CADTH

CADTH COMMON DRUG REVIEW

Clinical Review Report

Insulin glargine and lixisenatide injection (Soliqua)

(Sanofi-Aventis)

Indication: adjunct to diet and exercise to improve glycemic control in adults with type 2 diabetes mellitus inadequately controlled on basal insulin (less than 60 units daily) alone or in combination with metformin.

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Abbreviations

A1C	glycated hemoglobin
AE	adverse event
AIA	anti-insulin antibodies
ANCOVA	analysis of covariance
CDR	CADTH Common Drug Review
CI	confidence interval
DDP-4	dipeptidyl peptidase-4
EQ-5D-3L	EuroQol 5-Dimensions 3-levels
EQ-VAS	EuroQol visual analogue scale
FPG	fasting plasma glucose
GLP-1	glucagon-like peptide-1
iGlarLixi	fixed-ratio combination of insulin glargine/lixisenatide
IVRS/IWRS	interactive voice response system/interactive Web response system
IWQoL-Lite	Impact of Weight on Quality of Life–Lite
LSMD	least squares mean difference
MCID	minimal clinically important difference
mITT	modified intention-to-treat
MMRM	mixed-effects model with repeated measures
PPG	post-prandial plasma glucose
SAE	serious adverse event
SD	standard deviation
SE	standard error
SGLT2	sodium-glucose cotransporter-2
SMPG	self-monitored plasma glucose
T2DM	type 2 diabetes mellitus

Drug	Insulin glargine and lixisenatide (Soliqua)
Indication	An adjunct to diet and exercise to improve glycemic control in adults with type 2 diabetes mellitus inadequately controlled on basal insulin (less than 60 units daily) alone or in combination with metformin.
Reimbursement Request	As per indication
Dosage Form(s)	Subcutaneous injection
NOC Date	July 6, 2018
Manufacturer	Sanofi-Aventis Canada

Executive Summary

Introduction

Type 2 diabetes mellitus (T2DM) is a progressive metabolic disorder characterized by consistently elevated plasma glucose levels due to insulin resistance associated with alpha- and beta-cell dysfunction.[1] Prolonged impairment in glycemic control can result in damage to blood vessels, causing dysfunction and organ failure affecting the heart, brain, kidneys, retina, and lower limbs.[2] Diabetes is one of the most common chronic diseases in Canada, 90% of cases being T2DM. According to Diabetes Canada, there were an estimated 3.4 million Canadians (9.3% of the population) living with diabetes in 2015, and, by 2025, this number is expected to increase to 5 million people (12.1% of the population).[3] These factors have resulted in a heavy economic burden of diabetes in Canada.[3]

As T2DM progresses, insulin output further declines; therefore, exogenous insulin administration, with a product such as insulin glargine, is required in order to decrease levels of plasma glucose.[4] Although insulin is a benchmark in the treatment of T2DM, its optimization can be limited by side effects such as hypoglycemia and weight gain. Glucagon-like peptide-1 (GLP-1) analogues, such as lixisenatide, are potent plasma glucose–lowering drugs that mimic the effects of endogenous GLP-1, which stimulates release of insulin in the presence of elevated plasma glucose concentration, resulting in reductions in both fasting and post-prandial plasma glucose concentrations.[5] These actions are associated with decreased gastric emptying and induced satiety, which can provide beneficial effects on weight. GLP-1 analogues are also associated with gastrointestinal side effects, such as nausea, diarrhea, and vomiting.[6] Soliqua is a titratable fixed-ratio combination (iGlarLixi) of basal insulin glargine and the GLP-1 analogue lixisenatide, which is delivered as a once-daily injection. The Health Canada–approved indication for iGlarLixi is an adjunct to diet and exercise to improve glycemic control in adults with T2DM who are inadequately controlled on basal insulin (less than 60 units daily), alone or in combination with metformin.[7] It is available in a pen-injector format, containing 100 units/mL insulin glargine and 33 mcg/mL lixisenatide at a 3:1 ratio, which would allow daily doses of 15 units to 60 units of insulin glargine and 5 mcg to 20 mcg of lixisenatide.[7]

The objective of this review is to perform a systematic review of the beneficial and harmful effects of iGlarLixi for the treatment of adults with T2DM inadequately controlled on basal insulin (alone or with metformin).

Results and Interpretation

Included Studies

One multi-centre, parallel-group, open-label, randomized controlled superiority study met the criteria for inclusion for the CADTH systematic review. LixiLan-L (N = 736)[8] was a pivotal 30-week, active-controlled trial that investigated the efficacy and safety of iGlarLixi in adult patients with T2DM who were inadequately controlled on basal insulin, with or without metformin. Patients were randomized in a 1:1 ratio to iGlarLixi (N = 367) or insulin glargine (N = 369). The primary efficacy outcome was the mean change from baseline in glycated hemoglobin (A1C) at week 30. The secondary efficacy end points included change in body weight, fasting plasma glucose, and two-hour glucose excursion. Additional exploratory efficacy outcomes included the proportions of patients achieving an A1C < 7% and ≤ 6.5%, change in health-related quality of life measures, such as the EuroQol 5-Dimensions (EQ-5D) questionnaire and the Impact of Weight on Quality of Life–Lite (IWQoL-Lite) questionnaire, and changes in two-hour post-prandial plasma glucose over time. Safety outcomes were also measured, including mortality, treatment-emergent adverse events (AEs), serious AEs, withdrawals due to AEs, and notable harms, such as hypoglycemia, immunogenicity, and pancreatitis.

There were a number of limitations noted for this study. First, this study was open-label in its design, which increases potential for bias in reporting of subjective outcomes, such as the reporting of AEs and health-related quality of life. Second, outcomes in this study which were of interest for this review, such as two-hour post-prandial plasma glucose, health-related quality of life measures, risk of hypoglycemic events, and the proportion of patients achieving an A1C < 7% or ≤ 6.5%, were not appropriately adjusted for multiplicity, which would increase the risk of making type I error. Third, insulin glargine in this trial was capped at a dose of 60 units in order to match the maximum allowable insulin glargine dose in iGlarLixi. In a trial that is designed to demonstrate superiority of iGlarLixi versus insulin glargine, there is a concern for the impact of the use of a capped insulin dose in this trial on the clinical generalizability of the results. Finally, this study was limited by the duration of 30 weeks (a maximum of 39 weeks including run-in period), which would limit its ability to detect changes in more clinically important outcomes, such as cardiovascular-related outcomes and mortality.

Efficacy

At week 30, the change in A1C from baseline was found to be greater in the iGlarLixi group (–1.13%; standard deviation [SD] 0.057%) compared with insulin glargine alone (–0.62%; SD 0.055%), and the iGlarLixi group achieved a mean A1C value of 6.94% (SD 0.87%) compared with 7.48% (SD 0.91%) in the insulin glargine group. The difference between the two treatment groups was –0.52% (95% confidence interval [CI], –0.633% to –0.397%) in favour of the iGlarLixi group, and this difference was statistically significant ($P < 0.0001$). Although there is no established minimal clinically important difference for the change in A1C, the clinical expert consulted for this review considered this difference in treatment effect to be clinically relevant and over a duration in which it would be expected to see a meaningful change. Overall, there was a numerically higher proportion of patients in the iGlarLixi group who achieved an A1C less than 7.0% at week 30 (54.9% in the iGlarLixi group versus 29.6% in the insulin glargine group). A similar result was noted for the proportion of patients with an A1C equal to or less than 6.5% at week 30 (33.9% in the iGlarLixi group versus 14.2% in the insulin glargine group). It should be noted, however,

that the results for the proportion of patients achieving an A1C less than 7.0% and equal to or less than 6.5% should be considered exploratory, as they were not part of the statistical testing hierarchy and therefore not adjusted for multiplicity.

Patients treated with iGlarLixi also experienced a statistically significantly greater reduction in two-hour plasma excursion (least squares mean difference [LSMD] –3.43 mmol/L; 95% CI, –3.925 mmol/L to –2.939 mmol/L; $P < 0.0001$). Change in two-hour post-prandial plasma glucose from baseline to week 30 was not part of the statistical testing hierarchy and therefore should be considered exploratory given the increased risk of type I error.

There was no significant difference observed between the two groups with respect to the change in fasting plasma glucose from baseline to week 30, with an adjusted mean difference of 0.11 mmol/L (95% CI, –0.207 mmol/L to 0.428 mmol/L; $P = 0.4951$); however, these results should be considered exploratory, given that the statistical testing order failed, at the end point of change in insulin dose at week 30 before the testing for significance in fasting plasma glucose.

Mean body weight from baseline to week 30 was found to have decreased in the iGlarLixi group (–0.67 kg; standard error [SE] 0.181 kg) and there was an increase observed in the insulin glargine group (+0.70 kg; SE 0.178 kg). There was a statistically significant difference between groups for change in mean body weight from baseline to week 30 (adjusted LSMD –1.37 kg; 95% CI, –1.808 kg to –0.930 kg, $P < 0.0001$).

[redacted]

Two indirect treatment comparisons were reviewed (one submitted by the manufacturer and one was found through a CADTH Common Drug Review literature search). The manufacturer-submitted indirect comparison (IDC) compared the efficacy of iGlarLixi with currently available regimens for T2DM. The primary outcomes for this study included glycemic control end points, weight changes, and risk of hypoglycemic events. With regard to glycemic control, the only comparison that consistently showed a favourable result compared with iGlarLixi was basal insulin (once daily) + one oral antidiabetes drug. iGlarLixi was also found to be potentially better at reducing weight gain when compared with insulin regimens and DPP-4 inhibitors in conjunction with basal insulin, but not when compared with GLP-1 receptor agonists in conjunction with basal insulin (with the exception of albiglutide). Finally, iGlarLixi showed a favourable hypoglycemic profile against basal insulin regimens alone and against GLP-1 receptor agonists in conjunction with basal insulin, although results were not available for comparisons with combination of insulin degludec/liraglutide (iDegLira), liraglutide, dulaglutide, or any DPP-4 inhibitor. The IDC found in the literature (Evans et al. 2018)[9] examined phase III trials comparing iGlarLixi and iDegLira in insulin-experienced patients. iDegLira was found to be better than iGlarLixi at reducing A1C from baseline as well as reducing weight.

The two identified IDCs have several limitations, reducing the overall certainty in the results; the manufacturer's IDC is not up to date and is missing evidence published within the last two years, while the literature-identified IDC did not follow a systematic review approach and included only pivotal trials of various diabetes interventions. Other limitations have been identified in Appendix 7.

Harms

The percentage of patients reporting any treatment-emergent adverse reactions was similar for the iGlarLixi group (53.4%) and the insulin glargine group (52.3%). The percentage of patients who had experienced serious AEs was also similar between groups (5.5% versus 4.9%, respectively). The most frequently reported treatment-emergent AEs that occurred more frequently in the iGlarLixi group were nausea (10.4% compared with 0.5%), headache (5.8% compared with 2.7%), diarrhea (4.4% compared with 2.7%), and vomiting (3.6% compared with 0.5%). The rate of withdrawals due to AEs was low in both groups (< 3%); however, it was higher in the iGlarLixi group (2.7%) than in the insulin glargine group (0.8%). The most commonly cited reason for withdrawal in the iGlarLixi group was nausea (1.1%). There were three deaths observed during this trial, one belonging to the iGlarLixi group and two belonging the insulin glargine group. The cause of death for the patient in the iGlarLixi group was pneumonia, and for those in the insulin group, it was cardiopulmonary failure and gallbladder cancer.

The observed frequency of patients who experienced at least one event of documented symptomatic hypoglycemia (an event with typical symptoms of hypoglycemia with a measured plasma glucose concentration ≤ 3.9 mmol/L) for the iGlarLixi group was 40.0% and 42.5% for those on insulin glargine. The occurrence of severe hypoglycemia throughout the open-label treatment period of this study was numerically higher in the iGlarLixi group (1.1% in the iGlarLixi group and 0.3% in the insulin glargine group).

Allergic reactions were low in frequency and similar between patients in the iGlarLixi group (0) compared with those taking insulin glargine (0.3%). There was no documented occurrence of pancreatitis throughout this study.

Potential Place in Therapy[1]

Only about 40% of patients with T2DM treated with basal insulin, with or without other oral antidiabetes drugs, achieve A1C targets, and these individuals require additional therapy to improve glycemia. A traditional approach for managing these individuals has been the addition of prandial insulin from one to three times daily, but this therapy increases complexity and the number of injections and is associated with weight gain and hypoglycemia. There is an unmet need for patients requiring intensification beyond basal insulin for a simple and convenient therapy that will not increase hypoglycemia and will provide a weight benefit. GLP-1 receptor analogues are ideal drugs to combine with basal insulin, due to their simple titration regimens, improvement in A1C, and post-prandial plasma glucose, without increasing hypoglycemia and weight-loss benefits.

Fixed-ratio combinations of basal insulin with GLP-1 analogues allow for combining these two classes in a single injection. iGlarLixi has been studied in patients with T2DM suboptimally controlled on basal insulin, with or without up to two oral drugs, in the LixiLan-L trial.[8] The therapy of titrated iGlarLixi compared with insulin glargine was found to significantly improve A1C and lower body weight without increasing hypoglycemia. iGlarLixi was well tolerated, with lower rates of gastrointestinal adverse effects than other lixisenatide trials, likely due to the slow titration during the trial.

The trial data with iGlarLixi support using this drug in patients with an elevated A1C despite therapy with basal insulin, with or without metformin or other oral drugs. It also adds the

[1] This information is based on information provided in draft form by the clinical expert consulted by CDR reviewers for the purpose of this review.

convenience of a single injection with two drugs, rather than separate injections of basal insulin and a GLP-1 analogue. It may be particularly useful for patients with good fasting glucose control on basal insulin, but elevation in A1C and post-prandial hyperglycemia, especially after the largest daily meal. The weight benefit versus insulin alone is also important, given that about 85% of individuals with T2DM are overweight or obese.

iGlarLixi provides a novel way to combine a GLP-1 analogue with basal insulin in a convenient single injection for individuals with elevated A1C despite therapy with basal insulin. Its use in practice will be consistent with Diabetes Canada 2018 guidelines that recommend "a GLP-1 receptor analogue be considered as add-on therapy to basal insulin before initiating bolus insulin or intensifying insulin to improve glycemic control with weight loss and a lower hypoglycemia risk compared with single or multiple bolus insulin injections."[5]

Conclusions

One open-label, multi-centre, parallel-group randomized controlled trial in adults with T2DM who were inadequately controlled on basal insulin compared the use of iGlarLixi with insulin glargine for up to 30 weeks. There was a statistically significant improvement in A1C in favour of iGlarLixi compared with insulin glargine from baseline to week 30, and this difference was considered to be clinically relevant. Patients in the iGlarLixi group were also found to have a decrease in mean body weight after more than 30 weeks. There were no clinically relevant improvements in health-related quality of life outcomes observed when comparing iGlarLixi with insulin glargine. The percentage of patients experiencing at least one AE was similar between iGlarLixi and insulin glargine, with gastrointestinal effects reported at a higher frequency among patients taking iGlarLixi compared with those taking insulin glargine. The proportion of patients reporting symptomatic hypoglycemia was lower in the iGlarLixi group; however, there was a higher percentage of patients reporting severe symptomatic hypoglycemia in the iGlarLixi group compared with the insulin glargine group. There were no data available on the use of iGlarLixi beyond 30 weeks. The manufacturer-submitted IDC suggested that iGlarLixi is better than basal insulin combined with one oral antidiabetes drug for glycemic control between 20 to 30 weeks; comparisons between iGlarLixi and other treatment options in the analyses were inconclusive. The overall certainty of the results of the manufacturer-submitted IDC is limited, most notably because the literature search to inform the IDC was not up to date, and, therefore, the results do not reflect all available evidence.

Table 1: Key Efficacy and Safety Outcomes at Week 30 for iGlarLixi and Insulin Glargine in Patients with Type 2 Diabetes in the LixiLan-L Study

End Point	iGlarLixi (N = 367)	Insulin Glargine (N = 369)
Efficacy		
A1C, %	**N = 364**	**N = 364**
Mean baseline value (SD)	8.07 (0.68)	8.08 (0.73)
Mean end point value at week 30 (SD)	6.94 (0.87)	7.48 (0.91)
LS mean change from baseline (SE)[a]	–1.13 (0.057)	–0.62 (0.055)
LS mean difference of iGlarLixi versus insulin glargine [95% CI][a]	–0.52 [–0.633 to –0.397]	
P value[a]	< 0.0001	
2-hour glucose excursion (mmol/L)	**N = 329**	**N = 336**
Mean baseline value (SD)	7.01 (3.47)	7.14 (3.11)
Mean end point value at week 30 (SD)	3.11 (3.55)	6.71 (3.34)
LS mean change from baseline (SE)[b]	–3.90 (0.28)	–0.47 (0.27)
LS mean difference of iGlarLixi versus insulin glargine [95% CI][b]	–3.43 [–3.925 to –2.939]	
P value[b]	< 0.0001	
Body weight (kg)	**N = 365**	**N = 365**
Mean baseline value (SD)	87.81 (14.42)	87.09 (14.75)
Mean end point value at week 30 (SD)	87.48 (14.35)	87.96 (15.08)
LS mean change from baseline (SE)[a]	–0.67 (0.181)	0.70 (0.178)
LS mean difference of iGlarLixi versus insulin glargine [95% CI][a]	–1.37 [–1.808 to –0.930]	
P value[a]	< 0.0001	
Fasting plasma glucose (mmol/L)	**N = 364**	**N = 364**
Mean baseline value (SD)	7.33 (1.94)	7.32 (2.07)
Mean end point value at week 30 (SD)	6.78 (2.26)	6.69 (2.05)
LS mean change from baseline (SE)[a]	–0.35 (0.142)	–0.46 (0.138)
LS mean difference of iGlarLixi versus insulin glargine [95% CI][a,c]	0.11 [–0.207 to 0.428]	
P value[a,d]	0.4951	
EQ-5D-3L index value	[redacted]	[redacted]
Mean baseline value (SD)	[redacted]	[redacted]
Mean end point value at week 30 (SD)	[redacted]	[redacted]
LS mean change from baseline (SE)[a]	[redacted]	[redacted]
LS mean difference of iGlarLixi versus insulin glargine [95% CI][a,c]	[redacted]	
IWQoL-Lite total score	[redacted]	[redacted]
Mean baseline value (SD)	[redacted]	[redacted]
Mean end point value at week 30 (SD)	[redacted]	[redacted]
LS mean change from baseline (SE)[a]	[redacted]	[redacted]
LS mean difference of iGlarLixi versus insulin glargine [95% CI][a,c]	[redacted]	
Harms		
AEs	**N = 365**	**N = 365**
Patients with > 0 AEs, N (%)	195 (53.4)	191 (52.3)
Nausea	38 (10.4)	2 (0.5)
Nasopharyngitis	32 (8.8)	32 (8.8)
Headache	21 (5.8)	10 (2.7)
Diarrhea	16 (4.4)	10 (2.7)
Vomiting	13 (3.6)	2 (0.5)

End Point	iGlarLixi (N = 367)	Insulin Glargine (N = 369)
SAEs	**N = 365**	**N = 365**
Patients with > 0 SAEs, N (%)	20 (5.5)	18 (4.9)
Acute myocardial infarction	2 (0.5)	0
Hypoglycemia	2 (0.5)	1 (0.3)
Hypoglycemic unconsciousness	2 (0.5)	0
Unstable angina	2 (0.5)	0
WDAEs	**N = 365**	**N = 365**
WDAEs, N (%)	10 (2.7)	3 (0.8)
Nausea	4 (1.1)	0
Hypoglycemic unconsciousness	[redacted]	[redacted]
Dizziness	[redacted]	[redacted]
Other	[redacted]	[redacted]
Deaths	**N = 365**	**N = 365**
Number of deaths, N (%)	1 (0.3)	2 (0.5)
Death due to pneumonia	1 (0.3)	0
Death due to cardiopulmonary failure	0	1 (0.3)
Death due to gallbladder cancer	0	1 (0.3)
ARAC-adjudicated allergic events by patient	**N = 365**	**N = 365**
Any allergic event	0	1 (0.3)
Rhinitis allergic event	0	1 (0.3)
Injection-site reactions	**N = 365**	**N = 365**
Any injection-site reaction	0	2 (0.5)
Injection-site hypertrophy	0	1 (0.3)
Injection-site reaction	0	1 (0.3)

A1C = glycated hemoglobin; AE = adverse event; ARAC = Allergic Reactions Adjudication Committee; CI = confidence interval; EQ-5D-3L = EuroQol 5-Dimensions 3-levels; iGlarLixi = fixed-ratio combination of insulin glargine and lixisenatide; IWQoL-Lite = Impact of Weight on Quality of Life–Lite; LS = least squares; SAE = serious adverse event; SD = standard deviation; SE = standard error; WDAE = withdrawal due to adverse event.

[a] Mixed-effects model with repeated measures (MMRM) with treatment groups (fixed-ratio combination and insulin glargine), randomization strata of A1C (< 8.0%, ≥ 8.0%) at visit 5 (week –1), randomization strata of metformin use at screening (Yes, No), scheduled visit, treatment-by-visit interaction and country as fixed effects, and baseline average self-monitored plasma glucose value-by-visit interaction as a covariate.

[b] Analysis of covariance (ANCOVA) model with treatment groups (fixed-ratio combination and insulin glargine), randomization strata of A1C (< 8.0%, ≥ 8.0%) at visit 5 (week –1), randomization strata of metformin use at screening (Yes, No), and country as fixed effects and baseline two-hour post-prandial plasma glucose value as a covariate.

[c] Per step-down testing procedure. Analyses are considered exploratory.

Source: Clinical Study Report for LixiLan-L.[8]

Introduction

Disease Prevalence and Incidence

Diabetes mellitus is a metabolic disease characterized by persistent elevations in blood glucose (hyperglycemia).[2] This persistent elevated blood glucose causes damage to blood vessels on a microvascular (retinopathy, nephropathy, and neuropathy) and macrovascular (peripheral artery disease and cardiovascular disease) level.[2] 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 (T2DM), in which beta cells are unresponsive to insulin.[10] T2DM is more common than type 1 diabetes mellitus, accounting for approximately 90% of cases of diabetes mellitus.[10] T2DM typically occurs later in life, although this is changing with the current epidemic of childhood obesity in Western societies.[10] Poor diet and minimal exercise, and associated weight gain, are considered to be risk factors for T2DM.[10] The social determinants of health play an important role in developing diabetes and its complications, with the lowest income groups showing the highest risk.[3]

Diabetes mellitus significantly impacts the health of 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, and this number is projected to increase to 642 million by 2040.[2] 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 Canadian population) with diabetes in 2015, and, by 2025, this number will increase to 5 million people (12.1% of the Canadian population).[3] Patients with diabetes are also more likely to be hospitalized and to experience complications requiring specialist care. The economic burden of diabetes in Canada is expected to be about C$12.2 billion in 2010, and, by 2020, the diabetes-associated costs to the Canadian health care system are estimated to increase to C$16.9 billion per year.[3]

Standards of Therapy

Treatment regimens and therapeutic targets should be individualized in patients with T2DM. Treatment usually begins with lifestyle modification, including exercise and diet.[11] When lifestyle interventions are not sufficient to control blood glucose levels, pharmacological treatment becomes necessary.[11] There are a wide variety of classes of antidiabetes drugs available to treat T2DM, including insulin. Metformin is widely considered to be the first-line drug of choice for most patients, with a second or third agent added to metformin or used in combination for patients unable to achieve therapeutic targets.[12] Several oral antidiabetes drugs can be used alongside metformin, such as sulfonylureas, meglitinides, thiazolidinediones (TZDs), alpha-glucosidase inhibitors, dipeptidyl peptidase-4 (DDP-4) inhibitors, and sodium-glucose cotransporter-2 (SGLT2). Key characteristics of these classes of drugs are outlined in Table 2 and Table 3.[11] According to the Diabetes Canada guidelines, injectable drugs (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 therapy is insufficient or after patients are switched to basal insulin.[4,5] Although there are currently numerous therapeutic options and combination therapy strategies available, many patients do not achieve adequate glycemic control on oral antidiabetes treatments alone and require the addition of basal insulin to achieve target glycated hemoglobin (A1C) levels (i.e., < 7.0%).[11] Despite the use of a basal insulin, some

patients require further treatment to achieve or maintain this glycemic target. The addition of one or more injections of a prandial insulin before mealtime is an option; however, this approach also has disadvantages, including complexity, increased self–blood-glucose monitoring, risk of hypoglycemia, and weight gain.[4]

The latest joint position statement of the American Diabetes Association and the European Association for the Study of Diabetes suggested that GLP-1 receptor agonists may be a safer addition to basal insulin in comparison with prandial insulin for short-term outcomes and may be a more appealing option for overweight patients or for those who may find a basal-bolus insulin regimen to be too complex.[13] Although combination products are not specifically mentioned, this sentiment is echoed by the current Diabetes Canada clinical practice guidelines,[5] which recommends that a GLP-1 receptor agonist be considered before bolus insulin as add-on therapy in patients on a basal insulin who require antihyperglycemic treatment intensification, if there are no barriers to affordability or access.

Drug

Insulin glargine and lixisenatide fixed-ratio combination (iGlarLixi) is a multi-ingredient product that contains a long-acting insulin product (insulin glargine) and a GLP-1 receptor agonist (lixisenatide) in a single pen-injector format.[7] As T2DM progresses, endogenous insulin output further declines; therefore, exogenous insulin, such as insulin glargine, is required in order to decrease levels of plasma glucose.[4] Although insulin is a benchmark in the treatment of T2DM, its optimization can be limited by side effects, such as hypoglycemia and weight gain.[4] GLP-1 analogues, such as lixisenatide, are potent plasma glucose–lowering drugs that mimic the effects of endogenous GLP-1. GLP-1 stimulates the release of insulin in the presence of elevated plasma glucose concentration, resulting in reductions in both fasting and post-prandial plasma glucose concentrations.[14] These actions are associated with decreased gastric emptying and induced satiety, which provides beneficial effects on weight. GLP-1 analogues are also associated with gastrointestinal side effects, such as nausea, diarrhea, and vomiting.[5]

iGlarLixi contains 100 units/mL insulin glargine and 33 mcg/mL lixisenatide at a 3:1 ratio, which would allow doses of 15 units to 60 units of insulin glargine and 5 mcg to 20 mcg of lixisenatide to be administered once daily.[7] Health Canada has recently approved this fixed-ratio combination (iGlarLixi) product as an adjunct to diet and exercise to improve glycemic control in adults with T2DM who are inadequately controlled on basal insulin (less than 60 units daily), alone or in combination with metformin.[7] The recommended dosage of iGlarLixi is based on the patient's previous use of oral antidiabetes drugs or previous insulin requirement.

Table 2: Key Characteristics of GLP-1 Analogues, TZDs, DPP-4 Inhibitors, and Insulin

	GLP-1 Analogues	DPP-4 Inhibitors	Insulin/ Insulin Analogues	Basal Insulin/ GLP-1 Analogue Combination
Mechanism of Action	Mimic GLP-1, which: • Leads to insulin secretion • Inhibits glucagon release • Delays gastric emptying • Reduces food intake	Increase GLP-1 by inhibiting the DPP-4 enzyme, which inactivates GLP-1: • Leads to insulin secretion • Inhibits glucagon release • Delays gastric emptying • Reduces food intake	Substitute for endogenously secreted insulin	Mechanism of action associated with that of a GLP-1 analogue and insulin in combination
Indication[a]	Semaglutide: Once-weekly treatment of adult patients with T2DM to improve glycemic control, in combination with metformin, metformin and a sulfonylurea, metformin and basal insulin, or diet and exercise 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 antidiabetes 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-released, once weekly): T2DM that cannot be adequately controlled by diet and exercise alone. 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	Saxagliptin: T2DM in combination with metformin or a sulfonylurea, or 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, or in combination with metformin or a sulfonylurea and metformin, or insulin (with or without metformin) or pioglitazone, or metformin and pioglitazone, when these drugs, with diet and exercise, do not provide adequate glycemic control Linagliptin: T2DM as monotherapy or in combination with metformin or a sulfonylurea, or metformin and a sulfonylurea, when these drugs, with diet and exercise, do not provide adequate glycemic control	Patients with diabetes who require insulin for control of hyperglycemia	Soliqua: an adjunct to diet and exercise to improve glycemic control in adults with T2DM inadequately controlled on basal insulin (less than 60 units daily alone or in combination with metformin). Xultophy: an adjunct to lifestyle modifications for the once-daily treatment of adults with T2DM to improve glycemic control, in combination with metformin, with or without a sulfonylurea, when these combined with basal insulin (less than 50 units daily) or liraglutide (less than or equal to 1.8 mg daily do not provide adequate glycemic control)

	GLP-1 Analogues	DPP-4 Inhibitors	Insulin/ Insulin Analogues	Basal Insulin/ GLP-1 Analogue Combination
	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	Subcutaneous	Subcutaneous
Recommended Dosage	Varies by drug	Varies by drug	Titrated	Titrated
Serious Side Effects / 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	Contraindications: • DKA Warnings/precautions: • heart failure • pancreatitis • immune suppression	Serious warnings and precautions: • hypoglycemia • immune responses	Serious warnings and precautions: • hypoglycemia • immune response • pancreatitis • GI disorders Contraindications: pregnancy • hypersensitivity • hypoglycemic episodes

DKA = diabetic ketoacidosis; DPP-4 = dipeptidyl peptidase-4; GI = gastrointestinal; GLP-1 = glucagon-like peptide-1; MEN2 = multiple endocrine neoplasia syndrome type 2; MTC = medullary thyroid carcinoma; T2DM = type 2 diabetes mellitus.

[a] Health Canada indication.

Source: Product monographs.[15-28]

Table 3: 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 Increases degradation of glucose	Promotes insulin secretion by binding to the sulfonylurea receptor (SUR-1)
Indication[a]	Canagliflozin: • As monotherapy in patients with T2DM for whom metformin is inappropriate • In combination with metformin or a sulfonylurea when diet and exercise plus monotherapy with one of these drugs 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 • Combination therapy with insulin	T2DM which 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 drugs, as an adjunct to exercise and diet

	SGLT2 Inhibitors	Biguanides (Metformin)	Sulfonylurea
	(with or without metformin) when diet and exercise, and therapy with insulin (with or without metformin) do not provide adequate glycemic control Empagliflozin: In T2DM: • As monotherapy as an adjunct to diet and exercise to improve glycemic control in adult patients with T2DM		
Route of Administration	Oral	Oral	Oral
Recommended Dosage	100 mg to 300 mg once daily	850 mg to 1,000 mg twice daily	Varies by drug
Serious Side Effects / Safety Issues	Contraindications: • renal impairment (level of renal impairment varies by drug) Warnings and 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

LDL-C = low-density lipoprotein cholesterol; SGLT2 = sodium-glucose cotransporter-2; T2DM = type 2 diabetes mellitus.

[a] Health Canada indication.

Source: Product monographs.[15-28]

Objectives and Methods

Objectives

To perform a systematic review of the beneficial and harmful effects of insulin glargine and lixisenatide injection (100 units/mL + 33 mcg/mL) used as an adjunct to diet and exercise to improve glycemic control in adults with T2DM, when metformin combined with basal insulin (less than 60 units daily), or basal insulin alone, do not provide adequate glycemic control.

Methods

Studies selected for inclusion in the systematic review included pivotal studies provided in the manufacturer's submission to CADTH Common Drug Review (CDR) and Health Canada, as well as those meeting the selection criteria presented in Table 4.

Table 4: Inclusion Criteria for the Systematic Review

Patient Population	Adults with T2DM in who have experienced inadequate glycemic control on therapy with basal insulin (alone or in combination with metformin) Subgroups: • Age • Baseline A1C • Duration of T2DM • BMI • Previous diabetes therapy • Use of metformin at baseline • Renal function (eGFR)
Intervention	Insulin glargine (100 units/mL) + lixisenatide (33 mcg/mL), in doses of between 15 units insulin glargine + 5 mcg lixisenatide and 60 units insulin glargine + 20 mcg lixisenatide for administration once daily (alone or in combination with metformin)
Comparators	Basal insulin (with or without metformin) in combination with one or more of the following (as fixed-ratio combinations or as individual components): • SGLT2 inhibitors • Incretin mimetics (DPP-4 inhibitors and GLP-1 analogues) • Insulin/insulin analogues (including additional basal and prandial regimens) or • Placebo
Outcomes	**Efficacy outcomes:** • Mortality (all-cause, CV-related) • Diabetes-related morbidity (macrovascular, microvascular)[a] • Glycemic control (e.g., A1C, FPG, PPG, glucose excursion)[a] • Health-related quality of life (measured by a validated scale)[a] • Hospitalization (CV-related, all-cause) • Body weight[a] • Blood pressure • Health care resource utilization

Outcomes	**Harms outcomes:** • Mortality • AEs • SAEs • WDAEs • Notable harms (i.e., hypoglycemic events (severe versus mild/moderate), pancreatitis, immunogenicity, nausea/vomiting, diarrhea)
Study Design	Published and unpublished RCTs, phase III and IV

A1C = glycated hemoglobin; AE = adverse event; BMI = body mass index; CV = cardiovascular; DPP-4 = dipeptidyl peptidase-4; eGFR = estimated glomerular filtration rate; FPG = fasting plasma glucose; GLP-1 = glucagon-like peptide-1; PPG = post-prandial glucose; RCT = randomized controlled trial; SAE = serious adverse event; SGLT2 = sodium-glucose cotransporter-2; T2DM = type 2 diabetes mellitus; WDAE = withdrawal due to adverse event.

[a] Identified as important in the patient input.

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 All (1946–) 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 concepts were insulin glargine and lixisenatide.

No methodological filters were applied to limit retrieval to study type. Retrieval was not limited by publication year or by language. Conference abstracts were excluded from the search results. See Appendix 2 for the detailed search strategies.

The initial search was completed on June 18, 2018. Regular alerts were established to update the search until the meeting of the CADTH Canadian Drug Expert Committee on October 17, 2018. 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 (https://www.cadth.ca/grey-matters): health technology assessment agencies, health economics, clinical practice guidelines, drug and device regulatory approvals, advisories and warnings, drug-class reviews, and databases. 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 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 5, excluded studies (with reasons) are presented in Appendix 3: Excluded Studies.

