	311 (95)	157 (100)	150 (97)	220 (99)	217 (97)	220 (98)	219 (98)
Baseline, mean (SD)	89.11 (21.00)	87.39 (20.00)	65.60 (12.47)	65.99 (12.94)	86.74 (20.54)	87.47 (21.98)	74.59 (13.29)	74.19 (14.05)
Adjusted LS mean change from baseline at week 24 (SE)	–0.52 (0.29)	–1.80 (0.25)	0.06 (0.27)	–0.38 (0.28)	1.16 (0.33)	0.28 (0.33)	–0.07 (0.22)	–1.24 (0.22)
Adjusted LS MD versus placebo (95% CI)	–1.28 (–1.80, –0.75) NA[b]		–0.43 (–0.93, 0.06) *P* = 0.0857		–0.89 (–1.42, –0.35) *P* = 0.0012		–1.17 (–1.60, –0.74) *P* < 0.0001	
Mean change from baseline at last visit[a] (SE)	[redacted]	[redacted]	NA	NA	NA	NA	NA	NA
Weight loss responders, n (%)	[redacted]	[redacted]	157 (100)	150 (97)	NR	NR	NR	NR
≥ 5% body weight lost	[redacted]	[redacted]	7 (5)	11 (7)	NR	NR	NR	NR
< 5% body weight lost	[redacted]	[redacted]	150 (95)	139 (93)	NR	NR	NR	NR

ANCOVA = analysis of covariance; CI = confidence interval; CSR = Clinical Study Report; LIXI = lixisenatide; LS = least squares; MD = mean difference; NA = not applicable; NR = not reported; PLB = placebo; RCT = randomized controlled trial; SD = standard deviation; SE = standard error.

Note: All efficacy outcomes are based on the modified intention-to-treat population.

Last observation carried forward was used to impute missing data.

Means and mean differences were analyzed using an ANCOVA model with treatment groups (lixisenatide and placebo), randomization strata of screening A1C (< 8.0, ≥ 8.0%), randomization strata of metformin use at screening (yes, no), country as fixed effects, and baseline A1C value as a covariate in GETGOAL – L and GETGOAL – L – C. Instead of randomization strata of metformin use at screening (yes, no) as fixed effects in the ANCOVA model, randomization strata of sulfonylurea use at screening (yes, no) and randomization strata of thiazolidinediones use at screening (yes, no) were used in GETGOAL – L Asia and GETGOAL – DUO 1, respectively.

[a] "Last visit" refers to the final visit conducted in the extension phase of GETGOAL – L.

[b] End point in the statistical testing order failed before the testing for significance of change in body weight (statistical significance of this end point should not have been tested and should be considered exploratory).

Source: Riddle 2013,[4] GETGOAL – L CSR,[5] Riddle 2013,[6] GETGOAL – DUO 1 CSR,[7] Seino 2012,[8] GETGOAL – L Asia CSR,[9] and GETGOAL – L – C CSR.[10]

Rescue Therapy

All placebo-controlled trials reported the need for rescue therapy, with the exception of GETGOAL – L – C. Overall, a numerically similar number of patients received rescue therapy in the placebo group compared with the lixisenatide group in GETGOAL – L, GETGOAL – L Asia, and GETGOAL – DUO 1 (7%, 3%, and < 1% compared with 6%, 1%, and < 1%). No statistically significant difference was observed given that an end point in the statistical testing order failed before the testing for significance in the need for rescue therapy. Therefore, this end point is not corrected for multiple statistical testing and should be interpreted with caution.

[redacted] Details on the need for rescue therapy in the placebo-controlled trials are provided in Table 16.

Table 16: Summary of Rescue Therapy (Placebo-Controlled Randomized Controlled Trials)

End Point	GETGOAL							
	– L		– L Asia		– DUO 1		– L – C	
	PLB N = 167	LIXI N = 328	PLB N = 157	LIXI N = 154	PLB N = 223	LIXI N = 223	PLB N = 224	LIXI N = 224
Rescue therapy, n (%)								
During 24-week DB phase								
Yes	12 (7)	19 (6)	5 (3)	2 (1)	1 (< 1)	1 (< 1)	NR	NR
P value	NA[b]		NA[b]		NA[b]		NR	
During whole DB phase[a]								
Yes	[redacted]	[redacted]	NA	NA	NA	NA	NA	NA

CI = confidence interval; CSR = Clinical Study Report; DB = double-blind; LIXI = lixisenatide; LS = least squares; MD = mean difference; NA = not applicable; NR = not reported; PLB = placebo; RCT = randomized controlled trial; SD = standard deviation; SE = standard error.

Note: All efficacy outcomes are based on the modified intention-to-treat population.

Last objective carried forward was used to impute missing data.

[a] Includes rescue therapy administered during the extension phase of GETGOAL – L.

[b] End point in the statistical testing order failed before the testing for significance for the need of rescue therapy (statistical significance of this end point should not have been tested and should be considered exploratory).

Source: Riddle 2013,[4] GETGOAL – L CSR,[5] Riddle 2013,[6] GETGOAL – DUO 1 CSR,[7] Seino 2012,[8] and GETGOAL – L Asia CSR.[9]

Total Daily Basal Insulin Dose

In general, total daily basal insulin doses at baseline were similar between treatment groups in all placebo-controlled trials and were relatively variable across trials (ranged between 24.11 units per day and 57.65 units per day). In GETGOAL – L, GETGOAL – L Asia, and GETGOAL – L – C, a numerically greater reduction in the lixisenatide groups compared with the placebo groups were reported (–5.62 units per day, –1.39 units per day, and –2.98 units per day in the lixisenatide groups, and –1.93 units per day, –0.11 units per day, and –1.87 units per day in the placebo groups, respectively, at week 24). The adjusted mean difference in GETGOAL – L – C was –1.11 units per day (95% CI, –1.86 to –0.37), *P* = 0.0033, which was statistically significantly in favour of lixisenatide compared with placebo.

Contrarily, patients in GETGOAL – DUO 1 required more total daily basal insulin in both the lixisenatide and placebo groups; however, patients required a smaller increase in total daily basal insulin in the lixisenatide group compared with the placebo group (3.10 units per day compared with 5.34 units per day). The adjusted mean difference was –2.24 units per day (95% CI, –4.26 to
–0.22), *P* = 0.0300, which was statistically significantly in favour of lixisenatide compared with placebo. The results for change in total daily basal insulin were not part of the statistical testing hierarchy in GETGOAL – L and GETGOAL – L Asia, and their adjusted mean differences were –3.69 units per day (95% CI, –6.57 to –0.82) and –1.29 units per day (95% CI, –2.10 to –0.48), respectively.

[redacted]

[redacted] Details on the change in total daily basal insulin dose in the placebo-controlled trials are provided in Table 17.

Table 17: Change in Total Daily Basal Insulin Dose (Placebo-Controlled RCTs)

End Point	GETGOAL							
	– L		– L (Asia)		– DUO 1		– L – C	
	PLB N = 167	LIXI N = 328	PLB N = 157	LIXI N = 154	PLB N = 223	LIXI N = 223	PLB N = 224	LIXI N = 224
Change in total daily basal insulin (U)								
Baseline, n (%)	165 (99)	325 (99)	157 (100)	151 (98)	223 (100)	222 (100)	215 (96)	213 (95)
Baseline, mean dose (SD)	57.65 (34.73)	53.62 (33.97)	24.11 (14.18)	24.87 (14.02)	44.24 (19.86)	43.41 (18.87)	37.51 (16.07)	39.85 (19.15)
Adjusted LS mean change from baseline at week 24 (SE)	–1.93 (1.59)	–5.62 (1.32)	–0.11 (0.44)	–1.39 (0.46)	5.34 (1.26)	3.10 (1.26)	–1.87 (0.39)	–2.98 (0.39)
Adjusted LS MD versus placebo (95% CI)	–3.69 (–6.57, –0.82) NA[b]		–1.29 (–2.10, –0.48) NA[b]		–2.24 (–4.26 to –0.22) *P* = 0.0300		–1.11 (–1.86, –0.37) *P* = 0.0033	
Mean change from baseline at last visit[a] (SE)	[redacted]	[redacted]	NA	NA	NA	NA	NA	NA

ANCOVA = analysis of covariance; CI = confidence interval; CSR = Clinical Study Report; LIXI = lixisenatide; LS = least squares; MD = mean difference; NA = not applicable; PLB = placebo; RCT = randomized controlled trial; SD = standard deviation; SE = standard error.

Note: All efficacy outcomes are based on the modified intention-to-treat population.

Last observation carried forward was used to impute missing data.

Means and mean differences were analyzed using an ANCOVA model with treatment groups (lixisenatide and placebo), randomization strata of screening A1C (< 8.0, ≥ 8.0%), randomization strata of metformin use at screening (yes, no), country as fixed effects, and baseline A1C value as a covariate in GETGOAL – L and GETGOAL – L – C. Instead of randomization strata of metformin use at screening (yes, no) as fixed effects in the ANCOVA model, randomization strata of sulfonylurea use at screening (yes, no) and randomization strata of thiazolidinediones use at screening (yes, no) were used in GETGOAL – L Asia and GETGOAL – DUO 1, respectively.

[a] "Last visit" refers to the final visit conducted in the extension phase of GETGOAL – L.

[b] End point in the statistical testing order failed before the testing for significance for change in total daily basal insulin (statistical significance of this end point should not have been tested and should be considered exploratory).

Source: Riddle 2013,[4] GETGOAL – L CSR,[5] Riddle 2013,[6] GETGOAL – DUO 1 CSR,[7] Seino 2012,[8] GETGOAL – L Asia CSR,[9] and GETGOAL – L – C CSR.[10]

Active-Controlled Trial

Glycemic Control

Details pertaining to glycemic control outcomes in the active-controlled trial (GETGOAL – DUO 2) are provided inTable 18.

In general, baseline A1C was similar between treatment groups. Patients treated with lixisenatide, insulin glulisine once daily and insulin glulisine three times daily all experienced numerical reductions in A1C at week 26 (–0.63%, –0.58%, and –0.84%). The adjusted mean differences were –0.05% (95% CI, –0.17% to 0.06%) and 0.21% (95% CI, 0.1% to 0.33%) between lixisenatide and insulin glulisine once daily and insulin glulisine three times daily, respectively. Based on the adjusted mean differences and the pre-specified noninferiority margin for the change from baseline in A1C (0.4%), lixisenatide was considered noninferior to both insulin glulisine once daily and insulin glulisine three times daily (co-primary end points 1 and 2a) given that the upper bounds of the 95% CIs did not exceed the noninferiority margin of 0.4%.

The adjusted mean differences for patients who achieved an A1C < 7% were 3.7% (95% CI, –4.0% to 11.5%) and –7.3% (95% CI, –15.1% to 0.6%) when comparing lixisenatide to

insulin glulisine once daily and insulin glulisine three times daily, respectively. The adjusted mean difference for patients who achieved an A1C ≤ 6.5% was 2.7% (95% CI, –3.6% to 9.01%) between lixisenatide and insulin glulisine once daily. Numerically fewer patients achieved an A1C ≤ 6.5% with an adjusted mean difference of –10.5% (95% CI, –17.3% to –3.6%) between lixisenatide and insulin glulisine three times daily. The results for A1C responders were not adjusted for multiple statistical testing and should be considered exploratory; therefore, no statistical interpretations should be made.

Overall, baseline two-hour PPG was similar between treatment groups. Patients treated with lixisenatide experienced a numerically greater reduction in two-hour PPG compared with both insulin glulisine once daily and insulin glulisine three times daily at week 26. The reductions in two-hour PPG across all treatment groups ranged between –3.64 mmol/L and –1.41 mmol/L at week 26. The adjusted mean differences were similar in both insulin glulisine once daily and insulin glulisine three times daily treatment groups (–2.07 mmol/L [95% CI, –3.29 to –0.85] and –2.23 mmol/L [95% CI, –3.39 to –1.07], respectively). The results for PPG were not adjusted for multiple statistical testing and should be considered exploratory; therefore, no statistical interpretations should be made.

Baseline FPG was similar between treatment groups. The reductions in FPG across all treatment groups ranged between –0.23 mmol/L and –0.06 mmol/L at week 26. The adjusted mean differences in both the insulin glulisine once daily and insulin glulisine three times daily treatment groups were –0.01 mmol/L (95% CI, –0.32 to 0.30) and –0.17 mmol/L (95% CI, –0.48 to 0.143), respectively. The results for FPG were not adjusted for multiple statistical testing and should be considered exploratory; therefore, no statistical interpretations should be made.

In terms of glucose excursion, baseline values were similar between treatment groups. Patients treated with lixisenatide experienced a numerically greater reduction in glucose excursion compared with both insulin glulisine once daily and insulin glulisine three times daily at week 26. The reductions in glucose excursion across all treatment groups ranged between –3.03 mmol/L and –0.95 mmol/L at week 26. The adjusted mean differences were similar in both insulin glulisine once daily and insulin glulisine three times daily treatment groups (–1.61 mmol/L [95% CI, –2.76 to –0.45] and –2.08 mmol/L [95% CI, –3.19 to –0.97], respectively). The results for glucose excursion were not adjusted for multiple statistical testing and should be considered exploratory; therefore, no statistical interpretations should be made.

Generally, baseline average seven-point SMPG was similar between treatment groups. The reductions in average seven-point SMPG across all treatment groups ranged between –1.05 mmol/L and –0.78 mmol/L at week 26. The adjusted mean difference between patients treated with lixisenatide compared with insulin glulisine once daily at week 26 was –0.002 mmol/L (95% CI, –0.245 to 0.240). The reduction in average seven-point SMPG was numerically smaller in the lixisenatide group compared with the insulin glulisine three times daily group (0.269 mmol/L [95% CI, 0.028 to 0.510]). The results for average seven-point SMPG were not adjusted for multiple statistical testing and should be considered exploratory; therefore, no statistical interpretations should be made.

The co-primary end points (absolute change from baseline in A1C at week 26) were also analyzed in numerous pre-specified subgroups, and those highlighted in the CDR review protocol have been presented in Appendix 4; however, no formal statistical tests were performed. No numerical differences were observed in the adjusted mean differences between lixisenatide and insulin glulisine once daily for the change from baseline in A1C at

week 26 in any of the subgroups. A numerically smaller reduction in the change from baseline in A1C at week 26 was reported between lixisenatide and insulin glulisine three times daily in all subgroups with the exception of the A1C ≥ 8.0% (0.17% [95% CI, –0.03% to 0.36%]), no metformin use (0.17% [95% CI, –0.15% to 0.50%]), duration of diabetes ≤ 10 years (0.06% [95% CI, 0.12% to 0.24%]), total daily basal insulin dose < 45 units per day (0.18% [95% CI, –0.06% to 0.41%]), and duration of basal insulin dose ≥ 3 years (0.38% [95% CI, 0.18% to 0.58%]). The results for all subgroups were not adjusted for multiple statistical testing and should be considered exploratory; therefore, no statistical interpretations should be made. Detailed subgroup data are provided in Table 24 to Table 38in Appendix 4.

Sensitivity analyses to support the primary analysis were performed using an MMRM for the primary end points (absolute change from baseline in A1C at week 26) under the missing at random framework. A sensitivity analysis with 26-week completers (patients who completed the 26 weeks of treatment) using the observed week-26 values and the same ANCOVA model described for the primary analysis was also conducted. The results of all sensitivity analyses were similar in magnitude, direction, and statistical significance and were in support of the primary analyses in all treatment groups. The results of sensitivity analyses were not adjusted for multiple statistical testing and should be considered exploratory; therefore, no statistical interpretations should be made.

Table 18: Glycemic Control Outcomes (Active-Controlled Randomized Controlled Trial)

End Point	GETGOAL – DUO 2		
	LIXI N = 298	IG Once Daily N = 298	IG Three Times Daily N = 298
A1C (%)			
Baseline, n (%)	292 (98)	292 (98)	295 (99)
Baseline, mean (SD)	7.76 (0.56)	7.72 (0.58)	7.79 (0.60)
Adjusted LS mean change from baseline at week 26 (SE)	–0.63 (0.05)	–0.58 (0.05)	–0.84 (0.05)
Adjusted LS MD versus comparator (95% CI)		–0.05 (–0.17, 0.06)	0.21 (0.1, 0.33)
A1C responders,[a] n (%)			
≤ 6.5	60 (21)	52 (18)	91 (31)
Difference versus comparator (95% CI)		2.7% (–3.6, 9.0)	–10.5% (–17.3, –3.6)
< 7.0	123 (42)	112 (38)	145 (49)
Difference versus comparator (95% CI)		3.7% (–4.0, 11.5)	–7.3% (–15.1, 0.6)
Two-hour PPG (mmol/L)			
Baseline, n (%)	69 (23)	55 (18)	68 (23)
Baseline, mean (SD)	14.12 (3.62)	13.82 (3.52)	14.56 (3.48)
Adjusted LS mean change from baseline at week 26 (SE)	–3.64 (0.59)	–1.57 (0.60)	–1.41 (0.58)
Adjusted LS MD versus comparator (95% CI)		–2.07 (–3.29, –0.85)	–2.23 (–3.39, –1.07)
Glucose excursion (mmol/L)			
Baseline, n (%)	[redacted]	[redacted]	[redacted]
Baseline, mean (SD)	[redacted]	[redacted]	[redacted]
Adjusted LS mean change from baseline at week 24 (SE)	[redacted]	[redacted]	[redacted]
Adjusted LS MD versus comparator (95% CI)		[redacted]	[redacted]
Average seven-point SMPG (mmol/L)			
Baseline, n (%)	270 (91)	268 (90)	278 (93)
Baseline, mean (SD)	9.010 (1.746)	9.052 (1.743)	8.941 (1.545)
Adjusted LS mean change from baseline at week 26 (SE)	–0.784 (0.114)	–0.782 (0.113)	–1.053 (0.111)
Adjusted LS MD versus comparator (95% CI)		–0.002 (–0.245, 0.240)	0.269 (0.0283, 0.510)

End Point	GETGOAL – DUO 2		
	LIXI N = 298	IG Once Daily N = 298	IG Three Times Daily N = 298
FPG (mmol/L)			
Baseline, n (%)	295 (99)	295 (99)	294 (99)
Baseline, mean (SD)	6.58 (1.83)	6.85 (1.99)	6.65 (1.89)
Adjusted LS mean change from baseline at week 26 (SE)	–0.23 (0.14)	–0.21 (0.14)	–0.06 (0.14)
Adjusted LS MD versus comparator (95% CI)		–0.01 (–0.32 to 0.30)	–0.17 (–0.48 to 0.14)

A1C = glycated hemoglobin; CI = confidence interval; FPG = fasting plasma glucose; IG = insulin glulisine; LIXI = lixisenatide; LS = least squares; MD = mean difference; NR = not reported; PPG = postprandial glucose; RCT = randomized controlled trial; SMPG = self-monitored plasma glucose; t.i.d. = three times daily; SD = standard deviation; SE = standard error.

Note: Lixisenatide met the noninferiority margin of 0.4% when compared with both insulin glulisine once daily and insulin glulisine t.i.d.

P values not reported for any end point in GETGOAL – DUO 2.

All efficacy outcomes are based on the modified intention-to-treat population.

Last observation carried forward was used to impute missing data.

Means and mean differences were analyzed using an analysis of covariance model with treatment groups (lixisenatide, insulin glulisine once daily, and insulin glulisine three times daily), randomization strata of screening A1C (< 8.0, ≥ 8.0%), randomization strata of metformin use at screening (yes, no), country as fixed effects, and baseline A1C value as a covariate.

[a] End points other than the co-primary end points (absolute change from baseline in A1C for lixisenatide compared with insulin glulisine once daily and insulin glulisine three times daily) were not adjusted for multiple statistical testing and are therefore considered exploratory.

Source: Rosenstock 2016[11] and GETGOAL – DUO 2 Clinical Study Report.[12]

Body Weight

Details on the change in body weight in the active-controlled trial (GETGOAL – DUO 2) are provided in Table 19.

At baseline, the mean weights for patients were similar across treatment groups and ranged from 88.37 kg to 90.10 kg. Patients treated with lixisenatide experienced a reduction in body weight, whereas both patients treated with insulin glulisine once daily and patients treated with insulin glulisine three times daily experienced an increase in body weight at week 26. The changes in body weight across all treatment groups ranged from –0.63 kg to 1.37 kg at week 26. The adjusted mean differences were similar in both insulin glulisine once daily and insulin glulisine three times daily treatment groups and were statistically significantly in favour of lixisenatide (–1.66 kg [95% CI, –2.26 to –1.06] and –1.99 kg [95% CI, –2.59 to –1.40], respectively). Lixisenatide was found to be superior to insulin glulisine three times daily in the co-primary end point of change in body weight at week 26. The effect of lixisenatide on the change in body weight is presented in Figure 2.

Numerically more patients in the lixisenatide groups compared with both the insulin glulisine once daily and insulin glulisine three times daily groups achieved no weight gain (65% compared with 37% and 31%, respectively), weight loss of ≥ 2% body weight (33% compared with 11% and 11%, respectively), weight loss of ≥ 3% body weight (23% compared with 7% and 6%, respectively), and weight loss ≥ 5% body weight (12% compared with 4% and 2%, respectively).

The primary end point (change from baseline in body weight at week 26) was also analyzed in numerous pre-specified subgroups, and those highlighted in the CDR review protocol have been presented in Appendix 4; however, no formal statistical tests were performed. Overall, patients treated with lixisenatide experienced a numerically greater reduction in body weight compared with insulin glulisine once daily and insulin glulisine three times daily in all subgroups at week 26, with the exception of the mean difference in body weight

between lixisenatide and insulin glulisine three times daily in the age < 50 years subgroup (–1.49 kg [95% CI, –3.05 to 0.07]). The results for all subgroups were not adjusted for multiple statistical testing and therefore should be interpreted with caution. Detailed subgroup data are provided in Table 24 to Table 38 in Appendix 4.

Table 19: Body Weight Outcomes (Active-Controlled Randomized Controlled Trial)

End Point	GETGOAL – DUO 2		
	LIXI N = 298	**IG Once Daily N = 298**	**IG t.i.d. N = 298**
Body weight (kg)			
Baseline, n (%)	295 (99)	295 (99)	295 (99)
Baseline, mean (SD)	90.10 (17.39)	88.37 (15.88)	90.00 (17.21)
Adjusted LS mean change from baseline at week 26 (SE)	–0.63 (0.28)	1.03 (0.28)	1.37 (0.27)
Adjusted LS MD versus comparator (95% CI)		–1.66 (–2.26, –1.06) *P* value NR	–1.99 (–2.59, –1.40) *P* < 0.0001
Patients with no weight gain,[a] n (%)			
Responders	191 (65)	108 (37)	90 (31)
MD versus comparator (95% CI)		28.1% (20.5, 35.8)	34.2% (26.7, 41.7)
Weight loss responders,[a] n (%)			
≥ 2% weight reduction	97 (33)	33 (11)	32 (11)
MD versus comparator (95% CI)		21.7% (15.3, 28.1)	22.0% (15.6, 28.4)
≥ 3% weight reduction	69 (23)	21 (7)	18 (6)
MD versus comparator (95% CI)		16.3% (10.7, 22.0)	17.3% (11.8, 22.9)
≥ 5% weight reduction	36 (12)	11 (4)	7 (2)
MD versus comparator (95% CI)		8.5% (4.1, 12.9)	9.8% (5.7, 14.0)

CI = confidence interval; IG = insulin glulisine; LIXI = lixisenatide; LS = least square; MD = mean difference; NR = not reported; RCT = randomized controlled trial; t.i.d. = three time daily; SD = standard deviation; SE = standard error.

Note: Lixisenatide was superior when compared with insulin glulisine three times daily in the adjusted mean change from baseline at week 26.

P values not reported for any end point in GETGOAL – DUO 2.

All efficacy outcomes are based on the modified intention-to-treat population.

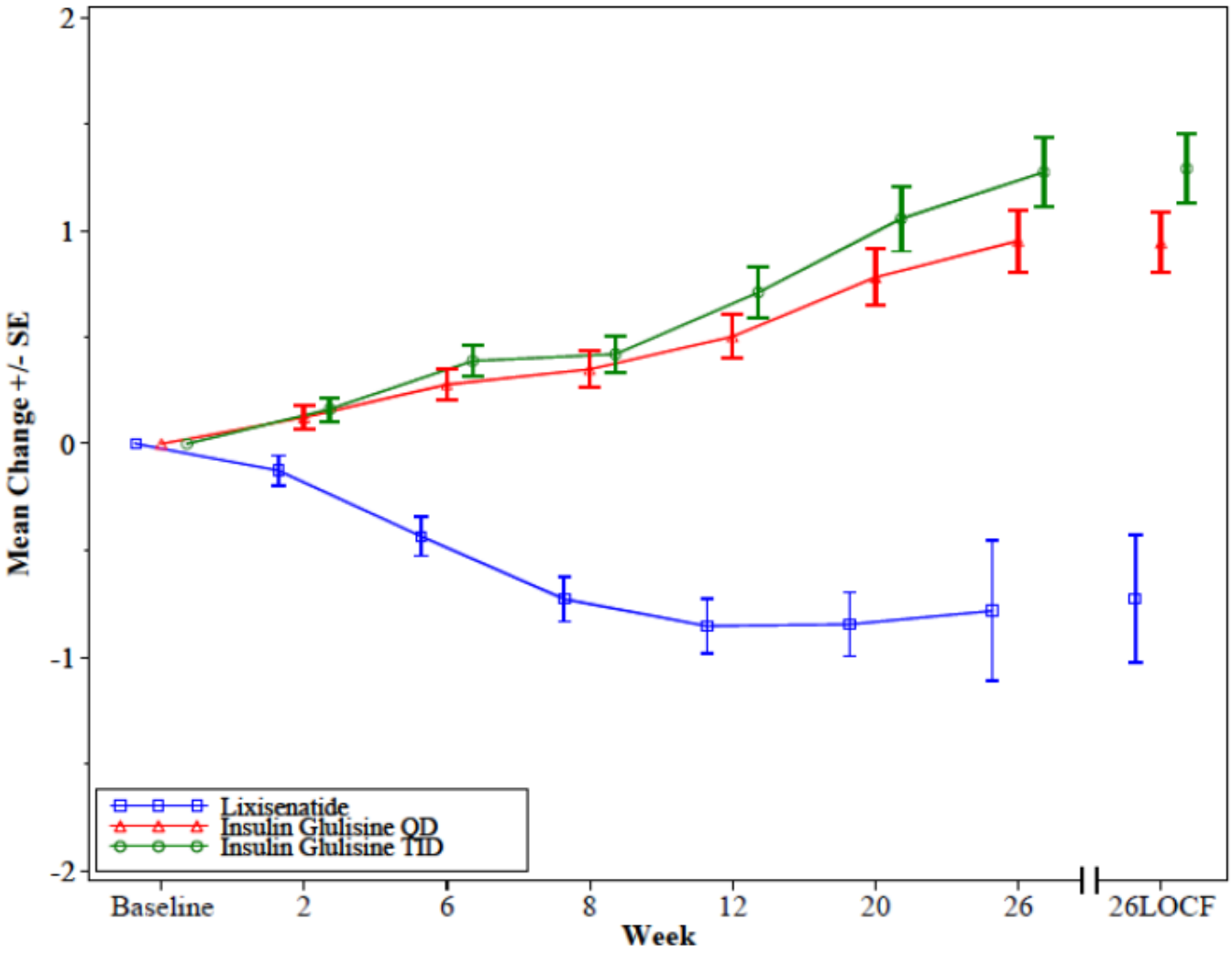
Last observation carried forward was used to impute missing data.

Means and mean differences were analyzed using an analysis of covariance model with treatment groups (lixisenatide, insulin glulisine once daily, and insulin glulisine three times daily), randomization strata of screening A1C (< 8.0, ≥ 8.0%), randomization strata of metformin use at screening (yes, no), country as fixed effects, and baseline A1C value as a covariate.

[a] End points other than the co-primary end points (absolute change from baseline in A1C for lixisenatide compared with insulin glulisine once daily and insulin glulisine three times daily) were not adjusted for multiple statistical testing and are therefore considered exploratory.

Source: Rosenstock 2016[11] and GETGOAL – DUO 2 Clinical Study Report.[12]

Figure 2: Change in Body Weight (Active-Controlled Randomized Controlled Trial)



LOCF = last observation carried forward; q.d. = once daily; SE = standard error.; t.i.d. = three time daily.

Note: End points other than the co-primary end points (absolute change from baseline in A1C for lixisenatide compared with insulin glulisine once daily and insulin glulisine three times daily) were not for multiple statistical testing and are therefore considered exploratory.

P values not reported for any end point in GETGOAL – DUO 2.

All efficacy outcomes are based on the modified intention-to-treat population.

LOCF was used to impute missing data.

Means and mean differences were analyzed using an analysis of covariance model with treatment groups (lixisenatide, insulin glulisine once daily, and insulin glulisine three times daily), randomization strata of screening A1C (< 8.0, ≥ 8.0%), randomization strata of metformin use at screening (yes, no), country as fixed effects, and baseline A1C value as a covariate.

Source: From the American Diabetes Association, Prandial options to advance basal insulin glargine therapy: testing lixisenatide plus basal insulin versus insulin glulisine either as basal-plus or basal-bolus in type 2 diabetes: the GetGoal Duo-2 trial, American Diabetes Association, 2016. Copyright and all rights reserved. Material from this publication has been used with the permission of American Diabetes Association.[11] CADTH does not own this work and permission should be sought from the copyright owner. GETGOAL – DUO 2 Clinical Study Report.[12]

Change in Total Daily Insulin Dose

Details pertaining to the change in total daily insulin dose in the active-controlled trial (GETGOAL – DUO 2) are provided in Table 20, Figure 3, and Figure 4.

In general, total daily basal insulin doses at baseline were similar across all treatment groups and ranged between 64.79 units per day and 67.45 units per day. Patients treated with lixisenatide required an increase in total daily basal insulin (0.70 units per day), whereas patients treated with insulin glulisine once daily and insulin glulisine three times daily required a reduction in their total daily basal insulin dose at week 26 (–0.06 units per day and –3.13 units per day, respectively). No statistically significant difference was observed in the adjusted mean difference between lixisenatide and insulin glulisine once daily (0.76 units per day [95% CI, –1.41 to 2.92]). Patients in the lixisenatide group required numerically more basal insulin than the insulin glulisine three times daily group with an adjusted mean difference of 3.83 units per day (95% CI, 1.66 to 6.00).