Results

Findings from the Literature

A total of one study was identified from the literature for inclusion in the systematic review (

Figure 1). The included study is summarized in Table 5. A list of excluded studies is presented in Appendix 3: Excluded Studies

Figure 1: Flow Diagram for Inclusion and Exclusion of Studies

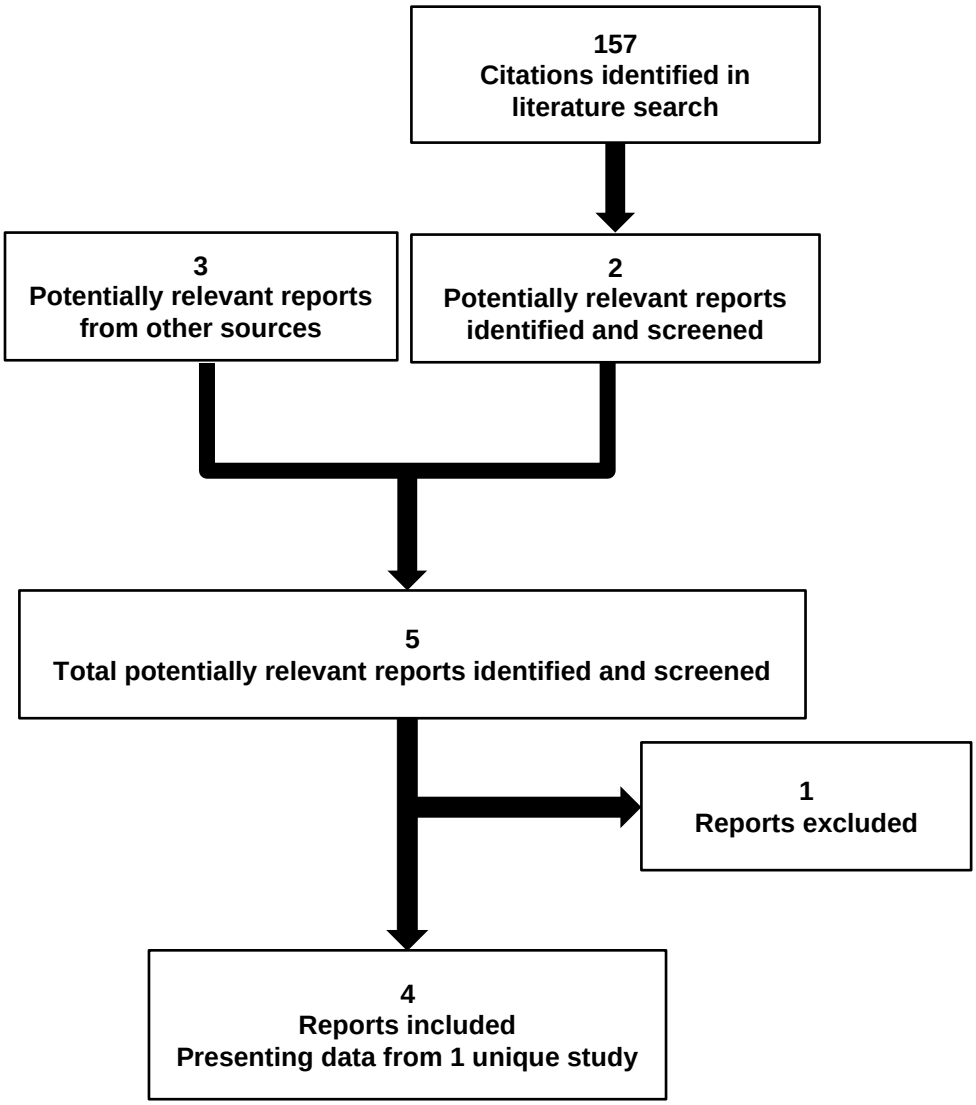


Table 5: Details of Included Studies

		LixiLan-L (405)
Designs and Populations	**Study Design**	Active-controlled, parallel-group, open-label RCT
	Locations	Australia, Canada, Chile, Czech Republic, Denmark, Estonia, Hungary, Lithuania, Mexico, Netherlands, Poland, Romania, Russia, Slovakia, Spain, Sweden, Ukraine, US
	Randomized	736
	Inclusion Criteria	• Adults with T2DM diagnosed at least 1 year prior to screening visit • Treatment with basal insulin for ≤ 6 months prior to screening, with a stable regimen (i.e., type of insulin and time/frequency of the injection) ≤ 3 months prior to screening • Stable basal insulin regimen (± 20%) between 15 and 40 units/day for ≤ 2 months prior to screening • If receiving basal insulin and 1 or 2 OADs, the OAD dose(s) must be stable ≤ 3 months prior to the screening, and the OADs can be 1 or 2 of metformin (≥ 1,500 mg/day or maximum tolerated dose), sulfonylurea, meglitinide, DPP-4 inhibitor, or SGLT2 inhibitor At screening: • A1C ≥ 7.5% or ≤ 10.0% • FPG ≤ 10.0 mmol/L for those receiving basal insulin in combination with two OADs or with one OAD other than metformin • FPG ≤ 11.1 mmol/L for those on basal insulin only or basal insulin plus metformin At the end of the 6-week run-in phase (before randomization): • A1C ≥ 7.0% or ≤ 10.0% • Mean fasting SMPG ≤ 7.8 mmol/L calculated for the seven days prior to randomization • Average insulin glargine daily dose ≥ 20 units or ≤ 50 units for the last three days before randomization
	Exclusion Criteria	• Age under the legal age of adulthood at screening visit • A1C < 7.5% or > 10% or BMI ≤ 20 or > 40 kg/m^2 at screening visit • History of hypoglycemia unawareness • History of metabolic acidosis, including diabetic ketoacidosis ≤ 1 year prior to screening visit • Use of oral or injectable glucose-lowering drugs other than those stated in the inclusion criteria in the 3 months prior to screening, including lixisenatide • Use of insulin other than basal insulin (e.g., prandial or pre-mixed insulin) in the year prior to screening, excluding short-term treatment (≤ 10 days) due to intercurrent illness • Previous discontinuation of treatment with GLP-1 agonist for safety/tolerability or lack of efficacy • History of pancreatitis (unless pancreatitis was related to gallstones and cholecystectomy was already performed), chronic pancreatitis, pancreatitis during a previous treatment with incretin therapies, pancreatectomy, stomach/gastric surgery • Renal function impairment with creatinine clearance < 30 mL/min or ESRD
Drugs	**Intervention**	• Soliqua 20 units/10 mcg (Pen A) if insulin glargine dose on the day before randomization < 30 units • Soliqua 30 units/10 mcg (Pen B) if insulin glargine dose on the day before randomization ≥ 30 units
	Comparator(s)	Insulin glargine (100 units/mL) alone to a maximum of 60 units daily
Phase	Run-in	6 weeks
	Open-label	30 weeks
	Follow-up	3 days
Outcomes	**Primary End Point**	Change in A1C from baseline to week 30
	Other End Points	• Change in FPG (measured in central laboratory) from baseline to week 30 • Change in 2-hour PPG and blood glucose excursion during a standardized meal test from baseline to week 30, at 30 minutes, 1 hour, or 2 hours • Change in body weight from baseline to week 30 • Change in 7-point SMPG profile from baseline to week 30 (each time point and average daily value) • Change in daily dose of insulin glargine from baseline to week 30 • Percentage of patients reaching A1C ≤ 6.5% and < 7.0% at week 30 • Percentage of patients requiring rescue therapy during treatment period • Change in patient-reported outcomes from baseline to week 30 (EQ-5D, IWQoL-Lite)

		LixiLan-L (405)
Notes	**Publications**	Aroda et al. (2016)[29]

A1C = glycated hemoglobin; BMI = body mass index; DPP-4 = dipeptidyl peptidase-4; EQ-5D = EuroQol 5-Dimensions questionnaire; ESRD = end-stage renal disease; FPG = fasting blood glucose; IWQoL-Lite = Impact of Weight on Quality of Life–Lite; OAD = oral antidiabetes drug; RCT = randomized controlled trial; SGLT2 = sodium-glucose cotransporter-2; SMPG = self-monitored plasma glucose; T2DM = type 2 diabetes mellitus.

Source: Clinical Study report for LixiLan-L,[8] Aroda et al. (2016);[29] two additional reports were included (FDA Medical and Statistical Review Reports).[30,31]

Included Studies

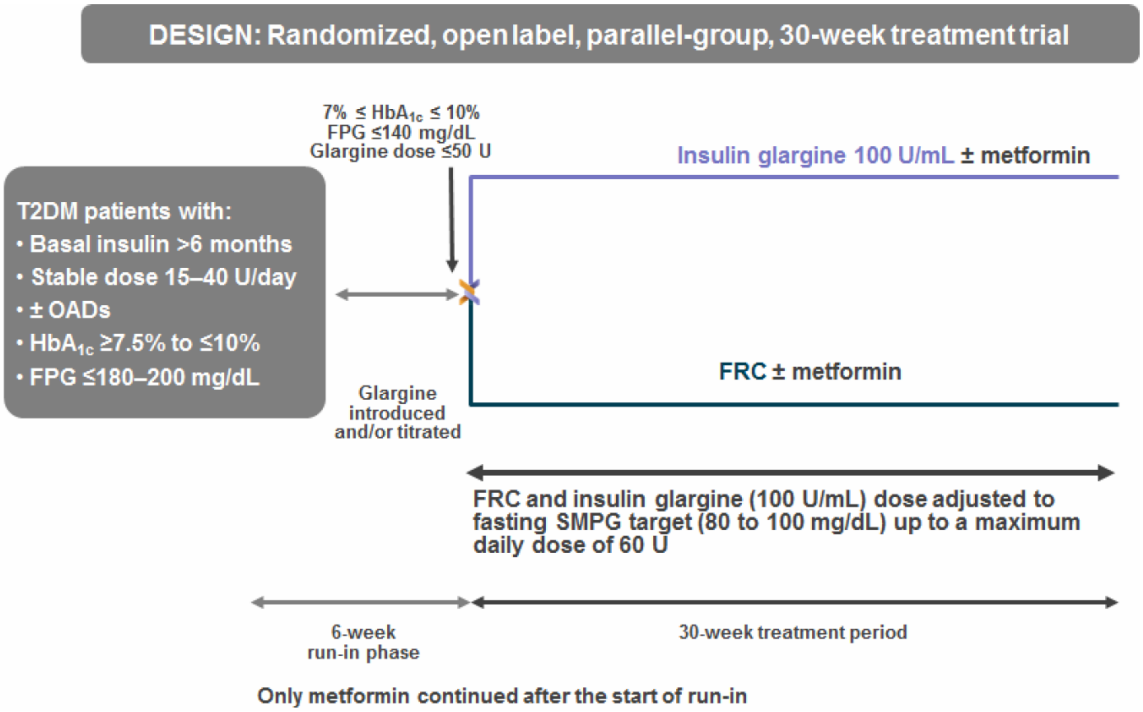
Description of Study

LixiLan-L (N = 736) was a randomized, 30-week, treat-to-target, active-controlled, open-label, parallel-group, superiority trial that enrolled patients who had been diagnosed with T2DM for at least one year at the time of screening with inadequate glycemic control, despite the use of a basal insulin, with or without the use of one to two oral antidiabetes drugs. This study included two treatment arms (iGlarLixi or insulin glargine alone), with or without the use of metformin in both arms, randomized at a 1:1 ratio.

Figure 2 provides an overview of the LixiLan-L study. This study was made up of four phases: a screening phase of up to two weeks, a six-week run-in phase, a 30-week treatment phase, and a three-day post-treatment safety phase. During the screening phase, patients had to be on a stable (± 20%) basal insulin dose of 15 units to 40 units and, for those randomized into the trial, a dose of ≤ 50 units at the end of the run-in phase. Eligible patients subsequently entered the run-in phase, in which the only basal insulin allowed was insulin glargine. As a result, patients who were receiving any other basal insulin were switched to insulin glargine at this time. During the run-in phase, patients were trained on the SoloSTAR pen device, after which they were expected to self-administer insulin glargine once daily at the same time every day. Dietary and lifestyle consultations were provided to all participants at the start of both the run-in and treatment phases. During the run-in phase, insulin glargine doses were adjusted based on daily measured fasting self-monitored plasma glucose (SMPG) to a target of 7.8 mmol/L in the seven days before the randomization visit, while avoiding hypoglycemia. Any oral antidiabetes drugs other than metformin that were previously being taken were discontinued. Patients previously taking metformin at a dose ≥ 1,500 mg per day or at a maximally tolerated dose were continued at a stable dose throughout the study. After the run-in phase, patients with an A1C of 7.0% or greater despite having a fasting plasma glucose (FPG) level of 7.8 mmol/L or lower, whose average insulin glargine daily dose for the previous 3 days was 20 units or more and up to 50 units, were randomized to either receive iGlarLixi or to continue on insulin glargine. Both treatments were administered with or without metformin. The maximum daily dose of insulin glargine was 60 units for both groups, and the maximum dose of lixisenatide was 20 mcg for the iGlarLixi group. At the time of randomization, patients were stratified by screening A1C value (< 8.0%, ≥ 8.0%) and metformin use (Yes or No).

Patients in this study were provided with protocol-specific training on the pen-injector devices, as well as the treatment schedules and dosage algorithms.

Figure 2: Design of LixiLan-L Study



FPG = fasting plasma glucose; FRC = fixed-ratio combination of insulin glargine and lixisenatide; HbA_{1c} = glycated hemoglobin; OAD = oral antidiabetes drug; T2DM = type 2 diabetes mellitus; U = units.

Source: Clinical Study Report for LixiLan-L.[8]

Populations

Inclusion and Exclusion Criteria

This trial aimed to include adult patients with T2DM for at least one year who had had previously been treated with a basal insulin for at least six months prior to their screening visit. The dose and regimen of their basal insulin, including the type of insulin and frequency of injection, were required to be stable for at least three months prior to screening, at a dosage of between 15 units and 40 units per day. Patients could be treated with one or two oral antidiabetes drugs at the time of screening; however, the oral antidiabetes drugs were required to be one or two of metformin, a sulfonylurea, meglitinide, a DPP-4 inhibitor, or an SGLT2 inhibitor. For patients receiving basal insulin in combination with two oral antidiabetes drugs (or with one oral antidiabetes drug other than metformin) to be considered for inclusion, they needed to have an FPG level of at most 10.0 mmol/L at screening, and for patients on basal insulin alone or basal insulin and metformin, they needed to have an FPG level of at most 11.1 mmol/L at screening. Those with an A1C less than 7.5% or greater than 10% were excluded from this trial, as well as those with a renal function impairment with a creatinine clearance < 30 mL/min or end-stage renal disease, for patients not treated with metformin.

Baseline Characteristics

The baseline characteristics of patients included in the LixiLan-L trial are shown in the Table 6. The treatment groups appeared to be balanced in terms of age, gender, and race, with race being predominantly white (91.7%). There was a higher percentage of patients with a creatinine clearance from 30 mL/min to 60 mL/min in the iGlarLixi group (4.9%) than in the insulin glargine group (2.5%).

Patients in this study had an overall mean duration of diabetes of 12 years, with a mean duration of three years using basal insulin. Screening A1C levels were similar between groups, with a mean A1C of 8.07% in the iGlarLixi group and 8.08% in the insulin glargine group. The overall mean daily dose of insulin glargine was approximately 35 units at the time of randomization.

There was a similar percentage of patients using metformin at screening, with 89.6% in the iGlarLixi group and 89.2% in the insulin glargine group. The percentage of patients using two oral antidiabetes drugs at screening was 43.6% and 37.9% in the iGlarLixi and insulin glargine groups, respectively, and the most frequently encountered combination was metformin plus a sulfonylurea.

Table 6: Summary of Baseline Characteristics in LixiLan-L Study

Baseline Characteristics		iGlarLixi (N = 367)	Insulin Glargine (N = 369)
Sex	Males, N (%)	165 (45.0)	179 (48.5)
Age	Mean (SD)	59.6 (9.4)	60.3 (8.7)
	Median (range)	60.0 (36, 85)	61 (32, 80)
	≥ 65 years, N (%)	110 (30.0)	120 (32.5)
Race	White, N (%)	337 (91.8)	338 (91.6)
	Black, N (%)	17 (4.6)	21 (5.7)
	Asian, N (%)	12 (3.3)	8 (2.2)
	Other, N (%)	1 (0.3)	2 (0.5)
Creatinine clearance[a] (mL/min), N (%)	30 to < 60	18 (4.9)	9 (2.5)
	60 to < 90	104 (28.4)	117 (31.9)
	≥ 90	244 (66.7)	241 (65.7)
Weight (kg)	Mean (SD)	87.71 (14.5)	87.11 (14.8)
	Median (range)	87.90 (44.3 to 127.5)	84.90 (44.8 to 135.6)
BMI (kg/m^2)	Mean (SD)	31.46 (4.27)	31.08 (4.17)
	Median (range)	31.31 (20.4 to 40.0)	30.76 (20.3 to 40.0)
	< 30, N (%)	156 (42.5)	158 (42.8)
	≥ 30, N (%)	219 (59.7)	212 (57.5)
Country of origin, N (%)	Canada, N (%)	[redacted]	[redacted]
	USA, N (%)	[redacted]	[redacted]
	Eastern Europe, N (%)	[redacted]	[redacted]
	Mexico, N (%)	[redacted]	[redacted]
	Russia, N (%)	[redacted]	[redacted]
	Other, N (%)	[redacted]	[redacted]
A1C at week 1, %	Mean (SD)	8.07 (0.68)	8.08 (0.73)
	Median (range)	8.00 (6.6 to 10.2)	8.10 (5.9 to 10.0)
FPG (mg/dL)	Mean (SD)	132.23 (35.11)	132.53 (38.24)

Baseline Characteristics		iGlarLixi (N = 367)	Insulin Glargine (N = 369)
	Median (range)	127.90 (57.6 to 282.8)	126.10 (59.4 to 309.9)
2-hour PPG (mg/dL)	Mean (SD)	265.31 (68.41)	269.75 (68.03)
	Median (range)	263.02 (63.1 to 466.6)	266.62 (88.3 to 495.4)
Average 7-point SMPG (mg/dL)	Mean (SD)	165.99 (28.54)	163.01 (28.89)
	Median (range)	163.79 (95.3 to 249.4)	161.75 (84.9 to 283.6)
Duration of diabetes (years)	Mean (SD)	12.02 (6.04)	12.13 (6.85)
	Median (range)	10.49 (1.1 to 36.7)	11.32 (1.0 to 42.7)
Duration of prior basal insulin treatment (years)	Mean (SD)	3.12 (3.06)	3.31 (3.08)
	Median (range)	2.15 (0.4 to 20.6)	2.29 (0.2 to 24.8)
Average daily dose of insulin glargine at randomization (units)	Mean (SD)	35.04 (9.22)	35.23 (8.63)
	Median (range)	35.00 (15.0 to 58.0)	36.00 (12.0 to 52.0)
Metformin use at screening, N (%)		[redacted]	[redacted]
Duration of metformin treatment (years)	Mean (SD)	[redacted]	[redacted]
	Median (range)	[redacted]	[redacted]
Daily dose of metformin at baseline (mg)	Mean (SD)	[redacted]	[redacted]
	Median (range)	[redacted]	[redacted]
Number of OAD use at screening, N (%)	No OAD	18 (4.9)	19 (5.1)
	1 OAD	189 (51.5)	210 (56.9)
	Metformin only	170 (46.3)	190 (51.5)
	Sulfonylurea only	16 (4.4)	14 (3.8)
	2 OADs	160 (43.6)	140 (37.9)
	Metformin + sulfonylurea	137 (37.3)	118 (32.0)
	Metformin + DPP-4 Inhibitor	20 (5.4)	18 (4.9)
Duration of first OAD use (years)	Mean (SD)	8.40 (5.51)	8.24 (5.64)
	Median (range)	7.75 (0.3 to 28.3)	7.41 (0.3 to 30.8)
Duration of second OAD use (years)	Mean (SD)	4.35 (3.53)	4.75 (4.95)
	Median (range)	3.55 (0.3 to 23.6)	3.05 (0.2 to 29.7)

A1C = glycated hemoglobin; BMI = body mass index; DPP-4 = dipeptidyl peptidase-4; FPG = fasting plasma glucose; iGlarLixi = fixed-ratio combination of insulin glargine and lixisenatide; OAD = oral antidiabetes drug; PPG = post-prandial glucose; SD = standard deviation; SMPG = self-monitored plasma glucose.

[a] Derived using Cockcroft–Gault.

Source: Clinical Study Report for LixiLan-L.[8]

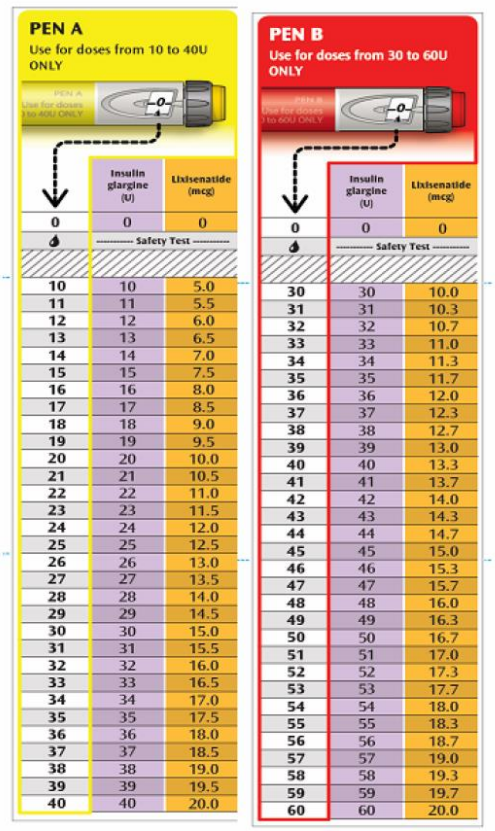
Interventions

Insulin Glargine/Lixisenatide Fixed-Ratio Combination (iGlarLixi)

The iGlarLixi used in the LixiLan-L trial was a sterile solution supplied in a pre-filled disposable SoloSTAR pen injector, with only the insulin glargine dose appearing in the pen dose window. In this study, two pens with two different ratios and dose ranges were used (Figure 1). Pen A contained 100 units/mL of insulin glargine and 50 mcg/mL of lixisenatide. This pen was used for a total daily dose of 10 units to 40 units of insulin glargine and delivered a fixed ratio of 2 units of insulin glargine following 1 mcg of lixisenatide (2:1). Therefore, each unit of insulin glargine was administered with 0.5 mcg of lixisenatide. Pen B contained 100 units/mL insulin glargine and 33 mcg/mL lixisenatide. This pen was used for a total daily dose of 41 units to 60 units of insulin glargine and delivered a fixed ratio of 3 units of insulin glargine following 1 mcg of lixisenatide (3:1). Therefore, each unit of insulin

glargine was given with 0.33 mcg of lixisenatide. The maximum daily dose within both pens was 60 units of insulin glargine and 20 mcg lixisenatide per day, which was only achieved concomitantly with Pen B. Of the two pens, only Pen B was submitted for approval to Health Canada.

Figure 3: Pens A and B Used in the Fixed-Ratio Combination Trial LixiLan-L



U = units.
Source: Clinical Study Report for LixiLan-L.[8]

iGlarLixi was administered subcutaneously once daily within one hour before breakfast. The dose of iGlarLixi was individualized based on the patient's need for insulin, clinical response, and previous insulin dose.

Patients who switched from basal insulin to iGlarLixi began treatment at a daily lixisenatide dose of 10 mcg using either Pen A (20 units insulin glargine) or Pen B (30 units insulin glargine), depending on the insulin glargine dose received on the day before randomization. During titration, either Pen A or Pen B was used, based on the required iGlarLixi daily dose. Pen A was used for patients with an insulin glargine dose less than 40 units and Pen B was used for doses between 41 units and 60 units. Throughout this study, patients who initiated treatment with Pen A who subsequently required a daily insulin glargine dose greater than 40 units were switched to Pen B.

Insulin Glargine

Those assigned to the comparator arm received insulin glargine, supplied as a sterile solution in a disposable pre-filled Lantus SoloSTAR pen injector. Each pen contained 300 units of insulin glargine in 3 mL of solution. According to its labelling instructions, insulin glargine was to be self-administered once daily at any time of the day but at the same time every day throughout both the run-in and treatment phases. The injection time was selected at the discretion of patients and investigators at the start of the run-in phase.

Patients already treated with insulin glargine entered the run-in phase taking the same dose received prior to screening. Patients receiving a different basal insulin were switched to insulin glargine at the start of the run-in phase. Patients previously taking insulin detemir were given 80% of the total daily dose at the start of run-in, and patients taking any basal insulin other than insulin glargine and insulin detemir at a once-daily interval were given the total daily dose at the start of run-in. Patients taking a basal insulin other than insulin glargine and insulin detemir more than once daily were given 80% of their total daily dose. Doses were adjusted in accordance with daily measured fasting SMPG, with a target of 7.8 mmol/L or lower, measured for seven days before the randomization visit, while avoiding hypoglycemia. The titration procedure for patients on insulin glargine for the seven days before randomization was at the discretion of the investigator. Small dose increases were permitted at this time in the case of hypoglycemia, at the investigator's discretion.

Patients subsequently randomized to insulin glargine had to administer the same daily dose on the day of randomization as the day before randomization. After this point, the dose was titrated on a weekly basis in accordance with the algorithm used for the iGlarLixi group.

Titration

In the randomization phase of the LixiLan-L study, the iGlarLixi and insulin glargine treatments were both titrated on a weekly basis using a treat-to-target approach, with a fasting SMPG target of 4.4 mmol/L to 5.6 mmol/L, inclusive. Any changes in dose were made on a weekly basis, in accordance with the median of fasting SMPG values from the previous three days, measured by patients using glucometers and accessories, which were sponsor-supplied, as shown in Table 7.

Table 7: Dose-Adjustment Algorithm for iGlarLixi and Insulin Glargine During the Randomization Phase of the LixiLan-L Study

Median of Fasting SMPG Values From the Last 3 Days	Dose Change (units/day)
> 7.8 mmol/L	+4
> 5.6 mmol/L and ≤ 7.8 mmol/L	+2
4.4 mmol/L to 5.6 mmol/L	No change
≥ 3.3 mmol/L and < 4.4 mmol/L	–2
< 3.3 mmol/L or occurrence of ≥ 2 symptomatic hypoglycemic event or 1 severe hypoglycemic event in the preceding week	–2 or –4 or at the discretion of the investigator or medically qualified designee

iGlarLixi = fixed-ratio combination of insulin glargine and lixisenatide; SMPG = self-monitored plasma glucose.

Source: Clinical Study Report for LixiLan-L.[8]

Titration monitoring was performed to ensure that the protocol-defined insulin dose-adjustment algorithm was being followed, which was designed to be identical for all treatments. Titration was monitored by a central team who were blinded to the treatment arm. The fasting SMPG values used for titration, daily insulin dose, and record of hypoglycemic events were extracted from the clinical database every two weeks to identify patients whose insulin dose was not titrated in line with the dosage algorithm. Titrations that occurred outside of the titration recommendations were addressed to the on-site monitoring team for investigator clarification.

The maximum daily dose of iGlarLixi was 60 units/20 mcg. If a daily iGlarLixi dose greater than 60 units/20 mcg was needed to maintain FPG or A1C below thresholds defined for rescue therapy, the dose was kept at 60 units/20 mcg and a rescue therapy was initiated. The administration of rescue therapy is further explained in the Rescue Therapy section.

Training

One disposable pen-injector device with an instruction leaflet was dispensed to each patient in both the iGlarLixi or insulin glargine arms, and that patient was instructed by study staff on proper use, storage information, and self-administration technique.

At the start of the run-in phase (week –6), all patients were trained using a training disposable Lantus SoloSTAR, and, at the start of the treatment phase (day 1), patients who were randomized to receive iGlarLixi were trained using a training disposable Pen A and Pen B.

Training could be repeated as often as it was deemed necessary by study site staff during both the run-in phase and the treatment phase, and patients were supplied with the appropriate number of pen-injectors in accordance with the dispensing scheme.

On the days of on-site visits, the iGlarLixi was self-administered before breakfast at the investigational site under the observation of staff.

Rescue Therapy

If all fasting SMPG values in three consecutive days were found to have exceeded the specific threshold values (Table 8), patients were instructed to contact the investigator and undergo a central laboratory FPG measurement (and A1C after week 12). In the case of FPG or A1C being above the thresholds, the investigator would ensure that there was not a reasonable explanation for these values, such as plasma glucose was not being measured after the patient had fasted at least eight hours, treatment was not being correctly titrated according to protocol, there was an intercurrent illness jeopardizing glycemic control, or compliance with treatment, as well as diet and lifestyle, was appropriate. If a reasonable explanation was not found after appropriate action was taken (e.g., assessing FPG, titrating insulin glargine or iGlarLixi appropriately, evaluating intercurrent illness, stressing compliance, further assessing FPG/A1C at next visit), or if a dose > 60 units was necessary to decrease FPG/A1C below the threshold, insulin glulisine was recommended to be added as rescue therapy. This administration was started as a single daily administration at the main meal of the day. No oral or injectable antidiabetic treatment other than short/rapid-acting insulin was permitted as rescue medication in either treatment group.

Table 8: Threshold Values for Rescue Therapy Throughout the LixiLan-L Study

Time Point Within Study	FPG Value
From week 8 up to but not including week 12	> 13.3 mmol/L
From week 12 up to and including week 30	> 11.1 mmol (or A1C > 8%)

A1C = glycated hemoglobin; FPG = fasting plasma glucose.

Source: Clinical Study Report for LixiLan-L.[8]

Outcomes

Efficacy Outcomes

A1C and Fasting Plasma Glucose

The primary end point in this trial was change from baseline to week 30 in A1C. The secondary efficacy end point was FPG. Both of these values derived from blood samples, which were drawn at screening, the end of the run-in phase, and at multiple time points over 30 weeks, including weeks 0, 8, 12, 24, and 30. Other efficacy outcomes included the percentage of patients achieving an A1C less than 7.0% and 6.5% or lower at week 30.

Body Weight

Body weight was measured at weeks –8, 0, 4, 8, 12, 18, 24, and 30.

Standardized Meal Test

Patients underwent a standardized meal challenge to assess fasting and post-prandial glucose (central laboratory values) as well as post-prandial glycemic excursions. The standardized meal was made up of approximately 600 kcal, and the quantity was identically delivered throughout the study. For the US, the test meal consisted of one Boost Plus and one Boost High Protein drink, and, for all other countries involved, the meal consisted of two Ensure Plus Drinks.

Meal tests were given during an on-site visit, at breakfast one week before randomization, and at the end of the 30-week treatment period. The standardized meal was consumed within a 15-minute period. Blood glucose was drawn 30 minutes prior to the start of the meal, just before the start of the meal (0 minutes), and 30, 60, and 120 minutes after the start of the meal. Fasting and post-prandial plasma glucose (PPG) blood samples drawn during the meal test were measured at a central laboratory.

Health-Related Quality of Life

Health-related quality of life was collected using the EuroQol 5-Dimensions 3-Levels (EQ-5D-3L) and Impact of Weight on Quality of Life–Lite (IWQoL-Lite). These questionnaires were completed by patients at weeks 0, 12, and 30 of the open-label randomization treatment period. The week 0 values collected were considered baseline values and were subsequently compared with values collected at week 30. These questionnaires were completed without any help from the investigator, site staff, friends, or relatives. For patients who required rescue therapy, these questionnaires were scheduled to be completed before initiation of rescue therapy as well as afterwards. For patients who withdrew from the study early, these questionnaires were completed on the last administration day of the product.

The EQ-5D-3L is a generic, preference-based measure of health-related quality of life. The first of two parts of the EQ-5D-3L is a descriptive system that classifies respondents (aged ≥ 12 years) based on the following five dimensions: mobility, self-care, usual activities,

pain/discomfort, and anxiety/depression. The EQ-5D-3L has three possible levels (1, 2, or 3) for each domain, representing “no problems,” “some problems,” and “extreme problems,” respectively. The EQ-5D-3L index score is generated by applying a multi-attribute utility function to the descriptive system. Different utility functions are available that reflect the preferences of specific populations (e.g., US or UK). Scores less than 0 represent health states that are valued by society as being worse than dead, while scores of 0 and 1.00 are assigned to the health states “dead” and “perfect health,” respectively. The lowest possible overall score (corresponding to severe problems on all five attributes) varies depending on the utility function that is applied to the descriptive system (e.g., −0.59 for the UK algorithm and −0.109 for the US algorithm). Although no minimal clinically important difference (MCID) for the EQ-5D-3L has been identified in T2DM, differences of 0.033 to 0.074 in the index score are typically considered clinically meaningful in other conditions.[32]

The second part is a 20 cm visual analogue scale (EQ-VAS) that has end points labelled 0 and 100, with respective anchors of “worst imaginable health state” and “best imaginable health state.”

The IWQoL-Lite questionnaire aims to measure patients’ weight-related quality of life. This is a 31-item, self-reported questionnaire composed of five domains: physical function, self-esteem, sexual life, public distress, and work. Overall scores range from 0 to 100, with higher scores representing better weight-related quality of life. There is no MCID for the IWQoL-Lite questionnaire identified in T2DM; however, in patients with general obesity, a range of 7 to 12 has previously been found.[33]

Compliance

Compliance with study treatments was based on a combination of patient diary checks and a visual check of the returned iGlarLixi or insulin glargine pens by site staff upon completion of a “Treatment Log Form.” The metformin start and end date of treatment, and total daily dose, were documented and checked by patient diary and patient interview.

Adverse Events and Serious Adverse Events

Adverse events (AEs) and serious AEs (SAEs) were assessed from baseline up to the end of the trial. All AEs and SAEs were collected from the time of informed consent and subsequently at each visit until the trial was completed. An AE was defined as any untoward medical occurrence in a patient administered a pharmaceutical product, which does not necessarily have a causal relationship with treatment. An SAE was defined as any untoward medical occurrence which resulted in death, required in-patient hospitalization or prolongation of hospitalization, was life-threatening, resulted in persistent or significant incapacity/disability, or was a medically important event.

Hypoglycemia

Documented symptomatic hypoglycemia was defined as an event in which typical symptoms of hypoglycemia were accompanied by SMPG of 3.9 mmol/L or lower. Severe symptomatic hypoglycemia was defined as an event requiring assistance of another person to actively administer carbohydrate, glucagon, or other resuscitative actions.

Antidrug Antibodies

Anti-lixisenatide antibodies were determined in the iGlarLixi and lixisenatide groups, and anti–insulin glargine antibodies in the iGlarLixi and insulin glargine groups. Blood samples taken at day 1 of the treatment period and at week 30 were measured for antidrug

antibodies by central laboratories. For determination of total concentration of lixisenatide (bound and unbound to anti-lixisenatide antibodies), plasma samples were analyzed using a validated enzyme-linked immunosorbent assay with a lower limit of quantification defined as 5.5 pg/mL.

Statistical Analysis

Determination of Sample Size

The sample size estimate was based on a mean difference in A1C between iGlarLixi and insulin glargine of 0.4% and a common standard deviation of 1.1%, using a t-test with two-sided 5% significance level. With 350 patients per group, the power would be least 95% power.

Primary End Point

The primary end point of this study was to demonstrate superiority of iGlarLixi to insulin glargine in A1C change from baseline to week 30.

The primary end point was analyzed using a mixed-effects model with repeated measures (MMRM), under the missing at random framework. The MMRM model included treatment group, randomization strata of A1C (< 8.0%, ≥ 8.0%) at visit 5 (week 1), randomization strata of metformin use at screening (Yes, No), visit (weeks 8, 12, 24, and 30), treatment-by-visit interaction and country as fixed effects, and baseline A1C value-by-visit interaction as covariates. The adjusted mean change in A1C from baseline to week 30 for each treatment group was estimated in the framework of this model, as well as the between-group difference and the 95% confidence interval.

Secondary End Points

Key secondary efficacy end points included change in two-hour glucose excursion, body weight, FPG, seven-point average SMPG, and percentage of patients reaching A1C less than 7.0% with no body weight gain. The analyses for continuous key secondary end points used an MMRM similar to the primary analysis, with differences between treatment groups and confidence intervals estimated within the framework of MMRM under the missing at random framework (see Missing Data section). The analysis for categorical key secondary end points used the Cochran–Mantel–Haenszel test adjusting for randomization strata.

Multiplicity Considerations

To control for type I error among secondary efficacy outcomes, a step-down testing procedure was applied. If the primary end point was statistically significant at the 5% level, a hierarchical testing procedure was performed to test the secondary outcomes in order. Testing was stopped if an end point was not statistically significant at the 5% level. Multiplicity adjustments were not performed on secondary efficacy variables, which are not included in Table 9. Secondary outcomes of interest in this review that were not adjusted for multiplicity include the percentage of patients reaching A1C less than 7.0% or 6.5% or lower at week 30, change in two-hour PPG from baseline to week 30, change in EQ-5D-3L questionnaire from baseline to week 30, and change in the IWQoL-Lite questionnaire from baseline to week 30.

Table 9: Statistical Hierarchy for Primary and Secondary Efficacy Outcomes in LixiLan-L Study

Priority Rank	Efficacy Outcome
Primary Outcome[a]	
1	Change in A1C in change from baseline to week 30
Secondary Outcomes[b]	
1	Change in 2-hour plasma glucose excursion during the standardized meal test from baseline to week 30
2	Change in body weight from baseline to week 30
3	Change in daily average of the 7-point SMPG from baseline to week 30
4	Percentage of patients reaching A1C < 7% with no body weight gain at week 30
5	Change in daily dose of insulin glargine from baseline to week 30
6	Percentage of patients reaching A1C < 7% with no body weight gain at week 30 and with no documented (PG ≤ 3.9 mmol/L) symptomatic hypoglycemia during the 30-week randomized treatment period
7	Change in FPG from baseline to week 30

A1C = glycated hemoglobin; FPG = fasting plasma glucose; PG = plasma glucose; SMPG = self-monitored plasma glucose.

[a] If the primary variable is statistically significant at the 5% level, a hierarchical testing procedure was performed to test the following secondary efficacy variables.

[b] Secondary efficacy variables were to be tested in a prioritized (1 to 7) order. Testing stopped when an end point was not statistically significant at the 5% level.

Source: Clinical Study Report for LixiLan-L.[8]

Exploratory End Points

The analysis of the patient-reported outcomes, such as EQ-5D and IWQoL-Lite, were performed on the modified intention-to-treat (mITT) population, assessing the change from baseline to week 30 using an MMRM model similar to that used for the primary end point.

Missing Data

The primary analysis was an MMRM analysis using all observations collected post-baseline, regardless of treatment discontinuation or initiation of rescue therapy, under the missing at random framework. The secondary efficacy outcome measurements of change in body weight and change in FPG from baseline to week 30 were also analyzed in this way.

To examine the impact of these missing data on results, a sensitivity analysis was conducted for the primary end point. Missing A1C values at week 30 were imputed using multiple imputations for patients who permanently discontinued from the study; specifically, the imputations used data from patients within their treatment group and randomization strata who had permanently discontinued the study treatment but had week 30 measurements (retrieved dropouts). Patients who completed treatment but did not have week 30 measurements were assumed to be missing at random. Their values were subsequently imputed using multiple imputations [redacted], and completed data were analyzed using an analysis of covariance (ANCOVA) model. In this study, it was stated that the planned imputations could not be performed due to limitations in the data, as the number of received dropouts was insufficient to build a reliable imputation model.

For secondary efficacy outcomes of change in two-hour PPG and blood glucose excursion during a standardized meal test, for which one post-baseline assessment was scheduled,

missing data at week 30 were imputed by last observation carried forward and the corresponding baseline value as a covariate to compare iGlarLixi and insulin glargine.

For health-related quality of life outcomes, such as the EQ-5D and the IWQoL-Lite, there was no apparent method in place for the handling of missing data.

Subgroup Analyses

Pre-specified subgroup analyses were performed on the primary outcome (change in A1C over 30 weeks) for the following:

- gender
- age group (< 50, ≥ 50 to < 65, and ≥ 65 years of age)
- race (Caucasian/white, black, Asian/other)
- ethnicity (Hispanic, non-Hispanic)
- baseline A1C (< 8.0, ≥ 8.0%)
- baseline BMI level (< 30, ≥ 30 kg/m^2)
- metformin use at screening (Yes, No)
- country
- oral antidiabetes drug use at screening (no oral antidiabetes drugs, one oral antidiabetes drug, or two oral antidiabetes drugs).

The treatment effects were conducted in the mITT population, excluding the assessments done after any introduction of rescue medication, and using the MMRM approach with treatment group (iGlarLixi or insulin glargine), randomization strata of A1C (< 8%, ≥ 8%), randomization strata of metformin use (Yes, No) at screening, visit, subgroup factor, treatment-by-visit, treatment-by-subgroup, visit-by-subgroup, treatment-by-visit-by subgroup factor, and country as fixed effects, and using baseline A1C value-by-visit interaction as a covariate. The adjusted estimates of treatment mean differences (iGlarLixi versus insulin glargine) with standard errors and 95% CIs were provided across subgroups.

Post Hoc Analyses

Additional information was received by the manufacturer regarding the disposition, efficacy, and safety outcomes for patients receiving Pen A (2 units:1 mcg ratio) compared with Pen B (3 units:1 mcg ratio) used in the study. A post hoc analysis was conducted by the type of pen used by patients throughout the study (Pen A only, Pen B only, and patients switching from Pen A to Pen B). The selected efficacy and safety outcomes included change from baseline to week 30 in A1C, body weight, and incidence of hypoglycemia. An MMRM analysis, which was similar to that used for the primary efficacy end point, and all scheduled measurements obtained during the study, was used.