Mean total daily insulin glulisine doses were [redacted] compared with 9.97 units per day and 20.24 units per day in the insulin glulisine once daily and insulin glulisine three times daily groups, respectively, [redacted] and week 26. Mean total daily insulin doses were [redacted] compared with 73.61 units per day and 81.05 units per day in the insulin glulisine once daily and insulin glulisine three times daily groups, respectively, [redacted] and week 26. The results for all changes in insulin were not adjusted for multiple statistical testing and should be considered exploratory; therefore, no statistical interpretations should be made.

Table 20: Change in Total Daily Insulin Dose (Active-Controlled RCT)

End Point[a]	GETGOAL – DUO 2		
	LIXI N = 298	IG Once Daily N = 298	IG t.i.d. N = 298
Change in total daily basal (glargine) insulin (U)			
Baseline, n (%)	292 (98)	294 (99)	294 (99)
Baseline, mean (SD)	67.45 (31.68)	64.79 (32.09)	65.05 (27.01)
Adjusted LS mean change from baseline at week 26 (SE)	0.70 (1.00)	–0.06 (1.00)	–3.13 (0.98)
Adjusted LS MD versus comparator (95% CI)		0.76 (–1.41, 2.92)	3.83 (1.66, 6.00)
Mean total daily insulin glulisine dose (U)			
Week 2 (SD)	NA	[redacted]	[redacted]
Week 26 (SD)	NA	10.44 (8.10)	21.53 (13.43)
Week 26 LOCF (SD)	NA	9.97 (7.80)	20.24 (13.04)
Mean total daily insulin dose (U)			
Week 2 (SD)	NA	[redacted]	[redacted]
Week 26 (SD)	NA	75.14 (40.48)	83.61 (33.52)
Week 26 LOCF (SD)	NA	73.61 (39.13)	81.05 (33.55)

CI = confidence interval; IG = insulin glulisine; LIXI = lixisenatide; LOCF = last observation carried forward; LS = least squares; MD = mean difference; NA = not applicable; NR = not reported; RCT = randomized controlled trial; t.i.d. = three time daily; SD = standard deviation; SE = standard error.

Note: *P* values not reported for any end point in GETGOAL – DUO 2.

All efficacy outcomes are based on the modified intention-to-treat population.

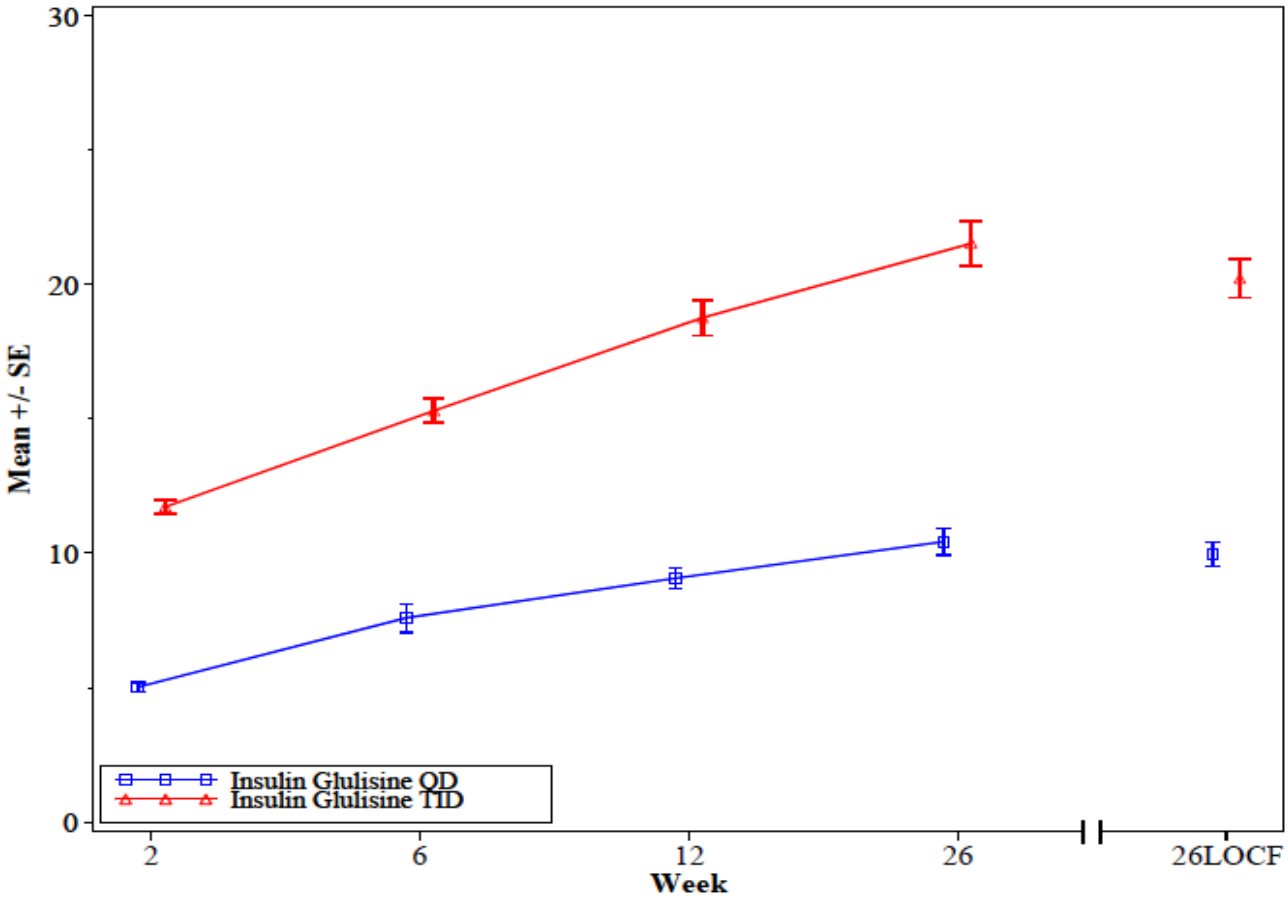
LOCF was used to impute missing data.

Means and mean differences were analyzed using an analysis of covariance model with treatment groups (lixisenatide, insulin glulisine once daily, and insulin glulisine three times daily), randomization strata of screening A1C (< 8.0, ≥ 8.0%), randomization strata of metformin use at screening (yes, no), country as fixed effects, and baseline A1C value as a covariate.

[a] End points other than the co-primary end points (absolute change from baseline in A1C for lixisenatide compared with insulin glulisine once daily and insulin glulisine three times daily) were not adjusted for multiple statistical testing and are therefore considered exploratory.

Source: Rosenstock 2016[11] and GETGOAL – DUO 2 Clinical Study Report.[12]

Figure 3: Change in Mean Daily Insulin Glulisine Dose (Active-Controlled RCT)



LOCF = last observation carried forward; q.d. = once daily; RCT = randomized controlled trial; SE = standard error; t.i.d. = three time daily.

Note: End points other than the co-primary end points (absolute change from baseline in A1C for lixisenatide compared with insulin glulisine once daily. and insulin glulisine three times daily) were not adjusted for multiple statistical testing and are therefore considered exploratory.

P values not reported for any end point in GETGOAL – DUO 2.

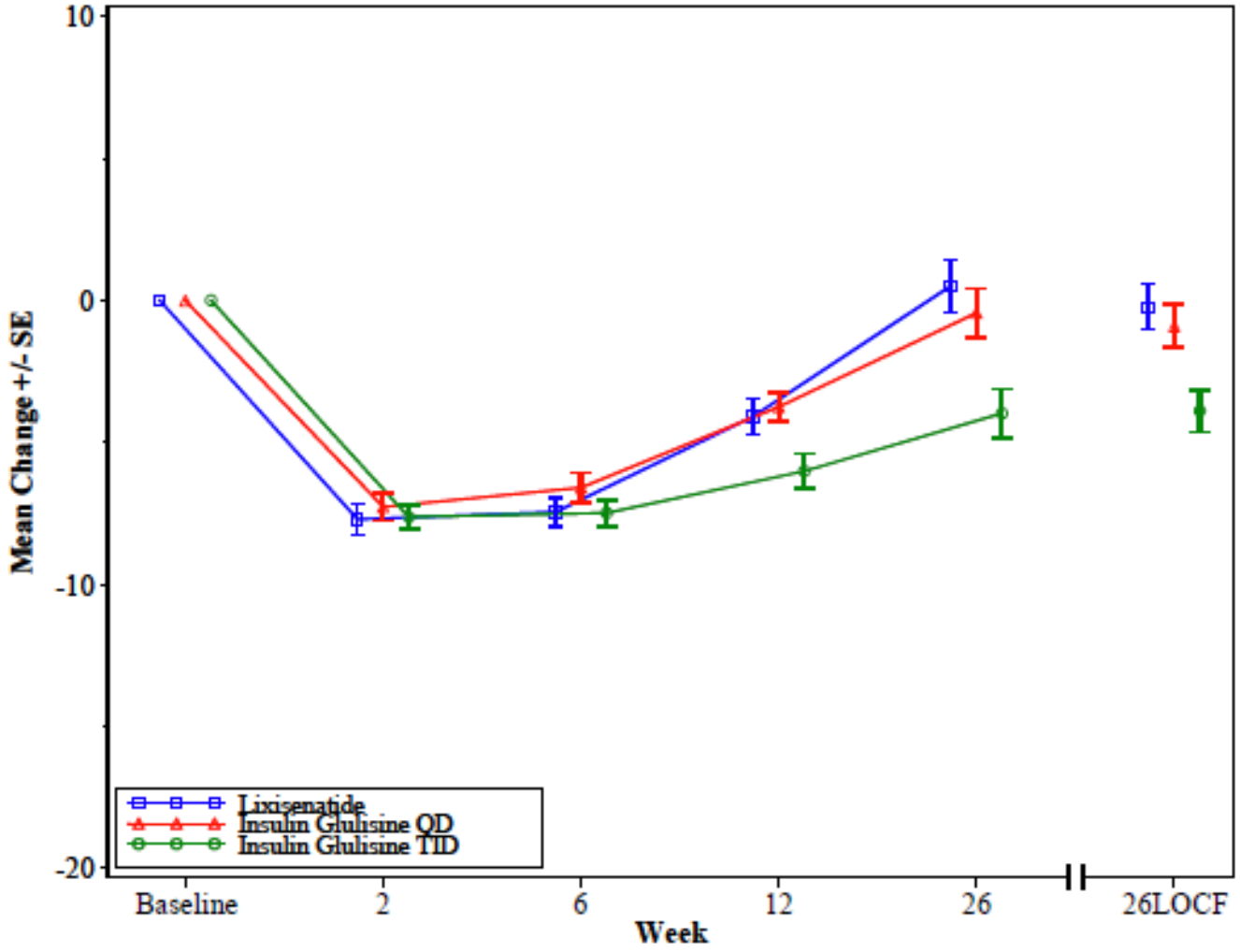
All efficacy outcomes are based on the modified intention-to-treat population.

LOCF was used to impute missing data.

Means and mean differences were analyzed using an analysis of covariance model with treatment groups (lixisenatide, insulin glulisine once daily and insulin glulisine three times daily), randomization strata of screening A1C (< 8.0, ≥ 8.0%), randomization strata of metformin use at screening (yes, no), country as fixed effects, and baseline A1C value as a covariate.

Source: GETGOAL – DUO 2 Clinical Study Report.[12]

Figure 4: Change in Mean Daily Insulin Glargine Dose (Active-Controlled RCT)



LOCF = last observation carried forward; q.d. = once daily; RCT = randomized controlled trial; t.i.d. = three time daily; SE = standard error.

Note: End points other than the co-primary end points (absolute change from baseline in A1C for lixisenatide compared with insulin glulisine once daily and insulin glulisine three times daily) were not adjusted for multiple statistical testing and are therefore considered exploratory.

P values not reported for any end point in GETGOAL – DUO 2.

All efficacy outcomes are based on the modified intention-to-treat population.

LOCF was used to impute missing data.

Means and mean differences were analyzed using an analysis of covariance model with treatment groups (lixisenatide, insulin glulisine once daily, and insulin glulisine three times daily), randomization strata of screening A1C (< 8.0, ≥ 8.0%), randomization strata of metformin use at screening (yes, no), country as fixed effects, and baseline A1C value as a covariate.

Source: GETGOAL – DUO 2 Clinical Study Report.[12]

[redacted]

[redacted]

Table 21: [redacted]

[redacted]	[redacted]		
	[redacted]	[redacted]	[redacted]
[redacted]			
[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]
[redacted]		[redacted]	[redacted]
[redacted]			
[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]
[redacted]		[redacted]	[redacted]
[redacted]			
[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]
[redacted]		[redacted]	[redacted]
[redacted]			
[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]
[redacted]		[redacted]	[redacted]
[redacted]			
[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]
[redacted]		[redacted]	[redacted]
[redacted]			
[redacted]	[redacted]	[redacted]	[redacted]

[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]

CI = confidence interval; IG = insulin glulisine; IWQOL-Lite = Impact of Weight on Quality of Life–Lite; LIXI = lixisenatide; LOCF = last observation carried forward; LS = least squares; MD = mean difference; NR = not reported; RCT = randomized controlled trial; SD = standard deviation; SE = standard error.

Note: *P* values not reported for any end point in GETGOAL – DUO 2.

All efficacy outcomes are based on the modified intention-to-treat population.

LOCF was used to impute missing data.

Means and mean differences were analyzed using an analysis of covariance model with treatment groups (lixisenatide, insulin glulisine once daily, and insulin glulisine three times daily), randomization strata of screening A1C (< 8.0, ≥ 8.0%), randomization strata of metformin use at screening (yes, no), country as fixed effects, and baseline A1C value as a covariate

[a] End points other than the co-primary end points (absolute change from baseline in A1C for lixisenatide compared with insulin glulisine once daily and insulin glulisine three times daily) were adjusted not for multiple statistical testing and are therefore considered exploratory.

Source: Rosenstock 2016[11] and GETGOAL – DUO 2 Clinical Study Report.[12]

Hospitalization Due to Hypoglycemia

No patients were hospitalized for hypoglycemia in the active-controlled trial (GETGOAL – DUO 2).

Harms

Placebo-Controlled Trials

Details pertaining to harms in the placebo-controlled trials are provided in Table 22.

Adverse Events

A numerically greater percentage of patients in the lixisenatide group experienced AEs compared with the placebo group in all trials (range between 64% and 89% versus 41% and 86%, respectively). The most commonly reported AEs that occurred more frequently in the lixisenatide treatment groups compared with the placebo groups were hypoglycemia (ranged between 25% and 44% compared with 19% and 41%, respectively), nausea (ranged between 23% and 40% compared with 5% and 10%, respectively), headache (ranged between 2% and 13% compared with 0% and 10%, respectively), diarrhea (ranged between 3% and 11% compared with 2% and 6%, respectively), vomiting (ranged between 9% and 18% compared with 1% and 2%, respectively), and decreased appetite (ranged between 2% and 7% compared with 0% and 1%, respectively). Overall, the frequency of AEs was relatively similar across trials; however, the difference in frequency of hypoglycemia in the lixisenatide group compared with the placebo group in GETGOAL – L Asia was greater than those observed in the other placebo-controlled-trials (44% compared with 24%). Contrarily, the difference in frequency of hypoglycemia in the lixisenatide group compared with the placebo group in [redacted]

Serious Adverse Events

SAEs were reported more frequently in the lixisenatide group compared with the placebo group (5% to 14% compared with 1% to 10%, respectively), with a similar frequency across all placebo-controlled trials.

Withdrawal Due to Adverse Events

A numerically greater percentage of patients in the lixisenatide group withdrew due to AEs compared with the placebo group in all trials (range between 4% and 11% versus 2% and 7%, respectively). The most commonly reported AEs leading to withdrawals that occurred more frequently in the lixisenatide treatment groups compared with the placebo groups were hypoglycemia, nausea, and vomiting. Overall, the frequency of WDAEs was relatively similar across trials.

Mortality

[redacted] one death in GETGOAL – L Asia and two deaths in GETGOAL – DUO 1; however, none of the deaths were considered to be related to study treatment by the investigators and adjudication committee. No deaths were reported in GETGOAL – L – C. Overall, the frequency of death was relatively similar across treatment groups trials.

Notable Harms

For some of the notable harms, a numerically greater percentage of patients experienced an event in the lixisenatide group compared with the placebo group in all the placebo-controlled trials: hypoglycemia ([redacted]44% versus 24%, 27% versus 19%, and 25% versus 20% for the lixisenatide groups versus the placebo groups in GETGOAL – L, GETGOAL – L Asia, GETGOAL – DUO 1, and GETGOAL – L – C, respectively), nausea ([redacted] 40% versus 5%, 27% versus 5%, and 23% versus 5% for the lixisenatide groups versus the placebo groups in GETGOAL – L, GETGOAL – L Asia, GETGOAL – DUO 1 and GETGOAL – L – C, respectively), diarrhea ([redacted]7% versus 3%, 7% versus 3%, and [redacted]for the lixisenatide groups versus the placebo groups in GETGOAL – L, GETGOAL – L Asia, GETGOAL – DUO 1 and GETGOAL – L – C, respectively), and vomiting ([redacted]18% versus 2%, 9% versus 1%, and 11% versus 1% for the lixisenatide groups versus the placebo groups in GETGOAL – L, GETGOAL – L Asia, GETGOAL – DUO 1, and GETGOAL – L – C, respectively). Occurrences of the remaining notable harms — specifically allergic reaction, pancreatitis, injection site reaction, and severe hypoglycemia — were approximately equal in both treatment groups across all the placebo-controlled trials, with the exception of injection site reaction in GETGOAL – DUO 1 (7% in the lixisenatide group compared with 2% in the placebo group).

Table 22: Harms (Placebo-Controlled Randomized Controlled Trials)

Adverse Events	GETGOAL							
	– L		– L Asia		– DUO 1		– C	
	PLB N = 167	LIXI N = 328	PLB N = 157	LIXI N = 154	PLB N = 223	LIXI N = 223	PLB N = 224	LIXI N = 224
Patients with > 0 AEs, n (%)	[redacted]	[redacted]	110 (70)	137 (89)	152 (68)	178 (80)	91 (41)	143 (64)
Most common AEs[a]								
Hypoglycemia	[redacted]	[redacted]	37 (24)	67 (44)	[redacted]	[redacted]	[redacted]	[redacted]
Nausea	[redacted]	[redacted]	7 (5)	61 (40)	11 (5)	61 (27)	12 (5)	51 (23)
Headache	[redacted]	[redacted]	3 (2)	16 (10)	[redacted]	[redacted]	[redacted]	[redacted]
Diarrhea	[redacted]	[redacted]	4 (3)	10 (7)	7 (3)	15 (7)	[redacted]	[redacted]
Nasopharyngitis	[redacted]	[redacted]	20 (13)	21 (14)	[redacted]	[redacted]	[redacted]	[redacted]
Vomiting	[redacted]	[redacted]	3 (2)	28 (18)	3 (1)	21 (9)	2 (1)	25 (11)
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Dizziness	[redacted]	[redacted]	8 (5)	13 (8)	[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Upper respiratory tract infection	[redacted]	[redacted]	1 (1)	7 (5)	[redacted]	[redacted]	[redacted]	[redacted]
Bronchitis	[redacted]	[redacted]	2 (1)	0	[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Asthenia	[redacted]	[redacted]	12 (8)	10 (7)	[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Dyspepsia	[redacted]	[redacted]	0	11 (7)	[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Abdominal discomfort	[redacted]	[redacted]	1 (1)	11 (7)	[redacted]	[redacted]	[redacted]	[redacted]
Decreased appetite	[redacted]	[redacted]	0	10 (7)	[redacted]	[redacted]	[redacted]	[redacted]
Constipation	[redacted]	[redacted]	4 (3)	8 (5)	[redacted]	[redacted]	[redacted]	[redacted]
Patients with > 0 SAEs, n (%)	[redacted]	[redacted]	9 (6)	10 (7)	10 (5)	17 (8)	2 (1)	11 (5)
Most common reasons[b]								
Coronary artery disease	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
WDAEs, n (%)	[redacted]	[redacted]	5 (3)	14 (9)	8 (4)	19 (9)	[redacted]	[redacted]
Most common reasons[b]								
Nausea	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Hypoglycemia	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Vomiting	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Number of deaths, n (%)	[redacted]	[redacted]	1 (1)	0	2 (1)	0	0	0
Notable harms, n (%)								
Hypoglycemia	[redacted]	[redacted]	37 (24)	67 (44)	[redacted]	[redacted]	[redacted]	[redacted]
Nausea	[redacted]	[redacted]	7 (5)	61 (40)	11 (5)	61 (27)	12 (5)	51 (23)
Diarrhea	[redacted]	[redacted]	4 (3)	10 (7)	7 (3)	15 (7)	[redacted]	[redacted]
Vomiting	[redacted]	[redacted]	3 (2)	28 (18)	3 (1)	21 (9)	2 (1)	25 (11)

Adverse Events	GETGOAL							
	– L		– L Asia		– DUO 1		– C	
	PLB N = 167	LIXI N = 328	PLB N = 157	LIXI N = 154	PLB N = 223	LIXI N = 223	PLB N = 224	LIXI N = 224
Allergic reaction	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Pancreatitis	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Injection site reaction	[redacted]	[redacted]	2 (1)	2 (1)	5 (2)	15 (7)	[redacted]	[redacted]
Severe hypoglycemia	[redacted]	[redacted]	0	0	0	1 (< 1)	NR	NR

AE = adverse event; CSR = Clinical Study Report; LIXI = lixisenatide; NR = not reported; PLB = placebo; SAE = serious adverse event; WDAE = withdrawal due to adverse event.
Note: Harms analyses are based on the safety population.
[a] Frequency ≥ 5%.
[b] Frequency ≥ 2%.

Source: Riddle 2013,[4] GETGOAL – L CSR,[5] Riddle 2013,[6] GETGOAL – DUO 1 CSR,[7] Seino 2012,[8] GETGOAL – L Asia CSR,[9] and GETGOAL – L – C CSR.[10]

Active-Controlled Trial

Details pertaining to harms in the active-controlled trial are provided in Table 23.

Adverse Events

A similar percentage of patients in the lixisenatide group experienced AEs compared with the insulin glulisine once daily group, and a numerically smaller percentage reported AEs when compared with insulin glulisine three times daily (74% versus 74% and 80%, respectively). The most commonly reported AEs that occurred more frequently in the lixisenatide treatment group compared with the insulin glulisine once daily and insulin glulisine three times daily groups were nausea (25% versus 2% and 1%, respectively), diarrhea (7% versus 3% and 1%, respectively), and vomiting (9% versus 2% and 2%, respectively). [redacted]

Serious Adverse Events

SAEs were reported by 4% to 5% of patients, with a similar frequency between treatment groups.

Withdrawal Due to Adverse Events

A numerically greater percentage of patients in the lixisenatide group withdrew due to AEs compared with the insulin glulisine once daily and insulin glulisine three times daily groups (5% versus 1% and 1%, respectively). [redacted]

Mortality

A total of three deaths occurred in GETGOAL – DUO 2; however, none of the deaths were considered to be related to study treatment by the investigators and adjudication committee. Overall, the frequency of death was relatively similar across treatment groups trials.

Notable Harms

For some of the notable harms, a numerically greater percentage of patients experienced an event in the lixisenatide group compared with the insulin glulisine once daily and insulin glulisine three times daily groups: nausea (25% versus 2% and 1%, respectively), diarrhea (7% versus 3% and 1%, respectively), and vomiting (9% versus 2% and 2%, respectively).

[redacted]

Table 23: Harms (Active-Controlled Randomized Controlled Trials)

Adverse Events	GETGOAL – DUO 2		
	LIXI N = 298	**IG Once Daily N = 298**	**IG t.i.d. N = 298**
Patients with > 0 AEs, n (%)	221 (74)	222 (74)	236 (80)
Most common AEs[a]			
[redacted]	[redacted]	[redacted]	[redacted]
Nausea	75 (25)	5 (2)	3 (1)
[redacted]	[redacted]	[redacted]	[redacted]
Diarrhea	20 (7)	10 (3)	4 (1)
[redacted]	[redacted]	[redacted]	[redacted]
Vomiting	26 (9)	5 (2)	6 (2)
[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]
Patients with > 0 SAEs, n (%)	11 (4)	11 (4)	14 (5)
Most common reasons[c]			
Coronary artery disease	[redacted]	[redacted]	[redacted]
WDAEs, n (%)	15 (5)	2 (1)	3 (1)
Most common reasons			
Nausea	[redacted]	[redacted]	[redacted]

Adverse Events	GETGOAL – DUO 2		
	LIXI N = 298	IG Once Daily N = 298	IG t.i.d. N = 298
Hypoglycemia	[redacted]	[redacted]	[redacted]
Vomiting	[redacted]	[redacted]	[redacted]
Number of deaths, n (%)	1 (< 1)	0	2 (1)
Notable harms, n (%)			
Hypoglycemia	[redacted]	[redacted]	[redacted]
Nausea	75 (25)	5 (2)	3 (1)
Diarrhea	20 (7)	10 (3)	4 (1)
Vomiting	26 (9)	5 (2)	6 (2)
Allergic reaction	[redacted]	[redacted]	[redacted]
Pancreatitis	[redacted]	[redacted]	[redacted]
Injection site reaction	[redacted]	[redacted]	[redacted]
Severe hypoglycemia	0	2 (1)	0

AE = adverse event; LIXI = lixisenatide; NR = not reported; PLB = placebo; SAE = serious adverse event; t.i.d. = three times daily; WDAE = withdrawal due to adverse event.

Note: Harms analyses are based on the safety population.

[a] Frequency ≥ 5%.

[b] Asymptomatic hypoglycemia.

[c] Frequency ≥ 2%.

Source: Rosenstock 2016[11] and GETGOAL – DUO 2 Clinical Study Report.[12]

Discussion

Summary of Available Evidence

Placebo-Controlled Trials

The evidence for this review as it pertains to the use of lixisenatide for the treatment of adults with type 2 diabetes mellitus in combination with a basal insulin (with or without metformin) was drawn from four similarly designed double-blind phase III multi-centre, multinational, placebo-controlled RCTs. GETGOAL – L (N = 495), GETGOAL – DUO 1 (N = 446), and GETGOAL – L – C (N = 447) randomized patients treated with a basal insulin (with or without metformin), while GETGOAL – L Asia (N = 311) randomized patients treated with a basal insulin (with or without sulfonylurea). All placebo-controlled trials used accepted methods to conceal allocation and randomize patients (interactive voice/Web response system). In addition, the use of the ANCOVA method of analysis would have ensured that the results were adjusted for variables including concomitant treatment with specified oral hypoglycemic drugs, baseline A1C, and country. Overall, there were numerically more WDAEs in the lixisenatide group compared with the placebo group; therefore, if the frequency of complete study withdrawals were greater in one group compared with the other group, randomization may have been compromised and the study results could be biased in favour of either treatment.

Although the placebo-controlled trials were double-blind RCTs, given that the AE profile associated with GLP-1 analogues (i.e., gastrointestinal AEs) is well known, some unblinding may have occurred.[34] As prior GLP-1 analogue experience was not an exclusion criterion in

any of the trials, some patients with prior experience may have surmised that the allocated treatment was lixisenatide. Unblinding may lead to biases such as under- or over-reporting of subjective outcomes (i.e., AEs) which can have an impact on the overall impression with lixisenatide treatment.

All placebo-controlled trials were designed to assess the efficacy and safety of treatment with 20 mcg lixisenatide in addition to permitted background therapy compared with placebo in addition to permitted background therapy over 24 weeks. A significant proportion of patients in the placebo-controlled trials were treated with metformin doses ≥ 2,500 mg per day. Some of the metformin doses in these ranges can exceed the maximum recommended dose by Health Canada, which is 2,550 mg per day.[35] Furthermore, a considerable portion of patients did not reach the lixisenatide dose recommended in the Canadian product monograph.[3] Daily basal insulin doses were titrated weekly based on target fasting SMPG between 4.4 mmol/L and 5.6 mmol/L, inclusive, which is inconsistent with Diabetes Canada's recommended target of 4.0 mmol/L to 7.0 mmol/L.[21] These discrepancies further limit the generalizability of the results to the type 2 diabetes mellitus population in Canada.

In each trial, the primary efficacy outcomes were the absolute change from baseline in A1C at week 24, which were analyzed using an ANCOVA model with appropriate stratifications. Those who required rescue therapy were not included in the A1C analysis and were not analyzed in the mITT population. The use of the LOCF method for handling missing data is a potential source of bias. Given that the overall benefits of lixisenatide on all glycemic control outcomes decrease over time. By using the LOCF method, the benefits of lixisenatide may be overestimated and result in a larger treatment effect due. Furthermore, the definition of the mITT population was inconsistent with the true definition of an ITT analysis, can bias the results, and may not preserve the integrity of randomization. This can potentially raise concerns given the number of missing patients in the A1C analysis, especially in the GETGOAL – L trial, wherein 7% of patients were excluded from the primary analysis. Furthermore, patients were excluded from the primary A1C analysis post-rescue treatment. Excluding these patients can overestimate the benefit of lixisenatide and bias the results by overestimating the treatment effect. However, sensitivity analyses to assess the impact of rescue medication were performed based on all scheduled A1C measurements during the main 24-week double-blind treatment period. Sensitivity analyses with 24-week completers using the observed week 24 values and the same ANCOVA model described for the primary analysis were also conducted. The validity of the sensitivity analyses on these end points may be biased given that patients were assumed to be missing at random.

Other outcomes of interest that were collected across all placebo-controlled trials include: the percentage of patients achieving target A1C; change from baseline in two-hour PPG, FPG, glucose excursion, average seven-point SMPG, and total daily basal insulin; body weight; and need for rescue therapy. Statistical testing hierarchies were used to examine secondary outcomes to control for type I error; however, the manufacturer does not appear to have adhered to its pre-specified testing strategy by continuing statistical testing for superiority after statistical insignificance was established. Overall, statistical testing should have stopped after the change in the FPG end point (third in the order of secondary analyses) in GETGOAL – L, the body weight end point (second in the order of secondary analyses) in GETGOAL – L Asia, the FPG end point (fifth in the order of secondary analyses) in GETGOAL – DUO 1, and the FPG end point (fifth in the order of secondary analyses) in GETGOAL – L – C. It is important to note that only the outcomes considered in the testing strategy that met statistical significance can be deemed acceptable, which implies that the results of the outcomes outside of the testing strategy (including all

subgroup analyses) should be considered as exploratory and be interpreted with caution because they were not appropriately adjusted for multiplicity, which increases the risk of making a type I error. Further, although subgroup analyses were presented for a number of relevant baseline factors, which were pre-specified, formal interaction tests and adjustments for multiple comparisons did not appear to have been made for these analyses. Given that subgroups typically do not maintain randomization (unless used as stratification variables for randomization, which was true of the A1C [< 8.0%, ≥ 8.0%] and metformin [yes, no] subgroups only), are likely underpowered (small sample size) to detect a statistically significant difference, and have an increased likelihood of type I error, these analyses should be treated as exploratory.