Analysis Populations

The randomized population was defined as all patients who had signed informed consent, with a randomized open-label treatment kit allocated and recorded in the interactive voice response system/interactive Web response system (IVRS/IWRS) database, regardless of whether the treatment kit was used.

The mITT population was defined as all randomized patients who had both a baseline assessment and at least one post-baseline assessment from any of the primary or

secondary efficacy end points, regardless of compliance with the study protocol. All efficacy analyses were based on the mITT analysis set.

Patient Disposition

Patient disposition throughout the LixiLan-L study is displayed in Table 10. In total, 1,930 patients were screened for inclusion, of which 912 (47.2%) were found ineligible for the run-in phase. Thus, 1,018 (52.7%) patients initiated the run-in phase, and 736 patients were randomized to begin the 30-week open-label treatment period with either iGlarLixi or insulin glargine alone. A total of 1,194 (61.9%) patients were recorded as screen failures, including 282 (14.6%) of patients who were recorded as failures throughout the run-in phase.

The percentage of patients permanently discontinuing treatment during the open-label treatment period was higher in the iGlarLixi group (29 patients [7.9%]) than in the insulin glargine group (10 patients [2.7%]). The most common reasons for discontinuation in the iGlarLixi group were AEs (3.3% in the iGlarLixi group versus 0.8% in the insulin glargine group) and other reasons (3.3% in the iGlarLixi group versus 1.6% in the insulin glargine group). The most common AEs in the iGlarLixi group that were cited as reasons for discontinuation were gastrointestinal tolerability and hypoglycemia.

Table 10: Patient Disposition in LixiLan-L Study

	iGlarLixi (N = 367)	Insulin Glargine (N = 369)
Screened, N	1,930	
Screen failures (not eligible for run-in phase), N (%)	912 (47.3)	
Run-in, N (%)	1,018 (52.7)	
Run-in failures, N (%)	282 (14.6)	
Randomized, N (%)	367	369
Randomized and treated, N (%)	365 (99.5)	365 (98.9)
Completed 30-week open-label treatment period, N (%)	336 (91.6)	355 (96.2)
Discontinued, N (%)	29 (7.9)	10 (2.7)
Adverse event, N (%)	12 (3.3)	3 (0.8)
Lack of efficacy, N (%)	0	0
Lost to follow-up, N (%)	1 (0.3)	0
Poor compliance, N (%)	4 (1.1)	1 (0.3)
Other reasons, N (%)	12 (3.3)	6 (1.6)
mITT population, N (%)	366 (99.7)	365 (98.9)
Had A1C measurement at week 30, N (%)	346 (94.3)	355 (96.2)
Missed A1C measurement at week 30, N (%)	346 (94.3)	355 (96.2)
Safety population, N	365	365

iGlarLixi = fixed-ratio combination of insulin glargine and lixisenatide; mITT = modified intention-to-treat.

Source: Clinical Study Report for LixiLan-L.[8]

Additional information was provided by the manufacturer regarding the disposition of patients receiving Pen A (2 units:1 mcg ratio) iGlarLixi to Pen B (3 units:1 mcg ratio). Results are displayed in Table 11, [redacted]

Table 11: Switch of Pen During Study Treatment Period for iGlarLixi Group in the Safety Population of LixiLan-L Study

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

[redacted]

Exposure to Study Treatments

Exposure and Adherence

Table 12 provides a summary of exposure and adherence to study treatments over time in the LixiLan-L study. In this study, the duration of exposure was defined from the date of the first administration of open-label treatment to the date of the last administration of open-label treatment with one additional day[redacted] Compliance with study medication was high and was similar between groups. [redacted]

Table 12: Duration of Exposure and Treatment Compliance Rates for Patients in the LixiLan-L Study

Days	[redacted]	
Duration of exposure, number of days		
Mean duration of study treatment, days (SD)	[redacted]	[redacted]
Missing duration	[redacted]	[redacted]
≥ 1 day	[redacted]	[redacted]
≥ 15 days	[redacted]	[redacted]
≥ 29 days	[redacted]	[redacted]
≥ 57 days	[redacted]	[redacted]
≥ 85 days	[redacted]	[redacted]
≥ 127 days	[redacted]	[redacted]
≥ 169 days	[redacted]	[redacted]
≥ 211 days	[redacted]	[redacted]
Treatment compliance, %		
Mean compliance rate, % (SD)	[redacted]	[redacted]
Patients with < 60%	[redacted]	[redacted]
Patients with ≥ 60% to < 80%	[redacted]	[redacted]
Patients with ≥ 80% to ≤ 100%	[redacted]	[redacted]
Patients with > 100%	[redacted]	[redacted]

[redacted]

SD = standard deviation.

Rescue Therapy

The percentage of patients requiring rescue therapy was low in both groups; however, it was lower for those receiving iGlarLixi (2.7%) than for those who received insulin glargine (6.0%).

Table 13: Number of Patients Requiring Rescue Therapy During the 30-Week Open-Label Treatment Period – mITT Population

Requiring Rescue Therapy, N (%)	[redacted]	[redacted]
Yes	[redacted]	[redacted]
Proportion difference versus insulin glargine [95% CI][a]	[redacted]	

[redacted]

CI = confidence interval; mITT = modified intention-to-treat.

Critical Appraisal

Internal Validity

- Baseline demographics appeared to be well-balanced between groups, with no major differences observed between treatment groups.
- The LixiLan-L study used a statistical hierarchy to examine secondary outcomes to control for type I error. Subsequent to testing for statistical significance of the primary efficacy variable, a testing hierarchy was performed on selected secondary efficacy variables. According to hierarchy rules specified in the protocol, the results for mean change in daily insulin glargine (fifth point in the hierarchy) did not meet the criteria for statistical significance and, therefore, statistical significance could not be concluded from beyond this point. However, the manufacturer does not appear to have adhered to its pre-specified testing strategy by continuing statistical testing after this point. Furthermore, outcomes such as change in two-hour PPG, health-related quality of life measures such as EQ-5D-3L and IWQoL-Lite, and the proportion of patients achieving an A1C < 7% or ≤ 6.5%, which were identified as outcomes of interest in this CDR protocol, were not adjusted for multiplicity. Therefore, any results from these outcomes should be considered as exploratory, since they were not appropriately adjusted for multiplicity, which would increase the risk of type I error.
- Subgroups identified in the LixiLan-L study were pre-specified and presented for a number of baseline factors, many of which were considered relevant in this CDR protocol. However, formal interaction tests and adjustments for multiple comparisons did not appear to have been made for these analyses. Additionally, given that subgroups typically do not maintain randomization (unless used as stratification variables for randomization, which were true of A1C [< 8.0%, ≥ 8.0%] and metformin [Yes, No] subgroups) and are often underpowered, these analyses should be treated as exploratory.
- All efficacy analyses were conducted using an mITT population, which 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. In the MMRM model, missing data were imputed using the last observation carried forward approach, specifically using post-baseline data; participants 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 ITT analysis. This could raise concerns, given the number of missing patients in the primary A1C analysis in the LixiLan-L study, in which 5% of patients were excluded in the iGlarLixi group, compared with 2.5% of patients in the insulin glargine group. Furthermore, patients were excluded from the primary A1C analysis post–rescue treatment. Excluding these patients can artificially inflate the benefit of iGlarLixi 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 30-week open-label treatment period, and a sensitivity analyses with patients who had completed 30 weeks were also conducted. The results of all sensitivity analyses were similar in magnitude, direction, and statistical significance as well as in support of the primary analyses in this trial. Although these analyses showed similar results as the primary data analysis, these analyses cannot fully account for the impact of missing data.

- There were missing data for health-related quality of life outcomes among patients at baseline ([redacted]) as well as at the end point (6.5% in the iGlarLixi group and 4.9% in the insulin glargine group), and there was no apparent framework in place to account for these missing values in the protocol. Missing data in these outcomes and the exclusion of these patients could be due to non-response bias and underestimate the variability in the results, which can potentially overestimate health-related quality of life results.
- Because the iGlarLixi had a cap of 60 units of insulin glargine that could be used daily, the insulin glargine group was also capped at this amount. According to the FDA medical review for this product, there were 99 patients (21%) in the iGlarLixi group and 112 patients (31%) in the insulin glargine group in this study who had a final insulin dose of 60 units. Thus, if a titration beyond 60 units had been permitted in the insulin glargine group, it may have led to a higher proportion of patients in this group being treated to target. Therefore, capping this dose in the insulin glargine arm could have biased the estimates of treatment efficacy.
- This study was open-label in its design. The manufacturer indicated that this was due to differences in the type and number of pens used to administer iGlarLixi (two pens at 2:1 and 3:1 fixed ratios) and insulin glargine. It was indicated in the clinical study report that neither the investigator nor the sponsor had access to the data for the primary efficacy end point, or the data for the standardized meal test end points from the baseline visit until the end of treatment, in an attempt to compensate for the lack of blinding in this study. Also, identifiable data on pens and injection times were masked and titration was monitored by a blinded central team, and allergic events were adjudicated in a blinded manner. However, there remains a potential for bias in reporting subjective outcomes such as AEs and health-related quality of life when treatment status is known.
- There was a higher rate of premature withdrawals in the iGlarLixi group compared with the insulin glargine group (29 patients [8%] versus 10 patients [3%], respectively), as well as an overall shorter duration of exposure in the iGlarLixi group (201.5 days in the iGlarLixi group versus 208.4 days in the insulin glargine group). Many of these discontinuations were due to AEs in the iGlarLixi group (3.3%) compared with the insulin glargine group (0.3%). Patients were not followed after discontinuation, and, due to the small amount of missing observations, it was stated that this was insufficient to build a reliable imputation model. It was assumed that the conclusions of statistical superiority of iGlarLixi over insulin glargine were unlikely to change because of the low number of received dropouts; however, this was not confirmed.

External Validity

- iGlarLixi was originally presented in the form of two pens, delivering insulin glargine and lixisenatide at different ratios. Pen A contained 100 units/mL of insulin glargine and 50 mcg/mL of lixisenatide (delivering insulin glargine/lixisenatide at a 2:1 ratio), and Pen B contained 100 units/mL of insulin glargine and 33 mcg/mL of lixisenatide (delivering insulin glargine/lixisenatide at a 3:1 ratio). Only Pen B is available in Canada, and, therefore, this formulary review was only intended to consider the use of Pen B. In the LixiLan-L study, Pen A and Pen B were designed to be used interchangeably, depending on the patient's required insulin glargine dose. If a patient in this study had a daily insulin glargine dose 40 units and less, they were instructed to use Pen A, and, if they had a daily insulin glargine dose between 41 and 60 units, they were instructed to use Pen B. Patients were not stratified by Pen A or B throughout the study, and pen type was not a pre-specified subgroup, so this information could not be fully separated.

As a result, the generalizability of the findings to patients using the fixed-ratio combination at a 3:1 ratio and taking doses of insulin glargine 40 units and less is uncertain. The clinical expert involved in this review commented that the switching from Pen A to Pen B would theoretically entail a transient dose reduction of lixisenatide coupled with a small rise in glargine dose, given what is known about dose-response data for lixisenatide. As a result, the clinical expert thought that any impact to pen switching throughout the trial would be minor and would not have an effect on overall results.

- A total of 1,930 patients were screened for inclusion in the LixiLan-L study, of which only 736 patients were randomized to begin the 30-week open-label treatment phase of this study. A total of 1,194 (61.9%) were recorded as screen failures. In this study, patients with an A1C less than 7.5% or greater than 10% were excluded, as well as those with a creatinine clearance < 30 mL/min or end-stage renal disease. Stringent inclusion and exclusion criteria could lead to the inclusion of a selected group of patients that may not be representative of the T2DM population in Canada who are inadequately controlled on basal insulin (less than 60 units daily), with or without metformin, and could limit the generalizability of the trial results.
- Patients in the LixiLan-L study were overwhelming white (91.7%), which is not entirely representative of the T2DM population in Canada, since Canada is home to a significant population of immigrants at a higher risk of T2DM. It was also not clear how many patients of Indigenous descent were included in the study population. As of 2011, people of South Asians, Chinese, and black heritage accounted for 61.3% of the total visible minority population, and Indigenous people accounted for 4.3% of the Canadian population.[10] Furthermore, there was a low representation of Canadian patients in the study (3.0%). As a result, the generalizability of this trial's results to the Canadian T2DM population may be limited.
- Because of the fixed-ratio components of iGlarLixi, the majority of patients in the LixiLan-L study were receiving ≥ 10 mcg to < 20 mcg of lixisenatide (70.8%) at the end of the treatment phase. According the product monograph for lixisenatide,[27] the recommended daily maintenance dose of lixisenatide is 20 mcg, meaning that there is a potential that patients taking lower doses may receive suboptimal treatment. A post hoc analysis was conducted by the manufacturer evaluating patients by their final lixisenatide dose and final insulin dose category, which suggested that a possible contribution of lixisenatide at doses between ≥ 10 and < 20 mcg on A1C change from baseline; however, very little is known about the effect of lixisenatide doses less than 10 mcg, and, because this analysis was not pre-specified, the contribution of lixisenatide at doses < 20 mcg remain uncertain.
- iGlarLixi has a dose limitation of 60 units of insulin glargine, which could affect generalizability of iGlarLixi to patients who require more than 60 units of insulin glargine daily. Furthermore, it is unknown whether iGlarLixi is superior to insulin glargine at doses beyond 60 units, since doses in the insulin glargine group were also capped at 60 units in order to match the dose limitation of the insulin glargine component in the iGlarLixi group. Therefore, it is unknown whether iGlarLixi would be a better treatment option than insulin glargine alone in a setting where basal insulin therapy was optimized without any dosage limitations.
- In this study, the treatment algorithm indicated that the dosage should increase no more than 4 units of insulin glargine (1.33 mcg lixisenatide) per week and should be targeted to bring down high morning FPG values between 4.4 mmol/L to 5.6 mmol/L in the preceding three days. According to the clinical expert involved in this study, this titration

was considered to be conservative for increasing insulin glargine and may not be appropriate for a T2DM population that is not yet at target and requires aggressive treatment. At the beginning of the treatment phase, patients were trained using a training disposable Pen A and Pen B, and training was to be repeated as often as deemed necessary by study site staff during both the run-in and treatment phases. This increased access to training would be difficult to generalize to the general diabetes population for whom injection technique may be suboptimal and experience with a fixed-ratio device may be limited.

- The LixiLan-L study was designed to have a treatment period of 30 weeks (39 weeks including run-in phase), which was an inadequate length of time to assess key clinical outcomes such as morbidity and mortality. T2DM is a chronic condition with risks of multiple serious complications that take years to develop; therefore, it is unlikely that a trial of this nature can be designed to assess these key outcomes. A1C is widely used as a surrogate marker for glycemic control; however, the exact nature of improvement required in A1C needed to achieve clinical benefit has not been fully elucidated. Furthermore, it is unclear whether the duration of the treatment period in the LixiLan-L study allowed for sufficient time to adequately assess health-related quality of life outcomes and whether the weight changes observed throughout the study period would have a meaningful impact on patients over time.

Efficacy

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

Glycemic Control

Table 14 displays the results for the glycemic outcomes of interest for this review. The results for mean change in A1C from baseline to week 30 were supportive of statistical superiority ($P < 0.0001$) of iGlarLixi to insulin glargine (–0.52%; 95% CI, –0.63 to –0.40) (Table 14). The mean change in A1C from baseline to week 30 was –1.13% (SD 0.057) in the iGlarLixi group and –0.62% (SD 0.055) in the insulin glargine group, which achieved mean A1C values of 6.94% (SD 0.87) and 7.48% (SD 0.91), respectively. The results of the sensitivity analyses of the change in A1C from baseline to week 30 were consistent with the results of the primary analysis.

There was no statistically significant difference in the mean change from baseline for FPG up until week 30 between the iGlarLixi group and the insulin glargine group (least squares mean difference [LSMD] 0.11 mmol/L; 95% CI, –0.207 to 0.428; $P = 0.4951$).

The LSMD in post-prandial glycemic control after a standardized liquid breakfast between iGlarLixi and insulin glargine was –3.4 mmol/L (95% CI, –3.92 to –2.94) in favour of iGlarLixi. Results were statistically significant at the 5% level for mean change in two-hour glucose excursion ($P < 0.0001$).

Table 14: Glycemic-Control Outcomes From Baseline at Week 30 for iGlarLixi and Insulin Glargine in Patients With Type 2 Diabetes in the LixiLan-L Study

End Point	N	iGlarLixi (N = 367)	N	Insulin Glargine (N = 369)
A1C (%)				
Mean baseline value (SD)	364	8.07 (0.68)	364	8.08 (0.73)
Mean end point value at week 30 (SD)	346	6.94 (0.87)	355	7.48 (0.91)
LS mean change from baseline (SE)[a]	364	–1.13 (0.057)	364	–0.62 (0.055)
LS mean difference of iGlarLixi versus insulin glargine [95% CI][a]	–0.52 [–0.633 to –0.397]			
P value[a]	< 0.0001			
Fasting plasma glucose (mmol/L)				
Mean baseline value (SD)	364	7.33 (1.94)	364	7.32 (2.07)
Mean end point value at week 30 (SD)	341	6.78 (2.26)	349	6.69 (2.05)
LS mean change from baseline (SE)[b]	364	–0.35 (0.142)	364	–0.46 (0.138)
LS mean difference of iGlarLixi versus insulin glargine [95% CI][b,c]	0.11 [–0.207 to 0.428]			
P value[b,c]	0.4951			
2-hour glucose excursion (mmol/L)				
Mean baseline value (SD)		7.01 (3.47)		7.14 (3.11)
Mean end point value at week 30 (SD)		3.11 (3.55)		6.71 (3.34)
LS mean change from baseline (SE)[d]		–3.90 (0.28)		–0.47 (0.27)
LS mean difference of iGlarLixi versus insulin glargine [95% CI][d]	–3.43 [–3.925 to –2.939]			
P value[d]	< 0.0001			

A1C = glycated hemoglobin; CI = confidence interval; iGlarLixi = fixed-ratio combination of insulin glargine and lixisenatide; LS = least squares; SD = standard deviation; SE = standard error.

[a] Mixed-effects model with repeated measures (MMRM) with treatment groups (fixed-ratio combination and insulin glargine), randomization strata of A1C (< 8.0%, ≥ 8.0%) at visit 5 (week –1), randomization strata of metformin use at screening (Yes, No), scheduled visit, treatment-by-visit interaction and country as fixed effects, and baseline average A1C% value-by-visit interaction as a covariate.

[b] Mixed-effects model with repeated measures (MMRM) with treatment groups (fixed-ratio combination and insulin glargine), randomization strata of A1C (< 8.0%, ≥ 8.0%) at visit 5 (week –1), randomization strata of metformin use at screening (Yes, No), scheduled visit, treatment-by-visit interaction and country as fixed effects, and baseline average FPG value-by-visit interaction as a covariate.

[c] As per step-down testing procedure, analyses are considered exploratory.

[d] Mixed-effects model with repeated measures (MMRM) with treatment groups (fixed-ratio combination and insulin glargine), randomization strata of A1C (< 8.0%, ≥ 8.0%) at visit 5 (week –1), randomization strata of metformin use at screening (Yes, No), scheduled visit, treatment-by-visit interaction and country as fixed effects, and baseline average two-hour glucose excursion value-by-visit interaction as a covariate.

Source: Clinical Study Report for LixiLan-L.[8]

Table 15 contains results observed for glycemic outcomes of interest that were not included in the statistical testing hierarchy and therefore considered to be inconclusive, as they have not been adjusted for multiplicity. With regard to the mean change in two-hour PPG results, treatment with iGlarLixi was found to lead to a greater reduction from baseline than treatment with insulin glargine (LSMD –3.33 mmol/L; 95% CI, 3.889 mmol/L to 2.774 mmol/L).

By week 30, the percentage of patients achieving an A1C less than 7.0% was found to be higher in the iGlarLixi group (54.9%) than in the insulin glargine group (29.6%), with a difference of 25.5% (95% CI, 18.9% to 32.1%). Similar results were seen for the percentage of patients reaching an A1C 6.5% or lower: 33.9% of patients in the iGlarLixi group achieved this target compared with just 14.2% in the insulin glargine group, with a difference of 39.2% (95% CI, 20.7% to 57.6%). These outcomes were also not adjusted for multiple statistical testing.

Table 15: Secondary Efficacy End Points Within the LixiLan-L Study, Unadjusted for Multiplicity – mITT Population

Value	iGlarLixi (N = 367)		Insulin Glargine (N = 369)	
	N	N (%) Achieving Target A1C	N	N (%) Achieving Target A1C
Mean change in 2-hour post-prandial plasma glucose during a standardized meal test				
Mean baseline value (SD)	332	14.85 (3.82)	340	14.97 (3.67)
Mean end point value at week 30 (SD)	332	9.91 (3.90)	340	13.41 (3.83)
LS mean change from baseline (SD)	–4.72 (0.322)		–1.39 (0.310)	
LS mean difference of iGlarLixi versus insulin glargine [95% CI][a]	–3.33 [–3.889 to –2.774]			
P value[a]	< 0.0001			
% patients with A1C ≤ 6.5% at week 30				
Number (%)	366	124 (33.9)	365	52 (14.2)
Proportion difference [95% CI] versus insulin glargine	19.76 [13.9 to 25.62]			
P value	< 0.0001			
% patients with A1C < 7% at week 30				
Number (%)	366	201 (54.9)	365	108 (29.6)
Proportion difference [95% CI] versus insulin glargine	25.52 [18.94 to 32.10]			
P value	< 0.0001			

A1C = glycated hemoglobin; CI = confidence interval; iGlarLixi = fixed-ratio combination of insulin glargine and lixisenatide; LS = least squares; mITT = modified intention-to-treat; SD = standard deviation.

[a] Mixed-effects model with repeated measures (MMRM) with treatment groups (fixed-ratio combination and insulin glargine), randomization strata of A1C (< 8.0%, ≥ 8.0%) at visit 5 (week –1), randomization strata of metformin use at screening (Yes, No), scheduled visit, treatment-by-visit interaction and country as fixed effects, and baseline two-hour PPG value-by-visit interaction as a covariate.

Source: Clinical Study Report for LixiLan-L.[8]

Health-Related Quality of Life Outcomes

Health-related quality of life, as measured by the change in total scores from two questionnaires (IWQoL-Lite and EQ-5D-3L), is reported in Table 16. [redacted]

Baseline values for the EQ-5D-3L perceived health status on the VAS were similar between treatment groups (Table 16). The change from baseline to week 30 was found [redacted].

Any statistical analysis of this end point should be considered exploratory because these outcomes have not been adjusted for multiplicity.

Table 16: Mean Change in Health-Related Quality of Life Outcomes Measured From Baseline to Week 30 Using MMRM in the LixiLan-L Study – mITT Population

Value	[redacted]	[redacted]
IWQoL-Lite total score		
Mean baseline value (SD)	[redacted]	[redacted]
Mean value at week 30 (SD)	[redacted]	[redacted]
LS mean change from baseline (SE)[a]	[redacted]	[redacted]
LS mean difference of iGlarLixi versus insulin glargine [95% CI] [a]	[redacted]	
EQ-5D-3L index value (based on a US population)		
Mean baseline value (SD)	[redacted]	[redacted]
Mean value at week 30 (SD)	[redacted]	[redacted]
LS mean change from baseline (SE)[b]	[redacted]	[redacted]
LS mean difference of iGlarLixi versus insulin glargine [95% CI][b]	[redacted]	
EQ-5D-3L perceived health status on VAS score		
Mean baseline value (SD)	[redacted]	[redacted]
Mean value at week 30 (SD)	[redacted]	[redacted]
LS mean change from baseline (SE)[c]	[redacted]	[redacted]
LS mean difference of iGlarLixi versus insulin glargine [95% CI][c]	[redacted]	

[redacted]

CI = confidence interval; EQ-5D-3L = EuroQol 5-Dimensions 3-levels; IWQoL-Lite = Impact of Weight on Quality of Life–Lite; LS = least squares; mITT = modified intention-to-treat; MMRM = mixed-effects model with repeated measures; SD = standard deviation; SE = standard error; VAS = visual analogue scale.

Body Weight

When comparing the iGlarLixi group and the insulin glargine group for change in body weight from baseline to week 30, there was a statistically significant difference between groups (LSMD –1.37 kg; 95% CI, –1.808 to –0.930; $P < 0.0001$). Patients in the iGlarLixi group were found to have decreased in weight, with a difference of –0.67 kg (SD 0.181), and patients in the insulin glargine group were found to have increased in weight, with a difference of +0.70 kg (SD 0.178).

Table 17: Change in Body Weight From Baseline at Week 30 for iGlarLixi and Insulin Glargine in Patients With Type 2 Diabetes in the LixiLan-L Study

Body Weight (kg)	N	iGlarLixi (N = 367)	N	Insulin Glargine (N = 369)
Mean baseline value (SD)	365	87.81 (14.42)	365	87.09 (14.75)
Mean end point value at week 30 (SD)	348	87.48 (14.35)	357	87.96 (15.08)
LS mean change from baseline (SE)[a]		–0.67 (0.181)		0.70 (0.178)
LS mean difference of iGlarLixi versus insulin glargine [95% CI][a]	–1.37 [–1.808 to –0.930]			
P value[a]	< 0.0001			

CI = confidence interval; iGlarLixi = fixed-ratio combination of insulin glargine and lixisenatide; LS = least squares; SD = standard deviation; SE = standard error.

[a] Mixed-effects model with repeated measures (MMRM) with treatment groups (fixed-ratio combination and insulin glargine), randomization strata of A1C (< 8.0%, ≥ 8.0%) at visit 5 (week –1), randomization strata of metformin use at screening (Yes, No), scheduled visit, treatment-by-visit interaction and country as fixed effects, and baseline mean body weight value-by-visit interaction as a covariate.

Source: Clinical Study Report for LixiLan-L.[8]

Other Efficacy Outcomes

Efficacy outcomes — such as changes in health care resource utilization, hospitalization, and blood pressure — were not reported in this study.

Subgroup Analyses

Table 18 shows the analysis by subgroup of patients (sex, age, race, ethnicity, BMI, baseline A1C, metformin use, and oral antidiabetes drug use at screening). There were no statistically significant differences in treatment effects found between subgroups when evaluating change in mean A1C from baseline to week 30. These results were not adjusted for multiplicity, and therefore should be interpreted with caution.

Table 18: Subgroup Analysis on Mean A1C (%) Change From Baseline in the LixiLan-L Study – mITT Population

Subgroup	iGlarLixi		Insulin Glargine		Treatment Difference iGlarLixi – Insulin Glargine [95% CI]
	N	LS Mean (SE)	N	LS Mean (SE)	
Sex					
Male	165	–1.05 (0.073)	175	–0.57 (0.070)	–0.48 [–0.65 to –0.30]
Female	199	–1.21 (0.069)	189	–0.66 (0.069)	–0.54 [–0.70 to –0.38]
Age (years)					
< 50 years	50	–1.29 (0.123)	41	–0.50 (0.132)	–0.79 [–1.123 to –0.456]
≥ 50 to < 65 years	204	–1.08 (0.070)	205	–0.69 (0.068)	–0.40 [–0.555 to –0.240]
≥ 65 years	110	–1.15 (0.085)	118	–0.53 (0.081)	–0.61 [–0.825 to –0.402]
Baseline A1C (%)					
< 8.0	165	–1.06 (0.085)	163	–0.58 (0.085)	–0.48 [–0.656 to –0.305]
≥ 8.0	199	–1.18 (0.078)	201	–0.63 (0.078)	–0.54 [–0.702 to –0.382]
Baseline BMI (kg/m^2)					
< 30	155	–1.12 (0.075)	156	–0.56 (0.073)	–0.56 [–0.745 to –0.381]
≥ 30	209	–1.14 (0.068)	208	–0.66 (0.066)	–0.48 [–0.635 to –0.324]
Metformin use at screening					
Yes	326	–1.10 (0.050)	324	–0.62 (0.049)	–0.48 [–0.600 to –0.350]

Subgroup	iGlarLixi		Insulin Glargine		Treatment Difference iGlarLixi – Insulin Glargine [95% CI]
	N	LS Mean (SE)	N	LS Mean (SE)	
No	38	–1.28 (0.136)	40	–0.43 (0.131)	–0.48 [–0.600 to –0.350]
OAD use at screening					
No OAD	18	–1.32 (0.202)	19	–0.57 (0.192)	–0.75 [–1.288 to –0.217]
1 OAD	187	–1.14 (0.074)	207	–0.57 (0.192)	–0.75 [–1.288 to 0.217]
2 OADs	159	–1.02 (0.083)	138	–0.56 (0.086)	–0.46 [–0.647 to –0.277]

A1C = glycated hemoglobin; BMI = body mass index; CI = confidence interval; iGlarLixi = fixed-ratio combination of insulin glargine and lixisenatide; OAD = oral antidiabetes drug; SE = standard error.

Source: Clinical Study Report for LixiLan-L.[8]

Harms

Only those harms identified in the review protocol are reported in this section (see 2.2.1, Protocol).

Adverse Events and Serious Adverse Events

Overall, the proportion of patients who experienced any AEs, SAEs, or death from any cause were comparable across treatment groups. Commonly reported AEs (frequency ≥ 5%) included nausea, nasopharyngitis, headache, diarrhea, influenza, upper respiratory tract infection, and vomiting. Nausea was more frequently reported in the iGlarLixi group (10.4%) compared with the insulin glargine group (0.5%). The proportion of patients in the iGlarLixi group who experienced at least one AE was similar (53.4%) to those in the insulin glargine group (52.3%), as well as the proportion experiencing at least one SAE (5.5% versus 4.9%, respectively). The reported SAEs occurring in at least two different patients (frequency ≥ 0.5%) included acute myocardial infarction, hypoglycemia, hypoglycemic unconsciousness, and unstable angina.

Withdrawals Due to Adverse Events

The frequency of withdrawals due to AEs was higher in the iGlarLixi group (2.7%) compared with the insulin glargine group (0.8%). The most commonly cited reason for withdrawal in the iGlarLixi group was nausea (1.1%). Other reasons for withdrawal cited in the iGlarLixi group were dizziness, hypoglycemic unconsciousness, pneumonia, and increased weight. The three patients in the insulin glargine group withdrew due to pregnancy, heart failure, and gall bladder cancer.

Mortality

The total number of deaths in this study was three: one in the iGlarLixi group and two in the insulin glargine group. The cause of death in the iGlarLixi group was pneumonia, and the cause of death for the two patients in the insulin glargine group was cardiopulmonary failure and gallbladder cancer.

Table 19: Adverse Events, Serious Adverse Events, Withdrawals Due to Adverse Events, Deaths, Allergic Reactions, and Injection-Site Reactions Observed in the LixiLan-L Study – Safety Population

	iGlarLixi (N = 365)	Insulin Glargine (N = 365)
AEs		
Patients with > 0 AEs, N (%)	195 (53.4)	191 (52.3)
Most common AEs[a]	Nausea, nasopharyngitis, headache, diarrhea, influenza, URTI, vomiting	
Nausea	38 (10.4)	2 (0.5)
Nasopharyngitis	32 (8.8)	32 (8.8)
Headache	21 (5.8)	10 (2.7)
Diarrhea	16 (4.4)	10 (2.7)
Vomiting	13 (3.6)	2 (0.5)
SAEs		
Patients with > 0 SAEs, N (%)	20 (5.5)	18 (4.9)
Most common SAEs[a]	Acute myocardial infarction, hypoglycemia, disturbances in consciousness, unstable angina	
Acute myocardial infarction	2 (0.5)	0
Hypoglycemia	2 (0.5)	1 (0.3)
Hypoglycemic unconsciousness	2 (0.5)	0
Unstable angina	2 (0.5)	0
WDAEs		
WDAEs, N (%)	10 (2.7)	3 (0.8)
Most common reasons	Nausea, disturbances in consciousness, dizziness	
Nausea	4 (1.1)	0
Hypoglycemic unconsciousness	[redacted]	[redacted]
Dizziness	[redacted]	[redacted]
Other	[redacted]	[redacted]
Deaths		
Number of deaths, N (%)	1 (0.3)	2 (0.5)
Death due to pneumonia	1 (0.3)	0
Death due to cardiopulmonary failure	0	1 (0.3)
Death due to gallbladder cancer	0	1 (0.3)
ARAC-adjudicated allergic events by patient		
Any allergic event	0	1 (0.3)
Rhinitis allergic	0	1 (0.3)
Injection-site reactions		
Any injection-site reactions	0	2 (0.5)
Injection-site hypertrophy	0	1 (0.3)
Injection-site reaction	0	1 (0.3)

[a] Frequency > 1%.

AE = adverse event; ARAC = Allergic Reactions Adjudication Committee; iGlarLixi = fixed-ratio combination of insulin glargine and lixisenatide; SAE = serious adverse event; WDAE = withdrawal due to adverse event.

Source: Clinical Study Report for LixiLan-L.[8]

Cardiovascular-Related Events

The percentage of patients experiencing a major cardiovascular event, displayed in Table 20, was low and similar between groups, [redacted]. The most commonly reported event was [redacted]

Table 20: Summary of Major Cardiovascular Events Occurring on Treatment in the LixiLan-L Study – Safety Population

Type, N (%)	[redacted]	[redacted]
Any	[redacted]	[redacted]
Cardiovascular death	[redacted]	[redacted]
Non-fatal myocardial infarction	[redacted]	[redacted]
Non-fatal stroke	[redacted]	[redacted]
Hospitalization for unstable angina	[redacted]	[redacted]
Hospitalization for heart failure	[redacted]	[redacted]
Coronary revascularization procedure	[redacted]	[redacted]

[redacted]

Notable harms

Pancreatitis

No patients in either group developed pancreatitis throughout the study.

Hypoglycemia

Table 21 shows the rate of occurrence of symptomatic hypoglycemia found in both iGlarLixi and insulin glargine arms. The rate of severe hypoglycemia, which was reported throughout this study, was low in both groups; however, it was found to have a higher incidence in the iGlarLixi group (1.1% in iGlarLixi group versus 0.3% in insulin glargine group).

Table 21: Summary of Symptomatic Hypoglycemia on Treatment in the LixiLan-L Study — Safety Population

Type	iGlarLixi (N = 365)	Insulin Glargine (N = 365)
Documented symptomatic hypoglycemia (plasma glucose ≤ 3.9 mmol/L)		
Number of patients with events, N (%)	146 (40.0)	155 (42.5)
Number of patients with events per patient year[a]	0.72	0.74
Documented symptomatic hypoglycemia as recorded on the dedicated eCRF, or documented, or probable		
Number of patients with events, n (%)	152 (41.6)	161 (44.1)
Number of patients with events per patient year[a]	0.75	0.77
Severe symptomatic hypoglycemia		
Number of patients with events, N (%)	4 (1.1)	1 (0.3)
Number of patients with events per patient year[a]	0.02	< 0.01

eCRF = electronic case report form; iGlarLixi = fixed-ratio combination of insulin glargine and lixisenatide.

[a] Calculated as number of events divided by the total patient years of exposure.

Source: Clinical Study Report for LixiLan-L.[8]

Immunogenicity

In this study, the rate of conversion from anti–insulin glargine antibody–negative status at baseline to positive status at week 30 was 15.2% in the iGlarLixi group and 11.4% in the insulin glargine group. There was also an increase in the amount of anti–insulin glargine antibody present among patients from baseline to week 30, which was 26.2% in the iGlarLixi group and 24.8% in the insulin glargine group at week 30 compared with 12.4% in the iGlarLixi group and 15.0% in the insulin glargine group at baseline (Table 22).

Table 22: Number With Anti–Insulin Glargine Antibody Status by Visit During the Treatment Period in the LixiLan-L Study — Safety Population

Visit	Anti–Insulin Glargine Antibody Status, n/N1 (%)	iGlarLixi (N = 365)	Insulin Glargine (N = 365)
Baseline	Positive	42/339 (12.4)	51/365 (15.0)
	Negative	297/339 (87.6)	288/339 (85.0)
Week 30	Positive	86/328 (26.2)	87/351 (24.8)
	Negative	242/328 (73.8)	264/351 (75.2)
	Conversion from negative at baseline to positive	50/328 (15.2)	40/351 (11.4)
Last on-treatment value	Positive	88/347 (25.4)	88/355 (24.8)
	Negative	259/347 (74.6)	267/355 (75.2)
	Conversion from negative at baseline to positive	51/347 (14.7)	41/355 (11.5)

iGlarLixi = fixed-ratio combination of insulin glargine and lixisenatide; n = number of subjects; N1 = total number of subjects with available data.

Source: Clinical Study Report for LixiLan-L.[8]

Table 23 displays the proportion of patients in the iGlarLixi group with anti-lixisenatide antibody status at baseline, week 30 as well as their last on-treatment value. [redacted]

Table 23: Number with Anti-Lixisenatide Antibody Status by Visit During the Treatment Period in the iGlarLixi Group in the LixiLan-L Study — Safety Population

Visit	Anti-Lixisenatide Antibody Status, n/N1 (%)	[redacted]
Baseline	Positive	[redacted]
	Negative	[redacted]
Week 30	Positive	[redacted]
	Negative	[redacted]
	Conversion from negative at baseline to positive	[redacted]
Last on-treatment value	Positive	[redacted]
	Negative	[redacted]
	Conversion from negative at baseline to positive	[redacted]

n = number of subjects; N1 = total number of subjects with available data.

[redacted]

Discussion

Summary of Available Evidence

One multi-centre, open-label, active-controlled randomized trial, LixiLan-L, met the criteria for inclusion in the CADTH CDR systematic review. This trial evaluated the superiority of iGlarLixi to insulin glargine in adult patients with a diagnosis of T2DM for at least one year, who were receiving treatment with basal insulin for at least six months prior to screening at a stable dose of 15 units to 40 units per day, with or without oral antidiabetes drugs, with an A1C between 7.5% and 10% at the time of screening. The primary efficacy end point in this study was a change from baseline to week 30 in A1C. Key secondary end points included change in body weight, FPG, seven-point SMPG, and daily dose of insulin glargine from baseline to week 30.

The mean age of participants ranged between 32 and 85 years, with a slightly higher proportion of women. The majority of study patients had, on average, a history of T2DM for 12 years, with a range between 1 year and 43 years. The A1C at screening ranged from 5.9% to 10.2%, with an overall mean of 8.08%. According to the clinical expert involved in this study, these patients represent an adult patient population inadequately controlled on basal insulin and are representative of a patient population who would be eligible for iGlarLixi.

Interpretation of Results

Efficacy

With respect to glycemic-control outcomes, this trial showed that there was a significant reduction in A1C levels from baseline to week 30 with iGlarLixi (–1.1%) compared with insulin glargine alone (–0.6%), with a mean difference of –0.52% (95% CI, –0.63 to –0.40; $P < 0.0001$). It is also worth noting that the mean A1C in the iGlarLixi group (6.94%) was under the target A1C identified in the trial of 7%, whereas the mean A1C was higher than the target A1C in the insulin glargine alone group (7.48%). The clinical expert consulted for

this review considered the difference in treatment effect observed between iGlarLixi and insulin glargine to be clinically relevant.

The percentage of patients achieving an A1C value below 7% and below 6.5% was found to be higher in the iGlarLixi group than in the insulin glargine group, with a statistically significant difference between groups. These outcomes, however, were not controlled for multiple statistical testing.

Additional glycemic-control values of interest for this CDR review included glucose excursion, PPG, and FPG. There was a statistically significant difference for a mean change in two-hour glucose excursion from baseline to week 30 (LSMD of iGlarLixi versus insulin glargine –3.43 mmol/L; 95% CI, –3.925 to –2.939; $P < 0.0001$). Although these values were only measured after one standardized meal of the day, the clinical expert involved in this CDR review found this difference to be clinically relevant, given that lixisenatide is considered more effective at controlling prandial levels than most other GLP-1 receptor agonists. The expert suggested that this outcome has been linked to reasons for elevated A1C levels in patients whose FPG is controlled. Similarly, there was a larger reduction from baseline to week 30 in two-hour PPG observed in the iGlarLixi group compared with the insulin glargine group (LSMD –3.33 mmol/L; 95% CI, –3.889 to –2.774). It is important to note, however, that this outcome was not appropriately adjusted for multiplicity and therefore should be considered exploratory. Finally, there was no significant difference observed between the iGlarLixi and insulin glargine groups with respect to the change in FPG from baseline to week 30, with the mean end point FPG values being 6.78 mmol/L in the iGlarLixi group and 6.69 mmol/L in the insulin glargine group (LSMD –0.11 mmol/L; 95% CI, –0.207 to 0.428; $P = 0.4951$). According to the clinical expert involved in this review, this result is expected, because lixisenatide functions primarily to reduce post-prandial glucose excursion, while insulin glargine primarily reduces FPG levels.

Statistical testing hierarchies were used to examine secondary outcomes to control for type I error, however, the manufacturer did not appear to adhere to its pre-specified strategy by continuing statistical testing for superiority after statistical insignificance was established. Overall, statistical testing should have stopped after the mean change in daily insulin glargine dose end point (fifth in the order of secondary analyses). The results for outcomes that lie outside the testing strategy and those that come after the statistical testing in the hierarchy should be considered inconclusive, due to the failure to control the type I error rate.

Health-related quality of life measures were included in this systematic review to provide a patient perspective of treatment with iGlarLixi and because this was considered an important outcome to patients, as reported in the patient input section (Appendix 1). The health-related quality of life outcomes measured in this trial were the patient-reported outcomes EQ-5D-3L and the IWQoL-Lite from baseline to week 30. Analyses of these outcomes were not adjusted for multiplicity, but the difference in treatment effect between iGlarLixi and insulin glargine alone was minimal.

Body weight was identified as an important outcome to patients in the patient input summary. Mean body weight decreased in the iGlarLixi group from baseline to week 30 by 0.67 kg and was found to have increased in the insulin glargine group by 0.70 kg during the same time frame (LSMD –1.37 kg; 95% CI, –1.808 to –0.930; $P < 0.0001$). While this difference was statistically significant, it is less than 2 kg (LSMD –1.37 kg; 95% CI –1.808 to –0.930). The clinical expert involved in this CDR review was encouraged by these results, due to the fact that insulin glargine alone is often associated with weight gain. The expert

also pointed out that both groups had increased their insulin glargine dose by 11 units throughout the 30 weeks of treatment, and, although this dose difference was small, the increase in insulin glargine dose was as well. Although any reduction in weight may be viewed as positive by patients, it is not known whether these changes translate into long-term health benefits. Furthermore, it is not clear whether this difference would have a meaningful impact on patients over a sustained length of time, since this study was over a short duration of 30 weeks.

An indirect treatment comparison (IDC) was submitted by the manufacturer, in addition to one indirect comparison identified by the literature search. For the manufacturer-submitted IDC, iGlarLixi was compared with all treatments that were likely to be indicated for patients with T2DM. Outcomes assessed included change from baseline in A1C%, proportion of patients with an A1C ≤ 7%, proportion of patients with an A1C ≤ 6.5%, change from baseline in body weight, risk of any hypoglycemic event, and risk of documented hypoglycemia. Using the Bayesian network meta-analysis (NMA) method for the outcome of A1C% change from baseline, and based on the fixed-effects model, iGlarLixi + one oral antidiabetes drug exhibited a favourable finding with a credible interval excluding the null versus basal insulin (once daily) + one oral antidiabetes drug (median difference –0.54; 95% credible interval [CrI], –0.69 to –0.38), and pre-mixed insulin (twice daily) (median difference –0.97; 95% CrI, –1.91 to –0.02), and an unfavourable finding with a credible interval excluding the null versus liraglutide 1.8 mg + basal insulin + one oral antidiabetes drug (median difference 0.66; 95% CrI, 0.04 to 1.27). The rest of the comparisons under the fixed-effects model showed credible intervals spanning the null. However, when compared with the results obtained from the random-effects model, iGlarLixi exhibited only a favourable finding (excluding the null) in the comparison with basal insulin + one oral antidiabetes drug (median difference –0.54; 95% CrI, –0.80 to –0.28); the rest of the comparisons under the random-effects model did not favour any treatment. Several limitations limit the generalizability of this study's findings. First, a search strategy appeared to have a cut-off of September 2016, meaning that many eligible trials found in the first published IDC were missed in this analysis. Second, sensitivity analyses in the Bucher IDC analysis, which could assess comparisons of high statistical heterogeneity, were not included. This was compounded by the fact that a high proportion of open-label studies were included in this analysis, with a wide range of follow-up times. The IDC found in the CDR literature search (Evans et al.)[9] assessed the use of iGlarLixi and a new fixed-ratio combination of insulin degludec/liraglutide (iDegLira). This IDC used a Bucher IDC analysis and Bayesian NMA framework, which would have allowed for wider number of comparisons of interest to be made, and used only phase III studies for its analysis. The results of this study seemed to favour iDegLira over iGlarLixi with respect to the change in A1C outcome, as well as for change in body weight. With respect to safety outcomes, it appeared that iDegLira showed consistently lower rates of severe or confirmed hypoglycemia compared with iGlarLixi.

The LixiLan-O study (N = 1,170) was a phase III, randomized, open-label, active-controlled, triple-arm, parallel-group, multinational, multi-centre trial.[34] The trial was designed to investigate the efficacy and safety of iGlarLixi against both its individual components (insulin glargine and lixisenatide) among patients aged ≥ 18 years with T2DM diagnosed at least one year before screening who had inadequate glycemic control despite treatment with metformin for at least three months, with or without a second oral antidiabetes drug. This trial was excluded from the main report after the indication of the iGlarLixi was amended to only include patients with inadequate glycemic control on basal insulin, and it

no longer fit in the selection criteria of the protocol. Results for this trial are provided in Appendix 6.

Harms

The frequency of AEs in patients treated with iGlarLixi and insulin glargine was similar between groups (53.4% in the iGlarLixi group versus 52.3% in the insulin glargine group). The incidence of SAEs was low (< 6%) and did not suggest association with specific treatments. Overall, the most common AEs occurring with iGlarLixi at a frequency above 5% were nausea (10.4%), nasopharyngitis (8.8%), and headache (5.8%). Other gastrointestinal AEs, such as diarrhea and vomiting, occurred at frequencies of 4.4% and 3.6%, respectively. According to the clinical expert involved in this study, this incidence of gastrointestinal events with iGlarLixi in this study is lower than expected, given the frequency of gastrointestinal AEs observed with lixisenatide monotherapy. The product monograph for lixisenatide reports the prevalence of nausea as 25.3%, vomiting as 9.8%, and diarrhea as 7.7%.[27] The slower titration of the lixisenatide component in the iGlarLixi in the LixiLan-L study, as well as the lower dose of lixisenatide, may have contributed to the lower frequencies of gastrointestinal AEs.

There were three deaths reported in this study. One of the deaths occurred in a patient on iGlarLixi and two occurred in patients on insulin glargine. These deaths were due to pneumonia, gallbladder cancer, and cardiopulmonary failure, and did not appear to be distributed with any clustering, or at a different frequency between treatment groups.

The percentage of patients with at least one episode of symptomatic hypoglycemia observed in this study was lower in the iGlarLixi group (40.0% in the iGlarLixi group and 42.5% in the insulin glargine group); however, the occurrence rate of severe symptomatic hypoglycemia was higher in the iGlarLixi group (1.1%) than in the insulin glargine group (0.3%). These results suggest that the risk of hypoglycemia known to be associated with insulin glargine and that of lixisenatide may be higher with patients taking iGlarLixi. In this study, patients with a history of hypoglycemia unawareness were excluded, and any concomitant use of a sulfonylurea was not allowed throughout the course of this study. It is known that the concomitant use of sulfonylureas with medications such as insulin glargine and GLP-1 agonists are associated with an increased risk of hypoglycemia. Currently, the product monograph for iGlarLixi provides a warning against the combined use of iGlarLixi with a sulfonylurea.[7]

The proportion of patients experiencing a major cardiovascular event was low and similar between treatment groups ([redacted]). The majority of events reported were for [redacted] The clinical expert involved in this study noted that the duration of this study was not sufficient to detect a meaningful difference between these two treatments in outcomes of this nature.

The presence of anti–insulin glargine antibodies and anti-lixisenatide antibodies were collected for this study because of concerns about immunogenicity with the use of lixisenatide. In this study, the rate of conversion of those with an anti–insulin glargine–negative status at baseline was found to be higher in the iGlarLixi group compared with the insulin glargine group (15.2% versus 11.4%). [redacted]

[redacted]. In terms of the effect on safety, the FDA medical review for this product reported a trend that was observed for patients with a higher concentration of anti-lixisenatide and a smaller reduction in A1C compared with those with lower concentrations.[30]

In the LixiLan-O study, the safety profile of iGlarLixi was found to carry risks associated with both its insulin glargine and lixisenatide components. Compared with insulin glargine, iGlarLixi was found to have a higher incidence of gastrointestinal AEs. iGlarLixi and insulin glargine were found to carry a higher incidence of hypoglycemia than lixisenatide alone. Lixisenatide and iGlarLixi were also found to have a higher incidence of product-related allergic reactions than insulin glargine alone.

Potential Place in Therapy[2]

Only about 40% of patients with T2DM treated with basal insulin, with or without other oral antidiabetes drugs, achieve A1C targets, and these individuals require additional therapy to improve glycemia. A traditional approach for managing these individuals has been the addition of prandial insulin from one to three times daily, but this therapy increases complexity and the number of injections and is associated with weight gain and hypoglycemia. There is an unmet need for patients requiring intensification beyond basal insulin for a simple and convenient therapy that will not increase hypoglycemia and will provide a weight benefit. GLP-1 receptor analogues are ideal drugs to combine with basal insulin, due to their simple titration regimens and improvement in A1C and PPG, without increasing hypoglycemia and with weight-loss benefits.

Fixed-ratio combinations of basal insulin with GLP-1 analogues allow for combining these two classes in a single injection. iGlarLixi has been studied in patients with T2DM suboptimally controlled on basal insulin, with or without up to two oral antidiabetes drugs, in the LixiLan-L trial.[8] The therapy of titrated iGlarLixi compared with insulin glargine was found to significantly improve A1C and lower body weight without increasing hypoglycemia. iGlarLixi was well tolerated, with lower rates of gastrointestinal AEs than other lixisenatide trials, likely due to the slow titration during the trial.

The trial data with iGlarLixi support using this drug in patients with an elevated A1C despite therapy with basal insulin, with or without metformin or other oral antidiabetes drugs. It also adds the convenience of a single injection with two drugs, rather than separate injections of basal insulin and a GLP-1 analogue. It may be particularly useful for patients with good fasting glucose control on basal insulin, but elevation in A1C and post-prandial hyperglycemia, especially after the largest daily meal. The weight benefit versus insulin alone is also important, given that about 85% of individuals with T2DM are overweight or obese.

iGlarLixi provides a novel way to combine a GLP-1 analogue with basal insulin in a convenient single injection for individuals with elevated A1C, despite therapy with basal insulin. Its use in practice will be consistent with Diabetes Canada 2018 guidelines that recommend “a GLP-1 receptor analogue be considered as add-on therapy to basal insulin before initiating bolus insulin or intensifying insulin to improve glycemic control with weight loss and a lower hypoglycemia risk compared with single or multiple bolus insulin injections.”[5]

[2] This information is based on information provided in draft form by the clinical expert consulted by CDR reviewers for the purpose of this review.

Conclusions

One open-label, multi-centre, parallel-group randomized controlled trial in adults with T2DM who were inadequately controlled on basal insulin compared the use of iGlarLixi to insulin glargine for up to 30 weeks. There was a statistically significant improvement in A1C in favour of iGlarLixi compared with insulin glargine from baseline to week 30, and this difference was considered to be clinically relevant. Patients in the iGlarLixi group were also found to have a decrease in mean body weight after more than 30 weeks. [redacted] The percentage of patients experiencing at least one AE was similar between iGlarLixi and insulin glargine, with gastrointestinal AEs reported at a higher frequency among patients taking iGlarLixi compared with those taking insulin glargine. The proportion of patients reporting symptomatic hypoglycemia was lower in the iGlarLixi group; however, there was a higher percentage of patients reporting severe symptomatic hypoglycemia in the iGlarLixi group. There were no data available on the use of iGlarLixi beyond 30 weeks. The manufacturer-submitted IDC suggested that iGlarLixi is better than basal insulin combined with one oral antidiabetes drug for glycemic control between 20 to 30 weeks; comparisons between iGlarLixi and other treatment options in the analyses were inconclusive. The overall certainty of the results of the manufacturer-submitted IDC is limited, most notably because the literature search to inform the IDC was not up to date, and, therefore, the results do not reflect all available evidence.

Appendix 1: Patient Input Summary

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

1. Brief Description of Patient Group(s) Supplying Input

One patient group, Diabetes Canada, provided the input for this submission. Diabetes Canada is a national health charity representing 11 million Canadians living with diabetes or pre-diabetes. The priorities of Diabetes Canada's mission are diabetes prevention, care, and cure. Diabetes Canada focuses on research and policy initiatives for better prevention and treatment strategies. The organization received funding from multiple pharmaceutical companies and organizations, including Sanofi Canada, which was one of five companies that provided more than $350,000 over the past two years. They had no help from outside their organization to collect and analyze data or to complete the submission.

2. Condition-Related Information

Information was gathered through online surveys of patients with type 2 diabetes and their caregivers, which were conducted in October 2016 and April 2018. A total of 847 people responded to the October 2016 survey — 790 patients with type 2 diabetes and 57 caregivers. Of those who responded to questions about age and time since diagnosis (n = 379), 70% were over the age of 55, with the largest number of respondents (56%, n = 211) in the age category 55 to 69 years, and 60% having lived with diabetes for more than 10 years. In the April 2018 survey (n = 12), 11 respondents were patients with type 2 diabetes and one was a caregiver. Information regarding age and time since diagnosis was provided by two patients: both were between the ages of 25 and 55, one had had diabetes less than a year, and the other for six to 10 years.

The patient group highlighted that diabetes is a chronic, progressive disease without a cure. The common symptoms of diabetes include extreme fatigue, unusual thirst, frequent urination and weight change (gain or loss). Diabetes requires considerable self-management, including eating well, engaging in regular physical activity, maintaining a healthy body weight, taking medications (oral and/or injectable) as prescribed, monitoring blood glucose, and managing stress. Poor glucose control is serious and problematic. Low blood glucose can precipitate an acute crisis, including confusion, coma, or seizure. High blood glucose over time can irreversibly damage blood vessels and nerves, resulting in blindness, heart disease, kidney problems, and lower-limb amputations, among other issues. The goal of diabetes management is to keep glucose levels within a target range to minimize symptoms and avoid or delay complications.

Most patients surveyed talked about the unfavorable effects diabetes has had on their lives. Patients describe diabetes as a "horrendous experience," "manageable but a bother," an "awful disease," and as inconvenient, frustrating, and exhausting. The condition affects all aspects of their lives, from eating and exercising to working and socialization. Patients are anxious and fearful of complications of the disease, and they face stigma. Patients who responded to the surveys indicated that they experienced the following symptoms or comorbidities: hyperglycemia; hypoglycemia; high blood pressure; high cholesterol; heart problems; mental health problems; kidney symptoms or disease; foot problems; eye problems; nerve damage; damage to blood vessels, heart, or brain; liver disease; weight gain; and sexual dysfunction.

The following are some comments from survey respondents:

"It is part of every decision I make on a daily basis regarding general health, exercise, nutrition, social activities, work etc."

"I feel like my body is breaking down 25 years ahead of its time."

"The fact that I have to consistently monitor myself and wonder if I'm going to lose my eyes is something I wouldn't wish on my worst enemy."

"I am a…mother…and hate the fact that I have developed diabetes and have to take medications for it… My kids have to know what to do if I pass out…"

3. Current Therapy-Related Information

Patients who responded to the October 2016 survey (n = 647) reported they have used (in the past or currently) the following antihyperglycemic drugs: metformin, glucagon-like peptide 1 (GLP-1) receptor agonists, sodium-glucose cotransporter-2 (SGLT2) inhibitors, combination of SGLT2 inhibitors and metformin, dipeptidyl peptidase-4 (DPP-4) inhibitors, combination of DPP-4 inhibitors and metformin, sulfonylureas, thiazolidinediones (TZDs), combination of TZDs and metformin, combination of TZDs and glimepiride, meglitinides, acarbose, and insulin. More than 60% of respondents (from the October 2016 survey) noted improvements in meeting target blood glucose levels (fasting, post-prandial, upon waking) and glycated hemoglobin (A1C) levels after initiation of their current medication regimen, compared with before (when they were not on treatment). About 46% patients said they were "better" or "much better" able to avoid hypoglycemia, and 39% said their current regimen helped them maintain or lose weight more effectively than in the past. Gastrointestinal side effects were "neither better nor worse" than previously in 39% of respondents. About two-thirds indicated they were either "satisfied" or "very satisfied" with the medication or combination of medications they are currently taking for their diabetes management. The factors were considered "quite important" or "very important" in choosing diabetes medications among respondents were, among others: keeping blood glucose at satisfactory level, avoiding low blood sugar, avoiding weight gain or facilitating weight loss, reducing risk of heart problems, and avoiding gastrointestinal issues (nausea, vomiting, diarrhea, pain) and urinary tract and/or yeast infections.

Three patients responded to questions about their medication use in the April 2018 survey. Metformin (3 patients), GLP-1 receptor agonists (1 patient), SGLT2 inhibitors (1 patient), DPP-4 inhibitors (1 patient), and sulfonylureas (1 patient) were used. Insulin use was reported as insulin glargine (1 patient) and rapid-acting (1 patient). All three patients reported that they were "better" or "much better" at achieving A1C targets with current medications than the previous regimen. They also identified the same factors as important in choosing medications as did the patients who participated in the October 2016 survey.

4. Expectations About the Drug Being Reviewed

Responders in both surveys indicated the desire for medications that have been proven safe and can normalize/stabilize blood glucose levels and improve A1C levels without causing weight gain or hypoglycemia. They wish for new treatments to enhance weight loss and improve health outcomes at an affordable cost. Ideally, they would like medications and diabetes devices to be covered in a timely manner by public and private plans. They want treatments that are easily administered, cause the least amount of disruption to lifestyle, and allow for flexibility with food intake and choices. They also want medications that will help avoid polypharmacy and eliminate the need for injections, while minimizing risk of any short-term medication-related side effects or long-term disease-related side effects. Several respondents hope future treatments will reverse or cure diabetes. In the October 2016 survey, some respondents commented on the advantage of having combination

medications available for diabetes treatment. Several spoke about how burdensome it is to take several oral and/or injectable medications for their management and stated that it would make a difference to their daily management and quality of life to reduce the number of drugs they administer.

The following are a few examples of comments from patients regarding their hopes and expectations for new treatments:

"Help with A1C, reduce weight gain, promote weight loss, supported by formulary to keep cost down."

"Manage diabetes effectively without needing such a large variety of medications."

"[T]he less medication [I] have to take, the better it is on my mental health."

Appendix 2: Literature Search Strategy

OVERVIEW	
Interface:	Ovid
Databases:	MEDLINE All (1946 to present) Embase (1974 to present) **Note:** Subject headings have been customized for each database. Duplicates between databases were removed in Ovid.
Date of Search:	June 18, 2018
Alerts:	Bi-weekly search updates until October 17, 2018
Study Types:	No search filters were applied
Limits:	No date or language limits were used Conference abstracts were excluded

SYNTAX GUIDE	
/	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#	Adjacency within # number of words (in any order)
.ti	Title
.ab	Abstract
.ot	Original title
.hw	Heading word; usually includes subject headings and controlled vocabulary
.kf	Author keyword heading word (MEDLINE)
.kw	Author keyword (Embase)
.pt	Publication type
.rn	CAS registry number
.nm	Name of substance word
medall	Ovid database code; MEDLINE All 1946 to present, updated daily
oemezd	Ovid database code; Embase 1974 to present, updated daily

MULTI-DATABASE STRATEGY	
1	S900007330.rn,nm.
2	(soliqua* or suliqua* or iglarlixi* or LixiLan* or "glargine/lixisenatide" or "lixisenatide/glargine" or "lantus/lyxumia" or "lyxumia/lantus" or "ave 0010/hoe 901" or "ave0010/hoe901" or "hoe 901/ave 0010" or "hoe901/ave0010").ti,ab,ot,kf,hw,rn,nm.
3	or/1-2
4	Insulin Glargine/ or (2ZM8CX04RZ or glargine* or lantus* or HOE 901 or HOE901 or HOE 71GT or LY 2963016m or MK-1293).ti,ab,ot,kf,hw,rn,nm.
5	(74O62BB01U or lixisenatide* or lyxumia* or adlyxin* or "ave 0010" or ave0010 or aqve 10010 or aqve10010 or ZP 10 or ZP10 or ZP 10A or ZP10A).ti,ab,ot,kf,hw,rn,nm.

MULTI-DATABASE STRATEGY	
6	4 and 5
7	3 or 6
8	7 use medal
9	*insulin glargine plus lixisenatide/
10	(soliqua* or suliqua* or iglarlixi* or LixiLan* or "glargine/lixisenatide" or "lixisenatide/glargine" or "lantus/lyxumia" or "lyxumia/lantus" or "ave 0010/hoe 901" or "ave0010/hoe901" or "hoe 901/ave 0010" or "hoe901/ave0010").ti,ab,kw.
11	or/9-10
12	*Insulin Glargine/ or (glargine* or lantus* or HOE 901 or HOE901 or HOE 71GT or LY 2963016m or MK-1293).ti,ab,kw.
13	*Lixisenatide/ or (lixisenatide* or lyxumia* or adlyxin* or "ave 0010" or ave0010 or aqve 10010 or aqve10010 or zp 10 or zp10).ti,ab,kw.
14	12 and 13
15	11 or 14
16	15 use oemezd
17	conference abstract.pt.
18	16 not 17
19	8 or 18
20	remove duplicates from 19

OTHER DATABASES		
PubMed	Searched to capture records not found in MEDLINE. 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 2018
Keywords:	Soliqua (insulin glargine and lixisenatide); type 2 diabetes
Limits:	No date or language limits used

Relevant websites from the following sections of the CADTH grey literature checklist *Grey Matters: a practical tool for searching health-related grey literature* (https://www.cadth.ca/grey-matters) were searched:

- Health Technology Assessment Agencies
- Health Economics
- Clinical Practice Guidelines
- Drug and Device Regulatory Approvals
- Advisories and Warnings
- Drug-Class Reviews
- Clinical Trial Registries
- Databases (free)
- Internet search.

Appendix 3: Excluded Studies

Table 24: Excluded Studies

Reference	Reason for Exclusion
LixiLan-O study	Indication

Appendix 4: Validity of Outcome Measures

Aim

To summarize the validity of the following outcome measures:

- Impact of Weight on Quality of Life–Lite (IWQoL-Lite)
- EuroQol 5-Dimensions 3-levels (EQ-5D-3L)

Table 25: Validity and Minimal Clinically Important Difference of IWQoL-Lite and EQ-5D-3L

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, Other conditions: 7 to 12	Kolotkin et al. (2003)[35]
EQ-5D-3L	EQ-5D-3L is a generic, health-related quality of life questionnaire.	Yes	Unknown for type 2 diabetes	van Reenen and Janssen (2015)[36] Health Quality Council of Alberta (2014)[37] McClure et al. (2017)[38]

EQ-5D = EuroQol 5-Dimensions 3-levels questionnaire; IWQoL-Lite = Impact of Weight on Quality of Life–Lite; MCID = minimal clinically important difference.

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. An estimated 80% of patients with diabetes 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. It was developed by Kolotkin et al. after the length of the original version proved cumbersome for research subjects.[39] The IWQoL-Lite was reduced to 31 items related to 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 assigned a score, ranging from 5 for "always true" to 1 for "never true."[39] The scores of all the items within a domain are added together to provide the domain score, and the sum of scores from all five domains provides the total score. Scores on the IWQoL-Lite (a total score and one for each of the domains) range from 0 to 100, with a 100 score representing the best and a 0 score representing the poorest quality of life.[39]

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.[35] IWQoL-Lite data were collected from 1,197 individuals who were obese seeking weight-loss treatment and gastric-bypass surgery in a clinical trial, of whom 225 had type 2 diabetes.[35] A number of statistical tests were done to assess the validity and reliability of the instrument. The 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 without diabetes, respectively, indicating acceptable internal consistency relative to a threshold of 0.70.[35] Within the group with diabetes, internal consistency 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 and without diabetes with the second-order IWQoL-Lite model. Moderate to strong correlations were found between body mass index (BMI) and IWQoL-Lite for both patients with and without diabetes, demonstrating construct validity.[35] Correlation coefficients ranged from –0.545 (sexual life) to –0.737 (public distress) for IWQoL-Lite scores and BMI to 0.705 for IWQoL-Lite total score and BMI among patients with diabetes.[35] However, the IWQoL-Lite instrument and validation study had a few limitations. Previous studies have investigated the relationship between IWQoL-Lite scores and measures of similar constructs such as the Short Form (36) Health Survey (SF-36), the Rosenberg self-esteem scale, the Marlowe–Crowne Social Desirability Scale, and global ratings, and have shown convergent and discriminant validity of this instrument; however, those studies were done in patients without diabetes.[39,40] These forms of validity were not investigated in this study among patients with diabetes. The IWQoL-Lite did not attempt to discriminate in the weight-related quality of life between patients with and without diabetes. This study also did not provide a minimal clinically important difference (MCID) for the IWQoL-Lite in obese patients with type 2 diabetes mellitus; however, in patients with general obesity, a range of 7 to 12 is typically found.[33]

EuroQol 5-Dimensions 3-levels

The EQ-5D-3L is a generic, preference-based, health-related quality of life instrument that has been applied to a wide range of health conditions and treatments, including type 2 diabetes.[32,41] The first of two parts of the EQ-5D-3L is a descriptive system that classifies respondents (aged ≥ 12 years) into one of 243 distinct health states. The descriptive system consists of the following five dimensions: mobility, self-care, usual activities, pain/discomfort, and anxiety/depression. Each dimension has three possible levels (1, 2, or 3) representing “no problems,” “some problems,” and “extreme problems,” respectively. Respondents are asked to choose one level that reflects their own health state for each of the five dimensions. A scoring function can be used to assign a value (EQ-5D-3L index score) to self-reported health states from a set of population-based preference weights.[32,41] The second part is a 20 cm visual analogue scale (EQ-VAS) that has end points labelled 0 and 100, with respective anchors of “worst imaginable health state” and “best imaginable health state,” respectively. Respondents are asked to rate their own health by drawing a line from an anchor box to the point on the EQ-VAS which best represents their own health on that day. Hence, the EQ-5D-3L produces three types of data for each respondent:

- a profile indicating the extent of problems on each of the five dimensions represented by a five-digit descriptor, such as 11121, 33211, etc.
- a population preference-weighted health index score based on the descriptive system
- a self-reported assessment of health status based on the EQ-VAS.

The EQ-5D-3L index score is generated by applying a multi-attribute utility function to the descriptive system. Different utility functions are available that reflect the preferences of specific populations (e.g., US or UK). The lowest possible overall score (corresponding to severe problems on all five attributes) varies, depending on the utility function that is applied to the descriptive system (e.g., −0.59 for the UK algorithm and −0.109 for the US algorithm). Scores of less than 0 represent health states that are valued by society as being worse than dead, while scores of 0 and 1.00 are assigned to the health states “dead” and “perfect health,” respectively. [32,41]

Evidence of the measurement properties of the EQ-5D in patients with type 2 diabetes was summarized in a systematic review by Janssen et al. (2011).[42] The authors concluded that construct, convergent, and discriminant validity of the EQ-5D was generally supported, based on data from 39 papers.[42] Test–retest reliability was found to be good to excellent, and responsiveness was acceptable.[42] Several studies reported ceiling effects.[42,43] A qualitative study suggested that EQ-5D had content validity in diabetes; however, it was missing some important factors that affect patients' quality of life, such as treatment or monitoring requirements, food awareness or restriction, activities, emotional functioning other than depression or anxiety, and social or relationship functioning.[44]

An MCID for the EQ-5D index score in patients with diabetes was not identified; however, in other conditions, it typically ranges from 0.033 to 0.074.[32]

Conclusions

The IWQoL-Lite is a self-administered questionnaire 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 internal consistency. The individual domains and total score of the IWQoL-Lite have a strong correlation with BMI. Convergent and discriminant validity of this instrument is proven in patients with diabetes. An MCID for the IWQoL-Lite in obese patients with type 2 diabetes mellitus was not identified, although a range of 7 to 12 is considered acceptable in patients with obesity.[33] The EQ-5D-3L is a widely used generic health status measure consisting of five self-reported health domains with three levels per domain. An MCID was not identified for type 2 diabetes.

Appendix 5: Detailed Outcome Data

Table 26: Change in A1C and Body Weight at Week 30 Using MMRM Where Patients in the iGlarLixi Group Used Pen B Only in the LixiLan-L Study — mITT Population

End Point	iGlarLixi Pen B Only (N = 146)	Insulin Glargine (N = 365)
A1C %	**N = 146**	**N = 364**
Mean baseline value (SD)	8.16 (0.70)	8.08 (0.73)
LS mean change from baseline (SE)[a]	–1.14 (0.082)	–0.61 (0.060)
LS mean difference of iGlarLixi versus insulin glargine [95% CI][a]	–0.53 [–0.684 to –0.369]	
P value	< 0.0001	
Body weight (kg)	**N = 146**	**N = 365**
Mean baseline	90.42 (13.90)	87.09 (14.75)
LS mean change from baseline (SE)[a]	–0.39 (0.265)	0.71 (0.18)
LS mean difference of iGlarLixi versus insulin glargine [95% CI][a]	–1.10 [–1.669 to –0.541]	
P value	0.0001	

A1C = glycated hemoglobin; CI = confidence intervals; iGlarLixi = fixed-ratio combination of insulin glargine and lixisenatide; LS = least squares; mITT = modified intention-to-treat; MMRM = mixed-effects model with repeated measures; SD = standard deviation; SE = standard error.

[a] Mixed-effects model with repeated measures (MMRM) with treatment groups (fixed-ratio combination and insulin glargine), randomization strata of A1C (< 8.0%, ≥ 8.0%), at visit 5 (week –1), randomization strata of metformin use at screening (Yes, No), scheduled visit, treatment-by-visit interaction and country as fixed effects, and baseline body weight value-by-visit interaction as a covariate.

Source: Manufacturer-provided additional data.[45]

Appendix 6: Summary of LixiLan-O Study

Aim

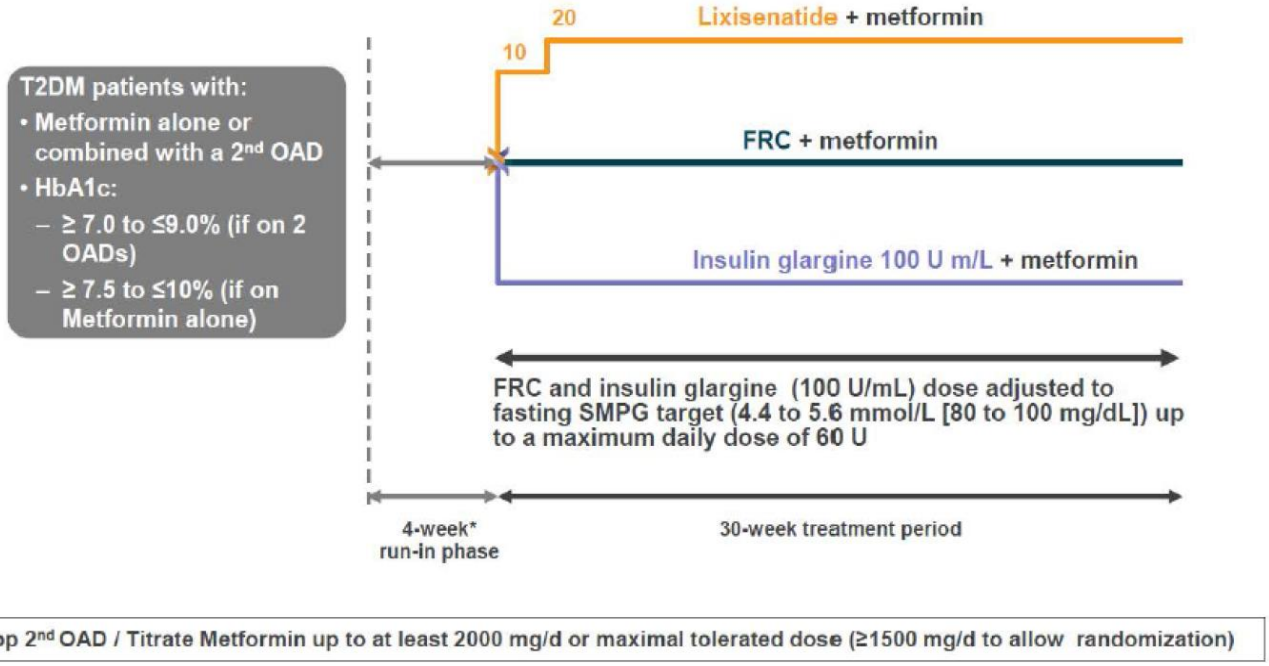
The following section provides a summary and critical appraisal of the LixiLan-O trial,[34] which was an open-label, active-controlled randomized trial designed to compare the titratable, fixed-ratio combination of insulin glargine/lixisenatide (iGlarLixi) with both of its individual components (insulin glargine and lixisenatide) in patients with type 2 diabetes mellitus who were insulin-naive by measuring a change in glycemic-control outcomes. This trial did not meet the inclusion criteria of this CADTH Common Drug Review (CDR) report because the indication for iGlarLixi includes only patients with inadequate glycemic control on basal insulin. Results for this trial are summarized in this appendix.

Methods

Description of Study

The LixiLan-O study[34] (N = 1,170) was a phase III, randomized, open-label, active-controlled, triple-arm, parallel-group, multinational, multi-centre trial. It was designed to investigate the efficacy and safety of iGlarLixi compared with both of its individual components (insulin glargine and lixisenatide) among patients aged 18 years and older with type 2 diabetes diagnosed at least one year before screening and with inadequate glycemic control despite treatment with metformin for at least three months, with or without a second oral antidiabetes drug. Patients were recruited through a screening period lasting up to six weeks, which included a screening phase of up to two weeks, followed by a four-week run-in phase during which patients were discontinued on any antidiabetes drug other than metformin, and metformin was optimized up to a daily dose of at least 2,000 mg or the maximum tolerated dose. Following the run-in phase, eligible patients with a glycated hemoglobin (A1C) level (≥ 7% and ≤ 10%), a fasting plasma glucose (≤ 13.9 mmol/L), and metformin dosage (≥ 1,500 mg/day or maximum tolerated dosage) within range and ability to adhere to study protocol were randomized using an interactive voice/Web response system in a 2:2:1 manner to receive either iGlarLixi, insulin glargine alone, or lixisenatide alone for a period of 30 weeks. All randomized patients were further stratified based on their A1C level, basal insulin use, and estimated glomerular filtration rate (eGFR). At the start of the run-in phase (week –6), all patients were trained using a training disposable Lantus SoloSTAR, as well as monitoring of glucose measurements, including glucometer dispensation. At the start of the treatment phase (day 1), patients who were randomized to receive iGlarLixi were trained using a training disposable Pen A and Pen B. The treatment phase lasted for 30 weeks, followed by a three-day post-treatment safety follow-up period after treatment discontinuation, except for those who prematurely discontinued study treatment. The primary efficacy end point was change in mean A1C level from baseline to week 30. The co-primary objectives of this study were to demonstrate superiority of iGlarLixi to lixisenatide in the A1C change from baseline to week 30 and to demonstrate the noninferiority of iGlarLixi to insulin glargine in A1C change from baseline to week 30.