Overall, the placebo-controlled trials included patients who were not necessarily representative of the type 2 diabetes mellitus population in Canada and may limit the generalizability of the results due to inclusion of patients with near target A1C and FPG, limited inclusion of patients ages ≥ 75 years, and inclusion of patients with lower body weight and BMI.

The GETGOAL – L Asia trial consisted of an entirely Asian population, and the majority of the GETGOAL – L – C trial consisted of Asian patients (87% Asian). The racial distribution in these trials would therefore not be entirely representative of the type 2 diabetes mellitus population in Canada and can potentially limit the generalizability of the trial results. Overall, no patients recruited in GETGOAL – L Asia were treated with metformin, which is widely considered to be the first-line drug therapy in patients with type 2 diabetes mellitus who are unable to achieve glycemic control with diet and exercise alone.[31]

Discrepancies in body weight and BMI compared with the type 2 diabetes mellitus population in Canada is especially apparent in the GETGOAL – L and GETGOAL – L – C trials. The clinical expert CDR consulted for this review noted that patients with higher weight and BMI would be considered ideal candidates for GLP-1 receptor agonist treatment for the fear of potential weight gain with other antidiabetic treatments; therefore, conducting studies with mostly Asian patients who tend to have lower BMI and body weight may not reflect the target population for the drug. The same clinical expert also highlighted that the patients recruited in the GETGOAL – L Asia and GETGOAL – L – C trials were treated with lower doses of total daily basal insulin at baseline compared with the type 2 diabetes mellitus population in Canada, also potentially limiting the generalizability of the trial results. It is important to note that the lower body weights and BMI in the Asian population may potentially explain the discrepancies in total daily basal insulin. Furthermore, incretin-based therapies, such as GLP-1 mimetics, are believed to be particularly effective in people of Asian or Japanese decent because of the underlying pathophysiology of diabetes in these groups.[32,33] Therefore, the effects of lixisenatide may have been overestimated in the GETGOAL – L Asia and GETGOAL – L – C trials.

Active-Controlled Trial

The evidence for this review as it pertains to the use of lixisenatide for the treatment of adults with type 2 diabetes mellitus in combination with a basal insulin (with or without metformin) was also drawn from one open-label, phase III, noninferiority, multi-centre, multinational, active-controlled RCT (GETGOAL – DUO 2 [N = 893]). The open-label study design necessitates caution when interpreting the results of analyses of all end points. Unblinding may lead to biases such as under- or over-reporting of subjective outcomes (i.e., AEs and HRQoL), which can impact the overall impression with lixisenatide treatment. Although A1C is an objective outcome, due to the open-label nature of the trial, basal insulin

can be modified based on active treatment, which can be a potential confounder. More importantly, the open-label design raises concerns of the extent to which insulin glulisine was optimally administered during the trial, especially since patients who were assigned to receive that treatment were asked to self-adjust their dose until their FPG had reached targets of < 5.6 mmol/L. Figure 3 indicates that patients may not have reached stable doses of insulin glulisine by the end of the study, indicating that the full effect of insulin glulisine may not be observed in the reported A1C due to the latent response of the measure. Suboptimal dosage of a direct comparator can lead to underestimation of the comparator's benefit, thereby artificially inflating the treatment effect of lixisenatide.

The active-controlled trial used accepted methods to randomize patients (interactive voice/Web response system). In addition, the use of a similar ANCOVA method of analysis would have ensured that the results were adjusted for variables including concomitant treatment with specified oral hypoglycemic drugs, baseline A1C, and country. Complete study withdrawals were not reported in GETGOAL – DUO 2. Overall, there were numerically more WDAEs in the lixisenatide group compared with the placebo group; therefore, if the frequency of complete study withdrawals was greater in one group compared with the other group, randomization may have been compromised and the study results could be biased in favour of either treatment. However, this concern is minimized in GETGOAL – DUO 2, wherein only 2% of patients were excluded from the primary analysis. In addition, a significant proportion of patients in the active-controlled trial were treated with metformin doses ≥ 2,500 mg per day. Some of the metformin doses in these ranges can exceed the maximum recommended dose by Health Canada, which is 2,550 mg per day.[35] Furthermore, a considerable portion of patients did not reach the lixisenatide dose recommended in the Canadian product monograph (20 mcg per day).[3] Daily basal insulin and daily insulin glulisine doses were titrated weekly and every three days, respectively, based on target fasting SMPG between 4.4 mmol/L and 5.6 mmol/L, inclusive, which is inconsistent with Diabetes Canada's recommended target of 4.0 mmol/L to 7.0 mmol/L.[21] These discrepancies further limit the generalizability of the results to the type 2 diabetes mellitus population in Canada.

In GETGOAL – DUO 2, the primary analysis was based on three co-primary end points analyzed using a similar ANCOVA model as the placebo-controlled trials (also appropriately stratified), and was analyzed in the mITT population using the LOCF procedure to impute missing data. The noninferiority margin used in GETGOAL – DUO 2 was similar to margins used in previous type 2 diabetes mellitus trials and consistent with the 2008 FDA draft guidance for diabetes mellitus, which accepts a noninferiority margin of 0.3% or 0.4% A1C percentage units; however, the selection of the 0.4% margin is considered less conservative.[28] Even though GETGOAL – DUO 2 was designed as a noninferiority trial, the primary efficacy outcomes were tested using data from the mITT population, which could potentially bias the results in favour of a finding of noninferiority. Furthermore, no secondary analyses using data from the more appropriate per-protocol population was conducted to corroborate the primary findings; therefore, results should be interpreted with caution. Furthermore, the definition of the mITT population was inconsistent with the true definition of an ITT analysis, can bias the results, and may not preserve the integrity of randomization. However, this concern is minimized in GETGOAL – DUO 2, wherein only 2% of patients were excluded from the primary analysis. Sensitivity analyses to support the primary analysis were performed using an MMRM as well as 26-week completers using the observed week-26 values and the same ANCOVA model described for the primary analysis. However, similarly to the placebo-controlled trials, the validity of the sensitivity analyses on these end points may be biased given that patients were assumed to be missing at random.

Other outcomes of interest that were collected include: the percentage of patients achieving target A1C; change from baseline in two-hour PPG, FPG, glucose excursion, and average seven-point SMPG; and change in body weight, change from baseline in total daily basal insulin, and HRQoL using the IWQOL-Lite questionnaire. No control for type I error was made for any outcomes other than the co-primary end points in GETGOAL – DUO 2, which implies that the results of all other outcomes (including all subgroup analyses) should be considered as exploratory and be interpreted with caution because they were not appropriately adjusted for multiplicity, which increases the risk of making a type I error. Further, although subgroup analyses were presented for a number of relevant baseline factors, which were pre-specified, formal interaction tests and adjustments for multiple comparisons did not appear to have been made for these analyses. Given that subgroups typically do not maintain randomization (unless used as stratification variables for randomization, which was true of the A1C [< 8.0%, ≥ 8.0%] and metformin [yes, no] subgroups only), are likely underpowered (small sample size) to detect a statistically significant difference, and have an increased likelihood of type I error, these analyses should be treated as exploratory.

Overall, GETGOAL – DUO 2 included patients who were not necessarily representative of the type 2 diabetes mellitus population in Canada and may limit the generalizability of the results due to stringent inclusion and exclusion criteria, inclusion of patients with near target A1C and FPG, limited inclusion of patients ages ≥ 75 years, and the inclusion of patients with lower body weight and BMI.

Interpretation of Results

Efficacy

Placebo-Controlled Trials

Patients treated with lixisenatide experienced a statistically significantly greater reduction in the primary end point of absolute change from baseline in A1C compared with placebo at week 24 in all placebo-controlled trials. It is important to note that the Health Canada reviewer report suggests the magnitude of effect observed with lixisenatide is modest compared with other drugs in the GLP-1 receptor agonist class, albeit clinically meaningful.[36] The primary end point (absolute change from baseline in A1C at week 24) was also analyzed in numerous pre-specified subgroups; however, no consistent trends could be identified in any of the subgroup data.

Overall, the placebo-controlled trials did not recruit many patients ages ≥ 75 years; however, only the GETGOAL – O trial provides evidence in this subgroup of patients and suggests consistent results.[29] The Health Canada reviewer report also highlights that the results from GETGOAL – O are consistent with the findings of the other placebo-controlled trials.[36] Sensitivity analyses to assess the impact of rescue medication were performed, as were sensitivity analyses with 24-week completers. The results of all sensitivity analyses were similar in magnitude, direction, and statistical significance, and were in support of the primary analyses in all placebo-controlled trials. However, the previously mentioned limitations related to the sensitivity analyses require caution when interpreting the results.

Overall, numerically more patients in the lixisenatide groups had an A1C < 7% compared with placebo groups in all placebo-controlled trials. Similar trends were noted for the proportion of patients with an A1C < 6.5%. The results for A1C responders were not part of the statistical testing hierarchy and should be considered exploratory; therefore, no

statistical interpretations should be made. Patients treated with lixisenatide also experienced a statistically significantly greater reduction in some of the secondary end points such as two-hour PPG and average seven-point SMPG compared with placebo at week 24 in all placebo-controlled trials (with the exception of the average seven-point SMPG in GETGOAL – L Asia). Numerical differences were observed in the average seven-point SMPG in GETGOAL – L Asia; however, given that an end point in the statistical testing order failed before the testing for significance in average seven-point SMPG, statistical significance of this end point should not have been tested and should be considered exploratory.

Patients treated with lixisenatide experienced a greater numerical reduction in glucose excursion compared with placebo at week 24; however, this end point was not part of the statistical testing hierarchy and should be considered exploratory, so no statistical interpretations should be made. Generally, no statistically significant differences in FPG were reported in patients treated with lixisenatide compared with placebo at week 24. A numerically greater reduction in FPG in GETGOAL – L Asia was observed compared with placebo; however, results should be considered exploratory given that an end point in the statistical testing order failed before the testing for significance in FPG (statistical significance of this end point should not have been tested). [redacted]

Baseline glycemic control characteristics and placebo responses varied considerably within and across placebo-controlled trials. The large placebo response rate may be due to suboptimal basal insulin therapy, which was optimized during the run-in phase, given that A1C is an outcome with latent response. Such a confounding factor may prevent an accurate estimation of comparative efficacy, though the direction of bias is unclear. NICE made similar comments on the variability of the placebo response and suggested that the variability in placebo response somewhat hampers assessment of lixisenatide's effects.[26]

The changes in body weight were statistically significantly in favour of lixisenatide compared with placebo in GETGOAL – DUO 1 and GETGOAL – L – C at week 24. No statistically significant difference in body weight was observed in GETGOAL – L Asia compared with the other placebo-controlled trials, whereas a numerically greater reduction in body weight was observed in GETGOAL – L; however, results should be considered exploratory given that an end point in the statistical testing order failed before the testing for significance in FPG (statistical significance of this end point should not have been tested). According to the clinical expert CDR consulted for this review, the effects of lixisenatide on body weight are relatively modest when compared with other GLP-1 receptor agonists. This is further supported with similar claims highlighted in the Health Canada reviewer report.[36] [redacted] No data were provided for weight loss responders in GETGOAL – DUO 1 and GETGOAL – L – C. The results for weight loss responders were not part of the statistical testing hierarchy and should be considered exploratory; therefore, no statistical interpretations should be made.

All placebo-controlled trials reported the need for rescue therapy with the exception of GETGOAL – L – C. Overall, a numerically similar number of patients received rescue therapy in the placebo group compared with the lixisenatide group in GETGOAL – L, GETGOAL – L Asia and GETGOAL – DUO 1 during the double-blind treatment phase. [redacted] The results for the need for rescue therapy were not part of the statistical testing hierarchy and should be considered exploratory; therefore, no statistical interpretations should be made.

Overall, patients treated with lixisenatide required statistically significantly less total daily basal insulin compared with placebo at week 24 in GETGOAL – DUO 1 and GETGOAL – L – C. Numerically greater reductions in total daily basal insulin were reported in the lixisenatide group compared with placebo at week 24 in both GETGOAL – L and GETGOAL – L Asia; however, change in total daily basal insulin was not part of the statistical testing hierarchies in either trial and therefore should be considered exploratory. The results for A1C responders were not part of the statistical testing hierarchy and should be considered exploratory; therefore, no statistical interpretations should be made. [redacted]

Overall, the placebo-controlled trials and the active-controlled trial did not address morbidity and mortality outcomes that are greatly important to patients; however, the ELIXA trial provides evidence for longer-term outcomes.[27] The ELIXA trial was designed to investigate the long-term effect of 20 mcg lixisenatide compared with placebo on cardiovascular morbidity and mortality using a composite of cardiovascular death, nonfatal myocardial infarction, nonfatal stroke, or hospitalization for unstable angina as the primary end point, and recruited patients with type 2 diabetes mellitus who recently experienced a spontaneous acute coronary syndrome event and were therefore at risk of a recurring cardiovascular event. Per FDA guidelines, the cardiovascular safety of lixisenatide would be established if the upper bound of the two-sided 95% CI was less than the pre-specified noninferiority margin of 1.3 for the efficacy end points with a superiority margin of less than 1.0. None of the end points (primary or secondary) or their individual components showed significant change in hazard ratio between lixisenatide and placebo; however, noninferiority versus placebo was met at the 1.3 noninferiority margin. Furthermore, lixisenatide was not proven superior to placebo at the 1.0 noninferiority margin. Similarly, the findings for absolute change from baseline in A1C also showed a statistically significant difference, albeit modest, between lixisenatide and placebo, and the safety profile of lixisenatide was consistent with previous studies.

Active-Controlled Trial

Patients treated with lixisenatide, insulin glulisine once daily and insulin glulisine three times daily all experienced numerical reductions in A1C at week 26. Based on the adjusted mean differences and the pre-specified noninferiority margin for the change from baseline in A1C

(0.4%), lixisenatide was considered noninferior to both insulin glulisine once daily and insulin glulisine three times daily (co-primary end points 1 and 2a) given that the upper bound of the 95% CI did not exceed the noninferiority margin of 0.4%. The primary end points were also analyzed in numerous pre-specified subgroups; however, no formal statistical tests were performed. Overall, no numerical differences in the change in A1C were observed between lixisenatide and insulin glulisine once daily in any of the subgroups at week 26. Contrarily, a numerically smaller reduction was observed with lixisenatide compared with insulin glulisine three times daily in all subgroups with the exception of the A1C ≥ 8.0%, no metformin use, duration of diabetes ≤ 10 years, total daily basal insulin dose < 45 units per day, and duration of basal insulin dose ≥ 3 years for the change from baseline in A1C at week 26. The results for all subgroups were not adjusted for multiple statistical testing and therefore should be interpreted with caution.

Overall, it is difficult to make any inference from results based on subgroups given that there were relatively small numbers of patients included in the analyses (trial may not have sufficient power to detect statistically significant differences in the key efficacy outcomes between treatment arms). Sensitivity analyses to support the primary analysis using an MMRM and 26-week completers were performed. The results of all sensitivity analyses were similar in magnitude, direction, and statistical significance, and were in support of the primary analyses in all treatment groups. However, the previously mentioned limitations related to the sensitivity analyses require caution when interpreting the results. Numerically more patients in the lixisenatide group had an A1C < 7% compared with the insulin glulisine once daily group, and similar trends were noted for the proportion of patients with an A1C < 6.5%. Contrarily, numerically fewer patients in the lixisenatide group had an A1C < 7% compared with the insulin glulisine group, and similar trends were noted for the proportion of patients with an A1C < 6.5%. The results for A1C responders were not adjusted for multiple statistical testing and are therefore subjected to inflated type I error and should be considered exploratory.

Overall, patients treated with lixisenatide also experienced a numerically greater reduction in some secondary end points, such as two-hour PPG and glucose excursion, compared with both insulin glulisine once daily and insulin glulisine three times daily at week 26. No numerical differences were observed in FPG compared with both insulin glulisine once daily and insulin glulisine three times daily at week 26. Patients treated with lixisenatide experienced a numerically greater reduction in average seven-point SMPG compared with insulin glulisine once daily but not insulin glulisine three times at week 26. The reduction in average seven-point SMPG was numerically smaller in the lixisenatide group compared with the insulin glulisine three times daily group. None of the secondary outcomes in GETGOAL – DUO 2 were adjusted for multiple statistical testing and so should be considered exploratory; therefore, no statistical interpretations should be made.

Patients treated with lixisenatide experienced a statistically significant reduction in body weight compared with both insulin glulisine once daily and insulin glulisine three times daily at week 26. Lixisenatide was found to be superior to insulin glulisine three times daily in the co-primary end point of change in body weight at week 26. The primary end point (change from baseline in body weight at week 26) was also analyzed in numerous pre-specified subgroups and demonstrated consistent results with the primary analysis with the exception of one subgroup (ages < 50 years). The results for all subgroups were not adjusted for multiple statistical testing and therefore should be interpreted with caution.

Overall, it is difficult to make any inference from results based on subgroups given that there were relatively small numbers of patients included in the analyses (trial may not have sufficient power to detect statistically significant differences in the key efficacy outcomes between treatment arms). The Health Canada reviewer report noted that the effect of lixisenatide on body weight appears to plateau at week 12, whereas patients treated with insulin glulisine once daily and three times daily continue to gain weight through week 26.[36] The trial length may therefore bias treatment effect on body weight against lixisenatide by underestimating the difference of change in body weight. Numerically more patients in the lixisenatide groups compared with both the insulin glulisine once daily and insulin glulisine three times daily groups achieved no weight gain, weight loss of ≥ 2% body weight, weight loss of ≥ 3% body weight, and weight loss ≥ 5% body weight. The weight loss responders end points were not adjusted for multiple statistical testing and should be considered exploratory; therefore, no statistical interpretations should be made.

Patients in the lixisenatide group required numerically more basal insulin than patients in the insulin glulisine three times daily group. The changes in insulin end points were not adjusted for multiple statistical testing and should be considered exploratory; therefore, no statistical interpretations should be made. Although the clinical expert CDR consulted for this review noted that the change in basal insulin was not clinically meaningful, the Health Canada reviewer report noted that, when administered in combination with basal insulin, lixisenatide allowed reductions of insulin doses with comparable or better glycemic control, which may contribute to minimizing insulin AEs, such as weight gain.[36]

GETGOAL – DUO 2 also evaluated HRQoL using the IWQOL-Lite questionnaire. Patients treated with lixisenatide typically had numerically higher scores in terms of the IWQOL-Lite total score and all of its domains compared with insulin glulisine once daily and insulin glulisine three times daily. Although, the minimal clinically important difference for the IWQOL-Lite in obese patients with type 2 diabetes remains unclear, differences of seven to 12 are typically clinically meaningful in other conditions. Given that the changes in the total score of the IWQOL-Lite and all of its domains do not meet these thresholds, the clinical importance of these differences remains unclear. The results for A1C responders were not adjusted for multiple statistical testing and should be considered exploratory; therefore, no statistical interpretations should be made.

Harms

Placebo-Controlled Trials

Numerically more patients in the lixisenatide group experienced AEs compared with the placebo group in all trials. The most commonly reported AEs that occurred more frequently in the lixisenatide treatment groups compared with the placebo groups were hypoglycemia, nausea, headache, diarrhea, vomiting, and decreased appetite, which is consistent with the gastrointestinal risk profile of GLP-1 agonists.[34] Overall, the frequency of AEs was relatively similar across trials; however, the difference in frequency of hypoglycemia in the lixisenatide group compared with the placebo group in GETGOAL – L Asia was greater than those observed in the other placebo-controlled-trials. The reason for the discrepancy remains unclear; however, it may be a consequence of the baseline characteristics of the patient population recruited in the GETGOAL – L Asia trial, given that the population consisted entirely of patients of Asian descent.

The definition hypoglycemia used in all of the placebo-controlled trials was inconsistent with the definition used by Diabetes Canada. Misclassification of events (hypoglycemia) may not

bias the study in favour of one treatment (assuming that blinding was maintained), but may overestimate or underestimate the true incidence of events.[21] In addition, hypoglycemia may have been an issue in the lixisenatide groups given that a considerable proportion of patients were not treated with the maximally tolerated dose of lixisenatide (20 mcg as reported in the product monograph). Furthermore, patients in the lixisenatide group also reported a greater reduction in their basal insulin compared with those in the placebo group, which may also suggest a mitigation strategy to avoid hypoglycemia. SAEs were reported more frequently in the lixisenatide group compared with the placebo group, with a similar frequency across all placebo-controlled trials.

Overall, numerically more patients in the lixisenatide group withdrew due to AEs compared with the placebo group in all trials. The most commonly reported AEs leading to withdrawals that occurred more frequently in the lixisenatide treatment groups compared with the placebo groups were hypoglycemia, nausea, and vomiting, which is consistent with the gastrointestinal risk profile of GLP-1 agonists.[34] Overall, the frequency of WDAEs was relatively similar across trials.

[redacted]one death in GETGOAL – L Asia and two deaths in GETGOAL – DUO 1; however, none of the deaths were considered to be related to study treatment by the investigators and adjudication committee. No deaths were reported in GETGOAL – L – C.

The occurrence of the remaining notable harms — specifically allergic reaction, pancreatitis, injection site reaction, and severe hypoglycemia — were approximately equal in both treatment groups across all the placebo-controlled trials, with the exception of injection site reaction in GETGOAL – DUO 1 (7% in the lixisenatide group compared with 2% in the placebo group).

Active-Controlled Trial

Numerically more patients in the lixisenatide group experienced AEs compared with the insulin glulisine once daily group, and numerically less reported AEs when compared with the insulin glulisine three times daily group. The most commonly reported AEs that occurred more frequently in the lixisenatide treatment group compared with the insulin glulisine once daily and insulin glulisine three times daily groups were nausea, diarrhea, and vomiting, which is consistent with the gastrointestinal risk profile of GLP-1 agonists.[34] Contrarily, one commonly reported AE occurred more frequently in the insulin glulisine once daily and insulin glulisine three times daily groups compared with the lixisenatide group: hypoglycemia. SAEs were reported with a similar frequency between treatment groups.

The definition hypoglycemia used in GETGOAL – DUO 2 was inconsistent with the definition used by Diabetes Canada.[21] Given that GETGOAL – DUO 2 was open-label in design, misclassification of subjective outcomes (e.g., AEs) may bias the study in favour of one treatment due to over- or under-reporting of harms. In addition, hypoglycemia may have been an issue in the lixisenatide groups given that a considerable proportion of patients were not treated with the maximally tolerated dose of lixisenatide (20 mcg as reported in the product monograph). Furthermore, patients in the lixisenatide group also reported a lesser reduction in their basal insulin compared with those in the insulin groups, which may also suggest reduced incidences of hypoglycemia compared with insulin.

Numerically more patients in the lixisenatide group withdrew due to AEs compared with the insulin glulisine once daily and insulin glulisine three times daily groups. The most commonly reported AEs leading to withdrawal that occurred more frequently in the

lixisenatide treatment groups compared with the insulin glulisine once daily and insulin glulisine three times daily groups were nausea and vomiting, which is consistent with the gastrointestinal risk profile of GLP-1 agonists.[34]

A total of three deaths occurred in GETGOAL – DUO 2; however, none of the deaths were considered to be related to study treatment by the investigators and adjudication committee.

The occurrence of the remaining notable harms — specifically allergic reaction, pancreatitis, injection site reaction, and severe hypoglycemia — was approximately equal in all treatment groups.

Potential Place in Therapy[a]

In patients with type 2 diabetes mellitus managed with oral diabetes agents in combination with basal insulin but A1C is not at target, there are limited options for improving glycemic control. In these cases, the fasting blood glucose is typically at target due to the use of basal insulin, but postprandial blood glucose remains elevated. A switch to a more intensive insulin regimen is required in most cases, such as the addition of prandial insulin injections (multiple daily injections) or a switch to twice-daily, pre-mixed insulin. Both of these alternative regimens are more work intensive, less convenient for patients, and have the potential to increase hypoglycemia. For some patients, the addition of a GLP-1 receptor agonist such as lixisenatide is a reasonable alternative; however, the use of this medication class for many patients is currently limited by cost.

According to the clinical expert CDR consulted for this review, the manufacturer's reimbursement request for lixisenatide appears to be clinically appropriate, given that the use of a GLP-1 receptor agonist is an appealing alternative to intensifying a patient's insulin regimen. The same clinical expert noted that the evidence reviewed for this CDR submission suggests that lixisenatide can reduce postprandial blood glucose in a clinically meaningful way when added to basal insulin with or without oral antidiabetic therapies. However, in patients with significantly elevated A1C (e.g., > 2.0% above target), it is less likely that the addition of lixisenatide alone could optimize glycemic control, and intensification of insulin therapy would likely still be required. The evidence also suggests that the risk of hypoglycemia is lower with lixisenatide compared with the addition of prandial insulin.

The clinical expert CDR consulted for this review noted that lixisenatide could be particularly useful in patients with lower health literacy who may struggle with complex insulin regimens, and patients who are elderly and frail, in whom hypoglycemia is avoided. Similarly, lixisenatide may also be preferred in patients who are overweight and obese, in whom the addition of short-acting insulin could predispose to weight gain. The same clinical expert noted that no specialized diagnostic testing would be required to identify patients in whom the addition of lixisenatide may be appropriate, and that clinicians would likely base their decision on A1C results as well as fasting and postprandial blood glucose testing, which would be routinely requested in this patient population.

The clinical expert highlighted one potential issue in the prescribing of lixisenatide. Given that there is a separate pen for each of the two drug doses (i.e., 10 mcg and 20 mcg), unlike other GLP-1 agonists where one pen can administer different doses, this implies that patients taking lixisenatide will be unable to self-titrate their dose based on tolerability per their physician's instructions, which could result in increased pharmacy faxes or physician visits for any changes in doses.

The clinical expert also highlighted that lixisenatide was found to be noninferior to placebo in terms of cardiovascular outcome in the ELIXA trial, which is reassuring for clinicians and patients. However, it should also be noted that other GLP-1 agonists have been shown to have cardiovascular benefit and that clinicians may prefer to use these agents, particularly in patients with high cardiovascular risk.

Conclusions

The CDR systematic review included four double-blind, phase III, placebo-controlled RCTs and one open-label, active-controlled RCT designed to assess the benefits of lixisenatide as an adjunct to diet and exercise to improve glycemic control in adult patients with type 2 diabetes mellitus in combination with a basal insulin (alone or with metformin).

Statistically significant differences in favour of lixisenatide compared with placebo were reported for the primary outcome (absolute change from baseline in A1C at week 24) in all placebo-controlled trials (GETGOAL – L [N = 495], GETGOAL – L Asia [N = 311], GETGOAL – DUO 1 [N = 446], and GETGOAL – L – C [N = 447]). Lixisenatide was also associated with benefits in some but not all secondary outcomes including change in two-hour PPG and change in body weight. Key limitations of the placebo-controlled trials include randomization potentially being compromised due to study withdrawals; concerns with the statistical testing across secondary end points; concerns with the imputation model and the definitions of ITT analysis and hypoglycemia; the lack of control for multiple statistical testing across subgroups of interest and sensitivity analyses; large placebo response; and the differences in patient and practice characteristics between the study centres included in the placebo-controlled trials and what would be seen in a Canadian setting (e.g., A1C and FPG near target, the mean age of patients, racial group, and the use of optimal standard antidiabetic practices). More patients in the lixisenatide group experienced AEs compared with the placebo group in all trials. The most commonly reported AEs that occurred more frequently in the lixisenatide treatment groups compared with the placebo groups were hypoglycemia, nausea, headache, diarrhea, vomiting, and decreased appetite, which is consistent with the gastrointestinal risk profile of GLP-1 agonists.

In addition, lixisenatide demonstrated noninferiority in the absolute change from baseline in A1C compared with insulin glulisine once daily and insulin glulisine three times daily using a noninferiority margin of 0.4% in three co-primary outcomes in GETGOAL – DUO 2: 1) noninferiority of lixisenatide versus insulin glulisine once daily in the change from baseline in A1C at week 26 using a noninferiority margin of 0.4%; 2a) noninferiority of lixisenatide versus insulin glulisine three times daily in the change from baseline in A1C at week 26 using a noninferiority margin of 0.4%; and 2b) superiority of lixisenatide versus insulin glulisine three times daily in the change from baseline in body weight at week 26. Lixisenatide was also associated with benefits in some, but not all, secondary outcomes including change in two-hour PPG.

Key limitations of GETGOAL – DUO 2 include its open-label design; concerns with the titration regimen of insulin, the imputation model, and the definitions of ITT analysis and hypoglycemia; lack of per-protocol analysis for noninferiority tests; randomization potentially being compromised due to study withdrawals; the lack of control for multiple statistical testing across all secondary end points, subgroups of interest, and sensitivity analyses; and the differences in patient and practice characteristics between the study centres included in the trial and what would be seen in a Canadian setting (e.g., A1C and FPG near target, the mean age of patients, racial group, and the use of optimal standard antidiabetic practices).

The most commonly reported AEs that occurred more frequently in the lixisenatide treatment groups compared with the placebo groups were nausea, diarrhea, and vomiting, which is consistent with the gastrointestinal risk profile of GLP-1 agonists. However, more hypoglycemic events were reported in patients treated with insulin glulisine once daily and insulin glulisine three times daily compared with lixisenatide.

Overall, it is important to note that lixisenatide was found to be noninferior to placebo in terms of cardiovascular outcomes in the ELIXA trial.

Appendix 1: Patient Input Summary

This section was prepared by CADTH staff based on the input provided by patient groups.

Brief Description of Patient Group(s) Supplying Input

Diabetes Canada is an organization dedicated to improving the lives of people with diabetes through education and services, research, knowledge translation, and advocating on patients' behalf. Their mission is delivered by a network of volunteers, employees, health care professionals, researchers, and partners. The programs and activities of Diabetes Canada are sponsored by a number of manufacturers and vendors of pharmaceuticals, supplies, and devices. No conflicts of interest were declared by Diabetes Canada in the preparation of the submission and the sponsors were not part of the process.

Condition-Related Information

Patient inputs were obtained through online surveys (social media and email blast) conducted in October 2016 and June 2017 in preparation for this submission. Overall, a total of 790 patients with type 2 diabetes mellitus and 57 caregivers of patients with type 2 diabetes answered the first survey, and 202 patients with type 2 diabetes mellitus and their caregivers responded to the second one.