Figure 4: Design of LixiLan-O study



FRC = fixed-ration combination; OAD = oral antidiabetes drug; $HbA1_c$ = glycated hemoglobin; SMPG = self-monitored plasma glucose; U = unit.

Source: Clinical Study Report for LixiLan-O. [34]

Population

Inclusion and Exclusion Criteria

The inclusion and exclusion criteria for the patients are listed in Table 27.

Table 27: Inclusion and Exclusion Criteria in the LixiLan-O Study

Type	Criteria
Inclusion Criteria	• Type 2 diabetes mellitus diagnosed at least one year prior to screening visit • Treatment for ≤ 3 months with metformin alone or metformin and a second OAD treatment that could be a sulfonylurea, meglitinide, or SGLT2 inhibitor, and who were not adequately controlled on treatment At screening: • FPG ≤ 10.0 mmol/L for those receiving basal insulin in combination with two OADs or with one OAD other than metformin • FPG ≤ 11.1 mmol/L for those on basal insulin only or basal insulin plus metformin At the end of the 6-week run-in phase (before randomization): • Mean fasting SMPG ≤ 7.8 mmol/L calculated for the seven days prior to randomization • Average insulin glargine daily dose ≥ 20 units or ≤ 50 units for the last three days before randomization
Exclusion Criteria	• A1C < 7.5% or > 10.0% for patients taking metformin alone, or A1C < 7.0% or > 9.0% for patients taking metformin with a second OAD treatment at screening visit • FPG > 13.9 mmol/L at the end of the screening period • Metformin maximum tolerated dosage less than 1,500 mg/day at the end of the screening period • Age under the legal age of adulthood at screening visit • Use of oral or injectable glucose-lowering drugs other than those stated in the inclusion criteria in the

Type	Criteria
	three months prior to screening, including lixisenatide • Use of insulin other than basal insulin (e.g., prandial or pre-mixed insulin) in the year prior to screening, excluding short-term treatment (≤ 10 days) due to intercurrent illness • Previous discontinuation of treatment with GLP-1 agonist for safety/tolerability or lack of efficacy • History of pancreatitis (unless pancreatitis was related to gallstones and cholecystectomy was already performed), chronic pancreatitis, pancreatitis during a previous treatment with incretin therapies, pancreatectomy, stomach/gastric surgery • Renal function impairment with creatinine clearance < 30 mL/min or ESRD

A1C = glycated hemoglobin; ESRD = end-stage renal disease; FPG = fasting blood glucose; GLP-1 = glucagon-like peptide-1; OAD = oral antidiabetes drug; SGLT2 = sodium-glucose cotransporter-2; SMPG = self-monitored plasma glucose.

Source: Clinical Study Report for LixiLan-O.[34]

Baseline Characteristics

Overall, the mean age of the patients was 58.4 years (standard deviation [SD] 9.3 years); 50.6% of the patients were male; and 90.1% were white. Mean body weight was 89.1 kg (SD 16.6 kg), and mean body mass index (BMI) was 31.7 kg/m^2. Of the patients, 26% were of 65 years or older, 24.9% had a creatinine clearance between 60 and < 90 mL/min, and 0.9% had a creatinine clearance between 30 and < 60 mL/min. More than half of the patients had an A1C level more than 8% (55.8%), and more than half (53.9%) had been using a sulfonylurea. These baseline characteristics had similar distribution across the three groups, including age, gender, race, A1C level, age at onset of diabetes, duration of diabetes, and diabetes and nondiabetes disease and medication history. Results are provided in Table 28.

Table 28: Summary of Baseline Characteristics in LixiLan-O Study

Baseline Characteristics		iGlarLixi (N = 469)	Insulin Glargine (N = 467)	Lixisenatide (N = 234)	All (N = 1,170)
Gender	Male, N (%)	222 (47.3)	237 (50.7)	133 (56.8)	592 (50.6)
Age	Mean (SD)	58.2 (9.5)	58.3 (9.4)	58.7 (8.7)	58.4 (9.3)
	Median (range)	59.0 (18 to 79)	59.0 (25 to 82)	59.0 (31 to 80)	59.0 (18 to 82)
	≥ 65 years, N (%)	133 (28.4)	114 (24.4)	59 (25.2)	306 (26.2)
Race	White, N (%)	417 (88.9)	421 (90.1)	216 (92.3)	1,054 (90.1)
	Black, N (%)	33 (7.0)	33 (7.1)	12 (5.1)	78 (6.7)
	Asian, N (%)	8 (1.7)	7 (1.5)	3 (1.3)	20 (1.7)
	Other, N (%)	11 (2.3)	6 (1.3)	3 (1.3)	20 (1.7)
Ethnicity	Hispanic, N (%)	85 (18.1)	87 (18.6)	51 (21.8)	223 (19.1)
	Non-Hispanic, N (%)	384 (81.9)	380 (81.4)	183 (78.2)	947 (80.9)
Creatinine clearance[a] (mL/min), N (%)	30 to < 60	4 (0.9)	3 (0.7)	3 (1.3)	10 (0.9)
	60 to < 90	117 (25.2)	128 (27.6)	44 (19.0)	289 (24.9)
	≥ 90	344 (74.0)	333 (71.8)	185 (79.7)	862 (74.2)
Weight (kg)	Mean (SD)	89.43 (17.16)	89.75 (16.36)	90.72 (16.25)	89.81 (16.66)
	Median (range)	88.90 (46.7 to 147.0)	88.50 (47.4 to 137.3)	91.00 (54.3 to 144.0)	89.10 (46.7 to 147.0)
BMI (kg/m^2)	Mean (SD)	31.64 (4.40)	31.66 (4.51)	31.99 (4.39)	31.72 (4.44)
	Median (range)	31.40 (18.9 to 40.1)	31.45 (21.0 to 41.5)	32.09 (20.2 to 40.3)	31.53 (18.9 to 41.5)
	< 30, N (%)	174 (37.1)	179 (38.3)	75 (32.1)	428 (36.6)
	≥ 30, N (%)	295 (62.9)	288 (61.7)	159 (67.9)	742 (63.4)

Baseline Characteristics		iGlarLixi (N = 469)	Insulin Glargine (N = 467)	Lixisenatide (N = 234)	All (N = 1,170)
Country of origin, N (%)	Canada, N (%)	3 (0.6)	6 (1.3)	2 (0.9)	11 (0.9)
	US, N (%)	133 (28.4)	150 (32.1)	79 (33.8)	362 (30.9)
	Western Europe, N (%)	60 (12.8)	52 (11.1)	28 (12.0)	140 (12.0)
	Eastern Europe, N (%)	164 (35.0)	143 (30.6)	67 (28.6)	374 (32.0)
	Mexico, N (%)	29 (6.2)	25 (5.4)	18 (7.7)	72 (6.2)
	Russia, N (%)	32 (6.8)	49 (10.5)	25 (10.7)	106 (9.1)
	Other, N (%)	48 (10.2)	42 (9.0)	15 (6.4)	105 (9.0)
A1C at week 1, %	Mean (SD)	8.17 (0.70)	8.20 (0.68)	8.28 (0.70)	8.20 (0.69)
	Median (range)	8.10 (6.8 to 10.4)	8.10 (7.0 to 10.0)	8.20 (7.0 to 10.0)	8.10 (6.8 to 10.4)
Randomization strata A1C at week 4	< 8%, N (%)	207 (44.1)	207 (44.3)	103 (44.0)	517 (44.2)
	≥ 8%, N (%)	262 (55.9)	260 (55.7)	131 (56.0)	653 (55.8)
FPG (mmol/L)	Mean (SD)	9.87 (2.35)	9.75 (2.32)	9.75 (2.19)	9.80 (2.31)
	Median (range)	9.70 (4.3 to 17.8)	9.30 (4.7 to 21.5)	9.70 (5.5 to 19.4)	9.60 (4.3 to 21.5)
2-hour PPG (mg/dL)	Mean (SD)	15.06 (3.61)	14.59 (3.60)	14.84 (3.35)	14.83 (3.56)
	Median (range)	15.10 (3.1 to 24.6)	14.50 (4.4 to 26.6)	14.95 (4.9 to 24.1)	14.80 (3.1 to 26.6)
Average 7-point SMPG (mg/dL)	Mean (SD)	10.51 (2.17)	10.38 (2.15)	10.43 (2.04)	10.44 (2.14)
	Median (range)	10.06 (5.2 to 16.8)	10.12 (5.8 to 18.3)	10.36 (6.0 to 17.2)	10.13 (5.2 to 18.3)
Duration of diabetes (years)	Mean (SD)	8.89 (5.51)	8.66 (5.59)	8.89 (6.26)	8.80 (5.69)
	Median (range)	8.14 (1.0 to 34.2)	7.60 (1.0 to 39.7)	7.65 (1.0 to 44.5)	7.69 (1.0 to 44.5)
Duration of metformin treatment (years)	Mean (SD)	6.42 (4.85)	6.46 (4.70)	6.12 (4.45)	6.38 (4.71)
	Median (range)	5.25 (0.3 to 34.2)	5.45 (0.3 to 26.4)	5.45 (0.2 to 24.7)	5.37 (0.2 to 34.2)
Daily dose of metformin at baseline (mg)	Mean (SD)	2,246.1 (456.8)	2,244 (444.7)	2,267.3 (427.4)	2,249.8 (445.9)
	Median (range)	2,000.0 (1,000 to 3,000)	2,000.0 (1,000 to 3,000)	2,000.0 (1,000 to 3,000)	2,000.0 (1,000 to 3,000)
Prior use of insulin, N (%)		11 (2.3)	14 (3.0)	4 (1.7)	29 (2.5)
Prior use of GLP-1 agonist, N (%)		[redacted]	[redacted]	[redacted]	[redacted]
Second OAD use at screening by class, N (%)	Number (Yes)	274 (58.4)	270 (57.8)	133 (56.8)	677 (57.9)
	Sulfonylurea	259 (55.2)	249 (53.3)	123 (52.6)	631 (53.9)
	Meglitinides	3 (0.6)	10 (2.1)	5 (2.1)	18 (1.5)
	SGLT2 inhibitor	2 (0.4)	2 (0.4)	0	4 (0.3)
	DPP-4 inhibitor	12 (2.6)	11 (2.4)	5 (2.1)	28 (2.4)
Duration of second OAD use (years)	Mean (SD)	3.98 (4.07)	4.61 (4.67)	3.94 (3.54)	4.22 (4.23)
	Median (range)	2.59 (0.3 to 21.3)	3.26 (0.3 to 25.4)	2.49 (0.3 to 16.0)	2.82 (0.3 to 25.4)

A1C = glycated hemoglobin; BMI = body mass index; FPG = fasting plasma glucose; GLP-1 = glucagon-like peptide-1; OAD = oral antidiabetes drug; PPG = post-prandial glucose; SD = standard deviation; SGLT2 = sodium-glucose cotransporter-2; SMPG = self-monitored plasma glucose.

[a] Derived using Cockcroft and Gault.

Source: Clinical Study Report for LixiLan-O.[34]

Interventions and Comparators

Dietary and lifestyle consultations were provided to all participants at the start of both the run-in and treatment phases. Background antidiabetes therapies received by the patients, including sulfonylureas, meglitinides, sodium-glucose cotransporter-2 (SGLT2) inhibitors, and dipeptidyl peptidase-4 (DPP-4) inhibitors, were discontinued and metformin treatment was optimized. Use of any weight-loss drugs, short/fast-acting insulin, or pre-mixed insulin, and systemic glucocorticoids were prohibited unless there were special circumstances.

Patients randomized to the iGlarLixi group were initiated on a dose of 10 units insulin glargine/5 mcg lixisenatide, maintained during the first week of treatment, and gradually increased, in line with the algorithm shown in Table 29. A treat-to-target approach was adopted when titrating the dose, with a fasting self-monitored plasma glucose (SMPG) target of 4.4 mmol/L to 5.6 mmol/L, inclusive, increasing once weekly based on median fasting SMPG values from the previous three days. SMPG values were measured by patients using supplied glucometers and accessories.

Patients randomized to receive insulin glargine received the marketed product Lantus (insulin glargine) in a SoloSTAR pen, in accordance with labelling documents. The starting dose of this product was also 10 units, and the titration algorithm, titration monitoring, and fasting SMPG targets were the same as for iGlarLixi (Table 29). In order to match the maximum dose with the iGlarLixi product of 60 units/20 mcg, the maximum dose of this product was capped at 60 units.

Patients randomized to the lixisenatide group self-injected the drug once daily with a pre-filled disposable pen, which was available at 10 mcg (initiation) and 20 mcg (maintenance) dose strengths. Patients were initiated at a dosage of 10 mcg daily for two weeks, then increased to a maintenance dose of 20 mcg daily from week 2 until the end of the treatment phase. Patients in the lixisenatide group were able to self-inject either before breakfast or dinner, as long as the injection was at the same time every day.

Table 29: Dose-Adjustment Algorithm for iGlarLixi and Insulin Glargine Groups for LixiLan-O Study

Median of Fasting SMPG Values From the Last Three Days	Dose Change (units/day)
> 7.8 mmol/L	+4
> 5.6 mmol/L and ≤ 7.8 mmol/L	+2
4.4 mmol/L to 5.6 mmol/L	No change
≥ 3.3 mmol/L and < 4.4 mmol/L	–2
< 3.3 mmol/L or occurrence of ≥ 2 symptomatic hypoglycemia or 1 severe hypoglycemia in the preceding week	–2 or –4 or at the discretion of the investigator or medically qualified designee

iGlarLixi = fixed-ratio combination of insulin glargine and lixisenatide; SMPG = self-monitored plasma glucose.

Source: Clinical Study Report for LixiLan-O.[34]

Outcomes

The efficacy and safety end points in the LixiLan-O trial are listed in Table 30. The co-primary objectives of this study were to demonstrate the superiority of iGlarLixi to lixisenatide in A1C change from baseline to week 30 and to demonstrate the noninferiority of iGlarLixi to insulin glargine in A1C change from baseline to week 30. If noninferiority was effectively demonstrated, statistical superiority of the iGlarLixi compared with insulin glargine on the A1C change from baseline to week 30 was tested according to the pre-

specified testing hierarchy. Unless otherwise specified, change from baseline to week 30 was completed for all outcomes.

Table 30: Efficacy and Safety End Points in the LixiLan-O Study

Level	End Points
Efficacy Outcomes	
Primary Outcome	Change in A1C (both noninferiority and superiority)
Secondary Outcomes	Percentage of patients reaching A1C ≤ 6.5% or < 7%
	Change in 2-hour post-prandial plasma glucose (at 30-minute, one-hour, and two-hour time points) and 2-hour plasma glucose excursion during a standardized meal test (at both 30-minute and one-hour time points)[a]
	Change in body weight
	Change in fasting plasma glucose
Exploratory Outcomes	Change in EQ-5D-3L
	Change in IWQoL-Lite
Safety Outcomes	
	AEs, SAE, WDAEs
	Symptomatic hypoglycemia (documented, probable, severe symptomatic hypoglycemia)
	Immunogenicity, anti-lixisenatide antibodies, and/or anti-insulin antibodies

A1C = glycated hemoglobin; AE = adverse event; EQ-5D-3L = EuroQol 5-Dimensions 3-levels; IWQoL-Lite = Impact of Weight on Quality of Life–Lite; SAE = serious adverse event; WDAE = withdrawal due to adverse events.

[a] This test was conducted in all patients in the iGlarLixi or insulin glargine groups, as well as those in the lixisenatide group injecting in the morning.
Source: Clinical Study Report for LixiLan-O.[34]

Statistical Analysis

Primary End Point

The primary end point of this study was the change from baseline to week 30 in A1C with two co-primary hypotheses: 1) to demonstrate superiority of iGlarLixi to lixisenatide in A1C change from baseline to week 30, and 2) to demonstrate the noninferiority of the iGlarLixi to insulin glargine for change in A1C from baseline to week 30. Noninferiority was tested prior to superiority.

A sample size of 450 patients in the iGlarLixi group and 450 patients in the insulin glargine group would ensure that the upper confidence limit of the two-sided 95% CI for the adjusted mean difference between the fixed-ratio combination group and the insulin glargine group in the A1C change from baseline to week 30 would not exceed 0.3% with more than 95% power. This calculation assumed a common standard deviation of 1.1% and a true difference in A1C between the treatment groups of zero.

For a demonstration of superiority of iGlarLixi to lixisenatide, a mean difference between the iGlarLixi and lixisenatide alone groups in the change in A1C from baseline of 0.4% was assumed, with a common standard deviation of 1.1% and a t-test at a one-sided 2.5% significance level with at least 95% power.

Based on a randomization ratio of 2:2:1, 1,125 patients were needed for this study (450 patients in the iGlarLixi group, 450 patients in the insulin glargine groups, and 225 patients in the lixisenatide group).

The co-primary superiority hypothesis of iGlarLixi against lixisenatide was tested at a two-sided 5% significance level, and the other co-primary end point of noninferiority of iGlarLixi against insulin glargine was tested using a one-sided statistical test with an alpha level of 0.025 and noninferiority margin of 0.3% A1C. Noninferiority was demonstrated if the upper bound of the two-sided 95% confidence interval for the difference in change in A1C from baseline to week 30 between iGlarLixi and insulin glargine was < 0.3%.

The primary end point was analyzed using a mixed-effects model with repeated measures (MMRM), under the missing at random framework. The MMRM model included treatment group, randomization strata of A1C (< 8.0%, ≥ 8.0%) at visit 5 (week 1), randomization strata of metformin use at screening (Yes, No), visit (week 8, 12, 24, and 30), treatment-by-visit interaction and country as fixed effects, and baseline A1C value-by-visit interaction as covariates. A sensitivity analysis for the primary end point used the same MMRM model (including all scheduled A1C values collected during the treatment phase, excluding those collected after discontinuation of treatment or introduction of rescue therapy), as well as additional sensitivity analyses using ANCOVA with missing data imputed by last observation carried forward. The adjusted mean change in A1C from baseline to week 30 for each treatment group was estimated in the framework of this model, as well as the between-group difference and the 95% confidence interval.

Secondary End Points

Key secondary efficacy end points included change in two-hour glucose excursion, body weight, and FPG. The analyses for continuous key secondary end points used an MMRM similar to the primary analysis, with differences between treatment groups and confidence intervals estimated within the framework of the MMRM. The analysis for categorical key secondary end points used the Cochran–Mantel–Haenszel test, adjusting for randomization strata.

Exploratory End Points

All adverse events (AEs) were summarized with descriptive statistics and by treatment status. The exploratory outcomes, such as health-related quality of life outcomes, were continuous and therefore analyzed using a similar MMRM model to the primary end point, described previously, on the mITT population.

Multiplicity Considerations

For the primary efficacy outcome, the co-primary hypothesis of statistical superiority of iGlarLixi to lixisenatide and noninferiority of iGlarLixi to insulin glargine was tested at the one-sided 2.5% significance level. If noninferiority was established, then a test of superiority of iGlarLixi over insulin glargine was performed at the two-sided 5% significance level.

Once the co-primary hypotheses were established, a step-down testing procedure was applied in order to control for type I error among secondary efficacy outcomes. A hierarchical testing procedure was performed to test the secondary outcomes in order. Testing was stopped if an end point was not statistically significant at the 5% level (two-sided). Multiplicity adjustments were not performed on secondary efficacy variables, which were not included in Table 31 or for exploratory outcomes.

Table 31: Statistical Hierarchy for Primary and Secondary Efficacy Outcomes in LixiLan-O

Priority Rank	Efficacy Outcome	Comparison
Primary Outcome[a]		
	Change in A1C in change from baseline to week 30	iGlarLixi versus lixisenatide (at $P < 0.05$ for superiority)
	Change of A1C in change from baseline to week 30	iGlarLixi versus insulin glargine (at an NI margin of 0.3%)
Secondary Outcomes[b]		
1	Change in 2-hour plasma glucose excursion during the standardized meal test from baseline to week 30	iGlarLixi versus insulin glargine
2	Change in fasting plasma glucose from baseline to week 30	iGlarLixi versus lixisenatide
2	Change in body weight from baseline to week 30	iGlarLixi versus insulin glargine
3	Change in daily average of the 7-point SMPG from baseline to week 30	iGlarLixi versus lixisenatide
4	Percentage of patients reaching A1C < 7% with no body weight gain at week 30	iGlarLixi versus insulin glargine
5	Change in daily average of the 7-point SMPG from baseline to week 30	iGlarLixi versus insulin glargine
5	Percentage of patients reaching A1C < 7% with no body weight gain at week 30 and with no documented (PG ≤ 3.9 mmol/L) symptomatic hypoglycemia during the 30-week randomized treatment period	iGlarLixi versus insulin glargine
6	Change in daily dose of insulin glargine from baseline to week 30	iGlarLixi versus insulin glargine
7	Change in FPG from baseline to week 30	iGlarLixi versus insulin glargine

A1C = glycated hemoglobin; FPG = fasting plasma glucose; iGlarLixi = fixed-ratio combination of insulin glargine and lixisenatide; PG = plasma glucose; SMPG = self-monitored plasma glucose.

[a] If the primary variable was statistically significant at the 5% level, a hierarchical testing procedure was performed to test the following secondary efficacy variables.

[b] Secondary efficacy variables were tested in a prioritized (1 to 7) order. Testing stopped when an end point was not statistically significant at the 5% level.

Source: Clinical Study Report for LixiLan-O.[34]

Missing Data

The primary analysis was an MMRM analysis using all observations collected post-baseline, regardless of treatment discontinuation or initiation of rescue therapy.

The MMRM model assumed missing data were missing at random (MAR). To examine the impact of these missing data on results, a sensitivity analysis was conducted for the primary end point; however, in the LixiLan-L study, it was stated that the number of received dropouts was insufficient to build a reliable imputation model. Missing A1C values at week 30 were imputed using multiple imputations for patients who permanently discontinued from the study; specifically, the imputations used data from patients within their treatment group and randomization strata who had permanently discontinued the study treatment but had week 30 measurements (retrieved dropouts). Patients who completed treatment but did not have week 30 measurements were assumed to be MAR. Their values were subsequently imputed using multiple imputations [redacted], and completed data were analyzed using an analysis of covariance (ANCOVA) model.

Subgroup Analyses

Subgroup analyses were to be performed on the primary outcome, change in A1C more than 30 weeks, according to the following baseline factors:

- Gender
- Age group (< 50, ≥ 50 to < 65, and ≥ 65 years of age)
- Race

- Ethnicity (Hispanic, non-Hispanic)
- Baseline A1C (< 8.0, ≥ 8.0%)
- Baseline BMI level (< 30, ≥ 30 kg/m^2)
- Country
- Oral antidiabetes drug use other than metformin use at screening (Yes, No)

Analysis Populations

The randomized population was defined as all patients who had signed informed consent, with a randomized open-label treatment kit allocated and recorded in the interactive voice response system/interactive Web response system (IVRS/IWRS) database, regardless of whether the treatment kit was used.

The modified intention-to-treat (mITT) population was defined as all randomized patients who had both a baseline assessment and at least one post-baseline assessment from any of the primary or secondary efficacy end points, regardless of compliance with the study protocol. All efficacy analyses were based on the mITT analysis set.

Patient Disposition

A total of 2,457 patients were screened for participation in the LixiLan-O study in 240 centres. Of these, 1,287 (52.4%) patients failed during the screening phase prior to the run-in phase, and 309 (12.9%) patients failed during the run-in phase before randomization, with no specific reasons cited. A total of 1,170 patients were randomized: 469 patients in the iGlarLixi group, 467 patients in the insulin glargine group, and 234 patients in the lixisenatide group. All patients received at least one dose of assigned medication; and they were included in the safety analyses. The efficacy analyses were conducted in the mITT population, which consisted of 1,170 randomized patients. A similar proportion of patients in the iGlarLixi and insulin glargine groups (6.2% and 5.8%) prematurely discontinued treatment, compared with 12% of patients in lixisenatide group. The most common reason cited for discontinuation was AEs, occurring in 9% of patients in the lixisenatide group, in 2.6% of patients in the iGlarLixi group, and 1.9% of patients in the insulin glargine group. The follow-up period was three days, and no patients were lost to follow-up. Table 32 summarizes the patient disposition data.

Table 32: Patient Disposition in LixiLan-O Study

	LixiLan-O Study			
	iGlarLixi (N = 469)	**Insulin Glargine (N = 467)**	**Lixisenatide (N = 234)**	**All**
Screened, N				2,457
Screen failures, N (%)				1,287 (52.4)
Run-in failures, N (%)				309 (12.6)
Randomized, N	469	467	234	1,170
Randomized and treated, N	469	467	233	
Completed 30-week open-label treatment period, N (%)	440 (93.8)	440 (94.2)	205 (87.6)	
Discontinued, N (%)	29 (6.2)	27 (5.8)	28 (12.0)	
Adverse event, N	12	9	21	
Lack of efficacy, N	1	0	3	
Lost to follow-up, N	0	0	0	

	LixiLan-O Study			
Poor compliance, N	8	9 (1.9)	4	
Other reasons, N	8	9 (1.9)	0	
mITT population, N (%)	468 (99.8)	466 (99.8)	233 (99.6)	1,167 (99.7)
Safety population, N	469	467	233	1,169

iGlarLixi = fixed-ratio combination of insulin glargine and lixisenatide; mITT = modified intention-to-treat.

Source: Clinical Study Report for LixiLan-O.[34]

Exposure

The percentage of patients requiring rescue therapy was highest (12.4%) in the lixisenatide group and was lower in both iGlarLixi (3.6%) and insulin (3.4%) groups. The proportion difference between the lixisenatide group and the iGlarLixi group was –8.78% (95% CI, –13.23 to –4.33). There was no significant proportion difference between the iGlarLixi and insulin glargine groups.

Table 33: Number of Patients Requiring Rescue Therapy During the 30-Week Open-Label Treatment Period — mITT Population

Requiring Rescue Therapy, N (%)	iGlarLixi (N = 468)	Insulin Glargine (N = 466)	Lixisenatide (N = 233)
Yes	17 (3.6)	16 (3.4)	29 (12.4)

iGlarLixi = fixed-ratio combination of insulin glargine and lixisenatide.

Source: Clinical Study Report for LixiLan-O.[34]

Results

Efficacy

Mean Change in A1C

Results for the primary efficacy end point (absolute change from baseline to week 30) are provided in Table 34. The primary objectives of this study, which were the determination of noninferiority of iGlarLixi compared with insulin glargine and statistical superiority of the iGlarLixi over lixisenatide, were met. The change from baseline to week 30 in A1C was –1.63% in the iGlarLixi group, –1.34% in the insulin glargine group, and –0.85% in the lixisenatide group, ending with a mean week 30 value of 6.50%, 6.81% and 7.31% in the iGlarLixi, insulin glargine, and lixisenatide groups, respectively.

Table 34: Mean Change in A1C (%) From Baseline to Week 30 Using Mixed-Effects Model With Repeated Measures (MMRM) — mITT Population

Outcome	N	iGlarLixi (N = 469)	N	Insulin Glargine (N = 466)	N	Lixisenatide (N = 233)
Baseline mean value (SD)	467	8.08 (0.71)	464	8.08 (0.69)	233	8.13 (0.72)
Week 30 mean value (SD)	443	6.50 (0.75)	446	6.81 (0.76)	221	7.31 (0.87)
Change from baseline to week 30 (SE)	467	–1.63 (0.038)	464	–1.34 (0.039)	233	–0.85 (0.052)
LSMD versus insulin glargine (95% CI),[a] *P* value[a]	–0.29 (–0.384 to –0.194) < 0.0001					
LSMD versus lixisenatide (95% CI),[a] *P* value[a]	–0.78 (–0.898 to –0.665) < 0.0001					

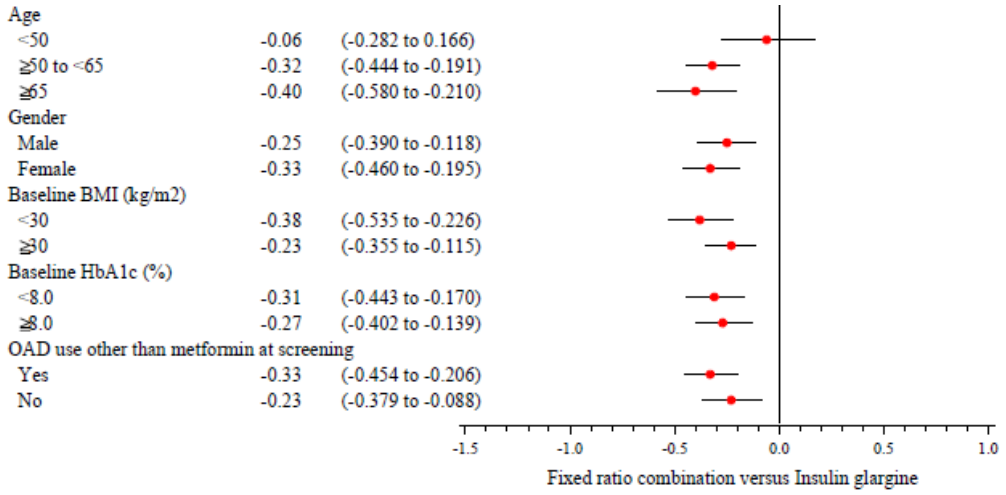
CI = confidence interval; iGlarLixi = fixed-ratio combination of insulin glargine and lixisenatide; LSMD = least squares mean difference; SD = standard deviation; SE = standard error.

[a] Mixed-effects model with repeated measures (MMRM) with treatment groups (fixed-ratio combination, insulin glargine alone, lixisenatide alone), randomization strata of A1C (< 8.0%, ≥ 8.0%) at visit 4 (week –1), randomization strata of second oral antidiabetes drug use at screening (Yes, No), visit (week 8, 12, 24, and 30), treatment-by-visit interaction, and country as fixed effects, and baseline A1C value-by-visit interaction as a covariate.

Source: Clinical Study Report for LixiLan-O.[34]

Results from the subgroup analyses showing change in A1C by baseline factors and country from baseline to week 30 are displayed in the forest plot shown in Figure 5.

Figure 5: Change in A1C Comparing iGlarLixi and Insulin Glargine by Pre-Specified Subgroups



BMI = body mass index; $HbA1_c$ = glycated hemoglobin; OAD = oral antidiabetes drug.
Source: Clinical Study Report for LixiLan-O.[34]

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. Although the primary objective was to establish noninferiority of iGlarLixi to insulin glargine with regard to change in A1C, superiority of iGlarLixi to insulin glargine was established from baseline to week 30 for the following end points: two-hour glucose excursion (least squares mean difference [LSMD] –2.13 mmol/L; 95% confidence interval [CI], –2.498 to –1.770; $P < 0.0001$), and body weight (LMSD –1.40; 95% CI, –1.891 to –0.910; $P < 0.0001$). In addition, superiority of iGlarLixi to lixisenatide was established from baseline to week 30 for change in mean FPG (LSMD –1.96 mmol/L; 95% CI, –2.246 to –1.682; $P < 0.0001$) and seven-point average SMPG (LSMD –1.40 mmol/L; 95% CI, –1.645 to –1.158; $P < 0.0001$). The results are summarized in Table 35.

The final test in the hierarchy order was the comparison between iGlarLixi and insulin glargine for mean change in FPG, respectively. This test was not found to be significant ($P = 0.1017$).

Table 35: Secondary Glycemic Outcomes at Week 30 for iGlarLixi, Insulin Glargine, and Lixisenatide in the LixiLan-O study

End Point	N	iGlarLixi (N = 468)	N	Insulin Glargine (N = 466)	N	Lixisenatide (N = 233)
2-hour glucose excursion (mmol/L)						
Mean baseline value (SD)	428	5.31 (2.86)	425	5.02 (2.96)	192	5.07 (2.54)
Mean end point value at week 30 (SD)[a]	428	2.81 (2.84)	425	4.80 (2.90)	192	1.70 (3.23)
LS mean change from baseline (SE)[b]	428	–2.49 (3.37)	425	–0.22 (2.86)	192	–3.37 (3.41)
LS mean difference of iGlarLixi versus insulin glargine [95% CI],[b] *P* value	–2.13 [–2.498 to –1.770] < 0.0001					
LS mean difference of iGlarLixi versus lixisenatide [95% CI][b]	0.91 [0.448 to 1.377]					
Body weight (kg)						
Mean baseline value (SD)	467	89.44 (17.16)	465	89.75 (16.34)	233	90.79 (16.25)
Mean end point value at week 30 (SD)	448	89.16 (17.34)	446	90.68 (16.03)	222	88.57 (16.20)
LS mean change from baseline (SE)[c]	467	–0.29 (0.182)	465	1.11 (0.183)	233	–2.30 (0.256)
LS mean difference of iGlarLixi versus insulin glargine [95% CI],[c] *P* value	–1.40 [–1.891 to –0.910] < 0.0001					
LS mean difference of iGlarLixi versus lixisenatide [95% CI][c]	2.01 [1.404 to 2.609]					
Fasting plasma glucose (mmol/L)						
Mean baseline value (SD)	465	9.88 (2.34)	465	9.75 (2.33)	232	9.79 (2.16)
Mean end point value at week 30 (SD)	436	6.32 (1.47)	438	6.53 (1.76)	216	8.27 (2.24)
LS mean change from baseline (SE)[c]	465	–3.46 (0.090)	465	–3.27 (0.091)	232	–1.50 (0.124)
LS mean difference of iGlarLixi versus insulin glargine [95% CI],[d] *P* value[d]	–0.19 [–0.420 to 0.038] 0.1017					
LS mean difference of iGlarLixi versus lixisenatide [95% CI],[d] *P* value	–1.96 [–2.246 to –1.682] < 0.0001					

CI = confidence intervals; iGlarLixi = fixed-ratio combination of insulin glargine and lixisenatide; LS = least squares; SD = standard deviation; SE = standard error.

[a] Last observation carried forward.

[b] Analysis of covariance (ANCOVA) model with treatment groups (fixed-ratio combination and insulin glargine), randomization strata of A1C (< 8.0%, ≥ 8.0%) at visit 5 (week –1), randomization strata of metformin use at screening (Yes, No), and country as fixed effects and baseline two-hour glucose excursion value as a covariate.

[c] Mixed-effects model with repeated measures (MMRM) with treatment groups (fixed-ratio combination and insulin glargine), randomization strata of A1C (< 8.0%, ≥ 8.0%) at visit 5 (week –1), randomization strata of metformin use at screening (Yes, No), scheduled visit, treatment-by-visit interaction and country as fixed effects, and body weight value-by-visit interaction as a covariate.

[d] Mixed-effects model with repeated measures (MMRM) with treatment groups (fixed-ratio combination and insulin glargine), randomization strata of A1C (< 8.0%, ≥ 8.0%) at visit 5 (week –1), randomization strata of metformin use at screening (Yes, No), scheduled visit, treatment-by-visit interaction and country as fixed effects, and fasting plasma glucose value-by-visit interaction as a covariate.

Source: Clinical Study Report for LixiLan-O.[34]

Secondary Efficacy End Points Unadjusted for Multiplicity

Results for exploratory end points are presented in Table 36. The change in two-hour post-prandial plasma glucose from baseline to week 30 was found to be larger in the iGlarLixi group than in either the insulin glargine group (LSMD –2.38 mmol/L; 95% CI, –2.794 to –1.963) or the lixisenatide group (LSMD –1.10 mmol/L; 95% CI, –1.627 to –0.573). There was also a higher percentage of patients reaching an A1C of 7.0% or lower in the iGlarLixi group compared with both the insulin glargine group (59.4%) and the lixisenatide group (33.0%). This was also seen in the results for the proportion of patients reaching A1C ≤ 6.5% in the iGlarLixi group (55.8%), compared with both the insulin glargine group (39.5%) and the lixisenatide group (19.3%).

[redacted]

Table 36: Secondary Efficacy End Point, Unadjusted for Multiplicity in the LixiLan-O Study

Efficacy End Points	N	iGlarLixi (N = 468)	N	Insulin Glargine (N = 466)	N	Lixisenatide (N = 233)
2-hour PPG (mmol/L)						
Mean baseline value (SD)	430	15.19 (3.63)	430	14.61 (3.64)	196	14.72 (3.32)
Mean end point value at week 30 (SD)[a]	430	9.15 (3.20)	430	11.35 (3.12)	196	9.99 (3.91)
LS mean change from baseline (SE)[b]	430	–6.04 (4.27)	430	–3.26 (3.54)	196	–4.73 (4.11)
LS mean difference of iGlarLixi versus insulin glargine [95% CI][b]	–2.38 [–2.794 to –1.963]					
LS mean difference of iGlarLixi versus lixisenatide [95% CI][b]	–1.10 [–1.627 to –0.573]					
Number of patients with A1C ≤ 6.5% or < 7% at week 30						
≤ 6.5%	261 (55.8)		184 (39.5)		45 (19.3)	
Proportion difference [95% CI] versus insulin glargine; *P* value	16.35% [10.13 to 22.58] < 0.0001					
Proportion difference [95% CI] versus lixisenatide; *P* value	40.61% [33.63 to 47.59] < 0.0001					
< 7%	345 (73.7)		277 (59.4)		77 (33)	
Proportion difference [95% CI] versus insulin glargine; *P* value	14.31 [8.37 to 20.25] < 0.0001					
Proportion difference [95% CI] versus lixisenatide; *P* value	40.61 [33.63 to 47.59] < 0.0001					
EQ-5D-3L index value based on a US population						
Mean baseline value (SD)	[redacted]					
Mean end point value at week 30 (SD)	[redacted]					
LS mean change from baseline (SE)[b]	[redacted]					

Efficacy End Points	N	iGlarLixi (N = 468)	N	Insulin Glargine (N = 466)	N	Lixisenatide (N = 233)
LS mean difference of iGlarLixi versus insulin glargine [95% CI][b]				[redacted]		
LS mean difference of iGlarLixi versus lixisenatide [95% CI][b]				[redacted]		
IWQoL-Lite total score						
Mean baseline value (SD)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Mean end point value at week 30 (SD)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
LS mean change from baseline (SE)[b]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
LS mean difference of iGlarLixi versus insulin glargine [95% CI][b]				[redacted]		
LS mean difference of iGlarLixi versus lixisenatide [95% CI][b]				[redacted]		

A1C = glycated hemoglobin; CI = confidence interval; EQ-5D-3L = EuroQol 5-Dimensions 3-levels; iGlarLixi = fixed-ratio combination of insulin glargine and lixisenatide; IWQoL-Lite = Impact of Weight on Quality of Life–Lite LS = least squares; PPG = post-prandial plasma glucose; SD = standard deviation; SE = standard error.

[a] Last observation carried forward.

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

Source: Clinical Study Report for LixiLan-O.[34]

Harms

Other Adverse Events

Table 37 shows the frequency of AEs found in the safety population. The proportion of patients who experienced any AE was 56.9% in the iGlarLixi group versus 48.6% in the insulin glargine group and 67.4% in the lixisenatide group, the most common AEs being nausea, diarrhea, and upper respiratory tract infections. Nausea occurred more frequently in patients taking lixisenatide, with a 24.0% incidence rate in this group, followed by 9.6% in the iGlarLixi group, compared with 3.6% in the insulin glargine group. The occurrence of diarrhea was the same between the iGlarLixi and lixisenatide groups (9.0% in each), compared with 3.5% in the insulin glargine group. The proportion of patients who experienced serious AEs was similar between groups (3.8% in the iGlarLixi group versus 4.1% and 3.9% in the insulin glargine and lixisenatide groups, respectively), and the most common serious AEs were bacterial infections, urinary tract infections, coronary artery disorders, and heart failure. AEs that led to treatment discontinuation occurred most frequently in the lixisenatide group (9.0%), many of these patients citing nausea and vomiting as the reason for discontinuation (4.3%). The proportion of AEs that led to treatment discontinuation in the iGlarLixi group was 2.6%, also citing nausea and vomited most commonly (0.9%). In the insulin glargine group, the proportion of AEs leading to treatment discontinuation was 1.9%. There were four deaths during this study. Two of these fatal events occurred in the insulin glargine group, and one each in the lixisenatide and iGlarLixi groups. The fatal events did not appear to have a difference in frequency between treatment groups. Allergic events were adjudicated by the Allergic Reactions Adjudication Committee (ARAC) for this study and were reported at a slightly higher frequency in the iGlarLixi group (1.3%) compared with the insulin glargine group [redacted] and the lixisenatide group (0.9%). Three of the six events in the iGlarLixi arm were deemed to be possibly

related to treatment, as well as the one anaphylactic reaction in the lixisenatide arm. No reactions documented in the insulin glargine arm were deemed to be related to treatment.

[redacted]

Table 37: Overall Summary of Harms Reported in the LixiLan-O Study

	iGlarLixi (N = 469)	Insulin Glargine (N = 467)	Lixisenatide (N = 233)
AEs			
Patients with > 0 AEs, N (%)	267 (56.9)	227 (48.6)	157 (67.4)
Most common AEs[a]	Nausea, diarrhea, upper respiratory tract infection; nasopharyngitis, headache		
Nausea	45 (9.6)	17 (3.6)	56 (24.0)
Diarrhea	42 (9.0)	20 (4.3)	21 (9.0)
Upper respiratory tract infection	33 (7.0)	23 (4.9)	12 (5.2)
Nasopharyngitis	26 (5.5)	25 (5.4)	15 (6.4)
Headache	24 (5.1)	15 (3.2)	18 (7.7)
SAEs			
Patients with > 0 SAEs, N (%)	18 (3.8)	19 (4.1)	9 (3.9)
Most common SAEs[a]	Bacterial infections, urinary tract infection, coronary artery disorders, heart failure		
Unspecified bacterial infection	[redacted]	[redacted]	[redacted]
Urinary tract infection	2 (0.4)	1 (0.2)	0
Coronary artery disorders	[redacted]	[redacted]	[redacted]
Heart failure	[redacted]	[redacted]	[redacted]
WDAEs			
WDAEs, N (%)	12 (2.6)	9 (1.9)	21 (9.0)
Most common reasons	Nausea and vomiting, urticaria, coronary artery disorders		
Nausea and vomiting	4 (0.9)	0	10 (4.3)
Urticaria	3 (0.6)	0	1 (0.4)
Coronary artery disorders	0	2 (0.4)	0
Other	5 (1.1)	7 (1.5)	10 (4.3)
Deaths			
Number of deaths on treatment, N (%)	1 (0.2)	2 (0.4)	1 (0.4)
Number of deaths post-treatment, N (%)	1 (0.2)	2 (0.4)	0
Any AE leading to death, N (%)	2 (0.4)	3 (0.6)	1 (0.4)
Death due to lung cancer	1 (0.2)	0	0
Death due to oral cancer	0	1 (0.2)	0
Death due to pulmonary edema	0	1 (0.2)	0
Death due to cardiopulmonary failure	1 (0.2)	1 (0.2)	0
Sudden death	0	0	1 (0.4)
ARAC-adjudicated allergic events by patient			
Any allergic event	6 (1.3)	3 (0.6)	2 (0.9)
Urticaria (hives)	3 (0.6)	1 (0.2)	1 (0.4)
Angioedema	3 (0.6)	0	0
Anaphylactic reaction	0	0	1 (0.5)
Allergic rhinitis	[redacted]	[redacted]	[redacted]
Injection-site reactions			
Any injection-site reaction	[redacted]	[redacted]	[redacted]

	iGlarLixi (N = 469)	Insulin Glargine (N = 467)	Lixisenatide (N = 233)
Bruising	[redacted]	[redacted]	[redacted]
Pain	[redacted]	[redacted]	[redacted]
Injection-site reaction	[redacted]	[redacted]	[redacted]
Discomfort	[redacted]	[redacted]	[redacted]
Irritation	[redacted]	[redacted]	[redacted]
Nodule	[redacted]	[redacted]	[redacted]
Papule	[redacted]	[redacted]	[redacted]
Rash	[redacted]	[redacted]	[redacted]
Erythema	[redacted]	[redacted]	[redacted]
Hemorrhage	[redacted]	[redacted]	[redacted]
Swelling	[redacted]	[redacted]	[redacted]
Warmth	[redacted]	[redacted]	[redacted]

AE = adverse event; ARAC = Allergic Reaction Assessment Committee; iGlarLixi = fixed-ratio combination of insulin glargine and lixisenatide; SAE = serious adverse events; WDAE = withdrawal due to adverse events.
[a]Frequency > 5%.
Source: Clinical Study Report for LixiLan-O.[34]

Hypoglycemia

Table 38 shows a summary of patients who were found to have symptomatic, probable, or severe hypoglycemia throughout the study. There was no increased frequency in patients experiencing documented symptomatic hypoglycemia (defined as an event with typical symptoms of hypoglycemia with a plasma glucose concentration of ≤ 3.9 mmol/L), with an incidence of 25.6% in the iGlarLixi group compared with 23.6% in the insulin glargine group. There were no severe cases of severe hypoglycemia in patients in either the iGlarLixi or lixisenatide groups, compared with one patient in the insulin group.

Table 38: Summary of Symptomatic Hypoglycemia on Treatment — Safety Population

Type	iGlarLixi (N = 469)	Insulin Glargine (N = 467)	Lixisenatide (N = 233)
Documented symptomatic hypoglycemia (plasma glucose ≤ 3.9 mmol/L)			
Number of patients with events, N (%)	120 (25.6)	110 (23.6)	15 (6.4)
Number of patients with events per patient year[a]	0.46	0.42	0.12
Documented symptomatic hypoglycemia as recorded on the dedicated eCRF, or documented, or probable			
Number of patients with events, n (%)	128 (27.3)	119 (25.5)	15 (6.4)
Number of patients with events per patient year[a]	0.49	0.45	0.12
Severe symptomatic hypoglycemia			
Number of patients with events, N (%)	0	1 (0.2)	0
Number of patients with events per patient year[a]	0	< 0.01	0

eCRF = electronic case report form; iGlarLixi = fixed-ratio combination of insulin glargine and lixisenatide.

[a] Calculated as number of events divided by the total patient years of exposure.

Source: Clinical Study Report for LixiLan-O.[34]

Immunogenicity

Anti-insulin antibodies (AIA) and anti-lixisenatide antibodies data were collected throughout this study, results of which are presented in Table 39. The proportion of positive AIA patients in the iGlarLixi group increased from baseline to 30 weeks from 0.5% at baseline to 21% at week 30, [redacted]. When comparing the proportion of positive AIA patients in the insulin glargine group, the number also grew from 0.2% at baseline to 8.9% at week 30, but the increase was not as large as that observed in the iGlarLixi group. [redacted]

Table 39: Number With Anti-Insulin and Anti-Lixisenatide Antibody Status by Visit During the Study in the iGlarLixi Group and the Insulin Glargine Group — Safety Population

Visit	Status		
Anti–insulin glargine antibody status, n/N1 (%)			
		iGlarLixi (N = 365)	**Insulin glargine (N = 365)**
Baseline	Positive	2/436 (0.5)	1/451 (0.2)
	Negative	434/436 (99.5)	450/451 (99.8)
Week 30	Positive	90/428 (21.0)	38/426 (8.9)
	Negative	338/428 (79.0)	388/426 (91.1)
	Conversion from negative at baseline to positive	81/428 (18.9)	38/426 (8.9)
Last on-study value	Positive	90/447 (20.1)	39/440 (8.9)
	Negative	357/447 (79.9)	401/440 (91.1)
	Conversion from negative at baseline to positive	81/447 (18.1)	39/440 (8.9)
Anti-lixisenatide antibody status, n/N1 (%)			
		iGlarLixi (N = 365)	**Lixisenatide (N = 233)**
Baseline	[redacted]	[redacted]	[redacted]
	[redacted]	[redacted]	[redacted]
Week 30	Positive	184/426 (43.2)	113/199 (56.8)
	Negative	242/426 (56.8)	86/199 (43.2)
	Conversion from negative at baseline to positive	164/426 (38.5)	96/199 (48.2)
Last on-study value	[redacted]	[redacted]	[redacted]
	[redacted]	[redacted]	[redacted]
	[redacted]	[redacted]	[redacted]

iGlarLixi = fixed-ratio combination of insulin glargine and lixisenatide; n = number of subjects; N1 = total number of subjects with available data.

Source: Clinical Study Report for LixiLan-O.[34]

Critical appraisal

Due to the similarities in design between the LixiLan-O and LixiLan-L studies, the limitations identified in the LixiLan-L study apply to the LixiLan-O study as well. Key limitations of this study include its open-label design, the lack of adjustment for multiplicity in outcomes considered clinically relevant to this review, and the imbalance between groups in the rate of premature discontinuations in this trial. The open-label design of this study, especially when evaluating subjective outcomes such as health-related quality of life outcomes and AE reporting, can increase potential for bias. Second, outcomes in this trial which were of interest to this review, such as two-hour post-prandial plasma glucose, health-related quality of life measures, and the proportion of patients achieving A1C lower than 7% or 6.5% or lower were not appropriately adjusted for multiplicity, which increases the risk of type I error. Finally, there was a higher rate of discontinuations noted in the lixisenatide monotherapy group (12.0%) compared with the iGlarLixi (6.2%) and insulin glargine (5.8%) groups. The majority of discontinuations in the lixisenatide group were due to AEs. This suggests patients were not MAR, which was the assumption of statistical model used in this study.

Conclusions

The LixiLan-O study was the only phase III trial that investigated the efficacy of the iGlarLixi in a population that was insulin-naive. This trial was an open-label, multi-centre, three-arm randomized controlled trial, which recruited adults with type 2 diabetes who were inadequately controlled on metformin for inclusion in a study comparing iGlarLixi against insulin glargine and lixisenatide alone for 30 weeks. iGlarLixi was shown to effectively lower A1C without an increase in weight and at a comparable rate of hypoglycemia, when it was compared with insulin glargine capped at 60 units. It was also shown to be superior in its reduction of A1C when compared with lixisenatide alone. There were no statistically significant improvements in health-related quality of life outcomes observed when iGlarLixi was compared with either of its monotherapy components. Compared with insulin glargine, iGlarLixi was found to have a higher incidence of gastrointestinal AEs. iGlarLixi and insulin glargine were found to carry a higher incidence of hypoglycemia than lixisenatide alone. Lixisenatide and iGlarLixi were also found to have a higher incidence of product-related allergic reactions than insulin glargine alone. However, there are key limitations to this study, which include its open-label design and a relatively short treatment period of 30 weeks.

Appendix 7: Summary of Indirect Comparisons

Background

The aim of this section is to review and critically appraise any indirect comparisons (IDCs) that compare the fixed-ratio combination of insulin glargine and lixisenatide injection (iGlarLixi) with any other treatment for type 2 diabetes mellitus (T2DM) in insulin-experienced patients.

Methods

One IDC was submitted by the manufacturer. In addition, a literature search was conducted to identify other published IDCs that would include a comparison with iGlarLixi in insulin-experienced T2DM patients.

Description of IDCs Identified

Two IDCs were identified: the manufacturer-submitted IDC, and Evans et al. (2018).[9] An overview of each is presented in Table 40.

Table 40: Overview of Included IDCs

	Manufacturer's IDC[46]	Evans et al. (2018)[9]
Patient Population	Insulin-exposed adult patients with T2DM not responding to basal insulin therapy	T2DM patients who have previously failed to achieve glucose control on basal insulin

Intervention	Any of the following interventions, alone or in combination:
	• Glucagon-like peptide-1 (GLP-1) analogues
	  ○ Albiglutide
	  ○ Exenatide
	  ○ Liraglutide
	  ○ Lixisenatide
	  ○ Taspoglutide
	  ○ Dulaglutide
	
	• Dipeptidyl peptidase-4 (DPP-4) inhibitors
	  ○ Alogliptin
	  ○ Dutogliptin
	  ○ Linagliptin
	  ○ Saxagliptin
	  ○ Sitagliptin
	  ○ Vildagliptin
	  ○ Melogliptin
	  ○ Carmegliptin
	  ○ Anagliptin
	  ○ Teneligliptin
	  ○ Gemigliptin
	
	• Insulin
	  ○ Long-acting insulin
	  ○ Intermediate-acting insulin
	  ○ Short-acting insulin or fast/rapid-acting insulin
	  ○ Premix insulin
	  ○ Combination of insulins
		iGlarLixi (fixed-ratio combination of insulin glargine and lixisenatide)

	Manufacturer's IDC[46]	Evans et al. (2018)[9]

	• Sodium-glucose cotransporter-2 (SGLT2) inhibitors
	  ○ Dapagliflozin
	  ○ Remogliflozin etabonate
	  ○ Empagliflozin
	  ○ Canagliflozin
	  ○ Tofogliflozin
	  ○ Ipragliflozin
	  ○ Sotagliflozin
	  ○ Ertugliflozin
	  ○ Luseogliflozin
	  ○ Sergliflozin
	
	• Sulfonylureas
	  ○ Carbutamide
	  ○ Acetohexamide
	  ○ Chlorpropamide
	  ○ Tolbutamide
	  ○ Glipizide
	  ○ Gliclazide
	  ○ Glibenclamide
	  ○ Glyburide
	  ○ Glibornuride
	  ○ Gliquidone
	  ○ Glisoxepide
	  ○ Glyclopyramide
	  ○ Glimepiride
	
	• Thiazolidinediones (TZDs)
	  ○ Rosiglitazone
	  ○ Pioglitazone
	  ○ Lobeglitazone
	  ○ Troglitazone
	  ○ Netoglitazone
	  ○ Rivoglitazone
	  ○ Ciglitazone
	  ○ Meglitinides
	  ○ Repaglinide
	  ○ Nateglinide
	
	• Premix
	• iGlarLixi (fixed-ratio combination of insulin glargine and lixisenatide injection)	

Comparators	Any of the interventions Placebo	iDegLira (fixed-ratio combination of insulin degludec and liraglutide)
Outcomes	• Mean change from baseline in A1C levels • Proportion of patients achieving a target A1C level (≤ 6.5% and ≤ 7.5%) • Body weight, change from baseline • Proportion/rates of patients experiencing any symptomatic hypoglycemia • Proportion/rates of patients experiencing documented hypoglycemia • Proportion/rates of patients experiencing severe hypoglycemia	• Change in A1C • Change in body weight • Daily insulin dose • Severe or blood-glucose–documented hypoglycemia • Documented symptomatic hypoglycemia

	Manufacturer's IDC[46]	Evans et al. (2018)[9]
	• Daily dose of insulin • Change in 2-hour post-prandial glucose and in blood glucose excursion during a standardized meal test from baseline • % of patients achieving a > 1% reduction in A1C • A1C < 7.0% with no weight gain and/or no hypoglycemia • Mean change in fasting plasma glucose levels • Mean change in post-prandial glucose levels • Mean change in body mass index/ blood pressure/ heart rate/ in lipid profile • Proportion of patients requiring dose escalation/average daily dose • Patient-reported outcomes (diabetes treatment satisfaction questionnaire, EQ-5D, SF-36, BDI-II score, etc.) • Hypoglycemia definition • Proportion/rates of patients experiencing hypoglycemic (all/daytime/nocturnal) events per type of hypoglycemia (all hypoglycaemias, severe, major, minor, confirmed, nocturnal, day time/ excursions) • Proportion of patients experiencing any/specific/serious adverse effects • Proportion of patients dying from all causes • Proportion of patients experiencing gastrointestinal adverse event/ weight gain/diarrhea/nausea/vomiting • Proportion of patients discontinuing treatment due to adverse events, lack of efficacy, or any reason • Time on drug or time to discontinuation (for any reason) • Proportion of patients with risk of cancer • Injection-site reactions	
Study Design	• Randomized clinical trials of a minimum of 20 weeks duration; included trials must have reported results within the 20 to 30 weeks' trial duration	• Phase III trials of the interventions

A1C = glycated hemoglobin; IDC = indirect comparison; EQ-5D-3L = EuroQol 5-Dimensions 3-levels; IWQoL-Lite = Impact of Weight on Quality of Life–Lite; T2DM = type 2 diabetes mellitus.

Source: CDR submission: Soliqua (insulin glargine and lixisenatide injection), 100 units/mL insulin glargine and 33 mcg/mL lixisenatide solution for injection in a pre-filled pen. Company: Sanofi-Aventis Canada Inc. [CONFIDENTIAL manufacturer's submission]. Laval (QC): Sanofi-Aventis Canada Inc.; 2018 May 17. Evans M, Billings LK, Hakan-Bloch J, Slothuus U, Abrahamsen TJ, Andersen A, et al. An indirect treatment comparison of the efficacy of insulin degludec/liraglutide (iDegLira) and insulin glargine/lixisenatide (iGlarLixi) in patients with type 2 diabetes uncontrolled on basal insulin. J Med Econ. 2018;21(4):340-7. Cai X, Gao X, Yang W, Ji L. Comparison between insulin degludec/liraglutide treatment and insulin glargine/lixisenatide treatment in type 2 diabetes: a systematic review and meta-analysis. Expert Opin Pharmacother. 2017;18(17):1789-98.

Review and Appraisal of IDCs

Manufacturer-Submitted IDC

Objectives and Rationale

The manufacturer-submitted IDC aimed to assess the treatment effect differences between the fixed-ratio combination of insulin glargine and lixisenatide injection and other pharmacotherapies for diabetes, where head-to-head evidence may be lacking. Specifically, the manufacturer-submitted IDC considered studies of adult patients with type 2 diabetes who were either insulin-naive or insulin-exposed who did not achieve glycemic control, where the intervention or comparator could be any of the following medication classes, alone or in combination: glucagon-like peptide-1 (GLP-1) analogues, dipeptidyl peptidase-4 (DPP-4) inhibitors, insulin, sodium-glucose cotransporter-2 (SGLT2) inhibitors, sulfonylureas, thiazolidinediones, meglitinides, pre-mixed insulin, the fixed drug combination under review, or placebo. Outcomes included, but were not limited to, glycated hemoglobin (A1C) changes, A1C responders, changes in body weight, hypoglycemia-related outcomes, and daily dose of insulin.

In our review of the manufacturer-submitted IDC, per the Health Canada–approved indication, the focus is on reporting and critically appraising the results of the insulin-experienced patient population.

Methods for Manufacturer-Submitted IDC

Study Eligibility, Selection Process, and Data Extraction

The manufacturer-submitted IDC provided clear pre-specified eligibility criteria for the inclusion of potential studies (Table 40). In addition, it described conducting a comprehensive search strategy of several bibliographical databases from 1980 to September 2016. A grey literature search was also conducted. Appropriately, screening of retrieved records was done by two independent reviewers; disagreement was referred to a third reviewer. Similarly, data extraction was conducted in parallel by two independent reviewers; disagreement was referred to a third reviewer.

Comparators

The manufacturer-submitted IDC described a plan to compare the fixed-ratio combination of insulin glargine and lixisenatide injection with all treatments that are likely to be indicated for patients with T2DM. The list of comparators is provided in Table 40.

Outcomes

The outcomes planned in the IDC included glycemic-control end points, weight changes, patient-reported quality of life measurements, and adverse events related to hypoglycemia and mortality (Table 40). The planned outcomes are similar to those reported in the CADTH Common Drug Review (CDR) protocol of the drug under review in the main clinical report. The manufacturer-submitted IDC described pooling the results of trials that have duration of 20 to 30 weeks.

Quality Assessment of Included Studies

The manufacturer-submitted IDC reported a descriptive quality assessment of the included trials based on factors related to randomization, allocation, baseline comparability, blinding, follow-up, selective reporting, statistical analysis, and other sources of bias. The manufacturer-submitted IDC described using the Jadad score for quality assessment; however, no plan was provided to investigate the impact of studies that were considered to be low quality or to have a high risk of bias.

Indirect Comparison Methods

The manufacturer-submitted IDC described using two different methods of analysis: the Bucher approach (adjusted indirect comparison) and a Bayesian network meta-analysis (NMA) approach. The Bayesian NMA was conducted using WinBUGS under a Markov chain Monte Carlo technique using the code recommended by the National Institute of Health and Care Excellence (NICE) Decision Support Unit. The manufacturer-submitted IDC reported using vague priors, sufficient burn-in iterations until model convergence (20,000 burn-in iterations), which was assessed visually and by using the Brooks-Gelman-Rubin (BGR) statistic, followed by at least 100,000 update iterations. The manufacturer-submitted IDC reported conducting the analysis under both fixed- and random-effects models and using the deviance information criterion (DIC) to compare the best model fit between the two approaches (i.e., if the model fit was better under one model versus the other, the results of the model with the better model fit would be reported). In addition, the manufacturer-submitted IDC reported using the total residual deviance as another indicator of the best model fit between the two approaches. Statistical heterogeneity was reported between direct pairwise comparisons using the I^2 statistic. The manufacturer-submitted IDC reported using the Monte Carlo error of less than 5% to determine an acceptable posterior estimate. Inconsistency between direct and indirect evidence was assessed using the inconsistency factor. The manufacturer-submitted IDC reported that the following sensitivity analyses were planned: Asian population, graphical data, and pooling treatments by their respective class. No rationale as to the reason for conducting these sensitivity analyses was provided. No subgroup analysis was planned. The results were reported as odds ratio for categorical outcomes and mean difference for continuous outcomes. Confidence intervals were reported for results obtained using the Bucher method, although the margins of the confidence interval were not explicitly specified (i.e., if it was a 95% confidence interval or lower). Results obtained from the Bayesian NMA methods were reported with a 95% credible interval range.

Results

The manufacturer-submitted IDC identified 108 eligible studies that fit their inclusion and exclusion criteria. Of these, only 13 contributed to the Bucher indirect comparison analysis, and 27 studies contributed to the Bayesian NMA analysis. The manufacturer-submitted IDC provided a list for reasons for exclusion of studies from the analysis, the main reasons being a comparative arm similar to the intervention arm (28 studies) and uncertainty regarding the basal insulin therapy (48 studies). Many of the outcomes reported by the trials are objective in nature and are sufficiently similar. The duration of the included trials varied in the range of 24 weeks to 52 weeks. However, the manufacturer-submitted IDC reported pooling the results of outcomes reported between 20 weeks to 30 weeks of the trial, regardless of the actual trial duration. A representation of the evidence network for each outcome is presented under the corresponding outcome heading.

The manufacturer-submitted IDC reported that the overall risk of bias in the included studies was low but did not provide the results of the individual assessment of each included study. A summary of the baseline and demographic characteristics of the enrolled patients in each study is presented in Table 41. The included studies represented a relatively large spectrum of combinations of insulin, oral antidiabetes drugs, GLP-1 receptor agonists, and DPP-4 inhibitor. The manufacturer-submitted IDC reported that all oral antidiabetes drugs were handled as a single class (i.e., background therapies). A breakdown of the initial and final average insulin dose in each study is presented in Table 42.

Table 41: Summary of Baseline Characteristics

Study Name	Blinding	Treatment Duration (Weeks)	Age (Years), Mean	Male, %	Diabetes Duration (Years), Mean	A1C at Baseline, %, Mean	BMI, Mean
Blonde et al. 2015 (AWARD 4)	Open-label	52	59.4	53.3	12.7	8.5	32.5
Mathieu et al. 2014 (BEGIN: VICTOZA ADD-ON)	Open-label	26	61.0	65.6	12.4	7.7	32.3
Buse et al. 2011	Single blind	30	59.0	56.5	12.0	8.4	33.5
Rodbard et al. 2016	Open-label	26	59.6	58.1	12.6	8.3	32.1
Buse et al. 2014 (DUAL 2)	Double-blind	26	57.5	54.5	10.5	8.8	33.7
Lingvay et al. 2016 (DUAL 5)	Open-label	26	58.8	50.3	11.5	8.3	31.7
Rosenstock 2016 et al. (GET GOAL-DU02)	Open-label	26	59.8	45.3	12.2	7.9	32.2
Riddle et al. 2013 (GET GOAL-L)	Double-blind	24	57.0	46.7	12.5	8.4	32.1
Mathieu et al. 2015	Double-blind	24	58.8	47.9	13.5	8.8	32.1
Hanefeld et al. 2011	Double-blind	26	63.0	61.2	11.1	7.3	32.2
Rosenstock et al. 2014 (HARMONY-6)	Open-label	52	55.6	47.0	11.0	8.5	NR
Vora et al. 2015 (LANSCAPE)	Open-label	24	61.6	72.5	13.0	8.6	31.1
Ligthelm et al. 2011	Open-label	24	52.7	56.7	11.2	9.0	33.8
Ahman et al. 2015 (LIRA ADD2 BASAL)	Double-blind	26	58.4	56.9	12.1	8.3	32.3
LIXILAN- L	Open-label	30	60.0	46.7	12.1	8.1	31.2
Liebl et al. 2009 (PREFER)	Open-label	26	60.1	NR	10.3	8.2	NR
Rosenstock et al. 2008	Open-label	24	54.7	52.5	11.1	8.9	34.5

Study Name	Blinding	Treatment Duration (Weeks)	Age (Years), Mean	Male, %	Diabetes Duration (Years), Mean	A1C at Baseline, %, Mean	BMI, Mean
Diamant et al. 2014 (The 4B study)	Open-label	30	59.0	53.0	11.5	8.3	32.5
Tinahones et al. 2014	Open-label	24	57.6	45.0	11.8	8.6	29.6
Yilmaz et al. 2007	Unclear	26	58.9	39.6	14.0	9.1	30.7
Yki-Jarvinen et al. 2013	Double-blind	52	60.1	52.2	NR	8.3	31.0
POZZILLI et al. 2016 (Award 9 trial)	Double-blind	28	60.4	NR	NR	8.4	32.7
Savvidou et al. 2016	Double-blind	26	63.0	39.4	11.3	8.2	32.8
Juurinen et al. 2009	Double-blind	24	56.0	55.5	9.4	7.5	32.9
Kumar et al. 2016	Open-label	26	58.1	56.6	11.5	8.4	30.1
Distiller et al. 2014	Open-label	24	51.7	50.0	12.4	9.0	39.7
Hood et al. 2015	Open-label	24	55.4	52.9	15.2	8.7	41.9

BMI = body mass index.

Source: CDR submission: Soliqua (insulin glargine and lixisenatide injection), 100 units/mL insulin glargine and 33 mcg/mL lixisenatide solution for injection in a pre-filled pen. Company: Sanofi-Aventis Canada Inc. [CONFIDENTIAL manufacturer's submission]. Laval, Quebec: Sanofi-Aventis Canada Inc.; 2018 May 17.

Table 42: Insulin Dose at Baseline and End Point

Study Name	Treatment Arm	Total Insulin Dose at Baseline (units/kg)	Total Insulin Dose at End Point (units/kg)	Calculated Insulin Change From Baseline
Blonde et al. 2015 (AWARD 4)	Basal (q.d.) + 1 OAD	0.59	1.42	0.83
	Dulaglutide1.5 mg (q.w.) + 1 OAD	0.61	1.03	0.42
	Dulaglutide 0.75 mg (q.w.) + 1 OAD	0.64	1.05	0.41
Mathieu et al. 2014 (BEGIN: VICTOZA ADD-ON)	Basal (q.d.) + liraglutide 1.2 mg (q.d.) + 1 OAD	0.7	0.55	–0.05
	Basal (q.d.) + 1 OAD	0.66	NR	0.19
Buse et al. 2014 (DUAL 2)	iDegLira 1.8 mg (q.d.) + 1 OAD	0.3	0.48	0.18
	Basal (q.d.) + 1 OAD	0.31	0.48	0.17
Lingvay et al. 2016 (DUAL 5)	iDegLira 1.8 mg (q.d.) + 1 OAD	0.18	0.47	0.29
	Basal (q.d.) + 1 OAD	0.37	0.74	0.37
Riddle et al. 2013 (GET GOAL-L)	Basal (q.d.) + Lixisenatide 20 mcg (q.d.) + 1 OAD	0.62	0.58	–0.04
	Basal (q.d.) + 1 OAD	0.65	0.64	–0.01
Rosenstock et al. 2016 (GET GOAL-DU02)	Basal (q.d.) + 1 OAD	0.735	0.83	0.21
	Basal (q.d.) + 1 OAD	0.72	0.89	0.4
	Basal (q.d.) + Lixisenatide	0.74	0.75	0.01

Study Name	Treatment Arm	Total Insulin Dose at Baseline (units/kg)	Total Insulin Dose at End Point (units/kg)	Calculated Insulin Change From Baseline
	20 mcg (q.d.) + 1 OAD			
Hanefeld et al. 2011	Basal (q.d.) + 2 OAD	0.36	0.3	–0.06
	Basal (q.d.) + 1 OAD	0.41	0.35	–0.06
Yki-Jarvinen 2013	Basal (q.d.) + Linagliptin 5 mg (q.d.) + 1 OAD	NR	NR	-
	Basal (q.d.) + 1 OAD	NR	NR	-
Mathieu et al. 2015	Basal (q.d.) + Sitagliptin 100 mg (q.d.) + 1 OAD	0.43	0.63	0.2
	Basal (q.d.) + 1 OAD	0.41	0.67	0.26
Ligthelm et al. 2011	Premix + 1 OAD	0.46	1.19	0.73
	Basal (q.d.) + 2 OAD	0.39	0.63	0.24
Ahman et al. 2015 (LIRA ADD2 BASAL study)	Liraglutide 8 mg+ basal (q.d.) + 1 OAD	0.54	0.41	–0.13
	Basal (q.d.) + 1 OAD	0.5	0.44	–0.06
Rosenstock et al. 2014 (HARMONY-6 trial)	Albiglutide 30 mg (q.w.) + Basal Insulin (q.d.) + 1 OAD	0.51	0.58	0.07
	Basal (q.d.) + 1 OAD	0.47	0.88	0.41
Liebl et al. 2009 (PREFER)	Premix	NR	0.74	-
	Basal (q.d.)	NR	0.96	-
Diamant et al. 2014 (The 4B study)	Basal (q.d.) + Exenatide 10 mcg (b.i.d.) + 1 OAD	0.675	0.64	–0.04
	Basal (q.d.) + 1 OAD	0.68	1.02	0.34
Rodbard et al. 2016	Premix	NR	1.11	-
	Basal (q.d.)	NR	1.34	-
Buse et al. 2011	Basal (q.d.) + 1 OAD	0.5	0.7	0.2
	Basal (q.d.) + Exenatide10 mcg (b.i.d.) + 10AD	0.51	0.66	0.15
Tinahones et al. 2014	Premix + 1 OAD	0.43	0.67	0.24
	Basal (q.d.) + 1 OAD	0.43	0.64	0.21
Yilmaz et al. 2007	Premix	0.6	0.74	0.14
	Premix + 1 OAD	0.62	0.53	–0.09
Rosenstock et al. 2008	Premix + 1 OAD	0.53	1.4	0.87
	Basal (q.d.) + 1 OAD	0.56	1.2	0.64
Aroda et al. 2016	iGlarLixi + 1 OAD	0.4	0.53	0.13
	Basal (q.d.) + 1 OAD	0.4	0.53	0.13
POZZILLI et al. 2016 (AWARD-9)	Dulaglutide 1.5 mg	0.42	NR	-
	Placebo	0.42	NR	-
Distiller et al. 2014	U-500 + metformin	2.01	2	–0.01
	U-500 + metformin + exenatide	2.12	1.9	–0.22
Hood et al. 2015	Insulin (t.i.d.)	2.5	2.8	0.3
	Insulin (b.i.d.)	2.4	2.7	0.3
Juurinen et al. 2009	Nateglinide 120 mg (t.i.d.)	0.83	0.83	0
	Placebo	0.72	0.74	0
Kumar et al. 2016	Basal (q.d.) + 1 OAD	NR	0.69	-
	Premix (q.d.) + 1 OAD	NR	0.69	-

Study Name	Treatment Arm	Total Insulin Dose at Baseline (units/kg)	Total Insulin Dose at End Point (units/kg)	Calculated Insulin Change From Baseline
Savivdou et al. 2016	Basal (q.d.) + Exenatide 10 mcg (b.i.d.) + 1 OAD	NR	NR	-
	Basal (q.d.) + RAI (t.i.d.) + 1 OAD	NR	NR	-
Vora et al. 2015 (LANSCAPE)	Premix (b.i.d.) + 1 OAD	0.49	1.03	-
	Basal (q.d.) + RAI (q.d.) + 1 OAD	0.46	0.99	-

b.i.d. = twice daily; NR = not reported; OAD = oral antidiabetes drug; q.d. = once daily; RAI = rapid-acting insulin; t.i.d. = three times daily.

Source: CDR submission: Soliqua (insulin glargine and lixisenatide injection), 100 units/mL insulin glargine and 33 mcg/mL lixisenatide solution for injection in a pre-filled pen. Company: Sanofi-Aventis Canada Inc. [CONFIDENTIAL manufacturer's submission]. Laval, Quebec: Sanofi-Aventis Canada Inc.; 2018 May 17.

While the manufacturer-submitted IDC outlined 25 outcomes in the protocol to be analyzed, only six outcomes have been reported in the submission. The manufacturer-submitted IDC described that these six outcomes were chosen to align with the NICE scope in reporting outcomes in T2DM studies. Specifically, the reported outcomes are A1C% change from baseline, proportion of patients with A1C 7% or lower, proportion of A1C 6.5% or lower, body weight change from baseline, risk of any hypoglycemic event, and risk of documented hypoglycemia. Of these outcomes, we have summarized here the A1C% change from baseline, proportion of patients with A1C 7% or lower, proportion of A1C 6.5% or lower, body weight change from baseline, and risk of any hypoglycemic event.

Results Using the Bucher IDC Method

The evidence network is presented in Figure 6. Using the Bucher method for the outcome of A1C% change from baseline, the fixed-ratio combination of insulin glargine and lixisenatide injection + one oral antidiabetes drug exhibited a favourable statistically significant finding versus insulin degludec + one oral antidiabetes drug (mean difference –0.86; CI, –1.4 to –0.32); and an unfavourable statistically significant finding versus liraglutide 1.8 mg + basal insulin + one oral antidiabetes drug (mean difference: 0.66; CI, 0.05 to 1.27), the rest of the comparisons under this outcome showed no statistically significant findings.

Using the Bucher method for the outcome of proportion of patients with less than 7% A1C, the fixed-ratio combination of insulin glargine and lixisenatide injection + one oral antidiabetes drug exhibited a favourable statistically significant finding versus pre-mixed insulin (twice daily) + one oral antidiabetes drug (odds ratio 2.56; CI, 1.58 to 4.14), pre-mixed insulin + any number of oral antidiabetes drug (odds ratio 2.37; CI, 1.53 to 3.67), and degludec (once daily) + one oral antidiabetes drug (odds ratio 4.95; CI, 2.64 to 9.3), the rest of the comparisons under this outcome showed no statistically significant findings.

Using the Bucher method for the outcome of proportion of patients with less than 6.5% A1C, the fixed-ratio combination of insulin glargine and lixisenatide injection + one oral antidiabetes drug exhibited a favourable statistically significant finding versus pre-mixed insulin + any number of oral antidiabetes drug (odds ratio 2.78; CI, 1.25 to 6.16), and degludec (once daily) + one oral antidiabetes drug (odds ratio 5.96; CI, 2.94 to 12.09); and an unfavourable statistically significant finding versus liraglutide 1.8 mg + basal insulin (once daily) + one oral antidiabetes drug (odds ratio 0.15, CI, 0.07 to 0.35), the rest of the comparisons under this outcome showed no statistically significant findings.