Type 2 diabetes is a chronic disease that stems from the inadequate production of insulin from the pancreas or ineffective use of insulin by the body, resulting in impaired glucose entry into the cells that subsequently raises blood glucose level. Common symptoms of diabetes are fatigue, thirst, and changes in body weight. Patients require considerable self-management, including diet, physical activity, body weight, blood glucose, and stress, in addition to diabetic medications. Lack of control of blood glucose can lead to a range of serious comorbidities such as cardiovascular diseases, blindness, kidney diseases, peripheral nerve damage, and erectile dysfunction. In addition to the physical problems, these complications have a negative impact on patients' quality of life as well as their psychosocial and financial well-being. Survey respondents emphasized that dietary requirements, lifestyle modification, and management of medications and side effects (weight gain) are associated with impaired work, travel, and social life as well as increased stress, anxiety, and financial burden. One participant aptly described the continuous challenges of everyday lives of patients with diabetes: "There is no 'day off' — no holiday away from diabetes."

Current Therapy-Related Information

Treatments for type 2 diabetes are usually targeted toward glycemic control; however, optimal blood glucose level is achieved by relatively few patients. Most patients, therefore, require multiple antidiabetic agents to reach their glycemic target. In addition, many current therapies fail to achieve glycemic control due to adverse events such as hypoglycemia, and due to significant weight gain. Metformin is usually the first-line treatment, which is supplemented by a range of medications, including glucagon-like peptide-1 (GLP-1) receptor agonists, insulin, sodium-glucose cotransporter-2 (SGLT2) inhibitors, sulfonylureas, dipeptidyl peptidase-4 (DPP-4) inhibitors, thiazolidinediones, meglitinides, and acarbose. Among the respondents, 44% to 59% reported improved blood glucose levels at various times of the day, improved glycated hemoglobin (A1C) levels, avoided hypoglycemia, and were satisfied with their medications.

Patients also identified that the mitigation of side effects, cost, and ease of administration (injection versus oral) are important considerations when choosing medications. Some respondents expressed the need for drugs “that are effective enough to allow for minimum, or no use, of other drugs” and provide a “life without concerns about complications because of diabetes.”

Expectations About the Drug Being Reviewed

There was no indication of patients taking lixisenatide in the survey; instead, information from patients and caregivers experienced with any type of GLP-1 receptor agonists were described in the submission. Among the patients who have had experience with GLP-1 receptor agonists, the majority reported this class of drugs to be effective in meeting their fasting, preprandial and postprandial blood glucose targets, A1C levels, and decreasing dependence on other medications. Weight loss was also noted in some cases.

Many patients switched from another medication or had this class of drugs included in their treatment regimen due to poor blood glucose control and to achieve improved diabetes management outcomes. One patient indicated that among members of her family with type 2 diabetes — including her — the use of a GLP-1 receptor agonist led to satisfactory control of diabetes, loss of weight, and avoided hypoglycemia, resulting in discontinuation of previously prescribed secretagogues. Another patient treated with a combination of sulfonylurea, a GLP-1 receptor agonist, and an SGLT2 inhibitor reported improved overnight fasting and A1C figures in addition to weight loss after the original treatment, metformin, was unsuccessful. On the other hand, several side effects were reported by a significant number of patients treated with GLP-1 receptor agonists, including extreme nausea and gastrointestinal effects, thirst, and dehydration. This required some patients to cut down their dosage of the drug while keeping a satisfactory A1C level.

When asked to rate the outcomes and side effects that the surveyed patients expect from their therapies, the vast majority responded that maintaining a satisfactory preprandial and postprandial blood glucose level throughout the day and preventing hypoglycemia, change in weight, heart problems, gastrointestinal effects, and high blood pressure were “important” to “very important” to them. Medications that are less costly, easy to administer, and minimize side effects were the preferred choice of treatments. Some opted for medications on the basis that they would avoid the requirement of multiple drugs and diabetes-associated complications, and provide more energy, better mental health, and an overall sense of well-being.

Appendix 2: Literature Search Strategy

Overview	
Interface:	Ovid
Databases:	Embase 1974 to present MEDLINE Daily and MEDLINE 1946 to present MEDLINE In-Process & Other Non-Indexed Citations Note: Subject headings have been customized for each database. Duplicates between databases were removed in Ovid.
Date of Search:	June 23, 2017
Alerts:	Weekly search updates until October 18, 2017
Limits:	No date limits Human only English only Conference abstracts were excluded

Syntax Guide	
/	At the end of a phrase, searches the phrase as a subject heading
.sh	At the end of a phrase, searches the phrase as a subject heading
MeSH	Medical Subject Heading
fs	Floating subheading
exp	Explode a subject heading
*	Before a word, indicates that the marked subject heading is a primary topic; or, after a word, a truncation symbol (wildcard) to retrieve plurals or varying endings
#	Truncation symbol for one character
?	Truncation symbol for one or no characters only
ADJ	Requires words are adjacent to each other (in any order)
ADJ#	Adjacency within # number of words (in any order)
.ti	Title
.ab	Abstract
.hw	Heading Word; usually includes subject headings and controlled vocabulary
.pt	Publication type
.rn	CAS registry number
pmez	Ovid database code; MEDLINE In-Process & Other Non-Indexed Citations, MEDLINE Daily and Ovid MEDLINE 1946 to Present
oemezd	Ovid database code; Embase 1974 to present, updated daily

Multi-Database Strategy	
#	**Searches**
1	(Lixisenatide* or adlyxin* or lyxumia*).ti,ab,kf,hw,ot.
2	(AQVE10010 or AQVE 10010 or "AVE 0010" or AVE0010 or ZP10 or ZP 10 or ZP10A or ZP 10A or "AVE 010" or AVE010 or "AVE 0010" or 74O62BB01U or UNII74O62BB01U or AVE0010 or 320367 13 3 or 32036713 3 or 320367 133 or "320367133").ti,ab,kf,hw,ot.
3	(320367 13 3 or 32036713 3 or 320367 133 or "320367133").rn,nm.
4	1 or 2 or 3
5	4 use ppez
6	exp *lixisenatide/
7	(Lixisenatide* or adlyxin* or lyxumia*).ti,ab,kw.
8	(AQVE10010 or AQVE 10010 or "AVE 0010" or AVE0010 or ZP10 or ZP 10 or ZP10A or ZP 10A or "AVE 010" or AVE010 or "AVE 0010" or 74O62BB01U or UNII74O62BB01U or AVE0010 or 320367 13 3 or 32036713 3 or 320367 133 or "320367133").ti,ab,kw.
9	6 or 7 or 8
10	9 use oemezd
11	5 or 10
12	exp animals/
13	exp animal experimentation/ or exp animal experiment/
14	exp models animal/
15	nonhuman/
16	exp vertebrate/ or exp vertebrates/
17	animal.po.
18	or/12-17
19	exp humans/
20	exp human experimentation/ or exp human experiment/
21	human.po.
22	or/19-21
23	18 not 22
24	11 not 23
25	24 not conference abstract.pt.
26	remove duplicates from 25

Other Databases	
PubMed	Same MeSH, keywords, limits, and study types used as per MEDLINE search, with appropriate syntax used.
Trial registries (Clinicaltrials.gov and others)	Same keywords, limits used as per MEDLINE search.

Grey Literature

Dates for Search:	June 20–21, 2017
Keywords:	Drug name, Indication
Limits:	No date limits used, English language only

Relevant websites from the following sections of the CADTH grey literature checklist, Grey Matters: a practical tool for evidence-based searching (http://www.cadth.ca/resources/finding-evidence/grey-matters), were searched:

- Health Technology Assessment agencies
- health economics
- clinical practice guidelines
- databases (free)
- Internet search
- open access journals.

Appendix 3: Excluded Studies

Reference	Reason for Exclusion
Aroda et al., 2016[37]	Intervention – irrelevant
Eto et al., 2015[38]	Study population – irrelevant
Farngren et al., 2016[39]	Outcomes – irrelevant
Meier et al., 2015[40]	Study design – irrelevant
Meneilly et al., 2017[29]	Study population – irrelevant
Miya et al., 2017[41]	Intervention – irrelevant
Pfeffer et al., 2015[27]	Indication other than the reimbursement request
Rosenstock et al., 2016[42]	Intervention – irrelevant
Rosenstock et al., 2016[43]	Intervention – irrelevant
Seino et al., 2015[44]	Intervention – irrelevant
Tonneijck et al., 2017[45]	Indication other than the reimbursement request
Wysham et al., 2017[46]	Intervention – irrelevant
Yamada et al., 2017[47]	Outcomes – irrelevant

Appendix 4: Detailed Outcome Data

Placebo-Controlled Trials

Table 24: [redacted]

[redacted]	[redacted]	
	[redacted]	[redacted]
[redacted]		
[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	
[redacted]	[redacted]	
[redacted]		
[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	
[redacted]	[redacted]	
[redacted]		
[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	
[redacted]	[redacted]	

A1C = glycated hemoglobin; ANCOVA = analysis of covariance; CI = confidence interval; LIXI = lixisenatide; NR = not reported; PLB = placebo; RCT = randomized controlled trial.

Note: All efficacy outcomes are based on the modified intention-to-treat population and do not include patients requiring rescue therapy.

Means and mean differences were analyzed using an ANCOVA model with treatment groups (lixisenatide and placebo), randomization strata of screening A1C (< 8.0, ≥ 8.0%), randomization strata of metformin use at screening (yes, no), country as fixed effects, and baseline A1C value as a covariate in GETGOAL – L and GETGOAL – L – C.

[a] Composite end point analyses were not part of the statistical testing hierarchy and are therefore considered exploratory.

Source: GETGOAL – L – C Clinical Study Report.[10]

Table 25: [redacted]

[redacted]	[redacted]							
	[redacted]		[redacted]		[redacted]		[redacted]	
	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
[redacted]								
[redacted]								
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]		[redacted]		[redacted]		[redacted]	
[redacted]								
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

[redacted]

A1C = glycated hemoglobin; ANCOVA = analysis of covariance; CI = confidence interval; CSR = Clinical Study Report; LIXI = lixisenatide; LS = least squares; MD = mean difference; NR = not reported; PLB = placebo; RCT = randomized controlled trial; SD = standard deviation; SE = standard error.

Note: All efficacy outcomes are based on the modified intention-to-treat population and do not include patients requiring rescue therapy

Means and mean differences were analyzed using an ANCOVA model with treatment groups (lixisenatide and placebo), randomization strata of screening A1C (< 8.0, ≥ 8.0%), randomization strata of metformin use at screening (yes, no), country as fixed effects, and baseline A1C value as a covariate in GETGOAL – L and GETGOAL – L – C. Instead of randomization strata of metformin use at screening (yes, no) as fixed effects in the ANCOVA model, randomization strata of sulfonylurea use at screening (yes, no) and randomization strata of thiazolidinedione use at screening (yes, no) were used in GETGOAL – L Asia and GETGOAL – DUO 1, respectively.

[a] Subgroup analyses were not part of the of the statistical testing hierarchy and were therefore considered exploratory.

Source: Riddle 2013,[4] GETGOAL – L CSR,[5] Riddle 2013,[6] GETGOAL – DUO 1 CSR,[7] Seino 2012,[8] GETGOAL – L Asia CSR,[9] and GETGOAL – L – C CSR.[10]

Table 26: [redacted]

[redacted]

[redacted]

A1C = glycated hemoglobin; ANCOVA = analysis of covariance; BMI = body mass index; CI = confidence interval; CSR = Clinical Study Report; LIXI = lixisenatide; LS = least squares; MD = mean difference; NR = not reported; PLB = placebo; RCT = randomized controlled trial; SD = standard deviation; SE = standard error.

Note: All efficacy outcomes are based on the modified intention-to-treat population and do not include patients requiring rescue therapy.

Means and mean differences were analyzed using an ANCOVA model with treatment groups (lixisenatide and placebo), randomization strata of screening A1C (< 8.0, ≥ 8.0%), randomization strata of metformin use at screening (yes, no), country as fixed effects, and baseline A1C value as a covariate in GETGOAL – L and GETGOAL – L – C. Instead of randomization strata of metformin use at screening (yes, no) as fixed effects in the ANCOVA model, randomization strata of sulfonylurea use at screening (yes, no) and randomization strata of thiazolidinedione use at screening (yes, no) were used in GETGOAL – L Asia and GETGOAL – DUO 1, respectively.

[a] Subgroup analyses were not part of the of the statistical testing hierarchy and were therefore considered exploratory.

Source: Riddle 2013,[4] GETGOAL – L CSR,[5] Riddle 2013,[6] GETGOAL – DUO 1 CSR,[7] Seino 2012,[8] GETGOAL – L Asia CSR,[9] and GETGOAL – L –C CSR.[10]

Table 27: [redacted]

[redacted]

[redacted]	[redacted]							
	[redacted]		[redacted]		[redacted]		[redacted]	
	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
[redacted]								
[redacted]	[redacted]		[redacted]		[redacted]		[redacted]	

A1C = glycated hemoglobin; ANCOVA = analysis of covariance; CI = confidence interval; CSR = Clinical Study Report; LIXI = lixisenatide; LS = least squares; MD = mean difference; NR = not reported; PLB = placebo; RCT = randomized controlled trial; SD = standard deviation; SE = standard error.

Note: All efficacy outcomes are based on the modified intention-to-treat population and do not include patients requiring rescue therapy.

Means and mean differences were analyzed using an ANCOVA model with treatment groups (lixisenatide and placebo), randomization strata of screening A1C (< 8.0, ≥ 8.0%), randomization strata of metformin use at screening (yes, no), country as fixed effects, and baseline A1C value as a covariate in GETGOAL – L and GETGOAL – L – C. Instead of randomization strata of metformin use at screening (yes, no) as fixed effects in the ANCOVA model, randomization strata of sulfonylurea use at screening (yes, no) and randomization strata of thiazolidinedione use at screening (yes, no) were used in GETGOAL – L Asia and GETGOAL – DUO 1, respectively.

[a] Subgroup analyses were not part of the of the statistical testing hierarchy and were therefore considered exploratory.

Source: Riddle 2013,[4] GETGOAL – L CSR,[5] Riddle 2013,[6] GETGOAL – DUO 1 CSR,[7] Seino 2012,[8] GETGOAL – L Asia CSR,[9] and GETGOAL – L – C CSR.[10]

Table 28: [redacted]

[redacted]	[redacted]							
	[redacted]		[redacted]		[redacted]		[redacted]	
	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
[redacted]								
[redacted]								
[redacted]	[redacted]	[redacted]					[redacted]	[redacted]
[redacted]								
[redacted]	[redacted]							
[redacted]								
[redacted]	[redacted]	[redacted]					[redacted]	[redacted]
[redacted]								
[redacted]	[redacted]							
[redacted]								
[redacted]	[redacted]	[redacted]					[redacted]	[redacted]
[redacted]								
[redacted]			[redacted]	[redacted]				
[redacted]								
[redacted]			[redacted]	[redacted]				
[redacted]								
[redacted]			[redacted]					
[redacted]								

[redacted]

A1C = glycated hemoglobin; ANCOVA = analysis of covariance; CI = confidence interval; CSR = Clinical Study Report; LIXI = lixisenatide; LS = least squares; MD = mean difference; NR = not reported; PLB = placebo; RCT = randomized controlled trial; SD = standard deviation; SE = standard error; TZD = thiazolidinedione.

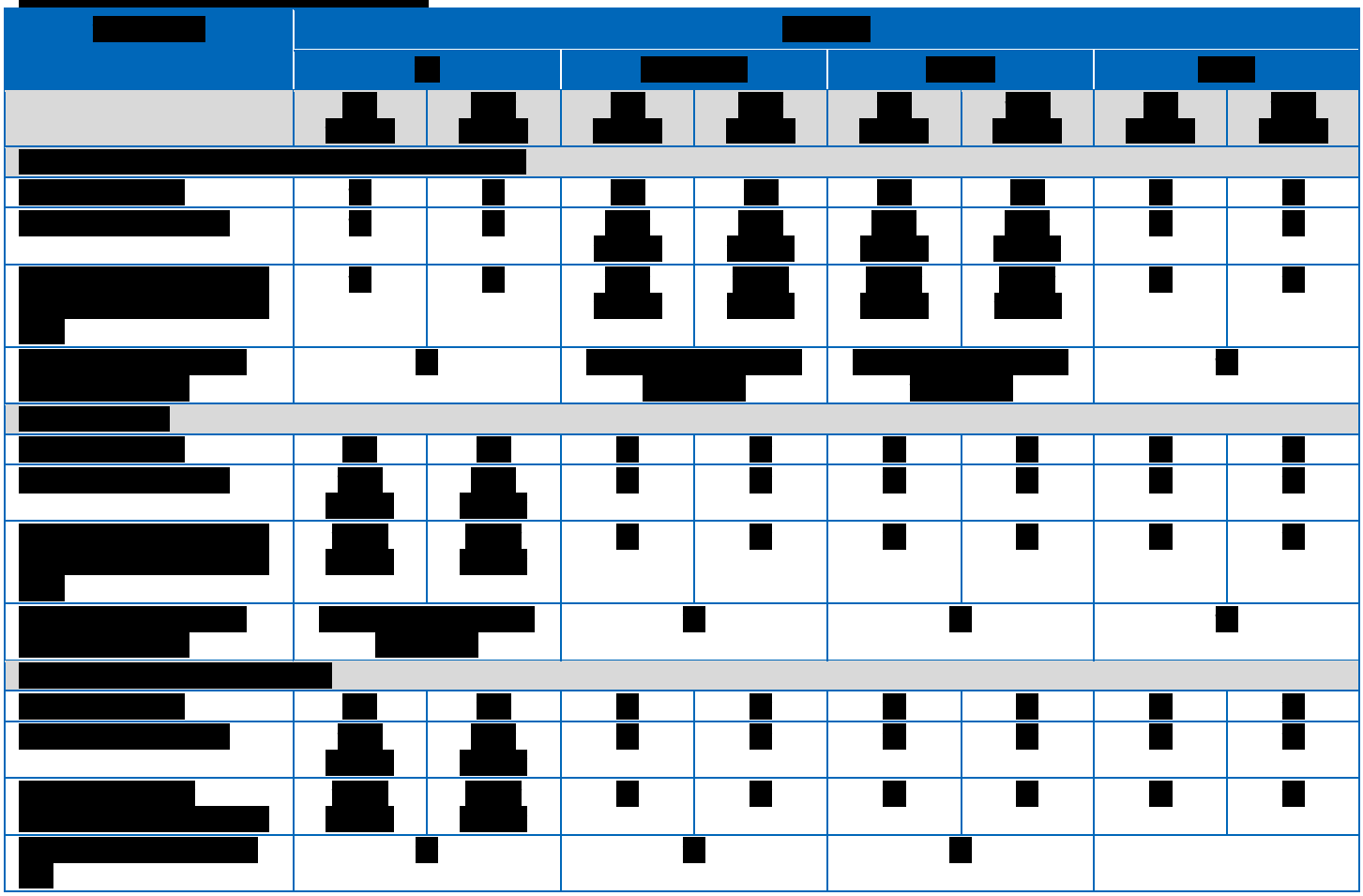
Note: All efficacy outcomes are based on the modified intention-to-treat population and do not include patients requiring rescue therapy.

Means and mean differences were analyzed using an ANCOVA model with treatment groups (lixisenatide and placebo), randomization strata of screening A1C (< 8.0, ≥ 8.0%), randomization strata of metformin use at screening (yes, no), country as fixed effects, and baseline A1C value as a covariate in GETGOAL – L and GETGOAL – L – C. Instead of randomization strata of metformin use at screening (yes, no) as fixed effects in the ANCOVA model, randomization strata of sulfonylurea use at screening (yes, no) and randomization strata of thiazolidinedione use at screening (yes, no) were used in GETGOAL – L Asia and GETGOAL – DUO 1, respectively.

[a] Subgroup analyses were not part of the of the statistical testing hierarchy and were therefore considered exploratory.

Source: Riddle 2013,[4] GETGOAL – L CSR,[5] Riddle 2013,[6] GETGOAL – DUO 1 CSR,[7] Seino 2012,[8] GETGOAL – L Asia CSR,[9] and GETGOAL – L – C CSR.[10]

Table 29: [redacted]



A1C = glycated hemoglobin; ANCOVA = analysis of covariance; CI = confidence interval; CSR = Clinical Study Report; LIXI = lixisenatide; LS = least squares; MD = mean difference; MMRM = mixed-effects models for repeated measures; NR = not reported; PLB = placebo; RCT = randomized controlled trial; SD = standard deviation; SE = standard error.

Note: All efficacy outcomes are based on the modified intention-to-treat population and do not include patients requiring rescue therapy, with the exception of the ANCOVA analysis including post-rescue therapy data.

[a] Sensitivity analyses were not part of the of the statistical testing hierarchy and were therefore considered exploratory.

[b] Multi-level model with random slopes and intercepts, with fixed-effect factors for treatment, visit, treatment-by-visit interaction, randomization strata of screening A1C (< 8.0%, ≥ 8.0 %), randomization strata of screening sulfonylurea use (yes, no), country, baseline A1C-by-visit interaction, and the number of days spent on rescue medications. Instead of the randomization strata of screening sulfonylurea use (yes, no) used in GETGOAL – L Asia, GETGOAL – DUO 1 used randomization strata of screening thiazolidinedione use (yes, no).

[c] MMRM with treatment groups (lixisenatide and placebo), visit, treatment-by-visit interaction, randomization strata of screening A1C (< 8.0%, ≥ 8.0%), randomization strata of metformin use at screening (yes, no), and country as fixed effects, and baseline A1C value and baseline A1C-by-visit interaction as covariates.

[d] Means and mean differences were analyzed using an ANCOVA model with treatment groups (lixisenatide and placebo), randomization strata of screening A1C (< 8.0, ≥ 8.0%), randomization strata of metformin use at screening (yes, no), and country as fixed effects, and baseline A1C value as a covariate in GETGOAL – L and GETGOAL – L – C. Instead of randomization strata of metformin use at screening (yes, no) as fixed effects in the ANCOVA model, randomization strata of sulfonylurea use at screening (yes, no) and randomization strata of thiazolidinedione use at screening (yes, no) were used in GETGOAL – L Asia and GETGOAL – DUO 1, respectively.

Source: Riddle 2013,[4] GETGOAL – L CSR,[5] Riddle 2013,[6] GETGOAL – DUO 1 CSR,[7] Seino 2012,[8] GETGOAL – L Asia CSR,[9] and GETGOAL – L – C CSR.[10]

Active-Controlled Trial

Table 30: [redacted]

[redacted]			
[redacted]			
[redacted]			
[redacted]			
[redacted]			
[redacted]			
[redacted]			
[redacted]			
[redacted]			
[redacted]			
[redacted]			
[redacted]			
[redacted]			
[redacted]			
[redacted]			

A1C = glycated hemoglobin; CI = confidence interval; IG = insulin glulisine; LIXI = lixisenatide; LS = least squares; MD = mean difference; NR = not reported; RCT = randomized controlled trial; t.i.d. = three time daily; SD = standard deviation; SE = standard error.

Note: All efficacy outcomes are based on the modified intention-to-treat population.

Means and mean differences were analyzed using an analysis of covariance model with treatment groups (lixisenatide, insulin glulisine once daily, and insulin glulisine three times daily), randomization strata of screening A1C (< 8.0, ≥ 8.0%), randomization strata of metformin use at screening (yes, no), and country as fixed effects, and baseline A1C value as a covariate.

[a] Composite end point analyses were not part of the statistical testing hierarchy and are therefore considered exploratory.

Source: Rosenstock 2016[11] and GETGOAL – DUO 2 Clinical Study Report.[12]

Table 31: [redacted]

[redacted]			
[redacted]			
[redacted]			
[redacted]			
[redacted]			
[redacted]			
[redacted]			
[redacted]			
[redacted]			
[redacted]			
[redacted]			
[redacted]			
[redacted]			
[redacted]			
[redacted]			

[redacted]	[redacted]		
	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]
[redacted]		[redacted]	[redacted]
[redacted]			
[redacted]			
[redacted]	[redacted]	[redacted]	[redacted]
[redacted]			
[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]
[redacted]		[redacted]	[redacted]
[redacted]			
[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]
[redacted]		[redacted]	[redacted]

A1C = glycated hemoglobin; CI = confidence interval; IG = insulin glargine; LIXI = lixisenatide; LS = least squares; MD = mean difference; NR = not reported; RCT = randomized controlled trial; SD = standard deviation; SE = standard error; t.i.d. = three times daily.

Note: All efficacy outcomes are based on the modified intention-to-treat population.

Means and mean differences were analyzed using an ANCOVA model with treatment groups (lixisenatide, insulin glulisine once daily, and insulin glulisine three times daily), randomization strata of screening A1C (< 8.0, ≥ 8.0%), randomization strata of metformin use at screening (yes, no), and country as fixed effects, and baseline A1C value as a covariate.

[a] Subgroup analyses were not adjusted for multiple statistical testing and were therefore considered exploratory.

Source: Rosenstock 2016[11] and GETGOAL – DUO 2 Clinical Study Report.[12]

Table 32: [redacted]

[redacted]	[redacted]		
	[redacted]	[redacted]	[redacted]
[redacted]			
[redacted]			
[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]
[redacted]		[redacted]	[redacted]
[redacted]			
[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]

[redacted]	[redacted]		
	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]
[redacted]		[redacted]	[redacted]
[redacted]			
[redacted]	[redacted]	[redacted]	[redacted]
[redacted]			
[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]
[redacted]		[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]
[redacted]		[redacted]	[redacted]

A1C = glycated hemoglobin; BMI = body mass index; CI = confidence interval; IG = insulin glargine; LIXI = lixisenatide; LS = least squares; MD = mean difference; NR = not reported; RCT = randomized controlled trial; SD = standard deviation; SE = standard error; t.i.d. = three times daily.

Note: All efficacy outcomes are based on the modified intention-to-treat population.

Means and mean differences were analyzed using an analysis of covariance model with treatment groups (lixisenatide, insulin glulisine once daily, and insulin glulisine three times daily), randomization strata of screening A1C (< 8.0, ≥ 8.0%), randomization strata of metformin use at screening (yes, no), and country as fixed effects, and baseline A1C value as a covariate.

[a] Subgroup analyses were not adjusted for multiple statistical testing and were therefore considered exploratory.

Source: Rosenstock 2016[11] and GETGOAL – DUO 2 Clinical Study Report.[12]

Table 33: [redacted]

[redacted]	[redacted]		
	[redacted]	[redacted]	[redacted]
[redacted]			
[redacted]			
[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]
[redacted]			
[redacted]			
[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]
[redacted]		[redacted]	[redacted]
[redacted]			
[redacted]			
[redacted]	[redacted]	[redacted]	[redacted]

[redacted]	[redacted]		
	[redacted]	[redacted]	[redacted]
[redacted]			
[redacted]			
[redacted]			
[redacted]			
[redacted]			
[redacted]			
[redacted]			
[redacted]			

A1C = glycated hemoglobin; CI = confidence interval; IG = insulin glargine; LIXI = lixisenatide; LS = least square; MD = mean difference; NR = not reported; RCT = randomized controlled trial; SD = standard deviation; SE = standard error; t.i.d. = three times daily.

Note: All efficacy outcomes are based on the modified intention-to-treat population.

Means and mean differences were analyzed using an analysis of covariance model with treatment groups (lixisenatide, insulin glulisine once daily, and insulin glulisine three times daily), randomization strata of screening A1C (< 8.0, ≥ 8.0%), randomization strata of metformin use at screening (yes, no), and country as fixed effects, and baseline A1C value as a covariate.

[a] Subgroup analyses were not adjusted for multiple statistical testing and were therefore considered exploratory.

Source: Rosenstock 2016[11] and GETGOAL – DUO 2 Clinical Study Report.[12]

Table 34: [redacted]

[redacted]	[redacted]		
	[redacted]	[redacted]	[redacted]
[redacted]			
[redacted]			
[redacted]			
[redacted]			
[redacted]			
[redacted]			
[redacted]			
[redacted]			
[redacted]			
[redacted]			
[redacted]			
[redacted]			
[redacted]			
[redacted]			
[redacted]			
[redacted]			
[redacted]			

[redacted]	[redacted]		
	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]
[redacted]		[redacted]	[redacted]

A1C = glycated hemoglobin; CI = confidence interval; IG = insulin glargine; LIXI = lixisenatide; LS = least squares; MD = mean difference; NR = not reported; RCT = randomized controlled trial; SD = standard deviation; SE = standard error; t.i.d. = three times daily.

Note: All efficacy outcomes are based on the mITT population

Means and mean differences were analyzed using an ANCOVA model with treatment groups (lixisenatide, insulin glulisine once daily, and insulin glulisine three times daily), randomization strata of screening A1C (< 8.0, ≥ 8.0%), randomization strata of metformin use at screening (yes, no), and country as fixed effects, and baseline A1C value as a covariate.

[a] Subgroup analyses were not adjusted for multiple statistical testing and were therefore considered exploratory.

Source: Rosenstock 2016[11] and GETGOAL – DUO 2 Clinical Study Report.[12]

Table 35: [redacted]

[redacted]	[redacted]	[redacted]	[redacted]
[redacted]			
[redacted]			
[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]
[redacted]		[redacted]	[redacted]
[redacted]			
[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]
[redacted]		[redacted]	[redacted]
[redacted]			
[redacted]			
[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]
[redacted]		[redacted]	[redacted]
[redacted]			
[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]
[redacted]		[redacted]	[redacted]

A1C = glycated hemoglobin; CI = confidence interval; IG = insulin glargine; LIXI = lixisenatide; LS = least squares; MD = mean difference; NR = not reported; RCT = randomized controlled trial; SD = standard deviation; SE = standard error; t.i.d. = three times daily.

Note: All efficacy outcomes are based on the mITT population

Means and mean differences were analyzed using an analysis of covariance model with treatment groups (lixisenatide, insulin glulisine once daily, and insulin glulisine three times daily), randomization strata of screening A1C (< 8.0, ≥ 8.0%), randomization strata of metformin use at screening (yes, no), and country as fixed effects, and baseline A1C value as a covariate.

[a] Subgroup analyses were not adjusted for multiple statistical testing and were therefore considered exploratory.

Source: Rosenstock 2016[11] and GETGOAL – DUO 2 Clinical Study Report.[12]

Table 36:

A1C = glycated hemoglobin; CI = confidence interval; IG = insulin glargine; LIXI = lixisenatide; LS = least squares; MD = mean difference; NR = not reported; RCT = randomized controlled trial; SD = standard deviation; SE = standard error; t.i.d. = three times daily.