Using the Bucher method for the outcome of body weight change from baseline, the fixed-ratio combination of insulin glargine and lixisenatide injection + one oral antidiabetes drug exhibited a favourable statistically significant finding versus linagliptin 5 mg (once daily) + basal insulin (once daily) + one oral antidiabetes drug (mean difference –1.09; CI, –1.53 to –0.65), basal insulin (once daily) + two oral antidiabetes drugs (mean difference –1.57; CI, –2.9 to –0.24), and pre-mixed insulin + any number of oral antidiabetes drug (mean difference –3.07; CI, –4.1 to –2.04); and an unfavourable statistically significant finding versus insulin degludec/liraglutide (iDegLira) 1.8 mg (once daily) + one oral antidiabetes drug (mean difference 1.75; CI, 1.05 to 2.45), liraglutide 1.8 mg + basal (once daily) + one oral antidiabetes drug (mean difference 1.73; CI, 0.11 to 3.35), basal insulin (once daily) + exenatide 10 mcg (twice daily) + one oral antidiabetes drug (mean difference 1.37; CI, 0.26 to 2.48), basal insulin (once daily) + dulaglutide 0.75 mg (once weekly) + one oral antidiabetes drug (mean difference 1.04; CI, 0.1 to 1.98).

Using the Bucher method for the outcome of proportion of any hypoglycemic event, the fixed-ratio combination of insulin glargine and lixisenatide injection + one oral antidiabetes drug exhibited a favourable statistically significant finding versus all available comparisons, specifically versus lixisenatide 20 mcg (once daily) + basal insulin (once daily) + one oral antidiabetes drug (rate ratio 0.61; CI, 0.48 to 0.77), basal insulin (once daily) + exenatide 10 mcg (twice daily) + one oral antidiabetes drug (rate ratio 0.63; CI, 0.46 to 0.86), and basal insulin (once daily) + two oral antidiabetes drug (rate ratio 0.43; CI, 0.32 to 0.58). The results of the outcomes using the Bucher method are summarized in Table 43.

The authors did not report any sensitivity or subgroup analysis on the studies included in Bucher IDC. Statistical heterogeneity in arms with direct meta-analysis was measured with the I^2 statistic and was considered low except in the following instances:

a. In the outcome of A1C 7% or lower; iDegLira 1.8 mg (once daily) + one oral antidiabetes drug versus basal insulin (once daily) + one oral antidiabetes drug (70.70%)
b. In the outcome of A1C 6.5% or lower; iDegLira 1.8 mg (once daily) + one oral antidiabetes drug versus basal insulin (once daily) + one oral antidiabetes drug (77.40%)
c. In the outcome of changes in body weight; basal insulin + one oral antidiabetes drug versus GLP + basal insulin + one oral antidiabetes drug (64.90%)
d. In the outcome of any hypoglycemic event; basal insulin (once daily) + one oral antidiabetes drug versus iDegLira 1.8 mg (once daily) + one oral antidiabetes drug (78.3%)

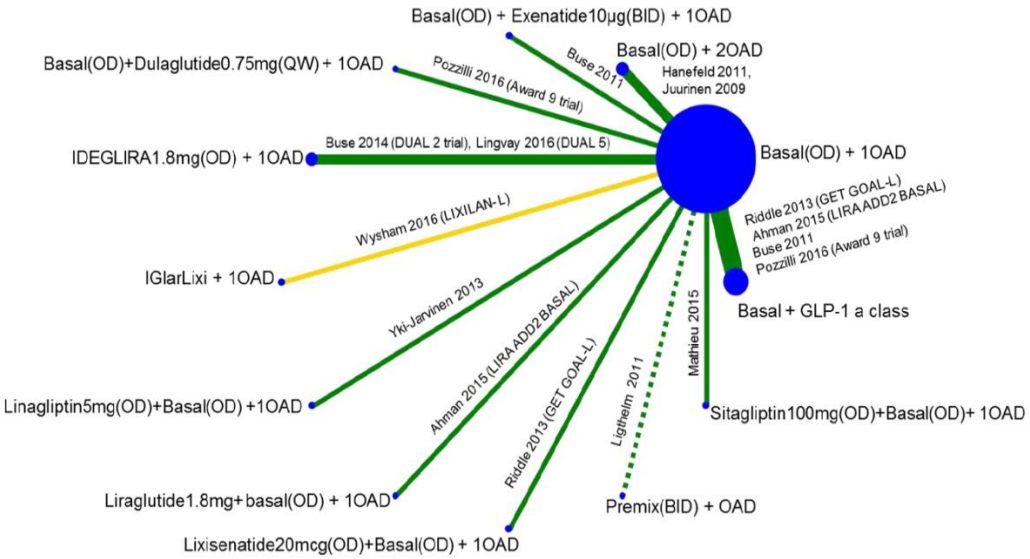
Table 43: Bucher IDC Results

Treatment	Outcomes				
Results Under the Bucher Method					
Fixed-Ratio Combination of Insulin Glargine and Lixisenatide Injection + 1 OAD Relative to:					
	A1C% Change, Mean Difference (95% CI)	**Proportion of A1C ≤ 7%, OR, (95% CI)**	**Proportion of A1C ≤ 6.5%, OR (95% CI)**	**Body Weight Change, Mean Difference (95% CI)**	**Any Hypoglycemic Event, RR (95% CI)**
Insulin + GLP-1 receptor agonist + Oral antidiabetes drug					
iDegLira 1.8 mg (q.d.) + 1 OAD	0.21 (–0.07 to 0.49)	0.8 (0.44 to 1.46)	0.83 (0.4 to 1.72)	**1.75 (1.05 to 2.45)**	NA
Liraglutide 1.8 mg + basal (q.d.) + 1 OAD	**0.66 (0.05 to 1.27)**	0.71 (0.48 to 1.05)	**0.15 (0.07 to 0.35)**	**1.73 (0.11 to 3.35)**	NA
Lixisenatide 20 mcg (q.d.) + basal (q.d.) + 1 OAD	–0.24 (–0.54 to 0.06)	1.06 (0.57 to 1.97)	0.75 (0.29 to 1.94)	–0.07 (–0.9 to 0.76)	**0.61 (0.48 to 0.77)**
Basal (q.d.) + Exenatide 10 mcg (b.i.d.) + 1 OAD	0.16 (–0.12 to 0.44)	1.51 (0.83 to 2.76)	0.82 (0.37 to 1.81)	**1.37 (0.26 to 2.48)**	**0.63 (0.46 to 0.86)**
Basal (q.d.) + Dulaglutide 0.75 mg (q.w.) + 1 OAD	0.23 (–0.04 to 0.5)	0.73 (0.41 to 1.29)	NA	**1.04 (0.1 to 1.98)**	NA
Basal + GLP-1 as class	0.14 (–0.17 to 0.45)	0.79 (0.39 to 1.61)	0.45 (0.14 to 1.45)	0.89 (–0.03 to 1.82)	**0.59 (0.49 to 0.72)**
Insulin + DPP inhibitor + Oral antidiabetes drug					
Linagliptin 5 mg (q.d.) + basal (q.d.) + 1 OAD	0.11 (–0.14 to 0.36)	NA	NA	**–1.09 (–1.53 to –0.65)**	NA
Sitagliptin 100 mg (q.d.) + basal (q.d.) + 1 OAD	–0.14 (0.32 to 0.04)	1.22 (0.76 to 1.93)	NA	NA	NA
Insulin + Oral antidiabetes drug					
Basal (q.d.) + 2 OAD	–0.18 (–0.41 to 0.06)	1.01 (0.44 to 2.34)	NA	**–1.57 (–2.9 to –0.24)**	**0.43 (0.32 to 0.58)**
Premix (b.i.d.) + 1 OAD	NA	**2.56 (1.58 to 4.14)**	NA	NA	NA
Premix (b.i.d.) + OAD (pooled Basal (q.d.) + 1 OAD and Basal (q.d.) + 2 OAD)	–0.44 (–0.9 to 0.02)	**2.37 (1.53 to 3.67)**	**2.78 (1.25 to 6.16)**	**–3.07 (–4.1 to –2.04)**	NA
Degludec (q.d.) + 1 OAD	**–0.86 (–1.4 to –0.32)**	**4.95 (2.64 to 9.3)**	**5.96 (2.94 to 12.09)**	–0.87 (–2.41 to 0.67)	NA

A1C = glycated hemoglobin; b.i.d. = twice daily; GLP-1 = glucagon-like peptide-1 agonist; iDegLira = insulin degludec/liraglutide fixed-ratio combination; NA = not available; OAD = oral antidiabetes drug; q.d. = once daily; OR = odds ratio; RR = rate ratio.

Source: CDR submission: Soliqua (insulin glargine and lixisenatide injection), 100 units/mL insulin glargine and 33 mcg/mL lixisenatide solution for injection in a pre-filled pen. Company: Sanofi-Aventis Canada Inc. [CONFIDENTIAL manufacturer's submission]. Laval, Quebec: Sanofi-Aventis Canada Inc.; 2018 May 17.

Figure 6: Network Diagram for A1C% Change From Baseline Under the Bucher Adjusted Indirect Comparison Method



BID = twice daily; OD = once daily; OAD = oral antidiabetes drug; QW = once weekly.

Source: CDR submission: Soliqua (insulin glargine and lixisenatide injection), 100 units/mL insulin glargine and 33 mcg/mL lixisenatide solution for injection in a pre-filled pen. Company: Sanofi-Aventis Canada Inc. [CONFIDENTIAL manufacturer's submission]. Laval, Quebec: Sanofi-Aventis Canada Inc.; 2018 May 17.

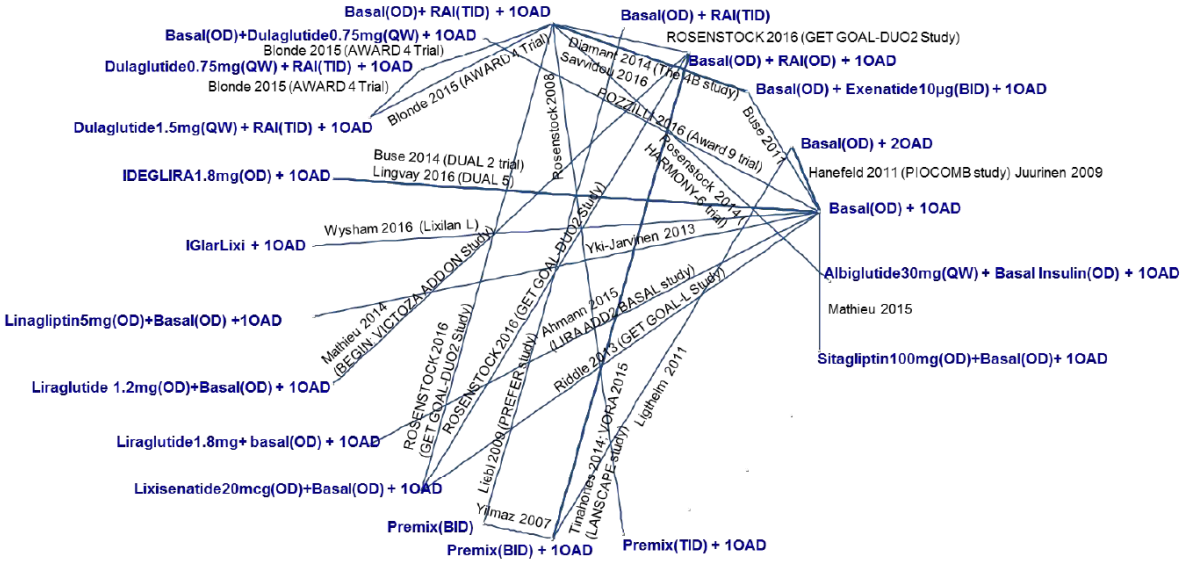
Results Using the Bayesian IDC Method

The results of the outcomes using the Bayesian NMA method are summarized in Table 44.

A1C% Change From Baseline

The manufacturer-submitted IDC described using the results of the fixed-effects model to present the main analysis. Based on the fixed-effects model, the fixed-ratio combination of insulin glargine and lixisenatide injection + one oral antidiabetes drug exhibited a favourable finding: basal insulin (once daily) + one oral antidiabetes drug (median difference –0.54; 95% CrI, –0.69 to –0.38), and pre-mixed insulin (b.i.d.) (median difference –0.97; 95% CrI, –1.91 to –0.02); and an unfavourable finding versus liraglutide 1.8 mg + basal insulin + one oral antidiabetes drug (median difference 0.66; 95% CrI, 0.04 to 1.27), the rest of the comparisons under the fixed effects did not favour any treatment. However, when compared with the results obtained from the random-effects model, iGlarLixi (iGlarLixi) only exhibited a favourable finding in the comparison against basal insulin + one oral antidiabetes drug (median difference –0.54; 95% CrI, –0.80 to –0.28); the rest of the comparisons under the random-effects model did not favour any treatment. A network diagram of the evidence network informing this outcome is presented in Figure 7.

Figure 7: Network Diagram for A1C% Change From Baseline Under the Bayesian Network Meta-Analysis Method



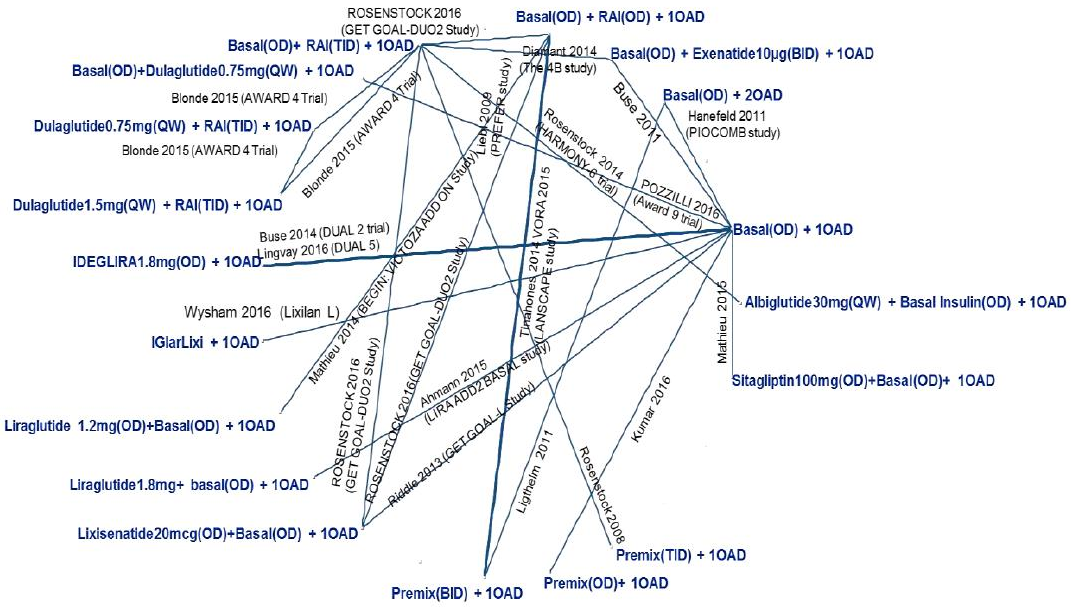
BID = twice daily; OAD = oral antidiabetes drug; OD = once daily; QW = once weekly; TID = three times daily.

Source: CDR submission: Soliqua (insulin glargine and lixisenatide injection), 100 units/mL insulin glargine and 33 mcg/mL lixisenatide solution for injection in a pre-filled pen. Company: Sanofi-Aventis Canada Inc. [CONFIDENTIAL manufacturer's submission]. Laval, Quebec: Sanofi-Aventis Canada Inc.; 2018 May 17.

Proportion of Patients With Less Than 7% A1C

Based on the fixed-effects model, the fixed-ratio combination of insulin glargine and lixisenatide injection + one oral antidiabetes drug exhibited a favourable finding versus basal insulin (once daily) + one oral antidiabetes drug (odds ratio 2.93; 95% CrI, 2.16 to 3.99), pre-mixed insulin (once daily) + one oral antidiabetes drug (odds ratio 2.56; 95% CrI, 1.59 to 4.16), and an unfavourable finding versus liraglutide 1.8 mg + basal insulin + one oral antidiabetes drug (odds ratio 0.34; 95% CrI, 0.19 to 0.58). The rest of the comparisons under this outcome did not favour any treatment. Results obtained from the random-effects model in this outcome are similar to the fixed-effects model with wider credible intervals. A network diagram of the evidence network informing this outcome is presented in Figure 8.

Figure 8: Network Diagram for Proportion of Patients With Less Than 7% A1C Under the Bayesian Network Meta-Analysis Method



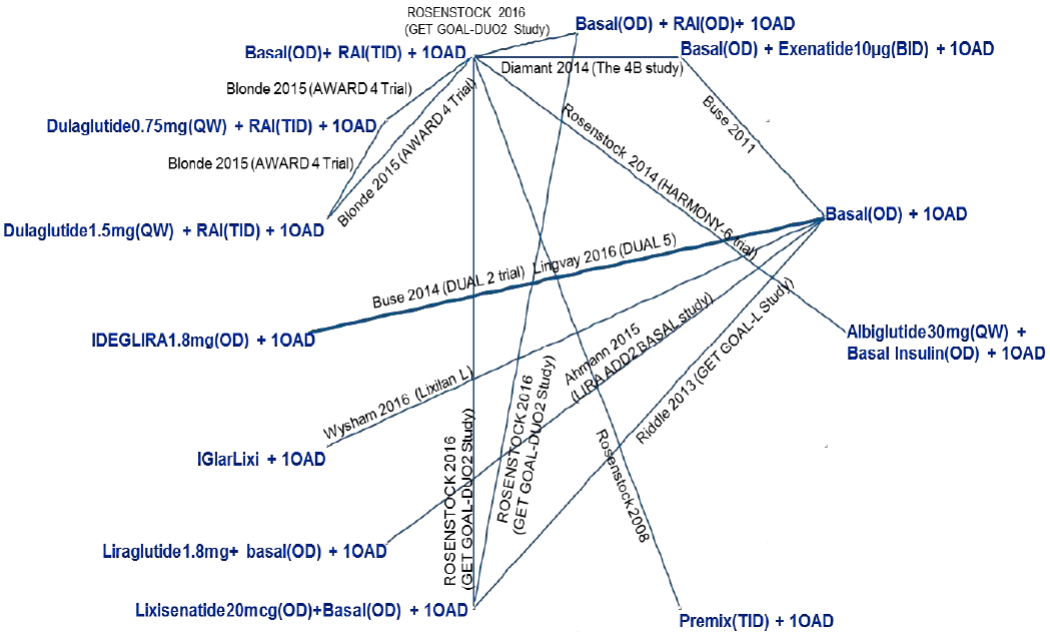
BID = twice daily; OAD = oral antidiabetes drug; OD = once daily; QW = once weekly; TID = three times daily.

Source: CDR submission: Soliqua (insulin glargine and lixisenatide injection), 100 units/mL insulin glargine and 33 mcg/mL lixisenatide solution for injection in a pre-filled pen. Company: Sanofi-Aventis Canada Inc. [CONFIDENTIAL manufacturer's submission]. Laval, Quebec: Sanofi-Aventis Canada Inc.; 2018 May 17.

Proportion of Patients With Less Than 6.5% A1C

For the outcome of proportion of patients with less than 6.5% A1C, and based on the fixed-effects model, the fixed-ratio combination of insulin glargine and lixisenatide injection + one oral antidiabetes drug exhibited a favourable finding versus basal insulin (once daily) + one oral antidiabetes drug (odds ratio 3.13; 95% CrI, 2.19 to 4.54); and an unfavourable finding versus liraglutide 1.8 mg + basal insulin + one oral antidiabetes drug (odds ratio 0.15; 95% CrI, 0.06 to 0.33), the rest of the comparisons under this outcome did not favour any treatment. Under the random-effects model, only the comparison against liraglutide 1.8 mg (once daily) + basal insulin (once daily) + one oral antidiabetes drug maintains a credible interval that excludes the null. A network diagram of the evidence network informing this outcome is presented in Figure 9.

Figure 9: Network Diagram for Proportion of Patients With Less Than 6.5% A1C Under the Bayesian Network Meta-Analysis Method



BID = twice daily; OAD = oral antidiabetes drug; OD = once daily; QW = once weekly; TID = three times daily.

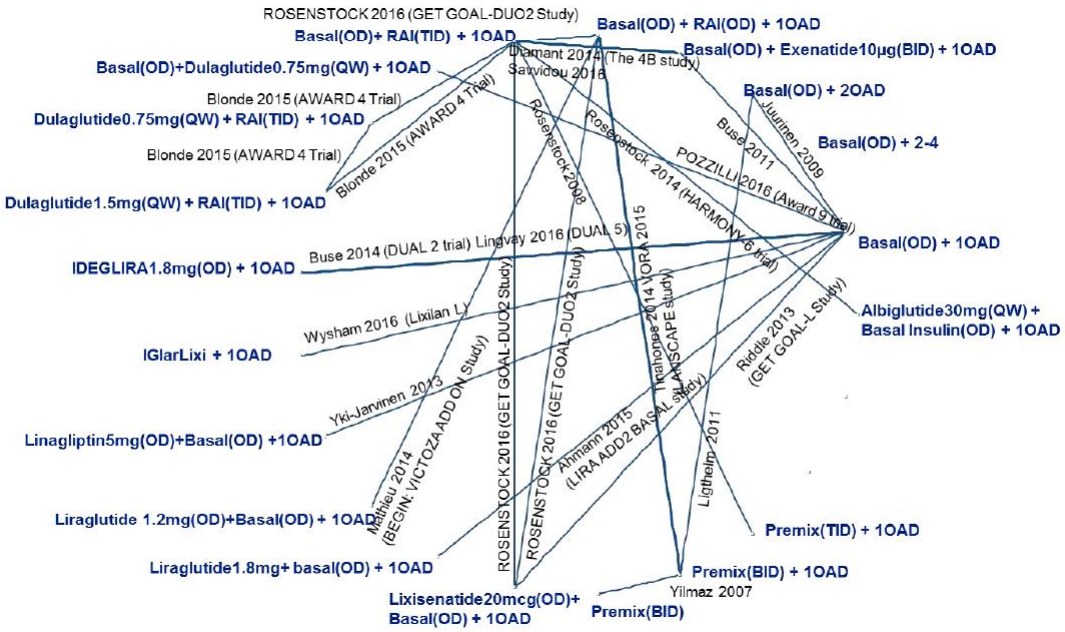
Source: CDR submission: Soliqua (insulin glargine and lixisenatide injection), 100 units/mL insulin glargine and 33 mcg/mL lixisenatide solution for injection in a pre-filled pen. Company: Sanofi-Aventis Canada Inc. [CONFIDENTIAL manufacturer's submission]. Laval, Quebec: Sanofi-Aventis Canada Inc.; 2018 May 17.

Change in Body Weight From Baseline

For the outcome of change in body weight from baseline, and based on the fixed-effects model, the fixed-ratio combination of insulin glargine and lixisenatide injection + one oral antidiabetes drug exhibited a favourable finding versus albiglutide 30 mg (once weekly) + basal insulin (once daily) + one oral antidiabetes drug (median difference –1.17; 95% CrI, –2.26 to –0.08), linagliptin 5 mg (once daily) + basal insulin (once daily) + one oral antidiabetes drug (median difference –1.09; 95% CrI, –1.59 to –0.59), basal insulin (once daily) + one oral antidiabetes drug (median difference –1.37; 95% CrI, –1.87 to –0.87), basal insulin (once daily) + two oral antidiabetes drug (median difference –1.27; 95% CrI, –2.34 to –0.2), pre-mixed insulin (b.i.d.) (median difference –3.49; 95% CrI, -5.76 to –1.25), pre-mixed insulin (twice daily) + one oral antidiabetes drug (median difference –2.81; 95% CrI, –3.82 to –1.8), pre-mixed insulin (three times daily) + one oral antidiabetes drug (median difference –2.17; 95% CrI, –3.46 to –0.89), basal insulin (once daily) + rapid-acting insulin (once daily) + one oral antidiabetes drug (median difference –2.21; 95% CrI, –3.18 to –1.24), and basal insulin (once daily) + rapid-acting insulin (three times daily) + one oral antidiabetes drug (median difference –2.67; 95% CrI, –3.61 to –1.75); and an unfavourable finding versus iDegLira 1.8 mg (once daily) + one oral antidiabetes drug (median difference 1.75; 95% CrI, 1.01 to 2.49), liraglutide 1.8 mg + basal insulin + one oral antidiabetes drug (median difference 1.73; 95% CrI, 0.09 to 3.37), liraglutide 1.2 mg (once daily) + basal insulin (once daily) + one oral antidiabetes drug (median difference 1.49; 95% CrI, 0.13 to 2.86), basal insulin (once daily) + exenatide 10 mcg (b.i.d.) + one oral antidiabetes drug (median difference 1.74; 95% CrI, 0.81 to 2.67), basal insulin (once daily) + dulaglutide 0.75

mg (once weekly) + one oral antidiabetes drug (median difference 1.04; 95% CrI, 0.07 to 2.01). Under the random-effects model, IGlarLixi (IGLARLIXI) only maintains a credible interval that excludes the null with the following comparisons: iDegLira 1.8 mg (once daily) + one oral antidiabetes drug, basal insulin (once daily) + one oral antidiabetes drug, pre-mixed insulin (b.i.d.), pre-mixed insulin (b.i.d.) + one oral antidiabetes drug, pre-mixed insulin (three times daily) + one oral antidiabetes drug, basal insulin (once daily) + rapid-acting insulin (once daily) + one oral antidiabetes drug, and basal insulin (once daily) + rapid-acting insulin (three times daily) + one oral antidiabetes drug. A network diagram of the evidence network informing this outcome is presented in Figure 10.

Figure 10: Network Diagram for Change in Body Weight From Baseline Under the Bayesian Network Meta-Analysis Method



BID = twice daily; OAD = oral antidiabetes drug; OD = once daily; QW = once weekly; TID = three times daily.

Source: CDR submission: Soliqua (insulin glargine and lixisenatide injection), 100 units/mL insulin glargine and 33 mcg/mL lixisenatide solution for injection in a pre-filled pen. Company: Sanofi-Aventis Canada Inc. [CONFIDENTIAL manufacturer's submission]. Laval, Quebec: Sanofi-Aventis Canada Inc.; 2018 May 17.

Proportion of Patients With Any Hypoglycemic Event

For the outcome of proportion of any hypoglycemic event, and under the fixed-effects model, the fixed-ratio combination of insulin glargine and lixisenatide injection + one oral antidiabetes drug exhibited a favourable finding versus all available comparisons, while noting that comparison against iDegLira and liraglutide combination therapies were not available. For this outcome, the manufacturer IDC described that the model did not converge under the random-effects model approach.

In addition, under the Bayesian NMA analysis, the manufacturer IDC reported a sensitivity analysis in which the comparators were pooled by class; this analysis is also presented in Table 44. It is notable that most findings that excluded the null under the fixed-effects model, when compared with findings from the random-effects model, ended up including the null in the credible interval range.

Table 44: Bayesian NMA Results

Treatment	Outcomes				
Results Under the Bayesian NMA Method					
Fixed-Ratio Combination of Insulin Glargine and Lixisenatide Injection + 1 OAD Relative to:					
	A1C% Change, Median Difference (95% CrI)	**Proportion of A1C ≤ 7%, OR (95% CrI)**	**Proportion of A1C ≤ 6.5%, OR (95% CrI)**	**Body Weight Change, Median Difference (95% CrI)**	**Any Hypoglycemic Event, RR (95% CrI)**
Insulin + GLP-1 receptor agonist + Oral antidiabetes drug					
iDegLira 1.8 mg (q.d.) + 1 OAD					
Fixed-effects model	0.17 (–0.05 to 0.40)	0.83 (0.55 to 1.24)	0.89 (0.56 to 1.42)	**1.75 (1.01 to 2.49)**	NA
Random-effects model	0.19 (–0.14 to 0.56)	0.81 (0.37 to 1.72)	0.84 (0.09 to 7.48)	**1.71 (0.15 to 3.13)**	NA
Liraglutide 1.8 mg + basal (q.d.) + 1 OAD					
Fixed-effects model	**0.66 (0.04 to 1.27)**	**0.34 (0.19 to 0.58)**	**0.15 (0.06 to 0.33)**	**1.73 (0.09 to 3.37)**	NA
Random-effects model	0.65 (–0.03 to 1.35)	**0.33 (0.13 to 0.84)**	**0.15 (0.01 to 2.02)**	1.73 (–0.42 to 3.89)	NA
Liraglutide 1.2 mg (q.d.) + basal (q.d.) + 1 OAD					
Fixed-effects model	0.17 (–0.21 to 0.55)	0.84 (0.37 to 1.86)	NA	**1.49 (0.13 to 2.86)**	NA
Random-effects model	0.17 (–0.36 to 0.66)	0.81 (0.24 to 2.62)	NA	1.49 (–0.79 to 3.61)	NA
Lixisenatide 20 mcg (q.d.) + basal (q.d.) + 1 OAD					
Fixed-effects model	–0.19 (–0.46 to 0.07)	1.21 (0.73 to 1.99)	0.99 (0.48 to 1.97)	–0.35 (–1.15 to 0.44)	**0.56 (0.45 to 0.68)**
Random-effects model	–0.2 (–0.58 to 0.19)	1.17 (0.49 to 2.7)	0.9 (0.07 to 9.8)	–0.36 (–1.98 to 1.12)	Model did not converge
Basal (q.d.) + Exenatide 10 mcg (b.i.d.) + 1 OAD					
Fixed-effects model	0.10 (–0.16 to 0.36)	1.17 (0.7 to 1.94)	0.67 (0.33 to 1.32)	**1.74 (0.81 to 2.67)**	**0.74 (0.6 to 0.93)**
Random-effects model	0.1 (–0.28 to 0.46)	1.2 (0.52 to 2.91)	0.67 (0.06 to 7.84)	1.72 (–0.01 to 3.25)	Model did not converge
Basal (q.d.) + Dulaglutide 0.75 mg (q.w.) + 1 OAD					
Fixed-effects model	0.23 (–0.06 to 0.52)	0.73 (0.41 to 1.28)	NA	**1.04 (0.07 to 2.01)**	NA
Random-effects model	0.23 (–0.18 to 0.65)	0.72 (0.29 to 1.86)	NA	1.04 (–0.7 to 2.8)	NA
Albiglutide 30 mg (q.w.) + basal insulin (q.d.) + 1 OAD					
Fixed-effects model	0.22 (–0.09 to 0.54)	0.73 (0.39 to 1.38)	0.43 (0.17 to 1.06)	**–1.17 (–2.26 to –0.08)**	**0.72 (0.54 to 0.98)**
Random-effects model	0.22 (–0.25 to 0.68)	0.73 (0.24 to 2.17)	0.41 (0.02 to 9.86)	–1.16 (–3.28 to 0.81)	Model did not converge

Treatment	Outcomes				
Results Under the Bayesian NMA Method					
Fixed-Ratio Combination of Insulin Glargine and Lixisenatide Injection + 1 OAD Relative to:					
	A1C% Change, Median Difference (95% CrI)	**Proportion of A1C ≤ 7%, OR (95% CrI)**	**Proportion of A1C ≤ 6.5%, OR (95% CrI)**	**Body Weight Change, Median Difference (95% CrI)**	**Any Hypoglycemic Event, RR (95% CrI)**
Dulaglutide 0.75 mg (q.w.) + RAI (t.i.d.) + 1 OAD					
Fixed-effects model	0.24 (–0.09, 0.58)	0.60 (0.32 to 1.10)	0.48 (0.22 to 1.05)	–0.51 (–1.72 to 0.67)	**0.33 (0.27 to 0.42)**
Random-effects model	0.24 (–0.24 to 0.71)	0.6 (0.2 to 1.74)	0.46 (0.02 to 10.78)	–0.5 (–2.66 to 1.51)	Model did not converge
Dulaglutide 1.5 mg (q.w.) + RAI (t.i.d.) + 1 OAD					
Fixed-effects model	0.29 (–0.04, 0.63)	0.66 (0.36 to 1.20)	0.41 (0.18 to 0.89)	0.53 (–0.67 to 1.73)	**0.40 (0.32 to 0.50)**
Random-effects model	0.29 (–0.2 to 0.76)	0.65 (0.22 to 1.92)	0.39 (0.01 to 9.14)	0.53 (–1.6 to 2.57)	Model did not converge
Insulin + DPP inhibitor + Oral antidiabetes drug					
Linagliptin 5 mg (q.d.) + basal (q.d.) + 1 OAD					
Fixed-effects model	0.11 (–0.16 to 0.38)	NA	NA	**–1.09 (–1.59 to –0.59)**	NA
Random-effects model	0.11 (–0.28 to 0.51)	NA	NA	–1.09 (–2.67 to 0.47)	NA
Sitagliptin 100 mg (q.d.) + basal (q.d.) + 1 OAD					
Fixed-effects model	–0.14 (–0.35 to 0.07)	1.22 (0.76 to 1.92)	NA	NA	NA
Random-effects model	–0.14 (–0.5 to 0.22)	1.21 (0.5 to 2.97)	NA	NA	NA
Insulin + Oral antidiabetes drug					
Basal (q.d.) + 1 OAD					
Fixed-effects model	**–0.54 (–0.69 to –0.38)**	**2.93 (2.16 to 3.99)**	**3.13 (2.19 to 4.54)**	**–1.37 (–1.87 to –0.87)**	**0.73 (0.66 to 0.8)**
Random-effects model	**–0.54 (–0.8 to –0.28)**	**2.93 (1.58 to 5.44)**	3.13 (0.5 to 19.06)	**–1.37 (–2.53 to –0.22)**	Model did not converge
Basal (q.d.) + 2 OAD					
Fixed-effects model	–0.16 (–0.41 to 0.09)	1.31 (0.69 to 2.48)	NA	**–1.27 (–2.34 to –0.2)**	**0.44 (0.33 to 0.59)**
Random-effects model	–0.16 (–0.51 to 0.2)	1.25 (0.46 to 3.15)	NA	–1.28 (–3.06 to 0.38)	Model did not converge
Premix (q.d.) + 1 OAD					
Fixed-effects model	NA	**2.56 (1.59 to 4.16)**	NA	NA	NA
Random-effects model	NA	**2.57 (1.06 to 6.29)**	NA	NA	NA
Premix (b.i.d.)					

Treatment	Outcomes				
Results Under the Bayesian NMA Method					
Fixed-Ratio Combination of Insulin Glargine and Lixisenatide Injection + 1 OAD Relative to:					
	A1C% Change, Median Difference (95% CrI)	**Proportion of A1C ≤ 7%, OR (95% CrI)**	**Proportion of A1C ≤ 6.5%, OR (95% CrI)**	**Body Weight Change, Median Difference (95% CrI)**	**Any Hypoglycemic Event, RR (95% CrI)**
Fixed-effects model	**–0.97 (–1.91 to –0.02)**	NA	NA	**–3.49 (-5.76 to –1.25)**	NA
Random-effects model	–0.98 (–2 to 0.01)	NA	NA	**–3.53 (-6.43 to –0.77)**	NA
Premix (b.i.d.) + 1 OAD					
Fixed-effects model	0.01 (–0.31 to 0.33)	1.02 (0.57 to 1.83)	NA	**–2.81 (–3.82 to –1.8)**	**0.53 (0.41 to 0.67)**
Random-effects model	0 (–0.44 to 0.42)	0.97 (0.36 to 2.43)	NA	**–2.81 (–4.67 to –1.14)**	Model did not converge
Premix (t.i.d.) + 1 OAD					
Fixed-effects model	–0.16 (–0.61 to 0.29)	1.49 (0.77 to 2.85)	1.00 (0.43 to 2.28)	**–2.17 (–3.46 to –0.89)**	**0.28 (0.22 to 0.35)**
Random-effects model	–0.17 (–0.73 to 0.4)	1.48 (0.49 to 4.47)	0.95 (0.04 to 22.51)	**–2.17 (–4.35 to –0.12)**	Model did not converge
Basal (q.d.) + RAI (q.d.) + 1 OAD					
Fixed-effects model	–0.19 (–0.49 to 0.13)	1.42 (0.83 to 2.42)	1.22 (0.56 to 2.62)	**–2.21 (–3.18 to –1.24)**	**0.46 (0.36 to 0.58)**
Random-effects model	–0.19 (–0.61 to 0.22)	1.37 (0.53 to 3.32)	1.14 (0.06 to 19.33)	**–2.2 (–4 to –0.57)**	Model did not converge
Basal (q.d.) + RAI (t.i.d.) + 1 OAD					
Fixed-effects model	0.06 (–0.20 to 0.33)	0.97 (0.58 to 1.61)	0.6 (0.29 to 1.21)	**–2.67 (–3.61 to –1.75)**	**0.29 (0.23 to 0.36)**
Random-effects model	0.06 (–0.33 to 0.44)	0.96 (0.39 to 2.33)	0.57 (0.04 to 7.56)	**–2.66 (–4.38 to –1.06)**	Model did not converge
Basal (q.d.) + RAI (t.i.d.)					
Fixed-effects model	–0.44 (–1.48 to 0.62)	NA	NA	NA	NA
Random-effects model	–0.46 (–1.58 to 0.68)	NA	NA	NA	NA
Comparators pooled by class					
Basal + 1 OAD					
Fixed-effects model	**–0.54 (–0.69 to –0.39)**	**2.93 (2.17 to 3.99)**	**3.12 (2.18 to 4.54)**	**–1.37 (–1.87 to –0.87)**	**0.73 (0.66 to 0.8)**
Random-effects model	**–0.54 (–0.86 to –0.22)**	**2.94 (1.05 to 8.15)**	3.14 (0.51 to 19.23)	–1.37 (–3.7 to 0.95)	0.72 (0.33 to 1.59)
Basal + 2 OAD					
Fixed-effects model	–0.16 (–0.41 to 0.08)	1.64 (0.92 to 2.91)	0.56 (0.2 to 1.57)	**–1.09 (–1.59 to –0.59)**	**0.44 (0.33 to 0.59)**
Random-effects model	–0.16 (–0.57 to 0.26)	1.49 (0.37 to 5.68)	0.71 (0.02 to 25.97)	–1.09 (–4.34 to 2.15)	0.44 (0.14 to 1.37)
Premix					

Treatment	Outcomes				
Results Under the Bayesian NMA Method					
Fixed-Ratio Combination of Insulin Glargine and Lixisenatide Injection + 1 OAD Relative to:					
	A1C% Change, Median Difference (95% CrI)	**Proportion of A1C ≤ 7%, OR (95% CrI)**	**Proportion of A1C ≤ 6.5%, OR (95% CrI)**	**Body Weight Change, Median Difference (95% CrI)**	**Any Hypoglycemic Event, RR (95% CrI)**
Fixed-effects model	**–0.99 (–1.93 to –0.06)**	NA	NA	**–2.98 (-5.16 to –0.8)**	NA
Random-effects model	–0.99 (–2.02 to 0.05)	NA	NA	–3.02 (-7.28 to 1.22)	NA
Premix + 1 OAD					
Fixed-effects model	–0.01 (–0.27 to 0.25)	1.44 (0.97 to 2.16)	0.5 (0.23 to 1.05)	–0.93 (–1.93 to 0.07)	**0.3 (0.24 to 0.37)**
Random-effects model	0 (–0.44 to 0.45)	1.37 (0.4 to 4.58)	0.63 (0.03 to 12.89)	–1.06 (–4.17 to 2.03)	0.37 (0.11 to 1.21)
Basal + RAI (q.d.) + 1 OAD					
Fixed-effects model	–0.18 (–0.43 to 0.07)	1.48 (0.97 to 2.24)	0.53 (0.27 to 1.05)	**–1.81 (–2.64 to –1)**	**0.3 (0.23 to 0.37)**
Random-effects model	–0.17 (–0.59 to 0.28)	1.51 (0.43 to 5.27)	0.64 (0.04 to 9.46)	–1.87 (–4.81 to 1.06)	0.38 (0.12 to 1.22)
Basal+ RAI (t.i.d.) + 1 OAD					
Fixed-effects model	0.06 (–0.17 to 0.28)	0.87 (0.58 to 1.3)	**0.3 (0.16 to 0.55)**	**–2.11 (–2.86 to –1.36)**	**0.29 (0.23 to 0.36)**
Random-effects model	0.08 (–0.31 to 0.52)	0.88 (0.25 to 3)	0.38 (0.04 to 4.23)	–2.2 (-5.07 to 0.65)	**0.28 (0.1 to 0.83)**
Basal + RAI (t.i.d.)					
Fixed-effects model	–0.47 (–1.52 to 0.59)	NA	NA	NA	NA
Random-effects model	–0.47 (–1.62 to 0.71)	NA	NA	NA	NA
iDegLira + 1 OAD					
Fixed-effects model	0.17 (–0.05 to 0.4)	0.83 (0.55 to 1.24)	0.89 (0.57 to 1.42)	**1.75 (1.02 to 2.48)**	NA
Random-effects model	0.2 (–0.2 to 0.66)	0.8 (0.22 to 2.82)	0.82 (0.09 to 7.55)	1.63 (–1.28 to 4.5)	NA
GLP + Basal + 1 OAD					
Fixed-effects model	0.1 (–0.11 to 0.31)	0.87 (0.6 to 1.26)	**0.36 (0.2 to 0.64)**	0.63 (–0.04 to 1.29)	**0.62 (0.5 to 0.75)**
Random-effects model	0.11 (–0.26 to 0.5)	0.87 (0.28 to 2.71)	0.43 (0.05 to 3.6)	0.82 (–1.76 to 3.47)	0.62 (0.23 to 1.64)
DPP-4 + Basal +1 OAD					
Fixed-effects model	–0.07 (–0.26 to 0.13)	1.22 (0.76 to 1.93)	NA	**–2.28 (–3.12 to –1.45)**	NA
Random-effects model	–0.04 (–0.43 to 0.37)	1.22 (0.28 to 5.25)	NA	–2.32 (-5.33 to 0.68)	NA
GLP + RAI (t.i.d.) + 1 OAD					
Fixed-effects model	0.26 (–0.02 to 0.54)	**0.56 (0.35 to 0.92)**	**0.22 (0.11 to 0.44)**	0.57 (–0.42 to 1.55)	**0.37 (0.29 to 0.45)**
Random-effects model	0.29 (–0.22 to	0.57 (0.11 to	0.28 (0.01 to	0.48 (–3.22 to	0.36 (0.09 to

Treatment	Outcomes				
Results Under the Bayesian NMA Method					
Fixed-Ratio Combination of Insulin Glargine and Lixisenatide Injection + 1 OAD Relative to:					
	A1C% Change, Median Difference (95% CrI)	**Proportion of A1C ≤ 7%, OR (95% CrI)**	**Proportion of A1C ≤ 6.5%, OR (95% CrI)**	**Body Weight Change, Median Difference (95% CrI)**	**Any Hypoglycemic Event, RR (95% CrI)**
	0.85)	2.85)	5.78)	4.17)	1.33)

A1C = glycated hemoglobin; b.i.d. = twice daily; CrI = credible interval; DPP-4 = dipeptidyl peptidase-4 inhibitor; GLP = glucagon-like peptide agonist; iDegLira = insulin degludec/liraglutide fixed-ratio combination; NA = not available; NMA = network meta-analysis; OAD = oral antidiabetes drug; OR = odds ratio; q.d. = once daily; q.w. = once weekly; RAI = rapid-acting insulin; RR = rate ratio; t.i.d. = three times daily.

Source: CDR submission: Soliqua (insulin glargine and lixisenatide injection), 100 units/mL insulin glargine and 33 mcg/mL lixisenatide solution for injection in a pre-filled pen. Company: Sanofi-Aventis Canada Inc. [CONFIDENTIAL manufacturer's submission]. Laval, Quebec: Sanofi-Aventis Canada Inc.; 2018 May 17.

The manufacturer-submitted IDC described three pre-specified sensitivity analyses for the results: studies with Asian population, studies with graphical data, and pooling treatments by their respective class. Of these, we have included the analysis of the pooled treatments in Table 44, as there is little evidence that the other two sensitivity analyses may affect the results. Under the fixed-effects model, the result shows that the fixed-ratio combination of insulin glargine and lixisenatide injection + one oral antidiabetes drug exhibited a favourable finding, with a credible interval excluding the null across all five outcomes when compared with the class of basal insulin + one oral antidiabetes drug. When compared with the class of basal insulin + two oral antidiabetes drugs, insulin glargine and lixisenatide injection + one oral antidiabetes drug exhibited a favourable finding, with a credible interval excluding the null only in the body weight and hypoglycemic episodes outcomes. No similar favourable outcomes across the five studies were noticed with comparisons against any of the other classes. However, it was noticed that insulin glargine and lixisenatide injection + one oral antidiabetes drug exhibited a favourable finding, with a credible interval excluding the null across all available class comparisons under the hypoglycemic outcome, although this outcome did not include a comparison with iDegLira + one oral antidiabetes drug. It is notable that most findings that excluded the null under the fixed-effects model, when compared with findings from the random-effects model, ended up including the null in the credible interval range except two, both comparing IGlarLixi (iGlarLixi) with basal insulin (once daily) + one oral antidiabetes drug under the outcomes of A1C change from baseline and proportion of patients with A1C 7% or lower.

In addition, the manufacturer's IDC showed that several meta-regression models were conducted that were not pre-specified in initial Methods section, specifically to address the potential impact of body mass index (BMI), disease duration, and baseline A1C levels. Overall, the results were similar to the base-case analysis. However, it was noted that controlling for BMI caused the results to be more favourable in terms of magnitude under the outcome of A1C change from baseline, but less favourable in terms of magnitude under the outcome of change in body weight. All regression analyses were conducted under the fixed-effects model.

The authors reported the deviance information criterion (DIC) and total residual deviance for each of their analyses. In addition, assessment of inconsistency was conducted, and no significant inconsistencies were found. Statistical heterogeneity (measured through the I^2) between nodes with direct connections and several studies was found to be high in the following instances:

- In the outcome of A1C ≤ 7%: iDegLira 1.8 mg (once daily) + one oral antidiabetes drug versus basal insulin (once daily) + one oral antidiabetes drug (70.70%).
- In the outcome of A1C ≤ 6.5%: iDegLira 1.8 mg (once daily) + one oral antidiabetes drug versus basal insulin (once daily) + one oral antidiabetes drug (77.40%).
- In the outcome of any hypoglycemic event: basal insulin (once daily) + rapid-acting insulin (RAI) (once daily) + one oral antidiabetes drug versus pre-mixed insulin (twice daily) + one oral antidiabetes drug (98.30%) and basal insulin (once daily) + one oral antidiabetes drug versus iDegLira 1.8 mg (once daily) + one oral antidiabetes drug (78.30%).
- In the pooled class outcome of A1C change from baseline: GLP + basal insulin + one oral antidiabetes drug versus basal insulin + one oral antidiabetes drug (71.20%), and DPP-4 + basal insulin + one oral antidiabetes drug versus basal insulin + one oral antidiabetes drug (71.20%).
- In the pooled class outcome of proportion of patients with ≤ 7% A1C: GLP + basal insulin + one oral antidiabetes drug versus basal insulin+ RAI (three times daily) + one oral antidiabetes drug (62.00%), and GLP + basal insulin + one oral antidiabetes drug versus basal insulin + one oral antidiabetes drug (85.60%).
- In the pooled class outcome of proportion of patients with ≤ 6.5% A1C: GLP + basal insulin + one oral antidiabetes drug versus basal insulin+ RAI (three times daily) + one oral antidiabetes drug (73.30%), GLP + basal insulin + one oral antidiabetes drug versus basal insulin + one oral antidiabetes drug (83.70%), and iDegLira + one oral antidiabetes drug versus basal insulin + one oral antidiabetes drug (77.40%).
- In the pooled class outcome of change in body weight: DPP-4 + basal insulin + one oral antidiabetes drug versus basal insulin + one oral antidiabetes drug (71.20%), and GLP + basal insulin + one oral antidiabetes drug versus basal insulin + one oral antidiabetes drug (71.30%).

Critical Appraisal

The manufacturer's IDC provided a comprehensive description of the methods, which included a clear population, intervention, comparisons, and outcomes. The manufacturer-submitted IDC report included a comprehensive literature search using several databases up to September 2016. Thus, it is likely that the manufacturer-submitted IDC missed several related trials that were published since that time, including comparators such as basal insulin plus SGLT2, which were consequently not included in the analysis. The manufacturer-submitted IDC reports an appropriately conducted screening and data extraction via two independent reviewers and a third reviewer to handle any disagreement. It also reports that there was an assessment of the quality of the included studies, but the results of such an assessment were not provided, nor was there any plan on how to handle studies that were deemed to be of low quality or high risk of bias. The manufacturer-submitted IDC's description of the approach used to conduct the Bayesian NMA was, overall, appropriate. This included conducting a sufficient number of burn-ins, measuring convergence through appropriate methods, conducting the analysis under both the fixed-

and the random-effects models, reporting on the DIC and residual heterogeneity, assessing statistical heterogeneity in direct comparisons, and assessing for inconsistency between direct and indirect evidence.

A comprehensive list of comparators, some of which are not marketed in Canada, were included. However, all of the reported results involve comparisons with drugs that are marketed in Canada. These comparators were considered to be appropriate in the Canadian setting, according to the clinical expert.

An important consideration when including a large number of trials is whether these trials are sufficiently similar, methodologically and clinically, to warrant valid comparisons. As two-third of the studies included in the analysis were open-label, it would have been beneficial for the manufacturer-submitted IDC to have conducted a sensitivity analysis on the non–open-label trials to assess the potential impact study design might have on the results, as open-label studies are more susceptible to show a bias in favour of the intervention. These sensitivity analyses could have been pre-specified as a priori. Baseline and demographic characteristics of the included studies were reported, and the clinical expert consulted by CADTH considered the studies to be, overall, similar. However, the clinical expert pointed out several studies that exhibited high A1C% at baseline. These studies are more susceptible to show larger effect size, and a sensitivity analysis may have been warranted. To this point, the manufacturer-submitted IDC reports conducting several meta-regressions to assess the impact of baseline BMI, disease duration, and A1C levels, which showed little difference from with the base-case analysis. These meta-regressions, however, were not part of the methods description reported in the manufacturer-submitted IDC and may have been conducted as post hoc analyses. The manufacturer-submitted IDC pooled all interventions and comparators, disregarding the type of oral antidiabetes drug that was used, and did not provide a sensitivity analysis to determine whether differences in the oral antidiabetes drug could have affected the results (e.g., a sensitivity analysis of studies that only allowed metformin as an oral antidiabetes drug), as some background therapies may affect some of the outcomes (e.g., sulfonylureas may increase the chance of hypoglycemia). While the manufacturer-submitted IDC did assess the statistical heterogeneity among the direct comparisons, it did not report any sensitivity/subgroup analysis that may have excluded several pairs of high statistical heterogeneity in order to assess the potential impact of such statistical heterogeneity. The outcomes reported were objective in nature, and the definition of any hypoglycemic event was sensitive to capture all definition of hypoglycemia across the studies. However, although the manufacturer-submitted IDC pre-specified capturing health-related quality of life outcomes, they were not reported. These outcomes are of interest to patients, and the lack of data for their assessment is an evidence gap.

A major limitation in interpreting the results obtained from the manufacturer-submitted IDC is that the authors used the results obtained from the fixed-effects model. The reasoning for this choice is largely that there was higher alignment between the direct meta-analysis results and the fixed-effects model results. Another common reason reported by the authors was the smaller standard deviation observed under the fixed-effects model. However, in the Methods section, the authors appropriately describe that the choice of the model will be based on model fitness, as measured through the DIC. The values of the DIC across outcomes are outlined in Table 45. Based on these results, the only justifiable use of results derived from the fixed-effects model are in the outcomes of any hypoglycemic event and in the pooled drug-class analysis, patients with or under A1C 7%. The rest of the outcomes show that the DIC values are smaller in the random-effects model, indicating better model

fit. In addition, the use of the random-effects model provides results that are generalizable outside of the evidence network, as it does not depend on the assumption of a true effect size across various studies. This, coupled with the fact that several direct meta-analysis comparisons exhibited high statistical heterogeneity, make the random-effects model a more appropriate choice for analysis.

Table 45: Differences in the Deviance Information Criterion Across Outcomes

Outcome	Deviance Information Criterion		Difference in the Deviance Information Criterion
	Fixed-Effects Model	Random-Effects Model	
A1C – change from baseline	–48.27	–45.97	–2.3
Patients with A1C 7% or lower	303.46	303.04	0.42
Patients with A1C 6.5% or lower	180.72	179.35	1.37
Body weight – change from baseline	46.41	47.95	1.54
Any hypoglycemia event	421.31	Model did not converge	NA
Pooled drug class – A1C – change from baseline	–40.38	–42.49	2.11
Pooled drug class – patients with A1C 7% or lower	284.17	295.93	–11.76
Pooled drug class – patients with A1C 6.5% or lower	200.27	185.05	15.22
Pooled drug class – body weight – change from baseline	100.03	47.87	52.16
Pooled drug class – any hypoglycemia event	340.07	208.80	131.27

A1C = glycated hemoglobin.

Source: CDR submission: Soliqua (insulin glargine and lixisenatide injection), 100 units/mL insulin glargine and 33 mcg/mL lixisenatide solution for injection in a pre-filled pen. Company: Sanofi-Aventis Canada Inc. [CONFIDENTIAL manufacturer's submission]. Laval, Quebec: Sanofi-Aventis Canada Inc.; 2018 May 17.

Other limitations in the manufacturer-submitted IDC include the following:

- The systematic review is not up to date: several new studies, including those with different comparators, have been published since the last date of the literature search that may influence the observed results.
- The reported outcome was not in accordance with the pre-specified list of outcomes: the authors report that the choice of the reported outcome was to align their review with outcomes described by NICE.
- The meta-regression analyses were not pre-specified.
- The differences in the included studies were not assessed using potentially relevant sensitivity analyses.

Review of Evans et al. (2018)[9]

Objectives and Rationale

The authors aimed to assess the treatment effect of iDegLira (fixed-ratio combination of insulin degludec and liraglutide) compared with iGlarLixi (fixed-ratio combination of insulin glargine and lixisenatide) in patients with T2DM who have previously failed to achieve adequate glucose control on basal insulin.

Methods for Evans et al. (2018)

Study Eligibility, Selection Process, and Data Extraction

The authors did not conduct a systematic review for their research question. The authors included only known phase III trials that were used by regulatory agencies to assess the interventions of interest. There was no description of any search strategy conducted or of a screening or data extraction process.

Comparators

The authors focused exclusively on comparing iDegLira (fixed-ratio combination of insulin degludec and liraglutide) with iGlarLixi (fixed-ratio combination of insulin glargine and lixisenatide), as informed by their respective phase III trials.

Outcomes

The authors reported on the following outcomes: change in A1C, change in body weight, daily insulin dose, severe or blood-glucose–documented hypoglycemia (defined as self-measured blood glucose ≤ 3.1 mmol/L), documented symptomatic hypoglycemia (defined as self-measured blood glucose ≤ 3.9 mmol/L). The authors did not explain whether a protocol existed or if these outcomes were pre-defined.

Quality Assessment

The authors did not explicitly describe a quality assessment process for the included studies.

Meta-Analysis and Indirect Comparison for Evans, 2018

The authors conducted two IDCs, one based on the Bucher indirect comparison method and one based on a Bayesian NMA approach. The authors describe that their Bayesian NMA was conducted with a non-informative prior distribution using the Markov chain Monte Carlo method, as implemented in the OpenBUGS software package. However, the authors did not provide information regarding the burn-ins, number of iterations until convergence, assessment of convergence, DIC values, total residual deviance/variance, or any attempts at assessing inconsistency between direct and indirect evidence. However, the authors mention that the network would be conducted with the fixed-effects generalized linear model.

Results of Evans et al. (2018)

Four trials were included: DUAL II, DUAL V, SWITCH 2, and LixiLan-L. Two trials informed the Bucher IDC analysis (DUAL II and LixiLan-L), and the authors pooled the basal insulin comparison arms of these trials. All four trials were used in the Bayesian NMA analysis, in which different types of basal insulin were treated as separate nodes. Two of the included studies had a double-blind design, while two had an open-label design. The reported study design and patients' baseline characteristics showed similarities across the trials; these are summarized in Table 46 and Table 47, as published. A representation of the evidence networks, as published in the IDC, is presented in Figure 11.

Table 46: Summary of Included Studies Characteristics

	LixiLan-L[13]	DUAL II[9]	DUAL V[12]	SWITCH 2[25]
Arms	IGlar U100 iGlarLixi	IDeg IDegLira	IGlar U100 IDegLira	IDeg IGlar U100
Inclusion criteria	Basal insulin >6 months Basal insulin 15–40 U/day 0–2 OADs (Metformin, SU, glinide SGLT2i, or DPP-4i) HbA_{1c} 7.5–10% (inclusive) SMPG ≤10–11.1 mmol/L Age ≥18 years	Basal insulin ≥90 days Basal insulin 20–40 U/day Metformin ± SU/glinide HbA_{1c} 7.5–10% (inclusive) BMI ≥27 Age ≥18 years	IGlar U100 ≥ 56 days IGlar U100 20–50 U/day Metformin HbA_{1c} 7.0–10% (inclusive) BMI ≤40 Age ≥18 years	Basal insulin ≥26 weeks Basal insulin ± OAD excluding SUs HbA_{1c} ≤ 9.5% BMI ≤45 Age ≥18 years
Run-in phase	6 weeks Discontinue all OADs except metformin Titrate IGlar U100 and metformin	None	None	None
Post run-in inclusion criteria	HbA_{1c} 7–10% (inclusive) SMPG ≤7.8 mmol/L IGlar U100 dose ≤50 U/day	N/A	N/A	N/A
Blinding	Open-label	Double-blind	Open-label	Double-blind
Concomitant	Metformin if used at screening	Metformin for all	Metformin for all	Continued pre-study OAD
Insulin caps	IGlar U100: 60 U iGlarLixi: 60 U	IDeg: 50 U IDegLira: 50 U	IGlar U100: No cap IDegLira: 50 U	IDeg: No cap IGlar U100: No cap
Titration target	4.4–5.6 mmol/L	4.0–5.0 mmol/L	4.0–5.0 mmol/L	3.9–5.0 mmol/L
Duration	30 weeks	26 weeks	26 weeks	32 × 2 weeks (64 weeks) in crossover design

BMI, body mass index; DPP-4i, dipeptidyl peptidase-4 inhibitor; IDeg, insulin degludec; IDegLira, insulin degludec/liraglutide; IGlar U100, insulin glargine 100 U/mL; iGlarLixi, insulin glargine/lixisenatide; N/A, not applicable; OAD, oral anti-diabetic drug; SGLT2i, sodium-glucose co-transporter-2 inhibitor; SMPG, self-measured fasting plasma glucose; SU, sulfonylurea; U, units.

Source: An indirect treatment comparison of the efficacy of insulin degludec/liraglutide (iDegLira) and insulin glargine/lixisenatide (iGlarLixi) in patients with type 2 diabetes uncontrolled on basal insulin, Evans M., et al.; Journal of Medical Economics, 2018, Taylor & Francis, reprinted by permission of the publisher (Taylor & Francis Ltd., http://www.tandfonline.com).

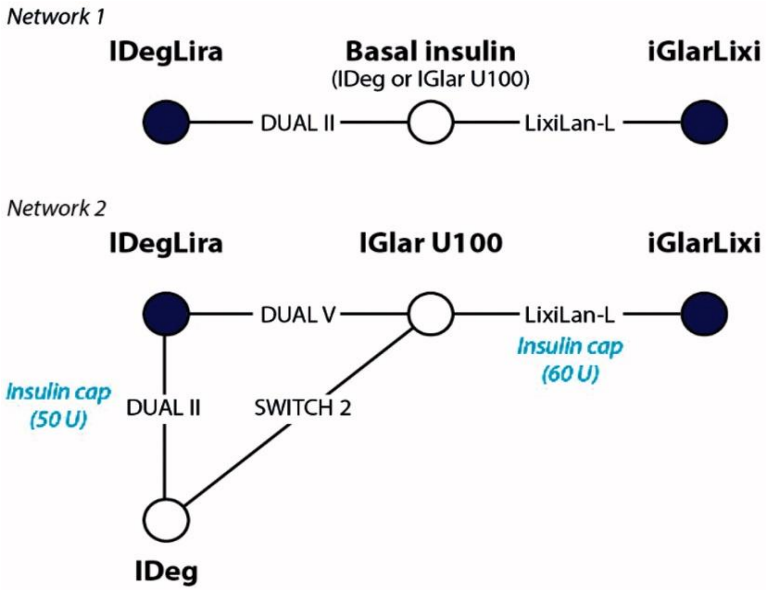
Table 47: Summary of Patients' Characteristics in the Included Studies

	LixiLan-L[a][13]		DUAL II[9]		DUAL V[12]		SWITCH 2[25]	
	iGlarLixi	IGlar U100	IDegLira	IDeg	IDegLira	IGlar U100	Total	
Sample size (*n*)	367	369	199	199	278	279	720	
Age (years)	60 ± 9	60 ± 9	57 ± 9	58 ± 11	58 ± 10	59 ± 9	61 ± 11	
White (%)	92	92	79	76	94	95	80	
Duration diabetes (years)	12 ± 7	12 ± 7	10 ± 6	11 ± 7	12 ± 7	11 ± 7	14 ± 8	
Insulin dose (units)	35 ± 9	35 ± 9	29 ± 8	29 ± 8	31 ± 10	32 ± 10	40[b] (IDeg/IGlar U100)	43[b] (IGlar U100/IDeg)
Weight (kg)	87.7 ± 14.5	87.1 ± 14.8	95.4 ± 19	93.5 ± 20	88.3 ± 17.5	87.3 ± 15.8	91.7 ± 19.5	
BMI (kg/m^2)	31.3 ± 4.3	31.0 ± 4.2	33.6 ± 6	33.8 ± 6	31.7 ± 4.4	31.7 ± 4.5	32.2 ± 5.6	
HbA_{1c} (%)	8.1 ± 0.7	8.1 ± 0.7	8.7 ± 0.7	8.8 ± 0.7	8.4 ± 0.9	8.2 ± 0.9	7.6 ± 1.1	
FPG (mmol/L)	7.3 ± 2.0	7.4 ± 2.1	9.7 ± 2.9	9.6 ± 3.1	8.9 ± 2.6	8.9 ± 2.9	7.6 ± 2.9	
Previous SU (%, yes)	40	40	50	50	0	0	0	

[a]Baseline values are post run-in period.
[b]Standard deviation not published.
Data are means ± standard deviation unless otherwise stated.
BMI, body mass index; FPG, fasting plasma glucose; IDeg, insulin degludec; IDegLira, insulin degludec/liraglutide; IGlar U100, insulin glargine 100 U/mL; iGlarLixi, insulin glargine/lixisenatide; SU, sulfonylurea.

Source: An indirect treatment comparison of the efficacy of insulin degludec/liraglutide (iDegLira) and insulin glargine/lixisenatide (iGlarLixi) in patients with type 2 diabetes uncontrolled on basal insulin, Evans M, et al.; Journal of Medical Economics, 2018, Taylor & Francis, reprinted by permission of the publisher (Taylor & Francis Ltd., http://www.tandfonline.com).

Figure 11: Network Diagram of Evans et al. (2018)



IDegLira = insulin degludec/liraglutide fixed-ratio combination; iGlarLixi = fixed-ratio combination of insulin glargine and lixisenatide; IGlar = insulin glargine; IDeg = insulin degludec; U = units.

Note: Network 1 represents the Bucher IDC, and Network 2 represents the Bayesian NMA.

Source: An indirect treatment comparison of the efficacy of insulin degludec/liraglutide (iDegLira) and insulin glargine/lixisenatide (iGlarLixi) in patients with type 2 diabetes uncontrolled on basal insulin, Evans M, et al.; Journal of Medical Economics, 2018, Taylor & Francis, reprinted by permission of the publisher (Taylor & Francis Ltd., http://www.tandfonline.com).

The outcomes presented by the authors indicate that iDegLira showed consistently favourable results (excluding the null), across both analysis networks, compared with iGlarLixi in terms of change in A1C% from baseline (–0.44%; 95% CrI, –0.71% to –0.17%) and change in body weight (–1.13 kg; 95% CrI, –1.96 kg to –0.30 kg). When assessing hypoglycemia, the authors report a lower rate ratio for iDegLira than iGlarLixi under the outcome of severe or blood glucose–confirmed hypoglycemia in the Bayesian NMA analysis (i.e., fewer patients exhibited the outcome under iDegLira than iGlarLixi) but not in the Bucher method analysis, while the outcome of symptomatic hypoglycemia did not show any results that excluded the null in either analysis. The results can be found in Table 48 and Table 49.

Table 48: Mean Difference of Change in A1C, Change in Body Weight, and Daily Insulin Dose Determined for Network 2 (Bayesian NMA) and Network 1 (Bucher IDC)

Outcomes	Mean difference (IDegLira vs iGlarLixi) (95% CI)	
	Network 1	Network 2 (Primary network)
Change in HbA_{1c} (%)	−0.53 (−0.77, −0.29)	−0.44 (−0.71, −0.17)
Change in body weight (kg)	−1.13 (−1.96, −0.30)	−1.42 (−2.50, −0.35)
Daily insulin dose (U)	0.3 (−2.2, 2.7)	−3.6 (−10.3, 3.3)

Source: An indirect treatment comparison of the efficacy of insulin degludec/liraglutide (iDegLira) and insulin glargine/lixisenatide (iGlarLixi) in patients with type 2 diabetes uncontrolled on basal insulin, Evans M, et al.; Journal of Medical Economics, 2018, Taylor & Francis, reprinted by permission of the publisher (Taylor & Francis Ltd., http://www.tandfonline.com).

Table 49: Rate Ratio of Hypoglycemia for Network 2 (Bayesian NMA) and Network 1 (Bucher IDC).

Outcome	Rate ratio (IDegLira vs iGlarLixi) (95% CI)	
	Network 1	Network 2 (Primary network)
Severe or BG-confirmed hypoglycemia[a]	0.66 (0.38, 1.16)	0.51 (0.29, 0.90)
ADA (SMPG ≤3.9 mmol/L) documented symptomatic hypoglycemia	1.17 (0.99, 1.38)	1.07 (0.90, 1.28)

[a]Defined as SMPG ≤3.1 mmol/L with or without symptoms in DUAL II and DUAL V, SMPG ≤3.1 mmol/L with symptoms in SWITCH 2, and SMPG ≤3.3 mmol/L with symptoms in LixiLan-L.

ADA, American Diabetes Association; BG, blood glucose; CI, confidence interval; IDegLira, insulin degludec/liraglutide; iGlarLixi, insulin glargine/lixisenatide; SMPG, self-measured plasma glucose; U, units.

Source: An indirect treatment comparison of the efficacy of insulin degludec/liraglutide (iDegLira) and insulin glargine/lixisenatide (iGlarLixi) in patients with type 2 diabetes uncontrolled on basal insulin, Evans M, et al.; Journal of Medical Economics, 2018, Taylor & Francis, reprinted by permission of the publisher (Taylor & Francis Ltd., http://www.tandfonline.com).

Critical Appraisal of Evans et al. (2018)

While the authors' use of the phase III trials alone meant that there is low methodological heterogeneity in the included studies, it also means that evidence that could have provided a better overall picture of the indirect evidence may have been missed. Clinical baseline characteristics were sufficiently similar, with the exception that the SWITCH 2 study exhibited lower values for baseline A1C and fasting plasma glucose. Outcomes described were objective and sufficiently similar in definition across included studies. In addition, the authors seem to have opted to use the fixed-effects model in their analysis. This, coupled with the previous point regarding lack of a systematic review, limits the results observed in the IDC to within the network (i.e., it cannot be generalized to the same comparison outside the network).

Another deficiency in the Evans et al. IDC is the lack of reporting on several pieces of information to allow the reader to better assess the validity of the reported results. We cannot determine whether the model used in the analysis converged properly; we are unable to determine any level of potential statistical heterogeneity; we are unable to determine whether the fixed-effects model was appropriate; and we cannot determine the level of consistency between direct and indirect evidence. Without these pieces of information, an assessment of the assumptions behind the use of IDCs cannot be made. As a result, there is high uncertainty involved in the results presented by Evans et al.

Discussion

Two IDCs were included: the manufacturer-submitted IDC[46] and the IDC by Evans et al.[9]. The manufacturer-submitted IDC was more comprehensive in the number of comparisons included, compared with Evan et al., which focused on comparing iDegLira with iGlarLixi. However, since the manufacturer-submitted IDC limited its search date to before September 2016, Evans et al. included studies that were published at a later date and would have been eligible in the manufacturer's IDC. Unlike the manufacturer-submitted IDC, Evans et al. did not conduct a systematic review; rather, the authors included phase III studies reviewed by regulatory agencies only. Both IDCs followed a similar methodological approach, conducting Bayesian NMA and a Bucher IDC analysis of the available evidence. Evans et al. suffers from limitations related to the lack of reporting information that would determine the validity of the assumptions underlying use of an indirect comparison (e.g., lack of inconsistency model) and the potential generalizability of the results (e.g., lack of clear reporting on whether a fixed- or random-effects model was used).[9,46] Limitations in the manufacturer's IDC include not being up-to-date and the lack of several sensitivity analyses that would have helped to better understand the effect of methodological and statistical heterogeneity among the included studies.

Comparing the results of the two IDCs for shared outcomes shows a divergence in the results of the outcome change in A1C. Evans et al. report results that favour iDegLira over iGlarLixi (with the exclusion of the null), whereas the manufacturer-submitted IDC reports a result that includes the null in the range (under the fixed-effects model). However, the results of changes in body weight were in the same direction in both studies and across both indirect methods, showing a result favouring iDegLira over iGlarLixi (with the exclusion of the null in the range). Although Evans et al. did report on hypoglycemia, showing a result that includes the null in the range, the manufacturer-submitted IDC was unable to report a comparison of these two drugs on this outcome. The divergence in the results of the

common outcomes in the same comparison between the two IDCs may indicate that, had the manufacturer-submitted IDC included more recently published trials, the reported outcome could be different. An overview of the common outcomes reported by both IDCs can be found in Table 50.

Table 50: Results of iGlarLixi and iDegLira, as Reported by the Manufacturer-Submitted IDC and Evans et al. (2018)

Outcome	IDC			
	Manufacturer-Submitted IDC		Evans et al., 2018	
	iGlarLixi versus iDegLira		iDegLira versus iGlarLixi	
	Bucher IDC (95% CI[a])	Bayesian NMA (95% CrI)	Bucher IDC (95% CI)	Bayesian NMA (95% CI[b])
Change in A1C%	0.21 (–0.07 to 0.49)	0.17 (–0.05 to 0.40)	**–0.53 (–0.77 to –0.29)**	**–0.44 (–0.71 to –0.17)**
Change in body weight (kg)	**1.75 (1.05 to 2.45)**	**1.75 (1.01 to 2.49)**	**–1.13 (–1.96 to –0.30)**	**–1.42 (–2.50 to –0.35)**
Any documented hypoglycemia	NA	NA	1.17 (0.99 to 1.38)	1.07 (0.90 to 1.28)

A1C = glycated hemoglobin; CI = confidence intervals; iGlarLixi = fixed-ratio combination of insulin glargine and lixisenatide; IDC = indirect comparison; iDegLira = insulin degludec/liraglutide fixed-ratio combination; NA = not applicable.

[a] As reported; the exact range is unknown.

[b] As reported by the authors; it is correctly the 95% credible interval.

Source: CDR submission: Soliqua (insulin glargine and lixisenatide injection), 100 units/mL insulin glargine and 33 mcg/mL lixisenatide solution for injection in a pre-filled pen. Company: Sanofi-Aventis Canada Inc. [**CONFIDENTIAL** manufacturer's submission]. Laval, Quebec: Sanofi-Aventis Canada Inc.; 2018 May 17. Evans M, Billings LK, Hakan-Bloch J, Slothuus U, Abrahamsen TJ, Andersen A, et al. An indirect treatment comparison of the efficacy of insulin degludec/liraglutide (iDegLira) and insulin glargine/lixisenatide (iGlarLixi) in patients with type 2 diabetes uncontrolled on basal insulin. J Med Econ. 2018;21(4):340-7.

In the manufacturer-submitted IDC, and across the two analyses, there was an overall consistent result in the common comparisons and outcomes between the Bucher IDC and the fixed-effects model Bayesian NMA. Overall, the results show that iGlarLixi is better at reducing weight when compared with insulin regimens and with DPP-4 inhibitors in conjunction with basal insulin, but not when compared with GLP-1 receptor agonist in conjunction with basal insulin (with the exception of albiglutide). Beyond the outcome of weight change, iGlarLixi shows a favourable hypoglycemic profile compared with basal insulin regimens alone, and compared with GLP-1 receptor agonist in conjunction with basal insulin, noting that this result was not available for the comparisons with iDegLira, liraglutide, dulaglutide, or any DPP-4 inhibitor. When considering glycemic control, the only comparison that consistently showed a result in favour of iGlarLixi across the three glycemic-control outcomes (A1C% change from baseline, proportion of A1C ≤ 7%, and proportion of A1C ≤ 6.5%) was with basal insulin (once daily) + one oral anti-hyperglycemic agent. In fact, iGlarLixi has consistently shown a worse glycemic-control profile across the three outcomes under the Bayesian NMA analysis when compared with liraglutide 1.8 mg + basal (once daily) + one oral antidiabetes drug. However, many of these results that exclude the null in their range no longer do so when viewed under the random-effects model, suggesting that generalizability of the outcomes from the fixed-effects model maybe limited. It is noted that, while the authors of the manufacturer's IDC used the results obtained from the fixed-effects model in the interpretation, the results of the random-effects model are more appropriate in most of the reported outcomes, based on DIC differences and the added generalizability.

Uncertainty in the results of the manufacturer's IDC stem mainly from the lack of an up-to-date search strategy and not including new trials that were published within the last two years. In addition, the impact of the high statistical heterogeneity observed in many direct

comparisons and the differences in the study design of the included trials were not assessed, adding another level of uncertainty in the observed findings.

While the IDC published by Evans et al. incorporated more recent evidence, it was limited in scope and was not a systematic review, leaving open the question of whether some studies were missed, or whether the inclusion of more comparators would have allowed more evidence to influence the iDegLira/iGlarLixi results. In addition, the authors did not report on several key pieces of information that would have allowed an assessment of the internal and external validity of the results presented. However, the Evans et al. IDC can inform us directly that there were several studies published that should have been included in the manufacturer's IDC.

Conclusion

Two studies reporting on an indirect treatment comparison of a fixed-ratio combination of iGlarLixi with other comparators were summarized: a manufacturer-submitted IDC, and one identified from the CDR literature search (Evans et al. 2018).

The IDC published by Evans et al. was not a systematic review and only looked at the phase III trials for iGlarLixi and iDegLira in insulin-experienced patients. Evans et al. reported that iDegLira was better than iGlarLixi in the outcomes of A1C change from baseline and weight gain.

The manufacturer-submitted IDC indicated that, overall, iGlarLixi is better at reducing weight when compared (under the fixed-effects model) with insulin regimens and with DPP-4 inhibitors in conjunction with basal insulin, but not when compared with GLP-1 receptor agonist in conjunction with basal insulin (with the exception of albiglutide). Beyond the outcome of weight change, iGlarLixi showed a favourable hypoglycemic profile when compared with basal insulin regimens alone, and with GLP-1 receptor agonists in conjunction with basal insulin, noting that these results were not available for the comparisons with iDegLira, liraglutide, dulaglutide, or any DPP-4 inhibitor. When considering glycemic control, the only comparison that consistently showed a favourable result compared with iGlarLixi across the three glycemic-control outcomes was with basal insulin (once daily) + one oral antidiabetes drug. iGlarLixi showed a worse glycemic-control profile across the three outcomes under the Bayesian NMA analysis when compared with liraglutide 1.8 mg + basal (once daily) + one oral antidiabetes drug. However, under the random-effects model, iGlarLixi demonstrated better glycemic-control profile and weight gain only in comparison with regimens that included some type of basal insulin + one oral antidiabetes drug, but not with other combinations.

Considering the lack of an up-to-date systematic review, the results presented here do not reflect the synthesis of all available evidence in the literature and considerably reduce the overall certainty in the observed results.

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