Note: All efficacy outcomes are based on the modified intention-to-treat population.

Means and mean differences were analyzed using an analysis of covariance model with treatment groups (lixisenatide, insulin glulisine once daily, and insulin glulisine three times daily), randomization strata of screening A1C (< 8.0, ≥ 8.0%), randomization strata of metformin use at screening (yes, no), and country as fixed effects, and baseline A1C value as a covariate.

[a] Subgroup analyses were not adjusted for multiple statistical testing and were therefore considered exploratory.

Source: Rosenstock 2016[11] and GETGOAL – DUO 2 Clinical Study Report.[12]

Table 37:

[redacted]	[redacted]		
	[redacted]	[redacted]	[redacted]
[redacted]			
[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]
[redacted]		[redacted]	[redacted]
[redacted]			
[redacted]			
[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]
[redacted]		[redacted]	[redacted]
[redacted]			
[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]
[redacted]		[redacted]	[redacted]

A1C = glycated hemoglobin; CI = confidence interval; IG = insulin glargine; LIXI = lixisenatide; LS = least squares; MD = mean difference; NR = not reported; RCT = randomized controlled trial; SD = standard deviation; SE = standard error; t.i.d. = three times daily.

Note: All efficacy outcomes are based on the modified intention-to-treat population.

Means and mean differences were analyzed using an analysis of covariance model with treatment groups (lixisenatide, insulin glulisine once daily, and insulin glulisine three times daily), randomization strata of screening A1C (< 8.0, ≥ 8.0%), randomization strata of metformin use at screening (yes, no), and country as fixed effects, and baseline A1C value as a covariate.

[a] Subgroup analyses were not adjusted for multiple statistical testing and were therefore considered exploratory.

Source: Rosenstock 2016[11] and GETGOAL – DUO 2 Clinical Study Report.[12]

Table 38: [redacted]

[redacted]	[redacted]		
	[redacted]	[redacted]	[redacted]
[redacted]			
[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]
[redacted]		[redacted]	[redacted]
[redacted]			
[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]
[redacted]		[redacted]	[redacted]
[redacted]			
[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]
[redacted]		[redacted]	[redacted]

[redacted]	[redacted]		
	[redacted]	[redacted]	[redacted]
[redacted]			
[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]
[redacted]		[redacted]	[redacted]

A1C = glycated hemoglobin; CI = confidence interval; IG = insulin glargine; LIXI = lixisenatide; LS = least squares; MD = mean difference; MMRM = mixed-effects models for repeated measures; NR = not reported; RCT = randomized controlled trial; SD = standard deviation; SE = standard error; t.i.d. = three times daily.

Note: All efficacy outcomes are based on the modified intention-to-treat population.

[a] Sensitivity analyses were not adjusted for multiple statistical testing and were therefore considered exploratory.

[b] MMRM with treatment groups (lixisenatide, insulin glulisine once daily, and insulin glulisine three times daily), visit, treatment-by-visit interaction, visit 7 (week 1) strata of A1C [< 8.0%, ≥ 8.0%], randomization strata of metformin use (yes, no), and country as fixed effects, and baseline A1C value and baseline A1C-by-visit interaction as covariates.

[c] Means and mean differences were analyzed using an analysis of covariance model with treatment groups (lixisenatide, insulin glulisine once daily, and insulin glulisine three times daily), randomization strata of screening A1C (< 8.0, ≥ 8.0%), randomization strata of metformin use at screening (yes, no), and country as fixed effects, and baseline A1C value as a covariate.

Source: Rosenstock 2016[11] and GETGOAL – DUO 2 Clinical Study Report.[12]

Appendix 5: Validity of Outcome Measures

Aim

To summarize the validity of the following outcome measure:

- Impact of Weight on Quality of Life–Lite questionnaire (IWQOL-Lite)

Findings

Impact of Weight on Quality of Life–Lite Questionnaire

Obesity is a major contributing factor to the impairment of quality of life among patients with diabetes, since an estimated 80% patients with type 2 diabetes mellitus also suffer from obesity, and 90% of newly diagnosed type 2 diabetes mellitus patients are overweight. The IWQOL-Lite, a shorter version of the full 74-item IWQOL questionnaire, is a self-administered, disease-specific tool designed to assess the effect of obesity on quality of life. This was developed by Kolotkin et al. after the length of the original version proved cumbersome for research subjects.[48] The IWQOL-Lite was reduced to 31 items that fall under five domains: physical function (11 items), self-esteem (seven items), sexual life (four items), public distress (five items), and work (four items). Each item has five response categories, ranging from “always true” to “never true.” Each category is assigned a score, with one being never true and five being always true.[48] The scores of all the items within a domain are added to provide the domain score, and the sum of scores from all five domains are added to provide the total score. The total score ranges from 0 to 100, with a higher score associated with a poorer quality of life.[48]

The impact of weight on quality of life and the psychometric properties of the IWQOL-Lite instrument among patients with diabetes were assessed by Kolotkin et al. IWQOL-Lite data from 1,197 individuals who are obese and seeking weight loss treatment and gastric bypass surgery in a clinical trial were collected, of which 225 had type 2 diabetes.[49] A number of statistical tests were done to assess the validity and reliability of the instrument. Internal consistency coefficient for the IWQOL-Lite total score using Cronbach’s alpha was calculated to be 0.981 and 0.980 for patients with diabetes and patients without diabetes, respectively, indicating excellent reliability.[49] Within the diabetic group, coefficients for the IWQOL-Lite scales/domains ranged from 0.843 (work) to 0.961 (physical function). Confirmatory factor analysis was done to test the scale structure and construct validity, and results showed comparable factor structure for both patients with diabetes and patients without diabetes with the second-order IWQOL-Lite model (items assigned to scales, and scales part of the higher order construct of weight-related quality of life). Moderate to strong correlations were found between BMI and IWQOL-Lite for both patients with diabetes and patients without diabetes, demonstrating construct validity.[49] Correlation coefficients ranged from –0.545 (sexual life) to –0.737 (public distress) for IWQOL-Lite scores and BMI, and 0.705 for IWQOL-Lite total score and BMI among patients with diabetes.[49] However, the IWQOL-Lite instrument and study had a few limitations. Even though previous studies have investigated the relationship between IWQOL-Lite scores and collateral measures such as the Short Form (36) Health Survey, Rosenberg self-esteem scale, Marlowe–Crowne social desirability scale, and global ratings, and have shown convergent and discriminant validity of this instrument, those studies were done in patients without diabetes.[48,50] However, this aspect of validity was not investigated in this study among patients with diabetes.

The absence of data on diabetic complications and comorbid conditions (diabetic retinopathy, peripheral vascular disease, coronary artery disease, peripheral sensory neuropathy, and depression), which are known to be associated with poorer health-related quality of life (HRQoL), is a limitation of this study. The IWQOL-Lite did not attempt to demonstrate discrimination in the weight-related quality of life between patients with and without diabetes. This study also did not provide a minimal clinically important difference for the IWQOL-Lite in patients with obesity and type 2 diabetes mellitus; however, in other conditions, a range of seven to 12 is typically found.[51]

Conclusion

The IWQOL-Lite is a self-administered questionnaire that is used to evaluate the effect of obesity on quality of life by measuring personal satisfaction in five key aspects of everyday life. Among patients with diabetes, this tool has demonstrated very high reliability. The individual domains and total score of the IWQOL-Lite have strong correlation with BMI, signifying construct validity. On the other hand, even though convergent and discriminant validity of this instrument is proven in other conditions, this has not been assessed in patients with diabetes. In addition, data showing correlation between IWQOL-Lite components and comorbidities associated with diabetes are lacking. A minimal clinically important difference for the IWQOL-Lite in patients with obesity and type 2 diabetes mellitus is not present, although a range of seven to 12 is considered acceptable in other conditions.[51]

Table 39: Validity and Minimal Clinically Important Difference of Outcome Measures

Instrument	Type	Evidence of Validity	MCID	References
IWQOL-Lite	IWQOL-Lite is a disease-specific tool to assess the impact of obesity on quality of life.	Yes	Unknown for diabetes; 7 to 12 for other conditions	[49]

IWQOL-Lite = Impact of Weight on Quality of Life–Lite questionnaire; MCID = minimal clinically important difference.

Appendix 6: Summary of the ELIXA Trial

Aim

The following section provides a summary and critical appraisal of the ELIXA trial (Evaluation of LIXisenatide in Acute coronary syndrome), which was designed to assess cardiovascular outcomes among patients with type 2 diabetes mellitus.[27]

Methods

Description of Study

The objective of this study was to evaluate the cardiovascular mortality and morbidity of lixisenatide among patients with type 2 diabetes mellitus who were at high cardiovascular risk due to a recent acute coronary event (myocardial infarction [MI] or unstable angina [UA]). The primary end point was defined as a composite of cardiovascular death, nonfatal MI, nonfatal stroke, or hospitalization for UA.

ELIXA was a randomized, double-blind, placebo-controlled, parallel-group, multi-centre, phase III, event-driven trial conducted in Canada and US, Central and South America and Mexico, Eastern Europe, Asia and Pacific islands, Africa, and Western Europe. Patients ages ≥ 30 years with type 2 diabetes mellitus who experienced an acute coronary event within 180 days before recruitment were identified following hospital admission, and then went through a screening process to assess eligibility. A one-week run-in period was conducted to train patients on self-administration of daily subcutaneous (SC) injection of unblinded placebo. Between 2010 and 2013, 6,068 lixisenatide-naive patients from 49 countries were enrolled and randomized using a centralized assignment system to receive SC injections of lixisenatide once daily or volume-matched placebo in a 1:1 double-blind manner in addition to locally determined standards of care. The median follow-up period for the patients was 25 months, which consisted of a two-week titration period at a dose of 10 mcg followed by a maintenance period at a dose of 20 mcg.

Populations

Inclusion and Exclusion Criteria

The inclusion and exclusion criteria for the patients are listed in Table 40.

Table 40: Inclusion and Exclusion Criteria of the ELIXA Trial

Inclusion Criteria	Exclusion Criteria
Spontaneous ACS (STEMI, non-STEMI, or UA)	Age < 30 years
• ACS presentation leading to acute care facility admission	Type 1 diabetes mellitus
• Increased cardiac biomarker (troponin or creatine kinase-MB) above ULN	History of metabolic acidosis
• ACS-related hospital admission within 180 days but later discharged	Use of other incretin-based therapies
History or newly diagnosed T2DM as defined by World Health Organization criteria: FPG ≥ 7.0 mmol/L or two-hour PPG ≥ 11.1 mmol/L on 2 separate occasions	Previous events of unexplained pancreatitis, chronic pancreatitis, pancreatectomy, stomach/gastric surgery, inflammatory bowel disease, personal or family history of medullary thyroid cancer, or genetic

Inclusion Criteria	Exclusion Criteria
	conditions that predispose to medullary thyroid cancer
	Percutaneous coronary intervention within 15 days, or coronary angiogram within 90 days post-screening or randomization
	Women who are or wish to be pregnant and lactating
	History of gastrointestinal disease resulting in prolonged nausea and vomiting
	Laboratory data at screening:
	• A1C < 5.5% or > 11.0%
	• Amylase and/or lipase > 3 × ULN
	• Calcitonin > 5.9 pmol/L
	• Alanine transaminase > 3 × ULN or total bilirubin > 1.5 × ULN
	• eGFR < 30 mL/min/1.73 m^2
	• Hemoglobin level < 6.21 mmol/L and/or neutrophils < 1500 cell/µL and/or platelets < 100,000/mm^3

ACS = acute coronary syndrome; eGFR = estimated glomerular filtration rate; FPG = fasting plasma glucose; PPG = postprandial glucose; pmol = picomole; STEMI = ST-segment elevation myocardial infarction; T2DM = type 2 diabetes mellitus; UA = unstable angina; ULN = upper limit of normal.
Source: ELIXA[27,52]

Baseline Characteristics

The patients had a mean age around 60 years, were mostly male (69.3%), white (75.2%), and overweight or obese (mean BMI just more than 30 kg/m^2). Patients had an average 9.3 years (8.25) of diabetes and a mean glycated hemoglobin (A1C) of 7.7% (1.30). The majority of patients were on statin (92.2%), Aspirin (94.4%), an angiotensin converting enzyme or angiotensin receptor blocker (84.9%), beta blocker (84.4%), thienopyridines (74.1%), and angiotensin converting enzyme inhibitor (60.3%). Of the 89.7% randomized patients who were on antidiabetic medications, 63.2% were on metformin and 37.8% were taking insulin. Baseline characteristics were similar in both treatment groups, including age, diabetes-related complications, medical and surgical history, and years of smoking for both current and past smokers. Details of patient baseline characteristics are summarized in Table 41.

Table 41: Summary of Baseline Characteristics

Characteristics	ELIXA	
	Placebo N = 3,034	**Lixisenatide N = 3,034**
Age, years, mean (SD)	60.6 (9.6)	59.9 (9.7)
Age ≥ 65 years, n (%)	1,040 (34.3)	1,003 (33.1)
Female, n (%)	938 (30.9)	923 (30.4)
Mean duration of diabetes, years (SD)	9.4 (8.3)	9.2 (8.2)
Mean glycated hemoglobin (A1C), (SD)	7.6 (1.3)	7.7 (1.3)
Diabetic retinopathy, n (%)	331 (10.9)	320 (10.5)
Diabetic neuropathy, n (%)	498 (16.4)	512 (16.9)
Mean body weight, kg (SD)	85.1 (19.6)	84.6 (19.2)
Mean BMI, kg/m^2 (SD)	30.2 (5.8)	30.1 (5.6)

Characteristics	ELIXA	
	Placebo N = 3,034	Lixisenatide N = 3,034
Race, n (%)[a]		
White	2,318 (76.4)	2,258 (74.4)
Hispanic ethnic group	903 (29.8)	865 (28.5)
Asian	367 (12.1)	404 (13.3)
Other	246 (8.1)	254 (8.4)
Black	103 (3.4)	118 (3.9)
Geographic region, n (%)[b]		
South or Central America	972 (32.0)	972 (32.0)
Eastern Europe	811 (26.7)	776 (25.6)
North America	403 (13.3)	404 (13.3)
Western America	377 (12.4)	354 (11.7)
Asia Pacific	329 (10.8)	374 (12.3)
Africa or near East	142 (4.7)	154 (5.1)
Current smoker, n (%)	354 (11.7)	355 (11.7)
Myocardial infarction before index ACS, n (%)	672 (22.1)	672 (22.1)
Medical history at randomization, n (%)		
Hypertension	2,340 (77.1)	2,295 (75.6)
Percutaneous coronary intervention	2,027 (66.8)	2,052 (67.6)
Heart failure	676 (22.3)	682 (22.5)
Coronary artery bypass grafting	249 (8.2)	258 (8.5)
Peripheral arterial disease	229 (7.5)	237 (7.8)
Stroke	188 (6.2)	143 (4.7)
Atrial fibrillation	190 (6.3)	176 (5.8)
Mean SBP, mm Hg (SD)	130 (17)	129 (17)
Mean heart rate, beats/min (SD)	70.2 (9.9)	70.2 (10.1)
Mean HDL cholesterol, mmol/L (SD)	2.3 (10.9)	2.3 (10.8)
Mean LDL cholesterol, mmol/L (SD)	4.3 (35.2)	4.3 (35.4)
Mean eGFR, mL/min/1.73 m^2) (SD)	75.2 (21.4)	76.7 (21.3)
Qualifying ACS event, n (%)		
STEMI	1,317 (43.4)	1,349 (44.5)
Non-STEMI	1,183 (39.0)	1,165 (38.4)
Unstable angina	528 (17.4)	514 (16.9)
Unclassified	6 (0.2)	6 (0.2)
Mean days from ACS to randomization (SD)	72.2 (43.9)	71.8 (43.4)
Ratio of urinary albumin to creatinine[c]		
Median (interquartile range)	10.5 (6.0 to 33.6)	10.2 (6.0 to 29.6)

ACS = acute coronary syndrome; eGFR = estimated glomerular filtration rate; HDL = High-density lipoprotein; LDL = Low-density lipoprotein; SBP = systolic blood pressure; STEMI = ST-segment elevation myocardial infarction; SD = standard deviation.

[a, b] Race and ethnic group were self-reported.

[c] Albumin measured in milligrams and creatinine in grams.

Source: ELIXA.[27]

Interventions and Comparators

Patients in the treatment group received an SC injection of lixisenatide once daily following randomization, with a starting dose of 10 mcg per day during the first two weeks, which was up- or down-titrated to a maximum of 20 mcg per day depending on safety and tolerability. Patients in the control group received a volume-matched placebo. A pen-type injector was used to self-inject the assigned treatments one hour before breakfast; however, it was allowed to be administered one hour before dinner if the investigators deemed better management of adverse events (AEs) and/or suitability for the patients' daily schedule by changing the dosage time. Both groups also received standard care for glycemic control per local clinical practice guidelines managed by the site investigators. Standard of care involved adjustment of glucose-lowering agents or the addition of antidiabetic medications other than prandial glucagon-like peptide-1 (GLP-1) receptor agonists or dipeptidyl peptidase-4 (DPP-4) inhibitors in order to achieve similar glycemic control in the two study groups. Of note, patients on basal insulin had a 20% decrease in their total dose.

Outcomes

Efficacy

All efficacy and safety outcomes were adjudicated by separate committees blinded to the treatment status of the patients. The primary end point was time to first occurrence of any of the following:

- death from cardiovascular causes, which can result from fatal MI resulting in death within 14 days, MI or complications related to heart failure (HF) including device failure, inconclusive death following a recent acute infarct, sudden death in otherwise stable subjects, fatal stroke, fatal pulmonary embolism, procedure-related death, or other cardiovascular-related death (cardiovascular deaths were distinguished from non-cardiovascular deaths, which were classified as a result of infection, malignancy, pulmonary, gastrointestinal, renal, accidental, suicidal, diabetes-related, and other causes)
- nonfatal MI; criteria for positive adjudication of MI were classified in three groups: spontaneous MI (elevated cardiac markers [CM] such as troponin or creatine kinase-MB > upper limit of normal (ULN), and either changes in ECG or clinical presentations of MI such as pain, dyspnea, and pressure), percutaneous coronary intervention-related MI within 48 hours of the procedure (CM 3 × > ULN), and coronary artery bypass graft–related MI within 72 hours of the procedure (elevated CM 5 × >ULN and new ECG changes)
- nonfatal stroke, where stroke was classified and defined as: ischemic stroke with or without hemorrhagic transformation confirmed by imaging, stroke with intracranial hemorrhage not due to a transformation of an ischemic stroke, or unknown from imaging
- hospitalization for UA, either due to worsening angina presented as pain, dyspnea, and pressure, or elevation in CMs indicative of myocardial injury but not MI

The secondary outcomes were composite of any of the following:

- the primary end points or hospitalization for HF, where HF was defined by symptoms (worsening dyspnea, orthopnea, paroxysmal nocturnal dyspnea, increasing fatigue), signs (rapid weight gain, pulmonary edema or rales, elevated jugular venous pressure, radiologic signs, peripheral edema, increasing abdominal distension or

ascites, S3 gallop, hepatojugular reflux/hepatomegaly, elevated B-type brain natriuretic peptide [BNP] or N-terminal pro b-type natriuretic peptide [NT-proBNP]), and treatments (intravenous diuretics, vasodilators or inotropes, mechanical fluid removal with ultrafiltration or dialysis, insertion of an intra-aortic balloon pump for hemodynamic compromise, initiation of oral diuretics or intensification of the maintenance oral diuretic dose)

- the primary end points, hospitalization for HF, or coronary revascularization procedures, where coronary revascularization was defined as any percutaneous coronary intervention or coronary artery bypass grafting for the management of acute coronary syndrome (ACS) either urgently or non-urgently
- ratio of urinary albumin to creatinine, measured by averaging two first-morning urine samples, one collected at week 0, week 24, week 76, week 108, and at the end-of-study visit, and the other before the day of each study visit

A number of additional end points were also measured, including: all-cause mortality, rates of the components of each of the composite end points, changes in the A1C level, body weight, and cardiometabolic biomarkers (e.g., A1C, fasting blood glucose [FPG], C-reactive protein, BNP, and NT-proBNP).

Harms

Measures of AEs included incidence of:

- hypoglycemia (symptomatic, blood glucose < 3.3 mmol/L, symptoms subsided after treatment) and severe hypoglycemia (symptomatic hypoglycemia requiring assistance, blood glucose < 2.0 mmol/L, symptoms subsided after treatment)
- any AEs
- laboratory measures:
  - serum chemistry: liver function (alanine aminotransferases, aspartate aminotransferases, alkaline phosphatase, total bilirubin), lipid parameters (total cholesterol, high-density lipoprotein cholesterol, low-density lipoprotein cholesterol, triglycerides), renal functions (creatinine, estimated glomerular filtration rate, blood urea nitrogen), neutropenia, thrombocytopenia, acute renal insufficiency, calcitonin, pancreatic enzymes (serum amylase and lipase), and electrolytes (sodium, potassium, chloride, calcium, phosphorus, bicarbonates)
- vital signs: heart rate, blood pressure
- pancreatitis
- any cancer, especially pancreatic neoplasms

Statistical Analysis

Data for demographic, medical and treatment history were collected and summarized by treatment group. All efficacy outcomes were analyzed using the intention-to-treat (ITT) population, which was defined as all patients according to their treatment status following randomization, regardless of treatment adherence or compliance. The comparative efficacy of lixisenatide and placebo for the primary and secondary outcomes were analyzed using Cox proportional hazards model adjusted for treatment groups and geographic region. Additionally, treatment effect for the primary composite end point was calculated by the following subgroups: gender, age, race, region, duration of diabetes, index ACS events, duration between ACS event and randomization, percutaneous coronary intervention post–ACS event and pre-screening, baseline A1C, BMI, and intake of antihypertension medications. For the primary and secondary outcomes, noninferiority of lixisenatide

compared with placebo was met if the upper boundary of the 95% confidence interval (CI) of the hazard ratio was less than 1.3 as recommended by the FDA. Superiority was met if the upper boundary of the 95% CI of the hazard ratio was less than 1.0. The cumulative incidence rate shown by Kaplan–Meier plots was used to depict the onset of primary and secondary cardiovascular outcomes over time. In addition to the composite measures, the time to first occurrence of each individual component of the primary and secondary cardiovascular end points were analyzed with the same adjusted Cox model, and Kaplan–Meier plots were generated similarly. Patients were followed-up to the end of the study period or death — whichever occurred first — regardless of treatment status. Unless otherwise specified, any cardiovascular end points that occurred after the study end date were not considered in the primary analyses. Among the patients, those without any of the primary cardiovascular outcomes by the end of the study period or until the last date with available information since randomization were considered right-censored observations.

In order to detect albuminuria over time, changes in ratio of urinary albumin to creatinine between the lixisenatide and placebo groups were analyzed from baseline to week 108 at different time points using an analysis of covariance (ANCOVA) model with treatment, region, baseline intake of angiotensin converting enzyme inhibitors and angiotensin receptor blockers as fixed effects and baseline ratio of urinary albumin to creatinine as a covariate. The last observation carried forward (LOCF) method was used to impute missing values for those with no information at week 108. The ratio was log-transformed, which was then back-transformed to provide per cent change based on geometric means as well as the corresponding 95% CI and *P* value. No formal testing was done for other end points such as FPG, A1C, and body weight; they were simply summarized using descriptive statistics.

The safety outcomes were analyzed using the safety population, which comprised any randomized patient who received at least one dose of either lixisenatide or placebo, or, for those who received both treatments, whichever was administered for the longest period. The on-treatment period was determined by the starting day of treatment up to three days after the last treatment. Safety assessment was performed in three time periods: the pre-treatment period consisting of time to informed consent up to first administration of treatment, the on-treatment period from the time to randomization up to three days after the last treatment dose received, and the post-treatment period following the on-treatment period starting four days after the last administration of treatment. The analyses were primarily focused on the on-treatment period. The summary of AE data was done by treatment group and organ class, using counts and percentages.

Multiplicity adjustment was in place to control for family-wise type I error rate using a hierarchical step-down procedure between the primary and secondary efficacy outcomes. If superiority for the primary composite end point was demonstrated using a one-sided alpha value of 0.025, the secondary end points were analyzed in the following order: time to first occurrence of any of the primary outcomes in addition to hospitalization for HF, per cent change in the ratio of albumin to creatinine, and time to first occurrence of any of the primary outcomes in addition to hospitalization for HF and coronary revascularization procedure. If the primary composite cardiovascular end point demonstrated superiority of lixisenatide over placebo, the secondary composite cardiovascular end points were claimed to be statistically significant at the upper bound of the 95% CI, otherwise they were not. The other secondary efficacy variables were not adjusted for multiple comparisons.

The sample size calculation estimated that 6,000 patients would need to be accrued to observe 844 primary outcomes assuming a 10% yearly event rate for the first year and a

7% yearly event rate thereafter (no rationale provided), which would provide the study 96% power to detect noninferiority and 90% power to detect superiority over placebo, assuming a true hazard ratio of 1.0 and 0.80, respectively.

A number of pre-specified sensitivity analyses were conducted. In order to test the robustness of the result obtained from the Cox model, sensitivity analyses were performed to analyze the primary composite end point using two additional methods: the Mantel–Haenszel method, and the exact method of assuming Poisson distribution to estimate the relative risk ratio and the associated 95% CI of lixisenatide over placebo. Another sensitivity analysis was conducted by excluding patients who had had the primary composite events 30 days after the discontinuation of lixisenatide or placebo (i.e., data from the on-treatment period only). The effect of potentially inaccurately adjudicating cardiovascular events was tested using two additional sensitivity analyses: one where all unknown deaths were imputed as cardiovascular deaths, and another where any cardiovascular events — including cardiovascular deaths as adjudicated by the local investigator, but not AEs adjudicated by the central committee — were included. Finally, an ad hoc Cox proportional hazards analysis adjusting for nominally significant baseline variables (age, estimated glomerular filtration rate, A1C, and previous stroke) was also conducted.

Patient Disposition

A total of 7,719 patients were screened for participation in the ELIXA trial in 828 centres. Of this, 92 patients failed during the screening period before run-in, and 1,559 failed during the run-in period before randomization. The reasons for failure were based on study exclusion criteria described previously. A total of 6,068 patients were randomized, 3,034 in each treatment group. All patients with the exception of five (three patients in the lixisenatide group and two in the placebo group) received at least one dose of medication they were assigned to; however, they were included in the ITT population. Five sites were closed due to non-compliance; however, the 11 patients from these sites were also included in the ITT population. More than 96% of patients who were randomized completed the study in both groups, which included around 7% patients who died during the study period (7.3% in the placebo and 6.8% in the lixisenatide group). The study discontinuation rate was comparable between the two groups; however, the treatment discontinuation rate was high in both groups, and more patients in the lixisenatide group discontinued treatment, citing AEs as the most common cause. Median follow-up period and number of patients lost to follow-up were similar in both groups. Table 42 summarizes the patient disposition data.

Table 42: Patient Disposition

Characteristics	ELIXA	
	Placebo (N = 3,034)	Lixisenatide (N = 3,034)
[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]

Characteristics	ELIXA	
	Placebo (N = 3,034)	Lixisenatide (N = 3,034)
[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]

ITT = Intention-to-treat.

[a] Including patients who took the medication on the day of their death, 51 for lixisenatide and 41 in placebo.

Source: ELIXA CSR[53]

Exposure to Study Treatments

[redacted] Details on patients' treatment duration and exposure are provided in Table 43.

Table 43: Exposure Dose and Duration

Exposure	ELIXA	[redacted]
Final dose of treatment, n (%)		
5 mcg	[redacted]	[redacted]
10 mcg	[redacted]	[redacted]
15 mcg	[redacted]	[redacted]
20 mcg	[redacted]	[redacted]
30 mcg	[redacted]	[redacted]
40 mcg	[redacted]	[redacted]
Duration of study treatment, days		
Mean, days (SD)	[redacted]	[redacted]
Median, days (min, max)	[redacted]	[redacted]
Cumulative duration of treatment exposure, patient years	[redacted]	[redacted]

Source: ELIXA Clinical Study Report.[53]

Critical Appraisal

Internal Validity

Patients were randomized to receive lixisenatide or placebo using a centralized assignment system. The demographic and other baseline characteristics were mostly balanced between the groups, including medical, surgical, metabolic, prior or concomitant medication history, and disease characteristics. Statistical differences seen for a few baseline variables were not clinically meaningful. Therefore, randomization appears to be successful.

Placebo was volume-matched with lixisenatide, ensuring blindness of treatment on patients' part. [redacted] The study outcomes were predefined and in compliance with regular clinical practice, therefore reducing the risk of misclassification. Adjudication of cardiovascular, pancreatic and allergic events was done by independent committee members blinded of the patients' treatment status. A separate data and safety monitoring committee had access to unblinded data and performed two interim analyses in order to rule out excess CV risk for lixisenatide compared with placebo following 122 and 300 positively adjudicated primary end points.

The first preliminary analysis was done to inform the executive team and sponsors of the noninferiority of lixisenatide compared with placebo if the upper boundary of the 96% CI of the hazard ratio was less than 1.8. The distinct noninferiority and CI margin were chosen to control for type I error and to meet New Drug Application submission with the FDA. The second interim analysis was done only if the 1.8 criterion had not been met in the first interim analysis. The statistical analysis procedure using Cox and ANCOVA model was appropriate for time to event data and continuous outcomes, respectively, accounting for confounders. The main result of no significant differences in rates of cardiovascular events by lixisenatide as an add-on to conventional therapies was robust following a number of sensitivity analyses which tested the appropriateness of the Cox model, adequacy of follow-up period, and effect of baseline imbalances. [redacted]

[redacted]Further, using the LOCF method to impute missing data may have biased the results in favour of noninferiority.

In order to control for family-wise type I error rate, a stepwise hierarchical testing order was established whereby time to first occurrence of any of the primary efficacy end points was analyzed first, followed by a number of secondary outcomes only if superiority of the primary end point was established at 0.05 alpha. Since the primary end point did not show superiority in favour of lixisenatide, the results of the secondary efficacy analyses were presented without any reference to statistical significance as established a priori. Imputation of missing values was done using the LOCF method. Analyses of the efficacy end points were done using the ITT population, which was defined as all randomized patients who received at least one dose of either lixisenatide or placebo, therefore preventing the effect of non-compliance in the results. The follow-up period of around 25 months was relatively longer involving an antidiabetic medication.

Of the 6,063 patients who were enrolled and received at least one dose of lixisenatide or placebo, rate of completion of study for 25 months was high in both groups (approximately 96%). Five patients did not receive the intended treatment they were assigned to, and vital status could not be ascertained in around 1% of patients in each group; therefore, it is unlikely to affect the results. In addition, the treatment compliance rate for the majority (94.3% for lixisenatide and 95.9% for placebo) of patients was high (80% to 100%); therefore, bias due to attrition or non-compliance is not of concern here.

The distributions of all cardiovascular end points were similar in both groups, including deaths from any cardiovascular and non-cardiovascular causes. AEs occurred at a higher frequency in the lixisenatide group and were mostly gastrointestinal in nature. This was reflected by the higher withdrawal rate in the lixisenatide group. GLP-1 agonists are commonly associated with gastrointestinal side effects, so these results are expected though they may compromise the blinding; however, since the patients were lixisenatide-naive, this is less likely to cause any bias.

External Validity

Patients in the ELIXA trial had a higher than normal cardiovascular risk, as they recently had a major ACS event. Data from wide demographic and clinical characteristics in the participating patients ensured representativeness and generalizability of the results. Notably, the study was done in six geographic regions across the world and included several race groups. In addition, a wide distribution in sex, BMI, smoking status, cardiovascular and renal disease history, and other confounding variables were included, extending the generalizability. Concomitant antihypertensive and antidiabetic that patients were on represent standard care practice.

Results

Cardiovascular End Points

Primary End Points

A total of 805 patients had the primary end point, which resulted in more than 95% and 88% power for the test of noninferiority and superiority, respectively. The primary composite end point (composite of death from cardiovascular causes, nonfatal MI, nonfatal stroke, or hospitalization for UA) occurred in 406 (13.4%) patients in the lixisenatide group and 399 (13.2%) patients in the placebo group, which translated to an adjusted hazard ratio of 1.02 (95% CI, 0.89 to 1.17), $P = 0.81$. Since the upper boundary of the 95% CI was less than 1.3

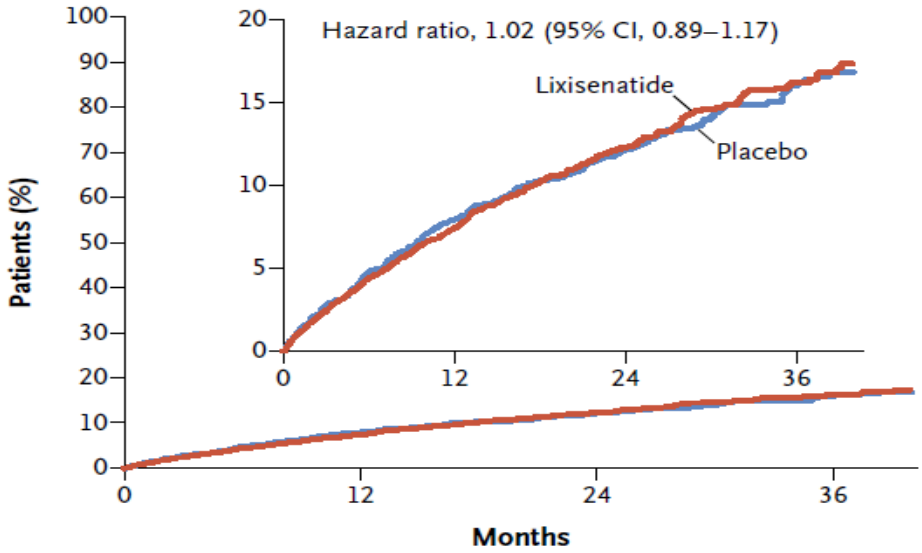
but not 1.0, the noninferiority of lixisenatide to placebo was proven ($P < 0.001$), but not superiority. The Kaplan–Meier plot shown in Figure 5 also showed no significant difference between the two treatment groups in time to event occurrence ($P = 0.81$). The incidence rate and adjusted hazard ratios for the primary end point, its components, and secondary end points are given in Table 44. Similar to the primary end point, there were no statistically significant differences in the adjusted hazard ratios of the individual components of primary end point between the two groups. However, the upper boundary of the 95% CIs of only death from cardiovascular causes and MI were below the noninferiority margin of 1.3; the other two were not, indicating the noninferiority result was mostly driven by the first two components of the composite primary end point. This could also be explained by the higher frequency of cardiovascular-related death and MI in the two study groups; however, the numbers were not strikingly different between the groups.

Table 44: Results for the Primary and Secondary Composite End Points, Its Individual Components, and Other Efficacy Outcomes

End Point	Placebo (N = 3,034)	Lixisenatide (N = 3,034)	Adjusted Hazard Ratio (95% CI)	*P* Value
Primary end point: death from CV causes, nonfatal stroke, nonfatal MI, or UA, n (%)	399 (13.2)	406 (13.4)	1.02 (0.89 to 1.17)	0.81
Patients with each primary end point event [a], n (%)				
Death from cardiovascular causes	158 (5.2)	156 (5.1)	0.98 (0.78 to 1.22)	0.85
MI	261 (8.6)	270 (8.9)	1.03 (0.87 to 1.22)	0.71
Stroke	60 (2.0)	67 (2.2)	1.12 (0.79 to 1.58)	0.54
UA	10 (0.3)	11 (0.4)	1.11 (0.47 to 2.62)	0.81
Secondary end points, n (%)				
Primary end point event, or hospitalization for HF	469 (15.5)	456 (15.0)	0.97 (0.85 to 1.10)	0.63
Primary end point, hospitalization for HF, or revascularization	659 (21.7)	661 (21.8)	1.00 (0.90 to 1.11)	0.96
Additional end points, n (%)				
Hospitalization for HF	127 (4.2)	122 (4.0)	0.96 (0.75 to 1.23)	0.75
Death from any cause	223 (7.4)	211 (7.0)	0.94 (0.78 to 1.13)	0.50

CI = confidence interval; CV = cardiovascular; HF = heart failure; MI = myocardial infarction; UA = unstable angina.
[a] Some patients had more than one component of the primary end point, and the numbers indicate the frequency of each individual component event, regardless of whether it was their first event.
Source: ELIXA.[27]

Figure 5: Kaplan–Meier Plot of the First Diagnosed Primary Composite End Point



Note: The inset shows the same data on an enlarged Y axis.
Source: From the New England Journal of Medicine, Pfeffer MA, Claggett B, Diaz R, Dickstein K, Gerstein HC, Kober LV, et al. Lixisenatide in patients with type 2 diabetes and acute coronary syndrome, volume 373(23), pages 2247-57, Copyright © (2017) Massachusetts Medical Society. Reprinted with permission from Massachusetts Medical Society.[27] CADTH does not own this work and permission should be sought from the copyright owner.

Subgroup Analyses

The results of the primary composite cardiovascular end point analyses showed consistency between treatment groups across all predefined and post-hoc subgroups, as shown in Figure 6. Although some heterogeneity was seen across geographic regions, the 95% CIs were overlapping and crossed unity.

Figure 6: Forest Plot for Analysis of the Primary Cardiovascular End Point by Subgroups

FIGURE CONTAINED CONFIDENTIAL INFORMATION AND WAS REDACTED AT THE REQUEST OF THE MANUFACTURER

Source: ELIXA Clinical Study Report.[53]

Sensitivity Analyses

[redacted]

[redacted]

Table 45: Sensitivity Analyses for the Primary Composite End Point

[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]

CI = confidence interval; HR = hazard ratio.
[a] One-sided *P* value corresponding to test of HR ≥ 1.3 versus HR < 1.3.
[b] Post-hoc adjustment for age, estimated glomerular filtration rate, glycated hemoglobin, and history of stroke.
Source: ELIXA CSR[53]

Secondary End Points

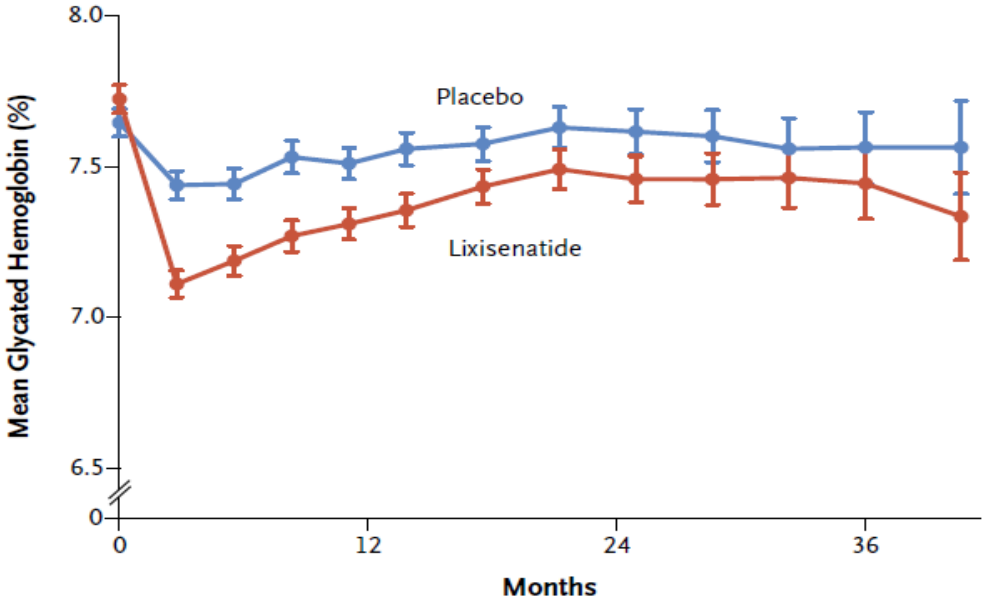
The secondary outcomes included the addition of hospitalization for HF and coronary revascularization to the primary composite end point, and neither showed no statistically significant differences in the hazard ratios between the two groups (0.97 [95% CI, 0.85 to 1.10], and 1.00 [95% CI, 0.90 to 1.11], respectively). Separate hazard ratios for hospitalization due to HF (0.96 [95% CI, 0.75 to 1.23]) and death from any causes (0.94 [95% CI, 0.78 to 1.13]) also showed no statistically significant difference between the two groups. Analysis of all deaths irrespective of causes showed no imbalance between the groups (hazard ratio: 0.937 [95% CI, 0.78 to 1.13]). Even though noninferiority margin was not pre-specified for the secondary outcomes, the upper limits of the 95% CIs were less than 1.3 in all cases. Details of these results are given in Table 44.

Clinical and Metabolic Effects

Glycated Hemoglobin

Even though the management of diabetes was not the main purpose of the trial, it was shown that treatment with lixisenatide led to a statistically significant reduction in mean A1C level compared with placebo (–0.6% versus –0.2%; $P < 0.001$), and the adjusted between-group differences of –0.27% (95% CI, –0.31 to –0.22), $P < 0.001$, was consistent throughout the total follow-up period, as shown in Figure 7. There were more hypoglycemic events in the lixisenatide group (16.6%) than the placebo group (15.2%), but the number of serious hypoglycemic episodes was lower in the lixisenatide group (16 reported events from 14 patients) compared with the placebo group (37 reported events from 24 patients).

Figure 7: Mean Change in A1C Level from Baseline to End of Study Visit

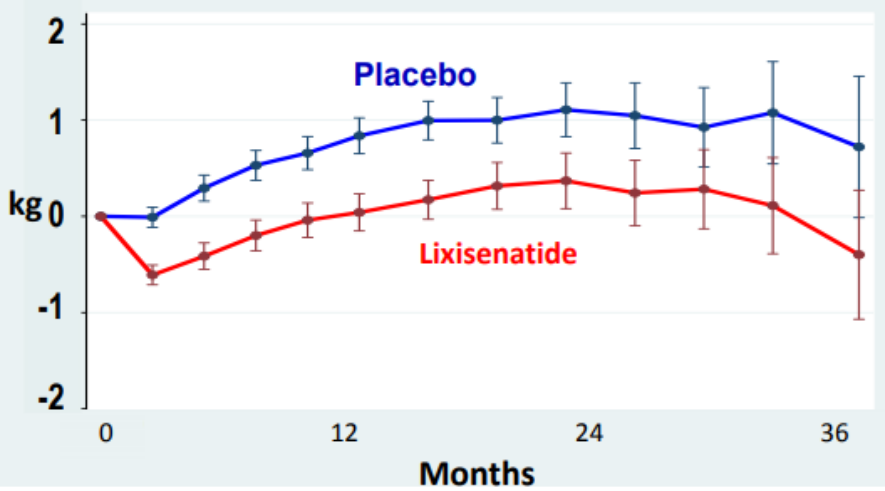


Source: From the New England Journal of Medicine, Pfeffer MA, Claggett B, Diaz R, Dickstein K, Gerstein HC, Kober LV, et al. Lixisenatide in patients with type 2 diabetes and acute coronary syndrome, volume 373(23), pages 2247-57, Copyright © (2017) Massachusetts Medical Society. Reprinted with permission from Massachusetts Medical Society.[27] CADTH does not own this work and permission should be sought from the copyright owner.

Change in Body Weight

Lixisenatide was associated with a small but significant change in body weight at 12 weeks, which then returned to the baseline level (mean change –0.6 kg in the lixisenatide group versus 0.0 kg in the placebo group, $P < 0.001$), and the average between-group difference of –0.7 (95% CI, –0.9 to –0.5), $P < 0.001$, in change in body weight was also consistent throughout the duration of the study, as shown Figure 8.

Figure 8: Mean Change in Body Weight Across Study Visits

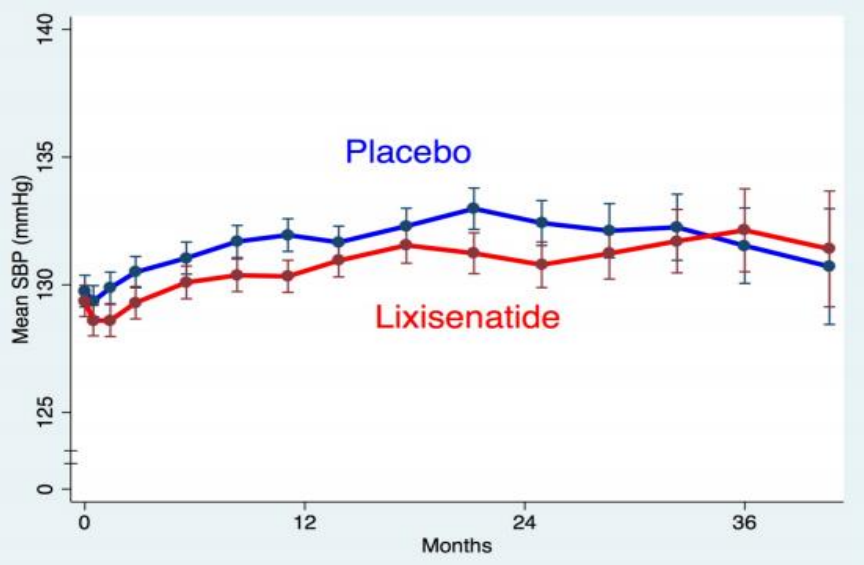


Source: From the New England Journal of Medicine, Pfeffer MA, Claggett B, Diaz R, Dickstein K, Gerstein HC, Kober LV, et al. Lixisenatide in patients with type 2 diabetes and acute coronary syndrome, volume 373(23), pages 2247-57, Copyright © (2017) Massachusetts Medical Society. Reprinted with permission from Massachusetts Medical Society [27] CADTH does not own this work and permission should be sought from the copyright owner.

Blood Pressure and Heart Rate

Lixisenatide was associated with a small average difference of –0.8 mm Hg (95% CI, –1.3 to –0.3) in systolic blood pressure throughout the follow-up period except at the later time points, which was statistically significant (*P* = 0.001), as shown in Figure 6. Heart rate also showed a small improvement in the lixisenatide group (on average 0.4 more beats per minute [95% CI, 0.1 to 0.6]) than placebo (*P* = 0.01).

Figure 9: Average Change in Systolic Blood Pressure Across Study Visits



SBP = systolic blood pressure.
Source: From the New England Journal of Medicine, Pfeffer MA, Claggett B, Diaz R, Dickstein K, Gerstein HC, Kober LV, et al. Lixisenatide in patients with type 2 diabetes and acute coronary syndrome, volume 373(23), pages 2247-57, Copyright © (2017) Massachusetts Medical Society. Reprinted with permission from Massachusetts Medical Society.[27] CADTH does not own this work and permission should be sought from the copyright owner.

Ratio of Urinary Albumin to Creatinine

The median ratio of urinary albumin to creatinine increased over time for both study groups. Even though there was a modest difference in the ratio of urinary albumin to creatinine in favour of lixisenatide over placebo (24% versus 34%, *P* = 0.004) from baseline to month 24, the median values at baseline, month 6, month 18, and month 24 were clinically similar, and post-hoc adjustment of A1C attenuated the difference (26% versus 32%, *P* = 0.07), as described in Table 46.

Table 46: Ratio of Urinary Albumin to Creatinine Between Treatment Groups

	Placebo (N = 2,803)	Lixisenatide (N = 2,803)	*P* Values
Baseline[a]	10.4 (5.9 to 32.6)	10.0 (6.0 to 28.0)	
Month 6	11.5 (6.1 to 39.3)	10.2 (6.0 to 30.3)	< 0.01
Month 18	12.5 (6.4 to 48.2)	11.1 (6.1 to 36.4)	< 0.01
Month 24[b]	13.4 (6.4 to 53.2)	11.9 (6.2 to 42.2)	< 0.01
% change (baseline to month 24)[c]	+34% (28% to 40%)	+24% (19% to 30%)	0.004
% change (baseline to month 24)[d]	+32% (26% to 38%)	+26% (20% to 31%)	0.07

[a] Among patients with baseline and at least one follow-up value.
[b] Last post-baseline observation carried forward.
[c] Pre-specified model, adjusting for baseline, treatment, region, and baseline use of angiotensin converting enzyme inhibitors and angiotensin receptor blockers.
[d] Post-hoc adjustment for both baseline and three-month glycated hemoglobin levels, *P* = 0.07.
Source: ELIXA.[27]

Harms

Adverse Events

[redacted] the frequency of SAEs was less in this group (20.6% versus 22.1% in the lixisenatide and placebo group, respectively). [redacted] Among the patients who received lixisenatide, 11.4% discontinued the treatment permanently, whereas this number was significantly different ($P < 0.001$) in the placebo group, 7.2%. [redacted] Table 47 lists the safety end points reported in the study.

Table 47: Treatment Emergent Adverse Events

Frequency of AEs, n (%)	Placebo (N = 3,032)	Lixisenatide (N = 3,031)
Patients with any AE	[redacted]	[redacted]
Patients with any SAE	669 (22.1)	625 (20.6)
Patients with any AE leading to death	[redacted]	[redacted]
Patients with WDAE	217 (7.2)	347 (11.4)
Most common AEs during the on-treatment period (incidence ≥ 5%)		
[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]
Notable harms		
[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]

Frequency of AEs, n (%)	Placebo (N = 3,032)	Lixisenatide (N = 3,031)
SAEs by affected organ class		
[redacted]		

AE = adverse event; SAE = serious adverse event; WDAE = withdrawal due to adverse event.

[a] Symptomatic hypoglycemia defined as plasma glucose value < 3.3 mmol/L.

[b] Severe symptomatic hypoglycemia defined as plasma glucose value < 2 mmol/L.

Source: ELIXA[27] and ELIXA Clinical Study Report.[53]

Discussion

In response to the FDA requirement of evaluating cardiovascular safety of antidiabetic drugs in 2008, the ELIXA trial was designed to investigate the long-term effect of lixisenatide compared with placebo on cardiovascular morbidity and mortality. This study therefore recruited patients with type 2 diabetes mellitus who recently experienced a spontaneous ACS event and were therefore at risk of a recurring cardiovascular event. Per FDA guideline, the cardiovascular safety of lixisenatide would be established if the upper bound of the two-sided 95% CI was less than the pre-specified upper bound of 1.3 for the efficacy end points; an upper bound less than 1.0 would indicate superiority. The primary end point was a composite of cardiovascular death, nonfatal MI, nonfatal stroke, or hospitalization for UA. Secondary end points were a combination of hospitalization for HF or revascularization added to the primary end point. With a sample size of 6,068 patients, of which 805 had the

primary end points, the study had a 95% power to detect noninferiority and more than 88% power to detect superiority. The median follow-up was 25.8 months.

None of the primary or secondary composite end points and their individual components showed significant change in hazard ratio between lixisenatide and placebo, and the upper bounds of the 95% CIs were within the pre-specified cut-off of 1.3 but not 1.0, indicating noninferiority of lixisenatide compared with placebo, but not superiority. This finding was concordant with a similar trial where DPP-4 inhibitors, saxagliptin, and alogliptin also showed noninferiority but not superiority to placebo as an add-on therapy to background antidiabetic medications. The vast majority of ELIXA patients also received concomitant cardiovascular medications, including beta blockers, statins, and platelet aggregation inhibitors, which may partially explain similar results in both groups. Similarly, a decrease in A1C was seen in both the lixisenatide and placebo group as both groups received up-titration or addition of other glucose-lowering agents in order to achieve glycemic control, although the decrease was significantly greater for lixisenatide. The safety profile of lixisenatide was consistent with previous studies, with no unexpected increase in AEs, particularly pancreatitis, pancreatic neoplasm, severe symptomatic hypoglycemia, or hospitalization due to HF. The majority of AEs were of gastrointestinal nature and mild to moderate in severity. The distribution of cardiovascular death, SAEs (notably cardiac arrhythmia, allergic reaction, pancreatitis, pancreatic cancer, thyroid cancer, lung cancer, renal impairment, and gastrointestinal disorders), and symptomatic hypoglycemia were comparable between the two groups.

Conclusion

Among patients with high cardiovascular risk as determined by recent cardiovascular event that required hospitalization, once-daily SC injection of 20 mcg lixisenatide as an add-on therapy to background antidiabetic medications for 25 months was noninferior to placebo for the composite occurrence of cardiovascular death, nonfatal MI, nonfatal stroke, hospitalization for UA or HF, and revascularization. Lixisenatide was associated with an improvement in A1C, and body weight remained unchanged; however, the differences are not considered clinically meaningful. Safety end points showed similar risk of overall rates of AEs in lixisenatide compared with placebo.

This study provided data for cardiovascular safety of lixisenatide with long-term use. Strengths of the study include robust design features (randomization; blinding; relatively low study attrition rate; and appropriately chosen, defined and measured efficacy and safety outcomes), long follow-up period, and a sound statistical analytic procedure.

Appendix 7: Summary of GETGOAL – O

Aim

The following section provides a summary and critical appraisal of the GETGOAL – O trial,[29] which was designed to evaluate the level of glycemic control among older patients with type 2 diabetes by measuring change in glycated hemoglobin (A1C).

Methods

Description of Study

GETGOAL – O was a phase III, randomized, double-blind, placebo-controlled, two-arm, parallel-group, multinational and multi-centre trial. The trial was designed to investigate the efficacy and safety of lixisenatide among patients ages ≥ 70 years from 73 centres in 13 countries (Canada, US, Australia, Peru, South Africa, and several Western European countries) who were not frail, had type 2 diabetes mellitus, and presented with commonly found clinical characteristics in the geriatric population, e.g., long-standing diabetes, on multiple antidiabetic treatments, renal impairment, polypharmacy, hypoglycemia, and unawareness of hypoglycemia. Patients were recruited through a seven-week screening period, comprising a three-week screening phase followed by a four-week run-in phase.

During the run-in phase, patients were trained on monitoring of blood glucose and injection of placebo, reporting of adverse events (AEs) and concomitant medications, hypoglycemia awareness, and management of symptoms typically presented in older patients. Following the run-in phase, eligible patients — as determined by their week-1 A1C level (< 7% and ≤ 10%) and ability to adhere to study protocol — were randomized in a 1:1 manner to receive lixisenatide or placebo once daily in the morning. The randomization was done using an interactive voice/Web response system, and a total of 350 patients were randomized, of which 340 received either placebo or lixisenatide. All randomized patients were further stratified based on their A1C level, basal insulin use, and estimated glomerular filtration rate (eGFR). The primary efficacy end point was absolute change in A1C level from baseline to week 24. The treatment phase lasted for 24 weeks, and a three-day safety follow-up period ensued after treatment discontinuation. A standardized 400-mL liquid meal test (600 kcal) was provide to the patients as breakfast on week 1 and week 24 half an hour after injection. Patients whose fasting blood glucose level exceeded a priori thresholds for three consecutive days required rescue therapy.

Population

Inclusion and Exclusion Criteria

The inclusion and exclusion criteria for the patients are listed in Table 48.

Table 48: Inclusion and Exclusion Criteria of the GETGOAL – O Trial

Inclusion Criteria	Exclusion Criteria
Patients with T2DM not adequately controlled by current antidiabetic treatments (only permitted drugs were metformin, sulfonylurea [except glibenclamide > 10 mg and gliclazide > 160 mg], meglitinide [except repaglinide > 6 mg], pioglitazone, and basal insulin) taken for at least 3 months before study	A1C ≤ 7% (≤ 53 mmol/mol) and > 10% (> 86 mmol/mol) or physicians' assessment of the individuals' diabetic condition at screening
Age ≥ 70 years	FPG > 13.9 mmol/L at screening
	Confirmed diagnosed hyperthyroidism or uncontrolled hypothyroidism
	Background therapy: Combined therapy of basal insulin and sulfonylurea or meglitinide, not stable antidiabetic regimen, background therapy started within 3 months of screening, history of other GLP-1 agonists (exenatide, liraglutide, lixisenatide, or others), recent use of weight loss drug
	BMI < 22 or > 40 kg/m², > 5 kg change in body weight within three months
	Severe renal impairment (eGFR < 30 mL/min/1.73 m^2)
	Amylase and/or lipase > 3 times ULN
	Previous incidence of severe hypoglycemia, in addition to unawareness of symptoms or events leading to unconsciousness, coma, or seizure within 6 months of screening
	Malnutrition (< 12 on MNA-SF)
	Moderate to severe cognitive impairment (< 24 on MMSE)
	Recent history of surgery or heart conditions (ischemic attacks, stroke, UA, or MI, CHF) and planning to undergo surgery within 6 months, liver disease
	Drug or alcohol abuse within 6 months
	Any severe or uncontrolled disease that preclude patients' from participation based on physicians' discretion, including but not limited to gastrointestinal disease associated with prolonged nausea and vomiting, history of unexplained or chronic pancreatitis, allergic reactions to GLP-1
	Inadequately controlled hypertension (SBP > 180 mm Hg or DBP > 95 mm Hg)

ACS = acute coronary syndrome; BMI = body mass index; CHF = congestive heart failure; DBP = diastolic systolic blood pressure; FPG = fasting plasma glucose; eGFR = estimated glomerular filtration rate; MI = myocardial infarction; MNA-SF = Mini Nutritional Assessment-Short Form; MMSE= Mini Mental State Examination; SBP = systolic blood pressure; T2DM = type 2 diabetes mellitus; UA = unstable angina; ULN = upper limit of normal.

Source: GETGOAL – O Clinical Study Report.[54]

Baseline Characteristics

Overall, the mean age of the patients was 74 years (3.9), 52% of the patients were male, and 71% were white. Mean body weight was 80 kg (15.7) and mean BMI was 30 kg/m^2 (4.1). Thirty-seven per cent of the patients were age ≥ 75 years, 28% had renal impairments, and 93% had a history of cardiovascular/cerebrovascular disorders mostly contributed by hypertension and dyslipidemia. More than half of the patients had A1C level more than eight, and about one-third were on basal insulin in addition to oral antidiabetic drugs. These baseline characteristics had similar distribution across the two groups, including distribution of eGFR, glycemic index, A1C, age at onset of diabetes, duration of diabetes, as well as diabetic and nondiabetic disease and medication history, although no comparative statistical tests were done. The results are given in Table 49.

Table 49: Summary of Baseline Characteristics

Characteristics	GETGOAL – O		
	Placebo N = 174	Lixisenatide N = 176	All N = 176
Age, years, mean (SD)	74.4 (3.8)	74.0 (4.0)	74.2 (3.9)
Age ≥ 75 years, n (%)	69 (39.7)	62 (35.2)	131 (37.4)
Male, n (%)	90 (51.7)	92 (52.3)	182 (52.0)
Ethnic origin, n (%)			
White	122 (70.1)	128 (72.7)	250 (71.4)
Asian	11 (6.3)	5 (2.8)	16 (4.6)
Other	41 (23.6)	40 (22.7)	81 (23.1)
BMI (kg/m^2)			
Mean (SD)	30.1 (4.5)	29.9 (3.7)	30.0 (4.1)
BMI < 30, n (%)	96 (55.2)	102 (58.0)	198 (56.6)
BMI ≥ 30, n (%)	78 (44.8)	74 (42.0)	152 (43.4)
Mean body weight, kg (SD)	80.1 (16.8)	80.8 (14.5)	80.5 (15.7)
eGFR (mL/min/1.73 m^2), n (%)			
≥ 30 to < 60	47 (27.0)	50 (28.4)	97 (27.7)
≥ 60	127 (73.0)	126 (71.6)	253 (72.3)
Mean FPG, mmol/L (SD)	8.9 (2.3)	8.8 (2.4)	8.9 (2.3)
Mean two-hour PPG (mmol/L), (SD)	14.8 (66.5)	15.1 (68.1)	15.0 (67.2)
Mean glucose excursion (mmol/L), (SD)	6.0 (57.0)	6.5 (56.7)	6.2 (56.9)
Mean seven-point SMPG (mmol/L), (SD)	9.9 (35.6)	9.7 (36.4)	9.8 (36.0)
A1C			
Week 1, mean (SD)	8.1 (0.7)	8.1 (0.7)	8.1 (0.7)
A1C % < 8.0, n (%)	[redacted]	[redacted]	[redacted]
A1C % ≥ 8.0, n (%)	[redacted]	[redacted]	[redacted]
Mean duration of diabetes (years), (SD)	14.6 (7.9)	13.6 (7.3)	14.1 (7.6)
Mean age at onset of type 2 diabetes (years), (SD)	59.7 (8.4)	60.4 (8.2)	60.1 (8.3)
Diabetic sensory or motor neuropathy, n (%)	51 (29.3)	58 (33.0)	109 (31.1)
Diabetic retinopathy, n (%)	21 (12.1)	28 (15.9)	49 (14.0)
Ratio of urinary albumin to creatinine (mg/g)			
< 30 (normoalbuminuria), n (%)	[redacted]	[redacted]	[redacted]
≥ 30 to < 300 (microalbuminuria), n (%)	[redacted]	[redacted]	[redacted]
History of cardiovascular/cerebrovascular disorder, n (%)	162 (93.1)	164 (93.2)	326 (93.1)
Background therapy, n (%)			
Basal insulin ± OADs	55 (31.6)	54 (30.7)	109 (31.1)
MET ± OADs (except SU)	57 (32.8)	52 (29.5)	109 (31.1)
SU + MET ± OADs	51 (29.3)	59 (33.5)	110 (31.4)
SU ± OADs (except MET)	8 (4.6)	11 (6.3)	19 (5.4)
OADs (except MET and SU)	1 (0.6)	0	1 (0.3)
Basal insulin			

Characteristics	GETGOAL – O		
	Placebo N = 174	Lixisenatide N = 176	All N = 176
Mean dose, U/day (SD)	[redacted]	[redacted]	[redacted]
Range (min, max)	[redacted]	[redacted]	[redacted]
Concomitant nondiabetic medications, n (%)			
Renin-angiotensin system agents	128 (73.6)	130 (73.9)	258 (73.7)
Analgesics	112 (64.4)	114 (64.8)	226 (64.6)
Lipid-modifying agents	108 (62.1)	110 (62.5)	218 (62.3)
Topical products for joint and muscular pain	104 (59.8)	98 (55.7)	202 (57.7)
Antithrombotic agents	103 (59.2)	94 (53.4)	197 (56.3)

BMI = body mass index; eGFR = estimated glomerular filtration rate; FPG = fasting plasma glucose; MET = metformin; OAD = oral antidiabetic drug; PPG = post prandial glucose; SMPG = self-monitored plasma glucose; SU= sulfonylurea.

Source: GETGOAL – O,[29] GETGOAL – O Clinical Study Report.[54]

Interventions and Comparators

Dietary and lifestyle consultation was provided to all patients before run-in period up to three months following treatment. Background antidiabetic therapies received by the patients needed to be stable for at least three months before screening. Patients self-administered once-daily injection of lixisenatide or volume and pen colour-matched placebo 30 minutes to 60 minutes before breakfast using a disposable pre-filled pen throughout the 24-week study period. A starting dose of 10 mcg of lixisenatide was given for the first two weeks; thereafter, the target maintenance dose of 20 mcg was given to everyone unless it was not tolerated, in which case the dosing was reduced to 10 mcg in the first eight weeks of treatment and kept stable thereafter.

Patients with an A1C level between 7.0 and 8.0 inclusive had their basal insulin level reduced by 20% upon starting lixisenatide treatment to avoid hypoglycemia. Patients who received sulfonylurea and had an A1C level between 7.0 and 8.5 saw a 25% reduction of sulfonylurea dose. The insulin or sulfonylurea dose was titrated based on the individuals' self-monitored plasma glucose (SMPG) values between week 4 and week 12, and in the absence of hypoglycemia, a baseline level of insulin or sulfonylurea was permitted. To ensure that glycemic parameters did not exceed predefined threshold values, rescue therapy was in place whereby routine fasting SMPG and fasting plasma glucose (FPG) were measured in patients. If all the values exceeded in an individual for three consecutive days, the individual had their measurements taken at a central location and appropriate therapy was given by the site investigator. The FPG thresholds varied by study period: > 15.0 mmol/L from week 1 to week 8, > 13.3 mmol/L from week 8 to week 12, and > 11.1 mmol/L or A1C > 9% from week 12 to week 24. Rescue medication included a 20% increase in basal insulin dose or an increase in any allowed antidiabetic background therapy according to investigators' discretion.

Permitted background antidiabetic therapies included metformin, basal insulin, meglitinides, pioglitazone, and sulfonylurea. However, basal insulin combined with sulfonylurea or meglitinides were not allowed due to increased risk of hypoglycemia if lixisenatide is added. In addition, glibenclamide (glyburide) dose > 10 mg, gliclazide > 160 mg, or repaglinide > 6 mg were not permitted. The background therapies also had to be unchanged for at least three months before screening. Use of any weight loss drugs, short- or fast-acting insulin or

premix insulin, and systemic glucocorticoid were prohibited unless under special circumstances.

Outcomes

The efficacy and safety end points in the GETGOAL – O trial are listed in Table 50. Unless otherwise specified, change from baseline to week 24 was done for all outcomes.

Table 50: Efficacy and Safety End Points in the GETGOAL – O Trial

Efficacy End Points		
Primary Outcomes	Absolute change in A1C level	
Secondary Outcomes	FPG	
	2-hour PPG change	Change in both of these parameters following the standardized liquid breakfast meal test was recorded from baseline to week 24
	Plasma glucose excursion	
	7-point SMPG score, defined as the change in the average and each time point of the 7 points	
	Body weight	
	Total daily dose of insulin (for patients receiving basal insulin)	
	% of patients requiring the rescue therapy during the 24-week period	
	% of patients reaching A1C target, defined as < 7.0%	
	Composite end points	
	> 0.5% (> 5.5 mmol/mol) reduction in A1C, and no symptomatic hypoglycemia (< 3.3 mmol/L)	
Exploratory Outcomes	QoL assessment using the SF-12 from baseline to week 23	
Safety End Points	Hypoglycemia, with or without symptoms, defined as accompanying plasma glucose ≤ 3.3 mmol/L or quick recovery following oral glucose	
	Gastrointestinal events	
	Any other AEs or SAEs, including allergic reactions, death and CV events	

AE = adverse event; CV = cardiovascular; ECG = electrocardiogram; FPG = fasting plasma glucose; MNA-SF= Mini Nutritional Assessment-Short Form; PPG = postprandial glucose; SAE = serious adverse event; SF-12 = Short Form 12; SMPG = self-monitored plasma glucose; QoL = quality of life; ULN = upper limit of normal.
Source: GETGOAL – O Clinical Study Report.[54]

Statistical Analysis

Primary Efficacy End Point

Sample size calculation was based on the assumption of a mean A1C difference of 0.4% between lixisenatide and placebo and a common standard deviation of 1.1%, which would provide the study at least 90% power if 340 randomized patients (170 per group) were recruited. A modified intention-to-treat (mITT) population was used to analyze all efficacy outcomes, which consisted of any patient who received at least one dose of lixisenatide or placebo and had both baseline and at least one post-baseline measurement taken for any of the primary or secondary outcomes. Appropriate descriptive statistics were used to summarize continuous and categorical baseline and demographic variables; however, no comparative tests were done to show differences in these characteristics between the groups.

Absolute change in A1C values during the on-treatment period (by excluding A1C values obtained after rescue therapy and/or 14 days after treatment discontinuation) from baseline to week 24 was analyzed using an analysis of covariance (ANCOVA) model with treatment,

week 1 A1C and eGFR level, basal insulin use at screening, and country modelled as fixed effects, and baseline A1C put as a covariate. The last observation carried forward (LOCF) method was used to impute missing week-24 A1C values in case patients discontinued the treatment before then. Data were presented as the least squares (LS) mean change from baseline to week 24 with respective standard errors and corresponding 95% CIs. Assumptions for ANCOVA model, normal distribution and homogeneity of variances, were tested by Shapiro–Wilk statistics and Levene's test, respectively, using model residuals.

Sensitivity Analyses

A number of sensitivity analyses were performed for the primary efficacy outcomes. If substantial deviations from the ANCOVA assumptions were observed, the normalized (Tukey's) rank transformation to the same ANCOVA model was performed. Another sensitivity analysis was done to assess the impact of imputed week-24 A1C values that were missing in the ANCOVA model for the primary efficacy end point. Mixed-effects models for repeated measures (MMRM) was done under the "missing at random" framework using post-baseline on-treatment A1C values where the same fixed effects and covariates were kept as in the original ANCOVA model. Another sensitivity analysis was done by using only on-treatment A1C values for patients who completed the 24-week double-blind period and did not require rescue therapy with the same original ANCOVA model. Finally, a multi-level model with random slopes and intercepts was used in order to assess the effect of rescue medications on the A1C change from baseline to the end of the treatment period plus an additional 14 days. This model included the same fixed effects as in the original ANCOVA model in addition to visit, treatment-by-visit interaction, country, baseline A1C-by-visit interaction, and the number of days spent on rescue medications.

Subgroup Analyses

The treatment effect of lixisenatide on the primary end point (absolute change in A1C from baseline to week 24) was analyzed using descriptive statistics and was summarized by the following subgroups:

- race
- ethnicity (Hispanic, not Hispanic)
- age group (< 75 years, ≥ 75 years)
- gender
- baseline BMI (< 30 kg/m², ≥ 30 kg/m²)
- baseline A1C (< 8.0%, ≥ 8.0%)
- basal insulin use at screening (yes, no)
- baseline eGFR (≥ 30 to <60 mL/min/1.73 m^2, ≥ 60 mL/min/1.73 m^2)
- background antidiabetic therapy use at screening
- country.

Secondary Efficacy End Points

All continuous secondary efficacy outcomes were analyzed using the ANCOVA model previously described, and the adjusted estimates of absolute mean (and standard error) and mean differences (with standard error and 95% confidence interval [CI]) between the treatment groups were provided. Likewise, summary statistics for all secondary end points at screening, run-in, baseline, on-treatment, and at week 24 were generated. All categorical secondary efficacy variables were analyzed by the Cochran–Mantel–Haenszel method stratified by treatment, A1C at baseline and at week 24, basal insulin use at screening, eGFR, and country.

Control for multiple comparisons was done only for the secondary outcomes because the primary efficacy end point of A1C change from baseline to week 24 was a single time measurement. Type I error rate in secondary efficacy outcome to address multiplicity issues was done using a step-down hierarchical testing procedure and only if the primary efficacy end point was statistically significant at the 5% level. The following testing order using two-sided statistical tests for the superiority of lixisenatide over placebo at the alpha level of 0.05 was in place, and the testing was stopped when an end point was found not to be statistically significant at the 5% level:

1. change in two-hour postprandial glucose (PPG) following the liquid standardized breakfast meal test from baseline to week 24
2. change in the daily average of the seven-point SMPG from baseline to week 24
3. change in body weight from baseline to week 24
4. change in FPG from baseline to week 24
5. percentage of patients requiring rescue therapy during the on-treatment period.

Safety and Exploratory End Points

All AEs were summarized with descriptive statistics and by treatment status. The exploratory outcomes, i.e., quality of life, were continuous in nature, and therefore analyzed using the aforementioned ANCOVA model. In addition, summary scores were created using appropriate descriptive statistics.

Patient Disposition

[redacted]Table 51 summarizes the patient disposition data.

Table 51: Patient Disposition

Characteristics	GETGOAL – O	
	Placebo (N = 174)	Lixisenatide (N = 176)
Randomized and treated, n (%)	[redacted]	[redacted]
Did not complete treatment, n (%)	[redacted]	[redacted]
Withdrawal by patient, n (%)	[redacted]	[redacted]
Reason for withdrawal, n (%)		
Adverse events	[redacted]	[redacted]
Lack of efficacy	[redacted]	[redacted]
Poor compliance to protocol	[redacted]	[redacted]
Other	[redacted]	[redacted]
Follow-up, weeks	[redacted]	[redacted]
Patient lost to follow-up, n (%)	[redacted]	[redacted]
mITT population for efficacy analyses	[redacted]	[redacted]
Safety population	[redacted]	[redacted]

mITT = modified intention-to-treat.

Source: GETGOAL – O Clinical Study Report.[54]

Exposure to Study Treatments

[redacted] Details on patients' treatment duration and exposure are provided in Table 52.

Table 52: Exposure Dose and Duration

Exposure	GETGOAL – O	
	Placebo (N = 174)	Lixisenatide (N = 176)
Final dose of treatment, n (%)		
10 mcg	[redacted]	[redacted]
20 mcg	[redacted]	[redacted]
Duration of study treatment		
Mean, days (SD)	[redacted]	[redacted]
Median, days (min, max)	[redacted]	[redacted]
Cumulative duration of treatment exposure, patient years	[redacted]	[redacted]

NR = not reported; SD = standard deviation.

Source: GETGOAL – O Clinical Study Report.[54]

Critical Appraisal

Internal Validity

The GETGOAL – O trial used an interactive voice/Web response system to randomize patients, and randomization and treatment allocation were regulated centrally. Demographic and baseline characteristics including disease and treatment status were similar in both the groups; therefore, the randomization process appears to be successful. Patients were blinded to the allocated treatment throughout the study period unless AEs required appropriate treatment. In addition, treatment kits were provided in a blinded manner, and committees that adjudicated efficacy and safety end points were blinded to patients' treatment status. However, prandial glucagon-like peptide-1 (GLP-1) receptor agonists are typically associated with gastrointestinal disorders, in which case some unblinding may occur among patients who received lixisenatide, potentially leading to an over- or under-reporting of subjective parameters or change of behaviours and thereby biasing the results. The primary and secondary outcomes, despite being objectively measured, may also be prone to bias if patients modify their background therapies or if patients surmised that their allocated treatment was lixisenatide.

The trial included a screening period to assess eligibility followed by a run-in period to train, and reporting patients on treatment administration, study protocol, and management of symptoms, which may positively affect high compliance to treatment (more than 98%). Patients on concomitant medications such as metformin, sulfonylurea, meglitinide, pioglitazone, and basal insulin were included in the trial; however, those who were on basal insulin in combination with sulfonylurea or meglitinide were excluded due to higher risk of hypoglycemia in these patients if lixisenatide was introduced. The follow-up period of 24 weeks may not be adequate to determine the pattern of treatment effect for all outcomes. Attrition/dropout rate from the treatment was similar in both groups at around 12%, with most citing AEs as the cause of treatment discontinuation.

The efficacy and safety outcomes were valid and appropriately chosen to reflect overall glycemic status, body weight, quality of life, and AEs, and were aligned with patients' needs. A1C correlates with the development of long-term complications of diabetes; FPG and PPG are considered supportive measure of efficacy of antidiabetic medications. PPG, seven-point SMPG, and body weight are more important in older patients. In addition, the

definitions of the efficacy and safety outcomes were pre-specified and are aligned with values used in clinical practice. Misclassification from inconstancies in outcome definition is therefore minimal

The study had enough power (90%) to detect a treatment effect of at least 0.4% difference in A1C. Patients in the trial were stratified by key factors that may affect the results, including A1C, basal insulin use, and eGFR level. All continuous primary and secondary end points were analyzed by ANCOVA and adjusted for relevant confounders. All categorical efficacy end points were analyzed by the Cochran–Mantel–Haenszel method stratified by A1C, basal insulin use, and eGFR level. Subgroup analyses for the primary and secondary outcomes did not show any significant heterogeneity in the treatment effect; however, the results are likely underpowered due to smaller sample size in the subgroups. Efficacy analyses were based on the mITT population, defined as all randomized patients who received at least one dose treatment dose and had measurements of baseline as well as at least one post-baseline data on any efficacy variables regardless of treatment compliance. All but two patients were excluded from the true intention-to-treat (ITT) set, thus lacking any concern for bias. Safety end points were analyzed in the safety population, which consisted of all randomized patients. Missing data were imputed using the LOCF method. However, this may be a potential source of bias if a treatment “waning” effect exists for lixisenatide such that patients in the lixisenatide group drop out or discontinue the treatment before benefits can be seen in the placebo group, leading to overestimation of the result. Multiplicity adjustment was done for the secondary efficacy outcomes. A step-down testing procedure was used to control for type I error in secondary efficacy analyses, which entailed following a testing hierarchy for the secondary end points if the primary end point was found to be significant at the 5% alpha level. Testing was stopped when a secondary end point was no longer significant at this level. It appears the order of testing as well as stopping rule was followed in the analyses.

In terms of the results, there was a marked decrease in A1C level as well as most secondary efficacy end points in the lixisenatide group compared with placebo even though patients in both treatment groups were considered to be on optimized antidiabetic therapies. A significant proportion of the patients had renal impairment (28%) and the majority (93.1%) had a history of cardiovascular/cerebrovascular conditions, as can be expected from patients of old ages. However, hypertension and dyslipidemia accounted for most cardiovascular/cerebrovascular conditions — not any diabetes-related complications. It should be noted that two-hour PPG was measured after intake of standardized liquid breakfast test, which showed marked reduction at 24 weeks; however, this result does not represent the composition, amount, and frequency of meals consumed regularly by the patients. This was also reflected by the greater reduction in two-hour PPG following standardized meal intake than the two-hour SMPG post-breakfast curve, which resulted from averaging SMPG values of the patients following each breakfast. Finally, a number of sensitivity analyses were performed to test the effect of adequacy of ANCOVA model, use of LOCF method in imputing missing values, and rescue therapy; results were consistent with the original findings. It should be noted, however, that patients who do not continue treatments or the study are more likely to have values different from patients who do, and LOCF or sensitivity analyses using MMRM method to impute missing data would not fully overcome this limitation.

External Validity

Overall, the study included patients who were older, and more than one-third of them were ages ≥ 75 years. This generalizes the results into a bigger community of patients with diabetes, a significant proportion of who are more than 70 years old. Since the diabetes-related complications and comorbidities are known to be higher among older patients, and since a significant proportion of GETGOAL – O trial patients had renal impairments and cardiovascular/cerebrovascular disorders, results from this trial can positively affect the generalizability of the effect of lixisenatide in the geriatric population. The majority of the patients were commonly on metformin, and approximately one-third were on sulfonylurea and basal insulin, which represents the general practice in Canada for patients with diabetes. The mean daily dose of metformin, meglitinides, pioglitazone, and sulfonylurea was also in compliance with Health Canada recommendations.[35] There was an even distribution of males and females in the trial. The patients were mostly Caucasian, with very few Black people.

The GETGOAL – O trial was limited to older patients who were non-frail; however, the specific criteria for frailty were not listed, therefore exclusion from the study may result from the subjective nature of assessment for frailty. As complications related to frailty are generally found in older individuals, excluding patients who are frail would not capture a substantial proportion of type 2 diabetes mellitus patients, thereby limiting its generalizability to only older patients who are relatively healthy and free of comorbidities. A few exclusion criteria were based on the physician's assessment of individual patients, and while they were typically seen in older patients, more severe cases were not included in the trial. More than half of the accrued patients (55.5%) were screening failures, and another 9.7% were run-in failures. The most common cause for failures was varied range of A1C. The mean A1C level in both groups was around 8.0, which was near target according to the clinical expert consulted for this CDR review. This was unusual for the typical type 2 diabetes mellitus patients in Canada and therefore may limit the generalizability of the results.

The mean body weight (80 kg) and BMI (30 kg/m^2) for the patients were on the lower end and do not reflect the general status of these parameters in older individuals according to the clinical expert. The trial population excluded any patients who were frail, which may further limit the generalizability of the results to the general status of older individuals. Body weight, for example, was decreased in both obese (BMI > 30 kg/m^2) and non-obese patients; however, this can have a detrimental effect on frail, underweight patients. Similarly, the impact of lixisenatide on nutritional status, hypoglycemia, and other safety end points as well as comorbidities were not determined in patients who are frail, which is more common with older age.

Results

Primary Efficacy End Points

Results for the primary efficacy end point (absolute change from baseline to week 24) are given in Table 53. The mean change in A1C was lower in the lixisenatide group (–0.57%) compared with placebo (0.06%). The adjusted LS mean difference between the two groups was statistically significant at –0.64% (95% CI, –0.81% to –0.46%). The Kaplan–Meier graph in Figure 10 shows this change in mean A1C over time for the two groups. There was a steady decrease in the mean A1C level for the lixisenatide group from baseline to week 24 but not for the placebo group. At the end of week 24, the mean A1C levels for the lixisenatide group and the placebo group were 7.36% and 8.01%, respectively. The

difference was in favour of lixisenatide, as shown by superiority in the LS mean of 0.64% (*P* < 0.0001); the effect was consistent irrespective of patients' age, renal function, and background antidiabetic therapy. The results are shown in Figure 10 and Table 53.

Table 53: Mean Change in Glycated Hemoglobin (%)

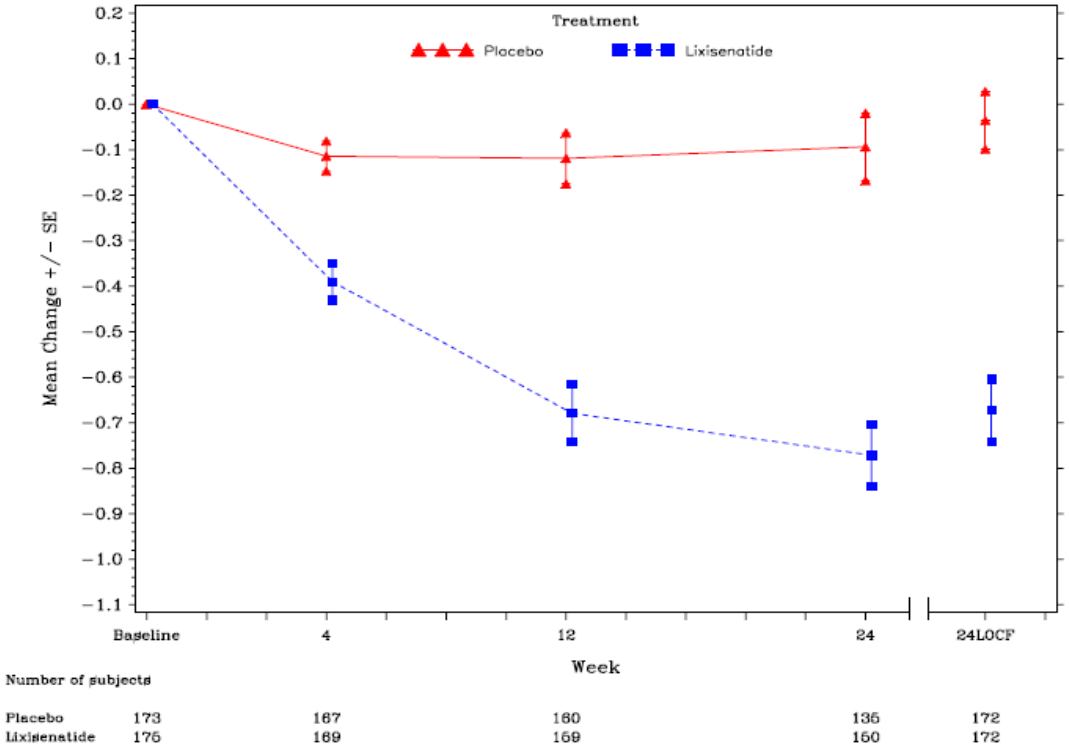
A1C (%)	GETGOAL – O	
	Placebo (N = 173)	**Lixisenatide (N = 175)**
Change from baseline to Week 24 (LOCF)		
Adjusted LS mean (SE)[a]	0.06 (0.072)	–0.57 (0.07)
Adjusted LS mean difference (SE) versus placebo[a]	—	–0.64 (0.08)
95% CI	—	–0.81 to –0.46
P value	—	< 0.0001

A1C = glycated hemoglobin; CI = confidence interval; LS = least squares; LOCF = last observation carried forward; SD = standard deviation; SE = standard error.

[a] Analysis of covariance model with treatment groups (lixisenatide and placebo), randomization strata of screening (week 1) A1C (< 8.0, ≥ 8.0%), basal insulin use at screening, estimated glomerular filtration rate (≥ 30 to < 60, ≥ 60 mL/min/1.73 m^2), and country as fixed effects, and baseline A1C value as a covariate.

Source: GETGOAL – O Clinical Study Report.[54]

Figure 10: Mean Change in Glycated Hemoglobin (%) by Treatment Groups



LOCF = last observation carried forward; SE = standard error.

Source: From the American Diabetes Association, Lixisenatide therapy in older patients with type 2 diabetes inadequately controlled on their current antidiabetic treatment: the GetGoal-O randomized trial, American Diabetes Association, 2017. Copyright and all rights reserved. Material from this publication has been used with the permission of the American Diabetes Association.[29] CADTH does not own this work and permission should be sought from the copyright owner. GETGOAL – O Clinical Study Report.[54]

Results from the subgroup analyses showing change in A1C by baseline factors and country from baseline to week 24 is given in the forest plot shown in Figure 11. The effect of lixisenatide on change in A1C did not show any heterogeneity by age, race, ethnicity, age group, gender, baseline BMI, baseline A1C, basal insulin use at screening, baseline renal function, or background antidiabetic therapy.

Figure 11: Change in Glycated Hemoglobin by Pre-Specified Subgroups

FIGURE CONTAINED CONFIDENTIAL INFORMATION AND WAS REDACTED AT THE REQUEST OF THE MANUFACTURER.

Source: GETGOAL – O Clinical Study Report.[54]

Secondary Efficacy End Points

Since the difference for change in A1C between lixisenatide and placebo was significantly different, a stepwise testing strategy was adopted to control for multiple comparisons of secondary efficacy outcomes as described previously. The following secondary efficacy end points showed significant decrease in the lixisenatide group compared with placebo from baseline to week 24: two-hour PPG (adjusted LS mean difference –5.05 mmol/L [95% CI, –5.96 to –4.13], $P < 0.0001$), glucose excursion (adjusted LS mean difference –4.46 mmol/L [95% CI, –5.23 to –3.68], P = not reported), daily seven-point SMPG (adjusted LS mean difference –0.96 mmol/L [95% CI, –1.39 to –0.52], $P < 0.0001$), and body weight (adjusted LS mean difference –1.32 kg [95% CI, –1.86 to –0.76], $P < 0.0001$). Lixisenatide was also shown to reduce A1C to the target level of < 7% more than the placebo (36.6% versus 14%, $P < 0.0001$). The results are summarized in Table 54, and the daily average of the seven-point SMPG score is given in Figure 12. From the figure, the highest difference in the average seven-point SMPG score at week 24 was observed following breakfast, which was sustained throughout pre- and post-lunch as well as before dinner and tapered off two hours post-dinner closer to, but still lower than, placebo.

Subgroup analysis to investigate the effect of BMI on change in body weight resulted in an LS mean difference of –1.26 kg (0.56) among patients with a BMI < 27 kg/m^2 (n = 48), and –1.30 kg (0.32) in patients with a BMI ≥ 27 kg/m^2 (n = 125), indicating little variability in weight loss by BMI. However, the BMI cut-off value of 27 kg/m^2 may not be considered the standard cut-off to differentiate individuals who are overweight and obese individuals from individuals who are neither overweight nor obese. Among the other outcomes, FPG reduction in both groups was not significantly different, percentage of patients requiring rescue therapy was lower in the lixisenatide group (five versus 18), basal insulin requirement fell in both groups, and the number of patients with a decrease in A1C > 0.5% and absence of hypoglycemia was close to three times higher in the lixisenatide group.

Table 54: Results of Secondary End Points

Efficacy End Points	GETGOAL – O	
	Placebo (N = 173)	Lixisenatide (N = 175)
Secondary Efficacy End Points		
Two-hour PPG (mmol/L)		
Change from baseline to week 24 (LOCF)		
Adjusted LS mean (SE)[a]	–0.07 (0.39)	–5.12 (0.39)
Adjusted LS mean difference (SE) versus placebo[a]	—	–5.05 (0.46)
95% CI	—	–5.96 to –4.13
P value	—	< 0.0001
Glucose excursion (mmol/L)		
Change from baseline to week 24 (LOCF)		
Adjusted LS mean (SE)[a]	[redacted]	[redacted]
Adjusted LS mean difference (SE) versus placebo[a]	—	–4.46 [redacted]
95% CI	—	–5.23 to –3.68
Seven-point SMPG (mmol/L)		
Change from baseline to week 24 (LOCF)		
Adjusted LS mean (SE)[a]	–0.19 (0.189)	–1.15 (0.186)
Adjusted LS mean difference versus placebo[a]	—	–0.96
95% CI		–1.39 to –0.52
P value	—	< 0.0001
Body weight (kg)		
Change from baseline to week 24 (LOCF)		
Adjusted LS mean (SE)[a]	–0.16 (0.22)	–1.47 (0.24)
Adjusted LS mean difference (SE) versus placebo[a]	—	–1.32 (0.27)
95% CI	—	–1.86 to -0.76
P value	—	< 0.0001
FPG (mmol/L)		
Change from baseline to week 24 (LOCF)		
Adjusted LS mean (SE)[a]	0.01 (0.21)	–0.30 (0.22)
Adjusted LS mean difference (SE) versus placebo[a]	—	–0.31 (0.26)
95% CI	—	–0.82 to 0.20
P value	—	0.23
Rescue therapy, n (%)		
Requiring rescue therapy	18 (10.4%)	5 (2.9)
Proportion difference (95% CI) versus placebo[a]	—	–7.8% (–13.12 to –2.41%)
P value[b]	—	0.003
% of patients with A1C < 7%, n (%)		
< 7%	24 (14.0%)	63 (36.6)
Proportion difference (95% CI) versus placebo[b]	—	22.7 (14.37 to 30.96)
P value	—	< 0.0001
Total basal insulin (U)		
Change from baseline to week 24 (LOCF)		

Efficacy End Points	GETGOAL – O	
	Placebo (N = 173)	Lixisenatide (N = 175)
LS mean (SE)[a]	–1.30 (1.07)	–2.97 (1.14)
LS mean difference (SE) versus placebo[a]	—	–1.67 (1.36)
95% CI	—	–4.38 to 1.04
Composite End Points		
A1C reduction > 0.5% and no symptomatic hypoglycemia with glucose < 3.3 mmol/L		
Response rate	37 (21.5%)	99 (57.6%)
Response rate difference (95% CI) versus placebo[b]	—	35.8% (26.71% to 44.97%)

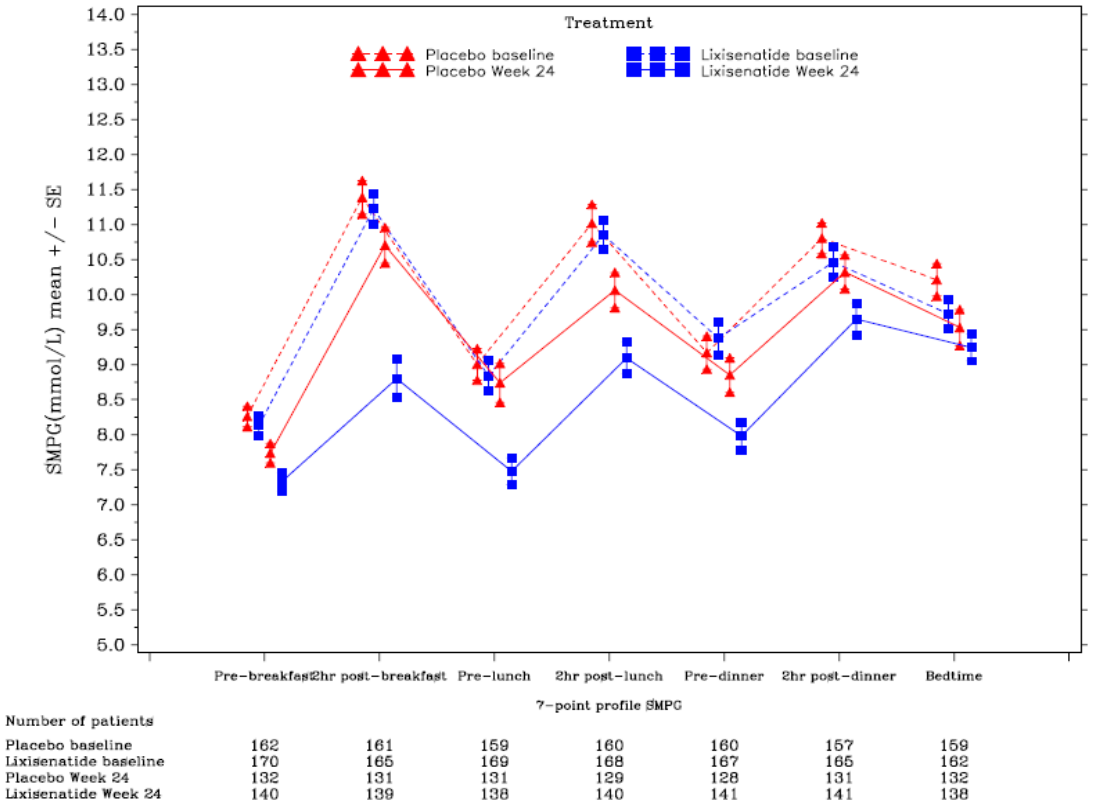
A1C = glycated hemoglobin; CI = confidence interval; FPG = fasting plasma glucose; LOCF = last observation carried forward; PPG = postprandial glucose; SD = standard deviation; SE = standard error; SMPG = self-monitored plasma glucose.

[a] Analysis of covariance model with treatment groups (lixisenatide and placebo), randomization strata of screening (week 1) A1C (< 8.0, ≥ 8.0%), basal insulin use at screening, estimated glomerular filtration rate (≥ 30 to < 60, ≥ 60 mL/min/1.73 m^2), and country as fixed effects, and baseline A1C value as a covariate.

[b] Based on Cochran–Mantel–Haenszel method stratified by randomization strata.

Source: GETGOAL – O Clinical Study Report.[54]

Figure 12: Plot of Average Seven-point Self-Monitored Plasma Glucose Profiles



SE = standard error; SMPG = self-monitored plasma glucose.

Source: From the American Diabetes Association, Lixisenatide therapy in older patients with type 2 diabetes inadequately controlled on their current antidiabetic treatment: the GetGoal-O randomized trial, American Diabetes Association, 2017. Copyright and all rights reserved. Material from this publication has been used with the permission of American Diabetes Association.[29] CADTH does not own this work and permission should be sought from the copyright owner. GETGOAL – O Clinical Study Report.[54]

Exploratory End Points

The Short Form 12 quality of life survey showed a small but statistically significant increase in the physical health composite score in the lixisenatide group (2.12) compared with the placebo group (0.39), with an LS mean difference of 1.73 (95% CI, 0.01 to 3.45) and effect size of 0.21 (Cohen classification). The change in mental health composite score was less pronounced (0.05 and –0.28 in lixisenatide and placebo, respectively), with an LS mean difference of 0.33 (95% CI, –1.57 to 2.22) between the two groups.

Table 55: Results of Exploratory End Points

Efficacy End Points	GETGOAL – O	
	Placebo (N = 173)	**Lixisenatide (N = 175)**
QoL — SF-12	n = 131	n = 138
Change in PCS from baseline to week 23 (LOCF)		
LS mean (SE)[a]	0.39 (0.74)	2.12 (0.73)
LS mean difference versus placebo[a]	—	1.73 (0.87)
95% CI	—	0.01 to 3.45
Change in MCS from baseline to week 23 (LOCF)		
LS mean (SE)[a]	–0.28 (0.81)	0.05 (0.81)
LS mean difference (SE) versus placebo[a]	—	0.33 (0.96)
95% CI	—	–1.57 to 2.22

A1C = glycated hemoglobin; CI = confidence interval; LOCF = last observation carried forward; LS = least squares; MCS = mental component summary; MNA-SF = Mini Nutritional Assessment-Short Form; PCS = physical component summary; SF-12 = Short Form 12; SE = standard error; QoL = quality of life.
[a] Analysis of covariance model with treatment groups (lixisenatide and placebo), randomization strata of screening (week 1) A1C (< 8.0, ≥ 8.0%), basal insulin use at screening, estimated glomerular filtration rate (≥ 30 to < 60, ≥ 60 mL/min/1.73 m^2), and country as fixed effects, and baseline A1C value as a covariate.
Source: GETGOAL – O Clinical Study Report.[54]

Safety End Points

Hypoglycemia

Among the lixisenatide group, incidences of hypoglycemia and symptomatic hypoglycemia were higher than the placebo group (17.6% versus 10.3% for hypoglycemia and 7.4% versus 5.7% for symptomatic hypoglycemia). This may be explained by the background therapy the patients received, specifically sulfonylurea in combination with lixisenatide. It was found that among patients with sulfonylurea as their background therapy, seven in the lixisenatide group and two in the placebo group had symptomatic hypoglycemia, whereas the incidence was lower for patients who received basal insulin (three versus seven in the lixisenatide group and the placebo group, respectively) and the same for those who received metformin with oral antidiabetic drugs (one in each group). Table 56 shows the incidence of symptomatic hypoglycemia by the type of background treatment.

Table 56: Number of Symptomatic Hypoglycemia by the Background Treatment Received

Symptomatic Hypoglycemia	Basal Insulin + OADs		MET + OADs (Except SU)		SU + MET + Other OADs	
	Placebo N = 55	Lixisenatide N = 54	Placebo N = 57	Lixisenatide N = 52	Placebo N = 51	Lixisenatide N = 59
Patients with events, n (%)	7 (12.7)	3 (5.6)	1 (1.8)	1 (1.9)	2 (3.9)	7 (11.9)
Patients with events per 100 patient years[a]	29.3	12.2	3.7	4.5	8.8	26.7

MET = metformin; OAD = oral antidiabetic drug; SU = sulfonylurea.
[a] Calculated as number of patients with events 3,100/total exposure + three days in patient years.
Source: GETGOAL – O. [29]

Other Adverse Events

Table 57 shows the frequency of AEs found in the safety population. The proportion of patients who experienced any treatment emergent AEs (71.0% and 67.8% in the lixisenatide group versus placebo group, respectively) and treatment emergent AEs leading to treatment discontinuation (8.5% and 5.7% in the lixisenatide group versus placebo group, respectively) were similar in the two groups, although the frequency was slightly higher in the lixisenatide group. Of the 350 randomized patients (176 in the lixisenatide group and 174 in the placebo group) that constituted the safety population, 15 patients in the lixisenatide group and 10 patients in the placebo group discontinued the treatment, citing gastrointestinal disorders as the main cause. Patients in the lixisenatide group experienced more nausea (25% versus 7.5%) and vomiting (5.7% versus 0.6%) than the placebo group. Among other notable outcomes, there were more infections in the placebo group (30.5%) than lixisenatide (23.3%). The same pattern was seen for musculoskeletal and connective tissue disorders (17.8% versus 10.8% in the placebo group and lixisenatide group, respectively). The placebo group also had one case of death (unrelated to the treatment) and acute pancreatitis.

Table 57: Number of Adverse Events

Adverse Events	GETGOAL – O	
	Placebo (N = 174)	**Lixisenatide (N = 176)**
Exploratory efficacy end points		
TEAE, n (%)		
Any TEAE	118 (67.8)	125 (71.0)
Serious TEAE	10 (5.7)	8 (4.5)
TEAE leading to discontinuation	10 (5.7)	15 (8.5)
TEAE leading to death	1 (0.6)	0
AEs by organ class, n (%)		
Infections and infestations	53 (30.5)	41 (23.3)
Nervous system disorders	19 (10.9)	21 (11.9)
Gastrointestinal disorders (overall)	36 (20.7)	71 (40.3)
Nausea	13 (7.5)	44 (25.0)
Diarrhea	13 (7.5)	19 (10.8)
Vomiting	1 (0.6)	10 (5.7)
Gastrointestinal disorders leading to discontinuation	1 (0.6)	10 (5.7)

Adverse Events	GETGOAL – O	
	Placebo (N = 174)	Lixisenatide (N = 176)
Musculoskeletal and connective tissue disorders (overall)	31 (17.8)	19 (10.8)
Arthralgia	8 (4.6)	4 (2.3)
Musculoskeletal pain	7 (4.0)	0
Hypoglycemia, n (%)		
Any hypoglycemia (symptomatic and asymptomatic)[a]	18 (10.3)	31 (17.6)
Symptomatic hypoglycemia		
Number of patients with events	10 (5.7)	13 (7.4)

AE = adverse event; TEAE = treatment emergent adverse event.
[a] Symptomatic hypoglycemia (plasma glucose ≤ 3.3 mmol/L) and asymptomatic hypoglycemia (plasma glucose ≤ 3.9 mmol/L).
Source: GETGOAL – O Clinical Study Report.[54]

Discussion

The GETGOAL – O trial was designed to evaluate the risk and benefits of lixisenatide in patients with type 2 diabetes mellitus who were elderly, not frail, and who had inadequate control of diabetes from their current treatment. Patients who were not frail and ages ≥ 70 years were included, and those with A1C values out of range and had moderate to severe cognitive impairments were excluded. Background therapies in most patients included metformin, sulfonylurea, meglitinides, and basal insulin. The patients received either lixisenatide (20 mcg) or placebo in addition to background medications, and were followed for 24 weeks. Change in A1C from baseline to week 24 was the primary outcome, and changes in two-hour PPG, glucose excursion, FPG, seven-point SMPG, body weight over the same time period, and frequency of patients reaching A1C target and requiring rescue therapy were considered secondary efficacy outcomes. In addition, physical and mental well-being as well as overall quality of life was assessed using the health-related quality of life measure Short Form 12. Any AEs, including hypoglycemia, were monitored.

A total of 350 patients were randomized to receive either lixisenatide (n = 176) or placebo (n = 174). At the end of the 24-week follow-up period, A1C level was significantly reduced in the lixisenatide group (adjusted LS mean difference –0.64%). This was largely attributed to a concomitant decrease in PPG that was maintained up to dinner time, as demonstrated by a standardized meal test and seven-point SMPG profile. In contrast, no clinically relevant effect on FPG was seen. There was a significant drop in body weight in the lixisenatide group (LS mean difference –1.32 kg). A small improvement in quality of life was also observed.

Lixisenatide was not associated with an unexpected increase in AEs or SAEs, and the treatment emergent AE distribution was similar in both groups. The most commonly reported AEs were nausea and vomiting. Patients in the lixisenatide group reported an increased frequency of hypoglycemia, which was found to result from concomitant intake of sulfonylurea.

Conclusions

Among older patients who are frail, lixisenatide 20 mcg per day in combination with background antidiabetic medications for 24 weeks was associated with a significant reduction in A1C, PPG and seven-point SMPG compared with placebo. A slight decrease in body weight was also found with lixisenatide, but no changes were seen in FPG levels. Among the patients who received lixisenatide, more patients reached target level of A1C compared with placebo, and it was also associated with improved overall quality of life. The risk of hypoglycemia and AEs for lixisenatide was comparable with placebo, and the safety profile, which included nausea and vomiting, was consistent with other known incretin-based therapies.

The GETGOAL – O trial was one of the few trials that investigated the efficacy of a GLP-1 agonist in patients who are older and have diabetes. Diabetes is very common with older age; however, few studies are specifically targeted toward geriatric populations, and patients older than 75 years are almost always excluded. Strengths of the study include a robust design ensuring randomization, blinding, relatively low treatment discontinuation rate; and high compliance with treatment and study protocol; appropriately chosen, defined, and measured efficacy and safety outcomes; and a sound analytic procedure. However, the relatively short follow-up, exclusion of patients who are frail, and relatively good baseline A1C, BMI and body weight among patients are key limitations of the study.

References

1. Meier JJ. GLP-1 receptor agonists for individualized treatment of type 2 diabetes mellitus. Nat Rev Endocrinol. 2012 Dec;8(12):728-42.
2. Fineman MS, Cirincione BB, Maggs D, Diamant M. GLP-1 based therapies: differential effects on fasting and postprandial glucose. Diabetes Obes Metab. 2012 Aug;14(8):675-88.
3. [Pr] Adlyxine™ (lixisenatide injection): 0.05 mg per mL (10 ug/dose), 0.1 mg per mL (20 ug/dose) solution for injection in a pre-filled pen [product monograph]. Laval (QC): Sanofi-aventis Canada Inc.; 2017 May 23.
4. Riddle MC, Aronson R, Home P, Marre M, Niemoeller E, Moissec P. Adding once-daily lixisenatide for type 2 diabetes inadequately controlled by established basal insulin: a 24-week, randomized, placebo-controlled comparison (GetGoal-L). Diabetes Care [Internet]. 2013 [cited 2017 Aug 16];36:2489-96. Available from: https://www.ncbi.nlm.nih.gov/pmc/articles/PMC3747925
5. Clinical study report no. EFC6016. A randomized, double-blind, placebo-controlled, 2-arm parallel-group, multicenter study with a 24-week main treatment period and an extension assessing the efficacy and safety of AVE0010 in patients with Type 2 diabetes insufficiently controlled with basal insulin [**CONFIDENTIAL** internal manufacturer's report]. Paris (FR): Sanofi; 2014 Nov 27.
6. Riddle MC, Frost T, Aronson R, Sauque-Reyna L, Souhami E, Silvestre L, et al. Adding once-daily lixisenatide for type 2 diabetes inadequately controlled with newly initiated and continuously titrated basal insulin glargine: A 24-week, randomized, placebo-controlled study (GetGoal-Duo 1). Diabetes Care [Internet]. 2013 Sep [cited 2017 Aug 16];36:2497-503. Available from: https://www.ncbi.nlm.nih.gov/pmc/articles/PMC3747901
7. Clinical study report no. EFC10781. A randomized, double-blind, placebo-controlled, 2-arm parallel-group, multicenter study with a 24-week double blind treatment period and an extension assessing the efficacy and safety of lixisenatide in patients with Type 2 diabetes insufficiently controlled with insulin glargine and metformin [**CONFIDENTIAL** internal manufacturer's report]. Paris (FR): Sanofi; 2012 May 2.
8. Seino Y, Min KW, Niemoeller E, Takami A, EFC10887 GETGOAL-L Asia Study Investigators. Randomized, double-blind, placebo-controlled trial of the once-daily GLP-1 receptor agonist lixisenatide in Asian patients with type 2 diabetes insufficiently controlled on basal insulin with or without a sulfonylurea (GetGoal-L-Asia). Diabetes Obes Metab [Internet]. 2012 Oct [cited 2017 Jul 7];14(10):910-7. Available from: https://www.ncbi.nlm.nih.gov/pmc/articles/PMC3466411
9. Clinical study report no. EFC10887. A randomized, double-blind, placebo-controlled, 2-arm parallel-group, multicenter study with a 24-week treatment period assessing the efficacy and safety of AVE0010 in patients with Type 2 diabetes insufficiently controlled with basal insulin with or without sulfonylurea [**CONFIDENTIAL** internal manufacturer's report]. Paris (FR): Sanofi; 2015 Jan 13.
10. Clinical study report no. EFC12382. A randomized, double-blind, placebo-controlled, 2-arm parallel-group, multicenter study with a 24-week treatment period assessing the efficacy and safety of lixisenatide in patients with type 2 diabetes insufficiently controlled with basal insulin with or without metformin [**CONFIDENTIAL** internal manufacturer's report]. Paris (FR): Sanofi; 2015 Sep 28.
11. Rosenstock J, Guerci B, Hanefeld M, Gentile S, Aronson R, Tinahones FJ, et al. Prandial options to advance basal insulin glargine therapy: Testing lixisenatide plus basal insulin versus insulin glulisine either as basal-plus or basal-bolus in type 2 diabetes: The GetGoal Duo-2 trial. Diabetes Care [Internet]. 2016 Aug [cited 2017 Jul 10];39(8):1318-28. Available from: http://care.diabetesjournals.org/content/diacare/39/8
12. Clinical study report no. EFC12626. A randomized, open-label, active-controlled, 3-arm parallel-group, 26-week study comparing the efficacy and safety of lixisenatide to that of insulin glulisine once daily and insulin glulisine three times daily in patients with Type 2 diabetes insufficiently controlled with insulin glargine with or without metformin [**CONFIDENTIAL** internal manufacturer's report]. Paris (FR): Sanofi; 2015 Jun 12.
13. Types of diabetes [Internet]. Toronto (ON): Diabetes Canada; 2017. [cited 2017 Aug 15]. Available from: http://www.diabetes.ca/about-diabetes/types-of-diabetes
14. Defronzo RA. Banting Lecture. From the triumvirate to the ominous octet: a new paradigm for the treatment of type 2 diabetes mellitus. Diabetes. 2009 Apr [cited 2017 Aug 15];58(4):773-95. Available from: http://www.ncbi.nlm.nih.gov/pmc/articles/PMC2661582
15. Global report on diabetes [Internet]. Geneva (CH): World Health Organization; 2016. [cited 2017 Aug 15]. Available from: http://apps.who.int/iris/bitstream/10665/204871/1/9789241565257_eng.pdf?ua=1
16. IDF diabetes atlas [Internet]. 7th ed. Brussels (BEL): International Diabetes Federation; 2017. [cited 2017 Aug 15]. Available from: http://www.diabetesatlas.org/
17. Diabetes statistics in Canada [Internet]. Toronto (ON): Diabetes Canada; 2017. [cited 2017 Aug 15]. Available from: http://www.diabetes.ca/how-you-can-help/advocate/why-federal-leadership-is-essential/diabetes-statistics-in-canada
18. An economic tsunami: the cost of diabetes in Canada [Internet]. Toronto (ON): Canadian Diabetes Association; 2009 Dec. [cited 2017 Aug 15]. Available from: http://www.diabetes.ca/CDA/media/documents/publications-and-newsletters/advocacy-reports/economic-tsunami-cost-of-diabetes-in-canada-english.pdf
19. Clinical practice guidelines for the prevention and management of diabetes in Canada. Can J Diabetes [Internet]. 2013 [cited 2017 Aug 16];37(Suppl 1):S1-S212. Available from: http://guidelines.diabetes.ca/app_themes/cdacpg/resources/cpg_2013_full_en.pdf
20. McCulloch DK. Management of persistent hyperglycemia in type 2 diabetes mellitus. In: Post TW, editor. UpToDate [Internet]. Waltham (MA): UpToDate; 2016 Mar 9 [cited 2017 Aug 16]. Available from: www.uptodate.com Subscription required.

21. Canadian Diabetes Association Clinical Practice Guidelines Expert Committee, Clayton D, Woo V, Yale JF. Hypoglycemia. Can J Diabetes. 2013 Apr;37 Suppl 1:S69-S71.

22. Inzucchi SE, Bergenstal RM, Buse JB, Diamant M, Ferrannini E, Nauck M, et al. Management of hyperglycaemia in type 2 diabetes, 2015: a patient-centred approach. Update to a position statement of the American Diabetes Association and the European Association for the Study of Diabetes. Diabetologia. 2015 Mar;58(3):429-42.

23. Standards of medical care in diabetes--2016. Diabetes Care [Internet]. 2016 [cited 2017 Aug 16];39(Suppl 1). Available from: http://care.diabetesjournals.org/content/suppl/2015/12/21/39.Supplement_1.DC2/2016-Standards-of-Care.pdf

24. Barnett AH. Lixisenatide: evidence for its potential use in the treatment of type 2 diabetes. Core Evid [Internet]. 2011 [cited 2017 Aug 15];6:67-79. Available from: http://www.ncbi.nlm.nih.gov/pmc/articles/PMC3195668

25. CPS [Internet]. Ottawa: Canadian Pharmacists Association. 2017 [cited 2017 Aug 15]. Available from: http://www.e-therapeutics.ca Subscription required.

26. Type 2 diabetes: lixisenatide. Evidence summary [Internet]. London (GB): National Institute for Clinical Excellence; 2013 Sep 24. [cited 2017 Aug 15]. Available from: https://www.nice.org.uk/guidance/esnm26/resources/type-2-diabetes-lixisenatide-pdf-1502680866716869

27. Pfeffer MA, Claggett B, Diaz R, Dickstein K, Gerstein HC, Kober LV, et al. Lixisenatide in patients with type 2 diabetes and acute coronary syndrome. N Engl J Med [Internet]. 2015 Dec 3 [cited 2017 Jul 7];373(23):2247-57. Available from: http://www.nejm.org/doi/pdf/10.1056/NEJMoa1509225

28. Guidance for industry: Diabetes mellitus: Developing drugs and therapeutic biologics for treatment and prevention [Draft guidance] [Internet]. Rockville (MD): Food and Drug Administration; 2008 Feb. [cited 2017 Aug 15]. Available from: https://www.fda.gov/downloads/Drugs/.../Guidances/ucm071624.pdf

29. Meneilly GS, Roy-Duval C, Alawi H, Dailey G, Bellido D, Trescoli C, et al. Lixisenatide therapy in older patients with type 2 diabetes inadequately controlled on their current antidiabetic treatment: the GetGoal-O randomized trial. Diabetes Care [Internet]. 2017 [cited 2017 Jul 10];40(4):485-93. Available from: http://care.diabetesjournals.org/content/diacare/40/4/485

30. Diabetes in Canada: Facts and figures from a public health perspective [Internet]. Ottawa (ON): Public Health Agency of Canada; 2017. [cited 2017 Aug 15]. Available from: https://www.canada.ca/en/public-health/services/chronic-diseases/reports-publications/diabetes/diabetes-canada-facts-figures-a-public-health-perspective/chapter-1.html

31. 2013 clinical practice guidelines quick reference guide [Internet]. Toronto (ON): Canadian Diabetes Association; 2013. [cited 2017 Aug 15; updated Nov 2016]. Available from: http://guidelines.diabetes.ca/cdacpg_resources/CPG_Quick_Reference_Guide_WEB.pdf

32. Seino Y, Kuwata H, Yabe D. Incretin-based drugs for type 2 diabetes: Focus on East Asian perspectives. J Diabetes Investig. 2016 Apr [cited 2017 Aug 15];7 Suppl 1:102-9. Available from: http://www.ncbi.nlm.nih.gov/pmc/articles/PMC4854513

33. Kim YG, Hahn S, Oh TJ, Park KS, Cho YM. Differences in the HbA1c-lowering efficacy of glucagon-like peptide-1 analogues between Asians and non-Asians: a systematic review and meta-analysis. Diabetes Obes Metab. 2014 Oct;16(10):900-9.

34. Sun F, Chai S, Yu K, Quan X, Yang Z, Wu S, et al. Gastrointestinal adverse events of glucagon-like peptide-1 receptor agonists in patients with type 2 diabetes: a systematic review and network meta-analysis. Diabetes Technol Ther [Internet]. 2015 Jan [cited 2017 Aug 14];17(1):35-42. Available from: http://www.ncbi.nlm.nih.gov/pmc/articles/PMC4290796

35. Glucophage®: metformin hydrochloride, manufacturer's standard, 500 mg and 850 mg tablets, oral antihyperglycemic agent [product monograph] [Internet]. Laval (QC): Sanofi-Aventis Canada Inc.; 2009 Oct 28. [cited 2017 Aug 15]. Available from: http://www.sanofi.ca/products/en/glucophage.pdf

36. Health Canada reviewer's report: Adlyxine (lixisenatide injection) [**CONFIDENTIAL** internal report]. Ottawa: Therapeutics Products Directorate, Health Canada; 2017.

37. Aroda VR, Rosenstock J, Wysham C, Unger J, Bellido D, Gonzalez-Galvez G, et al. Efficacy and safety of LixiLan, a titratable fixed-ratio combination of insulin glargine plus lixisenatide in type 2 diabetes inadequately controlled on basal insulin and metformin: the LixiLan-L Randomized Trial. Diabetes Care. 2016 Nov;39(11):1972-80.

38. Eto K, Naito Y, Seino Y. Evaluation of the efficacy and safety of lixisenatide add-on treatment to basal insulin therapy among T2DM patients with different body mass indices from GetGoal trials. Diabetol Metab Syndr [Internet]. 2015 [cited 2017 Jul 5];7:106. Available from: https://www.ncbi.nlm.nih.gov/pmc/articles/PMC4654794

39. Farngren J, Persson M, Ahren B. Effect of the GLP-1 Receptor Agonist Lixisenatide on Counterregulatory Responses to Hypoglycemia in Subjects With Insulin-Treated Type 2 Diabetes. Diabetes Care. 2016 Feb;39(2):242-9.

40. Meier JJ, Rosenstock J, Hincelin-Mery A, Roy-Duval C, Delfolie A, Coester HV, et al. Contrasting Effects of Lixisenatide and Liraglutide on Postprandial Glycemic Control, Gastric Emptying, and Safety Parameters in Patients With Type 2 Diabetes on Optimized Insulin Glargine With or Without Metformin: A Randomized, Open-Label Trial. Diabetes Care [Internet]. 2015 Jul [cited 2017 Jul 7];38(7):1263-73. Available from: http://care.diabetesjournals.org/content/diacare/38/7/1263

41. Miya A, Nakamura A, Miyoshi H, Cho KY, Nagai S, Kurihara Y, et al. Satisfaction of switching to combination therapy with lixisenatide and basal insulin in patients with type 2 diabetes receiving multiple daily insulin injection therapy: a randomized controlled trial. J Diabetes Investig. 2017 Mar 10.

42. Rosenstock J, Aronson R, Grunberger G, Hanefeld M, Piatti P, Serusclat P, et al. Benefits of LixiLan, a Titratable Fixed-Ratio Combination of Insulin Glargine Plus Lixisenatide, Versus Insulin Glargine and Lixisenatide Monocomponents in Type 2 Diabetes Inadequately Controlled on Oral Agents: The LixiLan-O Randomized Trial. Diabetes Care [Internet]. 2016 Nov [cited 2017 Jul 7];39(11):2026-35. Available from: http://care.diabetesjournals.org/content/diacare/39/11/2026

43. Rosenstock J, Diamant M, Aroda VR, Silvestre L, Souhami E, Zhou T, et al. Efficacy and safety of LixiLan, a titratable fixed-ratio combination of lixisenatide and insulin glargine, versus insulin glargine in type 2 diabetes inadequately controlled on metformin monotherapy: the LixiLan proof-of-concept randomized trial. Diabetes Care. 2016 Sep;39(9):1579-86.

44. Seino Y, Yabe D, Takami A, Niemoeller E, Takagi H. Long-term safety of once-daily lixisenatide in Japanese patients with type 2 diabetes mellitus: GetGoal-Mono-Japan. J Diabetes Complications [Internet]. 2015 Nov [cited 2017 Jul 10];29(8):1304-9. Available from: http://www.sciencedirect.com/science/article/pii/S1056872715002718

45. Tonneijck L, Muskiet MHA, Smits MM, Hoekstra T, Kramer MHH, Danser AHJ, et al. Postprandial renal haemodynamic effect of lixisenatide versus once-daily insulin glulisine in type 2 diabetes patients on insulin-glargine: an 8-week, randomised, open-label trial. Diabetes Obes Metab. 2017 Apr 27.

46. Wysham C, Bonadonna RC, Aroda VR, Puig DM, Kapitza C, Stager W, et al. Consistent findings in glycaemic control, body weight and hypoglycaemia with iGlarLixi (insulin glargine/lixisenatide titratable fixed-ratio combination) vs insulin glargine across baseline HbA1c, BMI and diabetes duration categories in the LixiLan-L trial. Diabetes Obes Metab. 2017 Apr 6.

47. Yamada Y, Senda M, Naito Y, Tamura M, Watanabe D, Shuto Y, et al. Reduction of postprandial glucose by lixisenatide vs sitagliptin treatment in Japanese patients with type 2 diabetes on background insulin glargine: a randomized phase IV study (NEXTAGE Study). Diabetes Obes Metab. 2017 Mar 26.

48. Kolotkin RL, Crosby RD, Kosloski KD, Williams GR. Development of a brief measure to assess quality of life in obesity. Obes Res [Internet]. 2001 Feb [cited 2017 Jul 25];9(2):102-11. Available from: http://onlinelibrary.wiley.com/doi/10.1038/oby.2001.13/full

49. Kolotkin RL, Crosby RD, Williams GR. Assessing weight-related quality of life in obese persons with type 2 diabetes. Diabetes Res Clin Pract. 2003 Aug;61(2):125-32.

50. Kolotkin RL, Crosby RD. Psychometric evaluation of the impact of weight on quality of life-lite questionnaire (IWQOL-lite) in a community sample. Qual Life Res. 2002 Mar;11(2):157-71.

51. Warkentin LM, Majumdar SR, Johnson JA, Agborsangaya CB, Rueda-Clausen CF, Sharma AM, et al. Weight loss required by the severely obese to achieve clinically important differences in health-related quality of life: two-year prospective cohort study. BMC Med [Internet]. 2014 Oct 15 [cited 2017 Aug 2];12:175. Available from: https://www.ncbi.nlm.nih.gov/pmc/articles/PMC4212133

52. Bentley-Lewis R, Aguilar D, Riddle MC, Claggett B, Diaz R, Dickstein K, et al. Rationale, design, and baseline characteristics in evaluation of LIXisenatide in acute coronary syndrome, a long-term cardiovascular end point trial of lixisenatide versus placebo. Am Heart J. 2015 May;169(5):631-8.

53. Clinical study report no. EFC11319. A randomized, double-blind, placebo-controlled, parallel-group, multicenter study to evaluate cardiovascular outcomes during treatment with lixisenatide in type 2 diabetic patients after an Acute Coronary Syndrome event [**CONFIDENTIAL** internal manufacturer's report]. Paris (FR): Sanofi; 2015 Jun 27.

54. Clinical study report no. EFC12703. A randomized, doubled-blind, placebo-controlled, 2-arm parallel-group, multicenter, 24-week study assessing the safety and efficacy of lixisenatide in older patients with type 2 diabetes inadequately controlled on their current diabetes treatment regimen [**CONFIDENTIAL** internal manufacturer's report]. Paris (FR): Sanofi; 2015 Sep 3.